4th Edition

Handbook of Dialysis Therapy

Allen R. Nissenson

Richard N. Fine

SAUNDERS
ELSEVIER

SAUNDERS
ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

HANDBOOK OF DIALYSIS THERAPY, 4th EDITION ISBN: 978-1-4160-4197-9

Library of Congress Cataloging-in-Publication Data

Handbook of dialysis therapy/edited by Allen R. Nissenson, Richard N. Fine. – 4th ed.
p. ; cm.
Rev. ed. of: Dialysis therapy/[edited by] Allen R. Nissenson, Richard N. Fine. 3rd ed. c2002.
Includes bibliographical references and index.
ISBN 978-1-4160-4197-9
1. Hemodialysis. I. Nissenson, Allen R. II. Fine, Richard N. III. Dialysis therapy.
[DNLM: 1. Renal Dialysis WJ 378 H236 2008]
RC901.7.H45D527 2008
617.4′61059–dc22 2007024577

Acquisitions Editor: Susan Pioli
Editorial Assistant: Joan Ryan
Senior Project Manager: David Saltzberg
Design Direction: Karen O'Keefe Owens

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

This book is dedicated to the memory of Hinda Rosenthal, whose compassion, intelligence, wit, and wise advice had been an invaluable inspiration to me professionally and personally.

Allen R. Nissenson, M.D.

I would like to dedicate this Edition of Dialysis Therapy to my dear friend and colleague, John E. Lewy, MD, whose untimely death as he approached his 72nd Birthday was a tragic loss to the entire Pediatric Nephrology community. John was a pioneer in the field of Pediatric Nephrology and his friendship and wisdom will be forever missed.

Richard N. Fine, M.D.

CONTRIBUTORS

Sergio R. Acchiardo, M.D.
Professor and Chief, Division of Nephrology,
The University of Tennessee Health Science Center,
Memphis, Tennessee

Rajiv Agarwal, MBBS, MD, DNB, FAHA, FASN
Professor of Medicine, Division of Nephrology,
Indiana University; Staff Physician, Department of Medicine,
VA Medical Center, Indianapolis, Indiana

Amira Al-Uzri, MD, MCR
Associate Professor of Pediatrics, Oregon Health & Science
University, Portland, Oregon

Connie Anderson, BSN, MBA
Director of Clinical Services, Northwest Kidney Centers,
Seattle, Washington

Vincent T. Armenti, MD, PhD
Professor of Surgery, Temple University School of Medicine;
Interim Surgical Director, Kidney Transplantation,
Temple University Hospital, Philadelphia, Pennsylvania

Stephen R. Ash, MD, FACP
Clinical Associate Professor, Indiana University Medical
Center, Indianapolis; Director of Dialysis, Department
of Nephrology, Arnett-Clarian Health System, Lafayette;
Chairman and Director of Research and Development,
HemoCleanse, Inc. and Ash Access Technologies, Inc.,
Lafayette, Indiana

Morrell Michael Avram, MD
Division of Nephrology, Long Island College Hospital,
Brooklyn, New York

Antonio Bellasi, MD
Division of Nephrology, University of Milan and
San Paolo Hospital, Milan, Italy

Mark R. Benfield, MD
Professor of Pediatrics, University of Alabama at Birmingham; Professor and Division Director of Pediatric Nephrology, Children's Hospital, Birmingham, Alabama

William M. Bennett, MD
Division of Nephrology, Legacy Good Samaritan Hospital, Portland, Oregon

Jeffrey S. Berns, MD
Associate Professor of Medicine, Renal, Electrolyte, and Hypertension Division, University of Pennsylvania School of Medicine; Penn Presbyterian Medical Center, Philadelphia, Pennsylvania

Anatole Besarab, MD
Clinical Professor of Medicine, Wayne State University School of Medicine; Director of Clinical Research, Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan

Christopher R. Blagg, MD, FRCP
Professor Emeritus of Medicine, University of Washington; Executive Director Emeritus, Northwest Kidney Centers, Seattle, Washington

Geoffrey A. Block, MD
Director of Clinical Research, Denver Nephrologists, PC, Denver, Colorado

Paola Boccardo, BiolSciD
Negri Bergamo Laboratories, Mario Negri Institute for Pharmacological Research, Bergamo, Italy

W. Kline Bolton, MD
Professor of Medicine and Chief of Nephrology, University of Virginia School of Medicine, Charlottesville, Virginia

Mary L. Brandt, MD
Professor and Vice Chair, Michael E. DeBakey Department of Surgery, Baylor College of Medicine; Department of Pediatric Surgery, Texas Children's Hospital, Houston, Texas

Eileen D. Brewer, MD
Professor and Head, Renal Section, Department of Pediatrics, Baylor College of Medicine; Chief, Renal Service, Texas Children's Hospital, Houston, Texas

Patrick D. Brophy, MD
Assistant Professor of Pediatrics (Pediatric Nephrology), University of Michigan; Department of Pediatrics and Communicable Diseases, CS Mott Children's Hospital, Ann Arbor, Michigan

Warren S. Brown, PhD
Professor of Psychology and Director of the Travis Research Institute, Graduate School of Psychology, Fuller Theological Seminary, Pasadena, California

Suphamai Bunnapradist, MD
Division of Nephrology, Maggiore Hospital, IRCCS, Milan, Italy

John M. Burkart, MD
Professor of Internal Medicine, Division of Nephrology and Director, Dialysis Units, Wake Forest University Medical Center, Winston-Salem, North Carolina

Vito M. Campese, MD
Department of Medicine, The New York University School of Medicine; North Shore University Hospital, Manhasset, New York

Ralph J. Caruana, MD
Professor of Medicine, Division of Nephrology, Hypertension and Transplantation, Medical College of Georgia, Augusta, Georgia

Darrell L. Cass, MD
Assistant Professor, Michael E. DeBakey Department of Surgery and Department of Pediatrics, Baylor College of Medicine; Co-Director, Texas Children's Fetal Center, Texas Children's Hospital, Houston, Texas

Vimal Chadha, MD
Assistant Professor of Pediatrics and Chief,
Pediatric Nephrology, Virginia Commonwealth University
Medical Center, Richmond, Virgina

Christopher T. Chan, MD, FRCPC
Assistant Professor of Medicine, University of Toronto;
Medical Director, Home Hemodialysis,
Toronto General Hospital, Toronto, Ontario, Canada

Chaim Charytan, MD
Clinical Professor of Medicine, Cornell University College
of Medicine, New York; Chief, Renal Division,
New York Hospital Medical Center of Queens, Flushing,
New York

William R. Clark, M.D.
Clinical Assistant Professor of Medicine, Nephrology Division,
Indiana University School of Medicine, Indianapolis, Indiana;
Vice President, Medical Strategy and Therapy Development,
Gambro, Inc., Lakewood, Colorado

Allan J. Collins, MD, FACP
Chronic Disease Research Group, Minneapolis, Minnesota

Carl H. Cramer II, MD
Lecturer, Department of Pediatric and Adolescent Medicine,
Division of Pediatric Nephrology, Mayo Clinic, Rochester

Terri L. Crawford-Bonadio, RN, CNN
Director of Professional Education, Fresenius Medical Care
North America, Lexington, Massachusetts

Declan de Freitas, MB, BAO, BCh, LRCP&SI, MRCPI
Registrar in Renal Medicine, Manchester Institute of
Nephrology and Transplantation, The Royal Infirmary,
Manchester, United Kingdom

José A. Diaz-Buxo, MD, FACP
Clinical Professor of Medicine, University of North Carolina,
Chapel Hill, North Carolina; Senior Vice President,
Home Therapies Development, Fresenius Medical Care
North America, Lexington, Massachusetts

Lesley C. Dinwiddie, MSN, RN FNP, CNN
Senior Vice President, Institute for Clinical Excellence, Education, and Research, Wheaton, Illinois

Eileen N. Ellis, MD
Professor of Pediatrics, University of Arkansas for Medical Sciences; Director, Pediatric Nephrology, Arkansas Children's Hospital, Little Rock, Arkansas

Janet A. Englund, MD
Associate Professor of Pediatrics, University of Washington; Associate Professor of Pediatrics, Section of Infectious Diseases, Children's Hospital and Regional Medical Center; Clinical Associate, Department of Infection Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington

Fabrizio Fabrizi, MD
Staff Nephrologist, Maggiore Hospital, IRCCS, Milan, Italy

Donald A. Feinfeld, MD, FASN
Professor of Clinical Medicine, Albert Einstein College of Medicine, Bronx; Nephrology Fellowship Program Director, Beth Israel Medical Center, New York, New York

Charles Jerome Foulks, MD
Professor of Medicine and Director, Division of Nephrology-Hypertension, Texas A&M University Health Science Center and College of Medicine, Scott & White Clinic and Hospital, Temple, Texas

Denis Fouque, MD, PhD
Professor of Nephrology, JE 2411-University Claude Bernard, Hôpital E. Herriot, Lyon, France

Miriam Galbusera, BiolSciD
Negri Bergamo Laboratories, Mario Negri Institute for Pharmacological Research, Bergamo, Italy

Dayong Gao, PhD
Professor of Mechanical Engineering, University of Washington, Seattle, Washington; Professor of Mechanical Engineering, University of Kentucky, Lexington, Kentucky

F. John Gennari, MD
Robert F. and Genevieve B. Patrick Professor of Medicine,
University of Vermont College of Medicine;
Attending Physician, Department of Medicine,
Fletcher Allen Health Care, Burlington, Vermont

Jeffrey Giullian, MD
Clinical Fellow, Division of Nephrology, Vanderbilt University,
Nashville, Tennessee

Stuart L. Goldstein, MD
Associate Professor of Pediatrics, Baylor College of Medicine;
Medical Director, Renal Dialysis Unit and Pheresis Service,
Texas Children's Hospital, Houston, Texas

Esther A. Gonzalez, MD
Associate Professor of Internal Medicine,
Division of Nephrology, Saint Louis University,
St. Louis, Missouri

William G. Goodman, MD
Professor of Nephrology, University of California,
Los Angeles, California

Frank A. Gotch, MD
Associate Clinical Professor of Medicine,
Division of Nephrology, University of San Francisco,
San Francisco, California

Leila Haghighat
Research Assistant, Division of Nephrology,
Stroger Hospital of Cook County, Chicago, Illinois

Nikolas B. Harbord, MD
Nephrology Fellow, Beth Israel Medical Center, New York,
New York

Elizabeth Harvey, MD, FRCPC
Associate Professor of Pediatrics, University of Toronto;
Division of Nephrology, Hospital for Sick Children, Toronto,
Ontario, Canada

Nicholas Andrew Hoenich, PhD
Lecturer in Clinical Science, School of Clinical Medical Sciences, Newcastle University; Clinical Scientist, Renal Unit, The Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom

Christer Holmberg, MD
Professor of Pediatrics, University of Helsinki; Head of Pediatric Nephrology and Transplantation, Hospital for Children and Adolescents, Helsinki, Finland

Clifford J. Holmes, PhD
Vice President, Scientific Affairs, Renal Division, Baxter Healthcare, McGaw Park, Illinois

Robert Hootkins, MD, PhD, FASN
Section Chief, Department of Nephrology and Hypertension, Austin Diagnostic Clinic, Austin, Texas

Daljit K. Hothi, MBBS, MRCPCH
Department of Pediatric Nephrology, Hospital for Sick Children, Toronto, Ontario, Canada

Susan Hou, MD
Professor of Medicine, Division of Nephrology. Loyola University Stritch School of Medicine, Chicago, Illinois

Alastair J. Hutchison, MBChB, FRCP, MD
Honorary Lecturer in Medicine, Manchester University Medical School; Clinical Director and Consultant in Renal Medicine, Renal Unit, Manchester Institute of Nephrology and Transplantation, Manchester, United Kingdom

Zhongping Huang, PhD
Assistant Professor of Mechanical Engineering, Widener University, Chester, Pennsylvania

Todd S. Ing, MD
Professor Emeritus of Medicine, Loyola University Chicago, Stritch School of Medicine, Maywood; Staff Physician, Department of Medicine, Veterans Affairs Hospital, Hines, Illinois

Curtis A. Johnson, PharmD
Professor Emeritus of Pharmacy and Medicine,
University of Wisconsin-Madison, Madison, Wisconsin

Kamyar Kalantar-Zadeh, MD, MPH, PhD
Associate Professor of Medicine and Pediatrics,
Division of Nephrology and Hypertension,
University of California, Los Angeles,
David Geffen School of Medicine, Los Angeles;
Director of Dialysis Expansion Program and Epidemiology,
Division of Nephrology and Hypertension, Harbor-UCLA
Medical Center, Torrance, California

André A. Kaplan, MD, FACP, FASN
Professor of Medicine, Division of Nephrology,
University of Connecticut Health Center; Medical Director,
University of Connecticut Dialysis Center; Chief, Blood
Purification, John Dempsey Hospital, Farmington, Connecticut

Toros Kapoian, MD, FACP
Associate Professor of Medicine, Division of Nephrology
and Hypertension, University of Medicine and Dentistry of
New Jersey-Robert Wood Johnson Medical School;
Medical Director, Kidney Center of New Jersey;
Robert Wood Johnson University Hospital; Medical Director,
Dialysis Clinic, Inc., North Brunswick, New Jersey

Elaine M. Kaptein, MD, FACP
Professor of Medicine, Division of Nephrology,
University of Southern California; Division of Nephrology,
LAC+USC Medical Center, Los Angeles, California

Pranay Kathuria, MD
Associate Professor of Medicine and Chief,
Section of Nephrology, University of Oklahoma College
of Medicine, Tulsa, Oklahoma

Jeffrey L. Kaufman, MD, FACS
Associate Professor of Surgery, Tufts University School of
Medicine, Boston; Vascular Surgeon, Baystate Medical Center,
Springfield, Massachusetts

William F. Keane, MD
Vice-President, External Medical and Scientific Affairs, Merck & Company, Inc., North Wales, Pennsylvania

Ramesh Khanna, MD
Professor of Medicine and Director, Division of Nephrology, University of Missouri- Columbia, Columbia, Missouri

Neenoo Khosla, MD
Assistant Professor of Nephrology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Paul L. Kimmel, MD, FACP, FASN
Professor of Medicine and Director, Division of Renal Diseases and Hypertension, George Washington University School of Medicine, Washington, DC

Carl M. Kjellstrand, MD, PhD, FACP, FRCP(C)
Clinical Professor of Medicine, Loyola University, Chicago; Vice President, Medical Affairs, Aksys Ltd., Lincolnshire, Illinois

Laura Kooienga, MD
Assistant Professor, Division of Renal Diseases and Hypertension, University of Colorado Health Science Center, Denver, Colorado

Peter Kotanko, MD
Krankenhuas der Barmherzigen Brueder, Abteilung Innere Medizin, Graz, Austria

Eugene C. Kovalik, MD, CM, FRCPCCS, FACP
Associate Professor of Medicine, Division of Nephrology, Duke University Medical Center, Durham, North Carolina

Matthias Kraemer, MD
Scientific and Medical Affairs, Fresenius Biotech GmbH, Bad Homburg, Germany

Anthony Langone, MD
Assistant Professor of Medicine, Division of Nephrology, Vanderbilt University; Medical Director, Kidney Transplantation, Veterans Affairs Hospital, Nashville, Tennessee

Peter F. Lawrence, MD
Professor of Surgery, Chief of Vascular Surgery, and Director of the Gonda Vascular Center, David Geffen School of Medicine, University of California, Los Angeles; University of California, Los Angeles, Center for Health Sciences, Los Angeles, California

Jeffrey J. Letteri, BS
Gambro, Inc., Lakewood, Colorado

Chi-Bon Leung, MB, FRCP
Senior Medical Officer, Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong

Adeera Levin, MD, FRCPC
Professor of Medicine, Division of Nephrology, University of British Columbia; Division of Nephrology, St. Paul's Hospital; Director, BC Provincial Renal Agency, Vancouver, British Columbia, Canada

Nathan W. Levin, MD
Professor of Clinical Medicine, Albert Einstein College of Medicine; Attending Physician, Beth Israel Medical Center; Medical and Research Director, Renal Research Institute, New York, New York

John Kenneth Leypoldt, PhD
Research Professor of Medicine and Adjunct Professor of Bioengineering, Department of Medicine, University of Utah; Research Service, VA Salt Lake City Health Care System, Salt Lake City, Utah

Philip Kam-Tao Li, MD, FRCP, FACP
Professor and Chief of Nephrology, Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong

Robert McGregor Lindsay, MD, FRCPC, FRCP(Edin), FACP, FRCP(Glasg)
Professor of Medicine, Division of Nephrology, The University of Western Ontario and London Health Sciences Centre, London, Ontario, Canada

Francisco Llach, MD
Professor and Director of Clinical Nephrology, Georgetown University Medical Center, Washington, D.C.

Margaret MacDougall, MD, PhD
Clinical Associate Professor of Medicine, SUNY Upstate Medical University, Syracuse, New York

Lionel U. Mailloux, MD, FACP
Associate Professor of Medicine, New York University School of Medicine; Senior Attending Physician, Department of Medicine, North Shore University Hospital, Manhasset; Attending Physician, Division of Nephrology, St. Francis Hospital and Heart Center, Roslyn, New York

Kevin J. Martin, MB, BCh, FACP
Professor of Internal Medicine and Director, Division of Nephrology, Saint Louis University, St. Louis, Missouri

Paul Martin, MD
Professor of Medicine and Associate Director, Division of Liver Diseases, Mount Sinai School of Medicine, New York, New York

Ziad A. Massy, MD, PhD
Professor of Pharmacology and Director, INSERM ERT 12, University of Picardie; Professor of Clinical Pharmacology and Nephrology, Amiens University Hospital, Amiens, France

Philip A. McFarlane, MD, PhD, FRCP(C)
Professor, Division of Nephrology, University of Toronto; Medical Director, Home Dialysis, St. Michael's Hospital, Toronto, Ontario, Canada

Rajnish Mehrotra, MD, FACP, FASN
Associate Professor of Medicine, David Geffen School of Medicine, University of California, Los Angeles; Director, Peritoneal Dialysis, Department of Medicine, Harbor-UCLA Medical Center; Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California

Mark M. Mitsnefes, MD, MS
Associate Professor of Pediatrics, University of Cincinnati; Pediatric Nephrology, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Neal Mittman, MD
Division of Nephrology, Long Island College Hospital, Brooklyn, New York

Michael J. Moritz, MD
Chief, Section of Transplantation, Lehigh Valley Hospital, Allentown, Pennsylvania

Laura L. Mulloy, DO
Professor of Medicine and Section Chief of Nephrology, Hypertension and Transplantation Medicine, Medical College of Georgia, Augusta, Georgia

Sean W. Murphy, MD
Associate Professor of Medicine, Divisions of Nephrology and Clinical Epidemiology, The Health Sciences Centre, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Dana Negoi, MD
Assistant Professor of Clinical Medicine and Medical Director, Medicine Specialty Clinic, University of Missouri, Columbia, Missouri

Alicia M. Neu, MD
Associate Professor of Pediatrics, The Johns Hopkins University School of Medicine; Medical Director, Pediatric Dialysis and Kidney Transplantation, Department of Pediatric Nephrology, The Johns Hopkins Hospital, Baltimore, Maryland

Bijan Nikakhtar, MD
Division of Nephrology, Georgetown University Medical Center, Washington, D.C.

Allen R. Nissenson, MD, FACP
Professor of Medicine, Associate Dean, Director, Dialysis Program, and Attending Physician, Department of Medicine, University of California, Los Angeles, Medical Center, Los Angeles, California

Pouneh Nouri, MD
Division of Nephrology, Georgetown University Medical Center, Washington, D.C.

Jed G. Nuchtern, MD
Associate Professor, Michael E. DeBakey Department of Surgery and Department of Pediatrics, Baylor College of Medicine, Houston, Texas

Matthew J. Oliver, MD
Division of Nephrology, Medical College of Georgia, Augusta, Georgia

Ali J. Olyaei, PharmD, BCPS
Associate Professor of Medicine, Division of Nephrology and Director, Clinical Trials, Oregon Health and Science University, Portland, Oregon

Madeleine V. Pahl, MD, FACP
Associate Professor of Medicine, Division of Nephrology, University of California, Irvine; Director of Renal Clinic, Division of Nephrology, University of California, Irvine, Medical Center, Orange, California

Patricia Painter, PhD
Associate Professor of Medicine, Division of Renal Medicine, University of Minnesota, Minneapolis, Minnesota

Biff F. Palmer, MD
Professor of Internal Medicine and Director, Renal Fellowship Training Program, Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas

Patrick S. Parfrey, MD, FRCPC
University Research Professor, Department of Medicine, Memorial University; Staff Nephrologist, Eastern Health, St. John's, Newfoundland, Canada

Ashley A. Perilloux, MS, RD
Pediatric Renal Dietitian, University of California,
Los Angeles/DaVita Pediatric Dialysis, Los Angeles, California

Phuong-Chi T. Pham, MD
Associate Clinical Professor of Medicine, Division of
Nephrology, David Geffen School of Medicine,
University of California, Los Angeles; Division of Nephrology,
Olive View-UCLA Medical Center, Sylmar, California

Phuong-Thu T. Pham, MD
Assistant Clinical Professor of Medicine, Kidney and
Pancreas Transplantation, David Geffen School of Medicine,
University of California, Los Angeles, California

Andreas Pierratos, MD, FRCPC
Associate Professor of Medicine, University of Toronto;
Head, Home Hemodialysis, Department of Medicine,
Humber River Regional Hospital, Toronto, Ontario, Canada

Joanne D. Pittard, MS, RN
Professor of Allied Health, Community Services Education,
Glendale Community College, Santa Monica, California

Patrick H. Pun, MD
Fellow in Nephrology, Duke University Medical Center,
Durham, North Carolina

Erik Qvist, MD, PhD
Professor, University of Helsinki; Pediatric Nephrology and
Transplantation, Hospital for Children and Adolescents,
Helsinki, Finland

Dominic S.C. Raj, MD, DM
Associate Professor of Medicine, Division of Nephrology,
University of New Mexico Health Sciences Center,
Albuquerque, New Mexico

Giuseppe Remuzzi, MD, FRCP
Director, Division of Nephrology and Dialysis,
Azienda Ospedaliera Ospedali Riuniti di Bergamo;
Research Coordinator, Negri Bergamo Laboratories,
Mario Negri Institute for Pharmacological Research,
Bergamo, Italy

Claudio Rigatto, MD, FRCPC, MACP, MSc
Assistant Professor of Medicine, University of Manitoba; Staff Nephrologist, Manitoba Renal Program, Winnipeg, Manitoba, Canada

Michael V. Rocco, MD, MSCE, FACP
Professor of Internal Medicine (Nephrology), Wake Forest University School of Medicine; Division of Nephrology, North Carolina Baptist Hospital, Winston-Salem, North Carolina

Rudolph A. Rodriguez, MD
Associate Professor of Medicine, Division of Nephrology, University of Washington; Section Head, Primary and Specialty Medicine Service Line, VA/Puget Sound Medical Center, Seattle, Washington

Claudio Ronco, MD
Director, Department of Nephrology, Dialysis, and Transplantation, St. Bortolo Hospital, Vicenza, Italy

Kai Rönnholm, MD, PhD
Professor, University of Helsinki; Pediatric Nephrology and Transplantation, Hospital for Children and Adolescents, Helsinki, Finland

Mitchell H. Rosner, MD
Assistant Professor of Medicine and Associate Chief for Faculty Development, Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia

John H. Sadler, MD
Associate Professor Emeritus of Medicine, Division of Nephrology, University of Maryland; President and Chief Medical Officer, Independent Dialysis Foundation, Baltimore, Maryland

Isidro B. Salusky, MD
Professor of Pediatrics, Associate Dean of Clinical Research, Director, Pediatric Dialysis Program, Director, General Clinical Research Center, David Geffen School of Medicine, University of California, Los Angeles, California

Ramin Sam, MD
Assistant Professor of Medicine, University of Illinois at Chicago Medical Center; Physician, Stroger Hospital of Cook County, Chicago, Illinois

Cheryl P. Sanchez, MD
Associate Professor of Pediatrics, University of Wisconsin School of Medicine and Public Health; Department of Pediatrics, University of Wisconsin Children's Hospital, Madison, Wisconsin

Scott G. Satko, MD
Assistant Professor of Medicine and Director, Nephrology Fellowship Program, Division of Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Franz Schaefer, MD
Professor of Pediatrics, University of Heidelberg; Chief, Division of Pediatric Nephrology, Hospital for Pediatric and Adolescent Medicine, Heidelberg, Germany

Rebecca J. Schmidt, DO, FACP, FASN
Professor of Medicine and Chief, Section of Nephrology, West Virginia University School of Medicine; West Virginia University Hospitals, Morgantown, West Virginia

Cornelis H. Schröder, MD, PhD
Professor of Pediatric Nephrology, University Medical Center, Wilhelmina Children's Hospital, Utrecht, The Netherlands

Gerald Schulman, MD, FAAN
Professor of Medicine, Director of Hemodialysis, Co-Director of Clinical Trials Center in Nephrology, Vanderbilt University Medical Center, Nashville, Tennessee

Steve J. Schwab, MD
Department of Medicine, Division of Nephrology, Medical College of Georgia, Augusta, Georgia

Michael H. Schwenk, PharmD
Division of Nephrology and Hypertension, The New York Hospital of Queens, Flushing, New York

Warren B. Shapiro, MD
Associate Professor of Clinical Medicine,
State University of New York Health Sciences Center
at Brooklyn; Co-Chief, Division of Nephrology and
Hypertension, Brookdale University Hospital and
Medical Center, Brooklyn, New York

Richard A. Sherman, MD
Professor of Medicine, Division of Nephrology,
University of Medicine and Dentistry of New Jersey—
Robert Wood Johnson School of Medicine, New Brunswick,
New Jersey

Jodi M. Smith, MD, MPH
Assistant Professor of Pediatrics, University of Washington;
Division of Nephrology, Children's Hospital and Regional
Medical Center, Seattle, Washington

Michael J.G. Somers, MD
Assistant Professor of Pediatrics, Harvard Medical School;
Director of Clinical Services, Division of Nephrology,
Children's Hospital Boston, Boston, Massachusetts

Evelyn Spanner, MSc, RD
Renal Program, London Health Sciences Centre, London,
Ontario, Canada

Bruce S. Spinowitz, MD, FACP
Associate Clinical Professor of Medicine and Associate
Chairman, Department of Medicine, New York Hospital
of Queens, Flushing, New York

John C. Stivelman, MD
Associate Professor of Medicine, Division of Nephrology,
University of Washington School of Medicine;
Chief Medical Officer, Northwest Kidney Centers,
Seattle, Washington

Cheuk-Chun Szeto, MD, FRCP
Professor, Department of Medicine and Therapeutics,
Prince of Wales Hospital, Chinese University of Hong Kong,
Shatin, Hong Kong

Alf M. Tannenberg, MD
Professor of Clinical Medicine, New York Medical College; Chief, Renal Service, Metropolitan Hospital Center, New York, New York

Karen B. Tipton, RN, BSN, CPN
Director, Renal Care Center, Children's Hospital of Alabama, Birmingham, Alabama

Avram Z. Traum, MD
Harvard Medical School; Division of Nephrology, Children's Hospital Boston, Boston, Massachusetts

Arthur Tsai, MD
Post-doctoral Fellow, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Zbylut J. Twardowski, MD, PhD
Professor Emeritus of Medicine, Division of Nephrology, University of Missouri, Columbia, Missouri

Antonios H. Tzamaloukas, M.D.
Professor of Medicine, University of New Mexico School of Medicine; Chief, Renal Section, New Mexico Veterans Affairs Health Care System; Staff Nephrologist, University of New Mexico Hospital; Nephrologist, Dialysis Clinics, Inc., Albuquerque, New Mexico

Raymond Vanholder, MD
Department of Internal Medicine, Nephrology Section, University Hospital, Ghent, Belgium

Nosratola D. Vaziri, MD, MACP
Professor of Medicine, Physiology and Biophysics, Division of Nephrology, University of California, Irvine; Chief, Division of Nephrology and Hypertension, University of California, Irvine Medical Center, Orange, California

Maureen Wakeen, RN, MS
Department of Medicine, Division of Nephrology, University of Wisconsin and University of Wisconsin Hospital, Madison, Wisconsin

Bradley A. Warady, MD
Professor of Pediatrics, University of Missouri-Kansas City School of Medicine; Associate Chairman, Department of Pediatrics, Chief, Section of Pediatric Nephrology, and Director, Dialysis and Transplantation, Children's Mercy Hospital, Kansas City, Missouri

Richard A. Ward, PhD
Professor of Medicine, Division of Nephrology, Kidney Disease Program, University of Louisville, Louisville, Kentucky

Steven J. Wassner, MD
Vice-Chair for Education and Chief, Division of Pediatric Nephrology and Hypertension, Penn State University College of Medicine; Department of Pediatrics, The Penn State Children's Hospital, The Milton S. Hershey Medical Center, Hershey, Pennsylvania

Steven D. Weisbord, MD, MSc
Assistant Professor of Medicine, Renal-Electrolyte Division, University of Pittsburgh School of Medicine; Staff Physician, Renal Section and Core Investigator, Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

John J. White, MD
Assistant Professor, Division of Nephrology, Medical College of Georgia, Augusta, Georgia

Suzanne H. White, RN, CNP
Nurse Clinician, Renal Care Center, Children's Hospital of Alabama, Birmingham, Alabama

James F. Winchester, MD
Chief, Division of Nephrology, Beth Israel Medical Center, New York, New York

David W. Windus, MD
Professor of Medicine, Renal Division, Washington University School of Medicine; Attending Physician, Barnes-Jewish Hospital, St. Louis, Missouri

Jay B. Wish, MD
Professor of Medicine, Case Western Reserve University;
Medical Director, Hemodialysis Services,
Division of Nephrology, University Hospitals Case
Medical Center, Cleveland, Ohio

Anthony R. Zappacosta, MD
Director of Dialysis, Campus Chief, Nephrology,
Department of Medicine, The Bryn Mawr Hospital,
Bryn Mawr, Pennsylvania

Stephen W. Zimmerman, MD
Professor Emeritus, Department of Medicine,
University of Wisconsin; Division of Nephrology,
Saint Mary's Hospital; Madison Area Renal Specialists,
Madison, Wisconsin

PREFACE

The dialysis population continues to grow both in the United States and worldwide. Emerging economies as well as developing nations have chosen to utilize resources to extend the lives of individuals afflicted with end-stage renal disease (ESRD).

Despite assiduous efforts to utilize renal transplantation as a viable option for potential recipients with ESRD, the increments in the number of transplants performed annually have been modest and certainly have been woefully inadequate compared to the annual growth in the dialysis population. Any such increments in the number of renal transplants performed annually have resulted, at least in the United States, from the increased availability of living donors. Limited availability of deceased donor organs continues to impede successful renal transplantation worldwide.

Consequently, patients require dialysis therapy for prolonged periods of time. This results in the development and/or progression of the consequences of uremia, and the associated co-morbid conditions: hypertension, cardiovascular disease, and those related to diabetes mellitus.

The objective of the initial edition of *Handbook of Dialysis Therapy* was to enlist the involvement of preeminent individuals in various areas of clinical dialysis, to address, in a succinct fashion, the pertinent clinical problems encountered in adults and children undergoing dialysis. The intent was to provide a "how-to" approach to help the potential reader to solve specific patient problems. *Dialysis Therapy* was developed to help nephrologists (pediatric and adults), nurses, technicians and other members of the health care team resolve the myriad of problems confronting the patients undergoing dialysis.

It has been almost a decade since the 3rd Edition of *Dialysis Therapy* and the practice of dialysis continues to be modified to meet the increasing complexity of the patient population and the technical and pharmaceutical advances. Many of the contributors to this edition of *Handbook of Dialysis Therapy* have contributed to previous editions; however, there are 29 new contributors to the 4th Edition who have brought a new perspective to the clinical problems of dialysis encountered.

Similarly, the format for this 4th edition has been updated from previous editions. In addition to adding new chapters, we have paid particular attention to the readability of the text, tables, and figures. Resizing of the book to make it more

portable and the abundant use of color are additional enhancements.

This book remains a problem solving tool and is complementary to our larger, more comprehensive textbook *Clinical Dialysis*, the 4th Edition, which was published in 2006.

We wish to thank all of our contributors for their outstanding work and hope that this book will be a useful reference for physicians, nurses, technicians, dieticians, social workers and administrators, all of whom assiduously attempt to optimize the clinical care of the dialysis population. The Editors wish to thank Susan Pioli, from Elsevier, whose invaluable assistance made the publication of this text possible.

Allen R. Nissenson, MD
Richard N. Fine, MD
Editors

Table of Contents

Section 7 IMPROVING OUTCOMES IN DIALYSIS PATIENTS

20 Quality, Safety, and Accountability, Jay B. Wish
21 Initiation of Dialysis Therapy, Scott G. Satko and John M. Burkart
22 Daily (quotidian) Hemodialysis, Andreas Pierratos, Chris Chan, and Phil McFarlane
23 NKF-K/DOQI (DOQI): Key Recommendations, Adeera Levin and Mike Rocco

Section 8 THE HEODIALYSIS PROCEDURE

24 Cannulation of Hemodialysis Vascular Access: Science and Art, Leslie C. Dinwiddie
25 Isolated Ultrafiltration, John J. White, Laura L. Mulloy, Ralph J. Caruana, and Todd S. Ing

Section 9 COMPLICATIONS DURING HEMODIALYSIS

26 Common Clinical Problems during Hemodialysis, Peter Kotanko and Nathan W. Levin
27 Hemodialysis-Associated Seizure Activity, Neenoo Khosla
28 Arrhythmias in Hemodialysis Patients, Claudio Rigatto and Patrick S. Parfrey
29 Prevention and Therapeutic Management of Bleeding in Dialysis Patients, Paola Boccardo, Miriam Galbusera, and Giuseppe Remuzzi
30 Hemolysis during Hemodialysis, Ramin Sam, Leila Haghighat, Carl M. Kjellstrand, and Todd S. Ing

Section 10 REUSE OF HEMODIALYZERS

31 Methods and Complications of Dialyzer Reuse, John K. Leypoldt

Section 11 ALTERNATIVE HEMODIALYTIC TECHNIQUES

32 Clinical Application of High-Efficiency Hemodialysis, Gerald Schulman
33 Continuous Renal Replacement Therapies: CAVH, CVVH, CAVHD, CVVHD and CVVHDF, Andre A. Kaplan
34 The Allient® Sorbent Hemodialysis System, Warren Shapiro
35 Convective Renal Replacement Therapies for Acute Renal Failure and End-Stage Renal Disease, Jeffrey J. Letteri, Claudio Ronco, Zhongping Huang, Dayong Gao, and William R. Clark

Section 12 PERITONEAL DIALYSIS: CLINICAL PRACTICE

36 Determination of Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD) Prescriptions, Scott G. Satko and John M. Burkart
37 Tidal Peritoneal Dialysis, Zbylut J. Twardowski
38 Peritoneal Dialysis Solutions, Declan de Freitas and Alastair Hutchison
39 Lymphatics, Peritoneal Fluid Losses and Peritoneal Dialysis, Ramesh Khanna

Section 13 PERITONEAL DIALYSIS: INFECTIOUS COMPLICATIONS

40 Abnormalities of Host Defense Mechanisms during Peritoneal Dialysis, Clifford J. Holmes
41 Peritoneal Catheter Exit-Site and Tunnel Infections, Zbylut J. Twardowski
42 Peritonitis in Peritoneal Dialysis Patients, Philip Kam-Tao Li, Chi-Bon Leung, Cheuk-Chun Szeto

Section 14 PERITONEAL DIALYSIS: NONINFECTIOUS COMPLICATIONS

43 Apparently Inadequate Peritoneal Membrane Function for Solute Removal, Zbylut J. Twardowski
44 Ultrafiltration Failure and Encapsulating Peritoneal Sclerosis (EPS), Dana Negoi and Ramesh Khanna
45 Hypotension in Peritoneal Dialysis Patients, Ramesh Khanna
46 Abdominal Catastrophes, Peritoneal Eosinophilia, and Other Unusual Events in Peritoneal Dialysis, Rajnish Mehrotra and Pranay Kathuria

Section 15 PERITONEAL DIALYSIS: INTRA-ABDOMINALPRESSURE-RELATED COMPLICATIONS

47 Abdominal Hernias in Continuous Ambulatory Peritoneal Dialysis, Michael H. Schwenk, Bruce S. Spinowitz, and Chaim Charytan
48 Dialysate Leaks, Michael H. Schwenk, Chaim Charytan, and Bruce S. Spinowitz
49 Hydrothorax and Peritoneal Dialysis, Michael H. Schwenk, Bruce S. Spinowitz, and Chaim Charytan

Section 16 ACID-BASE HOMEOSTASIS

50 Acid-Base Homeostasis in Dialysis, F. John Gennari

Section 17 NUTRITIONAL MANAGEMENT OF DIALYSIS PATIENTS

51 Nutritional Therpy in Maintenance Hemodialysis, Kamyar Kalantar-Zadeh
52 Nutritional Management in Peritoneal Dialysis, Robert M. Lindsay and Evelyn Spanner
53 Parenteral Nutrition in Patients undergoing Maintenance Dialysis, Denis Fouque and Raymond Vanholder

Section 18 GASTROINTESTINAL DISEASE

54 Liver Disease in Dialysis Patients, Fabrizio Fabrizi, Suphamai Bunnapradist, and Paul Martin
55 Ascites in Dialysis Patients, Alf M. Tannenberg

Section 19 THE HIV-INFECTED PATIENT

56 Care of the HIV-infected Dialysis Patient, Rudolph A. Rodriguez

Section 20 ANEMIA AND EPOETIN USE

57 Anemia in Patients with End Stage Renal Disease, Rebecca Schmidt and Anatole Besarab
58 Epoetin Use in Hemodialysis Patients, Arthur Tsai and Jeffrey S. Berns
59 Treatment of Anemia in Peritoneal Dialysis Patients, Curtis A. Johnson, Maureen Wakeen, and Stephen W. Zimmerman
60 Hypertension and Epoetin Use in Dialysis Patients, Nosratola D. Vaziri and M. V. Pahl
61 Epoetin and Iron Deficiency, Rajiv Agarwal
62 Refractoriness to Recombinant Human Epoetin (rHuEPO) Treatment, John C. Stivelman
63 Erythropoietin and Quality of Life in Chronic Kidney Disease, Steven D. Weisbord and Paul L. Kimmel
64 Target Hemoglobin, Mitchell H. Rosner and W. Kline Bolton

Section 21 CARDIOVASCULAR DISEASE

65 Hypertension in Chronic Dialysis Patients, Lionel U. Mailloux
66 Management of Ischemic Heart Disease, Heart Failure and Pericarditis in Hemodialysis Patients, Sean W. Murphy and Patrick S. Parfrey

Section 22 METABOLIC ABNORMALITIES

67 Management of Hyperlipidemia in Chronic Dialysis Patients, Ziad A. Massy and William F. Keane
68 Abnormalities of Thyroid Function in Chronic Dialysis Patients, Elaine M. Kaptein
69 Metabolic Abnormalities: Evaluation of Sexual Dysfunction, Biff F. Palmer

Section 23 NEUROLOGIC ASPECTS OF UREMIA

70 Management of Uremic Peripheral Neuropathy, Morrell Michael Avram and Neal Mittman
71 Electroencephalography in the Evaluation of Neurologic Function, Warren S. Brown
72 Impact of Anemia and Its Correction on Brain Function, Allen R. Nissenson

Section 24 UREMIC OSTEODYSTROPHY

73 Differential Diagnosis of Renal Osteodystrophy, Pouneh Nouri, Bijan Nikakhtar, and Francisco Llach
74 Phosphate Binders, L. Kooienga, A. Bellasi, and G.A. Block
75 Use of Vitamin D Sterols in Patients with ESRD, Kevin J. Martin and Esther A. Gonzalez
76 Aluminum-Related Bone Disease in Dialysis Patients, William G. Goodman
77 Management of Aluminum Toxicity, Antonios H. Tzamaloukas and Dominic Raj
78 Parathyroidectomy, Phuong-Chi T. Pham and Phuong-Thu T. Pham

Section 25 DIALYSIS AMYLOIDOSIS

79 Dialysis Amyloidosis, Sergio R. Acchiardo

Section 26 ACQUIRED CYSTIC KIDNEY DISEASE

80 Acquired Cystic Kidney Disease, Margaret MacDougall

Section 27 DIABETES

81 End Stage Renal Failure in the Diabetic Patient, Jeffrey Giullian and Anthony Langone
82 Choice of Insulin Administration Route in Diabetic Peritoneal Dialysis Patients, Jose A. Diaz-Buxo and Terri L. Crawford-Bonadio

Section 28 DRUG USE IN UREMIA

83 Principles of Drug Usage in Dialysis Patients. Ali J. Olyaei and William M. Bennett

Section 29 REHABILITATION AND PSYCHOSOCIAL ISSUES

84 Physical Activity and Functioning in Dialysis Patients, Patricia Painter
85 Rehabilitation of Adult Dialysis Patients: Physical, Psychosocial, and Vocational, John H. Sadler
86 Ethical Considerations in the Care of Dialysis Patients, Charles Foulks

Section 30 PEDIATRIC DIALYSIS

87 Vascular Access in Children, D. L. Cass
88 Infant Hemodialysis, Eileen N. Ellis
89 Urea Kinetic Modeling to Prescribe Hemodialysis in Children, Avram Z. Traum and Michael J.G. Somers
90 Anticoagulation in Children on Hemodialysis, Elizabeth Harvey and Daljit K. Hothi
91 Peritoneal Catheter Placement in Children, Mary L. Brandt and Eileen D. Brewer
92 Pediatric Peritoneal Dialysis Orders, Karen Tipton, Suzanne White, and Mark Benfield
93 Nutritional Management of Children on Peritoneal Dialysis, Ashley A. Perilloux and Isidro B. Salusky
94 Infant and Neonatal Peritoneal Dialysis, Alicia M. Neu
95 Dialysis in Inborn Errors of Metabolism, Franz Schaefer
96 Psychosocial Adjustment and Treatment of Children and Adolescents with ESRD, Erik Qvist, Kai Rönnholm, and Christer Holmberg
97 Growth in Children with ESRD, Steven J. Wassner
98 Adequacy of Peritoneal Dialysis in Pediatric Patients, Vimal Chadha and Bradley A. Warady
99 PET in Pediatric Patients, Cornelis H. Schröder
100 CRRT in Pediatric Patients, Carl H. Cramer II and Patrick D. Brophy
101 Prevention and Treatment of Bone Disease in Pediatric Dialysis Patients, Cheryl P. Sanchez
102 Management of Anemia in Children on Dialysis, Amira Al-Uzri

CHAPTER 1

Demographics of the End-Stage Renal Disease Population

Allan J. Collins, MD, FACP

Worldwide, the end-stage renal disease (ESRD) population has grown dramatically since the previous edition of this book. The previous edition reported data through 1997, whereas the current edition reports data up to 2004. The most striking changes center on the slowing of ESRD rates in several parts of the world, including the Netherlands, Scandinavia, and the United States. In some areas of the world, ESRD rates have in fact fallen to levels last seen 10 to 15 years ago. Despite remarkable progress in slowing the growth in the number of the new cases of ESRD, the prevalent populations continue to grow—mainly because of a reduction in death rates. This is particularly true in the United States, which had relatively higher mortality rates compared with other parts of the world. On the basis of these findings, government policies related to ESRD programs may need to address prevention strategies, to further reduce ESRD incident rates and to ease the disease burden in the ESRD-prevalent population.

In this chapter, data from the United States and other parts of the world are reviewed to provide background for subsequent chapters in this book. Tables and figures are from Chapters 2 and 12 in the United States Renal Data System (USRDS) *2006 Annual Data Report*. Table and figure numbering as extant in the *Report* is provided to allow readers to easily locate them in the *Report* or at the USRDS web site (*www.usrds.org*) should they choose to do so.

Growth of the End-Stage Renal Disease Population

International data on ESRD incidence and prevalence are presented in the USRDS *2006 Annual Data Report*. Five-year trends in incident rates are presented in Table 1.1 (Table 12.a in *Report*). Modest growth has been noted in most countries—the few exceptions being countries such as Australia and Canada. The major cause of renal failure worldwide centers on the increasing percentage of incident patients whose ESRD is due to

Table 1–1

Incidence of ESRD per Million Population[a]

Country/Province	2000	2001	2002	2003	2004
Australia	92	98	97	100	95
Austria	132	138	135	140	159
Bangladesh	6	6	6	8	—
Belgium, Dutch speaking	149	160	172	174	177
Belgium, French speaking	—	176	172	162	187
Canada	156	159	158	152	154
Chile	126	123	127	130	157
Croatia	—	112	118	131	155
Czech Republic	150	163	159	167	166
Denmark	132	140	132	133	133
Finland	95	91	94	95	94
Germany	175	184	174	186	194
Greece	157	167	167	179	195
Hungary	116	112	123	139	139
Iceland	57	77	70	73	75
Israel	165	167	177	183	191
Italy	131	125	126	133	161
Jalisco (Mexico)	195	205	232	280	346
Japan	242	251	256	262	267
Rep. of Korea	93	114	129	152	171
Luxembourg	134	187	144	157	174
Malaysia	79	89	97	102	110
Netherlands	95	101	102	102	105
New Zealand	109	120	119	115	110
Norway	90	95	93	96	101
Pakistan	—	—	26	32	—
Philippines	35	53	53	60	75
Poland	68	85	99	103	—
Russia	12	16	15	19	17
Scotland	109	104	110	121	115
Spain/Andalucia	—	112	122	121	123
Spain/Basque Ctry	121	123	102	142	129
Spain/Canary Isl.	146	172	147	167	—
Spain/Castile y Leon	—	—	—	111	115
Spain/Catalonia	145	144	149	149	136
Spain/Valencia	162	142	160	151	158
Sweden	130	127	129	122	122
Taiwan	353	370	394	401	376
Thailand	10	23	—	77	123
Turkey	115	141	118	112	121
United States	324	329	340	342	342
Uruguay	121	124	136	146	151

a. Table 12.a in *Report*.

Table 1–2

Percentage of Incident Patients with Diabetes

Country/Province	2000	2001	2002	2003	2004
Australia	22.3	25.3	26.7	25.8	30.1
Austria	33.0	32.3	34.6	33.4	32.6
Belgium, Dutch speaking	20.9	23.8	22.6	24.0	24.0
Belgium, French speaking	—	20.7	22.3	25.1	21.0
Canada	32.0	33.5	33.6	33.8	35.0
Croatia	—	28.7	28.8	26.9	29.0
Denmark	21.6	22.6	26.3	22.5	21.8
Finland	31.8	33.9	39.1	35.0	33.1
Germany	35.9	35.7	36.2	36.3	34.2
Greece	26.1	26.8	26.6	28.2	28.3
Hungary	20.9	21.1	26.2	25.5	29.5
Iceland	6.3	18.2	10.0	0.0	4.5
Italy	17.4	16.4	16.3	16.2	16.2
Jalisco (Mexico)	51.6	52.0	51.0	51.0	56.0
Japan	36.4	38.1	38.7	40.7	41.0
Rep. of Korea	40.7	41.5	40.7	42.5	43.4
Malaysia	44.0	45.9	49.1	51.7	54.7
Netherlands	16.4	16.2	17.5	16.6	17.0
New Zealand	35.9	37.9	44.5	41.0	39.6
Norway	15.1	14.5	12.1	15.8	17.3
Pakistan	—	—	40.0	40.0	—
Philippines	23.8	24.8	28.5	32.8	33.5
Poland	20.0	22.2	24.1	22.6	—
Russia	12.8	11.4	9.0	10.7	—
Scotland	18.2	18.1	18.5	18.9	16.1
Spain/Andalucia	—	18.3	20.5	19.3	20.8
Spain/Basque Ctry	14.8	13.4	20.3	13.2	18.3
Spain/Canary Isl.	43.6	46.5	48.0	42.7	—
Spain/Castile y Leon	—	—	—	21.7	24.6
Spain/Catalonia	20.0	20.2	21.0	21.8	22.2
Spain/Valencia	15.3	14.3	16.6	16.4	20.3
Sweden	25.5	25.3	23.8	24.0	24.9
Taiwan	32.4	38.0	39.6	40.0	39.4
Turkey	23.2	26.3	46.2	23.1	21.3
United States	46.0	46.2	45.7	45.7	45.6
Uruguay	17.7	21.2	20.0	29.6	21.8

a. Table 12.b in *Report*.

diabetes (Table 1.2; Table 12.b in *Report*). In the United States, incident rates appear to have stabilized—with rates in 2002, 2003, and 2004 being respectively 340, 343, and 342 cases per million population.

As shown in Figure 1.1 (Figure 2.4 in *Report*), the median age at dialysis initiation has reached 65.6 years in the United States, ranging from 67.5 years in the white population to a low of 59.4 years in Native Americans. The most striking trends in ESRD incidence are shown in Figure 1.2 (Figure 2.11 in *Report*); that is, those based on primary cause of renal disease. Incident rates due to diabetes have peaked and have begun to decline, with glomerulonephritis rates at levels last seen in the late 1980s. Figure 1.3 (Figure 2.12 in *Report*) shows the declines in incident

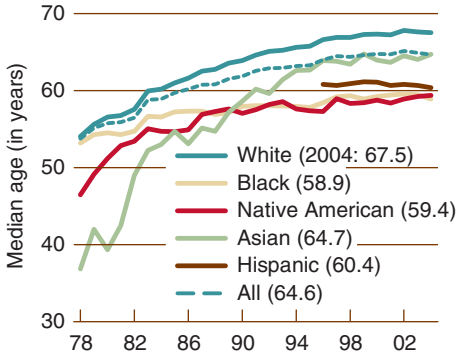


Figure 1–1

Median age of incident patients by race/ethnicity. (Figure 2.4 in *Report*.)

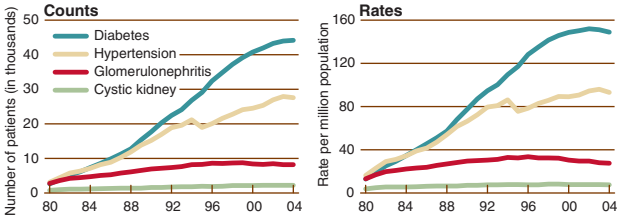


Figure 1–2

Incident counts and adjusted rates by primary diagnosis. (Figure 2.11 in *Report*.)

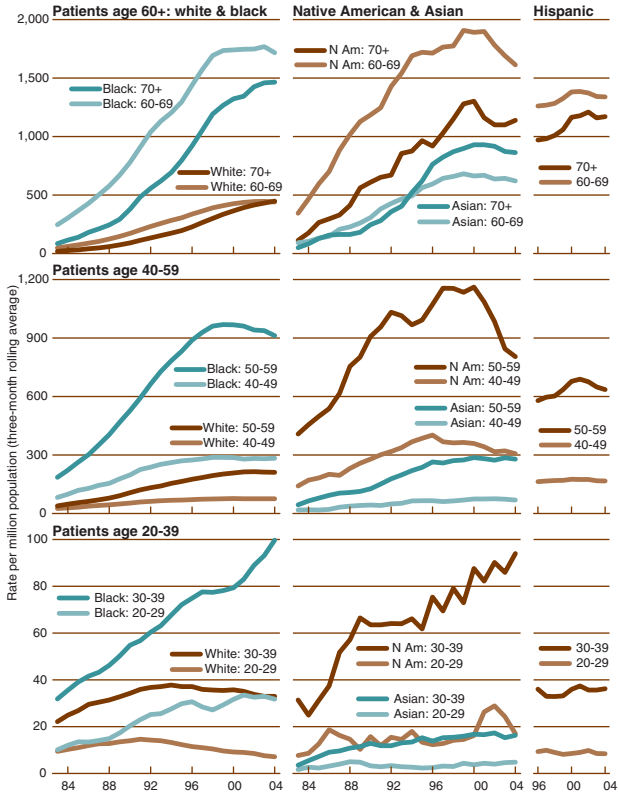


Figure 1–3

Adjusted incident rates of ESRD due to diabetes by age, race, and ethnicity. (Figure 2.12 in *Report*.)

rates due to diabetes for different age groups and races/ethnicities. For individuals 40 years old and older, incident rates of diabetes have generally peaked and have begun to decline. However, for individuals who are age 20 to 29 years and are entering ESRD with diabetes there are marked differences between the white and black populations—with continuing growth in the incident rates for blacks. These racial disparities, notable in the United States, may also be apparent in other multiracial countries.

As shown in Figure 1.4 (Figure 12.2 in *Repor*t), the countries with the highest ESRD incidence are Taiwan (with almost 380 cases per million population), followed by the Jalisco region of Mexico (at almost 350 per million), the United States (at 342 per million), and Japan (at approximately 270 per million). Patterns are similar for the prevalent populations, as shown in Figure 1.5 (Figure 12.5 in *Report*)—with Japan being first (at almost 1800 per million population), Taiwan second (at 1650 per million), and the United States third (at 1500 per million population).

Treatment Modality

Figure 1.6 (Figure 12.7 in *Report*) shows the mix of modality utilization, demonstrating differences between countries in the use of in-center hemodialysis, home hemodialysis, and peritoneal dialysis. Luxembourg has the highest use of in-center hemodialysis, at almost 99%. Japan is second, at approximately 95%. An increasing percentage of peritoneal dialysis is utilized in the Philippines, Scandinavian countries, Canada, Australia, and New Zealand—as well as Jalisco, Mexico, at almost 70%.

Utilization rates of peritoneal dialysis vary considerably by patient age and country. From Figure 1.7 (Figure 12.8 in *Report*), it is seen that patients less than 20 years old have a far greater representation in the peritoneal dialysis population—with about 40% of the reporting countries (including the United States) using continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD). With increasing age, there is a reduced utilization of peritoneal dialysis—particularly in those patients aged 65 to 74 years and 75 years and older. Regardless of age, however, Australia, New Zealand, and Iceland maintain the highest utilization rates of home CAPD/CCPD therapy compared to any other country.

Transplantation as a modality also varies considerably around the world. As seen in Figure 1.8 (Figure 12.9 in *Report*), the prevalence of functioning grafts varies by region—with parts of Spain as high as almost 600 prevalent functioning graft patients per million population. The lowest rates of prevalent transplants are in Malaysia, Turkey, Thailand, and Russia—at less than 10% of that noted in high-prevalent countries.

Rare Diseases and End-Stage Renal Disease

The USRDS has tracked a number of rare diseases and their trends for more than 10 years. For example, ESRD due to AIDS

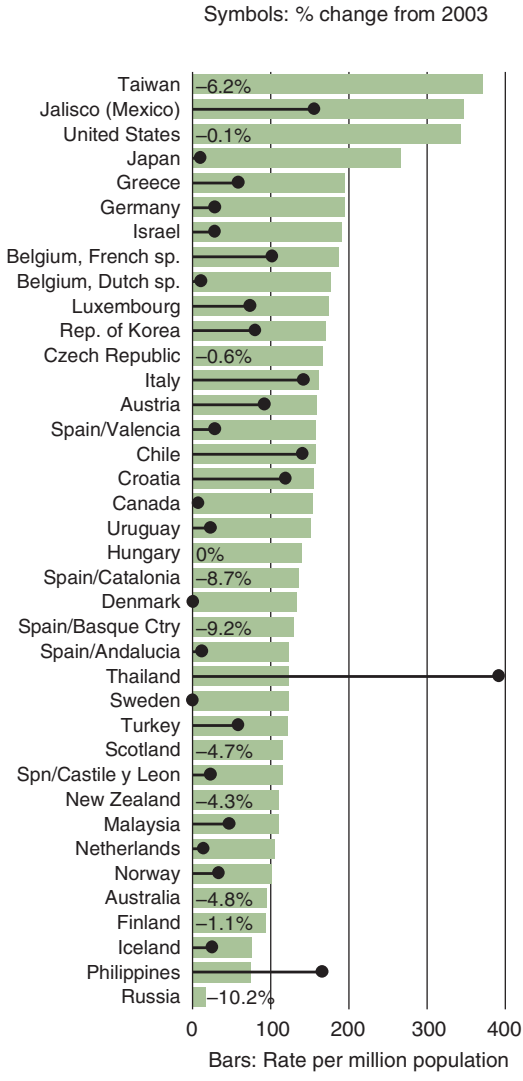


Figure 1–4

Incidence of ESRD in 2004. (Figure 12.2 in *Report*.)

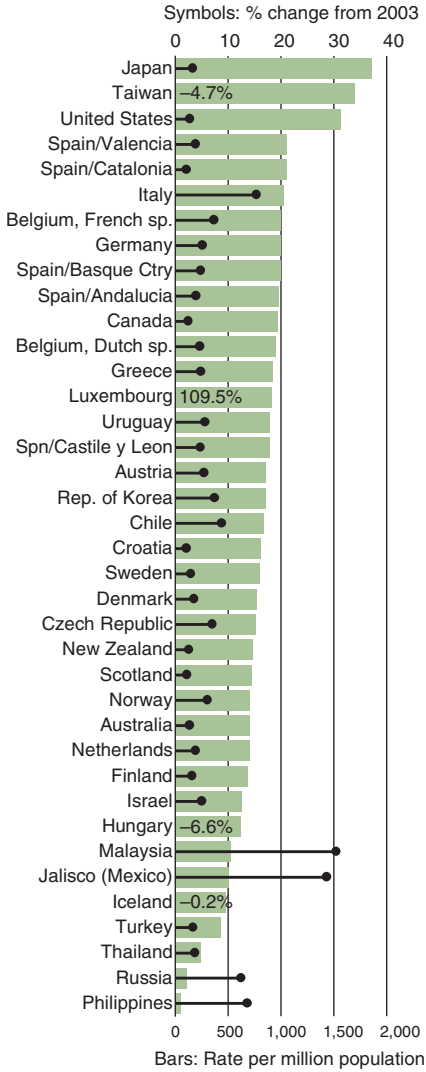


Figure 1–5

Prevalence of ESRD in 2004. (Figure 12.5 in *Report*.)

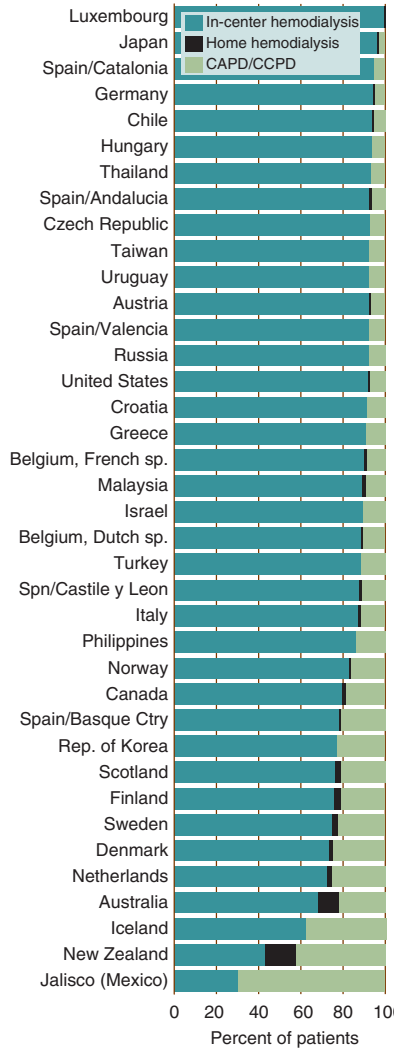


Figure 1–6

Percentage distribution of prevalent dialysis patients by modality in 2004. (Figure 12.7 in *Report*.)

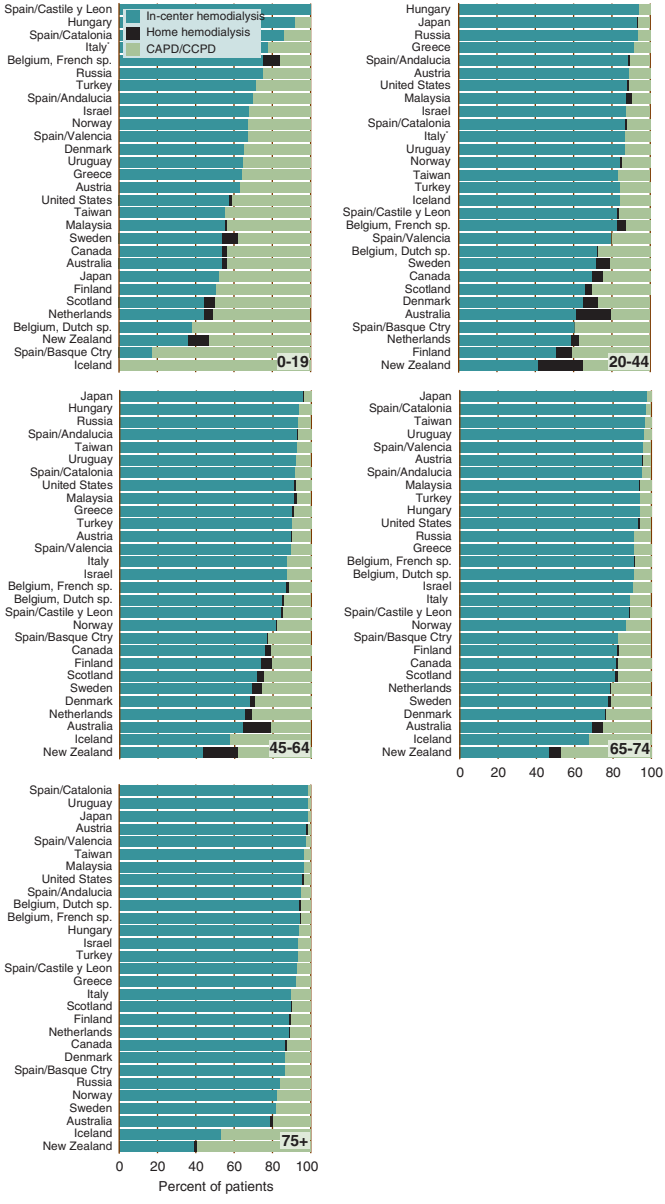


Figure 1–7

Percentage distribution of prevalent dialysis patients by age and modality in 2004. (Figure 12.8 in *Report*.)

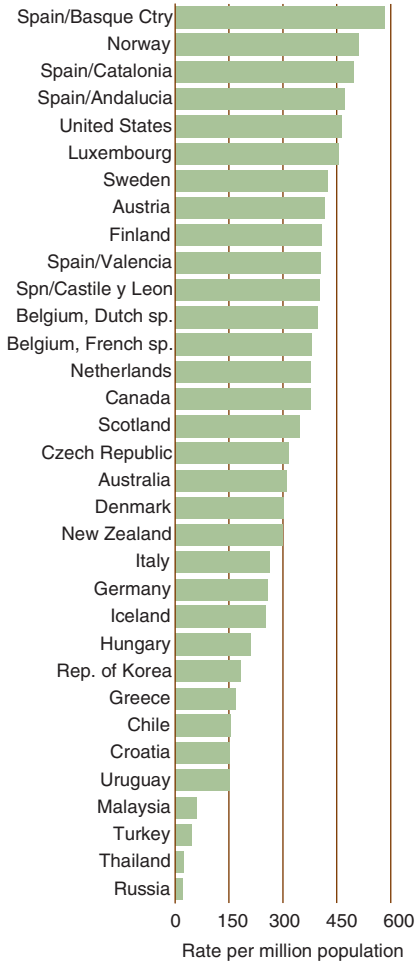


Figure 1–8

Prevalent rates of functioning grafts in 2004. (Figure 12.9 in *Report*.)

nephropathy has dramatically slowed—and the number of cases entering each year has been flat over the past 10 years (at approximately 800 cases) despite the increasing number of individuals with AIDS in the United States. These trends, which before 1995 showed increasing numbers of AIDS nephropathy patients, may reflect the newer AIDS treatments. Continued growth in the number of cases with kidney failure associated with post-nonrenal

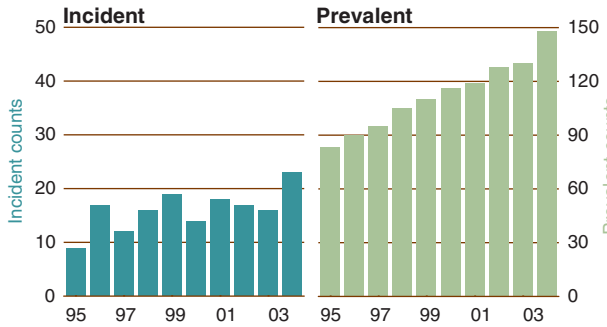


Figure 1–9

Patient counts for Fabry's disease. (Figure 2.23 in *Report*.)

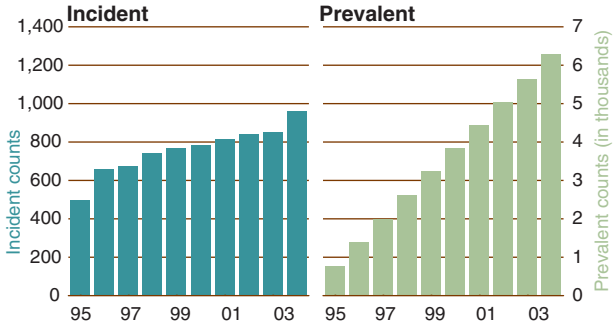


Figure 1–10

Patient counts for IgA nephropathy/Berger's and IgM nephropathy. (Figure 2.24 in *Report*.)

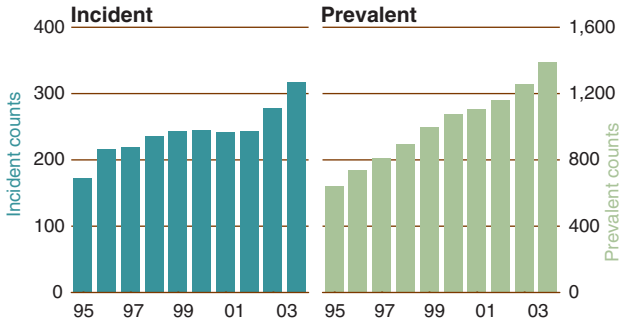


Figure 1–11

Patient counts for Wegener's granulomatosis. (Figure 2.25 in *Report*.)

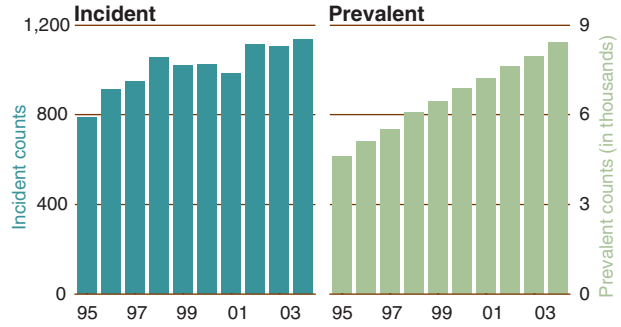


Figure 1–12

Patient counts for systemic lupus erythematosus (SLE nephritis). (Figure 2.26 in *Report*.)

transplantation have occurred over the past 10 years, with an almost fourfold increase in the number of cases.

Another area of major growth in rare diseases is that of multiple myeloma and light-chain nephropathy. Between 1995 and 2002, there was a steady increase in the number of incident patients with this diagnosis. However, in the past two years this growth has been attenuated—which may reflect different treatments in multiple

myeloma or a competing event of death before patients reach ESRD. Another important rare disease to track is Fabry's disease. Although only 10 to 20 Fabry's disease patients enter ESRD treatment per year, the fact that enzyme-replacement therapy has become available to these individuals makes this disease worthy of special attention. Over the past 10 years, there appears to be

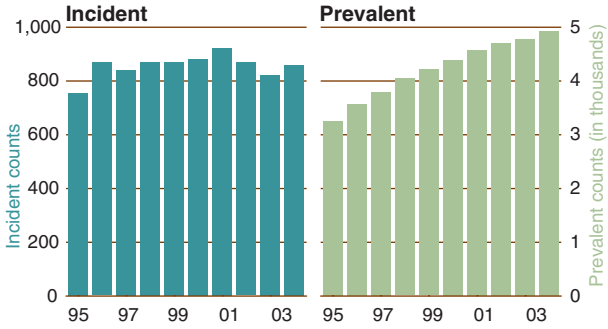


Figure 1–13

Patient counts for other secondary glomerulonephritis/vasculitis. (Figure 2.27 in *Report*.)

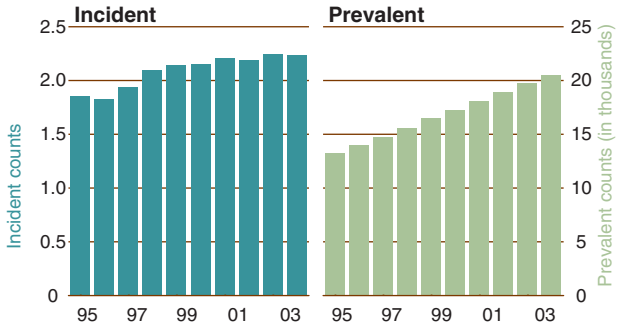


Figure 1–14

Patient counts for polycystic kidney disease. (Figure 2.28 in *Report*.)

an almost doubling in the number of Fabry's patients entering ESRD. This will need to be carefully monitored. Data on other rare diseases are presented in Figures 1.9 through 1.19 (Figures 2.23 through 2.33 in *Report*).

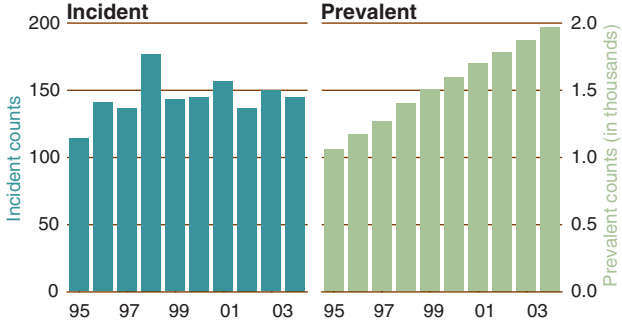


Figure 1–15

Patient counts for Alport's syndrome and other hereditary/familial disease. (Figure 2.29 in *Report*.)

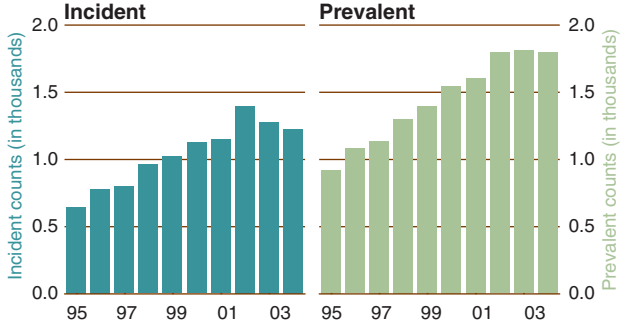


Figure 1–16

Patient counts for multiple myeloma and light-chain nephropathy. (Figure 2.30 in *Report*.)

Summary

The worldwide increase in the incidence of ESRD is clear. Diabetes mellitus remains the most common cause of ESRD worldwide, with an increasing percentage of individuals entering ESRD with this diagnosis every year. This is true in the United States, where the percentage of patients with ESRD due to diabetes is almost 44%. In Jalisco, Mexico, it is almost 57%; in

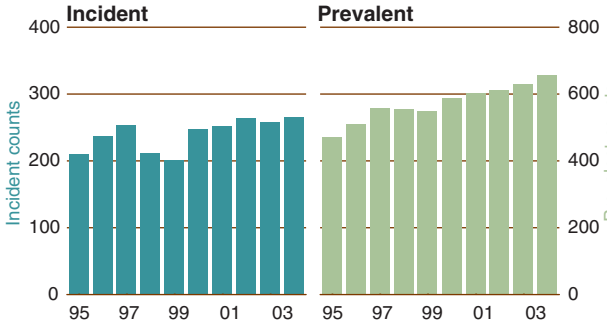


Figure 1–17

Patient counts for amyloidosis. (Figure 2.31 in *Report*.)

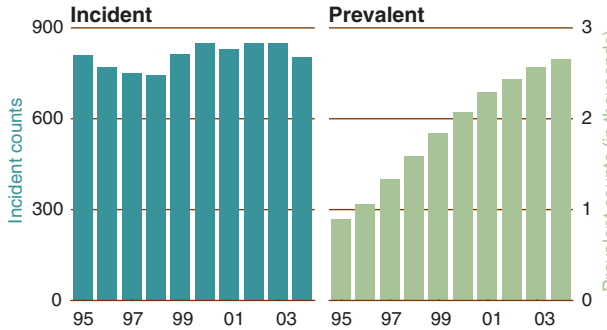


Figure 1–18

Patient counts for AIDS nephropathy. (Figure 2.32 in *Report*.)

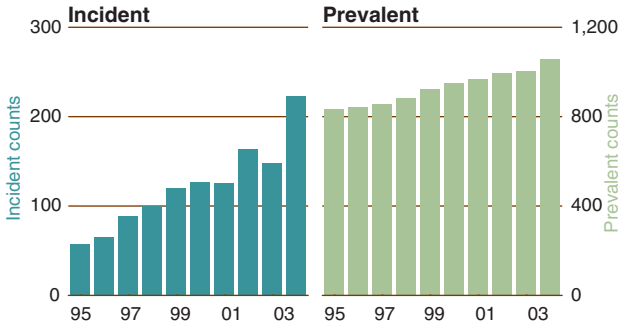


Figure 1–19

Patient counts for post-transplant (nonrenal) complications. (Figure 2.33 in *Report*.)

Malaysia, 56%; in Japan, 38%; and Taiwan and New Zealand, approximately 35%. This shows that diabetes is certainly a major cause of ESRD within developed and developing countries. Public health programs to address the burden of diabetes and the development of chronic kidney disease (which subsequently develops into ESRD) must be carefully considered.

New initiatives by the International Federation of Kidney Foundations and the International Society of Nephrology to raise public awareness about chronic kidney disease and thereby foster more prevention programs has led to the establishment of World Kidney Day, to be held annually on the second Thursday in March (first World Kidney Day: 9 March 2006). The emergence of chronic kidney disease prevention programs may lower the incident rates of ESRD. This has been shown in several countries besides the United States, such as the Netherlands and Scandinavian countries.

The existing dialysis population, however, continues to grow—placing increasing demands on the healthcare delivery system. Measures to improve the delivery of dialysis therapy, vascular access utilization, consideration of alternative dialysis modalities, the reduction of complications during the dialysis procedure, and management of other diseases are important to improve outcomes. These and many other areas are addressed in subsequent chapters of this book.

Recommended Reading

United States Renal Data System. *USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2006.

CHAPTER 2

Temporary Vascular Access for Hemodialysis

John J. White, MD; Matthew J. Oliver, MD; and Steve J. Schwab, MD

When immediate hemodialysis is necessary, rapid access to the circulation is essential. Acute vascular access is created by inserting a catheter into a central vein. Catheter access is temporary if the renal failure resolves or if another form of functional permanent access can be created. Unfortunately, catheters initially thought to be temporary when they are placed often go on to provide access for months to years. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) show that 60% of patients starting dialysis in the United States do so with an acute catheter. Consequently, catheters are now under a greater burden because they must be capable of providing adequate dialysis with a low rate of complications over longer periods of time.

Catheter Design

Although brand names such as Quinton catheter, VasCath, and PermCath are commonly used as slang to describe hemodialysis catheters, in actuality there is a wide assortment of available catheters. Catheters are designed to accommodate easy insertion and good positioning, and to provide maximal flows. Catheters differ by material, length, lumen size, lumen configuration, inlet/outlet holes, and method of connection to bloodlines (Figure 2.1). Temporary (nontunneled, uncuffed) catheters are primarily composed of polyurethane, which is stiff at room temperature to facilitate insertion but softens at body temperature to minimize vessel trauma. Tunneled cuffed catheters (long-term catheters) are primarily composed of silicone and silicone elastomers that are flexible and require a stylet and/or sheath for insertion.

The walls of the lumens of silicone catheters must be thicker than polyurethane catheters because silicone provides less structural support. Silicone and polyurethrane are less thrombogenic than materials such as Teflon and polyvinyl used in the past. Catheter lumen sizes range from 9 to 16 French (0.75- to 2.2-mm inner diameter). Catheter length varies greatly to accommodate

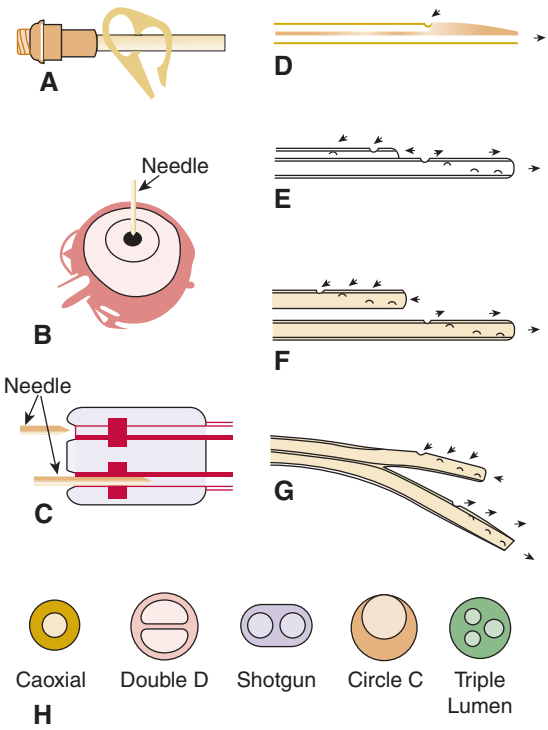


Figure 2–1

Hemodialysis catheter designs. Catheters traditionally connect to bloodlines with luer locks (A), but new implantable ports are accessed with dialysis needles (B, C). Lumens may be conjoined through their length (D, E), or completely (F) or partially separated (G). If the lumens are conjoined, various lumen configurations are available (H). The figure is approximate and is not intended to represent the exact design of any particular manufacturer's catheter.

proper positioning of the tip. In general, 15-cm temporary catheters are inserted in the right internal jugular vein, 20-cm catheters in the left internal jugular vein, and 20- or 24-cm catheters in the femoral vein to minimize recirculation and to reach the great veins. Tunneled cuffed catheters are much longer (up to 70 cm in overall length) to accommodate the creation of tunnels and

allow the tip to be placed in the right atrium or inferior vena cava as required.

The arterial and venous lumens can be completely separated (e.g., Tesio catheter), partially separated (Ash split catheter), or conjoined throughout their length. The lumens of conjoined catheters can be configured as a shotgun design (e.g., Niagara, Permcath), single round catheter with midline septum ("double D"; e.g., Opti-Flow), Circle C, coaxial (e.g., Duoflow), and triple lumen design (e.g., Trialysis). Inlet and outlet holes can be a single large hole or multiple small holes in various patterns. Traditionally, connector ports have been of luer lock design. Midline septums or shotgun designs theoretically prevent kinking.

Implantable devices (e.g., LifeSite, Dialock) allow dialysis needles to be inserted directly into subcutaneous ports. These devices are accessed by percutaneous puncture and consist of a titanium alloy port connected to a central venous silicone cannula. Two of these are implanted beneath the clavicle and tunneled in the right atrium via the jugular vein. When used with 70% isopropyl alcohol as a sterilant, retrospective and nonrandomized prospective studies have shown a decreased incidence of infection and catheter-related complications using these devices when compared to cuffed-tunneled catheters. Although promising, off-label use and a number of possibly related deaths in patients who were not candidates for other permanent access have drawn concerns from the Food and Drug Administration. Currently, these catheters are not available to the U.S. market.

Despite the myriad of designs and purported advantages, at present there is little evidence that one design is superior to others. Most catheters are tested in ideal circumstances and over short periods of time. Comparisons between devices have included few randomized controlled trials and have failed to show differences in clinically important outcomes such as solute clearance, rates of bacteremia, or catheter malfunction requiring intervention. For example, in a study comparing a twin-dialysis catheter system (Tesio), a split-tip design (Ash-Split), and a step-tip design (Opti-flow) there were no differences in catheter flow rates or rates of infection. The catheters only differed in time of insertion, with the split-tip and step-tip catheters being easier and faster to insert than the twin-dialysis system.

Catheter Insertion

Catheter insertion varies by operator, site of insertion, and insertion technique. The operator should be well experienced or be

supervised by an experienced operator. In general, tunneled cuffed catheters are inserted in operating rooms or clean interventional suites under fluoroscopy—with the operator gowned, gloved, and masked. Full surgical drapes are used, and the patient may be masked as well as given a mild sedative. Temporary catheters are generally inserted at the bedside or in the dialysis unit and do not warrant sterile precautions as rigorous as those required by tunneled cuffed catheters—but in general full-barrier precautions consisting of a mask, sterile gloves, gown, and a large drape should be used. The skin can be disinfected with chlorhexidine, povidone-iodine, or alcohol. Alcohol disinfects instantly, whereas povidone-iodine should be allowed to dry for 2 to 3 minutes to maximize antibacterial effect. Studies in nondialysis patients suggest that chlorhexidine reduces infection rates, but this has not been tested in dialysis patients.

When available, insertion should be performed with ultrasound guidance. Ultrasound allows the operator to examine the vein for anatomic abnormalities and to directly visualize insertion. Ultrasound guidance has been shown to minimize insertion complications in both the internal jugular and femoral sites and results in a decrease in immediate catheter dysfunction. Using ultrasound guidance, inexperienced operators can increase their success rate to 95%. The NKF-K/DOQI (Kidney Disease Outcomes Quality Initiative) guidelines support this practice.

The preferred site of placement is the right internal jugular vein. Catheters placed in the left internal jugular vein provide significantly less blood flow than right-sided catheters, and are nearly four times as likely to require removal for malfunction. Catheters should not be inserted into the subclavian vein if possible. Although studies have shown a decrease in infection rate with the use of subclavian catheters, these catheters have been associated with an increase in central vein stenosis (which may compromise future permanent access). In a prospective study in which patients underwent routine venography after removal of their first subclavian catheter, 52% of patients had subclavian vein thrombosis/stenosis. Half of these recanalized within 3 months, but the other half remained.

In practice, thrombosis/stenosis of the subclavian vein is often subclinical until an arteriovenous access is placed in the ipsilateral arm—after which severe arm swelling occurs. Treatment of the stenosis with angioplasty or stent is difficult and requires repeated procedures to maintain patency. Often the stenosis requires take-down of the permanent access and renders the arm unusable for future access. Thrombosis/stenosis of the internal jugular vein is

less frequent than the subclavian vein (approximately 6% in one series) and does not generally compromise future access unless it extends to the superior vena cava. Temporary catheters placed in the subclavian or internal jugular vein should have their position checked by chest X-ray or fluoroscopy before commencing dialysis. The tips of temporary catheters should rest in the superior vena cava (subclavian) or inferior vena cava (internal jugular vein). Temporary catheters are commonly placed in the femoral vein in bed-bound patients, but infection rates are higher than either neck location. Tunneled cuffed catheters may be placed in the femoral vein as well—and as a last resort catheters may be inserted via the translumbar and transhepatic routes.

Catheters can be dressed with either standard or adhesive dry gauze or breathable transparent dressings. Patients and caregivers may feel that an adhesive dressing better secures the catheter or better protects the exit site from contamination. Some randomized studies of nondialysis catheters show higher infection rates when catheters were dressed with nonbreathable dressings as compared with dry gauze. However, a large randomized study by Maki and colleagues of Swan-Ganz catheters showed no difference between dry gauze and breathable transparent dressings. Antibiotic ointments such as povidone-iodine and mupirocin, when used in conjunction with dry gauze dressings, reduce bacteremia related to temporary hemodialysis catheters. Ointment may not be as effective for tunneled cuffed catheters, but this has not been studied. Patients may resist povidone-iodine ointment when used with gauze dressing because leakage of ointment will stain clothes.

Many complications have been associated with hemodialysis catheter insertion. Some radiologic series report no serious complications despite hundreds of insertions. Average rates and ranges of complications in the literature are outlined in Table 2.1.

Catheter Performance

Dialysis catheter lumens must be of large bore in order to provide blood flows to achieve adequate clearance. It therefore follows that catheter malfunction occurs when the catheter cannot provide blood flow sufficient to achieve adequate dialysis. For short periods of dialysis, blood flows of 200 to 250 mL/minute are usually sufficient to correct the metabolic disturbances associated with renal failure. For longer use, blood flows greater than 300 cc/minute are generally needed to achieve adequate clearance and reduce treatment durations. The exact amount of blood flow

Table 2–1

Complications from Hemodialysis Catheter Insertion

Complication	Mean (%)	Range (%)
Arterial puncture	4.4	0–11.9
Local bleeding	4.0	0–18.1
Aspiration	2.2	NA[a]
Recurrent laryngeal palsy	1.6	NA
Hemo/pneumothorax	1.35	0–3.0
Air embolism	1.2	0–2.2
Cardiac arrhythmia	1.1	NA
Hemomediastinum	0.74	0–1.2
Vessel perforation	0.7	0–1.3
Pericardial tamponade	0.56	0.5–0.6
Retroperitoneal bleeding[b]	0.06	NA

a. NA = not available.
b. Femoral catheterization only.

and clearance required varies by patient. For acute dialysis, the dose prescribed can be significantly less than the dose delivered. This occurs for a variety of reasons unrelated to the device itself. However, femoral catheters are clearly associated with lower delivered dialysis dose.

Recirculation from catheters is generally negligible because the arterial inlet is usually positioned proximal to the venous outlet and there is a high blood-flow rate in the large central veins (e.g., superior vena cava at approximately 2 L/minute). Our studies indicate that there is essentially no recirculation from tunneled catheters placed in the right atrium. However, if the tip of the catheter is placed in an area of restricted blood flow or if the lumens are reversed recirculation increases. Recirculation of malfunctioning catheters is 7 to 8% if they are reversed, and 14 to 19% if well-functioning catheters are inadvertently reversed. If the tips of femoral catheters are too short to reach the venous segment of high blood flow, recirculation is high. One study found that femoral catheters shorter than 20 cm had recirculation of 26.3% versus 8.3% for those longer than 20 cm.

Catheter Malfunction

NKF-K/DOQI guidelines define catheter malfunction as failure to achieve blood flow rate equal to 300 mL/minute. The two primary mechanisms of malfunction are thrombosis and malposition of

the catheter relative to the central veins. Catheter malposition is more likely if the catheter never worked well (early malfunction). Malposition of the tip or kinking of the catheter have been reported in up to 68% of early malfunctions. Catheters with early malfunction should be imaged to diagnose malposition.

Late malfunction is more likely caused by thrombosis. Thrombosis can occur within the catheter lumen, at the catheter tip, or around the catheter (fibrin sheath); can involve the entire vein (mural thrombus); or can form in the right atrium. In a careful study of central venous catheters in oncology patients in whom all malfunctioning catheters were imaged, thrombosis was confirmed to be the cause in 64%. The incidence of the specific forms of thrombosis is poorly defined. Isolated studies report an incidence of mural thrombosis of 7.6% and fibrin sheaths of 60%. The latter catheters were imaged only if they were refractory to urokinase dwells. One-year patency rates for tunneled cuffed catheters are estimated at 30 to 74%. Efforts to prevent thrombosis have been disappointing. Fixed mini-dose warfarin has not proved effective, and systemic anticoagulation is generally undesirable.

Regardless of the etiology of malfunction, simple measures—such as patient repositioning, flushing the catheter with saline, rotating the catheter (uncuffed catheters), and lumen reversal—are usually tried to improve blood flow. It is not clear how effective these interventions are, but they are commonly performed. For instance, in one randomized study of temporary catheters 25 to 57% of dialysis treatments required lumen reversal (depending on the catheter design).

Catheters that are refractory to simple measures may be treated with thrombolytics, guide-wire insertion, guide-wire exchange, or catheter stripping. A thrombolytic dwell is usually the first line of treatment because it can be given in the dialysis unit. Currently available thrombolytics include streptokinase, reteplase, and alteplase (t-PA). Urokinase has been removed from the market. Streptokinase is highly antigenic. Reteplase has been shown to be effective for catheter malfunction but like urokinase has to be aliquotted and frozen. Alteplase has none of these issues and is the only FDA-approved thrombolytic for the treatment of catheter malfunction. During dwells, thrombolytic is infused into the catheter to fill the dead space in the lumen. Urokinase is usually given in a dose of 5000 units per mL, and t-PA in a dose of 1 to 2 mg/mL. Some protocols use a fixed amount of drug (e.g., 5000 units of urokinase or 1 mg of t-PA) followed by saline. Others use a fixed concentration per lumen.

The malfunctioning lumen only may be infused, or routinely both lumens may be infused regardless of which is malfunctioning. The drug is usually left to dwell for 20 to 60 minutes, but dwells of 1 to 4 days have been described. During the dwell, active drug can be periodically advanced toward the tip with saline. Thrombolytics are effective in approximately 80% of cases, even though most thrombus appears to reside outside the catheter lumen (Table 2.2). A direct comparison of urokinase with t-PA to treat catheter malfunction in oncology suggests that t-PA may be more effective. Larger doses of urokinase (250,000 units) and t-PA (50 mg) have been infused to treat refractory catheter malfunction or specific thrombotic complications (e.g., right atrial thrombus). Despite the increased dose, only minimal effects on bleeding parameters have been shown. The only major reported adverse event was an episode of hematuria requiring transfusion in a patient with known bladder cancer who was given 250,000 units of urokinase as a bolus.

Catheter malfunction may also be treated with guide-wire insertion, fibrin sheath stripping, or exchange over a guide wire. The immediate success of most techniques is good. However, the effect is short-lived and usually requires repeated intervention (Table 2.2). Guide-wire insertion has only been described in one report and is not recommended. Catheter exchange avoids femoral puncture, and any fibrin sheath may be disrupted at the time of the procedure with either a snare or balloon. One small study resulted in greater long-term patency rates for catheter exchange compared to fibrin sheath stripping. Catheter exchange does not increase the risk of subsequent infection. Therefore,

Table 2–2

Treatment of Catheter Malfunction

Immediate Intervention	Primary Success (%)[a]	Patency (Days)
Urokinase dwell	80	NA[b]
t-PA	91	30
Urokinase infusion	87	30
Guide-wire insertion	88	29
Catheter exchange	97	65
Catheter stripping	91	40

a. Success rates are averaged across available studies.
b. NA = not available.

catheter exchange is probably the best solution to catheter malfunction. However, this requires further investigation.

Catheter-Related Infections

Hemodialysis catheters can be complicated by exit site infections, tunnel infections, bacteremia, and distant infections (Figure 2.1). The exact definition of these infectious outcomes varies by source (see "Recommended Reading" for Centers for Disease Control definitions). A practical and simple definition of *exit-site infection* is "purulent drainage at the exit site." Redness, swelling, crusting, and pain may accompany this discharge—but these findings are more subjective than purulent drainage. Tunnel infections occur if inflammation extends 5 cm beyond the exit site or beyond the Dacron cuff. Bacteremia is defined by positive peripheral blood cultures in a patient with signs and symptoms of infection such as fever, chills, nausea, headache, hypotension, and elevated white blood cell count.

Bacteremia is confirmed to be catheter related if no other source is found and the same organism is cultured from the catheter (usually a semiquantitative culture from the tip), or if symptoms rapidly resolve after catheter removal. Distant infections occur when organisms seed during bacteremia. The most common distant infections are endocarditis (3.9–4.1%), osteomyelitis (0.5–5.9%), and septic arthritis (1.0–3.8%). Other reported complications are septic phlebitis, septic pulmonary emboli, spinal abscess, myocardial abscess, and septic death. The incidence and rate of infectious complications according to catheter type are outlined in Table 2.3.

Table 2–3

Infections Related to Hemodialysis Catheters[a]

Type of Infection (Number per 1000 CDs, %)	Temporary	Tunneled Cuffed
Exit-site infection	3.6 (9.0)	1.4 (22)
Tunnel infection	NA[b]	0.02 (0.2)
Bacteremia	6.2 (10.0)	1.8 (39)
Distant infection	1.1 (1.6)	0.4 (5.3)

a. Rates calculated from prospective studies if available. Distant infection includes endocarditis, spinal abscess, osteomyelitis, septic arthritis, and septic death.
b. NA = not available.

Gram-positive organisms cause approximately 75% of catheter-related bacteremias, with an increasing incidence of methacillin-resistant *Staphylococcus aureus*. The remainder are caused by gram-negative organisms (17%), fungi (1%), and mixed organisms (7%). A similar spectrum of organisms is cultured from exit-site infections. Coagulase-negative staphylococci and diphtheria frequently cause catheter-related infection, but can also be contaminants. Therefore, it is more likely that they are the true source if both blood culture bottles grow one of the organisms. The utility of cultures from catheters, cultures from dialysis lines connected to catheters, and surveillance cultures has not been established.

Patients with diabetes, immunosuppression, chronic kidney disease, a history of bacteremia, and *Staphylococcus aureus* nasal carriage are at increased risk for catheter-related bacteremia. Acute catheters inserted in the femoral vein are at greater risk than either internal jugular or subclavian sites. However, a recent study found no difference in infection rates for cuffed-tunneled femoral catheters compared to those placed in the internal jugular vein. Duration of placement is the most consistent risk factor (i.e., the longer the use the higher incidence of infection). A prospective study of temporary catheters reports the incidence of bacteremia to be approximately 10% for femoral catheters and internal jugular catheters after 1 week and 3 weeks of use, respectively. A recent study from the University of Alabama (Birmingham) showed that the overall likelihood of catheter-related bacteremia was nearly 50% at 6 months in their patients having tunneled catheters.

Prevention of Catheter-Related Infections

Duration of use is the strongest risk factor for infection. Therefore, minimizing the duration of use is the best method of preventing infection. The NKF-K/DOQI recommends that temporary femoral catheters remain in place for a maximum of 7 days, and that internal jugular vein catheters remain in place for a maximum of 3 weeks. If a catheter is still required, a tunneled cuffed catheter should be considered. There is no data to support the routine changing of other types of central venous catheters and this is generally not recommended. However, in bed-bound patients the risk of bacteremia at 1 week may justify the removal of the catheter and a subsequent "catheter holiday." A risk/benefit analysis of this strategy (compared to leaving the catheter in place) has not been rigorously performed as a randomized trial.

Table 2–4

Considerations for Accessing the Bloodstream Using Hemodialysis Catheters

- The catheter hubcaps or bloodline connectors should be soaked for 3 to 5 minutes in povidone-iodine and then allowed to dry prior to separation.
- Catheter lumens should be kept sterile.
- To prevent contamination, the lumen and tip should never remain open to the air. A cap or syringe should be placed on or within the catheter lumen, while maintaining a clean field under the catheter connectors.
- Patient should wear a surgical mask for all catheter procedures that remove the catheter caps and access the patient's bloodstream.
- Dialysis staff should wear gloves and a surgical mask or face shield for all procedures that remove the catheter caps and access the patient's bloodstream.
- A surgical mask for the patient and mask of face shield for the dialysis staff should be worn for all catheter-dressing changes.

Source: National Kidney Foundation. *Dialysis Outcome Quality Initiative: Clinical Practice Guidelines for Vascular Access*. New York: National Kidney Foundation 1997:47. Used with permission.

Meticulous handling of catheters also prevents infections. Starting at insertion, proper disinfection and sterile technique are crucial whenever the catheter is handled. The importance of these simple measures is emphasized and standardized in the NKF-K/DOQI guidelines (Table 2.4). For temporary catheters, 2% mupirocin placed at the exit site significantly reduced bacteremia rates (from 6.0 to 0.4 per 1000 catheter days) and 10% povidone-iodine ointment reduced bacteremia rates from 4.5 to 0.4 bacteremias per 1000 catheter days. Exit sites should be inspected at each dialysis treatment, and dressings should be changed weekly (or more often if warranted). There is mounting evidence to suggest that either citrate or antibiotic catheter locks (gentamicin with or without cefazolin) are more effective than heparin alone. A cost analysis is justified before widespread use.

Finally, in efforts to decrease catheter-related infection investigators have impregnated catheters with a variety of antiseptic (e.g. silver, chlorhexadine) and antibiotic materials (e.g., minocycline plus rifampin or gentamicin). Several studies

have been performed involving acute and long-term catheters, both tunneled and non-tunneled. Few have investigated hemodialysis catheters specifically. One study of acute (short-term) nontunneled hemodialysis catheters bonded with minocycline-rifampin compared to non-bonded catheters found a significant decrease in catheter-related infections (11 versus 0%, respectively). The majority of trials have reported a benefit of central venous antibiotic-bonded catheters. These devices seem to perform well in carefully conducted trials, but they are expensive and have potential drawbacks (such as a risk of allergic reaction and the emergence of anti-biotic resistance). Pending further study, we cannot currently recommend the use of antiseptic- or antibiotic-bonded catheters for acute or long-term hemodialysis.

Management of Catheter-Related Infection

Temporary catheters with exit-site infections should be removed immediately in light of the fact that the bacteremia rate is greater than 10% after 24 hours from the onset of exit-site infection. Exit-site infection from tunneled cuffed catheters may be treated with topical antibiotics. All other catheter-related infections should be treated with parenteral antibiotics. Antibiotics for tunnel infections should be active against staphylococci and streptococci. Methicillin-resistant *Staphylococcus aureus* (MRSA) should be treated empirically with vancomycin if there is a high prevalence of MRSA in the patient population. Exit-site infections and tunnel infections that do not respond to antibiotics should prompt catheter removal.

Treatment of catheter-related bacteremia is usually started in the dialysis unit in which the patient first develops symptoms. Empiric therapy with vancomycin (20 mg/kg initially post-dialysis, followed by 500 to 1000 mg after each treatment for maintenance) and gentamicin or tobramycin (1 mg/kg post-dialysis) is used to cover enterococci, MRSA, and gram-negative organisms. After cultures are available, vancomycin should if possible be replaced with a narrower-spectrum antibiotic such as cefazolin (2–3 g post-dialysis) to avoid the development of vancomycin resistance. If the catheter is temporary, or if the patient with a tunneled cuffed catheter is symptomatic, the catheter should be removed as soon as possible. For tunneled cuffed catheters, if the patient's symptoms are mild and resolve with antibiotics the catheter can be exchanged by guide wire within 24 to 48 hours.

Negative blood cultures are not necessary prior to catheter exchange. Nevertheless, some interventionalists insist on negative blood cultures. If no exit-site or tunnel infection is present, the same exit site and tunnel can be used. This technique eradicates infection 80 to 100% of the time. When an exit-site or tunnel infection is present, the catheter should be tunneled out through a new exit site. The success rate decreases to 64% with this technique. In a single-center nonrandomized comparison of guidewire exchange versus immediate removal, there was no significant difference in time to infection recurrence between the two techniques [relative risk for removal compared to exchange of 0.88 (95% CI, 0.45–1.79). Catheters should not be left in place and treated with antibiotics because there is only a 32% chance the infection will be eradicated.

Parenteral antibiotics should be continued for 3 weeks and are usually administered post-dialysis. Vancomycin, gentamicin, and the combination of the two can cause ototoxicity and should be used with caution when prescribed for more than 1 week.

Conclusions

Acute vascular access is synonymous with catheter use. but unfortunately catheter use is often not temporary. Although catheters are designed for use in acute renal failure and as a bridge to permanent access, they also play an increasing role as "permanent access" because many patients do not have reliable arteriovenous access. For end-stage renal disease patients initiating dialysis, early referral is the key to minimizing exposure to catheters. Ideally, a usable arteriovenous access should be ready when dialysis is started so that catheters are avoided altogether. Unfortunately, patients are often referred late or the need for dialysis is unanticipated and thus the patient begins dialysis with a catheter.

Frequently, the circumstances leading to catheter placement are out of the dialysis caregiver's control. After a catheter is inserted, however, it is imperative that a permanent access be placed as quickly as possible and that the catheter be removed as soon as the permanent access is functional. Furthermore, permanent accesses ultimately fail and catheters must fill the gap. Patients are becoming more dependent on catheters to provide adequate dialysis and are therefore at greater risk for the many complications associated with them. To improve vascular access for patients, we must continue to strive to better understand how to optimize catheter performance and minimize complications.

Recommended Reading

National Kidney Foundation. *Dialysis Outcome Quality Initiative: Clinical Practice Guidelines for Vascular Access*. New York: National Kidney Foundation 1997.

NKF-K/DOQI. Clinical Practice Guidelines for Vascular Access: Acute hemodialysis vascular access, noncuffed catheters. Am J Kidney Dis 2001;37(1):S146.

Evidence-based national guidelines that have become the standard of care for vascular access.

O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep 2002; 51(RR-10):1–29.

Guidelines for practictioners who insert catheters and for persons responsible for surveillance and control of infections in hospital, outpatient, and home healthcare settings.

Oliver, MJ. Acute dialysis catheters. Seminars in Dialysis 2001;14:432–35.

Reviews of temporary and tunneled dialysis catheters.

Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: Results from the DOPPS. Kidney Int 2002;61:305–16.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an ongoing observational study of hemodialysis patients in 12 countries. The study seeks to identify dialysis practices that contribute to improved mortality rates, hospitalization rates, health-related quality of life, and vascular access outcomes.

Schwab SJ. Acute hemodialysis vascular access. In UptoDate Online 14.2, *www.uptodate.com*.

Schwab SJ, Beathard G. The hemodialysis catheter conundrum: Hate living with them, but can't live without them. Kidney Int 1999;56:1–17.

Schwab SJ, Harrington JT, Singh A, et al. Vascular access for hemodialysis. Kidney Int 1999;55:2078–90.

Review and discussion focusing on arteriovenous fistulas and grafts.

CHAPTER 3

Evaluation for Vascular Access Dysfunction

David W. Windus, MD

Vascular access dysfunction commonly occurs in hemodialysis patients and results in inadequate dialysis, increased risk of thrombosis, access loss, and increased costs of care. Vascular access monitoring has been defined as the regular evaluation of patients with hemodialysis access by physical exam and dialysis characteristics for features suggestive of dysfunction. Vascular access surveillance has been defined as regular evaluation of the access for dysfunction using more technical methods. The desired goals of these methods are to choose a set of parameters predictive of an access complication, to allow for timely evaluation and correction of a problem, and to perform interventions that reduce thrombosis rate and prolong the usable life of the access.

Implicit in this monitoring and intervention strategy is that the underlying causes of access dysfunction and thrombosis are known and that the treatment of these problems prevents complications. The ability of access surveillance strategies to achieve these goals has been supported by some trials but not by others, and the goal of an ideal access evaluation strategy remains elusive. Despite a lack of a full consensus on the value and best surveillance technique, the focus on clinical indicators and hemodynamic abnormalities associated with access dysfunction for the past two decades has undoubtedly improved the overall care of the dialysis patient.

Approaches to access evaluation include physical exam, clinical- and dialysis-related abnormalities, measurements of flow and pressure, and assessment for structural abnormalities. Surveillance of arteriovenous grafts has been studied more thoroughly because of their higher complication and failure rate. On the other hand, surveillance for fistula failure has become a greater issue—in part due to placement of this access type in marginal situations. Differences between arteriovenous fistulas and grafts are highlighted in this chapter when possible. Although these methods are most often applied to patients on maintenance hemodialysis, some (e.g., physical exam and Doppler ultrasound) may be used for assessment of vascular access before initiation of dialysis. In

July of 2006, the updated National Kidney Foundation NKF-K/DOQI guidelines for vascular access were published. These guidelines continue to recommend a regular vascular access surveillance program using one of several available methods described in this chapter.

Clinical Indicators of Access Dysfunction

The physical examination is a simple and quick method for assessment of arteriovenous fistulas and grafts. The presence of abnormal findings or a change in the findings should prompt a more detailed evaluation of the vascular access. Nursing and technical staff should be encouraged to examine the vascular access before needle placement at each dialysis session. In addition, all dialysis accesses should be carefully examined on a regular basis by a qualified individual. Usually, there is a relatively rapid flow and drop of pressure through the access because of low resistance in the venous system. This results in an easily palpable thrill and loss of an arterial pulsation beyond the arterial anastomosis.

The physical examination of the arteriovenous fistula should include a search for pulsatile venous outflow and multiple collaterals. A pulsatile fistula suggests inadequate venous outflow due to a stenosis or veins of inadequate caliber. Multiple venous collaterals may prevent development of a dominant vein suitable for needle placement. The brief application of a partially inflated blood pressure cuff or tourniquet may aid in this assessment. An arteriovenous fistula that has been in use for some time can start enlarging at sites of repetitive needle puncture. If the patient or staff notes that these sites are enlarging rapidly over days to weeks, an outflow stenosis must be considered.

The physical examination of an arteriovenous graft includes palpation over the graft and venous outflow. The arterial pulsation should dissipate shortly after the arterial anastomosis. Evidence suggests that persistent pulsation throughout the graft with little or no detectable thrill is highly predictive of an outflow stenosis. The transition point from pulsation to thrill helps to localize the point of stenosis. Auscultation may also indicate the point of stenosis by the changed pitch of the bruit. Pseudoaneurysms develop in grafts, due in part to repetitive needle puncture in the same location. As with arteriovenous fistulas, rapid increase in size or increasing pulsatility should lead to prompt evaluation for outflow problems.

Dialysis-related Signs of Access Dysfunction

Several events or other findings related to the dialysis procedure should prompt concern that access problems are developing. Reduction of dialysis adequacy may be caused by deterioration of access function. Possible mechanisms include decreased blood pump speeds necessitated by arterial or venous pressure alarms, or increased access recirculation leading to reduction in effective clearance. Prolonged needle site bleeding at the end of dialysis is often due to development of access outflow stenoses. This event results from increased access pressure due to downstream stenosis and is the principle underlying using intra-access pressure as a screening test.

Vascular Access Flow

Determinants of Vascular Access Flow

The purpose for vascular access in end-stage renal disease (ESRD) patients is to provide sufficient blood flow for hemodialysis. Vascular access blood flow is a function of blood pressure, arterial inflow, and the presence of intragraft and venous outflow stenoses. Initial flow rates after arteriovenous graft placement can range from less than 1000 mL/minute to greater than 2000 mL/minute. The minimum desired blood flow is in the range of 400 to 500 mL/minute in order to prevent recirculation and reduced dialysis adequacy (see chapter on dialysis access recirculation). The maximum tolerated blood flow is below the level at which adverse elevations of cardiac output or vascular steal occur.

Low blood pressure can reduce vascular access blood flow and should be taken into account when interpreting and comparing results of sequential flow studies. This is particularly important with measurements taken during the dialysis treatment. The blood pressure should be recorded at the time of each flow measurement. Access flow falls about 10% during a 4-hour dialysis treatment. It is preferable to perform flow measurements in the early phase (initial 60–90 minutes) of the hemodialysis treatment in patients who experience large blood pressure drops during hemodialysis treatments.

Decreased Access Flow Rate

Declining vascular access flow is predictive of access thrombosis and stenosis. Access flow can be measured during dialysis by

several techniques and with Doppler ultrasound. In dialysis grafts, flow rates of less than 600 mL/minute are associated with a high risk of graft thrombosis in the following 3 to 6 months. A rapid decline in flow rate is also predictive of impending thrombosis. Flow declines of more than 25% in 6 months increase thrombosis risk more than a 13-fold. Earlier studies suggested that intervention based on low or declining blood flow prior to thrombosis reduces the future rate of access failure.

In arteriovenous fistulas, a flow rate below 500 mL/minute has been shown to be predictive of increased risk of thrombosis. Studies have also examined the effects of regular flow screening on outcomes of arteriovenous fistulas. Using a blood flow rate threshhold of less than 500 mL/minute yields approximately 60 to 70% sensitivity for detecting a stenosis. One study showed a sevenfold increase in angioplasty procedures after instituting a monthly flow surveillance program but no significant changes in thrombosis rate or access life. In sum, decreased flow rates in grafts and arteriovenous fistulas appear to be predictive of the presence of a stenosis and increased risk of thrombosis. On the other hand, when a surveillance program is applied to a general population of dialysis patients overall access survival does not improve consistently.

Recent evidence from several randomized controlled trials of intervention versus observation suggest a possible reduction in the number of patients experiencing graft thrombosis but no advantage to overall graft survival. It is important to note that the observation (control) groups in these trials also received interventions in response to other clinical indicators of graft dysfunction (as previously mentioned and outlined in Table 3.1). In one study, the group with interventions based on flow criteria (access flow <650 mL/minute) had 0.93 interventions per patient-years and the observation group had 0.61 interventions per patient-years. These results and those from other controlled trials of similar design suggest that higher-risk problems are often detected by clinical parameters and that the currently available studies are underpowered to detect access survival differences.

Measurement of Access Flow

Methods for measuring vascular access blood flow include ultrasound dilution and Doppler ultrasound. Alternative techniques for assessing access flow during the dialysis treatment are being evaluated. These methods include the use of ionic dialysance,

Table 3–1

Clinical Indicators of Access Dysfunction

- Deteriorating dialysis adequacy
- Prolonged needle bleeding
- Physical exam findings
- Arteriovenous fistula
- Arm swelling
- Pulsatile fistula
- Loss of thrill
- Fistula collapse during dialysis (inadequate inflow)
- Multiple collaterals
- Rapidly enlarging aneurysms
- Graft
- Arm swelling
- Pulsatile graft
- Loss of thrill
- Visible recirculation of saline
- Rapidly enlarging pseudoaneurysms

the Doppler ultrasound method based on variable pump flow, and an optidilutional method that assesses variation in bloodline hematocrit. In addition, vascular access flow rates have been measured with electromagnetic flow probes, but these can only be used in the operating room with an exposed blood vessel. The detection of true access recirculation suggests that an access flow less than delivered pump blood flow has occurred. A variety of methods have been described for measuring access recirculation. These are discussed later in this section. Magnetic resonance angiography has also been used to assess access flow.

The Ultrasound Dilution Method (Transonic Systems, Ithaca, NY)

This method uses two ultrasound flow probes specifically calibrated to the dialysis unit bloodlines, an analog/digital converter and flow measurement module, and a laptop computer with analysis software. The vascular access blood flow is derived from the dilution of blood by saline and from accurate measurements of flow in the bloodline (Figure 3.1). Ultrasound flow probes are placed on the arterial and venous bloodlines and measure sound velocity through the blood path. Access

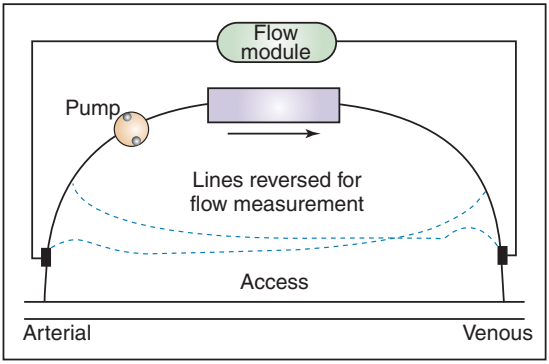


Figure 3–1

Schematic of an ultrasound dilution-based access flow measurement. The bloodlines are reversed during the flow measurement, enabling a bolus of saline to mix with access blood through the arterial needle and to be sampled through blood pulled in through the venous needle.

recirculation is first sought by releasing a bolus of saline with the bloodlines in the standard configuration. The bloodlines are then reversed, with the venous line returning to the arterial needle. With the blood pump turned to 300 mL/minute, a bolus of saline is released on the arterial side of the artificial kidney.

The initial dilution of blood by the saline is measured in the venous line returning to the arterial side of the access. This saline-blood mixture then enters the access and mixes with the flowing blood. Blood from the access (diluted by saline) is then pulled into the arterial line through the venous-side needle. The ratio of these dilutions factored by the known blood flow through the machine reflects access blood flow. The method is readily learned by a dialysis technician or nurse. The readings are usually obtained in duplicate and take about 10 to 15 minutes per patient. No additional supplies are required, and only a small amount of saline is needed for each study. The equipment should be recalibrated per manufacturer recommendations. Use of this method in patients with an arteriovenous fistula may give erroneous results if the venous needle is in one of several branches of the fistula.

Doppler Ultrasound

Doppler ultrasound estimates blood flow by calculating the product of velocity of blood flow times the cross-sectional area of the vascular access. The accuracy of flow measurement varies among the commercially available ultrasound machines. Peak velocity methods tend to overestimate flow, and mean velocity methods tend to underestimate flow rates. The time-domain correlation method appears to yield the most accurate flow rates. The ultrasound transducer is held at a fixed angle to the direction of blood flow. Several readings are taken and averaged. The equipment is costly and the technician must be trained to do the procedure. No additional supplies are required. Doppler ultrasound flow rates might help to determine maturation of arteriovenous fistulas.

Recommendations for Evaluation of Low Flow States

Low access blood flow rates associated with inadequate dialysis, access bleeding, increasing aneurysm size, or other technical problems with dialysis should be evaluated with an angiogram and repaired if a significant lesion is found. Evidence suggests that the risk of thrombosis increases as hemodialysis graft blood flow rates fall below 600 to 800 mL/minute. In addition, rapidly declining graft blood flows with sequential surveillance are also associated with a higher rate of thrombosis. The NKF-K/DOQI guidelines from 2006 recommend that patients with low graft blood flows undergo an angiogram to search for stenoses of the graft or venous outflow.

If a stenosis greater than 50% in diameter is found, treatment with balloon angioplasty or surgery is recommended. Recent evidence brings into question whether a preemptive intervention strategy holds for the general population of dialysis patients and for all stenosis greater than 50%. Further study is needed to determine if there are subsets of dialysis patients in which flow surveillance will have utility in reducing complications and extending access survival.

Some patients will be found to have low graft blood flow without apparent graft or venous outflow stenoses. Alternative causes of low flow are low arterial inflow due to atherosclerosis or fibromuscular hyperplasia, low blood pressure at the time of flow determination, and a technical error. Inflow stenoses are found in approximately 30% of cases if the arterial inflow and

anastomosis are carefully evaluated. Repeat flow studies and angiography (including the arterial circulation) may be indicated in persistent low flow states.

Vascular Access Pressure Surveillance

The pressure in the access reflects both inflow pressure and the resistance or impedance to outflow to the central venous circulation. Elevation of access pressure suggests that an outflow stenosis has developed. Several methods for assessing vascular access pressure have been evaluated. Access pressure can be measured with the blood pump running (dynamic) or off (static). In addition, a separate pressure transducer can be used or the pressure can be estimated indirectly from the venous drip chamber pressure transducer.

Usually, the pressure in the vascular access falls rapidly as blood flows against low resistance on its return to the central venous circulation. Flow impedance due to stenoses within the fistula or graft, at the graft venous anastomosis or in the venous outflow, raises the pressure at locations upstream to the stenosis. A schematic representation of this phenomenon is shown in Figure 3.2. Additional important factors contributing to the

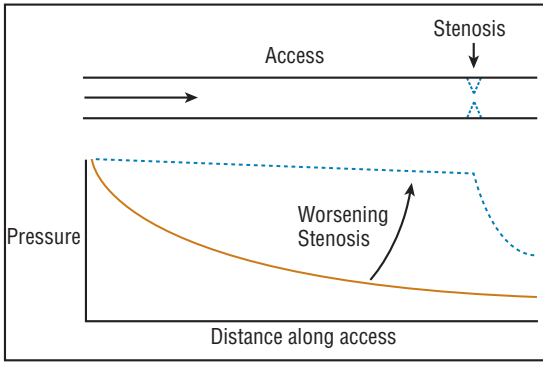


Figure 3–2

During usual circumstances, the intra-access pressure falls rapidly within the access. If an outflow stenosis is present, intra-access pressure is elevated.

pressure within the vascular access are patient blood pressure and the presence of arterial vascular disease.

Measurement of Intra-Access Pressure

The pressure within the vascular access can be directly measured from a needle inserted into the vascular access attached to a sensitive pressure transducer or estimated from the pressure transducer attached to the venous drip chamber of the hemodialysis machine. A direct measurement from the venous needle or the addition of a three-way stopcock on the venous return line while it is attached to the venous needle can be used to directly measure intra-access pressure. In either case, a line is connected to a sensitive pressure transducer and the pressure reading is taken with the blood pump stopped.

To avoid the need for special equipment and supplies, a simplified method for estimating the static intra-access pressure has been described. The dialysis needles are placed and attached in the usual configuration to the dialysis bloodlines. The pressure reading in the venous drip chamber is then recorded with the blood pump turned off. This pressure is the sum of the intra-access pressure and pressure due to the column of blood between the vascular access and the blood level of the venous chamber. The results of this method correlate with direct intra-access pressure measurement. A standard correction factor can be determined for the dialysis unit if all dialysis machines are the same and chair arm height is standard. These values are typically in the 10- to 20-mmHg range.

Interpretation of Intra-Access Pressure Measurements

The ratio of the intra-access pressure to mean arterial pressure is easily calculated. A ratio of greater than 0.5 is predictive of a more proximal stenosis greater than 50% in diameter and correlates with a reduction in graft blood flow. Repeat intra-access pressure measurement after angioplasty of a significant stenosis usually shows a decline to a ratio of less than 0.5. It has been reported that a screening and intervention program based on intra-access pressure surveillance causes a reduction in the thrombosis rate and in total interventions. The value of intra-access pressure surveillance as a predictor of stenosis or impending thrombosis has been found for arteriovenous fistulas is questionable.

Dynamic Venous Pressure

The venous drip chamber pressure with the blood pump running has also been used as an indirect assessment of intra-access pressure. During blood flow through the extracorporeal circuit, the pressure in the venous drip chamber is affected by blood flow rate, needle gauge, needle position, hematocrit, and intra-access pressure. It has been suggested that a venous drip chamber pressure of greater than 150 mmHg at a blood flow of 200 mL/minute with 16-gauge needles is predictive of an outflow stenosis.

More recently, a method termed the *dynamic venous access pressure ratio* has been described. This procedure incorporates 15-gauge needles, the effects of hematocrit, and higher blood pump speeds. This method reported 70 and 74% sensitivity of predicting graft complication in the next 3 and 6 months, respectively. The dynamic venous pressure measurement does not correlate well with flow surveillance results. This is thought to be due to a significant and variable contribution of the arterial inflow resistance to overall access flow. Currently, routine use of dynamic venous pressure as a primary surveillance method is not recommended.

Other Surveillance Methods

Color-flow Doppler studies are able to detect stenoses of the hemodialysis graft and venous outflow. Recent studies have differed on the utility of ultrasound surveillance for the detection of stenosis. In one of the studies, the ultrasound surveillance group was evaluated every 3 months for stenosis in addition to standard surveillance for dynamic venous pressure and flow measurements. The ultrasound surveillance group had a significantly longer cumulative access patency. Thrombosis rates were not given. In a recent prospective randomized controlled trial, AV grafts were screened every 4 months for the development of stenoses using ultrasound. The control group was monitored with clinical monitoring only. There was no difference in thrombosis rate or overall access survival comparing the two groups despite a 64% increase in the rate of angioplasty in the ultrasound group. Thus, recent evidence has not clearly established the utility of this structural screening method and further evaluation of this question is needed.

Vascular Access Surveillance Program

There is uniform agreement that dialysis staff should be attentive to clinical indicators of access dysfunction. It is recommended that all dialysis facilities have an organized system for the care

Table 3–2

Methods of Vascular Access Monitoring

- Clinical monitoring (see Table 3.1)
- Flow measurement
  - Ultrasound dilution
  - Doppler ultrasound
  - Others
- Pressure-based
  - Static intra-access pressure
  - Direct intra-access measurement
  - Indirect measurement via dialysis machine
  - Dynamic pressure (blood pump running)
- Structure-based
  - Color-flow Doppler
  - Angiography

of vascular access. This program should include experienced personnel responsible for record keeping and communication with nephrologists, surgeons, and interventional physicians. Each center should create and maintain a monitoring and surveillance strategy within the bounds of available methods at the center (see Table 3.2). The access should be examined at every dialysis session by the nurses and technicians, and dialysis adequacy should be monitored on a regular basis.

Many nephrologists prefer a preemptive approach to repair of access problems detected by surveillance methods to avoid deterioration of dialysis adequacy and unexpected thrombosis events. Surveillance techniques appear to have a sufficient sensitivity to detect and allow for further evaluation of hemodynamically significant stenoses and aid decision making regarding further access evaluation. It is likely that future research will identify subsets of patients and lesions that will be benefited by the more aggressive surveillance and intervention strategies available. In addition, as improved methods for preventing or treating thrombosis and stenosis become available surveillance may also increase in value.

Recommended Reading

Besarab A, Sullivan K, Ross RP, Moritz MJ. Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. Kidney Int 1995;47:1364–1373.

Description of a successful vascular access surveillance program using intra-access pressure monitoring.

May RE, Himmelfarb J, Yenicesu M, et al. Predictive measures of vascular access thrombosis: A predictive study. Kidney Int 1997;52:1656–62.
Compares access flow, recirculation, and dynamic venous pressure measurements as predictors of vascular access thrombosis.
Moist L, Churchill D, House A, Millward S, Elliott J, Kribs S, et al. Regular monitoring of access flow compared with monitoring of venous pressure fails to improve graft survival. J Am Soc Nephrol 2003;14: 2645–53.
Randomized controlled trial of graft surveillance with ultrasound-dilution flow measurements versus clinical monitoring showed improved detection of stenosis but did not change time to graft thrombosis or time to graft loss.
National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access, 2006. Am J Kidney Dis 2006;48 (1):S210–33.
These guidelines were developed based on studies and consensus opinion for detection of access dysfunction using monitoring, surveillance, and diagnostic testing.
Robbin ML, Oser RF, Heudebert GR, Mennemeyer ST, Allon M. Randomized comparison of ultrasound surveillance and clinical monitoring on arteriovenous graft outcomes. Kidney Int 2006;69:730–35.
Randomized controlled trial comparing the impact of ultrasound surveillance in addition to clinical monitoring. No additional benefit was found for ultrasound surveillance over clinical monitoring.
Tonelli M, Klarenbach S, Jindal K, Manns B. Economic implications of screening strategies in arteriovenous fistulae. Kidney Int 2006;69:2219–26.
This report analyzes the estimated costs of an arteriovenous fistula management program without flow surveillance and at two different flow rate thresholds (500 and 750 mL/minute) for intervention.

CHAPTER 4

Vascular Access for Hemodialysis in Adults

Peter F. Lawrence, MD

Introduction

Establishing and maintaining vascular access for hemodialysis has changed dramatically over the past decade. The prevalence of autogenous arteriovenous fistulae (AVFs) has increased, whereas the use of arteriovenous grafts (AVGs) and catheters has decreased proportionately. New graft materials and anastomotic techniques have been developed to gradually improve AVF and AVG patency. Techniques for noninvasive access monitoring are used for failing AVFs and AVGs, and percutaneous endovascular interventions have been increasingly used for failing or thrombosed AVFs and AVGs—although the limitations of procedures performed on the venous anastomosis have been increasingly recognized.

For many years, vascular access has been fragmented among several specialties and has lacked a quality assurance program. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-K/DOQI) has had a major impact by developing and implementing clinical practice guidelines for vascular access. The Fistula First program, instituted by the Centers for Medicare and Medicaid Services (CMS) and the National Kidney Foundation (NKF), has been used to implement the NKF-K/DOQI guidelines over the past four years. This chapter reviews the current recommendations that nephrologists, surgeons, and other dialysis staff should use to implement a multidisciplinary approach to establishing and maintaining vascular access for end-stage renal disease (ESRD) patients.

Vascular access continues to be a significant economic, surgical, and logistical problem for patients and their health care providers. In general, vascular access success is directly related to the frequency of use of hemodialysis catheters, the patency of the arteriovenous (AV) access (AVF versus AVG), and the prevalence of subsequent catheter and access complications (i.e., infection, malfunction, and thrombosis). The most cost-effective and lasting vascular access for hemodialysis is the native (AVF) fistula, but an increasing number of patients have exhausted their

autogenous veins and are required to have AVG or permanent cuffed dialysis catheters.

Unfortunately, in one study only 36.5% of ESRD patients were instructed to protect their forearm veins for subsequent AVFs—and subclavian catheters continue to be used for initial access (leading to continued problems with outflow stenosis and thrombosis). Because approximately 40% of ESRD patients have had less than 3 months of nephrology care, only 45% of patients starting dialysis and 60% of patients after 30 days of dialysis had a permanent access (i.e., AVF or AVG)—and subclavian catheters were used in 80% of patients.

Vascular Access History

It is important to understand how dramatically vascular access surgery has changed during the past 40 years, and particularly in the past 20 years. In 1966, Cimino-Brescia described the first radiocephalic AVF. In 1968, Dudrick described the first central line for total parenteral nutrition. In the late 1960s, the first ePTFE (expanded polytetrafluoroethylene) vascular grafts became available—and in 1973 Broviac developed the first tunneled right-atrial catheter. In 1980, Uldall reported the first short-term nontunneled double-lumen hemodialysis catheter. In 1995, Silva popularized the "all-autogenous" access philosophy—and in the same year the basilic vein transposition became an alternative when commonly used superficial veins were unavailable for conduit.

Barriers to Effective Vascular Access Management

Providing reliable and lasting vascular access should reduce morbidity, mortality, and health care costs. Optimal care requires the nephrologist, who is the ESRD team leader, to take an aggressive role in eliminating the common barriers discussed in the sections that follow.

Late Referrals to a Vascular Access Surgeon

In some large urban hospitals, 50% of all new ESRD patients simply appear in the emergency room with congestive heart failure—needing urgent dialysis. Large health plans need better systems to make an early referral to a vascular access surgeon. Bracelets should also be provided to patients to remind them and to alert other health care professionals to preserve superficial

upper extremity veins, particularly those selected for the access procedure.

Noncompliant Patients

Even when ESRD patients are referred to the vascular access surgeon, many patients deny they have a problem and are reluctant to have surgery. Once a patient starts urgent dialysis with a temporary catheter, many patients prefer the "painless" dialysis by catheter to the needle cannulation of an AVF or AVG. In these circumstances, vascular access education and support are essential. For outpatient vascular access procedures, many centers also report up to a 30% cancellation ("no show") rate. The elderly patient with multiple medical problems, the young patient in denial, and the indigent patient without transportation need individual attention by the dialysis staff, social worker, and family members to provide timely and efficient surgical care.

Poor Access Monitoring

Because it is not currently possible to control the biologic response to vascular access procedures (i.e., catheters, AVFs, and AVGs) and the resulting myointimal hyperplasia, all vascular accesses have a limited patency. Identifying failing accesses can lead to interventions that prolong the function of each vascular access, reduce the number of catheters, and improve care of ESRD patients. Each dialysis unit should have a routine non-invasive monitoring system for vascular access sites.

No Dedicated Facilities

To limit the number and duration of temporary catheters, AVF creation or AVG placement should occur within 1 week of referral to a vascular access surgeon. Furthermore, a failed or thrombosed AVF or AVG should initially have an endovascular procedure or open surgical intervention within 48 hours. At most institutions, there is no operating room, radiology suite, or clinic area specifically dedicated to or standing by to accomplish these goals in an outpatient setting. Most vascular access procedures are added on to an existing, usually overbooked, schedule.

Vascular access procedures are often bumped for other medical and surgical emergencies, particularly at large trauma, transplant, or general hospitals. ESRD patients then become inpatients, and/or require temporary catheters, and/or miss dialysis sessions.

One solution to this problem is to develop a dedicated vascular access surgical center. Such a center provides one-stop service for clinic evaluation, noninvasive vascular testing, catheter placement, endovascular interventions (i.e., angioplasty, lysis, and stenting), and outpatient surgery (i.e., AVF and AVG procedures). A business plan will demonstrate that a dedicated vascular access center can reduce overall costs, morbidity, and mortality while increasing patient and staff satisfaction.

No Vascular Access Team

When a vascular access problem arises, dialysis staff often scramble to find an interventionalist to solve the problem immediately. Without a dedicated and integrated vascular access team, results are variable and new surgical and endovascular approaches may not be explored. Preoperative venous mapping for AVFs, routine noninvasive monitoring for access problems, and more complex and time-consuming surgical procedures may not be done because reimbursement is poor and not offset by a large clinical volume. The director of a dialysis unit must establish and lead a multi-disciplinary team to meet NKF-K/DOQI guidelines and to implement Fistula First and other CMS performance measures.

No Integrated Care Plan

Over the past decade, vascular access for hemodialysis has become more complex, more demanding, and more costly. Each dialysis unit, through its multidisciplinary vascular access team, will need to assess its local resources and translate the NKF-K/DOQI guidelines into an effective integrated vascular access care plan. A database is essential for tracking every patient's vascular access history: access sites, monitoring results, secondary interventions, and subsequent complications. With a plan and database, every unit should be able to establish an effective quality improvement program for vascular access.

Evaluation for Access

Once the decision has been made that a patient needs hemodialysis, the access procedure is based on the anticipated length of dialysis needed (days, months, or lifetime) and on the unique characteristics of each patient—such as life expectancy, co-morbidities, location of dialysis (home or center), compliance of the patient, and psychosocial needs. Each access method has its advantages and

challenges, and the best access site and method for one patient may be different for another.

Acute Dialysis Access

Immediate dialysis requires placement of a catheter in a central large-caliber vein so that enough flow can be generated to dialyze a patient in <4 hours. There is currently no AVF that can be used immediately for hemodialysis, and AVGs have a higher complication rate if used immediately. Therefore, temporary-access catheters are often used when dialysis must be performed in less than 3 to 4 weeks and there is inadequate time for the chronic access fistula or graft to mature. Several graft companies have developed and are promoting prosthetic hybrid grafts that can be used immediately with a lower risk of hematoma, thrombosis, and infection.

Currently, most patients who need immediate access should therefore have a temporary central hemodialysis catheter placed. Occasionally, for medical or social reasons, these temporary-access catheters become "permanent temporary access." This may occur when a patient with a temporary hemodialysis catheter becomes acutely or chronically ill and is unable to undergo a permanent access procedure, or when a chronic access procedure cannot be performed due to anatomic limitations such as superior vena caval syndrome.

The placement of temporary dialysis catheters has a low risk when performed by an experienced physician. An uncuffed hemodialysis catheter can be percutaneously placed at the bedside, but must be replaced prior to hospital discharge because it can be dislodged and cause excessive hemorrhage or infection. Therefore, the uncuffed catheter should not be used as an outpatient solution. Uncuffed catheters should be replaced with a cuffed catheter, which is more durable, rarely dislodges, has a lower infection rate, and can be used with outpatients.

Selection of Optimal Site for Temporary Access

Temporary access is best achieved in a central upper extremity or neck vein that provides direct access to the superior vena cava and right atrium. When the tip of the catheter is left in this location, the flow is high and the risk of thrombosis is low. In most patients, central veins are patent and easily accessible, but occasionally prior catheters or central deep vein thrombosis (particularly in hypercoagulable patients) has occluded them.

Internal Jugular Vein

The internal jugular vein is optimal for acute temporary access because it is large, usually patent, and directly connected to the superior vena cava. In addition, if a temporary catheter thromboses the internal jugular vein, the thrombus rarely limits the ability to perform a permanent access procedure in the arm vein—which drains into the subclavian vein and ultimately into the superior vena cava. In addition, complications during placement (such as bleeding) are easy to control with direct compression—and pneumothorax is uncommon with internal jugular vein catheters.

Subclavian Vein

These veins are the second choice for temporary hemodialysis catheters. Although subclavian veins are relatively easy to access, there is a significant risk of stenosis in the vein months to years after the catheter is removed—and this stenosis may lead to high venous resistance, a swollen arm, and ultimately AVF or AVG failure. In addition, subclavian veins are difficult to compress if they are lacerated or bleed during line placement—and pneumothorax is a higher risk than with internal jugular catheters.

Femoral Vein

A femoral vein catheter is a lesser choice for acute access, because it is located in a region that has a higher bacterial content and therefore a higher risk of infection. In addition, thrombosis of the catheter is associated with a higher risk of symptomatic venous thrombosis in the lower extremity and with pulmonary embolism, and long-term sequelae of leg swelling and venous ulceration.

Technique for Placement of Temporary Venous Catheters

The technique for the placement of temporary venous catheters requires knowledge of anatomic landmarks (Figure 4.1) to reduce the incidence of failure and complications.

Percutaneous Noncuffed Dialysis Catheters

Percutaneous noncuffed dialysis catheters can be placed rapidly in almost any setting. However, if possible the procedure should be done under ultrasound guidance (Figure 4.2). These catheters

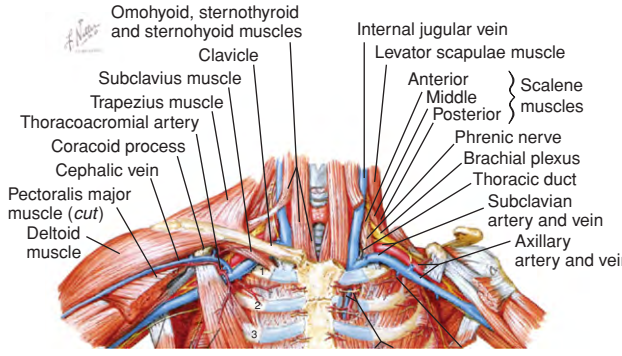


Figure 4–1

Anatomy of the central neck and arm veins. Knowledge of the anatomy of these veins and their relationship to the arteries, muscles, and lung is critical to increase the likelihood of success with percutaneous access and to avoid complications such as pneumothorax and arterial puncture.

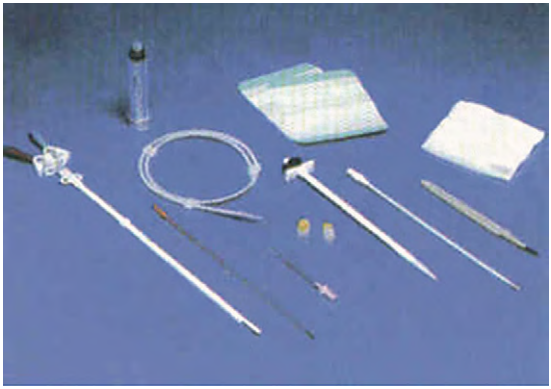
do not require fluoroscopic guidance, but a chest X-ray must be performed at the completion of the procedure to confirm the proper location of the catheter in the superior vena cava and to assess for pneumothorax.

Cuffed Venous Catheters

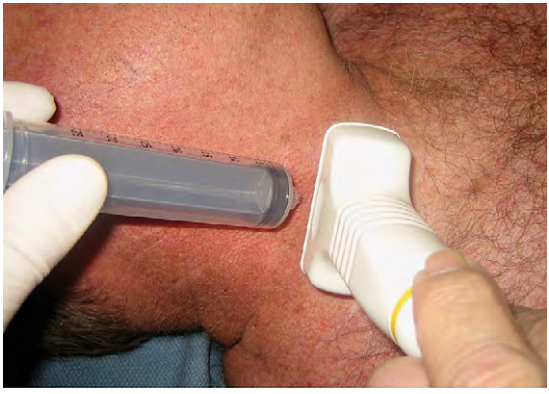
Cuffed catheters must be placed in a setting equipped with ultrasound and fluoroscopy (Figure 4.3). Use of ultrasound improves the ease of venous puncture and reduces the risk of arterial puncture. Fluoroscopy facilitates the advancement of a large-caliber sheath, the positioning of the catheter in the superior vena cava, and investigation of the catheter path for kinks.

Permanent dialysis

Placement of permanent access must be a planned procedure. It requires consideration of multiple factors, the most important of which are discussed in the sections that follow. In general, however, autogenous (nonartificial graft) access is superior in terms of long-term patency and resistance to infection.



A



B

Figure 4–2

Placement of a temporary dialysis catheter. For immediate access, a noncuffed dialysis catheter is frequently placed (A). The internal jugular vein is the preferred site, but subclavian veins are also acceptable. These catheters can be placed at the bedside (B). The highest success (and lowest complication rate) occurs when ultrasound is used to identify the central vein and assist in the venapuncture.

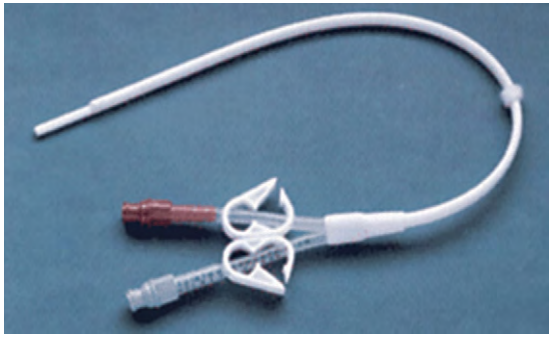


Figure 4–3

Cuffed venous dialysis catheter. A cuffed catheter can provide longer-term dialysis with a lower infection rate than a noncuffed catheter. For optimal results and reduced complications, a cuffed catheter requires ultrasound guidance during venapuncture and fluoroscopy to confirm the placement in the superior vena cava.

NKF-K/DOQI and Fistula First Guidelines

The National Kidney Foundation began the Dialysis Outcomes Quality Initiative to develop clinical practice guidelines (Table 4.1) for vascular access. A workgroup of experts reviewed more than 3000 articles and extrapolated the best-practice literature to what they thought would be realistic optimal standards of practice.

Table 4–1

Patient Evaluation and Access Placement (NKF-K/DOQI) Guidelines

- Patient H&P Exam Prior to Permanent Access Selection
- Diagnostic Evaluation Prior to Permanent Access Selection
- Order of Preference for Placement of AV Fistulae
- Type and Location of Dialysis AV Graft Placement
- Type and Location of Tunneled Cuffed Catheter Placement
- Acute Hemodialysis Vascular Access: Noncuffed Catheters
- Preservation of Veins for AV Access
- Timing of Access Placement
- Access Maturation

Consequently, they published 38 guidelines "to advise healthcare providers and patients as to what constitutes optimal clinical practice" (Vascular Access NKF-K/DOQI Guidelines, p. 3). These guidelines were based on 55 "evidence," 27 "evidence/opinion," and 62 "opinion" statements. The guidelines were updated in 2001, and are scheduled to be updated again between 2006 and 2007.

These practice guidelines, although not rigorously tested, are now regarded as the standard of practice. Importantly, patient demographics or other risk factors do not stratify the expected secondary (or cumulative) patencies for AVF and AVG. Furthermore, CMS has now adopted many of these guidelines as clinical performance measures that affect the more than 3000 dialysis centers in the United States. The Fistula First program (Table 4.2) is CMS's implementation program for the NKF-K/DOQI guidelines. Because the entire NKF-K/DOQI guidelines for vascular access cannot be listed here, key recommendations are listed in Table 4.1.

Vascular Access Evaluation

A patient whose serum creatinine is greater than 4 mg/dL should be referred to a vascular access surgeon. A vascular access surgeon is a general, vascular, transplant, or urologic surgeon who has the training, experience, and commitment to evaluate and manage patients requiring specialized intravascular access for dialysis, pheresis, bone marrow transplantation, total parenteral nutrition, or other chemotherapy. Before the surgical evaluation,

Table 4–2

Fistula First Program Guidelines for Success

- Routine Quality Assessment of Vascular Access
- Timely Referral to Nephrologist
- Early Referral to Surgeon for "AVF Only" Evaluation & Timely Placement
- Surgeon Selection Based on Outcomes, Willingness, and Ability
- Full Range of Appropriate Surgical Approach to AVF Evaluation and Placement
- Secondary AVF Placement in Patients with AV Grafts
- AVF Placement in Patients with Catheters Where Indicated
- Cannulation Training for AV Fistulas
- Monitoring and Maintenance to Ensure Adequate Access Function
- Education for Caregivers and Patients
- Outcomes Feedback to Guide Practice

the nephrologist and dialysis staff should have evaluated the patient for dialysis, educated the patient and his/her family about ESRD, and chosen a treatment modality [e.g., CAPD (continuous ambulatory peritoneal dialysis), hemodialysis, or preemptive living-donor renal transplantation].

Many educational materials, programs, and support groups are available through the National Kidney Foundation and medical equipment manufacturers. Particularly useful to patients and their families are two easily understood brochures: "Central Line Access" and "Hemodialysis Access" (Krames Communications). The nephrologist should also obtain the appropriate insurance authorization for a referral to the vascular access surgeon. This is usually a referral rather than a consultation because the surgical evaluation will usually include subsequent vascular access management.

The most common ICD-9-CM code is 459.9 for vascular insufficiency, with secondary codes for ESRD (e.g., 580–589.xx) and other co-morbidities (e.g., diabetes 250.x or hypertension 403.xx). The purpose of the surgical evaluation is to determine the best site for hemodialysis access, to identify patients at high risk for access failure, to assess operative risk for the surgical procedure(s), and to educate the patient to obtain informed consent. As outlined later in the chapter, the vascular access evaluation is usually an expanded problem-focused or comprehensive outpatient clinic visit.

Physical Exam

The most important determinant of successful dialysis access is to have a patient with CKD (chronic kidney disease) evaluated by an access surgeon before dialysis is required and to identify the optimal artery and vein for an AVF. Once evaluated, the patient should have the applicable armed marked (Figure 4.4) and all future IVs and blood draws should be limited to the hand of the arm *not undergoing* the access procedure.

Handedness

Most patients prefer that their nondominant forearm be used for dialysis. Therefore, if all other factors are equal the nondominant forearm is used for the first access procedure.

Allen's Test

Good arterial pressure and a noncalcified artery are optimal for long-term function of permanent dialysis access. Because there is variability in arterial anatomy, an Allen's test (Figure 4.5)

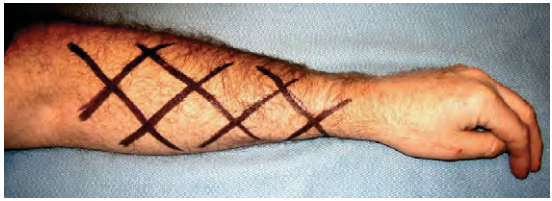


Figure 4–4

Arm marking prior to access procedures. Once a patient is known to require dialysis in the future, the best site should be selected by physical exam of the arm arteries and arm veins. It may also require duplex imaging of the veins and noninvasive testing of the arteries, particularly for subsequent access procedures. Once selected, the arm should be marked and further venous and arterial procedures prohibited in the arm. Hand veins should be used primarily for IVs. Inadequate superficial veins are one of the most common reasons for initial access procedure failure.

should be used to assess for both patency of the ulnar and radial artery and cross-collaterals in the palmar arches of the hand between the two systems. Patients without good collaterals may still have the AVF performed on an artery in the arm with a positive Allen's test, but great care must be taken to avoid occlusion of the artery.

Tourniquet Test

In patients who have not had excessive vein damage from blood draws or IVs of the arm veins, the adequacy of the veins can be determined by physical examination—augmented with a tourniquet. Veins that are >2 mm in diameter, but more importantly are flexible and distensible (and those that are close to the skin surface), are optimal for AVF creation. When the physical exam is unclear, duplex ultrasound mapping should be done to assess the patency of the arm veins. Many access centers perform duplex ultrasound of the veins in all patients.

Arm Size and Swelling

The size of the arm and presence or absence of swelling are important determinants of a functional AVF or AVG. Obese arms and patients with arm edema are both poor candidates for AVF unless other alternative sites are also poor. Occasionally,

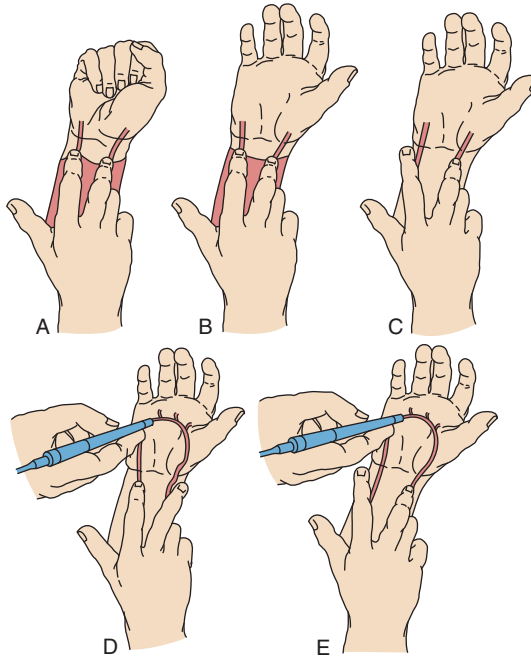


Figure 4–5

Allen's test is used to determine whether the arterial supply of the hand is adequate and whether the hand arch connects the ulnar and radial arteries. Arteries should not be ligated or occluded during an access procedure if the Allen's test shows poor collaterals.

superficial arm veins are so deep that they must be moved to the surface to be accessed.

Noninvasive Testing

Arterial Assessment

- *Physiologic Doppler analysis:* A Doppler can be used to determine the quality of the flow signal and to determine whether there is a proximal or distal stenosis. Triphasic signals indicate patent vessels and good arterial inflow.

- *Segmental pressures:* In patients without easily palpable pulses in the upper extremities, segmental pressures can identify hemodynamically significant stenoses. Patients with an arm pressure of <90% of the contralateral arm have a very high risk of steal phenomenon if an artery in the arm is used for access. A Doppler can also be used to perform a modified Allen's test.
- *Ultrasound of upper extremity arteries:* Ultrasound may be necessary in patients with calcified arteries to determine the patency of the vessel, in that falsely elevated arterial pressures will be present with "stiff arteries." In addition, ultrasound can estimate the amount of calcification and identify the best location for placing an arterial anastomosis.

Venous Assessment

In regard to vein mapping, although a physical exam and tourniquot test can determine the adequacy of veins in most patients many access surgeons use duplex ultrasound routinely to determine the size and the patency of superficial arm veins (Figure 4.6). Basilic veins, which are increasingly being used for autogenous AVF, are difficult to assess on physical exam and need to be assessed for patency by duplex scan. In addition, duplex ultrasound should

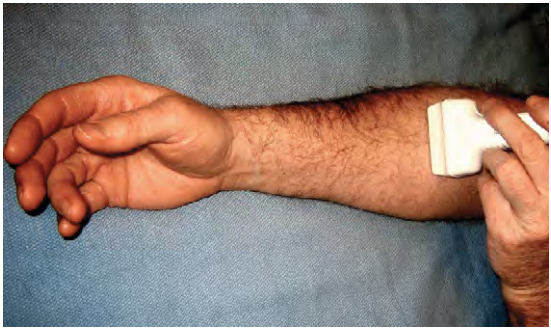


Figure 4–6

Duplex vein mapping. Duplex scanning of the arm veins is particularly useful if the veins do not distend with a venous tourniquet or if there have been multiple IVs and venapunctures in the arm being proposed for access. In the OR, a soft catheter can also be passed up the vein to confirm its patency.

routinely be performed on the subclavian vein in any patient who has had a temporary central venous catheter placed in the subclavian vein on the side where a permanent access procedure is being planned. Stenoses reduce the probability of long-term patency and should be dilated prior to access (alternatively, a contralateral access procedure performed).

Optimal Conduits

Upper Extremity Vein

An upper extremity vein is the optimal conduit for chronic hemodialysis access. The cephalic or the basilic vein can be used for conduit, and occasionally one of these can be transposed to create an optimal fistula. If the quality of the vein is in doubt upon physical exam, duplex ultrasound mapping should be used to determine patency and to examine for stenoses.

Transposed Veins

Many access surgeons prefer autogenous veins, to the extent that they will harvest lower extremity veins for upper extremity conduit—although the reported series show that transposed veins are not superior to prosthetic vein.

Prosthetic Grafts

Prosthetic grafts are used when autogenous conduit is not available. They have similar patencies, irrespective of the conduit material, and thus the type of conduit is based on access surgeon preference.

- *PTFE:* This is the most commonly used conduit, due to excellent handling characteristics and incorporation into the tissue. Most access surgeons use a 6- or 8-mm graft, with the size determined by the donor artery and recipient vein. In the upper arm, a 4- × 7-mm tapered or "stepped" graft is used by some to reduce the likelihood of steal phenomenon—which occurs when a large artery is connected to a large vein through a large conduit.
- *Dacron:* This graft is used by some access surgeons and has a similar patency to other prosthetics.
- *Combined PTFE/Dacron:* This graft has been fused into a composite material to take advantage of the characteristics of each, and is proposed when immediate access is required. The Dacron seals better after needle withdrawal, and the PTFE has a smoother surface and theoretically lower thrombosis rate.

Optimal Sites

There should be a systematic progression from one access site to another, in an attempt to use every site available for chronic angioaccess. In spite of this optimal progression, any access procedures will dilate all veins in the arm—which may lead to the development of veins and arteries at sites that were initially suboptimal. However, the optimal progression is from distal to proximal and from vein to prosthetic (Figure 4.7a through 4.7d).

Wrist

The Brescia-Cimino fistula (Figure 4.8) connects the radial artery to the cephalic vein. With a high patency; good flow; and low risk of infection, steal, or other complications, it should be the first choice for most patients. In diabetics and obese patients, the

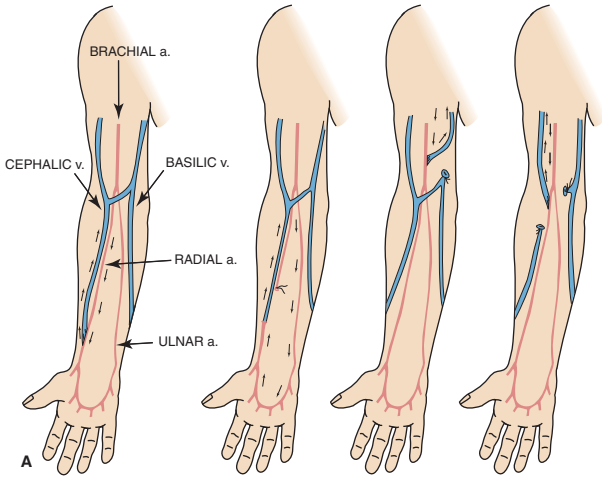


Figure 4–7

Optimal progression of access procedures. The optimal progression of access is from the nondominant upper extremity distally to proximally, using autogenous veins (A, B). Next, the dominant arm should be used. Once all autogenous veins have been exhausted, prosthetic graft should be used in the same progression. When upper extremity access sites have been depleted, the lower extremities can be used (C, D). The progression suggested is based on the durability of the conduit and likelihood of complications such as access thrombosis, steal syndrome, and infection.

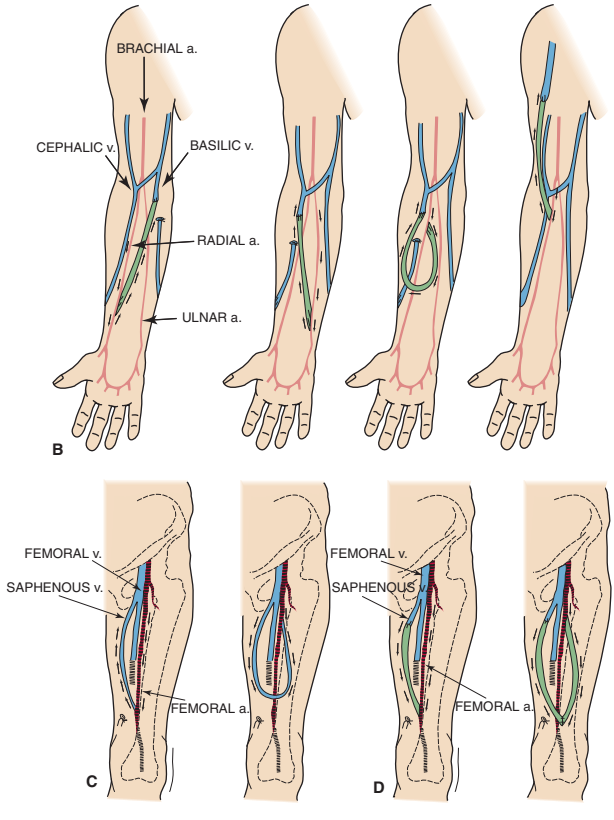


Figure 4–7

Cont'd

radial artery may be small or the cephalic vein may be small and deep in the subcutaneous tissue. In these cases, another fistula may be a better first choice. If autogenous tissue is not available, a straight graft from the radial artery to the median cubital vein is an acceptable prosthetic alternative.

Forearm

The basilic vein in the forearm is also an excellent conduit for hemodialysis, although it needs to be transposed to the radial

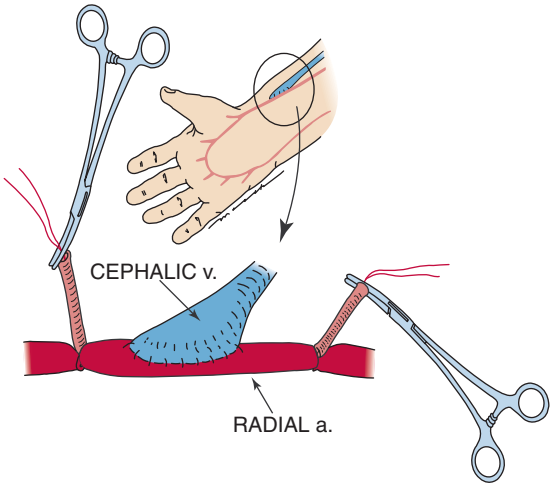


Figure 4–8

Brescia-Cimino AVF. The best initial choice for an access procedure is an AVF between the cephalic vein and the radial artery at the wrist. This procedure, if performed by an experienced access surgeon, has a high success rate with a low complication rate. There are several variations in technique, including end-to-side versus side-to-side and wrist versus snuffbox.

region for good function. Mobilization of the basilic vein, with retunneling, is superior to other conduits when the cephalic vein is not available in the forearm. A prosthetic alternative is a forearm loop AVG, which is placed from the distal brachial artery or proximal radial artery to the median cubital vein. Unfortunately, this procedure has a lower patency than any procedure with autogenous vein.

Upper Arm

Autogenous vein remains the conduit of choice, even when lower arm vein is not available. Brachial artery to cephalic vein and basilic vein transposition are two procedures that have high patencies and lower complication rates. When all autogenous veins have been used, an upper arm AVG between the brachial artery and the basilic, brachial, or axillary vein is an acceptable alternative.

Femoral Region

Because of the bacterial colonization of the femoral region, autogenous AVFs or prosthetic AVGs are less desirable in this location. However, when all arm sites have been used a femoral access may be the only option. As long as the arterial perfusion is good, AVFs and AVGs can be constructed in a similar manner to that of the arm—but with lower patency due to infectious complications.

Unusual Locations

Axillary-axillary/femoral-popliteal: When all conventional access sites have been exhausted, the access surgeon must use creativity to obtain a permanent access site. Connecting any large artery to any large vein will in desperate situations result in a functional chronic access site.

Anesthesia for Access Procedures

Anesthesia Selection

The anesthetic procedure selected should be based on the location within a facility where the procedure is being performed (patient room, angio suite, operating room), the extent of the procedure (central access line versus AVG), the experience of the physician or access surgeon performing the procedures, and patient preference. Many patients request general anesthesia for all access procedures, including central venous lines, although many procedures can and should be done under local anesthesia.

When a patient is young and well controlled medically (normal potassium, fluid status, and so on), the anesthetic choice should take into greater consideration their personal preference. As patients get sicker and older, the anesthetic choice may be more dependent on their health status. Recent myocardial infarction, recent stroke, fluid overload, hyperkalemia, and mental status changes may mandate the type of anesthesia—as well as the suitability for any permanent access procedure. The options range from local anesthesia and regional arm or neck block to MAC (monitored anesthesia care) conscious sedation or general anesthesia.

Problems for Anesthesia and the Operating Room

In Europe and Japan, creating AVFs or placing AVGs in the upper extremity is usually done with local anesthesia alone and an operating room nurse or technician monitoring vital signs. In the United States, most patients demand (and surgeons prefer) general or regional anesthesia. All surgeons, however, use general anesthesia when performing vascular access procedures in the

chest and abdomen—and usually when performing procedures in the lower extremity (where regional anesthesia can also be used). Surgery for emergencies, such as uncontrolled bleeding from an access site or excision of an infected AVF or AVG, is also performed under general anesthesia.

Urgent surgical cases, such as persistent lymphatic drainage from the surgical incision and ligation or banding because of steal syndrome, are usually addressed using regional or local anesthetic. Interventional radiologists use local anesthesia with intravenous sedation and appropriate monitoring by a nurse or radiology technician. Anesthesiologists are always concerned that they may have to change from local or regional anesthesia to general anesthesia. Consequently, any ESRD patient requiring an anesthesiologist must conform to the preoperative rules governing general anesthesia. Next to patients not appearing for scheduled surgery, anesthetic concerns are the most common reason for delay or cancellation of elective vascular access cases.

Patients on Coumadin must also hold their medication for 3 days and have the prothrombin time (PT) drawn. On the day of surgery, anesthesia staff will draw a serum potassium (K^+) from all ESRD patients, another PT from anticoagulated patients, and finger-stick or serum blood sugar from diabetic patients. Patients are also required to be NPO (nothing by mouth). If the K^+ is 5.0 to 6.0 mEq/L, most anesthesiologists will delay the case to treat the patient with glucose and insulin and then recheck the K^+. If the K^+ is >6.0 mEq/L, most anesthesiologists will cancel the case. The patient will then need urgent dialysis and the surgery will be rescheduled. Nephrologists must be diligent about controlling the K^+ before surgery. If the PT is <2.0 INR (international normalized ratio), regional anesthesia can be used.

Regional anesthesia is not used if the PT is =2.0 INR. Except for diabetic patients in ketoacidosis or hyperosmotic coma, hyperglycemia should be treated with insulin and the case should not be delayed. Because of the potential risk of aspiration, especially in diabetic patients, the anesthesiologist will cancel or delay (for 6–8 hours) elective cases if the patient is not NPO. Patients with positive hepatitis C or HIV serology require extra vigilance to protect operating room and other nursing personnel. Elective cases should be canceled for unstable angina, congestive heart failure (e.g., rales, orthopnea, or room air oxygen saturation <94%), a recent change in cardiac rhythm (e.g., new-onset atrial fibrillation or bradycardia), and active infection, except when excising an infected access.

Contraindications to Performing AVF/AVG Procedures

Vascular access and endovascular procedures (such as AVF creation, AVG placement, PTA, and thrombolysis) are elective procedures. Absolute contraindications to permanent dialysis access AVF or AVG include patient refusal, noncompliance with medical therapy, local infection, and inability to tolerate a regional procedure. Permanent (i.e., tunneled, cuffed) catheters rather than AVF or AVG should also be placed in patients with a life expectancy of less than 6 months (e.g., terminal cancer; AIDS; and end-stage liver, heart, or lung disease patients who are not transplant candidates).

Peripheral Vascular Disease

Peripheral vascular disease can create significant technical problems with vascular anastomoses, increase the risk of steal syndrome (discussed previously), and lead to decreased patency of the access. Smoking cessation should be encouraged and hyperlipidemias treated. The saphenous veins are usually preserved for peripheral or cardiac bypasses rather than for AVFs. Thigh AVGs are also not usually placed in a lower extremity that has had an amputation (e.g., below- or above-the-knee amputations). With significant preexisting vascular disease, the incisions for placing the thigh AVG may break down—leading to infection, AVG loss, and further surgery.

Chronic and Intradialytic Hypotension

Patients with systemic hypotension (systolic blood pressure <100 mmHg) and/or bradycardia (pulse <60 bpm) are usually not candidates for AVGs because their AVGs are likely to thrombose. AVFs will, however, tolerate a lower systolic blood pressure, heart rate, and access blood flow (<100 mL/minute). Intradialytic hypotension (IDH) occurs in 25 to 50% of hemodialysis treatments and can lead to AVG thrombosis, gastrointestinal symptoms, and cerebral and cardiac ischemia.

Although many patient factors, dialysate composition, and the dialysis process itself contribute to IDH, the most common factors are diabetic autonomic neuropathy (i.e., orthostatic hypotension), underlying cardiac dysfunction (i.e., left ventricular hypertrophy and poor ejection fraction), dehydration (e.g., low dry weight, ileostomy), and antihypertensive medications. The nephrology staff must make every effort to identify and correct factors leading to chronic or intradialytic hypotension.

Cardiac Disease

Upper extremity AVF and AVG procedures, hemodialysis catheters, and most CAPD catheter placements are usually performed under local or regional anesthesia with intravenous sedation. Because most vascular access procedures are elective, surgeons and anesthesiologists often require a cardiology evaluation for patients with chronic hypotension, suspected low-ejection fraction, bradycardia and other arrhythmias, and valvular or ischemic cardiac disease. Patients with significant cardiac disease are probably not candidates for more complex procedures requiring general anesthesia, such as AVGs in the neck, chest wall, abdomen, or thigh. Patients with prosthetic heart valves should avoid permanent catheters. Their anticoagulation, if any, is managed the same as for any other surgical procedure—with admission, heparin anticoagulation, and restarting Coumadin following the procedure.

Morbid Obesity

With more adipose tissue, duplex ultrasonography is usually required to locate superficial veins for AVFs. Furthermore, veins are usually superficialized or transposed so that the dialysis unit can cannulate them. Infiltrations are common, and many patients then have AVGs placed. The risk of AVG infections is probably increased because of greater dissection, longer operating times, associated diabetes, and inadequate personal hygiene. Excessive perspiration with resultant candida infection and greater numbers of skin flora in the axilla and groin can be a significant problem for proximal arm and thigh AVGs. Meticulous technique is required to prevent a perigraft hematoma, seroma, or lymph collection that may lead to an infected AVG.

Infection, Skin, and Potential Wound Problems

Because long-term access procedures are elective, active hidradenitis, cellulitis, or other superficial infections near the operative site must be adequately treated before any elective access procedure can be performed. Whenever possible, incisions for access surgery are made away from eczematous or psoriatic skin lesions. Some elderly or steroid-dependent patients may have fragile, thin, and sometimes almost transparent skin on their upper extremities. In these patients, electrocautery must be used cautiously and AVGs tunneled along a deeper subcutaneous plane.

Thigh AVGs should not be placed in patients with bladder or bowel incontinence, an overlying panniculus with intertriginous candida or other fungal infection, or poor personal hygiene. The following precautions are also recommended to reduce access

infections. All patients should receive intravenous cefazolin (or, if penicillin allergic, vancomycin) in the operating room. Electrocautery is used to reduce wound hematomas. "Weeping" ePTFE grafts should be controlled with a 5- to 10-minute application of a thrombin-based gel. A well-adherent, porous, stretchable tape (e.g., Hypafix) with dry sterile gauze is used. Hypafix can stretch to accommodate postoperative swelling, and tape "burns" can be avoided. The dressing should remain intact until the patient is seen in the clinic.

Hypercoagulable States

When a patient has recurrent access thromboses (e.g., more than two episodes within 6 months) the surgeon must carefully look for a reason, which include the following: intradialytic hypotension, inappropriate compression of the access, stenosis or occlusion of the venous anastomosis or its outflow, intra-access stenosis, and poor arterial inflow. If these causes are ruled out, a hypercoagulable state should be considered. Although most ESRD patients have abnormal platelet function, some patients may have spontaneous clumping of platelets. Nephrotic syndrome causes a loss of antithrombin III.

Ten percent of systemic lupus erythematosus patients may have a lupus anticoagulant. Patients with a history of deep venous thrombosis may have antithrombins (3–8%), protein C defects (3–8%), protein S deficiency (5–10%), heparin cofactor 2 deficiency, anticardiolipin antibodies, and other coagulation defects. Activated protein-C resistance (APCR) occurs in approximately 5% of the general population. Sickle cell patients have higher blood viscosity and need periodic erythropheresis. When a hypercoagulable state is suspected, a hematologist should be consulted. Although some tests can be done immediately (e.g., APCR), most specialized testing can only be done 2 months after any thrombotic event or thrombolytic therapy. If a patient has lost more than two AVGs to recurrent thromboses, one option is to place a catheter and obtain a hypercoagulation screen 2 months later.

Placement of another AVG should be delayed until the test results are available. Another option is to place another AVG and empirically start Coumadin. Unfortunately, systemic anticoagulation of ESRD patients with an AVF or AVG has a narrow therapeutic window. Either the Coumadin dose is subtherapeutic or the patient bleeds from the needle sites. ESRD patients with hypertension probably have an increased risk of stroke, and spontaneous vitreous bleeding is a risk in diabetic patients.

Therefore, empiric Coumadin therapy should be carefully discussed with the patient and the entire medical team.

Complications of Access

Anatomic Problems

In regard to this section, see Tables 4.3 and 4.4. The most common anatomic problem reported by vascular access surgeons is "small vessels" in the adult ESRD patient. Sometimes this is simply due to an anatomic variant such as high bifurcation of the brachial artery or a superficial ulnar artery in approximately 10 and 3% of patients, respectively. High bifurcation of the brachial artery is an early division of the brachial into the radial and ulnar arteries proximal to the antecubital fossa, most commonly near the axilla.

A superficial ulnar artery is an ulnar artery superficial to the flexor muscles of the forearm and may be incorrectly identified as the brachial artery. If found by duplex ultrasonography, this variant does allow more proximal arterial revisions of an ulnar-basilic AVF. Relatively small nonatherosclerotic arteries of the adult (i.e., radial or ulnar <1.6-mm diameter, brachial artery <3-mm diameter) are usually seen in small women. Because the risk of steal syndrome is high with small arteries, the diameter of the arterial anastomosis must be decreased (e.g., by using a 4- to 6-mm stepped or 4- to 7-mm tapered ePTFE AVG). Wong showed that using radial arteries and/or cephalic veins with diameters <1.6 mm leads to early AVF failure. Silva reported improved patency rates when using arteries =2.0 mm (in luminal diameter), veins =2.5 mm for AVFs, and veins =4.0 mm for all AVGs.

Table 4–3

Post-access Placement Management (NKF-K/DOQI)

Monitoring, Surveillance, and Diagnostic Testing
- Monitoring Primary AV Fistulae for Stenosis
- Recirculation Methodology, Limits, Evaluation, and Follow-up

Prevention of Complications: Infection
- Infection Control Measures
- Skin Preparation Technique for Permanent AV Accesses
- Catheter Care and Accessing the Patient's Circulation

Table 4–4

Management of Complications (NKF-K/DOQI): When to Intervene

- Managing Potential Ischemia in a Limb Bearing an AV Access
- AVG for Stenosis, Infection, Graft Degeneration, and Pseudoaneurysm Formation
- Primary AV Fistulae
- Treatment of Stenosis Without Thrombosis in AVG and AVF
- Treatment of Central Vein Stenosis
- Treatment of Thrombosis and Associated Stenosis in Dialysis AV Grafts
- Treatment of Thrombosis in Primary AV Fistulae
- Treatment of Tunneled Cuffed Catheter Dysfunction
- Treatment of Infection of Dialysis AV Grafts
- Treatment of Infection of Primary AV Fistulae
- Treatment of Infection of Tunneled Cuffed Catheters
- Treatment of Pseudoaneurysm of Dialysis AV Grafts
- Aneurysm of Primary AV Fistulae

Inadequate Maturation and Flow

The most common complication of access surgery is inadequate maturation. Selecting an artery with good flow, selecting a vein that is >2.5 mm preoperatively and admits a 7F catheter in the OR, and meticulous surgical technique with loupe magnification when constructing the anastomosis increases the likelihood of vein maturation. Patients who are physically active and regularly squeeze a rubber ball can improve the maturation time of an AVF.

Infection

Infection is a significant problem, particularly when prosthetic conduit is used. If infection occurs early and involves the graft, it can occasionally be treated with antibiotics. However, late infections that involve the graft usually require either complete graft removal or excision of the infected portion with bypass around the infection.

Arm Edema and Outflow Stenosis

Patients who develop arm edema after an access procedure usually have a stenosis in the vein proximal to the AVF or

AVG. When this occurs, the vein must be interrogated with a duplex ultrasound, magnetic resonance venogram, or fistulogram and dilated to reduce the outflow stenosis. Occasionally, an unrecognized outflow vein occlusion requires takedown of the AV connection to eliminate massive edema.

Thrombosis

Thrombosis of an AVF or AVG is usually caused by stenosis of the outflow vein, but can also be due to stenoses within the conduit or stenosis of the arterial anastomosis. With AVG thrombosis, revision of the venous anastomosis of the graft is usually required to regain and maintain graft patency. Repeated dilatations of the AVG venous anastomosis are futile and excessively expensive in terms of cost and patient time and should not be performed. Dilatation or revision of other venous stenoses is useful to regain fistula or graft patency. Techniques to declot the graft with lytic agents and mechanical devices can be used, followed by angiogram to identify the site of stenosis and correct it.

Aneurysm

Aneuryms occur in AVFs and AVGs due to repeated puncture of the vein wall or the graft wall. When aneurysms enlarge or are filled with thrombus, the segment of the conduit should be replaced. However, the segment should not be sacrificed. Repair of the aneurysm or bypass can often be performed without the need for placement of a temporary dialysis catheter.

Steal Syndrome

Steal occurs when there is a combination of a large high-flow fistula or graft and a small artery or arterial stenosis or occlusion. Steal syndrome is a significant concern in vascular access surgery because it can lead to ligation of the access, permanent neurologic disability, and litigation. Preoperative risk assessment, intraoperative decision making, and early postoperative (i.e., within 48 hours) monitoring of susceptible patients is therefore important.

In general, patients with normal radial and/or ulnar pulses are unlikely to develop steal syndrome. Unless there is a palpable distal posterior tibial or dorsalis pedis pulse, most surgeons will not place a thigh AVG. The greater flow in a thigh AVG coupled

with greater vascular disease in the lower extremity increases the risk of lower extremity tissue loss. Steal syndrome is more likely to occur in patients with diabetes, small arteries (i.e., radial or ulnar <1.6 mm, brachial <3 mm), absent wrist pulses, Raynaud's phenomenon, vasculitis (e.g., systemic lupus erythematosus), amputations, and other significant peripheral vascular disease. Diabetics with wrist pulses do not require digital plethysmography but should be evaluated 24 hours postoperatively.

As previously discussed, small arteries should not be used for access. Patients without brachial artery pulses should have preoperative arteriography and appropriate intervention. Patients without wrist pulses but a palpable brachial pulse, Raynaud's phenomenon, vasculitis, or amputations should have preoperative and/or intraoperative digital plethysmography. A preoperative digital pressure (DP) <50 mmHg or a digital-to-brachial pressure index (DBI) <0.6 is usually predictive of steal syndrome, and creating an AVF or placing an AVG in that arm should be avoided. After AVF creation or AVG placement, the surgeon should verify that distal perfusion is adequate—usually by a persistent wrist pulse or occasionally by digital plethysmography.

Loss of a distal pulse in the operating room indicates a technical problem with the arterial anastomosis or excessive access flow. If the DP is <50 mmHg or the DBI is <0.6 after an AVF is created or an AVG is placed, banding with ePTFE of the AVF or plication of the AVG should be performed. Although banding a graft with chronic steal syndrome has been used to reduce flow, the most common procedure for this problem is a DRIL (revacuclarization-interval ligation) (Figure 4.9) procedure, in which the hand is revascularized with a bypass and the interval artery is ligated.

Summary

Over the past 15 years, establishing and maintaining vascular access for hemodialysis patients has changed dramatically. The number, age, and co-morbidities of ESRD patients have increased. The increasing use of central venous catheters allowed the vast majority of vascular access operations to be elective outpatient procedures. Our goals are now to increase the use of AVFs and to decrease the use of AVGs and catheters.

Our success depends on early vascular access referral, creative vascular access surgeons, routine monitoring, and aggressive secondary interventions. For those patients who require an AVG, we need a better understanding of NIH to achieve better patencies. Although further studies are required, the best graft patency

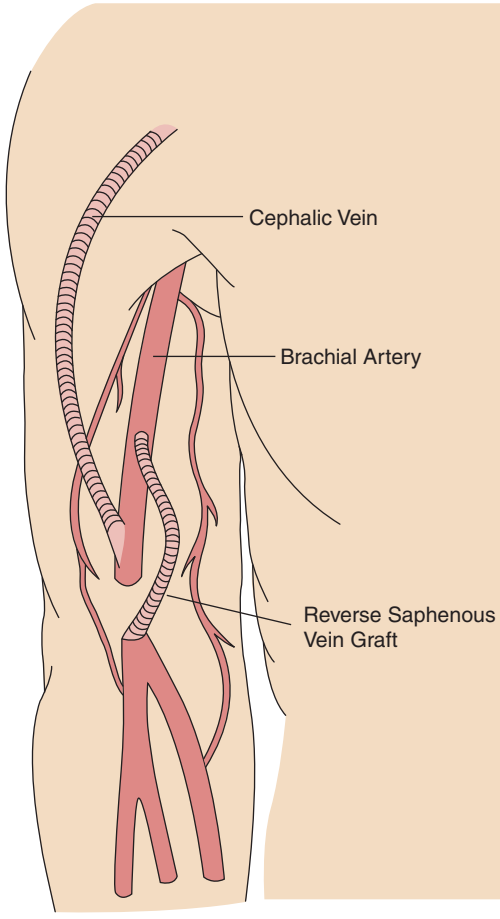


Figure 4–9

DRIL procedure. This procedure was designed to address steal of arterial flow from the hand after an access procedure in the upper extremity. Since there may not be additional access sites available, the DRIL procedure salvages the access site for continued use while increasing flow to the hand. To prevent steal syndrome initially, the size of the anastomosis between the artery and the vein should be limited.

Table 4–5

Quality of Care Standards (NKF-K/DOQI)

- Goals of Access Placement: Maximizing Primary AV Fistulae
- Goals of Access Placement: Use of Catheters for Chronic Dialysis
- Center-Specific Thrombosis Rate
- Infection Rate
- Primary Access Failure Rate: AV Grafts
- Primary Access Failure Rate: Tunneled Cuffed Catheters
- Primary Access Failure: Native AV Fistulae
- Cumulative Patency Rate of Dialysis AV Grafts
- Cumulative Patency Rate of Tunneled Cuffed Catheters
- Cumulative Patency Rate of Primary AV Fistulae

may come from a 6-mm straight, carbon-lined, hooded ePTFE with a local drug-delivery system and low-dose aspirin therapy. Intradialytic monitoring of vascular access sites prolongs AVF and AVG function. Percutaneous transluminal angioplasty and thrombolysis is preferred to surgical thrombectomy and revision. Although these changes have increased the number of interventions and the costs of vascular access care, we hope that overall quality of care has improved.

The optimal mix of pre-ESRD assessment, surgical technique, monitoring, and subsequent interventions by a multidisciplinary team, however, is still undefined. Quality programs (Table 4.5) should be used to assess the center-specific rates of use of tunneled cuffed catheters, primary native AVFs, and AVGs, and of thrombosis infection and maturation rates. If these parameters are regularly measured and assessed, the quality of care for patients will improve, the cost to the health care system will be reduced, and the strain on overburdened ORs will be improved. In short, an integrated and comprehensive program for vascular access should be the goal of all hemodialysis centers.

Recommended Reading

Gibson KD, Gillen DL, Caps MT, et al. Vascular access survival and incidence of revisions: A comparison of prosthetic grafts, simple autogenous fistulas and venous transposition fistulas from the United States Renal Data System Dialysis Morbidity and Mortality Study. Journal of Vascular Surgery 2001;34(4):694–700.

Jennings W, Spergel L. Tools for Achieving Fistula First Goals. Fistula First, National Vascular Access Improvement Initiative at *www.fistulafirst.org*.

Owen WF. Guidelines for Hemodialysis Adequacy. National Kidney Foundation NKF-K/DOQI 2000 at *www.kidney.org/professionals/kdoqi/guidelines_updates/doqiuphd_i.html*.

Patel ST, Hughes J, Mills JL. Failure of arteriovenous fistula maturation: An unintended consequence of exceeding Dialysis Outcome Quality Initiative guidelines for hemodialysis access. Journal of Vascular Surgery 2003;38(3):439–45.

Silva MB, Hobson RW, Pappas PJ, et al. Vein transposition in the forearm for autogenous hemodialysis access. Journal of Vascular Surgery 1997;26(6):981–88.

CHAPTER 5

Major Complications from Vascular Access for Chronic Hemodialysis

Jeffrey L. Kaufman, MD

At a minimum, complications from hemodialysis access sites are a local nuisance, requiring a brief day-stay procedure for revision. However, they can be life-threatening, expensive, and the cause of a prolonged hospitalization. Complications require careful attention because they often decrease hemodialysis efficiency or interrupt the normal dialysis schedule. They are labor intensive for the entire dialysis support team. They are a frustrating imposition on the patient's family. The most common causes of access-site failure are aberrant flow, site thrombosis, and infection. Less common problems include conduit degeneration, steal/ischemia, and edema (Table 5.1).

Permanent Central Venous Catheters

Placement Complications

All central venous catheters share potential complications that include pneumothorax, hemothorax, inadvertent arterial puncture, and chylothorax. Puncture of mediastinal structures is possible during placement, with injury or hemorrhage involving the pericardium or a hemithorax. It is also possible for a catheter tip to be positioned outside the venous system with initially no symptoms.

Because hemodialysis catheters come in a wide range of models and lengths, there is variability in the placement of the entrance site for the catheter tunnel. Some surgeons use a short pocket for the catheter cuff, which facilitates placement but predisposes to spontaneous catheter avulsion and loss of the barrier seal function of the cuff. Others place the cuff deep from the entrance, which prevents spontaneous dislodgment but makes removal more difficult. It is helpful for the patient to understand how the catheter will be positioned, because some exit sites will prove to be uncomfortable if the catheter is left in place long-term.

Table 5–1

Complications from Permanent Hemodialysis Access

Infection
- Catheter infection
- Catheter-related septic central venous thrombosis
- Localized graft infection, including primary blowout with skin erosion
- Total graft infection
- Mycotic aneurysm involving anastomoses
- Endocarditis
- Port infection or erosion with contamination
- Metastatic infection

Emboli
- Arterial
- Venous (pulmonary embolism)
- Septic pulmonary embolism
- Air embolism

Thrombosis
- Catheter or port thrombosis
- Central venous thrombosis
- Graft thrombosis
- Adjacent arterial thrombosis
- Sleeve thrombosis around catheters
- Superficial phlebitis

Hemorrhage
- Perigraft hematoma
- Perianastomotic hematoma
- False aneurysm
- Conduit degeneration

Ischemia/obstruction
- Steal
- Intimal flap
- Neointimal fibrous hyperplasia involving graft, native artery, outflow vein
- Venous outflow obstruction/recirculation
- Graft lumen stenosis/laminated thrombus
- Central vein stenosis/obstruction

Seroma, lymphocele
Edema
Carpal tunnel syndrome
Neuralgia, hypesthesia, hyperesthesia
Wound problems from surgery
Port mechanical torsion, catheter fracture, or separation

It is particularly important to discuss this with women, who may experience discomfort when the catheter receives pressure from underwear. Patients may need to be warned that after a dialysis catheter is removed there may remain visible scars on the chest or neck. A surgical or angiography suite (including outpatient surgical units) is the most appropriate site for catheter placement, in order to preserve sterility. Fluoroscopy is the ideal means of determining the catheter position before finishing the procedure. Ultrasound evaluation of the jugular vein prior to placement prevents injury to the carotid artery by allowing understanding of the relative position of the vein to other structures in the neck. In addition, jugular vein thrombosis or stenosis will be appreciated.

During placement, all wires and dilators should pass smoothly. If a wire kinks or a dilator "hangs up," vein laceration is possible. Deep pain in the neck or chest is ominous, implying impending tissue injury. The patient should be positioned slightly head-down to prevent air embolism. If an arterial laceration occurs with a dilator or with the large-diameter catheter, control of hemorrhage will likely require formal repair or placement of a covered arterial stent. If a subclavian catheterization is necessary, one should try to avoid a puncture at the extreme medial position in the angle between the clavicle and the chest wall.

A catheter placed there may be "scissored" and divided over time, with possible embolization of the intravenous fragment into the heart or pulmonary artery. Catheters in the groin share all of these considerations, but one difference applies to the inadvertent arterial placement of a temporary (non-Silastic) catheter in the femoral artery retrograde to the iliac. In such an instance, it is generally best to remove the catheter immediately. However, in seriously ill patients receiving an urgent dialysis treatment it is acceptable to give heparin to prevent arterial thrombosis and proceed with dialysis before removing the catheter.

One must be certain that the catheter is not decreasing blood flow to the leg, and special care must be given to prevention of arterial emboli from the return line. If any symptoms of ischemia occur in the leg, the procedure is terminated immediately and a vascular surgeon is consulted. If the groin is chosen for cannulation with a temporary catheter, one must be certain not to enter the superficial femoral artery—which, due to its smaller size and more commonly significant involvement with atherosclerosis, is more easily lacerated or dissected than the common femoral.

Dialysis Catheter Infections

Exit site infections with minimal exit-site drainage or erythema about the catheter can be treated with IV antibiotics and dressing changes. Low-grade infection of a chronic dialysis catheter may be manifested by no more than a fever. If there is any doubt about such a catheter, it can be exchanged over a guide wire under local anesthesia (and the tip cultured). High fevers, leucocytosis, rigors, or overt bacteremia indicate a major catheter infection. For these, IV antibiotics and catheter removal are necessary. This also applies when there is extrudable pus from the entry site or erythema along a subcutaneous tunnel. Failure to appreciate infection may lead to accumulation of a septic thrombus at the catheter tip, septic embolization, or endocarditis.

Vein Wall Injury and Thrombosis

Large-diameter catheters, even when made of relatively bioinert Silastic, can cause intimal injury leading to thrombosis and stenosis. Common is the sleeve of material that surrounds a dialysis catheter from its entry site to the tip, and the hallmark of this is inability to aspirate blood from the proximal lumen. The differential diagnosis includes partial thrombosis of a catheter lumen and position such that the orifice of the lumen abuts the central vein wall. Ideally, many of these problems are prevented by placing the catheter tip just into the right atrium. If a catheter is bound by a sheath, it may be stripped using angiographic techniques and wire snares. Alternatively, the sheath can be ruptured with a balloon-tipped catheter. Catheter replacement is another option, but the new catheter must not be replaced into the old sheath.

Complete central vein thrombosis is a very significant complication, most notable because of destruction of the vein as an access site. Superior vena cava syndrome from catheter-related thrombosis is extremely rare. Thrombi related to a central venous catheter can cause pulmonary emboli, but this is also rare. Central vein thrombi may recanalize over time, but they may do so with enough associated scarring and contracture that the venous segment becomes useless for further instrumentation. If an ipsilateral arteriovenous fistula is placed distal to such an injured segment, the resulting extremity edema can be significant—especially if there is a low serum albumin level from malnutrition or nephrotic syndrome.

The diagnosis of catheter-associated thrombosis is made by duplex ultrasonography in most instances. Venography or CT

scans of the area may be needed in some cases where ultrasonography is indeterminate. The ideal treatment of acute thrombosis from a catheter includes removal of the foreign body and often a brief course of heparin, which may be given as a subcutaneous low-molecular-weight preparation in order to avoid hospitalization. For massive thrombosis, there is a rationale for local or systemic thrombolytic therapy followed by heparin anticoagulation. This is especially important if there is a plan to use the distal extremity for an arteriovenous fistula or graft. The patient with major or recurrent thrombosis should be studied for acquired or familial hypercoagulability.

Catheter-Related Septic Central Venous Thrombosis (CRSCVT)

Infection of a dialysis catheter in association with central venous thrombosis is an ominous but fortunately uncommon complication. The diagnosis is based on continued bacteremia after catheter removal in the presence of documented central venous thrombus. The infection, most commonly from *Staphylococcus*, is treated with a course of parenteral and oral antibiotics given for 6 weeks in a manner analogous to the treatment of endocarditis. Because the offending thrombus may be a sleeve coating the catheter or partially occluding the central vein, and because the patient is usually very ill, the physician must maintain a high index of suspicion for CRSCVT—especially when there is no edema of the ipsilateral extremity. If untreated, CRSCVT can lead to endocarditis or septic pulmonary embolism.

The technical issue is where to access the circulation while treatment is initiated and whether a new catheter will become infected. Temporary groin puncture for one or two sessions will often suffice for dialysis while the bacteremia comes under control, and after a week of therapy a new Silastic catheter placed in a new site will remain free of clot and infection. Patients with CRSCVT should receive a careful evaluation for primary placement of, or conversion to, an autogenous dialysis fistula—especially if ultrasonography reveals an intact basilic system in an arm. A controversial point is whether heparin should be given during the initial therapy for this type of infection. Heparin may be useful in decreasing the inflammatory response associated with active venous thrombosis, but there is no evidence that it prevents septic pulmonary embolization.

Mechanical Problems

Catheters improperly fixed to the skin can be avulsed within the first 2 weeks after placement. Surgeons are usually aware of this and will carefully suture the catheter to the skin, as well as provide a secure dressing from the device to the skin. In time, however, a catheter subjected to pulling forces may well develop exposure and avulsion of the barrier Dacron cuff—leading to hemorrhage or loss of the access site. Air embolism is also a potential complication at the time the catheter falls out. Catheter avulsion is not usually a problem for patients with normal mentation, but for those with dementia there must be a regimen to ensure that the catheter is not accidentally removed.

Catheter fracture can occur with external clamping. Silastic material can become brittle at sites of repeated compression. A partially fractured catheter should be clamped, to prevent blood loss or air embolism, and replaced as an emergency procedure to maintain the access site. To prevent this problem, clamping of catheters should be allowed only where indicated by the manufacturer. Intravenous fracture of catheters due to pressure from the clavicle were previoulsy noted. The embolized fragment is removed with radiographic baskets or snares, and the remainder of the dialysis catheter is replaced at the same entry site if possible.

Long-Term Subcutaneous Dialysis Access Ports

All of the complications associated with catheters are found related to implanted ports, such as the LifeSite. Unique complications related to ports come from the need for a subcutaneous pocket, in which a port may rotate if not carefully sutured; the development of a hematoma or seroma in the pocket; pain from the device; and port erosion of skin. Some female patients have complained about the appearance of the port puncture site when it is placed medially on the upper chest.

Permanent Hemodialysis Access

Autogenous fistulas are favored over prosthetic grafts because of their greater longevity, lessened ongoing cost, and lessened risk of mechanical complications. Despite these advantages, all access constructions are associated with potentially serious problems stemming from infection, circulatory embarrassment, hemorrhage, thrombosis, edema, and seroma formation.

Assessment of Extremity Perfusion and Fistula Flow

Complications relating to placement of dialysis access are often worse in the patient who starts with abnormal circulation in the extremity. This is not to imply that a patient with abnormal circulation should not have an attempt at access there, but prediction of the patient at risk for trouble will facilitate planning if access failure occurs. The baseline vascular examination starts with palpating pulses, recognizing that in people with ESRD distal occlusive disease may be masked by edema or effects of prior surgery.

Capillary refill and skin color are inaccurate measures of perfusion. Severe inflow disease in the subclavian-axilllary segments may be defined by a lower brachial blood pressure on one side. A Doppler stethoscope can be used to determine blood flow patterns, but grading blood flow with this instrument is subjective unless one has special bidirectional equipment. A bedside Allen test using a Doppler stethoscope is not helpful in predicting steal (see material following), with the exception of identifying the uncommon patient who has virtually total flow to the hand coming from the radial artery. This is a patient for whom a Cimino fistula can readily result in hand ischemia.

In the vascular laboratory, pulse volume recordings are used to document extremity and digital flow. Pulse volume waveforms can be used to identify patients with major occlusions when Doppler occlusion pressures cannot be obtained due to vascular calcification. Patients with highly abnormal baseline distal circulation should be considered at high risk for steal. They can have conventional access constructions placed, but their hand perfusion should be monitored closely thereafter in order to prevent irreversible ischemic changes in the digits.

Although the most serious sign of steal is gangrene, patients may develop small non-healing ulcers at the sites of finger sticks for glucose testing, digital stiffness, paronychias, or severe pain. If these changes occur, the patient should have urgent conversion of the access site to another area. In addition, patients with such calcification may be at risk for acute arterial occlusion from fracturing of plaques at the time of access placement. Ready access to vascular laboratory equipment will facilitate the diagnosis of this problem should it occur.

Based on the resting examination of an arm prior to placement of a construction, it is difficult to determine overall arterial sufficiency that will allow high blood flow volumes in an access

site. A minor stenosis of the inflow artery at rest may have no effect on distal blood pressure or flow in the arm, yet it may become very significant after placement of the conduit, where flow volumes can increase by 10 times.

Surveillance of Access Sites

Many complications relating to dialysis access are best evaluated using noninvasive testing in the vascular laboratory. In some centers, routine surveillance of access sites is performed with duplex ultrasonography—which can provide flow characteristics, flow volume, and determination of the diameter of the flow lumen. Stenoses, false aneurysms, and other conduit abnormalities can be readily determined with duplex scanning. If in doubt, a fistulogram should be obtained to define significant stenoses—which can also be assessed at the same time by pullback pressure measurement.

Thrombosis

Thrombosis is the most common complication. The diagnosis is often first made by the patient, who notes loss of a palpable pulse or thrill in the construction. Examination of the site may reveal loss of a machinery bruit, and there may be aspiration of clot when the site is punctured. A Doppler stethoscope will demonstrate absence of a flow signal. If an outflow thrombus has acutely formed, the graft may have an accentuated pulsation without forward Doppler flow. It is important to recognize this situation, which is not common, because the patient can be quickly anticoagulated with heparin to avoid total graft thrombosis—and urgent mechanical lysis, balloon angioplasty, or surgery will be easier performed on the site. For autogenous fistulae with multiple venous channels, thrombosis may be accompanied by increased flow volume in collateral veins or increased distal edema.

In the last decade, the management of clotted access sites has been revolutionized using methods of interventional radiology (IR)—also known under the concept of "interventional nephrology." The mainstay technique is mechanical lysis augmented by balloon angioplasty of luminal defects. In some institutions, thrombolysis with urokinase or other agents has been preferred. However, the results are in general no better than with saline alone. Lysis techniques also include the Angiojet. IR procedures are generally very well tolerated,

and most complications relate to volume overload from contrast administration or problems with excessive sedation for the procedure. Some clot from the graft will embolize to the lung during the washout procedure in most cases, but this is usually asymptomatic.

There are no reports of paradoxical embolization of this type of clot through a patent foramen ovale, but it is theoretically possible. The advantage of catheter techniques is that the anatomic defect causing thrombosis is both diagnosed and treated at the same setting. In addition, those sites that are hopeless for angioplasty are brought to the surgeon with a more precise plan for operative revision. Ideally, a problem access site will have function restored in a manner that will allow elective reconstruction of the problem as a day-stay procedure.

Because the goals of treatment for the clotted access site are safe restoration of flow, preservation of access sites for the future, and preservation of dialysis treatment continuity, it is important for interventional staff and surgeons to work together closely and to communicate carefully with the dialysis unit staff. In addition, catheter procedures can have associated complications that require surgery: Puncture sites may fail to seal, leading to significant hemorrhage. Balloon catheters can rupture, leading to fragment retention or embolization. If there is a close working relationship between the surgeons and catheter intervention staff, complications will receive better treatment.

Thrombectomy

Despite the advances of catheter technology in treating thrombosed access sites, surgery is still commonly necessary for acute thrombosis. Most often, such a site is known to have an anatomic problem and a decision is made that it is so significant a defect that it will be repaired only when the site fails. Realizing this, surgeons treating these sites should not perform a thrombectomy alone in most cases. They should perform a revision that targets the flow defect, and if they cannot the site should be replaced to a new anatomic region.

Revision is most commonly necessary for a stenosis at the venous outflow, and this is invariably due to neointimal fibrous hyperplasia (NFH, or intimal hyperplasia). Options include placement of a patch angioplasty to widen the venous anastomosis or interposition of a new conduit to a new venous outflow. Generally, a better long-term result is obtained with the latter. If the conduit has degenerated with dilatation to form an aneurysm, or if there

are large false aneurysms, the extension to a new outflow can be combined with a longer segmental interposition comprising half the extent of the access site. If one leaves a segment of incorporated graft, it can be used acutely to maintain continuity of dialysis without a central venous catheter.

Laminated thrombus is commonly found to cause a stenosis within a synthetic conduit. This pale leathery material can cause weblike stenoses or diffuse-flow lumen narrowing. To remove this material, a surgeon can use a uterine curette or a special wire thrombectomy catheter. Red to tan, a firm thrombus may be adherent across the arterial and venous anastomoses. On the arterial side, the meniscus of this material must be removed or the construction will clot again. On the venous side, this material will adhere firmly to areas of NFH and there will be a failure of back-bleeding when the thrombectomy is performed.

In this circumstance, the surgeon must be careful to avoid repeated passage of balloon thrombectomy catheters into the outflow veins, which will suffer a diffuse intimal injury from instrumentation. This will lead to more NFH and recurrent failure. Ideally, a site freshly revised or thrombectomized will have intraoperative imaging to verify that no problem remains. Many surgeons use C-arm fistulography, and some use color-flow duplex ultrasonography for this purpose. The complications of thrombectomy and revision of access sites are the same as those for primary access placement overall, but there is in addition the rare problem of embolization of clot into the inflow artery and its distal bed—causing a significant degree of ischemia (see material following). It must be emphasized that if there is any question about the quality of access site flow after an intervention a central venous catheter should be placed such that continuity of treatments is preserved.

Hypercoagulability

Suspicion will arise that a patient is hypercoagulable based on repeated thrombosis of technically sufficient access sites. Before coming to this conclusion, one must be certain that repeated technical error by the surgeon is not the cause and that there is no arterial insufficiency causing low flow volumes in the constructions. Patients at risk for hypercoagulability include those:

- Refractory to heparin
- Who have known clotting abnormalities, such as a baseline subnormal prothrombin time

- Who clot an access site despite a therapeutically elevated prothrombin time from warfarin
- With paradoxically excessive bleeding during surgery (possible platelet aggregation abnormality)
- Who undergo "heparin-free" dialysis without clotting the dialyzer
- With repeated thrombosis of central vein catheters, even more so of the central veins themselves
- With a family history of thrombosis
- With a history of venous thrombosis, especially more than once (thrombophilia)

Theoretically, the population receiving dialysis should mirror the population at large in the incidences of factor V-Leiden and prothrombin GS-20210a, which are the familial hypercoagulability markers for which laboratory tests are currently available. There is no evidence supporting routine testing for these alleles before vascular access is constructed. For patients who repeatedly clot access constructions, these tests can be readily performed—as well as measurement of proteins C, S, and antithrombin III and anticardiolipin antibody levels (antiphospholipid antibody).

A pragmatic approach to the problem of repeated thrombosis requires the surgeon to verify adequacy of a construction's hemodynamics such that flow is ideally more than 600 mL/minute and there is no tendency to kink or occlude the construction by the patient's body habitus or position. If these are acceptable, the patient may require warfarin to keep the access flowing—and rare patients have required prolonged treatment with low-molecular-weight heparins. Another alternative is for the surgeon to explore conversion of the site to autogenous, especially with a translocated basilic vein. When erythropoietin was first used, many surgeons were concerned that the elevation of hematocrit would lead to an increase in viscosity of blood that would in turn cause access sites to clot. There is no evidence to support this contention. There are rare patients with a history of repeated thrombosis who will be forced to use central catheters long-term.

Circulatory Embarrassment

NKF-K/DOQI guidelines mandate monitoring of access hemodynamics. Flow abnormalities can stem from venous occlusive disease or stenosis, conduit degeneration or lamination of clot, and arterial inflow insufficiency. Often, all segments of an established access site will become diseased simultaneously. The site defined as having a hemodynamic abnormality should be studied by ultra-

sound or fistulography, and there should be a plan for immediate interventional repair of any critical lesion found.

NFH is the most commonly acquired lesion, more often on the venous side than arterial. There are no certain means of preventing these lesions other than for the surgeon to use precise and gentle technique, preferably not injuring the vessel intima through excessive handling at the time of surgery. Some surgeons have found that use of anastomotic stapling will lower NFH rates in comparison with conventional suturing. In addition, excessively rough passage of balloon thrombectomy catheters will cause denudation of venous intima—leading to outflow destruction over time. On the arterial side, rough technique will lead to clamp injury—which will in turn cause a stenosis (problematic for access flow if it is on the afferent side of the anastomosis), which is potentially a cause of severe ischemia to the hand or arm if it is on the efferent side.

Anatomic variation can also lead to blood flow abnormality in an access site, often with sluggish flow and thrombosis. Between 7 and 15% of people will have a variant position of the brachial artery bifurcation. A surgeon finding a small "brachial" artery in the antecubital fossa or upper arm should be alerted to the fact that such an abnormality may be present. The small artery diameter may predispose to low flow volumes and early thrombosis. Revision to a larger proximal artery inflow may be needed.

Vascular Steal

Although insufficient flow is problematic because it leads to thrombosis of an access construction, a more dangerous and increasingly common problem is steal—which can lead to significant dysfunction or damage to the affected extremity. For steal to occur, three factors must be present: disease in the inflow arteries such that they cannot dilate to meet access flow demands, disease in the distal vessels such that they have higher than normal resistance to flow, and a low-resistance access construction conduit. Symptoms can range from a hand that is cold or numb only during treatments to mononeuropathy with intrinsic muscle weakness in the hand to rest pain in the extremity with gangrene.

Predicting the patient who will develop steal is difficult. Patients with diabetes and nonpalpable radial arteries are at primary risk, as are patients with obviously hardened palpable brachial arteries. An Allen test can be used to try to predict steal, but it is of poor predictive power. The effects of radial artery occlusion

can be performed with a handheld Doppler stethoscope, but there is no noninvasive test that can predict what will happen to hand flow when the ulnar artery feeds across the wrist into a high-flow fistula.

The diagnosis of the steal phenomenon is possible at the bedside with only a Doppler stethoscope. One checks for baseline digital blood flow at the level of the proximal phalanges and compares subjective flow patterns before and after temporary access site occlusion. If occlusion causes flow to increase, especially if it goes from none to vigorous with visible hyperemia of digits, the diagnosis is certain. Further documentation of suspected steal is possible using pulse volume recordings of digits before and after fistula occlusion, or by using color-flow duplex ultrasonography to evaluate flow into the extremity. For minor steal, the access site can be followed—reserving repair or revision for the patient who does not demonstrate adaptation to the symptoms. For major steal that threatens the limb, an urgent procedure is indicated. This can range from revision to a new arterial inflow site, bypass around the access site (the DRIL procedure), banding or flow limitation to the site, or purposeful thrombosis or ligation of the site.

Uncommon Complications

There are three rare complications that stem from high-flow access constructions. First is excessive arterial dilatation proximal to the access inflow. This induced arteriomegaly can be associated over time with thrombosis of native arterial segments, with resultant severe distal ischemia. Fortunately, there are no reports of gangrene or amputation from this phenomenon. Second, and also rare, is exacerbation of congestive heart failure from high cardiac output. Unless the underlying cardiac lesion can be repaired, the patient truly suffering this problem will require chronic central venous catheterization for dialysis rather than a high-flow access site.

Finally, there is induced carpal tunnel syndrome from high-volume access flow across the wrist. This is a phenomenon that can occur when there is access inflow based on the radial artery and when the proximal radial artery side of the construction becomes narrowed. Flow is then dependent on collaterals from the ulnar artery coming across the carpal row and retrograde into the distal radial artery. If this collateralization is very large, it can compress the median nerve and cause symptoms. The diagnosis of this phenomenon can be made by compression of

the ulnar artery, which almost immediately brings some relief to the hand. Flow across the base of the palm can be demonstrated by duplex ultrasonography. Definitive treatment is by revision of the access inflow anastomosis to eliminate the proximal stenosis.

Arterial Occlusion

Acute arterial occlusion from access construction or revision is fortunately uncommon. Occlusion of a single-branch artery in the forearm distal to a brachial access site is usually asymptomatic, unless there has been previous instrumentation with arterial thrombosis at the wrist—as might occur with a radial artery cannulation. Total brachial artery occlusion may result in severe symptoms of hand ischemia, especially if combined with an element of vascular steal. The etiology may be a clamp injury, an intimal flap from fracture of a calcified artery, or a technical error in suturing the conduit to the artery.

Retrograde thrombosis may also very rarely occur as a complication of sudden outflow occlusion of a conduit while a patient is being dialyzed, where clot is pumped by the dialyzer. Urgent repair in these cases is required. Thrombectomy of access sites can result in embolization of clot into the distal arterial runoff of an extremity, but this is fortuitously uncommon. A more common problem is acute intimal injury from passage of the thrombectomy catheter or instruments, often a curette, from the conduit into the native vessel. Again, immediate symptoms of ischemia should be recognized by the surgeon and immediately repaired if there is any question about the viability of the extremity.

Chronic arterial occlusion after access site construction is most often related to induced NFH. Any instrumentation of an artery (even more so, of veins) will lead to destruction of intima—with deposition and degranulation of platelets. The resultant release of platelet-derived growth factor and other less-well-defined stimulating kinins will lead to proliferation of subintimal fibroblasts and creation of a stenosis. This can progress to complete occlusion in rare cases. The key time period for appearance of this disease in arteries is from 6 to 24 months after instrumentation, but NFH can occur in as few as 6 weeks.

The treatment is primarily preventive, by keeping intimal injury to the minimum through careful technique and minimal manipulation of balloon catheters in the native vessels. Antiplatelet drugs also play a role in decreasing the risk of occurrence of this disease for coronary and peripheral vascular bypasses,

but there are only a few reports that support improved patency in access sites if antiplatelet drugs are administered. If the distal extremity is symptomatic due to arterial lesions related to an access site, the treatment is conventional bypass or patch angioplasty of the affected vessel. Balloon angioplasty or stenting may prove alternatives in selected cases.

Early Postoperative Complications Related to Access Placement

Problems Related to Wound Care During Surgery

Gentle tissue handling is extremely important in placing dialysis access conduits, and wound problems are even more an issue when reoperations are performed for access sites with complications. Skin preparation for surgery optimally includes a long-acting iodinated agent, such as Duraprep, or one containing chlorhexidine. All patients receive prophylactic antibiotics before procedures, except for those for whom minor autogenous constructions are planned. There is no evidence supporting antibiotics for a wrist Cimino fistula or antecubital vein-brachial fistula. Agents of choice include single doses of cefazolin (most commonly used), vancomycin, and levofloxacin.

Antibiotics are often included in wound irrigation solutions. Infection risk also stems from poor tissue handling technique and problems in wound closure. Care must be taken to avoid hematomas and trauma to subcutaneous fat. Prolonged or forceful retraction (or excessively tight closure of subcutaneous fat) can lead to fat necrosis, which is manifested later by drainage of cloudy fluid from a wound. Electrocautery, especially for hemostasis, should be used with care in order to avoid fat necrosis. A dire complication of sloppy tissue handling is edge necrosis of a wound, which can lead to exposure of a conduit. These considerations are particularly important for translocated basilic vein constructions, especially in obese patients for whom there may be substantial wound healing problems.

Neuralgia from access constructions occurs from several causes. First is direct injury to adjacent nerves at the time of construction placement. Second is pain related to ligation or clipping of a small cutaneous nerve, where there is late development of a neuroma. This has been observed in the forearm and wrist, as there is a small cutaneous branch of the radial nerve that is prone to injury during creation of autogenous fistulas.

Third, there is the problem of puncture into or near a cutaneous nerve overlying an access conduit. The patient with this problem will have severe pain from a dialysis needle, or there may be development of chronic pain and dysesthesias in the scar tissue that inevitably overlies an access conduit. Fourth, there is the problem of access conduits placed under or near surgical scars. Some patients experience significant pain when dialysis needle punctures are necessary through scars. For this reason, conduits are best routed away from prior areas of surgery if possible. Finally, neuralgia may be the major sign of early steal—and if this is not addressed protracted ischemic neuropathy in the hand may result.

Hemorrhage

Hemorrhage immediately after initiation of flow into a hemodialysis conduit is fortunately uncommon. Persistent bleeding from suture holes in PTFE conduits is a nuisance in some patients. It is avoided by careful suturing technique, and some surgeons prefer PTFE suture rather than polypropylene with a belief that the holes in the graft are smaller yet better filled by the suture—causing less bleeding. Bleeding is also prevented by avoiding too much heparin during the procedure, especially in patients on chronic warfarin therapy where anticoagulation reversal has not occurred.

When bleeding from suture holes occurs, the heparin effect can be reversed with protamine. However, care must be taken to avoid hypotension from excessively rapid administration of this drug. DDAVP is also useful in achieving hemostasis in these cases. Historically, surgeons have often used topical clotting agents incorporating bovine thrombin to achieve hemostasis, but recent publications have voiced concerns about exposure of dialysis patients to thrombin. Hemorrhage at the venous anastomosis during a thrombectomy and revision procedure is not unusual, especially as a paradoxical problem in patients with a coagulopathy such as an anticardiolipin antibody. This type of bleeding is controlled with patience, as previously noted.

Early hemorrhage along a PTFE conduit into the subcutaneous tissues is avoided by creating a tight tunnel with a small-diameter tunneling device. It is a problem more likely to occur when a plastic graft is tunneled in the proximal arm where an autogenous fistula remains open at the wrist. Compression of the arm with a gently applied elastic bandage can also

control this diffuse oozing into the tunnel. In the past, peri-graft hemorrhage from puncture was avoided by allowing a period of 4 to 6 weeks for the graft to incorporate into tissue after placement.

In more recent practice at many centers, this period of waiting has been shortened to 1 to 2 weeks, if the surgeon uses tight tunnels for routing the graft. Nevertheless, a perigraft hematoma can be a major, disabling complication. It can cause skin breakdown that exposes the graft, and it can form a nidus for infection to occur. Perigraft hemorrhage is best managed in consultation with the surgeon who initially placed the graft. Perigraft hematoma causes reddening of skin overlying the conduit, and thus the differential diagnosis is an acute graft infection. A small hematoma can become secondarily infected even several weeks after graft placement. The surgeon who placed the conduit must be involved in the decision making regarding these conduits, whether to give antibiotics and local care to the extremity or to remove the graft.

Edema

Edema may occur soon after placement of a high-flow access construction. Edema will occur when there is a stenosis or occlusion of veins central to the venous outflow, and swelling will be accentuated in patients with anasarca. Fistulograms, including imaging of the veins in the thoracic outlet through to the superior vena cava, will be helpful in determining the best treatment for the swollen arm after access placement. Where there is a stenosis, balloon angioplasty may relieve venous hypertension. Although stents have been tried for these lesions, they carry the drawback that intimal hyperplasia may be accelerated in the dilated segment—causing early reocclusion. In rare cases, veno-veno bypass will relieve edema from venous hypertension. Also in rare cases, intractable edema from fistula flow will require access ligation.

Edema may also occur merely from the fact of multiple-access operations in an arm. Troublesome edema has occurred in the central tissues within a looped forearm or groin graft. Such edema may be a phenomenon of no clinical significance, but it may also herald subclinical graft infection. In such cases, the site should be rested without puncture, the extremity elevated, and consideration made to the use of gentle compression with elastic bandages.

Technical Problems and Miscellaneous Difficulties

Conduit position can cause a major functional problem. Surgeons should become familiar with the patient's usual position in a dialysis chair, such that the access conduit is placed in a position that does not hinder puncture. In addition, the conduit must be positioned close to the skin but not too shallow. If a conduit is too deep to the skin, conventional needles may pop out of the conduit with patient movement—leading to a massive arm hematoma. If too shallow, skin erosion may occur with graft exposure. Translocated basilic vein constructions must be long enough to provide room for the dialysis needles, and this usually requires mobilization of the vein well down the forearm. Some patients have limited shoulder mobility due to arthritis or previous injury. Placing a conduit far to the medial volar aspect of such an extremity will prevent the conduit from being cannulated.

Perigraft seroma is a troublesome complication generally limited to PTFE conduits. Plasma may be seen to "weep" through grafts that have come in contact with wetting agents (surfactants) such as povidone-iodine or alcohol. Seroma may be prevented by using barrier plastic draping or Duraprep on the skin, although no controlled trials have confirmed this clinical impression. Patients with low serum protein levels may also be prone to seromas, as are those undergoing redo operations and procedures in the groin. Some seromas may respond to careful aspiration drainage. Rather than risk infection of a graft from repeated manipulation, a persistent seroma may require wound exploration (in order to ligate the leaking lymphatic channel) and a careful reclosure—or graft removal and replacement of the conduit in a new site.

Aneurysms occur at anastomoses, within conduits as they degenerate, as a manifestation of graft sepsis, and as a result of chronic hemodynamic stress in the inflow artery or outflow vein. Aneurysms may cause pain or visible deformity in the extremity. When this occurs, the site may be revised to eliminate the aneurysmal segment. This is most easily done by splicing a new conduit in parallel to the diseased segment, thereby allowing continuity of access site function. The most dangerous acute problem from aneurysmal change is skin erosion, especially when it is associated with localized sepsis in the conduit.

The patient may have thinned skin over the access graft, with damage due to repeated puncture in the same site. A small puncture eschar may fail to heal, leading to erosion and exposure of

the conduit. Massive hemorrhage is usually preceded by a "herald bleed" controlled with local pressure. Dialysis nurses must be taught that eschars overlying grafts or bleeding erosions must be brought to the attention of a surgeon. Nurses must also learn to differentiate the appearance of skin where a "buttonhole" access puncture technique is used from skin that is threatening erosion. A shallow subcutaneous position of a conduit may predispose to erosion, as may be the case for patients taking therapeutic doses of steroids.

Surgical repair of exposed sites or erosions is aimed at maintaining access site function overall while rerouting blood away from the diseased segment and skin ulcer. Through the site of erosion, the diseased conduit can be removed—usually without making a massive skin incision. The area of contamination is locally drained or placed on wet dressings for secondary closure. In the case of a catastrophic hemorrhage, primary ligation and removal of the contaminated graft is often necessary—with temporary access by a central venous catheter. Local skin suture over a site of erosion is generally unsuccessful, leading to more extensive sepsis in the area. There have been a few case reports of rotational cutaneous flaps used to treat this type of graft exposure, with mixed results. A course of IV antibiotics is often necessary in the immediate perioperative period after such a graft catastrophe.

In the past, there has been no adverse effect on renal transplantation by the creation or maintenance of hemodialysis access. Recently, cryopreserved veins have become available for use as prosthetic conduits in vascular surgery, and some have been used for dialysis constructions. Some transplantation surgeons have been concerned about the possibility of these allogenic conduits causing immunosensitization. There is no evidence that xeno-conduits (bovine carotid) have an adverse effect on transplantation.

Graft Infection

Infection is only rarely a perioperative problem for autogenous fistulas, unless it stems from contamination of a perianastomosis hematoma or lymphocele. With the extensive incisions necessary, these are more often a problem for upper arm translocated vein procedures. As long as an autogenous conduit has tissue coverage—with elevation of the limb, control of local tissue necrosis, antibiotic support, and proper dressing care these

wounds will heal. The major concern for translocated basilic veins is ischemia and contamination involving side branches of the vein, which are at risk for blowout. If a wound separation in the arm threatens such a conduit, the best treatment is aggressive wound debridement in the OR with a proper tension-free wound closure and with closed suction drainage of any associated collections.

Infections involving prosthetic grafts can remain localized, with formation of a perigraft seroma or abscess, or they may present with a systemic bacteremia and metastatic sepsis throughout the body. If graft sepsis is questioned, surgical consultation is necessary. A duplex scan can be used to determine the presence of a perigraft collection. This loss of graft incorporation into the surrounding soft tissue is one of the main signs of infection. This fluid can be carefully aspirated for Gram stain and culture. Rarely, dialysis technicians will notice turbid fluid draining from a puncture site after a treatment: This should be taken as a serious matter. The fluid should be cultured, and the patient brought to the attention of his physicians. Radiolabeled white cell or gallium scans are occasionally also useful in the diagnosis of graft infection.

One of the more impressive signs of infection is the sudden development of an anastomotic false aneurysm in a previously stable graft, particularly if there is overlying erythema or tenderness. A graft infection may point through an area of skin erosion or through an old incision, first with a "herald bleed" and later with a catastrophic hemorrhage.

Although some cases of graft infection have been cured with antibiotics alone, most cases require resection of the affected graft. After graft removal, the patient receives dialysis through a central venous catheter until he is clinically free of bacteremia with IV antibiotics. Therapy is guided by cultures of the excised graft. In most cases, graft infection does not involve the totality of a graft and the surgeon will often find that the anastomoses remain incorporated into surrounding tissue. In this situation, the graft is removed by ligating the outflow vein and completely taking down the venous anastomosis.

At the arterial side, a small hood of graft can be left on the artery to act as a patch angioplasty over the anastomosis. This is covered completely by autogenous tissue. If the entire arterial anastomosis must be removed, closure of the artery will require an autogenous vein patch angioplasty with a soft tissue closure—often with rotation of an adjacent muscle as a vascularized flap. If the local artery must be ligated, and thereafter it is determined

that the ipsilateral hand or foot has demonstrable Doppler flow, nothing more in the acute phase should be done. For chronic ischemia thereafter, bypass operations are very successful—even in the upper extremity. If graft removal and arterial ligation result in absence of Doppler flow in the extremity, a vascular surgeon should perform an urgent bypass procedure—routing the new conduit through an uncontaminated subcutaneous tunnel.

Anesthesia for Access Surgery

It is generally assumed that patients with ESRD are at higher than average risk for cardiopulmonary complications should general anesthesia be required for surgery. Therefore, multiple small procedures under local or regional anesthesia seem safer and better tolerated than extensive ones under general anesthesia. The ready availability of temporary central vein catheters to bridge periods of access failure facilitates this flexible approach.

Most procedures are performed on a day-stay basis under local or regional anesthesia. Ideally, even urgent procedures are arranged for morning surgery time in order to allow for recovery from sedation, the performance of any necessary afternoon dialysis, and transportation to home. For short procedures, lidocaine suffices. However, for longer operations bupivicaine will allow 2 to 3 hours of anesthesia. These procedures would be impossible without sedation with propofol, fentanyl, or midazolam. General or conduction anesthesia is necessary for central axillary/subclavian procedures or for groin grafts.

It is not unusual to find severe hyperkalemia or hyperglycemia in a patient with a clotted access site presenting for surgical thrombectomy. These abnormalities can occur even when the patient has never suffered a break in his or her usual hemodialysis schedule or a known decrease in the quality of hemodialysis prior to the thrombosis. The availability of point-of-care laboratory measurement of metabolic parameters (I-Stat) at least theoretically improves the safety of urgent angioaccess procedures because patients with significant abnormalities can be treated with an aggressive dialysis session using a temporary dialysis catheter prior to their revisional surgery.

The complications from dialysis access procedures include sudden cardiac death and acute (“flash”) pulmonary edema. Perioperative myocardial infarctions are fortunately rare, but under the stress of a prolonged procedure with insufficient local anesthesia or sedation induction of dysrhythmias and transient coronary insufficiency do occur. Medication reactions during

surgery are also rare. Physicians in the OR nevertheless need to be cautious about rapid administration of protamine (it is best to avoid excessive heparin in the first place), inadvertent intravenous administration of bupivicaine, and excessive amounts of iodinated contrast or intraoperative fistulography.

Virtually all procedures are best performed under monitored anesthesia care. Strictly local anesthesia without monitoring can be used for removal of central venous catheters, placement of temporary nontunneled dialysis catheters, and ligation of access sites. In a young cooperative patient, a Cimino fistula can be performed without sedation—as can a tunneled Silastic catheter.

Surgeons must be sensitive to the fact that some patients will experience severe discomfort after even a relatively minor access site revision, such that their pain is not well controlled using oral narcotic analgesics after surgery. To avoid complications from excessive sedation, and to prevent the patient or his family from having severe anxiety or anger about the process of access surgery, patients with severe pain should be observed overnight and treated with parenteral narcotics as necessary.

Recommended Reading

Books

Adams ED, Sidawy AN. *Nonthrombotic Complications of Arteriovenous Access for Hemodialysis.* 1692–1705.

Bohannon WT, Silva MB. *Venous Transpositions in the Creation of Arteriovenous Access.* 1677–83.

Lumsden AB, Bush RL, Lin PH, Peden EK. *Management of Thrombosed Dialysis Access*. 1684–91.

This is a comprehensive source among recent texts dealing with dialysis access construction, hemodynamics, and complications.

Rutherford, RB (ed). *Vascular Surgery, Sixth Edition*. Philadelphia: Elsevier Saunders 2005.

Sidaway AN (ed.). *Arteriovenous Hemodialysis Access*.

Weiswasser J, Sidawy AN. *Strategies of Arteriovenous Dialysis Access*. 1669–76.

Articles

The following are a selection from the recent literature on significant complications and their management.

Doelman C, Duijm LE, Liem YS, Froger CL, Tielbeek AV, et al. Stenosis detection in failing hemodialysis access fistulas and grafts: Comparison of color Doppler ultrasonography, contrast-enhanced magnetic resonance angiography, and digital subtraction angiography. *Journal of Vascular Surgery* 2005;42(4):739–46.

Gousheh J, Iranpour A. Association between carpel tunnel syndrome and arteriovenous fistula in hemodialysis patients. *Plastic & Reconstructive Surgery* 2005;116(2):508–13.

Hingorani A, Ascher E, Kallakuri S, Greenberg S, Khanimov Y. Impact of reintervention for failing upper-extremity arteriovenous autogenous access for hemodialysis. *Journal of Vascular Surgery* 2001;34(6):1004–09.

Knoll GA, Wells PS, Young D, Perkins SL, Pilkey RM, Clinch JJ, et al. Thrombophilia and the risk for hemodialysis vascular access thrombosis. *Journal of the American Society of Nephrology* 2005;16(4):1108–14.

Knox RC, Berman SS, Hughes JD, Gentile AT, Mills JL. Distal revascularization-interval ligation: A durable and effective treatment for ischemic steal syndrome after hemodialysis access. *Journal of Vascular Surgery* 2002;36(2):250–55.

Konner K. The anastomosis of the arteriovenous fistula: Common errors and their avoidance. Nephrology Dialysis Transplantation 2002;17(3):376–79.

Patel AA, Tuite CM, Trerotola SO. Mechanical thrombectomy of hemodialysis fistulae and grafts. *Cardiovascular & Interventional Radiology* 2005; 28(6):704–13.

Patel ST, Hughes J, Mills JL Sr. Failure of arteriovenous fistula maturation: An unintended consequence of exceeding dialysis outcome quality, initiative guidelines for hemodialysis access. *Journal of Vascular Surgery* 2003; 38(3):439–45.

Ryan SV, Calligaro KD, Dougherty MJ. Management of hemodialysis access infections. *Seminars in Vascular Surgery* 2004;17(1):40–44.

Tashjian DB, Lipkowitz GS, Madden RL, Kaufman JL, Rhee SW, Berman J, et al. Safety and efficacy of femoral-based hemodialysis access grafts. J Vasc Surg 2002;35:691–93.

Teruya TH, Abou-Zamzam AM Jr., Limm W, Wong L, Wong L. Symptomatic subclavian vein stenosis and occlusion in hemodialysis patients with transvenous pacemakers. *Annals of Vascular Surgery* 2003;17(5):526–29.

Vogel PM, Parise C. Comparison of SMART stent placement for arteriovenous graft salvage versus successful graft PTA. *Journal of Vascular & Interventional Radiology* 2005;16(12):1619–26.

Weng FL, Berns JS. Complications of percutaneous treatment of thrombosed hemodialysis access grafts. *Seminars in Dialysis* 2003;16(3):257–62.

CHAPTER 6

Dialysis Access Recirculation

Richard A. Sherman, MD, and Toros Kapoian, MD

Recirculation occurs when blood returning from the venous (postdialyzer) line reaches the arterial (predialyzer) line without having passed through the capillary circuit where uptake of urea (and other solutes) from the tissues takes place. When recirculation occurs via retrograde flow in the vascular access, it is called access recirculation. When it occurs via the heart (as it does uniformly with arteriovenous accesses), it is called cardiopulmonary recirculation (Figure 6.1).

Measurement of Access Recirculation

Access recirculation is typically quantitated by measuring the concentration of urea at three sites: the arterial and venous lines and a systemic site. It is calculated using the formula

$$\% \text{ Recirculation} = 100\ [(S - A) / (S - V)],$$

where A, V, and S are the BUN (blood urea nitrogen) concentrations in the arterial (A), venous (V), and systemic (S) samples. For many years, the systemic site used for blood sampling was a vein in the arm contralateral to the access site. If the BUN in the arterial and systemic samples did not differ, there was no dilution of the arterial line urea concentration by venous line blood and recirculation was absent (0%). Generally, values of 5 to 15% were found to be present in most patients with apparently well-functioning AV accesses.

Access recirculation was poorly understood until recent years because of a lack of appreciation that during hemodialysis arterial concentrations of dialyzed solutes (e.g., urea) are lower than venous concentrations (AV disequilibrium) because of cardiopulmonary recirculation. Thus, the peripheral vein BUN routinely exceeded that in arterial line blood—a difference largely responsible for the apparent recirculation values of 5 to 15% that were routinely observed. Also contributing to the false elevations in recirculation was venovenous disequilibrium (a difference in BUN in different veins), which was a consequence of regional blood flow inequalities.

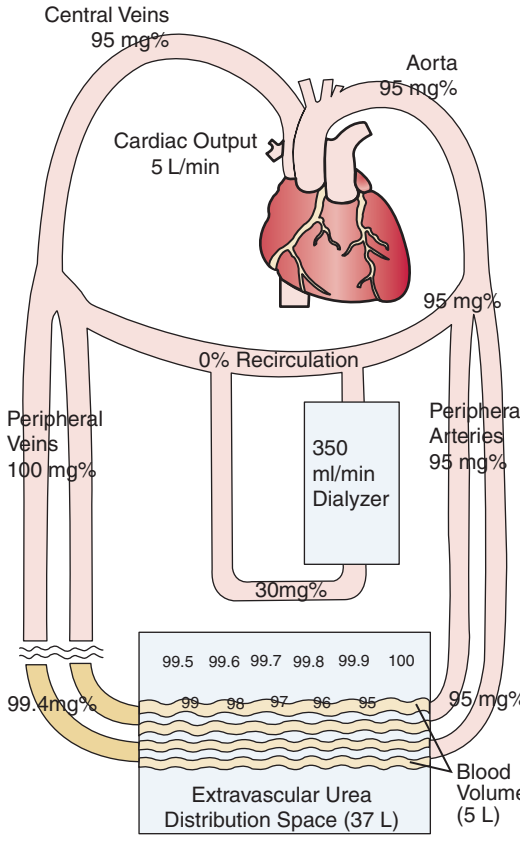


Figure 6–1

The theoretical changes in BUN early in dialysis in a 70-kg patient with a cardiac output of 5 L/minute, a dialyzer blood flow rate (BFR) of 350 mL/minute, and a 70% dialyzer urea extraction. Arterial blood can pass directly to the veins via the AV access without passing through the capillaries where "urea refill" of this blood can occur. This short circuit is called cardiopulmonary recirculation and results in AV disequilibrium in BUN concentrations. *(From Sherman RA. Recirculation revisited. Semin Dial 1991; 4:221–23, with permission.)*

Because of these considerations, it is now recommended that the systemic sample be obtained from the arterial line. This sample must be obtained using a protocol designed to ensure that the BUN in this specimen is not falsely low due to contamination by recirculated blood, nor falsely high due to a rebound in BUN that occurs when the delay in obtaining the sample after dialyzer blood flow is stopped (or slowed) exceeds 10 to 15 seconds. This rebound is a consequence of the elimination of cardiopulmonary recirculation (and its associated depression in arterial BUN) that follows the interruption of dialysis.

The protocol in Table 5.1 addresses these issues and has been validated and recommended by the Dialysis Outcomes Quality Initiative (NKF-K/DOQI) of the National Kidney Foundation. The only significant inherent errors that occur by using this method are those due to laboratory variation in BUN measurement. Using this methodology, recirculation values of less than 5% are considered normal, greater than 10% abnormal, and 5 to 10% potentially abnormal if confirmed.

Implications of Access Recirculation

The presence of recirculation in a properly cannulated AV access indicates that access blood flow is less than dialyzer blood flow. However, an access whose intrinsic blood flow is only marginally more (<100 mL/minute) than dialyzer blood flow may show modest amounts of recirculation if the arterial and venous needles

Table 6–1

Protocol for Urea-based Measurement of Recirculation

Perform the test after approximately 30 minutes of treatment and after turning off ultrafiltration.

1. Set the pump speed to 500 mL/minute (or maximum achievable rate).
2. Draw the arterial (A) and venous (V) line samples.
3. Immediately reduce the blood flow rate to 120 mL/minute.
4. Turn the blood pump off exactly 10 seconds after reducing the blood flow rate.
5. Clamp the arterial line immediately above the sampling port.
6. Draw the systemic arterial sample (S) from the arterial line port.
7. Unclamp the line and resume ultrafiltration and dialysis.
8. Measure BUN in A, V, and S samples, and calculate percent recirculation (R) using the formula $R = [(S - A) / (S - V)] \times 100$.

are close together. The caveat "properly cannulated" should not be taken lightly. Unrecognized reversal of the arterial and venous lines explained the presence of recirculation in 31 to 82% of cases reported by three different dialysis centers.

Although recirculation points toward low-access blood flow, the absence of recirculation does not necessarily indicate that baseline access blood flow exceeds dialyzer blood flow. When a stenosis (sometimes termed *stricture*) is present in the access between the arterial and venous needles, the dialysis circuit bypasses the stenosis and allows the "stenosis-limited" access blood flow to transiently increase during treatment.

The measurement of recirculation is potentially valuable in the recognition of low-access blood flow, a major risk factor for access thrombosis and a cause of unexplained reductions in dialysis delivery. True access recirculation is absent in a great majority of patients with AV accesses. Its presence in a patient with a properly cannulated AV graft indicates that access blood flow is significantly less than the usual dialyzer blood flow rate of 350 to 500 mL/minute. Because the risk of access thrombosis in an AV graft rises as blood flow rate falls below 600 to 800 mL/minute, recirculation in an AV graft indicates a critically low access blood flow rate and a graft that is at very high risk of thrombosis.

The susceptibility of AV grafts to thrombosis with low blood flow probably accounts for the relative rarity of recirculation in this setting. Most grafts clot before flow is low enough to produce recirculation. In contrast, recirculation is an earlier marker for thrombosis risk in patients with an autologous AV fistula that tends to remain patent with lower blood flows. Thus, even though access stenosis is more common with AV grafts than with AV fistulas recirculation is more likely to be observed in fistulas than in grafts.

These observations suggest that recirculation is of minimal value as a screening tool for access stenosis in patients with AV grafts. Its value is substantially greater in fistulas not only for the reasons noted previously but because the major clinical screening tool for access stenosis, venous (or intra-access) pressures, is of substantially less value in fistulas than a graft. Pressures often do not rise with venous stenosis in fistulas because of the presence of collateral blood flow around the stenosis.

Due to the inefficiencies of dialyzing blood with depressed solute levels, recirculation will reduce dialysis delivery. Recirculation values of 15 and 25% will reduce Kt/V by approximately 10

and 20%, respectively, for typical dialysis regimens. Although recirculation can have a major impact on dialysis delivery, it is responsible for only a minority of the reductions in Kt/V found on monthly testing. Seeking abnormalities in access anatomy in patients with these reductions without documentation that recirculation is present is usually unrewarding. Closer examination (e.g., review of actual dialysis time, delivered dialyzer blood flow, blood sampling procedure) is more likely to reveal the cause of the decline in dialysis delivery.

Alternative Means of Measuring Access Recirculation

Both high– and low–"tech" procedures can be used to detect recirculation. A variety of sophisticated devices are available (or in development) that alter venous line blood in some way and then seek to detect the presence of that altered blood in arterial line blood—thus indicating that recirculation has occurred. Some of these induced alterations include temperature (cooling), light transmission or ultrasound dilution (added saline), electrical conductivity (added hypertonic saline), and hemoconcentration (ultrafiltration). The best validated and most widely used technique is ultrasound dilution (Transonic Systems, Ithaca, New York). These devices are predominantly used for the measurement of access blood flow rate, a value determined from the amount of recirculation induced by reversing the blood lines on the dialysis circuit. Under these conditions, access blood flow approximates the product of dialyzer blood flow rate and [(1 – R)/R], where R is the recirculation fraction. Using this same approach, a rough estimate of access blood flow can also be made from urea-based measurement of recirculation—although line reversal is needed in the typical setting in which access blood flow exceeds dialyzer blood flow.

Recirculation can also often be detected with one's fingertip and observation of the venous and arterial line pressure gauges. In a normally functioning access, blood that is not taken up by the arterial needle continues antegrade past the venous needle. Interruption of this flow by finger pressure on the access between the needles tends to reduce venous pressure (the extent of the reduction depends on the amount of "excess flow") and has little effect on the arterial pressure. However, if recirculation is present the flow between the needles is retrograde and the venous pressure increases sharply if a venous stenosis is present.

Much less commonly, an arterial-side stenosis is responsible for the recirculation. Under these circumstances, the arterial pressure (always "negative") may become more negative with the fingertip maneuver. An inflow (arterial) stenosis should also be suspected when the arterial needle regularly "sucks." The arterial line tubing tends to collapse and/or the arterial pressure is highly negative. When recirculation is due to reversed lines, finger pressure between the needles will immediately interrupt dialysis with both venous and (negative) arterial pressure rising sharply. This occurs because all blood flow is cut off to the arterial line and all outflow is cut off for the venous line.

Indications for the Measurement of Access Recirculation

The measurement of recirculation has a limited, although important, role in dialysis patient management. In a new AV vascular access, correct needle placement must be confirmed—given the relatively high frequency of inadvertent reversed lines. This can be done using a bedside test (one of which was described previously), an access flow monitor (e.g., Transonic), or an urea-based recirculation test. Such an assessment should be done in the first few weeks after access use is initiated.

In AV grafts, recirculation is not appropriate as a routine screening test given the rarity of recirculation in this setting and its late development in the natural history of graft failure. It can, however, be useful in selected circumstances such as confirming a suspicion of low access blood flow and with a decrease in Kt/V that is otherwise unexplained. When recirculation is found in a properly cannulated AV graft, some urgency is advised in proceeding to fistulography and prompt surgical or interventional radiologic follow-up (as indicated). AV grafts frequently fail in the hiatus between the initial detection of recirculation and its evaluation and therapy.

In autologous AV fistulae, the role of recirculation in access surveillance is currently uncertain. Although recirculation is much more likely to be the sole indicator of fistula pathology, the frequency of such pathology is relatively low. Measuring recirculation every 2 to 3 months in patients with autologous AV fistulae should be considered, although a skillful routine physical examination of the access may be equally useful. The routine measurement of access flow makes the measurement of recirculation for access screening purposes unnecessary.

Recirculation in Central Venous Catheters

Central vein catheters are in widespread use. The measurement of and interpretation of recirculation is different in these catheters than with AV accesses. Four noteworthy points follow.

- Recirculation can be measured using the same technique as with AV accesses, although the issue of AV disequilibrium is irrelevant because central vein blood is used for all measurements.
- A low level of recirculation (less than 10%) is typical in central vein catheters, even though central vein blood flow far exceeds dialyzer blood flow rate. Retrograde flow following atrial contraction has been postulated as the cause for this finding.
- High levels of recirculation can result from the use of central vein catheters in veins with low intrinsic blood flow rates, such as the femoral veins. When this site is accessed, catheters should be at least 19.5 cm. Small catheters (e.g., 15 cm) have been reported to have recirculation values of up to 38%. Very high recirculation values (79%) have also been seen in defective catheters that allow blood to flow directly from the venous lumen to the arterial lumen.
- Unlike AV accesses, line reversal with central vein catheters usually increases recirculation only modestly (5–10%).

Recommended Reading

Besarab A, Sherman RA. The relationship of recirculation to access blood flow. Am J Kidney Dis 1997;29:223–29.

Demonstrates that access recirculation is a function of access blood flow.

Kapoian T, Steward CA, Sherman RA. Validation of a revised slow-stop recirculation method. Kidney Int 1997;52:839–42.

Presents the methodology and validation of the urea-based recirculation protocol adopted by the National Kidney Foundation-Dialysis Outcomes Quality Initiative.

Sherman RA. Recirculation revisited. Semin Dial 1991;4:221–23.

An explanation for the difference in intradialytic BUN concentrations in arterial and venous blood samples.

Sherman RA, Kapoian T. Recirculation, urea disequilibrium, and dialysis efficiency: Peripheral arteriovenous versus central venovenous vascular access. Am J Kidney Dis 1997;29:479–89.

Reviews the issues and interfaces of recirculation, urea disequilibrium, and dialysis efficiency for central venous and AV accesses.

CHAPTER 7

Peritoneal Access Devices and Placement Techniques

Stephen R. Ash, MD, FACP

Requirements for a Perfect Peritoneal Dialysis Catheter

Peritoneal dialysis (PD) catheters are the most successful long-term transcutaneous devices in the practice of medicine. Tunneled internal jugular catheters, suprapubic tubes, chest tubes, and the drive lines of implanted artificial hearts provide adequate hydraulic function (without infection) for months. PD catheters can provide excellent hydraulic function and avoid infection for years. However, in spite of their overall success the hydraulic function and biocom-patibility of PD catheters is far from perfect. Failure of peritoneal catheters is catastrophic for delivery of PD. Catheter failure contributes to dropout from PD in up to 1/3 of patients on PD therapy.

Perfect hydraulic function of a peritoneal catheter would mean that the catheter allows fluid to flow out of the peritoneal cavity with the same ease and recovery as inflow and that all of the peritoneal fluid is drained completely. Common experience indicates that this is not the case. At the same hydraulic pressure gradient, flow into a PD catheter is almost always faster than outflow. This is because the limiting resistance to flow in the latter part of outflow is not the resistance of the catheter and tubing but the hydraulic resistance of small spaces between the catheter and surrounding tissues when the intraperitoneal volume becomes small. Bernoulli and hydraulic pressures bring tissues closer to the catheter as outflow proceeds and volume diminishes. The ouflow rate decreases when the abdomen is drained about 3/4 of the usual fill volume. Toward the end of outflow the flow becomes very slow, almost imperceptible.

Routinely at the end of outflow there is 300- to 500-mL intraperitoneal residual volume trapped in the peritoneum. The deceleration of flow of PD catheters near the end of outflow is a source of frustration, but we have learned how to provide PD in spite of it. Patients on CAPD are taught to qualitatively judge the flow rate of their catheters by feeling the temperature of the

tubing, inserting bubbles in lines, and other tricks. They end outflow effectively when it appears there will be minimal further outflow of fluid. Naturally, the outflow volume varies more than 10%—even with the same solution in over the same period of time.

For cycler therapy, machines have built-in end-of-outflow determinations, set at 50 mL/minute or less—although this value is somewhat arbitrary. High-flow-rate PD schedules such as "tidal" treatment are designed to leave a residual of a liter or so in the peritoneum so that outflow can always be at a maximal rate and overall flow through the peritoneum maintained at a high level. If the residual volume is too high, efficiency is lost due to poor mixing within the peritoneum. If the residual volume is too low, time is lost when the peritoneal drainage slows down during each outflow.

Outflow failure is defined as failure to drain the same amount of PD fluid that is infused, or that is known to be within the peritoneum. Although there are many other causes, including pericatheter leak and excess peritoneal permeability, omental attachment to the catheter is the major cause. Omental attachment brings neighboring tissues closer to the peritoneal catheter, resulting in a "ball-valve" effect in which tissues completely obstruct the catheter—causing outflow to cease while there is significant intraperitoneal volume. Catheters migrate because they are attached to omentum, and outflow failure is due to the omental attachment—not the higher position in the abdomen.

From a hydraulic standpoint, fluid can run uphill as easily as downhill—and outflow can proceed to drain through a superiorly placed catheter, though obviously less rapidly than if the catheter is in the middle of a pool of PD fluid in the pelvis. Biocompatibility of an implanted device means that it operates without altering the physiology, anatomy, bacteriology, biochemistry, or reparative function of neighboring tissues. The evolution of chronic PD catheters reflects the goals of attaining adequate hydraulic function and perfect biocompatibility, which includes the following features.

- Peritoneal membrane without sclerosis or adhesions
- Abdominal wall without leaks or hernias
- Subcutaneous tract without infection
- Skin exit site without infection
- Peritoneum without infection and without adhesions between viscera or to the catheter
- Catheter surface without persistent biofilm and not harboring bacteria after a peritonitis episode

Tenckhoff first described the coiled and straight version of his double-cuff PD catheter in 1968. Since then there has been some effort at modification of the catheter, for the most part with the goal of improving outflow and preventing omental attachment. There have been few attempts at changes in materials, but the most popular PD access devices today remain the curled and straight Tenckhoff catheters.

Types of Chronic Peritoneal Catheters

Chronic PD catheters are constructed of soft materials such as silicone rubber or polyurethane. The intraperitoneal portion usually contains 1-mm side holes, but one version has linear grooves or slots rather than side holes. All chronic PD catheters have one or two extraperitoneal Dacron (polyester) cuffs that promote a local inflammatory response. This produces a fibrous plug to fix the catheter in position, prevent fluid leaks, and prevent bacterial migration around the catheter.

Currently, the method chosen for placement of the catheter and the experience of the operator have more effect on the outcome of the catheter than the catheter design. As shown in Figure 7.1, there appears at first to be a bewildering variety of chronic peritoneal catheters. However, each portion of the catheter has only a few basic design options. There are four designs of the intraperitoneal portion.

- Straight Tenckhoff, with an 8-cm portion containing 1-mm side holes
- Curled Tenckhoff, with a coiled 16-cm portion containing 1-mm side holes
- Straight Tenckhoff, with perpendicular silicone discs (Toronto-Western or Oreopoulos-Zellerman catheter)
- T-fluted catheter (Ash Advantage), a T-shaped catheter with grooved limbs positioned against the parietal peritoneum

There are three basic shapes of the subcutaneous portion between the muscle wall and the skin exit site.

- Straight, or a gently curved straight catheter
- A permanent 150-degree bend or arc (Swan Neck)
- A permanent 90-degree bend, with another 90-degree bend at the peritoneal surface (Cruz Pail Handle catheter)

There are three positions and designs for Dacron (polyester) cuffs.

- Single cuff around the catheter, usually placed in the rectus muscle but sometimes on the anterior surface of the rectus (depending on the procedure used to implant the catheter)

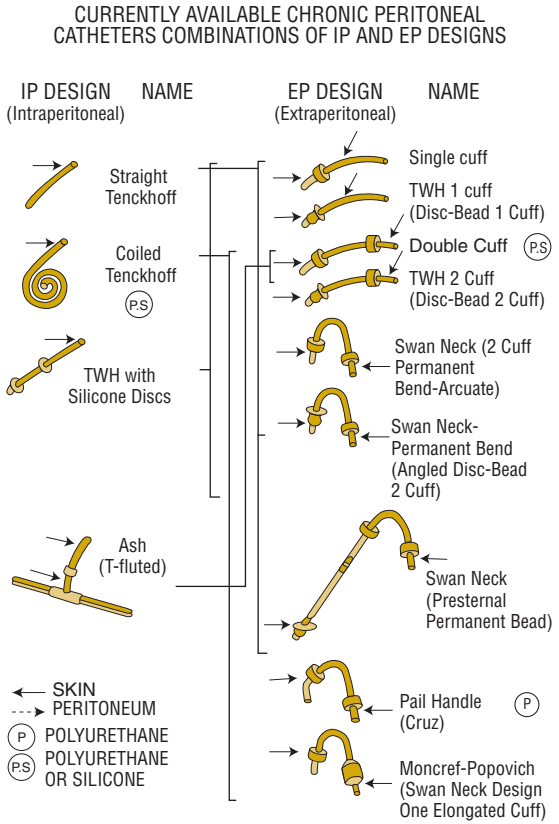


Figure 7–1

Currently available peritoneal catheters in combinations of intraperitoneal and extraperitoneal designs. All catheters are of silicone except where indicated by P or PS.

- Dual cuffs around the catheter: one in the rectus muscle and the other in subcutaneous tissue
- Disc-ball deep cuff, with parietal peritoneum and posterior rectus sheath sewn between a Dacron disc and a silicone ball and a second subcutaneous cuff (Toronto-Western and Missouri catheters)

There are three internal diameters for adult PD catheters, each having an outer diameter of approximately 5 mm (Figure 7.2).

- 2.6-mm, the standard Tenckhoff catheter size (also Swan-Neck catheter, Missouri Swan-Neck catheter, and Toronto-Western catheter)
- 3.1-mm, the Cruz catheter
- 3.5-mm, the Flex-Neck and Advantage catheters

There are two materials of construction.

- Silicone rubber (nearly all catheters)
- Polyurethane (Cruz catheter)

The various intraperitoneal designs are all created to diminish outflow obstruction. The shape of the curled Tenckhoff catheter and the discs of the Toronto-Western catheter hold visceral peritoneal surfaces away from the side holes of the catheter. The grooves of the Advantage catheter distribute flow over the surface of the limbs that contact the parietal peritoneum, providing a much larger surface area for drainage than side holes provide. An irritated omentum attaches firmly to side holes of a catheter

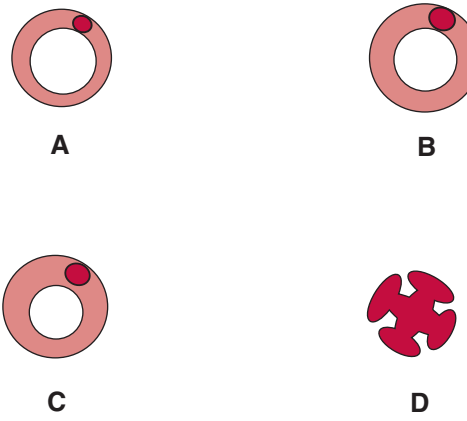


Figure 7–2

Comparison of cross-sectional dimensions of the intraperitoneal portion of several peritoneal catheters: *A*, Flex-Neck Tenckhoff catheter (silicone); *B*, Cruz Tenckhoff catheter (polyurethane); *C*, standard Tenckhoff (silicone); and *D*, one intraperitoneal limb of the T-fluted catheter (Ash Advantage, silicone). Small oval indicates barium-impregnated stripe.

but only weakly to grooves on a catheter (as demonstrated by the Blake surgical drain, with grooves on the catheter surface).

The subcutaneous catheter shapes all provide a lateral or downward direction of the exit site. A lateral or downward direction minimizes the risk of exit infection. An upward-directed exit site collects debris and fluid, increasing the risk of exit site infection. The optimal location for the standard deep cuff is within the rectus muscle (described in material following). The subcutaneous cuff provides additional protection from bacterial contamination of the subcutaneous tunnel. The disc-ball deep cuff is fixed in position by the peritoneum and posterior rectus sheath, and thus catheters with a disc-ball deep cuff cannot migrate outward. Similarly, the T shape of the Advantage catheter places the intraperitoneal limbs against the parietal peritoneum (preventing outward migration of the catheter).

The larger internal diameter of the Cruz and Flex-Neck catheters (Figure 7.2) provides lower hydraulic resistance and more rapid dialysate flow during inflow and the early phase of outflow. In the latter part of outflow, the resistance to flow is determined largely by the spaces formed by peritoneal surfaces as they approach the catheter—rather than the inside of the catheter. The Advantage catheter provides much larger entry ports for drainage of peritoneal fluid, and limited clinical studies have demonstrated faster drainage of the peritoneum in early and late phases of outflow and a decrease in residual peritoneal volume at the end of outflow.

Changing the material of construction of peritoneal catheters has not changed the incidence of complications of the catheters. Polyurethane catheters do not have a lower incidence of persistent peritonitis or omental attachment leading to outflow failure. Polyurethane catheters appear to have a weaker bond to the Dacron cuff, and loosening of this bond can create pericatheter leaks. Degradation of the tubing of polyurethane PD catheters has also occured in a few patients, resulting in catheter fragmentation. This type of complication is rarely seen in polyurethane central venous catheters.

Proper Location of Components of Chronic Peritoneal Catheters

There is general agreement on the proper location of the components of chronic peritoneal catheters (Figures 7.3 and 7.4).

- The intraperitoneal portion should be between the parietal and visceral peritoneum and directed toward the pelvis to the right or left of the bladder.

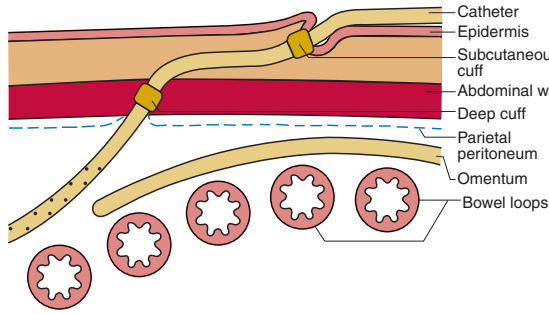


Figure 7–3

Proper relationship of peritoneal cuffs to abdominal musculature, parietal and visceral peritoneum, and skin exit site for straight Tenckhoff catheter.

- The deep cuff should be within the medial or lateral border of the rectus sheath.
- The subcutaneous cuff should be approximately 2 cm from the skin exit site.

Placing the deep cuff within the abdominal musculature promotes tissue ingrowth and therefore minimizes pericatheter hernias, leaks, catheter extrusion, and exit site erosion. At the parietal peritoneal surface, the squamous epthelium reflects along the surface of the catheter to reach the deep cuff. If the deep cuff is outside the muscle wall, the peritoneal extension creates a potential hernia. At the skin surface, the stratified squamous epithelium follows the surface of the catheter until it reaches the superficial cuff. If the exit site tunnel is longer than 3 cm, the squamous epithelium disappears and granulation tissue is left—leading to an exit site with continued "weeping" of serous fluid. The potential for exit site infection is increased.

Some peritoneal catheters have components that provide greater fixation of the deep cuff within the musculature. When the Missouri and Toronto-Western catheters are placed, the ball is inside the peritoneum and the Dacron disc is outside the peritoneum. When the T-fluted (Ash Advantage) catheter is placed, the flutes open into position adjacent to the parietal peritoneum and perpendicular to the transrectal portion. With all of these catheters, outward migration of the catheter is impossible.

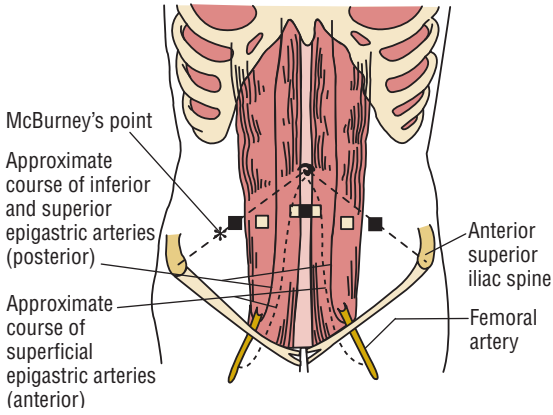


Figure 7–4

Major blood vessels and landmarks of the anterior abdominal wall. Open squares represent the preferred and safest points for location of the deep cuff of a chronic peritoneal catheter within the medial or lateral border of the rectus muscle. Solid squares indicate the external landmarks used during blind insertion of a needle or cannula at the start of peritoneoscopic or blind catheter placement: 1/2 the distance between the anterior superior iliac spine for the lateral border of the rectus and 2 cm below the umbilicus for medial border of the rectus.

The presternal catheter has an exit site on the anterior chest wall, connecting to a standard Tenckhoff or Missouri catheter within the peritoneum. A long tunneled segment connects the intraperitoneal portion and the exit site portions (Figure 7.5). A Dacron cuff is present in the abdominal musculature and near the exit site. The rate of exit site infection appears to be very low with this catheter, although randomized and prospective trials have not been conducted comparing exit infection rates with catheters having abdominal exit sites. The presternal exit site allows patients to bathe without wetting the exit site, and is helpful in patients with pendulous abdomens and difficulty in cleaning or bandaging their exit site. An alternative for such patients is to place the PD catheter high along the left lateral rectus border, so that the exit site resides above the panniculus.

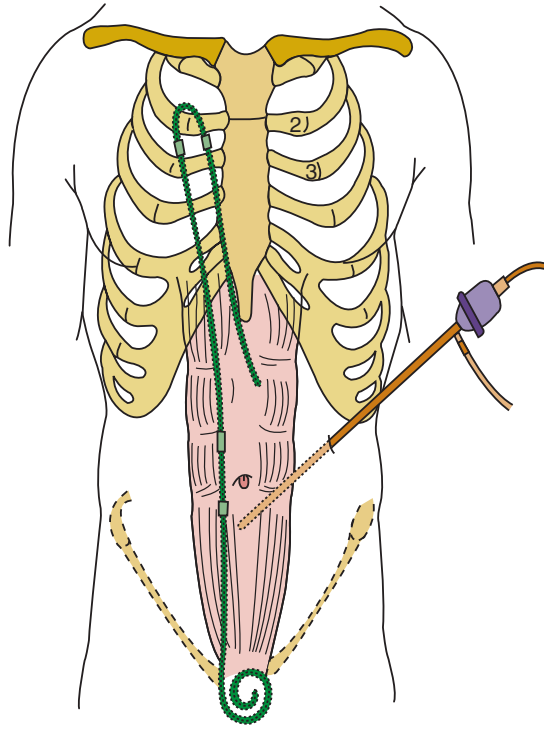


Figure 7–5

A presternal exit site for a standard curled Tenckhoff catheter, shown with laparoscope used for placement and positioning. *(Courtesy of Dr. John Crabtree.)*

Position of Peritoneal Dialysis Catheter Components

In placement of peritoneal catheters it is necessary to choose a deep cuff location free of major blood vessels (Figure 7.4). The superficial epigastric arteries course from the femoral artery and ligament toward the umbilicus, anterior to the rectus sheath. The inferior epigastric arteries lie behind the rectus muscles, roughly in the middle of the rectus sheath. Considering the position of

these arteries, the safest locations for placing the deep cuff are in the medial or lateral borders of the rectus muscle.

For procedures using a cannula or needle insertion, the lateral border of the rectus is located halfway between the anterior superior iliac spine and the midline. The medial border is located approximately 1 cm from midline, below the umbilicus. The exact location of the medial and lateral border of the rectus muscle can be determined more precisely using ultrasound (such as with the Site-Rite). This also allows a scan of the parietal peritoneal surface for any bulky adhesions.

Effects of Catheter Design on Success of the Catheter

Randomized prospectively controlled studies have generally shown little effect of catheter design on the success of peritoneal catheters, although one study by Nielson demonstrated a longer 3-year survival of coiled versus straight Tenckhoff catheters. If properly placed, dual-cuff Tenckhoff catheters have a lower incidence of exit site infection and longer lifespan than single-cuff catheters—although properly placed single-cuff catheters can work as well. Curled Tenckhoff catheters have a lower incidence of outflow failure than straight catheters. Swan Neck catheters appear to have a lower incidence of exit site infection than those with straight subcutaneous segments. Nonrandomized studies of specific catheters have indicated various advantages, including that catheters with the best fixation of the deep cuff (such as the Missouri and Advantage catheters) have a very low incidence of exit site infection.

Some silicone Tenckhoff catheters (such as the Flex-Neck) have a larger internal diameter and thinner walls (Figure 7.2). These catheters are more pliable and create less tension between deep and superficial cuffs during the normal patient activities. This may result in a lower incidence of pericatheter leaks and hernias, and fewer exit site and tunnel erosions, although any real advantages are as yet unproven. An early problem with Flex-Neck catheters was that they were prone to crimping in the subcutaneous tunnel if angled sharply. However, if physicians follow the supplied template to create the subcutaneous tunnel with a gentle downward curve, crimps in the subcutaneous tract are eliminated.

Flex-Neck catheters, like the Cruz catheter, have a higher rate of inflow and initial outflow than those with standard smaller internal diameters. Outflow rate is not dependent merely on the

hydraulic resistance of the catheter, but also on the hydraulic resistance of tissue spaces around the catheter tip. Rapidity of flow at the end of outflow for the Cruz catheter is partly due to the 90-degree angle of the catheter at the parietal surface, which positions the coiled portion next to the parietal peritoneal surface. Properly placed, Flex-Neck and some Tenckhoff-type catheters can have nearly overall outflow rates similar to the Cruz catheter. For catheters with larger lumens, care must be taken to avoid kinks during placement.

The Advantage catheter contains fluted limbs that remain adjacent to the parietal peritoneum, ensuring a stable position of the catheter without extrusion of the deep cuff or exit site erosion (similar to the disc-ball and the older column-disc catheters). Advantage catheters placed in patients beginning PD and those with previous Tenckhoff failures demonstrate a 1-year survival of 90%, higher than the 50 to 80% survival of Tenckhoff catheters in most studies but similar to results in some studies. During follow-up of 42 patients with Advantage catheters in place for up to 4 years, only one patient developed a pericatheter leak (resolved by delaying CAPD)—and no patient has developed a pericatheter hernia or late exit infection. Outflow rate of PD fluid is on average equal to the best-functioning Tenckhoff catheters (including the Flex-Neck catheters of large internal diameter).

The total outflow volume of exchanges is more consistent with the Advantage catheter. In CAPD exchanges with the same glucose concentration and dwell time, the Advantage catheter has a standard deviation of 2% versus 10% for Tenckhoff catheters. The more consistent peritoneal outflow is probably due to more complete drainage of the peritoneum, with a diminished residual volume (but this is not wholly proven). Diminished residual volume is important in that if residual volume is decreased by 300 to 500 cc the inflow volume can be increased by the same amount, thus increasing the peritoneal clearance by 10 to 20% without increasing patient discomfort by overfilling the abdomen.

Advantage peritoneal catheters may diminish the risk of outflow failure, but do not eliminate this risk. Omentum does not directly attach to the intraperitoneal portion of the catheter, but after peritonitis or other irritation omentum may surround the long grooved intraperitoneal limbs and trap them against the parietal peritoneum. Infusion of iodine dye during fluoroscopy demonstrates that with this type of omental entrapment the dye does not pass freely in many directions out of the grooves of the catheter, but rather stays near the catheter and exits from the ends of the limbs. Laparoscopic removal of adhesions and uncovering

of the catheter can result in a perfectly functioning PD catheter, but in some cases the adhesions reform. Negative aspects of the Advantage catheter include the fact that it is somewhat more complicated to insert, although it can be placed by dissection, laparoscopy, or peritoneoscopy.

A special slotted "key tube" and guide are needed to hold the ends of the catheter together so that it can be inserted through the quill guide of a peritoneoscopic or laparoscopic placement or through a peritoneal opening during surgical placement. The catheter limbs open automatically when the tube and guide are retracted. Another problem with this catheter is that if the peritoneal fluid contains a considerable amount of blood or fibrin the small openings between the fluted limbs and the central T portion can block off. This usually resolves with some in/out flushes by a 20-cc syringe with saline, but sometimes locking the catheter with tPA is necessary. Ongoing improvements in the T-shaped catheter should help to resolve these problems, making it less likely to obstruct with fibrin and making placement more like a standard Tenckhoff catheter. Removal of the catheter is no more complicated than a Tenckhoff. After dissecting the deep cuff free of tissue, gentle traction collapses the intraperitoneal limbs.

All PD catheters can serve as a nidus for infection, requiring removal in the cases of persistent peritonitis. None of the new designs or materials has changed this propensity. Peritoneal catheters with a long-term and effective antibacterial surface are still an elusive goal, but several new approaches to sterilization of biofilm are now being evaluated. Another challenge is to limit the growth of adventitial tissue around and onto catheters, as in fibrous sheathing of central venous catheters and omental attachment to peritoneal catheters. Of course, these materials would have to be applied to the intravascular or intraperitoneal surfaces of the catheters and not in the subcutaneous space or on the cuffs.

Catheters for Continuous-Flow Peritoneal Dialysis

Nighttime cycler automated PD is an attractive option for dialysis patients, but has never fulfilled the promise of providing the same daily clearance as CAPD. Continuous-flow PD (CFPD) is a treatment in which dialysate enters and drains from the abdomen from two separate intraperitoneal points, at a continuous rate. CFPD has been attempted over the last 40 years, and has been

shown to have the potential to double or triple peritoneal clearance rates versus CAPD. Therefore, CFPD could provide excellent uremic therapy without the need for daytime exchanges—and could also provide excellent therapy of acute renal failure.

CFPD requires two intraperitoneal access points: one for inflow of dialysate and the other for outflow. Because there is no interruption of inflow to allow outflow, flow rates are determined only by the rate at which the draining catheter can reproducibly drain the abdomen. In some patients using standard catheters, dialysate flow rates of up to 300 mL/minute can be maintained through the peritoneum with CFPD. With use of an external dialyzer to "regenerate" the dialysate, clearances of urea, creatinine, and urate respectively average 57, 35, and 39 mL/minute in adult patients. At 170 mL/minute of dialysate flow, urea and creatinine clearances have respectivley averaged 31 and 23 mL/minute. Recent studies with dialyzer-regenerated PD fluid and using dual Tenckhoff catheters have confirmed urea clearances of 50 mL/minute or more in several patients with acute renal failure.

CFPD has also been used principally for fluid overload. In six pediatric patients with ARDS due to sepsis or SIRS, CFPD at 10 to 30 mL/kg/hour with two Tenckhoff catheters resulted in a decrease of body weight by an average of 33% and an improvement in alveolar-arterial oxygen gradient. With CFPD, the time-averaged clearance of PD can theoretically exceed that of daily 4-hour HD (Hemodialysis) and come close to those of CVVH (Continuous Veno-Venous Hemofiltration) or CVVHD (Continuous Veno-Venous Hemodiafiltration) and approach the KoA (Mass-Transfer Area Coefficient) or maximal clearance theoretically obtainable from the peritoneum. These high dialysate flow rates seem unrealistic today only because we are accustomed to using expensive prepackaged dialysate and gravity flow. However, if PD machines reappear that can proportion fluid on site—or if sorbent-based regenerative systems are commercialized—peritoneal dialysate will be available at just about any flow rate desired.

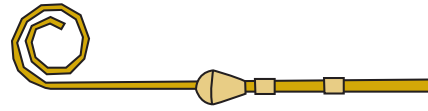
A major requirement for CFPD to be successful is to have effective drainage of the peritoneum at relatively high flow rates. Theoretically, this is not difficult because the standard Tenckhoff can drain the abdomen at 300 mL/minute or more under gravity flow in CAPD during the early part of outflow. However, flow from Tenckhoff catheters is always somewhat variable. With CAPD exchanges, if there is a diminution in flow this merely represents a slower outflow and some inconvenience. In CFPD, at 300 mL/minute it is possible to build up an extra liter of fluid in the peritoneum in only a few minutes. The Advantage

"t-fluted" peritoneal catheter generally provides higher flow rate and more complete drainage of peritoneal fluid than the standard Tenckhoff catheter, but not in all patients. With some modifications, this catheter may provide faster and more reliable drainage for CFPD—using a second site for infusion of fluid into the peritoneum or one limb of the T-shaped catheter for infusion and one for drainage.

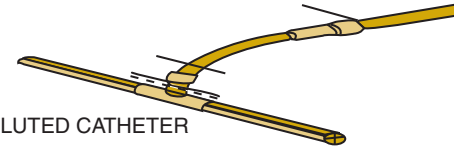
For CFPD to be acceptable in use as a home therapy, it will be necessary to have one skin entry site for the catheter (rather than two). Most of the research done to date has been performed using two separate catheters, with separate peritoneal entry sites. The abdominal viscera and omentum between the two catheters helps prevent "shunting" of fluid in the peritoneum between the entry and exit points. To avoid having two skin exit sites, it is possible to have two widely separated peritoneal entry points for catheters—with subcutaneous tubes leading to a single exit-site tubing. Another approach is to build a single-body dual-lumen catheter with an entry and exit port for the PD fluid. Several such catheters have been designed (Figure 7.6). This approach is simpler, but has a risk that fluid can shunt or short-circuit along the catheter body from the entry to exit port. For this reason, several dual-lumen PD catheters have channels that deflect the inflow fluid along the parietal peritoneum or in directions opposite the drainage ports.

One final challenge for CFPD is control of intraperitoneal volume, which is especially complicated due to the fact that ultrafiltration is somewhat unpredictable during PD. Intraperitoneal volume is very important to maximizing clearance of CFPD. Too large a volume increases shunting and too small a volume recruits too little peritoneal area. A simple approach is to control pressure at the exit point of the peritoneum. Compliance of the peritoneum is relatively constant for each patient. Therefore, controlling intraperitoneal pressure is essentially the same as controlling intraperitoneal volume.

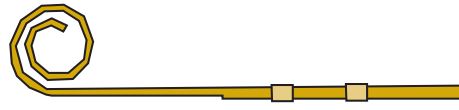
Controlling pressure at the outlet catheter port is easily accomplished. Placing the drain bag just above the umbilicus controls this pressure accurately. However, if there is resistance through the intraperitoneal drain the intraperitoneal pressure may be higher than the pressure at the outflow port. Thus, for this pressure control system to work the drainage catheter must drain PD fluid with minimal resistance around the catheter (as discussed previously). For Tenckhoff or other catheters with excellent function, this pressure control system effectively controls intraperitoneal volume during CFPD.



15F DUAL LUMEN CATHETER WITH DIFFUSER



T-FLUTED CATHETER



DOUBLE LUMEN COILED PERITONEAL DIALYSIS CATHETER

DOUBLE LUMEN STRAIGHT PERITONEAL DIALYSIS CATHETER

14F COILED PERITONEAL DIALYSIS CATHETER

Figure 7–6

Several designs for single-body dual-lumen catheters for continuous-flow peritoneal dialysis.

Methods of Implantation of Peritoneal Dialysis Catheters

Acute peritoneal catheters are inserted into the abdomen blindly, through a midline site just below the umbilicus. The abdomen is first prefilled by making a small skin incision and advancing an

IV catheter into the peritoneum at this site, removing the central needle, and attaching an intravenous tubing set to infuse 2 L of saline or dialysate. This catheter is removed, and the acute catheter with internal pointed stylet is advanced through the abdominal wall in the same location. The stylet is withdrawn slightly, and the catheter is advanced in a direction roughly parallel to the parietal peritoneum toward the pelvis.

When obstruction is felt, indicating impingement on adhesions or bowel loops, the catheter is redirected until it can be advanced the full length into the peritoneum. The stylet is withdrawn, and the movable wings advance to the skin surface. The wings are sutured to the skin. The catheter is used for 3 days of peritoneal dialysis therapy, and then removed. Chronic PD catheters are placed by one of four methods, outlined in the following sections.

Dissection

Dissection is a surgical technique in which layers of tissue are separated under direct vision. A 3- to 5-cm "primary" skin incision is made, followed by a 2- to 3-cm incision through the rectus muscle. The parietal peritoneum is identified, incised, and lifted to create an air space between parietal and visceral peritoneum. The catheter and internal stylet are advanced by feel into the peritoneum, until the deep cuff is within the rectus muscle (for Tenckhoff-type catheters). For the Missouri and Toronto-Western catheters, the ball is advanced into the abdomen and the parietal peritoneum sewn between the ball and Dacron disc.

Blind Puncture

Blind puncture involves puncture of the abdomen by a needle, dilatation of the tract, and advancement of the catheter through the same tract without visualization. The abdomen is prefilled with fluid, and a needle is inserted through the muscle wall. A guide wire is then placed, the tract dilated, and the catheter inserted through a split sheath (similar to that used for internal jugular catheters). When the deep cuff stops at the external rectus, the split sheath is separated and removed, leaving the deep cuff in location just outside the abdominal musculature. A variation on the blind technique is fluoroscopic placement, in which the position of the needle is confirmed by injection of radiographic dye—with the distribution of the dye indicating infusion to the peritoneal space. The guide wire is advanced under fluoroscopy to ensure that it enters the pelvis.

Peritoneoscopy

In peritoneoscopy, a 2.2-mm Peritoneo-scope (Y-TEC) is used to inspect the peritoneum and select the proper location of the peritoneal catheter—which follows the same course when the scope is removed. The procedure is done under local anesthesia entirely, or in combination with light conscious sedation. A cannula, internal trocar, and surrounding quill guide are inserted into the abdomen; the intraperitoneal position is confirmed using the scope; and then about 1 L of air is infused to create a pneumoperitoneum. The cannula is advanced between visceral and parietal peritoneum under vision, the scope and cannula are removed, the quill is expanded with dilators, and the peritoneal catheter is advanced through the quill.

The deep cuff enters the musculature by expanding the quill, with the cuff implantor tool advancing the cuff so that the outer portion is just below the external rectus sheath. Peritoneoscopic placement is also used for the Advantage catheter. A second spiral guide encloses the catheter, with the intraperitoneal limbs folded forward. This spiral guide is advanced through the quill guide, and when the quill guide and spiral guide are retracted the limbs open against the parietal peritoneum. The deep cuff is automatically positioned within the rectus muscle. A laparoscopic variation of the Y-TEC procedure used by surgeons is similar, with only a few exceptions to is the procedure described previously.

The laparoscopic variation utilizes two punctures, typically under general anesthesia, although local anesthesia can be used. The first puncture, typically at the umbilicus, is for the laparoscope itself (either 5.0 or 10.0 cm in diameter) using standard laparoscopic insertion techniques. Air insufflation (up to 3 L) is accomplished via a Verres needle or the cannula of the laparoscope. The quill guide assembly is inserted as described previously, after the initial visualization and under direct vision externally and internally. The balance of the procedure is the same.

Laparoscopy

Several recent publications have described the use of laparoscopic techniques for the placement of peritoneal catheters. These techniques use the same 5- to 10-mm-diameter cannulas generally used for laparoscopic surgery, and are performed with automated inflation of several liters of CO_2 to the peritoneum and under general anesthesia. The trocars are much larger than the 2.2-mm peritoneoscope used in the Y-TEC system. Advancing the PD

catheter through a 10-mm cannula into the abdomen makes it difficult to ensure that the deep cuff is placed within the musculature until after the cannula is removed. Advancing the PD catheter through a 5-mm split-sheath cannula means that the cuff is in most cases left outside the anterior rectus sheath.

In spite of the excellent visualization of the peritoneum with laparoscopic placement techniques, several studies have shown that catheters placed in this manner have a high frequency of pericatheter leak due to the large hole made in the musculature by a 10-mm cannula or the external cuff location after placement by a 5-mm cannula. As opposed to catheters placed with specially designed equipment in peritoneoscopy, catheters placed by the laparoscopic technique have not been proven in general to have improved outcomes versus those placed by dissection. However, laparoscopy does provide knowledge of intraperitoneal anatomy—which may be helpful in placement of PD catheters in patients with previous surgeries and multiple adhesions.

In fact, the visibility of the peritoneum is considerably higher than with the small peritoneoscope. In addition, adhesion lysis is possible for patients with extensive adhesions. Fixation of the omentum to the upper peritoneum is possible for patients with extensive greater omentum. Laparoscopy can also be used for repositioning PD catheters. In difficult cases, laparoscopy (versus dissective placement) may be a preferable technique for PD catheters because of the improved visualization, knowledge of adhesions, and procedural options.

The goal of peritoneoscopic and laparoscopy techniques is to directly visualize intraperitoneal structures and select the optimal location for the catheter position. The catheter course chosen can avoid bowel loops, adhesions, and omentum, and can ensure that the catheter rests against the paritetal peritoneum (as always recommended). In the peritoneoscopic technique, neither the rectus sheath/muscle nor the parietal peritoneum is incised—and the initial puncture through the rectus muscle is only about 2.5 mm in diameter. Thus, the layers of the anterior abdominal wall remain intact and tightly surround catheter and cuff after placement. In laparoscopic techniques, the entry site for cannulas is considerably larger but the catheter can also be placed through a smaller separate entry point (such as with the quill, cannula, and trocar).

Tunneling the catheter is similar for each method of insertion. The exit site is determined by laying the catheter over the skin in a gentle downward bend (for straight subcutaneous segment

catheters) or in an arcuate course (for Swan Neck catheters). The exit site is selected at a point 2 cm external to the subcutaneous cuff (if present). A "secondary" incision is made by inserting a number 11 scalpel blade to the hub. A Tunnelor tool or similar device is advanced through the subcutaneous fat from the secondary incision to the primary incision. The tip of the catheter is attached to the Tunnelor tool, and the tip brought through the secondary incision. Hemostats are lightly applied to the external tubing and drawn into the tunnel. When the tips of the hemostats reach the desired position of the subcutaneous cuff, the tips are spread and the hemostat removed. The catheter is pulled through the exit site and the subcutaneous cuff is drawn into the tunnel, to rest 2 cm from the exit site.

Each technique of catheter placement has its advantages and disadvantages, and the overall success of the catheters is highly dependent on the method of placement. Dissective techniques securely place the deep cuff within the abdominal musculature. However, the incision in the abdominal musculature requires surrounding tissues to first close the wound and then grow into the deep cuff before the deep cuff is secure. Pericatheter leaks are frequent if the catheter is used immediately after placement. The dissective approach provides no visualization of adhesions and free spaces within the peritoneum. The catheter may be advanced into loops of bowel, or near adhesions, and early outflow failure of the catheter.

Blind placement procedures are convenient, can be performed anywhere in a hospital, and have the advantage of being low cost. Bowel perforation is an occasional complication, however, and no visualization of the peritoneal space is provided to avoid impingement of the catheter tip on adhesions or visceral surfaces. The deep cuff is placed outside the abdominal musculature, not within the rectus sheath.

Peritoneoscopic placement allows the best visualization of the peritoneal space. This avoids placing the catheter under bowel loops, under omentum, or against adhesions. The quill expands to enable the deep cuff to advance into the musculature. The Y-TEC procedure can be performed in any room in the hospital. Specialized equipment must be purchased, however, and the physician must have some training in peritoneoscopic techniques. Tenckhoff catheters can be placed by any of the methods described previously. The disc-and-ball Missouri or Toronto-Western catheters, however, can only be placed by dissection techniques.

Effects of Placement Techniques on Catheter Success

The success of peritoneal catheters depends more on placement technique than on the catheter design. Reviews of numerous publications have shown that peritoneoscopic placement results in the lowest incidence of early and late catheter infection, probably due to a lower amount of trauma around the catheter during placement and firm position of the deep cuff. Early outflow failure is minimized by ensuring that the catheter is placed next to the parietal peritoneum. Pericatheter leak is minimized by the firm location of the deep cuff within musculature.

Peritoneoscopically placed catheters may be used immediately for PD treatments to support the patient by PD in almost any schedule except full-volume CAPD, as long as the cuff is securely placed within the muscle. It is better to wait at least 2 weeks before starting dialysis, but practical nighttime cycler or manual exchange therapy can be implemented 1 to 2 days after placement of a PD catheter by peritoneoscopy—as long as the abdomen is dry during days and the patient is ambulatory.

Two randomized controlled studies have confirmed that catheter survival is approximately twice as long for those placed by peritoneoscopy versus catheters placed by dissective techniques. However, the outcomes of surgically placed catheters in these trials were hardly satisfactory, with about 50% survival of the catheters at 1 year. Many studies of catheters placed by dissective technique (surgical) have demonstrated a 1-year catheter survival rate of greater than 80%, and some recent publications by John Crabtree have demonstrated near 100% success of PD catheters placed by laparoscopy (with omental fixating procedures as needed) over 6 months of follow-up.

A meta-analysis of success of PD catheter placement by surgery versus laparoscopy showed no significant differences in outcome but a trend toward better outcome with laparoscopic techniques (especially peritoneoscopic techniques) (Oritz, J Am Soc Nephrol 2004;15:2735–46). Thus, it appears that the type of technique used for catheter placement is less important than the skill, care, and experience of the operator.

Burying the Peritoneal Dialysis Catheter

PD catheters need to "mature" after placement, with fibrous tissue ingrowth into the cuffs and development of a fibrous tunnel. The fully ingrown catheter is more resistant to infection of cuffs and

the surface of the catheter. Traditional surgical implantation of Tenckhoff catheters involves immediate exteriorization of the external segment through the skin, so that the catheter can be used for supportive PD or for intermittent infusions during the "break-in" period. To prevent blockage and to confirm function, the catheter is flushed weekly with saline or dialysate. Each exchange carries the same risk of peritonitis as in CAPD therapy. The catheter must also be bandaged and the skin exit site kept clean in the weeks after placement, to avoid bacterial contamination of the exit site. The patient must therefore be trained in some techniques of catheter care.

It has always been difficult to decide when to place a PD catheter in a patient with chronic renal insufficiency. If the catheter is placed too early, the patient may spend weeks to months caring for a catheter that is not used for dialysis. If the catheter is placed after the patient becomes uremic, it is often used for PD therapy without a break-in period.

Moncrief and Popovich devised a placement technique in which the entire peritoneal catheter can be buried under the skin some weeks to months before it is used. The catheter burying technique was first described for placement of a modified Tenckhoff catheter with a 2.5-cm-long superficial cuff, but the technique has been adopted for standard dual-cuff Tenckhoff catheters. In the original technique, the external portion of the catheter was brought through a 2- to 3-cm skin exit site (much larger than the usual 0.5-cm incision). The catheter was then tied off with silk suture, and then coiled and placed into a "pouch" created under the skin. The skin exit site was then closed. Weeks to months later, the original skin exit site was opened and the free end of the catheter was brought through the original skin large exit site.

The technique of burying PD catheters after placement allows maturation to occur before use of the catheter, much as with fistulas and grafts. It also allows the time of catheter insertion to be separated from the time of use, and avoids requiring the patient to learn how to care for the catheter site or observe the catheter site for potential complications. At the time of initiation of dialysis, the patient and physician can focus attention on the proper performance of the technique and patient response rather than on function of the catheter. The patient can be trained in full-volume CAPD techniques rather than in break-in or cycler techniques used for immediately exteriorized catheters.

Another goal of burying the PD catheter was to improve tissue ingrowth to cuffs by preventing cuff contamination during

ingrowth of tissue into the cuffs and tunnel. It also avoids risk of bacterial contamination during early pericatheter leaks. Burying the catheter effectively eliminates early pericatheter leaks during catheter use, and decreases the incidence of peritonitis rate. In one study with 66 months of follow-up, patients with the buried Tenckhoff catheter had peritonitis infection rates of 0.017 to 0.37 infections per year versus 1.3 to 1.9 infections per year in control patients. In a study of 26 buried Tenckhoff catheters, incidence of infection complications during PD was 0.8 infections per year and catheter-related peritonitis was only 0.036 per patient-year. A retrospective study confirmed a significantly lower catheter infection and peritonitis rate in patients having had buried catheters, as well as a significantly longer catheter life—although the procedure was not effective when used for single-cuff catheters.

The incidence of exit site infections is not generally decreased in catheters that are buried and exteriorized. This may be explained due to an increase in trauma near the exit site during burying and exteriorizing the catheter. A large exit site is created when the catheter is buried, and a similarly large site is recreated when the catheter is exteriorized. Creating a pouch under the skin requires a considerable amount of dissection and trauma near the exit site. The size of the pocket limits the length of catheter that can be coiled and buried under the skin, limiting the external length of the catheter after exteriorization.

The exit site must be opened widely to remove the catheter, because the coil rests in a position distant from the skin exit site. Subcutaneous adhesions to the silk suture around the catheter further restrict removal. Increased trauma near the exit site during placement and exteriorization of the catheter may have caused an increased incidence of early exit infection with this technique. In one study of "embedded" catheters in 26 adult patients (with mean subcutaneous residence of 79.5 days), 2 patients developed local seromas and 12 developed subcutaneous hematomas (5 of which were revised surgically). At catheter "activation," there were at least two flow problems: 9 patients developed fibrin thrombi (2 requiring operative clearance) and 4 patients had omental catheter obstruction (4 requiring omentectomy). When burying the Tenckhoff catheter by standard techniques, there were a total of 27 complications in 26 catheter placements—with 13 of these complications requiring corrective surgery.

When catheters are placed by the Y-TEC procedure, the quill and cannula of the system can be reassembled and used to bury the external portions of dual-cuff Tenckhoff and Advantage

catheters. The catheter exit site is made slightly larger than the standard exit site. The quill and cannula are inserted through this exit site to create a long straight tunnel for the external end of the catheter. The catheter is blocked with an internal plug (removed from the tunneling tool) rather than with an external silk suture. We have used this technique to bury and then remove more than 40 Tenckhoff and Advantage catheters.

There have been few early complications of insignificant hematoma (3%), seroma (0%), exit infection (3%), or outflow failure (0%), and all catheters have functioned after exteriorization. Nephrologists can bury and exteriorize PD catheters with greater ease and lower trauma than they can do so using surgical procedures, and can possibly obtain improved results. A kit specifically for burying the PD catheter should be soon available on the market, providing a suitable plug for the catheter and avoiding the need for reassembling the quill or using a standard Tunnelor tool for burying the catheter.

A curious aspect of the burying technique is that it seems contrary to "the rules" of catheter break-in. In immediately exteriorized catheters, it is necessary to infuse and drain dialysate or saline (with or without heparin) at least weekly to prevent outflow failure or obstruction of the catheter. However, with the completely buried catheter there is no infusion of any fluid for periods up to 1 year. Why is this possible? It may be that stress and strain on the catheter, air within the catheter, and catheter compliance associated with the newly placed catheter that is not buried allow some fluid to enter and exit the side holes during patient movement.

The buried catheter has less motion, and with a secure blockage there is very little fluid inflow/outflow through the holes during normal activity. Further, the infusion of saline or dialysate during break-in techniques adds a bioincompatible fluid to the abdomen at a time before the catheter is "biolized" or protein/lipid coated. The catheter becomes biolized in the absence of dialysate or saline in the peritoneum. When PD is begun, the catheter is already biolized and is less likely to develop omental attachment, even in patients with active omentum.

Summary

Although the Tenckhoff curled and straight peritoneal catheters are remarkably successful and are the standard peritoneal catheters today, they are also less than perfect. Problems of outflow failure, pericatheter leaks, and infection result in significant loss of access

and sometimes result in modality failure. Alternative catheter designs are available and should be used if patients have complications with standard Tenckhoff catheters. Eventually, outflow failure and catheter infection may be solved with new catheter designs and materials. Nighttime cycler therapy may become more effective through CFPD or other machine and fluid improvements. PD may then become an even more successful and better utilized modality for home dialysis.

The success of peritoneal catheters depends mostly on the care, skill, and experience of the person placing them. It depends only in part on the design of the catheter used, or the technique for placement. An increasing number of nephrologists are placing their own PD catheters by the peritoneoscopic and blind techniques (with or without fluoroscopy). Published results confirm that these techniques generally produce outcomes equal to or better than dissective or laparoscopic techniques.

By placing their own catheters, nephrologists may be able to provide placements and PD on a more timely basis, and thus increase the proper use of PD in the ESRD population. Burying the PD catheter gives additional flexibility in providing peritoneal access, allowing the catheter to be placed weeks to months before it is needed—while avoiding patient effort in exit site care and catheter flushes before PD is actually implemented.

Recommended Reading

Amerling R, Glezerman I, Savransky E, Dubrow A, Ronco C. Continuous flow peritoneal dialysis: principles and applications. Semil Dial. 2003 Jul-Aug; 16(4):335–40.

Ash SR. Chronic peritoneal dialysis catheters: Effects of catheter design, materials and location. Semin Dial 1990;3:39–46.

An overview of all peritoneal catheter designs, with major conclusion that skill and technique of implantation has more effect on catheter success than does catheter design.

Ash SR. Bedside peritoneoscopic peritoneal catheter placement of Tenckhoff and newer peritoneal catheters. Adv Perit Dial 1998;14:75–79.

Description of the Y-TEC technique for catheter implantation, and analysis of success of catheters placed by this technique.

Ash SR, Janle EM. T-fluted peritoneal dialysis catheter. Adv Perit Dial 1993;9:223–26.

First description of the catheter now known as the Advantage catheter.

Ash SR, Carr DJ, Diaz-Buxo JA. Peritoneal access devices: Hydraulic function and biocompatibility. In Nissenson AR, Fine RN, Gentile DE (eds.), *Clinical Dialysis*. Norwalk, CT: Appleton & Lange 1995:295–321.

A review of the hydraulic principles determining peritoneal dialysis catheter function, and an overview of all catheter designs.

Eklund BH. Surgical implantation of CAPD catheters: Presentation of midline incision, Lateral placement method and review of 100 procedures. Nephrol Dial Transplant 1995;10:386–90.

Excellent review of surgical techniques for catheter placement.
Eklund BH, Honkanen EO, Kala A-R, Kyllonen LE. Peritoneal dialysis access: Prospective randomized comparison of the Swan Neck and Tenckhoff catheters. Perit Dial Int 1995;15:353–56.
One of the few prospectively randomized trials to include differing PD catheter designs.
Eklund B, Honkanen E, Kyllonen L, Salmela K, Kala A-R. Peritoneal dialysis access: Prospective randomized comparison of single-cuff and double-cuff straight Tenckhoff catheters. Nephrol Dial Transplant 1997;12:2664–66.
Another prospective randomized trial of two PD catheter designs.
Gadallah MF, Pervez A, El-Shahawy, et al. Peritoneoscopic versus surgical placement of Tenckhoff catheters: A prospective study on outcome. J Am Soc Nephrology 1996;7:A0904.
Prospective trial comparing surgical and peritoneoscopic placement techniques for PD catheters.
Gokal R, Alexander S, Ash S, et al. Peritoneal catheters and exit site practice: Toward optimum peritoneal access, 1998 update. Perit Dial Int 1998;18:11–33.
Review and concensus article regarding PD catheters, placement techniques, and care.
Kim D, Burke D, Izatt S, et al. Single- or double-cuff peritoneal catheters? A prospective comparison. Trans Am Soc Artif Intern Organs 1984;30:232–35.
Comparison study of two PD catheter designs.
Lye WC, Kour NW, van der Straaten JC, et al. A prospective randomized comparison of the Swan Neck, coiled, and straight Tenckhoff catheters in patients on CAPD. Perit Dial Int 1996;16(1):S333–35.
Randomized comparative study of two PD catheter designs.
Moncrief JW, Popovich RP, Simmons EE, et al. The Moncrief-Popovich catheter: A new peritoneal access technique for patients on peritoneal dialysis. Trans Am Soc Artif Intern Organs 1994;39:62–65.
Original description of the technique for "burying" PD catheters and description of a catheter with longer SQ cuff.
Nielsen PK, Hemmingsen C, Friis SU, Ladefoged J, Olgaard K. Comparison of straight and curled Tenckhoff peritoneal dialysis catheters implanted by percutaneous technique: A prospective randomized study. Perit Dial Int 1995;15:18–21.
Comparative study of two PD catheter designs.
Pastan S, Gassensmith C, Manatunga AK, Copley JB, Smith EJ, Hamburger RJ. Prospective comparison of peritoneoscopic and surgical implantation of CAPD catheters. Trans Am Soc Artif Intern Organs 1991;37:M154–56.
Prospective trial comparing surgical and peritoneoscopic implantation of PD catheters.
Roberts M, Ash SR, Lee DBN. Innovative peritoneal dialysis: Flow-through and dialysate regeneration. ASAIO J 1999;45:372–78.
Review of all studies of continuous-flow peritoneal dialysis.
Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Catheter-related interventions to prevent peritonitis in peritoneal dialysis: A systematic review of randomized, controlled trials. J Am Soc Nephrol 2004;15:2735–46.
Excellent review of various techniques of catheter care.
Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. Trans Am Soc Artif Intern Organs 1968;14:181–87.
First description of the Tenckhoff straight and curled catheters.
Twardowski ZJ. Presternal peritoneal catheter. Adv Ren Replace Ther 2002;9(2):125–32.
Description of the presternal catheter design and patient advantages.

CHAPTER 8

Complications of Acute Peritoneal Catheter Insertion

Anthony R. Zappacosta, MD

Percutaneous placement of peritoneal dialysis access remains a useful procedure. It can be accomplished using the standard Seldinger technique involving needle puncture followed by guide wire, dilator, and peel-away sheath. For the initial blind puncture, many centers routinely use the Veress needle—a spring-loaded blunt-tipped needle originally developed by gynecologists. This step is followed by placing a standard single-cuff Tenckhoff catheter with the Seldinger technique.

This procedure has replaced use of the original stiff acute peritoneal catheter in many programs, which was associated with a higher incidence of peritonitis because of the lack of a cuff and a subcutaneous tunnel separating the peritoneal entrance of the catheter from the skin exit site. The catheter placement site wound is less than 2 cm compared to 6 or 7 cm for a surgically placed catheter. Most centers have nephrologists skilled in placing catheters who directly manage the patient. This direct involvement in establishing dialysis access usually optimizes the procedure and increases the reliability of access.

Complications of Percutaneous Placement

Complications of percutaneous placement are listed in Table 8.1. There is a reduced risk of vessel and visceral perforation with surgical placement in patients who are likely to have adhesions, and the inadvertent preperitoneal catheter position is also unlikely with this approach. However, barring these complications there are no differences in the incidence of other complications between surgically and percutaneously placed catheters.

The incidence of bowel perforation with percutaneous puncture of the peritoneum is variously reported to be 0 to 1.3%. The risk can be minimized by referring for surgical catheter placement those patients who are likely to have adhesions. We do not use percutaneous placement in patients with more than one abdominal scar, those who have had abdominal surgery within the past 10 years, or any patient who has had a particularly severe

Table 8–1

Complications Specific to Percutaneously Placed Peritoneal Catheters

- Viscus perforation
- Vessel laceration
- Preperitoneal catheter position and dialysate installation

protracted episode of peritonitis. The signs and symptoms of bowel perforation are generally easy to interpret. The patient may develop profuse watery diarrhea with installation of dialysate, or there will be a foul odor when the dilator stylet assembly is removed just prior to advancing the Tenckhoff catheter. Dialysate will be cloudy and/or contain particulate matter. We manage bowel perforation by discontinuing peritoneal dialysis, removing the catheter, substituting hemodialysis, and administering antibiotics. Our surgical consultants and the literature support an initial, conservative, nonsurgical approach to managing such a puncture wound of the bowel.

Bladder perforation is usually avoidable by having the patient void or otherwise emptying the bladder by catheterization before puncturing the abdomen. If the bladder is perforated, it is usually manifested by an increase in urine volume positive for glucose. We manage bladder perforation by removing the peritoneal catheter and leaving a urinary catheter in place. Peritoneal dialysis can be resumed immediately by placing the catheter again. The urinary catheter is left in place for at least a week to ensure bladder healing.

The incidence of serious hemorrhage requiring transfusion is approximately 0.4%. This is usually due to bleeding from the abdominal wall musculature, although rarely an intra-abdominal vessel is lacerated. This hemorrhage is managed by rapid-exchange peritoneal dialysis and supportive care with transfusions as needed. Because we can never be certain that the bleeding is not from an intra-abdominal site, we do not add heparin to the dialysate. Blood clot blockage of the catheter is avoided by rapid-exchange dialysis. The bleeding in our experience has stopped within 24 hours in most cases.

Preperitoneal installation of the catheter dialysate rarely occurs in skilled hands. This is manifested by an unusual amount of pain

upon installation of dialysate and little or no outflow drainage. The catheter, of course, must be removed and placement attempted again.

Hydrothorax occurs in less than 1% of patients and is manifested by very poor if any drainage of dialysate, dyspnea, and abnormal chest radiograph findings (unilateral pleural effusion). We manage hydrothorax by thoracentesis, leaving an intrapleural catheter in place to drain the pleural space completely. Once that has occurred, a sclerosing agent (usually tetracycline) is instilled—which will cause the two layers of the pleura to adhere and prevent hydrothorax from recurring. Peritoneal dialysis must be discontinued until this procedure has been completed, and we wait at least 1 week before resuming peritoneal dialysis in patients with this complication.

Peritonitis can occur at any time after a catheter is placed. It is treated as any other peritonitis occurring during CAPD (Continuous Ambulatory Peritoneal Dialysis). Antibiotics are instilled into the abdomen, and heparin is used to eliminate the problem of fibrin encasement—which is otherwise a common complication of peritonitis. We try to minimize additions to the dialysate bags when doing rapid exchanges in order to reduce the likelihood of contaminating the dialysate. We routinely add potassium to every other bag, instead of every bag, during continuous rapid-exchange peritoneal dialysis—and this is usually sufficient to prevent potassium depletion and hypokalemia.

Exit-site or tunnel infection can occur within a few days of acute catheter placement, and we manage this complication with antibiotics in the same way it is managed in CAPD patients. We have had to remove approximately 14% of catheters placed because of tunnel-exit infection.

Complications of Dialysate Flow

Table 8.2 lists dialysate flow-rate problems. Catheter migration to a subdiaphragmatic location occurs in 4% of catheters and almost always results in difficult drainage manifested by a slow outflow rate with normal inflow. However, we have had patients with migrated catheters for over 5 years that have functioned normally. A laparoscopic technique is now available to reposition such catheters. We have also documented catheter migration from the pelvis to the subdiaphragmatic region and back again into the pelvis.

Fibrin encasement presents with normal or slow inflow rate but little or no outflow of dialysate. This problem occurs after

Table 8–2

Dialysate Flow Problems

Manifestation	Potential Cause
Inflow rate normal, outflow rate normal, but only approximately half of volume drains out	Lack of seal at peritoneal catheter junction with subcutaneous leaking
Inflow rate normal, outflow rate slow, effluent volume variable	Catheter migration to subdiaphragmatic location with consequent omental trapping
Bowel trapping due to constipation	
Hydrothorax	
Slow inflow, no outflow	Fibrous encasement Catheter kink in tunnel Catheter luminal obstruction

peritonitis or pancreatitis, but we have also seen it in uncomplicated catheter placements in diabetic patients. It is nearly completely preventable by the addition of heparin, up to 5000 U/2 L of dialysate, once a day or several times a week We routinely add 5000 U of heparin to the peritoneum (in a volume of approximately 30 mL) every few days between dialysis sessions in order to prevent fibrin encasement.

Subcutaneous leaking of dialysate around an incomplete seal of the peritoneum-catheter junction is not uncommon, and it occurs especially with increases in intra-abdominal pressure but also can occur in a supine patient in an intensive care unit. It is manifested by pitting edema in the lower abdomen or genital edema. Typically before this occurs, several exchanges will have occurred with a normal flow rate to outflow drainage—but only about half of the inflow volume will be recovered in the drainage bag. There is no remedy for this problem except to wait for the peritoneum-catheter junction to become watertight and to avoid dwell time. We have generally been able to continue dialysis without dwell time, and the leak eventually seals off. This may take several days and is often recurrent. Unfortunately, dwell time cannot be increased to greater than a few minutes. Otherwise, the leak and edema worsen. The edema is generally reabsorbed in a few days.

Exit-site leaks are also common and predispose the patient to tunnel and exit-site infections. We avoid using the catheter when there is an exit-site leak of dialysate.

Luminal obstruction with fibrin is manifested by no dialysate flow, either in or out. It is not common, but when it occurs generally the obstruction is easily dislodged by squeezing the bag forcefully or flushing the catheter with saline. A kink in the catheter tunnel may occur rarely and is easily identified because inflow will be impossible and typically manual pressure against the tunnel during inflow will restore flow rate, confirming the kink.

Recommended Reading

Asif A, Byers P, Vieira CF, Merrill D, et al. Peritoneoscopic placement of peritoneal dialysis catheter and bowel perforation: Experience of an interventional nephrology program. Am J K Dis 2003;42:1270–74, 2003.

Crabtree JH, Fishman A. A laparoscopic method for optimal peritoneal dialysis access. Pert Dial Access Surg 71:135–43.

Nolph K (ed.). *Peritoneal Dialysis, Third Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 1989.

Textbook with extensive bibliography and much practical information.

Zappacosta A, Perras S. *Continuous Ambulatory Peritoneal Dialysis*. Philadelphia: Lippincott 1984.

A how-to book on management of CAPD patients.

CHAPTER 9

Water Treatment Equipment for In-Center Hemodialysis: Including Verification of Water Quality and Disinfection

Richard A. Ward, PhD

A water treatment system provides water in which levels of contaminants known to be toxic to dialysis patients are consistently less than those required by regulation (Table 9.1). The system provides this water at the correct temperature, pressure, and flow rate for operation of the facility's equipment—including equipment for dialysate preparation, dialyzer reprocessing, and concentrate preparation.

Selecting a Water Treatment System

All dialysis facilities require a water treatment system because no water supplier can be relied on to provide water that consistently meets the prescribed standards. Systems should be acquired from vendors with expertise in water treatment for dialysis.

Developing System Specifications

Because no two dialysis facilities are exactly alike, each facility should develop its own specifications before acquiring a water treatment system (Table 9.2). (Although the process presented here describes the acquisition of a new water treatment system, it is equally applicable to evaluating or expanding an existing system.)

If a system is used for multiple purposes, demand for water may fluctuate markedly. For example, dialyzer reprocessing may intermittently increase water consumption by 30 to 50% over that used to prepare dialysate. Thus, the water system must be sized to cope with peak demand. Data on required water flow rates, pressures, and temperatures can be obtained from dialysis equipment manufacturers. The water treatment system should be oversized by 20 to 25%, because consumption usually increases

Table 9–1

Maximum Concentrations of Contaminants Permitted in Water Used for Hemodialysis Applications[a]

Rights were not granted to include this table in electronic media. Please refer to the printed publication.

as patient numbers increase and production rates tend to decrease slightly as equipment ages.

In the United States, current regulations set limits of 200 CFU/mL and 2 EU/mL for bacteria and endotoxin (respectively) in water

Table 9–2

Steps in Developing Specifications for a Water Treatment System

Step	Procedure
1.	Determine applications for which water will be used. Estimate water consumption and required delivery pressures.
2.	Define product water quality for each application.
3.	Evaluate quality of feed water.
4.	Compare feed water quality with required product water quality and determine the reduction needed for each contaminant.
5.	List water purification options and determine the preferred system configuration.
6.	Prepare request for bids.

used for hemodialysis applications and in the final dialysate. More stringent limits have been set in other countries. For example, in Europe the limit for endotoxin is 0.25 EU/mL. Evidence is accumulating that even higher levels of dialysate purity may reduce some of the long-term morbidity associated with hemodialysis. For this reason, some advocate the use of "ultrapure" water and dialysate, which are defined as containing less than 100 CFU/L and less than 0.03 EU/mL of endotoxin.

Information on the water supply available to the facility is obtained by testing water collected at the facility, and from the local water supplier. Water samples obtained at the facility are tested for the contaminants listed in Table 9.1. If the water supplier uses chloramines to disinfect the water, information on the levels used throughout the year should be obtained. Information on the flocculent used to clarify the water should also be requested to determine whether alum is used. (Chloramines and aluminum are severely toxic to dialysis patients, and extreme care must be taken to ensure their removal.) The water system is always designed to cope with the worst-case feed-water quality.

The required product water quality should be compared with that of the feed water. Next, a list should be prepared of the purification processes that can achieve the necessary reductions in contaminant levels. From this list, a preferred system configuration can be developed. A detailed algorithm for selecting a water treatment system for a specific application has been

published by the Food and Drug Administration (HHS Publication FDA 89-4234).

Design Considerations

Table 9.3 presents some of the major questions to be answered in arriving at a preferred configuration.

Water Purification Processes

Reverse osmosis is the primary water purification process of choice in most applications. Although an ion exchange process produces higher-quality water with regard to ionic contaminants, it contributes to microbiologic contamination and has higher operating costs than does reverse osmosis. Reverse osmosis effectively reduces the level of inorganic contaminants in the water by at least a factor of 10 and the level of bacteria by a factor of 10^3 to 10^5. Such reductions are usually sufficient to produce water meeting the requirements listed in Table 9.1.

Chloramines are an important exception to this general rule. Chloramines are highly toxic to dialysis patients and are being used increasingly as an alternative to chlorine in water supplies. Carbon adsorption is the usual way of removing chloramines from water. All water treatment systems should include two carbon adsorption beds connected in series and placed before the reverse osmosis unit (to remove chlorine that degrades some reverse osmosis membranes). In addition, reverse osmosis membranes

Table 9–3

Questions to Be Considered in Configuring a Water Treatment System

Step	Procedure
1.	What purification processes are needed to produce water of the required purity?
2.	How should the processes be sequenced to maximize efficiency and minimize maintenance?
3.	How should the feed water be pretreated to prolong the life of the major purification equipment?
4.	Is a supplementary water heater needed to maintain feed-water temperatures in the winter?
5.	Should the distribution system include a storage tank?

act as a microbiologic barrier against bacteria that proliferate in carbon adsorption beds. Not all carbons are equally effective in removing chloramines. If granular activated carbon is used for chloramine removal, it should have an iodine number of at least 900. (This restriction may not apply to other forms of carbon, such as catalytic carbon.) Further, water must remain in contact with the carbon for sufficient time to allow chloramine adsorption to occur. For chloramine removal by granular activated carbon, an empty bed contact time (EBCT) of 5 minutes for each bed must be specified.

Occasionally, carbon does not provide adequate removal of chloramines because of the nature of the water supply (high levels of organic material) or municipal water treatment practices (use of high pH or inhibitors to control corrosion). In such circumstances, it may be necessary to pretreat the feed water to the carbon adsorption beds with anion exchange resins (to scavenge large organic molecules) or acid injection to adjust the pH into the optimal range for removal of chloramines by carbon. Alternatively, chloramines may be eliminated by injection of sodium metabisulfite, which reduces chloramines to chloride ions.

Calcium and magnesium can be removed by reverse osmosis, but they may foul the reverse osmosis membranes and shorten the membrane's life. Thus, a softener to remove calcium and magnesium should be installed between the carbon adsorption beds and the reverse osmosis unit. The softener should be sized to avoid exhaustion during dialysis.

Other pretreatment may include a multimedia depth filter (sediment filter) to remove suspended solids and a 5-μm particle filter following the carbon beds to remove entrained particles that may damage the reverse osmosis unit pump and membranes. All filters must have an opaque housing or some other means to inhibit algae growth.

The performance of both reverse osmosis units and carbon adsorption beds is influenced by water temperature. A hot and cold water blending valve should be installed at the inlet to the water treatment system to maintain feed water temperature in the range specified for each item of purification equipment. In areas with marked seasonal fluctuations in temperature, an on-demand gas-fired water heater may be installed. A simple heat exchanger can be used to prewarm the feed water using the reject stream from the reverse osmosis unit.

Based on these considerations, the system shown in Figure 9.1 will produce acceptable water for dialysis in most settings. In circumstances in which there are very high levels of some ionic

contaminants in the feed water, the use of a two-stage reverse osmosis unit (or reverse osmosis followed by a mixed bed ion exchange system) may be necessary. If ion exchange is used, it should be followed by an ultrafilter to remove any bacteria added to the purified water from the ion exchange resin.

Water Distribution System

Once water meeting the standards outlined in Table 9.1 is produced, it must be distributed to its point of use at the flow rate and pressure required by the dialysis equipment and without degrading its quality. The water distribution system usually consists of a storage tank and a distribution loop, which takes water from the tank to its point of use and returns unused water to the tank (Figure 9.1). Although storage tanks are susceptible to bacterial growth and can be difficult to disinfect, they offer flexibility in coping with peak water demands and provide a margin of safety should the water supply or a component of the water purification cascade fail. If a storage tank is used, it should be no bigger than necessary, have a tight-fitting lid and a conical bottom, drain from the lowest point, and be designed for easy disinfection of all its internal surfaces.

The distribution loop is constructed from inert materials and designed to minimize bacterial proliferation. The piping material

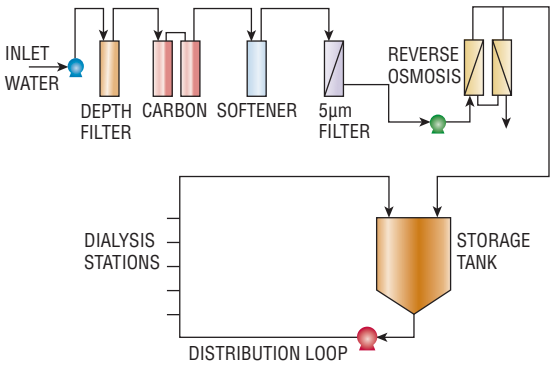


Figure 9–1

Configuration of a typical water treatment and distribution system.

is commonly nonplasticized polyvinyl chloride, joined by solvent welding. Other materials, such as cross-linked polyethylene or polyvinylidene fluoride, may be needed if the distribution system incorporates hot water or ozone disinfection. Piping and other fittings installed beyond the water treatment device used to remove contaminating metal ions (usually a reverse osmosis unit) must not contain brass, copper, aluminum, or galvanized parts because these will leach toxic metals into the purified water.

The distribution loop must not contain areas of stagnant flow where bacteria can proliferate (e.g., branched piping systems, closed pressure vessels or surge tanks, oversized storage tanks, or dead-ended pipes). Pipe diameters should be selected to achieve the greatest flow velocity possible. Velocities of at least 1 m/s can usually be achieved without requiring excessive pressures. An ultrafilter, installed at the point where the water is used, is a further means of ensuring that water of high microbiologic quality is provided to the dialysis equipment.

Purchasing a System

With the design and specifications completed, vendors can be asked to submit bids for a water treatment system. While it is not necessary to specify the preferred system in the bid request, it is useful for evaluating the bids received. In bids, vendors should provide details on system operation, monitoring, maintenance, disinfection, and safety features—as well as on utility requirements for system components.

Once bids are received, they must be evaluated with respect to capital cost and to ensure that the proposed system meets the facility's requirements and that it will not have excessive operating costs or maintenance requirements (Table 9.4). If the system is to be supplied or installed by more than one vendor, be sure that all components are compatible. Similarly, if a system expansion is planned make sure that any new components do not require more feed water than existing components can provide. In the United States, all major components of the water treatment system should comply with Food and Drug Administration regulations.

Quality Control for the Water Treatment System

In general, once a water treatment and distribution system has been installed and its ability to provide water meeting the criteria

Table 9–4

Questions to Be Considered in Evaluating a Potential Water Treatment System

Step	Procedure
1.	If the system differs from the facility's "preferred" system, will it produce water of the desired quality?
2.	Can each component of the proposed system adequately supply all downstream components?
3.	Has detailed information been provided on initial testing and validation of the system once it is installed?
4.	Are utility requirements listed?
5.	Have monitoring procedures for all components been described?
6.	How will the distribution system be disinfected? Are procedures provided for disinfection of the system, including rinse-out of any chemical disinfectant? Is the method of disinfection compatible with the materials used in the system?
7.	Have guidelines for maintenance and troubleshooting of system components been included?
8.	Will training in the operation and maintenance of the system be provided to facility staff?
9.	Does the system conform to any existing regulations?

listed in Table 9.1 has been verified the dialysis facility is responsible for maintaining the system so that it continues to produce water of the appropriate quality. Left alone, the performance of any water treatment system deteriorates over time. Feed-water quality may change, components with finite capacity will exhaust, and bacteria will contaminate distribution systems.

These changes may result in catastrophic failure of the system, resulting in patient injury or expensive repairs. A well-designed quality control program must be implemented to safeguard against such failures. Even then, failure of a critical component (such as the pump used to circulate water through the distribution system) may result in a temporary disruption of water supply to dialysis machines. There should be a contingency plan to cover this eventuality.

The quality control program consists of monitoring and maintenance. Monitoring detects changes in system performance before they adversely affect the quality of water produced.

Maintenance prevents deterioration in system performance and deals with unexpected events when they occur.

Written procedures should be developed for all monitoring and maintenance functions, and responsibility for performing these procedures must be clearly delineated. Results of all monitoring and maintenance should be recorded in log books, which will provide a record of system performance and serve as a baseline for assessing deviations in performance. Data should also be summarized graphically to facilitate trend analysis. Staff should be provided with clear guidelines for action should values of monitored parameters exceed preset limits. The logs should be independently reviewed on a regular basis.

Monitoring

Monitoring provides information on product and feed-water quality, and on the performance of individual system components. Product-water quality must be monitored to ensure that it continues to meet the standards listed in Table 9.1. Feed-water quality is monitored to ensure that it does not deteriorate beyond that assumed in system design. Additional information on changes in feed-water quality can be obtained through regular communication with the local water supplier.

Water quality is monitored by determining contaminant levels in water samples. After the initial performance of the water treatment system is verified, product water should be analyzed for all chemical contaminants listed in Table 9.1 every 6 to 12 months. Between these analyses, changes in product-water conductivity and percent rejection by the reverse osmosis unit can be used as a guide to changes in total ionic contaminants in the water.

The frequency of testing for microbiologic contaminants should be such that increasing levels of bacteria and endotoxin are detected, and corrective action taken, before they respectively exceed 200 CFU/mL and 2 EU/mL. After initial installation of the system, or when problems are being experienced, samples should be obtained at least weekly. As experience achieves stable low levels of bacteria and endotoxin, the frequency of sampling can be decreased (which should not be less than once per month). Meticulous care must be exercised in obtaining samples (Table 9.5), particularly those intended for microbiologic testing.

Levels of contaminants listed in Table 9.1 are determined by sending a water sample to a water-testing laboratory. Chloramines are an important exception to this rule: chloramines must be monitored at least daily, and the analysis must be done onsite.

Table 9–5

Procedure for Obtaining Water Samples for Analysis

Step	Procedure
1.	Sample as close as possible to the point where the water will be used.
2.	Use a sample port that provides direct access to the stream to be sampled. For samples intended for microbiologic testing, avoid using quick-connect devices or flexible tubing connected to valves.
3.	Be sure the water treatment system has been in operation for at least 30 minutes.[a]
4.	Open the sampling valve and allow at least 1 L of water to flow to waste (30–60 s).
5.	Collect a clean catch sample and close the valve.

a. Samples for testing the hardness of water leaving a softener should be collected toward the end of the day.

Chloramines are determined as the difference between total chlorine and free chlorine using a DPD (N,N-diethyl-o-phenylenediamine) test kit, dip-and-read test strips, or an online chloramine monitor. Samples for microbiologic testing must be drawn before the system is disinfected and processed within 30 minutes, or stored on ice and processed within 24 hours.

Bacterial cultures must be performed using a sensitive culturing technique and a medium capable of detecting bacteria that proliferate in a nutrient-poor environment. Blood agar or the calibrated loop technique must not be used. The spread plate or membrane filtration techniques, using tryptic soy agar and incubation at 35 to 37ºC for 48 hours, are recommended in the United States. Use of other media (Reasoners 2A or tryptone glucose extract agar), combined with lower incubation temperatures (23–28°C) and longer incubation times (168 hours), may increase the recovery of bacteria. Endotoxin concentrations are determined by the limulus amebocyte lysate (LAL) assay.

Equipment performance is monitored to determine when replacement of exhausted components is required or when maintenance of permanent equipment is needed. Daily monitoring of the performance of individual system components provides ongoing assurance that product-water quality is being maintained (Table 9.6). A temperature monitor should be incorporated in the blending valve used to provide constant temperature water to the system.

Table 9–6

Parameters Used to Monitor the Performance of Water Treatment System Components

Purification Process	Monitored Parameter	Derived Parameter	Frequency of Monitoring
Filtration	• Inlet pressure	Pressure drop[a]	Daily
	• Outlet pressure	Pressure drop	Daily
	• Product water flow rate	Pressure drop	Daily
Softener	• Product water hardness		Daily
Carbon adsorption bed	• Inlet pressure	Pressure drop[a]	Daily
	• Outlet pressure	Pressure drop	At least daily
	• Product water chloramine concentration	Pressure drop	
Reverse osmosis	• Feed-water conductivity	% Rejection[b]	Daily
	• Product-water conductivity	% Rejection	Daily
	• Feed-water flow rate	% Recovery[c]	Daily
	• Product-water flow rate	% Recovery	Daily
	• Inlet pressure	Pressure drop[a]	Daily
	• Outlet pressure	Pressure drop	Daily
	• Feed-water temperature		
Ion exchange	• Product-water specific resistance		Continuous

a. Pressure drop (ΔP) is defined as the difference between the inlet and outlet pressures.
b. Percentage rejection is defined as $100 \times (1 - \text{Product-Water Conductivity} / \text{Feed-Water Conductivity})$.
c. Percentage recovery is defined as $100 \times (\text{Product-Water Flow Rate} / \text{Feed-Water Flow Rate})$.

Pressure gauges should be installed before and after each component of the water treatment system to monitor fouling of the component by debris or bacteria. An increasing pressure drop across filters may indicate bacterial proliferation. All conductivity and resistivity meters must be temperature compensated. Because deionizers can release toxic effluent when they exhaust, they must be monitored continuously. The monitor must be connected to audible and visible alarms that are activated if the specific resistance decreases to below 1 megohm/cm.

Maintenance

System maintenance includes replacement of exhausted components and preventive measures designed to sustain system performance. The ion exchange beds of softeners and deionizers have a finite capacity and must be regenerated or replaced. Softeners are regenerated onsite using an automated cycle activated outside the facility's normal operating hours. Refined salt should be used for regeneration. Rock salt contains impurities that may damage the control mechanisms of the softener. Deionizers are not regenerated onsite. They are obtained ready-to-use from a vendor. The vendor must certify that the resins are not mixed with resins from other industrial applications during regeneration.

Carbon adsorption beds also have a finite capacity and are replaced on a rotating basis. When a water sample obtained between the two beds indicates that the first bed is no longer removing all chloramines from the water, the first bed is removed (replaced by the second bed) and a new bed is added in the second position. Carbon adsorption beds cannot be regenerated and must be replaced by beds containing new carbon.

Multimedia depth filters are regenerated onsite using an automated backwash cycle. Cartridge filters are difficult to regenerate and are replaced once the pressure drop reaches the maximum value suggested by the filter manufacturer. Reverse osmosis units require regular maintenance to sustain their performance. If product water flow rate or percent recovery of product water decreases by more than 10% under constant operating conditions, the reverse osmosis membranes should be cleaned. The cleaning agent used depends on the membrane material, and specific procedures for cleaning and restoring membranes should be obtained from the manufacturer at the time of purchase.

Disinfection is required to prevent unacceptable bacterial counts from occurring in the purified water. Bacterial counts

should not be used to indicate when disinfection is required. Rather, disinfection should be performed on a regular schedule—and cultures taken and endotoxin levels checked to verify that the disinfection schedule is adequate. In the United States, action levels of 50 CFU/mL for bacteria and 1 EU/mL for endotoxin have been established to help prevent levels of bacteria and endotoxin from exceeding the limits outlined in Table 9.1. If monitoring reveals the presence of bacteria or endotoxin at or above the action level, the water treatment and distribution system should be disinfected to prevent bacteria or endotoxin levels from progressing to the limits outlined in Table 9.1 and the disinfection schedule should be reevaluated.

Disinfection should include the water purification system, the entire water distribution system, any systems used to prepare and distribute bicarbonate concentrate, and the individual dialysis machines. In particular, a there should be a procedure to disinfect the water line connecting the dialysis machine to the water distribution system because this line is not disinfected during routine disinfection of the dialysis machine according to the manufacturer's instructions. Disinfection can be effected with a variety of chemical germicides, depending on the materials used to construct the system. Procedures for disinfecting the reverse osmosis system, including specification of the chemicals and concentrations to be used, should be obtained from the manufacturer at the time of purchase.

A number of chemicals may be used to disinfect the water distribution system. Commercially available peracetic acid preparations are effective cleaning and disinfecting agents, provided the distribution system does not contain gaskets or O-rings made of Buna-N. If an existing system contains Buna-N components, they must be replaced by equivalent components made of Viton (DuPont, Wilmington, DE) or EPDM (ethylene propylene diene monomer)—which are compatible with peracetic acid. Alternatively, sodium hypochlorite or formaldehyde may be used. Distribution systems may also be disinfected by nonchemical methods, such as ozone or hot water.

Repeated contamination of the distribution system with the same organism may indicate biofilm formation. Biofilm can be difficult to eliminate from the distribution system once it becomes established. Bleach circulated at high velocities and ozone are generally the most effective agents for biofilm removal. Their effectiveness may be enhanced by pretreating the piping system with a descaling agent, such as citric acid.

Selected References

AAMI. *Dialysate for Hemodialysis* (ANSI/AAMI RD52:2004). Arlington, VA, Association for the Advancement of Medical Instrumentation 2004.
Provides guidance on the preparation of dialysate for hemodialysis, including water purification and distribution.
AAMI. *Water Treatment Equipment for Hemodialysis Applications* (ANSI/AAMI RD62:2001). Arlington, VA: Association for the Advancement of Medical Instrumentation 2001.
Contains the standards of performance for water treatment systems used for hemodialysis applications and the underlying rationale of those standards.
Bland LA. Microbiological and endotoxin assays of hemodialysis fluids. Adv Renal Replac Ther 1995;2:70–79.
Discusses the necessary components of a surveillance program for microbiologic contamination of water used for hemodialysis applications.
Luehmann DA, Keshaviah PR, Ward RA, Klein E. *A Manual on Water Treatment for Hemodialysis*. Rockville, MD: U.S. Department of Health and Human Services 1989 (HHS Publication FDA 89-4234).
A how-to manual that presents a practical approach to the design and maintenance of water treatment systems for hemodialysis.
Marion-Ferey K, Pasmore M, Stoodley P, Wilson S, Husson GP, Costerton JW. Biofilm removal from silicone tubing: An assessment of the efficacy of dialysis machine decontamination procedures using an in vitro model. J Hosp Infect 2003;53:64–71.
A comparison of the effectiveness of biofilm removal with and without first descaling with dilute acid.
Ward RA. Dialysis water as a determinant of the adequacy of dialysis. Semin Nephrol 2005;25:102–11.
A review of water quality requirements for hemodialysis.
Ward RA. Ultrapure dialysate. Semin Dial 2004;17:489–97.
A review of the evidence supporting the use of ultrapure dialysate for hemodialysis.

CHAPTER 10

Single-Patient Hemodialysis Machines

Richard A. Ward, PhD

Single-patient hemodialysis machines deliver a patient's dialysis prescription by controlling blood and dialysate flows through the dialyzer. In addition, they incorporate monitoring and alarm systems that protect the patient against adverse events that may arise from equipment malfunction during the dialysis treatment. The basic components of a single-patient machine are shown in Figure 10.1. This chapter briefly reviews these components and their functions.

Extracorporeal Blood Circuit

The extracorporeal blood circuit consists of an access device (needles or catheter), blood tubing, blood pump, and dialyzer. It usually also includes a pump for continuous administration of heparin during dialysis. The role of the blood circuit is to deliver blood to the dialyzer at the prescribed flow rate and then return the blood to the patient. This goal must be achieved without damaging blood components and without loss of circuit integrity that may lead to blood loss or the entry of air or other harmful substances, such as bacteria, into the blood.

Urea clearance, and therefore the delivered Kt/V for urea, depends in large part on the effective blood flow rate through the extracorporeal circuit. This blood flow is established using a roller pump (also known as a rotary peristaltic pump). These pumps generally allow flows in the range of 50 to 600 mL/minute. The blood flow rate setting on the pump is based on the speed of the pump (revolutions/minute) and the volume of the pump segment of the blood tubing set. Because the volume of the pump segment depends on its diameter, the diameter of the pump segment must match the preset value in the machine or be selected at the time of treatment in those machines that allow different diameter pump segments to be used. The blood flow rate displayed by most single-patient machines is based on the pump speed and the tubing diameter.

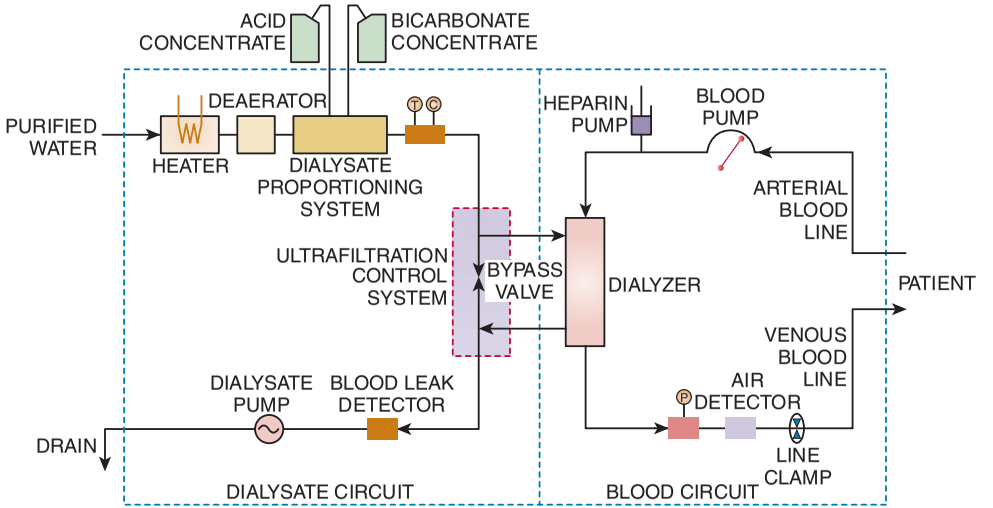


Figure 10–1

Basic components of a single-patient hemodialysis machine, including required monitoring and safety features (C = conductivity monitor, P = pressure monitor, T = temperature monitor). Details of the dialysate proportioning system and the ultrafiltration control system are indicated in Figures 10.2 and 10.3.

The actual blood flow rate may be substantially less than the displayed value, leading to a lower than anticipated urea clearance. The difference in flow rates arises because subatmospheric pressure (also known as negative pressure) in the arterial blood line deforms the cross section of the pump segment, leading to a decrease in its volume. The decrease in blood flow rate is greatest under circumstances that lead to the lowest pressures in the arterial blood line, such as high blood-flow rates and small-diameter access needles. Some newer single-patient machines display a corrected blood flow rate calculated using a software algorithm and the pressure measured at the inlet to the blood pump.

Heparin is used to suppress clotting stimulated by the extracorporeal blood circuit. The heparin is usually administered as a bolus dose, predialysis, followed by a constant infusion throughout the treatment. Single-patient hemodialysis machines are equipped with a syringe pump to infuse the heparin into the arterial blood line between the blood pump and the dialyzer.

Dialysate Circuit

The principal functions of the dialysate circuit are to prepare dialysate from concentrate and water, to deliver it to the dialyzer at the prescribed temperature (generally 35–37ºC) and flow rate, and to control fluid removal from the patient. Most current machines allow the composition of the dialysate and the fluid removal rate to be varied during the treatment according to some predetermined profile.

Dialysate Preparation

Dialysate is prepared by the addition of electrolyte concentrate to warmed and deaerated water. Pressure and temperature changes may cause water or dialysate to degas in the fluid pathway of the machine. The air bubbles formed by degassing can compromise the operation of ultrafiltration control systems and lead to loss of effective membrane area if the air accumulates in the dialyzer. Therefore, dissolved air is removed from the incoming water by applying a partial vacuum in a deaeration chamber located after the water heater.

Essentially all dialysis is performed with bicarbonate-containing dialysate. Because carbonate salts will precipitate from concentrated bicarbonate solutions in the presence of calcium and magnesium ions, two separate concentrates must be used to prepare bicarbonate-containing dialysate. One concentrate

(the bicarbonate concentrate) contains sodium bicarbonate, and in some cases some sodium chloride. The other concentrate (the acid concentrate) contains all remaining dialysate constituents, including a small amount of acid needed to establish the bicarbonate buffer system in the final dialysate.

The acid is usually acetic acid, although concentrates containing citric acid are also available. Two types of proportioning system are used to prepare dialysate. The first type of proportioning system uses pumps with fixed stroke volumes to mix concentrate and water to form the final dialysate (Figure 10.2a). Two pumps meter the acid and bicarbonate concentrates. A third pump may meter water, as shown in Figure 10.2a, or the final dialysate. This type of proportioning system is the most common type in use today. A conductivity sensor is used to monitor the composition of the final dialysate. The second type of proportioning system uses peristaltic pumps coupled to conductivity monitors to adjust the amount of concentrate mixed with water to yield a preset conductivity (Figure 10.2b).

Because conductivity is used to control the concentrate pump, these systems incorporate a second set of conductivity sensors for safety monitoring. A variation of dynamic proportioning uses a powder cartridge, instead of a liquid, for the bicarbonate concentrate (Figure 10.2c). A portion of the heated deaerated water is passed through a cartridge containing sodium bicarbonate powder. Mixing of the resulting bicarbonate concentrate with water and acid concentrate is controlled by a conductivity monitor. This system reduces the handling of containers of liquid concentrates by dialysis unit staff and the risk of bacterial contamination associated with liquid bicarbonate concentrate.

The different approaches to preparing bicarbonate-containing dialysate have resulted in a variety of proportioning ratios for concentrate and water. Ratios of concentrate to water in common use include 1:1.225:32.775, 1:1.83:34, and 1:1.72:42.28 (acid concentrate:bicarbonate concentrate:water). Each proportioning ratio requires its own particular acid and bicarbonate concentrates. Some machines are designed for use with a single proportioning ratio, whereas other machines can be set to use different proportioning ratios. Because machines monitor dialysate composition based on conductivity, use of the wrong concentrates can lead to dialysate of the correct conductivity but the wrong composition. Therefore, failure to use the correct machine setting or to use the correct concentrates with a given machine can lead to patient injury.

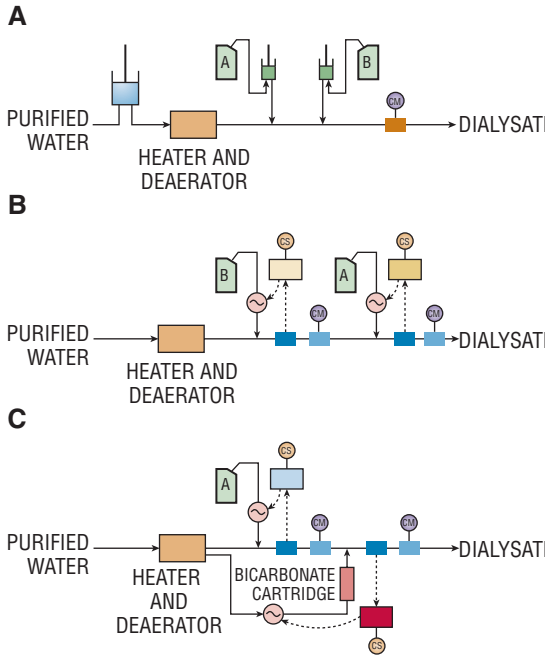


Figure 10–2

Typical dialysate proportioning systems. *A*, Fixed-volume proportioning of water, acid concentrate, and bicarbonate concentrate. *B*, Dynamic proportioning using conductivity measurement to control the acid and bicarbonate concentrate pumps. *C*, Dynamic proportioning using a powder cartridge to prepare the bicarbonate concentrate online (A = acid concentrate, B = bicarbonate concentrate, CM = conductivity monitor, CS = conductivity set point). Broken lines indicate control circuits.

Use of hypernatremic dialysate at the beginning of dialysis may reduce the incidence of hypotension and other intradialytic complications by minimizing the development of osmotic disequilibrium as urea is rapidly removed. For this reason, single-patient machines allow the dialysate sodium concentration to be varied according to some preselected profile. Proportioning systems using fixed-volume pumps vary the dialysate sodium

concentration of the dialysate by varying the stroke rate of the acid concentrate pump. Dynamic proportioning systems vary the dialysate sodium by changing the set-point of the conductivity sensor in the dialysate conductivity control system. Some single-patient machines also allow the bicarbonate concentration of the dialysate to be varied.

There is increasing evidence that low levels of microbiologic contaminants in the dialysate contribute to long-term morbidity in hemodialysis patients. To help minimize such contamination, most current single-patient machines allow the user the option of including an ultrafilter in the dialysate line immediately before the dialysate enters the dialyzer. The ultrafilter, which removes bacteria and endotoxin from the dialysate, is disinfected when the machine is disinfected (see material following) and its performance is validated for a given time or number of treatments.

Fluid Removal

Older single-patient hemodialysis machines had no means of controlling fluid removal from the patient during dialysis. Removal of the desired amount of fluid required knowledge of the ultrafiltration coefficient of the dialyzer and relied on the ability of the machine operator to set the pressures in the blood and dialysate compartments of the dialyzer to achieve the appropriate ultrafiltration rate. Both the ultrafiltration coefficient and the pressures are subject to significant error, which frequently led either to inadequate or to excessive fluid removal. In particular, highly permeable dialyzers (high-flux and high-efficiency dialyzers) could not be used safely with these machines.

Current single-patient hemodialysis machines incorporate volumetric ultrafiltration control systems that allow use of all currently available dialyzers. Two systems are in use: one based on flow sensors and the other based on a balancing chamber (also known as a flow equalizer; Figure 10.3). Flow-sensor systems use bearingless turbine or electromagnetic flow meters to measure the dialysate flow rates entering and leaving the dialyzer (Figure 10.3a). A microprocessor-based control system controls the dialysate compartment pressure to achieve the desired ultrafiltration rate. Some systems incorporate a pair of flow sensors on both the dialysate inlet and outlet lines.

The calibration of the sensors can be checked during dialysis by bypassing the dialyzer for a brief period (during bypass, the inlet and outlet sensors should register the same flow rate).

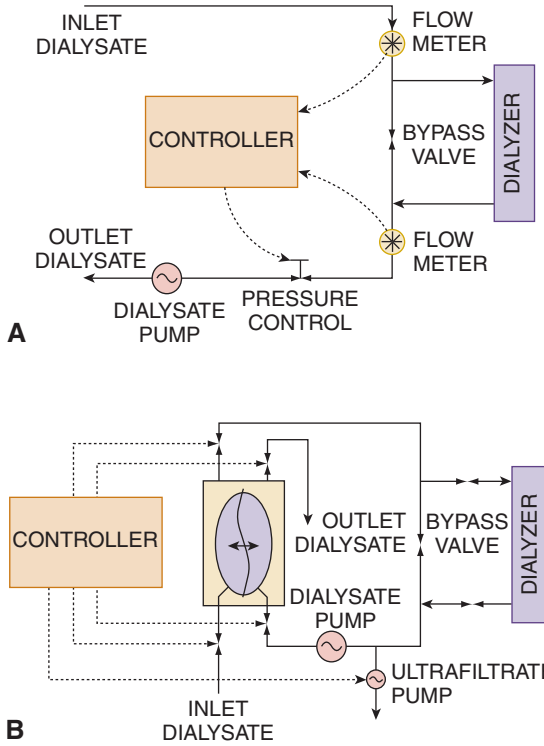


Figure 10–3

Typical ultrafiltration control systems. *A*, Flow sensor-based system. *B*, Balancing chamber system in which the left side of the balancing chamber meters fresh dialysate and the right side meters spent dialysate. Broken lines indicate control circuits. Note that in practice two balancing chambers are used, operating in sequence.

The dynamic range of the flow sensors limits the range of dialysate flow rates that can be used by these machines to 350 to 700 mL/minute. Balancing chamber systems incorporate a fixed-volume chamber divided by a flexible membrane (Figure 10.3b). A set of actuated valves is used to control flow into and out of the balancing chamber. With the valves positioned so that

the dialyzer is isolated from the balancing chamber, one side of the balancing chamber is filled with fresh dialysate—causing an equivalent volume of spent dialysate to be discharged to drain from the other side of the chamber.

The valve positions then change to create a closed loop between the balancing chamber and the dialyzer. The fresh dialysate is pumped into the dialyzer, displacing an equal volume of spent dialysate—which returns to the other side of the balancing chamber. In this way, inlet and outlet dialysate flows are matched exactly. Two balancing chambers operate in sequence: while one balancing chamber is exchanging dialysate with the dialyzer, the other is filled with fresh dialysate—sending the spent dialysate to drain. Net ultrafiltration is achieved using a separate pump that removes fluid from the dialysate outlet line between the dialyzer and the balancing chamber.

Balancing chamber systems do not have the same limitations on flow rates as flow-sensor systems. For standard hemodialysis applications, balancing chamber systems typically allow the use of a wider range of dialysate flow rates (300–1000 mL/minute) than is possible with flow-sensor systems. Machines with balancing chamber systems may be adapted to allow even lower dialysate flow rates for continuous renal replacement therapies such as slow low-efficiency daily dialysis.

Monitoring and Control

Single-patient hemodialysis machines incorporate a number of features to monitor the dialysis treatment and to protect the patient from the adverse consequences of equipment failure. All single-patient hemodialysis machines are required to have monitoring systems to protect the patient against certain hazardous conditions (Table 10.1). Single-patient hemodialysis machines are also required to have a lockout mechanism to prevent the machine from being used during the disinfection or cleaning cycle (see material following). These safety devices, and other monitors, are described in more detail elsewhere in this book.

More recently, monitoring systems have been introduced that acquire online treatment data for computer-based medical records and automatically measure physiologic and other treatment-related variables that can be used to monitor and control the delivery of dialysis in real time (Table 10.2). Automated measurement of blood pressure is now a standard option on most single-patient dialysis machines. Other monitoring systems are able to provide a continuous measurement of hematocrit or

Table 10–1

Required Safety-Monitoring Systems for Single-Patient Hemodialysis Machines

Monitor	Location	Alarm Condition	Protects Against
Pressure	Venous blood line	Blood line separation or occlusion	Blood loss
Air bubble or foam	Venous blood line	Pre-pump line separation	Air embolus
Temperature	Dialysate	Temperature outside preset range	Hemolysis (>42ºC), energy loss (<35ºC)
Conductivity	Dialysate	Conductivity outside preset range	Hypo- or hyperosmolar dialysate, low- or high-bicarbonate dialysate
Hemoglobin	Dialysate	Dialyzer membrane rupture	Blood loss

Table 10–2

Optional Automated Therapy Monitoring and Control Systems for Single-Patient Hemodialysis Machines

Monitored Variable	Derived Treatment Information
Machine parameters (flow rates, pressures, treatment time, ultrafiltration rate, etc.)	Computerized treatment record
Blood pressure (oscillometric method)	Blood pressure and heart rate
Conductivity clearance (dialysate)	Dialyzer clearance, delivered urea Kt/V, access blood flow rate
Hematocrit or plasma protein concentration	Relative change in blood volume
Thermal energy balance	Maintenance of a constant body temperature

plasma protein concentration during dialysis or to intermittently measure the ionic clearance of the dialyzer, also known as conductivity clearance. These systems, which are available as options on a limited number of single-patient machines, allow some assessment of treatment delivery in real time.

Changes in hematocrit and plasma protein concentration provide a measure of changes in vascular volume during dialysis that may be helpful in guiding ultrafiltration rates to avoid excessive decreases in vascular volume and intradialytic hypotension. Conductivity clearance provides a close approximation to urea clearance and can be used to estimate the delivered dose of dialysis in terms of urea Kt/V as a treatment progresses and the delivered Kt/V for each treatment. The ability to obtain a treatment-by-treatment estimate of Kt/V may provide a better guide to the overall delivery of dialysis than a single blood-based measurement performed once per month.

Measurement of conductivity clearance may also be used to determine the flow rate through a patient's blood access as part of an access surveillance program. Single-patient machines from one manufacturer also include as an option a system for monitoring and controlling thermal energy exchange between the patient and the dialysate. This system can be used to maintain a constant body temperature during dialysis, which may help reduce intradialytic hypotensive complications.

Cleaning and Disinfection

Single-patient hemodialysis machines must be cleaned and disinfected regularly to prevent buildup of chemical and bacterial deposits in the dialysate flow path. The use of bicarbonate-containing dialysate increases the risk that calcium and magnesium carbonate will deposit in the dialysate circuit. Such deposits can interfere with conductivity-based monitoring systems and flow-meter–based ultrafiltration control systems. To prevent the buildup of carbonate deposits, machines are rinsed with acetic acid (vinegar) or citric acid. Bacterial buildup in the dialysate flow path is a common cause of bacterial and endotoxin contamination of the dialysate. This problem can be severe if the bacteria form a biofilm. Therefore, single-patient hemodialysis machines must be disinfected at least daily with a chemical disinfectant such as sodium hypochlorite (bleach).

Some machines also incorporate a hot water disinfection cycle that can be used as an alternative to chemical disinfection. No matter whether disinfection is achieved with chemicals or hot

water, none of the currently available single-patient machines incorporates a way to disinfect the water supply line between the connection to the purified water distribution system and the concentrate mixing chamber through which chemical germicide is introduced (or the heater used to generate hot water for disinfection). All current machines require the operator to develop a separate cleaning and disinfection protocol for this section of line to prevent its colonization with biofilm that will continually reinfect the fluid pathways of the machine.

Recommended Reading

AAMI. *Hemodialysis Systems* (ANSI/AAMI RD5:2003). Arlington, VA: Association for the Advancement of Medical Instrumentation 2003.
Contains the standards of performance for single-patient hemodialysis machines in the United States, and the underlying rationale of those standards.
Ahmed J, Besarab A, Lubkowski T, Frinak S. Effect of differing blood lines on delivered blood flow during hemodialysis. Am J Kidney Dis 2004;44:498–508.
Compares actual and displayed blood flow rates at different pressures for different blood tubing sets.
Polaschegg HD, Levin NW. Hemodialysis machines and monitors. In Jacobs C Kjellstrand CM, Koch KM, Winchester JF (eds.). *Replacement of Renal Function by Dialysis, Fourth Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 1996:333–79.
A comprehensive review of the operation of single-patient hemodialysis machines.
Ward RA, Ronco C. Dialyzer and machine technologies: Application of recent advances to clinical practice. Blood Purif 2006;24:6–10.
Briefly reviews recent technological innovations for monitoring and control of therapy with single-patient dialysis machines.

C H A P T E R 1 1

Single-Needle Dialysis

Matthias Kraemer, PhD

In single-needle dialysis (SND), access to the blood circulation of the patient is performed by a single device with only one lumen. This may be a single cannula, or a single-lumen catheter (SLC). The availability of only a single lumen for extracting blood from the patient into the extracorporeal circuit and for returning cleared blood requires an alternating-flow schedule, which is characteristic for SND. In the arterial phase, blood is extracted from the patient during a time interval t_A. In the venous phase, blood is returned during an interval t_V. During these phases, the extracted volume V_S has to be stored within the extracorporeal system. A dialysis with a double-lumen catheter or a (very rarely used) double-lumen cannula is usually not regarded as an SND due to the absence of the alternating-flow scheme.

Basic Setups of the Extracorporeal Circuit for Single-Needle Dialysis

SND today is typically performed using one of two basic setups[1] of the extracorporeal circuit (with minor variations), which have existed for more than 30 years (Figure 11.1). Arterial and venous lines are connected to the cannula via a Y-piece. In the "pump/clamp" system shown in Figure 11.1a, the arterial line leads to the blood pump and dialyzer. At the beginning of the arterial phase, clamp A is opened, clamp V is closed, and the blood pump is started. The dialyzed blood is pumped into a closed compliance chamber Co with a flow Q_A.

With increasing blood volume stored in the chamber, the remaining air is compressed. When pressure reaches a predefined upper limit (e.g., 300 mmHg), the venous phase is activated by stopping the blood pump, closing clamp Cla, and opening clamp Clv. The compressed air in the compliance chamber Co drives the accumulated blood into the venous line and through the cannula back to the patient. As soon as the decreasing pressure in Co reaches a predefined lower limit (e.g., 100 mmHg), the arterial phase is activated and the described cycle starts again.

In the more frequently used "double-pump" system shown in Figure 11.1b, an arterial blood pump fills the compliance

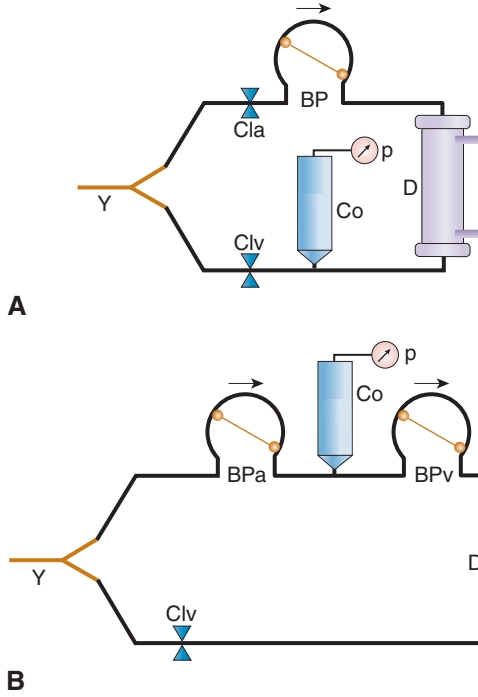


Figure 11–1

Basic setups of currently used extracorporeal circuits for SND. *A*, System with a single blood pump and clamps (pump/clamp system). *B*, System with two blood pumps positioned pre-dialyzer (BP = blood pump, Cl = clamp, Co = compliance chamber, p = pressure sensor, D = dialyzer, a = arterial, v = venous).

chamber Co during the arterial phase. The second venous pump is halted, and the clamp Clv is closed. During the venous phase—again activated when the predefined upper pressure limit is reached (e.g., 180 mmHg)—the arterial pump is halted, clamp Clv opens, and the venous pump is started. The compliance chamber is emptied by the blood pump BPv at the flow rate Q_V, and blood flows through the dialyzer back to the patient until reaching a lower pressure limit (e.g., 80 mmHg) in Co—which

activates the arterial cycle again. In both settings, control of blood pumps and clamps as a function of measured pressure in Co is of course performed automatically by a control unit of the dialysis machine. Aside from the pressure in Co, other parameters can be used to control the SND circuit (see material following).

In SND systems, leaks that allow the entry of air may occur also in the venous tube segment (between cannula and venous clamp Clv), which is under negative pressure during the arterial phase. This is a specific risk of SND systems because at least part of this air volume will be pumped into the patient during the following venous phase. Therefore, no injection ports should be located downstream of the air detector.

Single-Needle Dialysis Cycle Control

The total single-needle (SN) cycle time t_C is the sum of the duration of the arterial (t_A) and venous (t_V) phases. The volume $V_S = Q_A \times t_A$ pumped in the arterial phase is called the stroke volume. The volume pumped back to the patient in the venous phase is $V_V = V_S - UFR \times t_C$ (UFR = ultrafiltration rate). The flows Q_A and Q_V are typically set to the same level when double-pump setups are used, but an access vessel tending to collapse at high Q_A may require a setting $Q_V > Q_A$. Figures 11.2a and b show typical pressures, flows, and times in a single-pump system. Figure 11.2c shows flows and times in a double-pump system. The average blood flow is the blood volume pumped to the dialyzer (stroke volume V_S) per cycle time t_C, which can be expressed as a function of flows as follows (in case of constant Q_A and Q_V):

$$Q_M = \frac{V_S}{t_C} = \frac{Q_A \bullet (Q_V + UFR)}{Q_A + Q_V}$$

Timing and flows during the SN cycle are defined by setting V_S, Q_A, Q_V, and UFR. The stroke volume V_S is usually set between 30 and 50 mL. Under this condition, SND leads to a fluctuation of the intracorporeal blood volume of the patient of about 1%. Much higher V_S might lead to hemodynamic instability, reduced clearance, and clotting in the case of ongoing ultrafiltration (UF). With smaller V_S, unavoidable recirculation (see material following) leads to a decrease in effective clearance.

For control of switching between arterial and venous phases, different parameters have been used. If (as explained previously in regard to the example shown in Figure 11.1) both the end of the arterial and venous phases are determined by specified pressure

limits (e.g., in a closed compliance chamber), a pressure-pressure control is used. This appears to be the control mode most frequently used (the typical operational characteristics of the rigid air-filled compliance chamber are shown in Figure 11.3). An arterial or venous phase can also be terminated after a fixed time, or if a specified volume of blood is accumulated in the compliance chamber. In the latter case, volume may be measured automatically by height sensors in a rigid compliance chamber, by weight, or from the operation of a blood pump (e.g., the number of revolutions). Aside from time-time, pressure-pressure, and volume-volume controls, mixed controls (pressure-time, volume-time, pressure-volume, and so on) have been developed. The first parameter refers to control of the arterial phase; the second to control of the venous phase. Time-time controls have not found acceptance because they require additional adjustments [setting all of t_A, t_V, Q_A, Q_V, and UFR tends to violate the requirement that $Q_A \times t_A = Q_V \times t_V + UFR \times (t_A + t_V)$].

The monitoring of cycle timing can provide an additional protective system for SND. In the commonly used systems with pressure-pressure control, but also in some systems controlled by pressure and volume, measurement of the cycle time t_C or the cycle phases t_A and t_V is mostly performed, to provide additional safety. If the upper pressure limit for switching from arterial to venous phase is not reached within the expected time window $t_A + \Delta t$, the blood pumps will be stopped and the venous clamp closed. Such a condition might be caused by blood loss to the environment, a defective pressure sensor that might lead to line rupture, or other problems. The interval Δt is the tolerance window for cycle phase duration and determines the response time of the system.

Technical Components and Setup Variants

During the history of developments for SND, a large variety of setups of extracorporeal circuits for SND and of specific components for these circuits have been designed.[4] These developments were stimulated by the requirement to obtain a safe and reliable performance, or the intention to reduce complexity, decrease costs, achieve maximum obtainable clearance, and achieve a continuous or even constant flow through the dialyzer. Figure 11.4 shows some examples for further setups of the extracorporeal circuit for SND discussed during the history of SND. The main characteristics that vary between setups are explored in the sections that follow.

Number and Type of Pumps

In most single-pump systems, the energy required to return the blood to the patient during the venous phase has been stored previously within the compliance chamber during the arterial phase (e.g., by air compression). However, a system with six clamps has been designed that uses the same pump for both the arterial and venous phase (Figure 11.4d). In two-pump systems, there is one separate pump for arterial and venous phase each. Two-pump heads driven alternately by the same motor unit

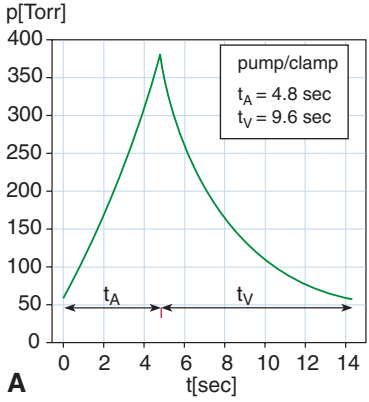


Figure 11–2

Examples for cycle timing, pressure in the compliance chamber, and blood flows in single-needle setups with a rigid closed air-filled compliance chamber (Windkessel). *A*, Compliance chamber overpressure p (pressure exceeding environmental pressure). *B*, Blood flows during arterial and venous phase in a pump/clamp system as in Figure 11.1a (VS = 40 mL, V0 = 150 mL). *C*, Blood flows during arterial and venous phase in a double-pump system as in Figure 11.1b (VS = 40 mL) if QA has to be kept lower than QV (see text). Whereas the double pump system achieves only an average blood flow of QM = 167 mL/minute, the double-pump system achieves QM = 222 mL/minute despite a lower QA and without critically high venous pressures and flows during the venous phase. A double-pump system with QA = QV = 500 mL/minute would lead to a total cycle time of only tA + tV = 9.6 seconds and would allow one to achieve QM = 250 mL/minute.

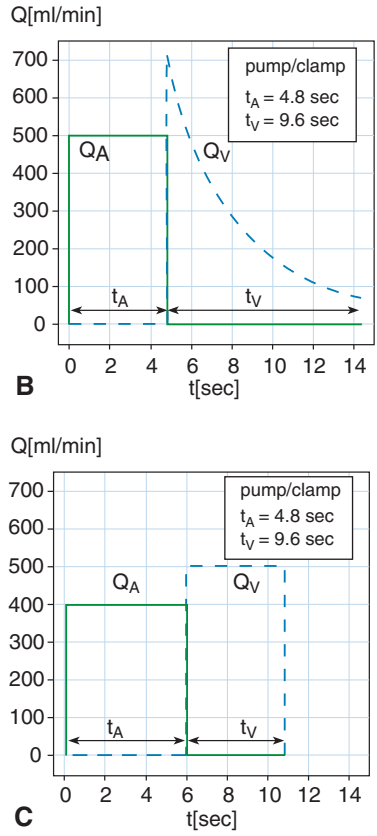


Figure 11–2

Cont'd

and using a clutch system have been developed. A three-pump system has been designed in which the third pump generates a constant dialyzer flow between two compliance chambers (Figure 11.4b).

Roller pumps are in general use in SND. Several other pumps (especially hydraulic, pneumatic, and piston pumps) have also

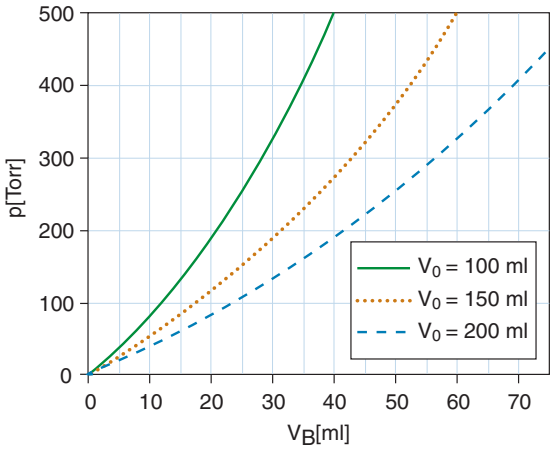


Figure 11–3

Characteristics of a rigid closed air-filled compliance chamber (Windkessel). The compliance chamber overpressure p (pressure exceeding environmental pressure) is plotted as a function of blood volume VB in the compliance chamber. Pressure-volume functions strongly depend on the total chamber volume V0.

been used. In these pump types, the pump chamber can be used as the compliance chamber. Recently, such a pneumatic pump system has been made available (Renal Solutions) that can be used both for SND and double-needle dialysis (DND) with the same bloodline system. Bidirectional pumps have been used, which pump blood through the dialyzer into the compliance chamber—and back to the patient through the same blood path. However, the recirculating volume of such systems is obviously very high.

Relative Position of Dialyzer and Compliance Chamber (Co)

In single-pump systems, the compliance chamber has been positioned behind the dialyzer (Figure 11.1a) or before the dialyzer. The compliance chamber is located downstream of

the pump in most setups. The dialyzer is always located downstream of the pump. In double-pump systems with a single compliance chamber, the chamber is positioned between pumps. The dialyzer may either be between pumps (before or behind the compliance chamber) or behind the venous pump. The configuration of pumps, compliance chamber, and dialyzer largely determines the pressures in the dialyzer during the SN cycle. In the earlier dialysis machines with transmembrane pressure (TMP)–controlled UF, the configuration was very relevant for proper UF control.

Several configurations have therefore been designed for purposes of better UF control (Figure 11.4a). In modern dialysis machines with volumetric UF control, UF is not influenced by the position of the dialyzer. Another consequence of the configuration is the pressure variation during the SN cycle. Many configurations lead to large (Figures 11.1a and 11.4a) and rapid fluctuations. Large fluctuations of pressure were regarded as promoting back-filtration in phases of low pressure (see material following). Configurations with the dialyzer downstream of the venous pump (Figure 11.1b) allow us to realize low-pressure fluctuations.

Number and Type of Compliance Chambers

Several types of compliance chambers have been described: the closed chamber (Windkessel, Figure 11.1), the open chamber (no pressure rise during filling), the elastic bag, the collapsible bag, and the pressurized bag (Figure 11.4c). The open chamber and the collapsible bag are passive systems. That is, they provide volume store for blood but cannot store energy for generating blood flow during the venous phase. Therefore, they are not appropriate in single-pump systems. The other compliance systems are active systems.

The closed chamber stores energy in compressed air, the elastic bag stores energy in the extended bag material, the pressurized bag stores energy in (for example) a compressed spring. The stored energy has to be provided by the arterial pump during the arterial phase, and can be used to drive blood flow during the venous phase. In some historical systems with parallel plate dialyzers, additional compliance chambers could be avoided because the dialyzer provided a substantial compliance volume—which is not the case with today's hollow fiber dialyzers. Systems with two or more compliance chambers also have been described (Figures 11.4b and 11.4d).

Number and Type of Clamps

Whereas setups with one or two clamps (Figure 11.1) are frequently used, systems without separate clamps and with a higher number of clamps have been developed. In setups with no clamp or with one clamp, one or two occlusive pumps provide the line

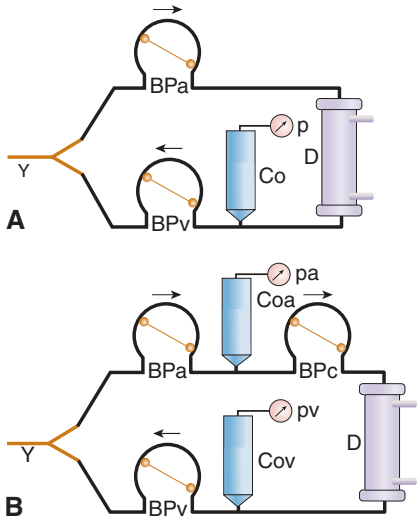


Figure 11–4

Additional "historic" setups for the extracorporeal circuit of SND systems. *A*, Older two-pump system allowing for simple adjustment of transmembrane pressure (TMP) for control of UF in TMP-controlled UF systems. This setup leads to larger pressure variations during the single-needle cycle than the setup shown in Figure 11.1b. *B*, Setup with three pumps and two compliance vessels according to Leonard. The circulation pump provides a constant flow through the dialyzer. *C*, Single-pump system with a compliance bag pressurized by a spring, allowing a more constant venous flow than in the usual setup (Figure 11.1a). *D*, Single-pump system with six clamps, described by Leppert, in which the pump is continuously running and is alternately switched into the arterial and venous branch (clamps in active venous phase shown). (BP = blood pump, Cl = clamp, Co = compliance chamber, Cos = compliance sac, p = pressure sensor, D = dialyzer, a = arterial, and v = venous.)

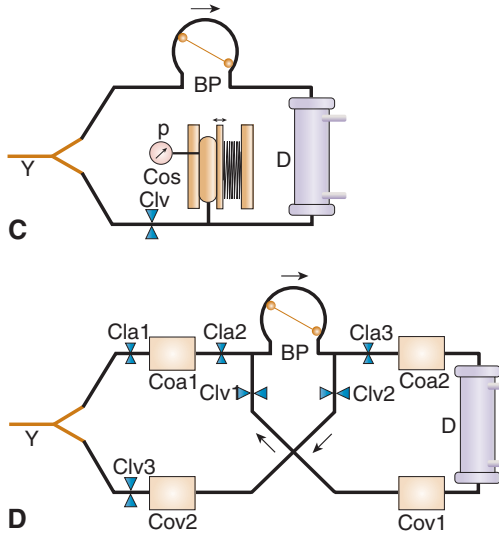


Figure 11–4

Cont'd

clamping required for proper function in both lines. However, currently used systems have always at least the venous clamp (downstream of the venous air detector). Furthermore, the use of clamps—especially if they are located close to the needle—can reduce compliance effects that contribute to recirculation (see material following). Systems with more than two clamps are rare (see Figure 111.4d, in which four of six clamps are required for switching the single pump between arterial and venous line in order to avoid a second pump).

The Efficiency of Single-Needle Dialysis Systems

The clearance of uremic toxins achievable with SND systems is limited especially as a consequence of the alternating-flow scheme. In addition, recirculation is increased against DND at the same average blood flow—which further decreases clearance. Many efforts have been made to improve the efficiency of SND

systems, within the inherent limitations just mentioned. Maximizing the average blood flow is an obvious requirement. Some designers of SND systems have assumed that achieving a continuous or even constant flow would increase clearance. These issues are discussed in more detail in the following.

Clearance Limitation Due to Alternating-Flow Scheme

SND systems can use only about half the dialysis time for moving blood from the patient to the dialyzer. This derives from the fact that both the blood extracted from and returned to the patient have to pass the same lumen, and the achievable average blood flow Q_M in SND is only about half the DND flow. When switching a patient from DND to SND, there is about a 50% loss in clearance if the flow in the arterial and venous phases remains the same as the flow used before in DND. This loss could of course be reduced by increasing Q_A and Q_V. However, the potential to increase blood flows is usually small in conventional dialysis. The limiting factors are that Q_A and Q_V should not exceed fistula flow Q_F, and that there is a risk that higher flows may cause fistula damage and mechanical hemolysis of blood cells. Typically, average flows of only Q_M = 200 to 250 mL/minute are achievable.

Clearance Reduction Due to Recirculation

A second disadvantage of SND is that clearance is further reduced by the presence of recirculation, which tends to be higher than in DND. Additional recirculation is inherent to SND.[7] At the beginning of the arterial phase, the volume in the needle or catheter (between Y-connection and access) is still filled with cleared blood from the venous phase. This blood volume is then pumped back to the dialyzer and is thus recirculating. This first component of recirculating volume V_{REC1} is quite small (typically 0.1–0.2 mL for a cannula if special SN cannulas are used; approximately 1 mL for a catheter).

The second component of recirculating volume V_{REC2} derives from the compliance of the tube system. At the end of the venous phase, the tube system around the Y-connection (between the arterial and venous occlusions at a length of approximately 2–3 m) becomes somewhat extended by the positive venous pressure. At the beginning of the arterial phase, the pressure becomes negative and the tube system slightly collapses. The volume

difference between extended and collapsed states is to a large extent also recirculating volume. This volume depends also on flow rates and needle type, because both largely affect the pressure change. A separate line for arterial pressure measurement further increases V_{REC2}. A typical V_{REC2} of 3 to 10 mL has been reported,[1] with up to 50% contribution from the arterial pressure measurement line. V_{REC2} could be largely reduced by using an arterial and venous clamp positioned very close to the Y-connection. However, such clamps introduce additional discomfort for the patient and have rarely been used.

The third component of recirculating volume, V_{REC3}, derives from access recirculation. Assuming a blood access by fistula or graft, access recirculation in DND is flow of cleared blood from the venous to the arterial needle (which occurs if the extracorporeal flow Q_B exceeds the access flow Q_F). In SND, access recirculation arises if Q_F does not meet the flow demand during the arterial phase ($Q_A > Q_F$). In this condition, cleared blood—which has been returned to the access during the previous venous phase and is now located downstream of the needle—is moved back into the needle (unless the access vessel collapses).

Whereas access recirculation in DND can be avoided if $Q_F > Q_B$, it is obvious that SND at the same average flow $Q_M = Q_B$ requires at least twice this access flow ($Q_F > Q_A = 2 \times Q_M = 2 \times Q_B$) to avoid access recirculation. However, the situation in SND is even worse. Even if Q_F slightly exceeds Q_A, some cleared blood (which entered the access vessel from the needle at the end of the venous phase) may be sucked back immediately at the beginning of the arterial phase because the cleared blood was not swept away fast enough. It was recommended[7] that $Q_F \approx 1.5 \times Q_A$ should be used to avoid this effect. Therefore, if a Q_M of (for example) 250 mL/minute is used the access recirculation would exceed 50% at an access flow Q_F = 250 mL/minute, would still be some percent at Q_F = 500 mL/minute, and would reach 0% at about Q_F = 750 mL/minute.

The total recirculation R depends on the recirculating volumes and the stroke volume V_S: $R = (V_{REC1} + V_{REC2} + V_{REC3}) / V_S$. Recirculating volumes are largely dependent on flows Q_A, Q_V, and Q_F ; on V_S; on arterial and venous pressures during the cycle; on choice of access device; and on position of the access device in the access vessel. Even without access recirculation, R may reach 6 to 30% for stroke volumes of 30 to 50 mL. Using high flows (Q_M = 200–250 mL/minute) in combination with accesses delivering low flows (Q_A< 400 mL/minute) may lead to an excessively high R and thereby unacceptable clearance

reductions. These arguments demonstrate that the risk of a clinically very significant reduction in toxin removal due to recirculation is higher in SND than in DND. Monitoring the access function and avoiding unrecognized loss in clearance is therefore highly recommended. Modern systems using larger stroke volumes achieve $R \approx 5$ to 10% in the case of sufficient access flows Q_F.

Maximizing the Average Blood Flow

SND systems have limitations in achieving larger clearances, as explained previously. Therefore, it is essential to achieve the highest possible average blood flow Q_M if SND is used for standard dialysis therapy—with about 3 times 4 hours of treatment weekly. Achievable flows Q_A and Q_V are limited by access performance, maximum possible cannula dimensions, and the increasing risks of hemolysis and access vessel damage at high flows. Under these restrictions, a maximum Q_M can be achieved if both Q_A and Q_V are constant and at an acceptable upper limit for the patient.

Single-pump setups with a Windkessel compliance chamber are less appropriate for this purpose. They show a largely decreasing flow in the venous phase (Figure 11.2b). Because already the maximum flow at the beginning of the venous phase should not exceed the maximum Q_V, the achievable mean Q_V and thereby the mean Q_M are significantly lower than in double-pump setups (Figures 11.2b and 11.2c). A higher Q_M can be achieved with single-pump setups if other compliance chambers are used that show a more constant pressure-volume characteristic (in contrast to that shown in Figure 11.3)—as with, for example, elastic bags or specific systems for pressurizing bags. Such compliance chambers allow at least a reduction in the variability of Q_V, but do not seem as yet to be widely used (probably for practical reasons).

Continuous or Constant Blood Flow Through the Dialyzer

Several of the more complex setups of the extracorporeal circuit designed for SND had the aim of providing a continuous or even constant flow through the dialyzer. This was achieved, for example, by a third pump providing constant flow (Figure 11.4b)—or by two compliance chambers, upstream and downstream of the dialyzer, providing nonconstant but continuous

flow. The underlying assumption for such designs was that a more continuous flow through the dialyzer is beneficial for solute removal and leads to a higher average clearance than the discontinuous flow achieved with simpler setups. A more detailed analysis,[6,8] however, shows that this is not correct. To provide an explanation, toxin molecules of a specific type (e.g., urea) in a small volume segment of blood that just enters the dialyzer are examined in the following.

The toxin molecules move from blood into dialysate by diffusion, perpendicular to the dialyzer axis along a concentration gradient. The fraction of molecules that reaches the dialysate compartment during passage of the dialyzer depends essentially on the time t_P the molecules remain within the hollow fibers (aside from molecular weight). As long as t_P does not change, the fractional toxin removal is largely independent of whether the blood flow through the dialyzer Q_D is constant or whether Q_D shows a discontinuous pulsatile flow scheme (e.g., $Q_D = 0$ during arterial phase, $Q_D = 2 \times Q_M$ during venous phase).

Under typical conditions of a stroke volume V_S = 40 mL, a dialyzer blood compartment volume of V_D = 100 mL, and the mentioned pulsatile flow scheme, the volume segment entering the dialyzer would experience two to three arterial phases with $Q_D = 0$ within the dialyzer, and venous phases of length $V_D / (2 \times Q_M)$. At a Q_M of 200 mL/minute leading to a cycle time t_C = 12 seconds, passage time would be (15 + 2 × 6) seconds = 27 seconds or (15 + 3 × 6) seconds = 33 seconds—both of which are close to the passage time under constant-flow conditions of 30 seconds. Therefore, a significant deviation of the clearance under pulsatile and constant-flow conditions would not be expected.

Generally, the variability in passage time increases with increasing ratio V_S/V_D. If V_S approaches V_D or even exceeds V_D, the variability becomes large. For example, for V_D = 80 mL and V_S = 100 mL there would be zero to one arterial phases with $Q_D = 0$—leading to passage times between 12 and 27 seconds (compared to 24 seconds under constant-flow conditions). Under such conditions, the pulsatile flow scheme can lead to lower clearances than the constant-flow scheme. However, as long as $V_S < 0.5 \times V_D$ (which is usually the case) both schemes show practically identical clearance levels for small molecules as urea. There are even studies demonstrating that pulsatile flow may lead to less protein deposition on the membrane and to higher clearances for larger molecules compared to constant flow with the same average flow Q_M. Probably pulsatile flow

promotes convective exchange between blood and dialysate compartement, which increases clearance. The conclusion from these considerations and investigations is that the complexity and high costs of SND setups for achieving continuous or constant flow appear to be unjustified.[8]

Advantages and Disadvantages of Single-Needle Dialysis

The obvious advantage of SND in the case of using needles for blood access is that only one needle has to be inserted. This is of benefit to the patient, who experiences less puncture-related trauma, and to the nurse. In addition, there have been several reports that the 50% reduction in the number of punctures required when switching from DND to SND leads to a similar reduction in access-related problems. Such problems may also depend on the technique of access puncture. However, it seems generally accepted that less frequent punctures lead to less damage of the access vessel and to increased access survival.

SND provides an inherent safety feature in the case of needle dislodgement. In the case of venous needle disconnection in DND, the dialysis machine continues to extract blood from the patient without returning it—which can rapidly lead to a life-threatening condition. However, needle disconnection in SND will lead to aspiration of air into the extracorporeal circuit. The machine will alarm within a short time, as soon as the air reaches the venous level detector.

SND is superior to DND when a catheter is used for blood access.[6] Using an SLC requires the use of an SND machine setup, whereas a double-lumen catheter (DLC) is operated with an DND setup. The SND setup is preferable because SLCs are superior to DLCs with respect to dialysis efficiency. Twice the flow can be achieved with SLCs (assuming the same outer diameters). The flow through a lumen is proportional to the pressure drop along the lumen and inversely proportional to the square of the lumen cross section (strictly, only in the case of circular cross sections; Hagen-Poiseulle law). The maximum flow (at the maximum allowed pressure drop) through the SLC is therefore approximately four times as high as through the DLC (because the ratio of the lumen cross sections of SLC and DLC is approximately 2). Because only half the time can be used for pumping blood to the dialyzer using the SLC, the average flow that can be achieved with the SLC is about twice the flow achievable with the DLC. An SLC in combination with SND

therefore allows us to achieve much higher clearances and is therefore preferable. The same argument holds when comparing the single-lumen SN access with the rarely used double-lumen SN access.

Aside from these advantages, SND has a considerable number of disadvantages versus DND. The main disadvantage certainly is the restricted clearance. As discussed in the previous chapter, the maximum achievable clearance in SND is less than half the maximum DND clearance due to the alternating-flow scheme and the increased recirculation. This is still true if the SND system has been optimized for achieving high clearances (e.g., by using a double-pump setup with $Q_A = Q_V$, the optimal needle and filter, and so on). In consequence, SND is not appropriate for high-efficiency dialysis.

When SND is used in a standard thrice-weekly dialysis setting, relatively high average flow rates have to be used to achieve a sufficient toxin removal (about Q_M = 250 mL/minute and more, depending on urea distribution volume, treatment time, dialyzer clearance, and so on). SND in such a standard therapy setting is therefore an "at-the-limits" treatment, quite different from conventional DND. Q_A and Q_V are very high, as well as the absolute arterial and venous pressures. The risks of access damage and subclinical or even severe hemolysis[9] are increased due to the high and pulsatile flows and excessive pressures. In addition, a much higher access flow is required to avoid access recirculation. A careful selection of components (especially the access needle or catheter) and a monitoring of access flow and pressures are strongly recommended to avoid the previously mentioned complications.

Backfiltration has also been discussed as a possible disadvantage of SND in earlier years.[10] Several of the setups of the extracorporeal circuit led to largely varying transmembrane pressures during the SN cycle, promoting backfiltration of dialysis fluid into blood strongly during part of the cycle. However, modern dialysis machines produce ultrapure dialysate and therefore back-filtration of such high-quality dialysate into blood is no longer a problem for the patient and does not need to be avoided. This conclusion is further supported by the fact that (according to Polaschegg) the undesired transport of possible dialysis fluid contaminations also occurs by back-diffusion from dialysis fluid into blood (which frequently has been ignored). The transport by back-diffusion usually strongly exceeds the transport by back-filtration. Because back-diffusion is unavoidable in hemodialysis, the reduction of back-filtration alone cannot

efficiently avoid the transport of contaminants into blood.[6] With the use of sterile dialysis fluid, back-filtration is no longer a relevant problem of SND.

Another disadvantage is that many physiologic monitoring and control features of the dialysis machine available for DND are not available for SND. Since the beginning of the 1990s, several devices (e.g., for measurement of recirculation and access flow, for dialysis dose, and for control of blood volume and body temperature) have been introduced. An adaptation of such systems for SND is technically difficult because the physical parameters (e.g., temperature, optical density, and conductivity) measured in the extracorporeal circuit are subject to large oscillations caused by the alternating-flow scheme and recirculation effects. Many of the systems are not usable in SND mode, and the therapeutic benefits of these systems are therefore not available for patients on SND.

Another potential disadvantage is the increased technical complexity of SN systems (and therefore increased treatment cost). The additional technical components required to perform an SND largely depend on the specific setup used. For example, in setups providing constant blood flow through the dialyzer (Figure 11.4b) technical complexity is high—whereas the currently used setups (Figure 11.1) have a moderately increased complexity versus the DND setup.

It is essentially the treatment mode that determines whether the advantages of SND outweigh its disadvantages. Whereas in higher-efficiency treatments (e.g., standard hemodialysis) SND is clearly inferior, the restricted clearance and the limitations in using monitoring and control equipment become less relevant in treatments with long weekly dialysis times (especially with nocturnal dialysis or continuous therapy).

Clinical Applications of Single-Needle Dialysis

In conventional hemodialysis treatment, with three treatments of about 4 hours weekly DND is the dominating therapy mode—and SND clearly is not recommended due to the poor achievable clearances. Even when high flows Q_A and Q_V of 400 to 500 mL/minute are used, a sufficient dose of dialysis can only be achieved in patients with low weight. Nevertheless, the use of SND may be temporarily required under specific conditions. As long as the patient has to be dialyzed using a central venous catheter because of critical blood access or ongoing access revi-

sion, SND is the preferred treatment mode (as explained previously). SND also must be performed if the access allows the placement of only one needle (e.g., due to infections or stenoses of the access).

However, especially in such accesses requiring the use of SND, it is often not possible to achieve high flows. Therefore, fistulas or grafts not appropriate for placement of two needles should be revised if possible—to switch back to the more efficient DND mode. SND should not be regarded as a long-term treatment option for patients with critical access. If SND cannot be avoided, it is especially important to carefully check whether a sufficient dialysis dose is achieved. Specific caution for the timing of taking blood samples for urea kinetic modeling is required to avoid inconsistent results caused by the alternating-flow scheme.[11]

In consequence of the previously mentioned applications, SND is a less often (but not rarely) used therapy mode in a standard hemodialysis setting. In a study on type and surveillance of vascular accesses in the Netherlands,[12] it was reported that SND in 1996 was frequently used in 14% of patients (and occasionally in another 7%)—probably reflecting a relatively high frequency of access problems requiring catheter use. Forty-six percent of the dialysis centers preferred SLCs (requiring use of SND to DLCs). SND was more often used in the earlier years of hemodialysis, before the limitations of this mode in toxin removal became obvious. According to Hoenich,[4] 42.3% of treatments in Europe in 1978 were SND treatments—with highest use (60.3%) in Belgium. Today, standard hemodialysis machines can usually be retrofitted with SN equipment. Most holiday dialysis units offer SND.

There are a number of other dialysis therapy modes in which the low achievable clearance of SND is not a problem. Generally, these are modes in which the total weekly dialysis time is much higher than the standard time of approximately 12 hours. For example, the continuous therapy in patients with acute renal failure is performed at lower flows. SND with a single-lumen central venous catheter appears to be the recommended treatment mode. In nocturnal dialysis for chronic patients, there is no need for high blood flows due to the long duration and/or high frequency of treatments.

Especially for daily overnight home hemodialysis, SND has often beeen mentioned as the optimal choice of access—and has been used in several home dialysis studies. The inherent safety against undetected blood loss is another strong argument for using SND. The probability for needle disconnection may be regarded as especially high if the patient prepares for dialysis

alone, and the risk of a lethal outcome also is increased if the patient is alone during the treatment. Still another argument for using SND in daily overnight home hemodialysis is that the number of punctures required weekly (6×1) is kept on the same level as in standard DND (3×2), which avoids additional damage to the access due to the increased treatment frequency.

Several specialized home hemodialysis machines are already on the market. Some of them allow one to perform SND. A technical problem that has in part been addressed by some device manufacturers is the noise generation during the nocturnal application. Noise generated by pumps and clamps of SND systems should be low enough not to prevent the patient from sleeping.

There are also some applications of the SN technology outside dialysis (e.g., in apheresis or hemoperfusion procedures).

Summary

SND has been in the picture during the entire history of dialysis. Even the first treatment by Kolff was an SND (despite its not having many similarities to today's extracorporeal circuits for SND). Systems more similar to current setups have been described by Twiss (1964), Kopp (1972), and Ringoir (1974). However, SND certainly has not been a key topic in scientific discussions and technical development in recent years. A search in PubMed revealed only 21 papers between 1990 and the beginning of 2006, and only 9 papers since 1994 (in several of these papers SN is only a side topic). A search of current congress abstracts reveals that there are hardly any contributions related to SND.

It appears that much of the complexity introduced during the historic development of SND technology is no longer required today: The issue of backfiltration is not relevant if sterile dialysis fluid is used. Continuous or constant flow has been shown to have no advantages. Therefore, SND is a treatment option today performed with the relatively simple technical setups shown in Figure 11.1—with reliability and safety of operation being the primary requirements. SND has well-known restrictions for use in standard and high-efficiency therapy, but is well suited for applications in which high clearances are not required.

References

1. Polaschegg HD, Levin NW. Hemodialysis machines and monitors. In Hörl WH, Koch KM, Lindsay RM, Ronco C, Winchester JF (eds), *Replacement of Renal Function, Fifth Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2004:325–449.

2. Kopp KF, Gutch CF, Kolff WJ. Single-needle dialysis. ASAIO Trans 1972;18:75–81.
3. Van Waeleghem JP, Boone L, Ringoir S. New technique on the one needle system during hemodialysis. Proc EDTNA 1973;1:10–16.
4. Hoenich NA, Downing N, Pearson S, et al. Review of mechanical systems for single-needle dialysis. In Ringoir S, Vanholder R, Ivanovich P (eds), *First International Symposium on Single-Needle Dialysis*. Cleveland: ISAO Press 1984:22–37.
5. Leonard EF. Flow patterns of single-needle dialysis. In Ringoir S, Vanholder R, P Ivanovich (eds), *First International Symposium on Single-Needle Dialysis*. Cleveland: ISAO Press 1984:13–21.
6. Polaschegg HD. Single-needle technik: Neu überdacht. Aktuelle Nephrologie 1994;3:685–92.
7. Gotch FA. Models to predict recirculation and its effect on treatment time in single-needle dialysis. In Ringoir S, Vanholder R, Ivanovich P (eds). *First International Symposium on Single-Needle Dialysis*. Cleveland: ISAO Press 1984:47–62.
8. Polaschegg HD, Wojke R. Constant blood flow during single-needle dialysis is unnecessary. Int J Artif Organs 1993;16(7):505–09.
9. Dhaene M, Gulbis B, Lietaer N, et al. Red blood cell destruction in single-needle dialysis. Clinical Nephrology 1989;31(6):327–31.
10. Giorgetti M. Backfiltration (BKF) in single needle dialysis. EDTNA-ERCA Journal 1997;23(3):41–44.
11. Wright MJ, Lindley EJ, Swales D, et al. Consistent timing of the post-dialysis blood sample is necessary to prevent undertreatment in single needle dialysis. Nephrol Dial Transplant 2000;15(4):554–55.
12. Ezzahiri R, Lemson MS, Kitslaar PJEHM, et al. Haemodialysis vascular access and fistula surveillance methods in The Netherlands. Nephrol Dial Transplant 1999;14:2110–15.

CHAPTER 12

Safety Monitors in Hemodialysis

Joanne D. Pittard, MS, RN

Hemodialysis monitors include machines, devices, protocols, and personnel. The major goal is to ensure patient safety during the hemodialysis procedure. All tasks that check, observe, keep track of, and control the hemodialysis treatment are monitoring procedures. These important tasks are too often lightly dismissed. This chapter focuses on the fluid delivery system and extra-corporeal circuit, their respective monitoring devices, and their functions, locations, performance standards, and management. Monitoring of the patient and hemodialysis prescription pre-, during, and postdialysis are covered in other sections of this book.

Definitions and Overview

The fluid delivery system is commonly called "the machine." The fluid delivery system prepares a body temperature electrolyte solution called dialysate. The dialysate flows through the dialysate compartment of the dialyzer (artificial kidney), where dialysis occurs. A blood pump circulates the patient's blood through the extracorporeal circulation (outside the body) to the blood compartment of the dialyzer and back to the patient. The two major categories monitored are the dialysate circuit and blood circuit. We can easily remember these categories by associating them with their respective fluid pathway.

Dialysate Circuit

The function of the dialysate circuit is to:

- Prepare the dialysate solution for safe exposure to the patient's blood
- Monitor the dialysate for conductivity and temperature
- Circulate the dialysate through the dialyzer
- Regulate ultrafiltration by volumetric control of the dialysate
- Monitor the effluent dialysate for blood leaks prior to going to the drain

Blood Circuit

The function of the blood circuit is to:

- Circulate the blood outside the body through the dialyzer
- Anticoagulate the patient's blood
- Maintain blood in a sterile state
- Monitor the extracorporeal blood circuit for arterial and venous pressures and the integrity of the circuit for the presence of air and blood leaks

The blood circuit consists of a blood tubing set (arterial and venous), blood side of the dialyzer, intravenous (IV) normal saline and administration line, and heparin syringe and infusion line. The blood and dialysate are separate circuits that interface at the dialyzer membrane. The machine design must involve extensive monitoring of both circuits. Specific warning alarms must be initiated when the machine's preset limits are exceeded and/or an unsafe condition exists.

Single-Patient Machinery

The vast majority of dialysis facilities in the United States use single-patient fluid delivery systems. This type of equipment is self-contained, preparing dialysate only for the individual machine. Some dialysis facilities use central delivery systems with central manufacture of dialysate. Although that system is more economical, it is less safe than the individual machines. The discussion here focuses on single-patient machinery. A few safety issues unique to a central delivery system are explored.

Control Panel and Monitor Display

All modern fluid delivery systems have a frontal control panel (Figure 12.1) by which pressure and other limits may be set and system parameters may be viewed. The control panel and monitor display on the face of the machine will have audible and visual warning alarms as a mandatory part of safe dialysis monitoring.

Monitor Failure

Machine monitors are either mechanically or electrically operated, or a combination of both. All monitors can fail. Murphy's law (If anything can go wrong, it will) should be remembered and accepted as fact. Murphy's law is attributed to an engineer

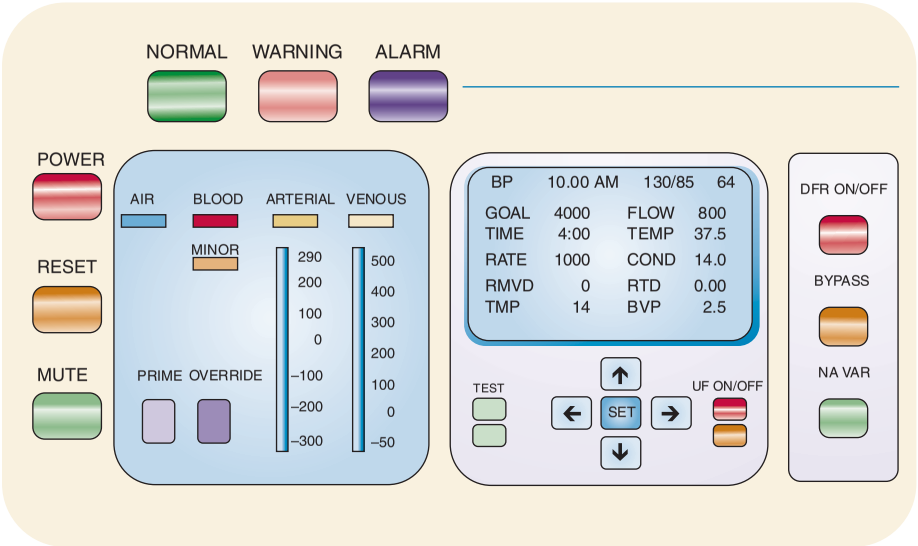


Figure 12–1

Control panel and monitor display. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

working at the Los Alamos laboratories in the 1950s. The truth of this statement can be reworded to "If you can think of a possible disaster with the present equipment, take the necessary precautionary steps immediately or it will happen." If one can access misadventure and incident reporting, virtually every possible projected failure of a monitor has occurred and has resulted in patient/staff injury or death.

Fail-safe, a Misnomer

Machine monitors are frequently thought to be fail-safe devices, but they are not. A truly fail-safe device cannot be overridden to cause harm either by electronic or human intervention. By this narrow definition, there are no fail-safe dialysis machine monitors. Because all dialysis machine monitors can fail, they ought to be simple to operate and accurate—and should signal a warning when they are out of limits or not working properly. Any important factor requires dual monitoring: the machine monitor device and dialysis personnel. No machine, computer, or device can replace the continuous surveillance of hemodialysis personnel.

Dialysate Circuit

Figure 12.2 displays components of the dialysate fluid path. Dialysate monitoring includes prescription, composition (conductivity and pH), temperature, flow, pressure, effluent, absence of impurities (cleaning and disinfecting agents), potential pyrogenic agents, and microbiologic testing. Each monitor or control is discussed in order of the usual flow of fluid, from the water inlet solenoid valve to the effluent dialysate drain line.

Why Discuss the Details of Dialysis Machinery?

Each dialysis treatment exposes the end-stage renal disease (ESRD) patient's blood to hundreds of liters of dialysate. The dialysate should be of pharmaceutic grade because dialysate is essentially an intravenous (IV) solution. The machinery that manufactures dialysate can silently and quickly cause a patient serious injury or death because of contaminants or incorrect solute concentration. Even more distressing, if the machinery manufactures a substantially hypotonic fluid but at a concentration that does not cause hemolysis the patient may rapidly develop

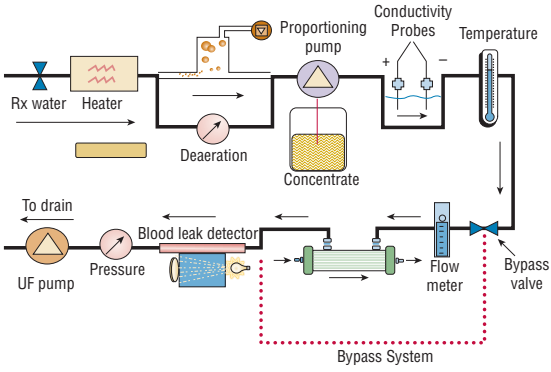


Figure 12–2

Fluid pathway simplified. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

water intoxication, cerebral edema, seizures, and noncardiogenic pulmonary edema—signs and symptoms that the dialysis staff will misinterpret as requiring more ultrafiltration and more dialysis!

With current therapy using blood flow rates of 300 to 450 mL per minute (mL/minute), the entire patient's circulating blood may be exposed to toxic chemicals or a hemolytic state in less than 15 minutes. Death can be both swift and the cause undiagnosed, even with postmortem examination. Each component of the dialysate circuit discussed, if it malfunctions, may induce hemolysis.

Water Inlet Solenoid and Monitoring

The water inlet solenoid permits the flow of treated water into the dialysis machine when the main power switch is activated, and stops the flow when the main power is turned off. Treated water enters the machine via a water inlet valve with water pressure usually between 20 and 105 pounds per square inch (psi). The treated water for hemodialysis must meet the Association for the Advancement of Medical Instrumentation (AAMI) standards.

Not all machines have a water inlet solenoid. Allowing water to flow into the machine without activating the machine's main power switch can cause problems in bacterial buildup in that portion of the fluid pathway.

The inlet water pressure can be measured using a dial-type manometer. This mechanism may malfunction or leak in the On or Off position. There are neither published performance standards nor standard alarms for this device. Many machines have a continuous audible warning alarm, to alert the staff of problems. If an alarm condition exists that indicates inadequate water flow or pressure, its role may be to prevent water from being overheated by the water heater. Overheated dialysate causes gross hemolysis.

Heater and Heater Monitoring

The heater raises the temperature of the incoming water to approximately body temperature. Heating partially degasses the cold water, which improves the mixing of water and dialysate concentrate. A thermistor feedback circuit usually controls the electrical heating elements. The heater may have a coarse adjustment control inside the machine and a fine adjustment control on the front panel. There may be a simple bimetallic dial thermometer within some machines, which although not alarmed provides visual observation of its function. Internal factory-set controls should limit dialysate temperature to between 33 (92) and 39°C (102°F). The fine adjustment control knob on the front panel of the machine should not be capable of overriding this setting.

Deaeration System and Monitoring

The deaeration system removes dissolved gases by exposing water to subatmospheric pressures generated by a vacuum pump. The gases coalesce, form bubbles, and are vented to the atmosphere by a bubble trap. Improper or inadequate removal of dissolved gases in dialysate can be a hidden cause of several serious dialysis problems, including the following.

- False blood-leak alarms
- False conductivity alarms
- Interference with volumetric control function
- Decreased dialysis efficiency by air bubbles trapped on the dialyzer membrane that reduces functional dialyzer surface area

Frequent false blood-leak alarms or rapid fluctuations in conductivity can indicate a malfunction of the vacuum pump. The machine should be removed from service and undergo maintenance. If the dialysate inflow and/or outflow lines are not correctly attached to the dialyzer, air can be pulled into the system. Proper technique by the dialysis staff who set up the dialysis machinery prior to dialysis and who secure the quick disconnects of the dialysate lines on the dialyzer dialysate ports will prevent this problem.

Mixing Device and Monitoring

The mixing device, also known as the proportioning system, proportions treated water and dialysate concentrate to create dialysate of the correct ionic concentration. The proportioning system ratio depends on the type of dialysate concentrate used and the type of fluid delivery system. Typical mixing ratios of *water* to *dialysate* concentrate are:

- 34:1 or 44:1 for acid concentrate
- 20:1 or 25:1 for bicarbonate concentrate

The supply of treated water and dialysate concentrate generates dialysate flow rates between 500 and 1000 mL/minute. The two basic types of proportioning systems are fixed-ratio mixing and servo-controlled mixing. Fixed-ratio mixing uses diaphragms or piston pumps to deliver a set volume of water and concentrate to the mixing chamber. Servo-controlled mechanisms continuously monitor the dialysate composition with conductivity sensors that adjust the amount of concentrate mixed with water to maintain a variable or set composition.

In machines that add concentrate by a servo-controlled mechanism until the dialysate reaches a desired conductivity, a second independent conductivity and pH monitor must cause an alarm if the conductivity is incorrect. If acid and bicarbonate inputs are reversed, or if the wrong concentrates are used for a bicarbonate machine, the servo loops may make a solution of acceptable ionic strength (correct conductivity) but of lethal ionic composition. In this case, the pH monitor or concentrate pump speed monitor becomes critical. However, not all machines are equipped with pH monitors and this deadly event will not be diagnosed. The conductivity and pH monitor will verify proper mixing with a fixed-ratio proportioning system. Equipment using servo-controlled mechanisms requires a diligent and trained staff to ensure that the proper dialysate concentrate is attached to the proper concentrate lines on the machine.

Dialysate Prescription and Monitoring

Dialysis personnel must confirm that the physician's orders prescribing the dialysate content match the delivered prescription of dialysate. The dialysate prescription is not static. Some physicians model and individually tailor sodium, potassium, calcium, magnesium, and dextrose. A major problem with using many individualized dialysate formulas in one facility is the increase in risk of error by personnel. The more variables that exist in a dialysis unit the greater the inherent risk of staff errors.

Staff must check and verify all dialysate concentrate containers for the appropriate content. Each container must be clearly labeled. No unlabeled dialysate concentrate container should be used. Labels must include each electrolyte; the amount, time, and date mixed; and the name of the person performing the task. All additives must be properly recorded on the labels. This is especially important for the bicarbonate concentrate that must be used within a 24-hour period after mixing. The correct dialysate concentrate must be attached to the correct concentrate port on the dialysis machine.

Composition and Conductivity of Dialysate

Analysis of the dialysate for the proper composition is necessary after it has been mixed and prior to exposing it to the dialyzer and patient. All modern fluid delivery systems have conductivity cells and meters. Total conductivity of dialysate is measured as a simple assessment and surrogate for dialysate ionic content. A conductivity cell is connected to a meter that displays the total ionic concentration of dialysate. Conductivity cells should be made of high-quality corrosion-resistant materials. The conductivity of an electrolyte solution increases as the temperature increases. Conductivity cells used to monitor dialysate should be temperature compensated.

Measuring Conductivity

In dialysis, conductivity is usually measured using a two-electrode system. The electrodes are connected to a constant current and an ammeter (Figure 12.3). An electric current is passed through the solution between the electrodes. The ammeter measures the flow of current (the inverse of electrical resistance) that passes through the solution between the electrodes. The conductivity measurement is an estimate of the total ionic

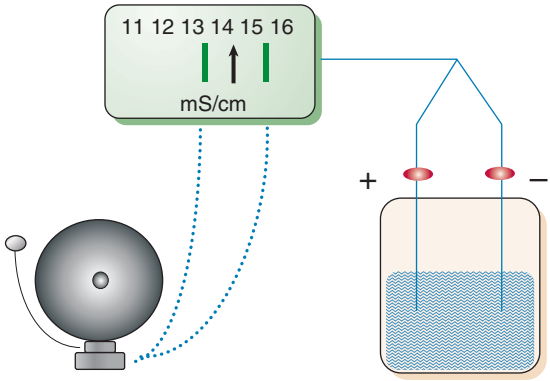


Figure 12–3

Conductivity monitor. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

content of the dialysate, and does not measure or reflect specific ions or electrolytes. The conductivity meters usually read the conductivity in millimhos per centimeter (mmhos/cm) or milliSiemens per centimeter (mS/cm). A range of 12.5 to 16.0 mS/cm is acceptable for a standard dialysate solution. This range varies slightly from facility to facility, depending on the dialysate formula in use.

Monitoring Conductivity

Conductivity meters on dialysis machines have external and internal limits set. Some machines may have three internal conductivity sensors set at different intervals of control. The conductivity, or dialysate ionic composition, is so important that this monitoring redundancy is a commonsense safeguard against single-monitor failure. The closest-tolerance internal high/low limits are set at ±5%. The last set of conductivity monitoring may be set at 50% of normal conductivity. If the first two monitors fail, the patient (without any alarms being triggered) will receive a massive infusion of hypotonic dialysate. Because different mixtures of ions have different conductivities, it is

mandatory that the dialysate formulas determine the established conductivity setting.

All facilities must have an established acceptable conductivity range, and this range should be publicly posted. Any deviation in the conductivity limits set should cause a conductivity alarm. A conductivity alarm causes three actions on the dialysis machine: an audible alarm, a visual alarm, and activation of the bypass system. The bypass system diverts the dialysate to the drain before it can enter the dialysate inflow line leading to the dialyzer. Thus, exposure of the patient's blood in the dialyzer to an incorrect or unsafe dialysate composition is avoided.

No Intradialytic Conductivity Adjustments

Only a qualified and trained machine technician should adjust the external or internal conductivity limits. Under no circumstances should they be adjusted during the dialysis treatment. They must be properly adjusted and preset before the dialysis treatment. Serious and fatal accidents have occurred due to improper adjustments of the conductivity limits. It is advised that readings of the conductivity meter for accuracy be taken by performing an independent analysis of the dialysate. This must be done before preparing the dialyzer for patient use and before the dialysis treatment is initiated.

The most common method of performing an independent analysis of the machine's conductivity is the use of various portable conductivity meters that measure the total conductivity. Another option less used is to send a dialysate specimen for laboratory analysis that measures each electrolyte level. When using independent analysis, be sure that the reference conductivity meter is calibrated accurately before use. All standard solutions should be fresh and should render acceptable readings. If independent verification of the dialysate conductivity does not validate the conductivity meter, do not dialyze the patient with that machinery. A complete resolution of the problem is necessary before dialysis. Failure to resolve a problem before dialysis only invites a potential disaster. It is best to bring in another dialysis machine and start over.

Low Conductivity and Monitoring

A low-conductivity alarm is the most common type of conductivity alarm (Figure 12.4). The usual cause is a lack of concentrate in one or both acid and bicarbonate concentrate

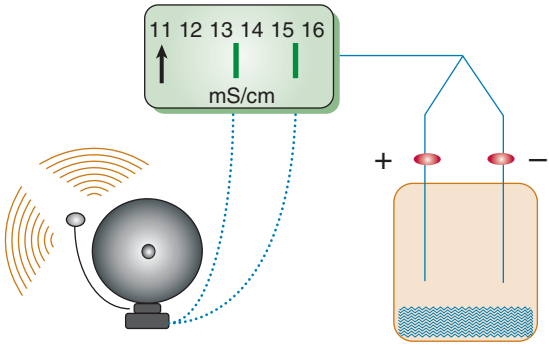


Figure 12–4

Low-conductivity alarm. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

containers. Rarely, a low-conductivity alarm is due to incorrect dialysate concentrate. If the internal or external low-conductivity limits are not adjusted properly and/or the machine does not go into the bypass mode, the patient's blood is exposed to hypotonic dialysate. Exposure to hypotonic dialysate can be fatal within a few minutes. Hypotonic dialysate causes a hypo-osmolar state, and even without acute hemolysis water intoxication can occur—which can also be lethal.

There must be an adequate amount of dialysate concentrate in the container(s) before starting dialysis. Dialysis staff should not rely on the conductivity meter to monitor dialysate concentrate supplies. Although hypotonic dialysate can be deadly, the dialysis staff's response to this alarm is invariably nonchalant and cavalier.

True, if the dialysis machine goes into the bypass mode there is no harm to the patient. However, when the dialysis machine is in the bypass mode no dialysis is taking place and the time lost on dialysis is rarely if ever made up with a longer dialysis time the next dialysis session. If one accepts that the average dialysis in the United States comprises not the maximal amount of dialysis time but probably the minimal amount of dialysis time, placing the dialysis machinery in bypass routinely will shorten the patient's life span. Newer-model fluid delivery machines have

timers that stop with a dialysate circuit alarm. This ensures that the patient receives their allocated time on dialysis.

High Conductivity and Monitoring

High-conductivity alarms (Figure 12.5) can result from inadequate water flow to the proportioning system, untreated incoming water with an excess of calcium, or incorrect hookup of dialysate concentrate to the dialysis machine. A common serious cause of high conductivity occurs when two acid concentrate containers are connected to the dialysis machine instead of one acid container to the acid port and one bicarbonate container to the bicarbonate port. If the dialysis machine goes into bypass mode, there is no harm to the patient. However, if the internal or external high-conductivity limits have not been set correctly the patient's blood is exposed to hypertonic dialysate—with the possibly of a hyperosmolar coma ensuing.

Newer-model fluid delivery systems have automatic built-in adjustment of conductivity limits for sodium variation, which causes an increase in conductivity. If sodium variation is done incorrectly, the patient will leave dialysis thirsty and in a hyperosmolar state and will attempt to relieve that thirst with free

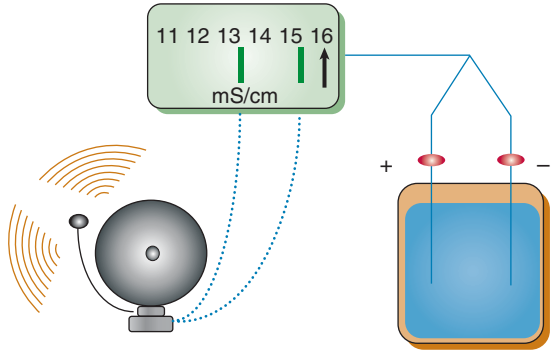


Figure 12–5

High-conductivity alarm. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: [publisher] 2003, with permission.)*

water. That will result in a marked expansion of their extracellular volume, which can lead to malignant hypertension.

If a conductivity alarm occurs during the dialysis treatment, the bypass mode is activated. While correcting the alarm condition, the dialysis staff must not adjust the external or internal conductivity limits. Adjusting the conductivity limits during an alarm condition overrides the bypass mode and endangers the patient's life. If the alarm situation cannot be corrected, the treatment must be stopped and the patient moved to another dialysis machine.

Acid-Base (pH) Control and Monitoring

Most newer-model fluid delivery systems will not go into conductivity if the pH is too high or too low. However, the majority of dialysis clinics still perform independent pH tests before each dialysis. Fluid delivery machines using bicarbonate dialysate may or may not have pH monitors. There may be a pH meter on the front display panel with lights that activate when an alarm condition occurs.

The pH of dialysate is commonly checked by use of a pH paper test strip or bicarbonate pH test strips. With the pH paper test strips, the color change of the dialysate-soaked test strip is compared with a list of colors for various pH values. The bicarbonate pH test strips interpret the results by comparing the indicator pad to the color chart on bottle labels. An acceptable range for test results is a pH of 7.5 ± 0.5 (7.0–8.0). If the pH is below or above the acceptable limits and the conductivity meter is within acceptable limits, do not dialyze. Both the pH and conductivity must be in acceptable limits before initiating dialysis.

Bypass System, Monitoring, and Rinse Mode

The bypass system diverts dialysate (Figure 12.6) directly to drain away from the dialyzer to avoid exposure of the patient's blood to unsafe dialysate. The dialysate bypass valve (located in the incoming dialysate circuit pre-dialyzer) is activated by high/low conductivity, high/low pH, or high/low temperature. It is imperative that dialysis staff verify and check that the bypass valve diverts the dialysate to drain.

There is no monitor for its failure or function on most machines. A light on the front panel of the machine indicates when the machine is in the bypass mode. In addition, an audible

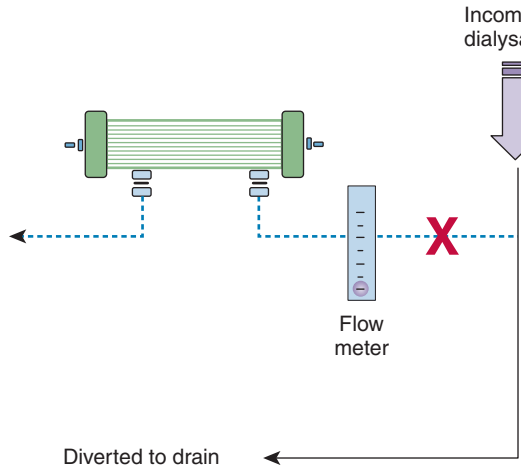


Figure 12–6

Bypass valve activated. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

alarm usually occurs. If there is a float located in the dialysate inflow line (indicating flow), the float will drop to the bottom of the indicator. There is usually a manually operated control to initiate the bypass mode. Failure of the bypass valve during dialysis is a critical and dangerous situation.

The rinse mode on dialysis machines overrides the bypass system. It allows rinsing and disinfection of the entire fluid pathway. It should never be activated while a patient is on dialysis. In newer-model machines, the blood pump cannot be activated when the machine is in the rinse mode. However, this is not true for all dialysis machines in use today.

Dialysate Temperature

The dialysate temperature is usually maintained between 37 and 38°C (98.6 and 100.4°F) throughout the dialysis treatment. An internal temperature sensor (Figure 12.7) monitors the dialysate temperature continuously. In some cases, the actual temperature

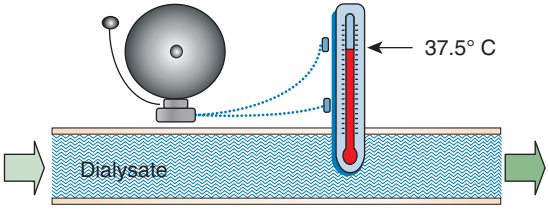


Figure 12–7

Dialysate temperature. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

reading is displayed on the front panel of the machine. Other machines have lights on the front panel that indicate an alarm condition. Most fluid delivery machines have high and low temperature monitor alarms. Some older-model machines have only high-temperature alarms. If the high or low internal temperatures exceed the preset internal limits, three actions result: an audible alarm, a visual alarm, and activation of the bypass mode.

Temperatures Greater Than 106°F

The usual causes of high dialysate temperature are either a malfunctioning water heater with a temperature controller or a water flow restriction. The internal high limit should be set at no higher than 41°C (105.8°F). Normal red blood cells (RBCs) begin to hemolyze at 42°C. Overheated dialysate has been known to precipitate cardiac arrhythmias.

Although it is true that the efficiency of diffusion during dialysis is increased with increased dialysate temperature, without excellent electronic temperature monitoring this is a dangerous way to increase dialysis efficiency. Under no circumstances should the high limit be adjusted above 41°C. Several articles in the literature suggest that the upper limits be set at 42°C (107.6°F), which is probably too high and may cause hemolysis. It should be remembered that uremic RBCs are more osmotically fragile and have a shorter half-life than normal RBCs. It is reasonable to assume that these uremic

RBCs are more sensitive to all mechanical and thermal causes of trauma than normal RBCs.

Temperatures Less Than 98.6°F

Some nephrologists use lower-temperature dialysate in the belief that this promotes a more stable blood pressure response to high ultrafiltration. If low-temperature dialysate is used, the total dialysis time needs to be increased by about 8% for every 3°C below 98.6°F because that is the theoretical loss in diffusivity with temperature decrease. Low dialysate temperatures may induce venous vessel spasm and make it impossible to obtain maximum blood flows through the artificial kidney. With dialysate temperatures below 98.6°F, patients will complain of being cold and ask for a blanket—and some will actually shiver in an attempt to increase their core body temperature. An increase in cardiac irritability in patients with coronary vessel disease may be observed.

Microbiology

The dialysate solution is very clean, but not sterile. Most dialysis facilities in the United States use reverse osmosis systems to filter the feed water. Theoretically, the product water should be sterile. It is very pure. However, as the water courses through the plastic piping of the dialysis unit to the dialysis machine and traverses through the fluid pathway it comes in contact with bacteria, endotoxins, pyrogens, and other impurities.

All fluid pathways in the dialysis machines must be routinely rinsed, cleaned, and disinfected. The rinsing and cleaning process keeps the internal environment of the dialysis machine clean and free of cellular debris or deposits for proper operation. The disinfection eliminates bacterial growth and prevents the risk of pyrogen reactions. The same is true for all dialysate concentrate containers that store dialysate concentrate. Each dialysis facility uses different techniques to achieve this end.

Inadequate cleaning and disinfection of the water treatment system, dialysate delivery system, and dialysate concentrate containers leads to high bacterial counts. Inadequate disinfection can be due to lack of frequent disinfection, too low concentrations of cold chemical disinfectants, and inadequate contact time of the disinfectant.

Microbiologic Monitoring

Monitoring is done to check for the presence of bacteria and/or endotoxins (Table 12.1). Microbiologic monitoring tests for the presence of live bacteria. A water sample is placed in a culture media and incubated for one or more days. The number of living bacteria in a set volume is reported as the colony count or colony-forming units per milliliter (cfu/mL). Microbiologic monitoring requires that the total viable microbial counts are not to exceed 200 cfu/mL in water used to prepare dialysate, or 2000 cfu/mL in proportioned dialysate exiting the dialyzer. Microbial test results must be documented. Microbial counts exceeding the industry standards require analysis and a more frequent and vigorous disinfecting routine. It is recommended that action be taken if levels exceed 50 cfu/mL for water (Table 12.1).

AAMI requires a minimum of once-a-month testing. The testing is to validate the proper disinfection of equipment. The sample for testing the fluid delivery system is taken "at the termination of dialysis at the point where dialysate exits the dialyzer." Industry standards recommend additional sampling. Samples from dialysate concentrate containers and mixing tanks should be taken after the longest time period between disinfection of these containers and after the longest storage time for the concentrate.

Test for Endotoxins

Endotoxins are bacterial lipopolysaccharides. They are substances released from cell walls when a microorganism is broken down or dies. Their origin is usually from gram-negative

Table 12–1

Microbiological Monitoring

Fluid	Bacteria (CFU/mL)	Endotoxin (EU/mL)
Water to prepare dialysate, to reprocess dialyzers, and to prepare germicides	< 200	< 2.0
Dialysate exiting dialyzer	< 2000	< 5.0
Bicarbonate concentrate	< 200	< 2.0
Minimum testing frequency	Monthly	Monthly

bacteria. The presence of endotoxins is measured using the limulus amebocyte lysate (LAL) assay. The LAL concentration should be less than 2 endotoxin units (EU) per milliliter (< 2 EU/mL). It is recommended that action be taken if levels exceed 1.0 EU/mL.

Bacteria in Bicarbonate Concentrate

Acid dialysate concentrate is bacteriostatic. However, the bicarbonate powder used to make bicarbonate concentrate can be contaminated with bacteria, molds, and/or pyrogens. Failure to properly clean and disinfect all areas where water and dialysate travel leads to bacterial growth, usually pseudomonas, in the fluid pathways.

Pyrogens

High bacterial counts predispose to pyrogen reactions. The most common type of pyrogen is from fragments of dead bacteria. However, any type of cellular debris (even if it is sterile) can cause pyrogen reactions. An increase in pyrogen reactions is associated with the use of high-flux dialyzers and bicarbonate dialysate. The lack of adequate removal of bacteria and bacterial end products from the dialysate solutions and/or fluid pathway of the dialysis machines is invariably the principle cause of these pyrogenic reactions. Dialysis facilities that practice scrupulous water disinfection and control, even with reuse of dialyzers, have virtually no pyrogenic reactions.

Some literature invokes the increased porosity of the high-flux membrane to whole bacteria as a substantial cause of pyrogen reactions. However, even in dialysis units using reprocessed high-flux dialyzers correcting the high microbial counts of the feed water and delivered dialysate invariably eliminates all pyrogen reactions.

Cleaning and Disinfection

It would seem obvious that cleaning and disinfection of the dialysis machinery should only be done after all patients have been completely disconnected. Although obvious, there are several reported instances of patients being “bleached” or “cooked” when the respective cleaning procedure was begun before all patients were disconnected.

Central System Hazard

A central fluid delivery system that services more than one room carries the enormous risk of this lethal misadventure. A careful and thorough bed and chair check by two individuals must be performed to verify that no patient is on dialysis in that setting.

Routine Cleaning

Routine cleaning of fluid delivery systems is accomplished by rinsing with purified water (AAMI standard) and acid cleaning of the fluid pathway on a daily basis. Acid cleaning minimizes the buildup of calcium precipitate associated with bicarbonate dialysate. Acid cleaning does not disinfect the machine. Acid cleaning is accomplished with the use of acetic acid (5%) or vinegar, citric acid, peracetic-based disinfectants, and acid concentrate. A minimum of a 5-minute water rinse is recommended before acid cleaning. A thorough rinse of the dialysis machine must be done before patient use or chemical disinfection. Acetic acid can easily be tested for residuals by using pH test paper.

Fluid Delivery System Disinfection

Disinfection of the fluid delivery system is done by heat and/or chemical disinfection. Disinfection is done usually once each week, or more often if necessary. Frequency of disinfection depends on routine bacterial counts and the orders of the medical director. Samples for bacterial counts should be taken before disinfection.

Heat Disinfection

Certain model fluid delivery machines are equipped to use heat disinfection. In most cases, this is done on a daily basis. Heat disinfection occurs with water heated to about 85°C in the internal fluid pathway of the dialysis machine. The average length of heat exposure is about 30 minutes. It is important to follow the manufacturer's recommendations. If the machine is to be used following heat disinfection, it is critical to allow the proper cooling-down cycle before patient use. Most machines using heat disinfection have a built-in safety feature that will not allow the machine to go into the "dialyze" mode until the temperature has dropped below 42°C.

Chemical Disinfection

Chemical disinfection may be done with a variety of chemicals. The most common chemical disinfectants in use are sodium hypochlorite, peracetic acid, and formaldehyde. A thorough water rinse is essential when using corrosive chemicals for disinfection. When using chemical disinfectants, it is important to remember that all disinfectants require a certain amount of contact time. High microbial counts in water require longer contact times. Fluid pathways that have dead spaces, blind loops, or inactive dialysis stations that are improperly shunted to drain are especially hazardous. All dead spaces are difficult to disinfect. All machines require labeling with a sign indicating the presence of the chemical disinfectant and the need for residual testing before the disinfection is deemed complete.

Sodium Hypochlorite

Sodium hypochlorite (bleach) is a cold disinfectant. It is available in different concentrations ranging from 5 to 10%. The advantages of sodium hypochlorite are its low cost, its effectiveness, and its safety. Free chlorine is a strong oxidant. It effectively cleans and eliminates any cellular debris in the fluid pathway that may interfere with the machine operation.

Residual testing for sodium hypochlorite is simple and done with chlorine reagent test strips that test down to 0.5 parts per million (ppm). The residual test is very sensitive. Sodium hypochlorite in minute amounts greater than 1:25,000 produces hemolysis. Some dialysis units clean their bicarbonate concentrate plastic containers with bleach but do not carefully rinse or test for residual chlorine before refilling with bicarbonate concentrate. This allows bleach to be dialyzed into the patient, causing a low-level persistent hemolysis that is ignored or attributed to functional iron deficiency. Failure to perform residual testing will result in acute hemolysis or slow hemolysis that may go undetected.

Formaldehyde

Formaldehyde is a cold sterilant that effectively kills all microorganisms, including spores and resistant viruses, when used in proper concentrations and given adequate contact time. There are several reports of serious to deadly septicemia, with inadequate formaldehyde concentrations being used to disinfect the fluid path of dialysis machinery. It is the most common periodic disinfectant used for fluid delivery systems.

It is an inexpensive and stable solution with a long shelf life. Formaldehyde is a gas that is dissolved in water to form the compound formalin. Formalin is the saturated solution of formaldehyde in water. A 100% formalin solution is equivalent to 37 to 40% formaldehyde. In dialysis, a 4% formaldehyde (11% formalin) concentration is used.

Concentrations lower than 4% formaldehyde do not adequately kill *Mycobacterium chelonae* in water. The formaldehyde gas is irritating to the eyes and has an offensive odor. Gloves must always be worn when handling formaldehyde to prevent dermatitis and allergic sensitivities. The room must be well ventilated. Any splashing must be minimized. A face shield gives total protection to the face. Minimally, eye protection (goggles) must be worn when handling formaldehyde.

Formaldehyde has no cleaning properties. Formaldehyde denatures protein and fixes most cellular debris. Therefore, before its use the fluid pathway requires water rinsing and use of another chemical substance to remove any existing cellular debris and deposits. The fluid pathway of the fluid delivery machines is filled with formaldehyde after cleaning to destroy all microorganisms. Generally, the formaldehyde is left in the machines overnight for effective contact time.

Sensitive residual testing is now available. Indicator test strips are now on the market to test for residual formaldehyde to a sensitivity of 1.0 ppm. The same principles apply to this cold sterilant as described for peracetic acid. In the past, safety tests for formaldehyde used Schiff's reagent. Schiff's reagent will test to 5 ppm. The newer indicator test strips are more sensitive. There have been several outbreaks of feed water being contaminated with residual formaldehyde, which led to a number of dialysis patients on single-patient machines becoming seriously ill with shock, coma, and semilethal consequences.

Peracetic Acid

The use of a stabilized mixture of peracetic acid, hydrogen peroxide, and acetic acid is probably the cold sterilant of choice for fluid delivery systems. Unlike formaldehyde, this mixture leaves no toxic residues. It decomposes into oxygen and acetic acid after reacting with organic material. The odor is pungent—similar to the smell of vinegar. The mixture of peracetic acid, hydrogen peroxide, and acetic acid acts as a cleaning agent in addition to a cold sterilant. The mixture is a strong oxidant that readily cleans all cellular debris, precipitates, and scale in the machines when used routinely. As a cold sterilant, it is effective

with an 11-hour contact time. Because it is a strong oxidant, the manufacturer's recommendations must be followed carefully so that materials in the machines will not be adversely affected.

Test strips are available to check for the presence or absence of the peracetic acid mixture. Indicator test strips ensure the presence of this cold sterilant in the machines. After the peracetic acid mixture is rinsed from the machine, residual test strips test for the absence of the peracetic acid mixture. The residual testing is very sensitive, testing down to <1 ppm.

Because the peracetic acid mixture is a strong oxidant, its handling requires careful attention to avoid chemical burns. Gloves and face protection are mandatory. Accidental contact exposure to this chemical requires water flushes and medical attention similar to those described for formaldehyde. Regardless of the type of cleaning or disinfecting agent used in the facility, a thorough water rinse must be done prior to adding chemicals and after cleaning and disinfection. Safety tests must be done after the final rinse to validate the absence of the chemical used. It is dangerous to rely on a timed rinse without the use of a valid safety test. Residual testing prevents patient injury due to chemical exposure.

Dialysate Pressure Monitor and Management

The dialysate pressure monitor monitors ultrafiltration pressures. It is a critical function of dialysis therapy that ensures accurate and safe fluid removal from the patient. One method of regulating the patient's ultrafiltration is by application of transmembrane pressure (TMP). Calculating the TMP is explained in the chapter on pre- and posthemodialysis assessment. This applies to conventional fluid delivery systems. Newer machine models have ultrafiltration/volumetric control circuits. The dialysis personnel set the goal for the desired fluid removal, set the duration of dialysis, and activate the ultrafiltration control mode. The machine will automatically calculate and apply the required transmembrane pressure to achieve the desired ultrafiltration.

Volumetric control systems have different design features. A common design uses balancing chambers to precisely measure fluid volume entering and leaving the dialyzer. These machines automatically adjust the TMP. Volumetric control systems use matched pumps, usually diaphragm pumps. The pumps are controlled by valves and are integrated after proportioning of dialysate. Valves located above and below the balancing chambers open and close to direct the flow of fresh and used

dialysate. Fresh dialysate is pushed out to dialyzer, whereas used dialysate is pushed out to drain. The two chambers alternate functions, creating a constant flow of fresh dialysate. The system is a closed loop, with both chambers exactly balanced. Air is removed from the used dialysate, in a separation chamber, to ensure accurate measurement.

To ensure proper functioning of matched pumps and appropriate sealing of the valves, it is recommended that a pressure-holding test be performed pre-dialysis. This tests the integrity of the diaphragms to ensure that they are free from defects or flaws. Bad valve seals can cause inaccurate ultrafiltration that is potentially catastrophic with high-flux dialyzers. These tests can be performed manually or automatically, depending on the machine model.

Blood-Leak Detector and Monitoring

This monitor functions by transmitting filtered or unfiltered light through a column of effluent dialysate that has exited the dialyzer (Figure 12.8). Tears or leaks in the dialyzer membrane cause RBCs to leak into the dialysate, interrupting the light transmission. The machine response to a blood-leak alarm is

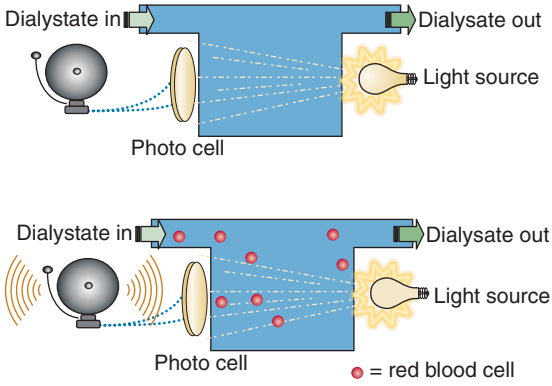


Figure 12–8

Blood-leak detector. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

to effect audible and visual alarms, stop the blood pump, and engage the venous line clamp. It is recommended that a blood-leak detection threshold be set at 0.25 to 0.35 mL of whole blood per liter of dialysate. False blood-leak alarms can be caused by the presence of air bubbles in the path or by cloudy or dirty optical lenses.

If the machinery indicates this alarm, a stat Hemastix (benzidine test strip) must be taken at the dialysate drain line. A positive Hemastix test indicates a blood leak. If the Hemastix is weakly positive and the patient is on a hollow-fiber dialyzer, it is possible to closely monitor the patient, observe the dialysate outflow for increased turbidity (indicates air bubbles or RBCs), and wait a few minutes. The leaking fibers may seal or clot off. During this time, remove the ultrafiltration, decrease the blood flow rate, and attend the patient on a one-to-one ratio. If the patient cannot be continuously monitored, replace the dialyzer.

If the repeat Hemastix is negative, continue dialysis. If the blood-leak alarm continues, or if blood is visible in the dialysate lines, stop dialysis and change the dialyzer per-unit protocol. The dialyzer should be discarded. After a blood leak, it is important to clean the optical path of the blood-leak detector. Always maintain a narrow range of sensitivity. Do not dialyze a patient with a faulty blood-leak detector. A major blood leak can be fatal.

Dialysate Flow and Monitoring

The dialysate flow rates may be preset or adjustable. The usual dialysate flow rate for conventional dialyzers is a minimum of 500 mL/minute. For high-efficiency and high-flux dialyzers, it is usually 700 to 800 mL/minute. It is counterproductive and provides an inefficient dialysis to use high blood flow rates with a high-efficiency or high-flux dialyzer with a dialysate flow of less than twice the blood flow rate. Adequate dialysate flow is essential for an efficient dialysis. These alarm conditions include low incoming water pressure to the machine, dialysate pump failure, and obstruction in the flow path and power failure.

Most machines have a continuous audible alarm with these conditions. There usually are no alarms that alert the staff when the dialysate flow rate is set too low (e.g., at 500 mL/minute instead of 800 mL/minute). Dialysis personnel must be diligent in monitoring this aspect. Dialysis personnel must monitor the dialysate effluent line to the drain to ensure that it is not obstructed and that it is properly placed in the drain. An obstruction can

cause back-pressure into the dialysate compartment and may decrease the dialysate flow rate.

Electrical Safety

Dialysis machines pose a risk of electrical shock to a patient or staff member. All electronic equipment must be inspected and tested on a periodic basis. The staff members, most frequently in the patient care areas, must accept responsibility for identifying and reporting any potential hazardous conditions. All electric components should be adequately isolated from liquid leaks and the outside of equipment shielded from liquid spills. Electric components must be plugged into the correct socket, and grounded plugs used. Electrical safety classes and safe use of equipment is mandatory for all dialysis personnel.

The Blood Circuit

The blood (extracorporeal) circuit (Figure 12.9) monitors pressures in the arterial and venous bloodlines, and the integrity of the circuit for the presence of air and blood leaks. The four

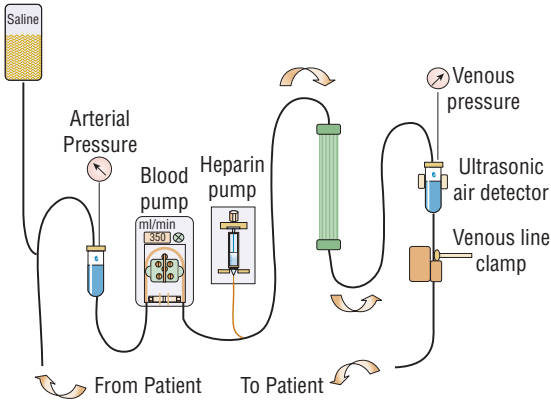


Figure 12–9

Blood (extracorporeal) circuit. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

main blood circuit monitors (Figure 12.10) are arterial pressure monitor, venous pressure monitor, air-foam detector, and blood-leak detector. The blood-leak detector acts as a blood circuit alarm but is entirely incorporated within the dialysate circuit and has already been described. The machinery responds to blood circuit alarms by effecting audible and visual alarms, stopping the blood pump, and engaging the venous line clamp to stop the blood flow through the blood circuit. Additional areas to monitor in the blood circuit are blood flow rate, heparin therapy, and normal saline supply.

Arterial Pressure Monitor and Pre-blood Pump

The arterial pressure monitor measures the pressure in the arterial bloodline between the patient's arterial access and the blood pump (Figure 12.9). With the blood pump set to blood flow rates greater than 200 mL/minute to as high as 450 mL/minute, the pressure in this blood tubing segment is commonly subatmospheric to negative. This portion of the blood circuit can

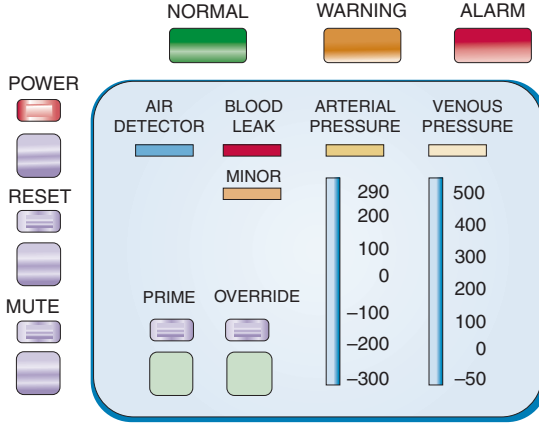


Figure 12–10

Blood circuit monitors. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

be a source of air entry into the blood circuit and is considered a high-risk area.

The arterial pressure monitor is leak free, with adjustable high/low limits (Figure 12.11)—which read negative and positive pressures in mmHg (10% accuracy). This monitor requires a filter to prevent viruses, bacteria, or blood from being refluxed back into the arterial pressure monitor. This filter is essential because viral hepatitis has been transmitted by contamination of air devices. These filters or fluid barriers are called isolators and/or transducer filters/protectors. They protect the monitor from blood contamination and the spread of infection between patients. Make sure the pressure monitor lines are unclamped and patent during dialysis. Some bloodlines have collapsible pillow-shaped segments, which can initiate a false alarm.

During setup, priming, and rinsing of the dialyzer, the high/low limits are opened. As soon as the dialysis treatment is initiated, the dialysis personnel must set the low (or negative) pressure limit just below the reading at the desired blood flow. Upper and lower monitor limits should be set within 50 to 100 mmHg of actual reading to detect problems. Newer-model machines will automatically adjust the high/low limits approximately 50 mmHg above and below the actual pressure. Setting the low arterial limit close to the actual pressure (about 50 mmHg below that pressure) will detect early drops in blood pressure with arteriovenous (AV) fistulae. Some units limit the minimum arterial limit to –100 mmHg.

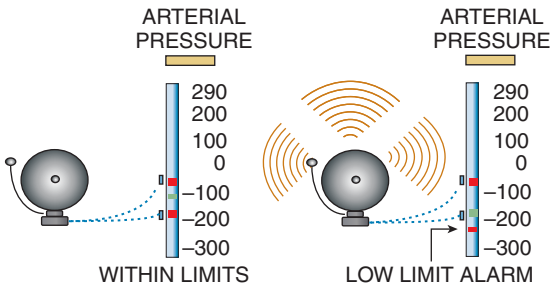


Figure 12–11

Arterial pressure. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

The greater the vacuum the greater the risk of air entering this tubing segment from any crack, improperly glued or fitted joint, sample port, saline infusion line, or patient's access. It is advisable to set the high limit just below zero, which will pick up a disruption of the arterial bloodline from the fistula needle. The usual causes of a low-limit arterial pressure alarm are a drop in blood pressure (only with AV fistulae), a kink in the arterial bloodline between the access and blood pump, malpositioned arterial needle or problem with arterial access, and a clotted arterial line. Always check the circuit for air bubbles.

The usual causes of a high-limit arterial pressure alarm are bloodline separation (only if the upper limit is set below 0 mmHg), an unclamped saline infusion line, an increase in patient blood pressure, a leak in the circuit between patient and monitor, and torn blood tubing in the pump segment. It is important to check for leaking blood. The appropriate response to pressure alarms is to mute the audible alarm, investigate the problem, correct the problem, and restart the blood pump by pressing the Reset/Restart button. Do not restart the blood pump until the problem is corrected for patient safety. Failure to correct the problem will cause the alarm to reoccur.

Venous Pressure Monitoring

The venous pressure monitor, located post-dialyzer (Figure 12.9), monitors pressure at the venous drip chamber, the segment between the drip chamber and the patient's venous access, and the added intra-access pressure. The resistance to the blood flow entering the venous access causes the pressure to be positive (Figure 12.12), above 0 mmHg. The venous pressure monitor's structure and standards are similar to those described for the arterial pre-blood pump monitor. This pressure monitor requires protection by a filter or transducer fluid barrier.

Causes of a high-venous-pressure alarm are a kink in the venous bloodline between the drip chamber and the patient's venous access, a clot in the venous drip chamber and/or downstream to the patient, and a malpositioned venous needle or problem with the venous access device. Causes of a low-venous-pressure alarm are bloodline separation or disruption of connections between the blood pump to and including the venous access, a kink in the bloodline post-dialyzer and pre-venous drip chamber, a clotted dialyzer, and a lowering of the blood pump speed.

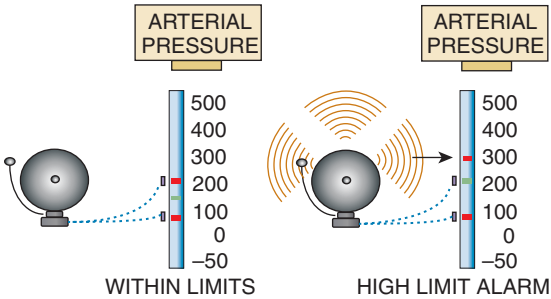


Figure 12–12

Venous pressure. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

Note that setting the low limit close to the operating pressure of the venous drip chamber can alert to a disruption of the blood circuit between the blood pump and venous access site. With a disruption of the circuit, the venous pressure will drop to 0 mmHg. It should be remembered that the venous pressure monitor reflects P_{BO} in the equation $TMP = P_{BO} - P_{DO}$. High venous pressures can result in ultrafiltration rates that are too high unless an ultrafiltration-controlled machine is being used.

Air-Foam Detector

The air-foam detector monitors blood in the venous tubing (Figure 12.13) for the presence of air, foam, and microbubbles. It must be reemphasized that with almost all internal AV fistulae/grafts and all venovenous dialysis a significant subatmospheric pressure exists between the arterial access and the roller pump. There are many junctions and heat-sealed joints in this portion of the circuit. If the heparin infusion line is in the negative-pressure segment rather than post–blood pump, it may increase the risk for air entry. After the blood pump, the blood circuit is at considerable positive pressure and air can enter only by pumping or injecting it into the remainder of the circuit. Air embolism is a preventable and very serious dialysis misadventure.

Two types of air-foam detectors are in use: the ultrasonic and the reflected light detectors. It is believed that only the

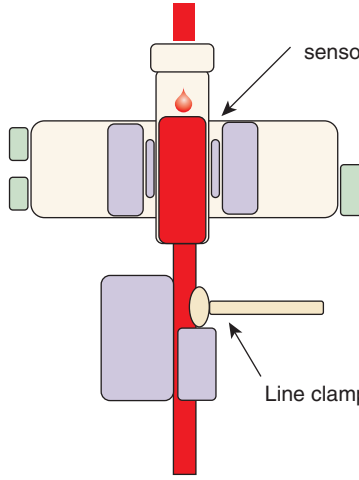


Figure 12–13

Air-foam detector. *(From Pittard J. Hemodialysis Nursing Training Manual, Seventh Edition. Santa Monica, CA: Hemodialysis, Inc. 2003, with permission.)*

ultrasonic device is currently being sold. Nevertheless, many of the reflected light devices are still in use. Surprisingly, there are no standards for permissible detection of air because either type of detector readily identifies gross air displacement of blood in the venous drip chamber when properly armed and functioning. Microbubbles from 5 to 500 μm in diameter represent a different problem because they stream along with the blood flow. These microbubbles are entrained in the bloodstream.

Although both types of monitors can detect microbubbles, their guaranteed detection requires a sensitivity setting that may result in many false alarms due to turbulence in fluid flow. The compromise is a sensitivity adjustment of the ultrasonic devices such that some false alarms occur that require the attention of dialysis personnel. In certain situations, entrained microbubbles can go undetected and cause clinical air embolism. The current standards for these devices require response to air in blood, a blood and saline mixture, or saline. Only the ultrasonic device can meet this requirement. A dangerous aspect of the reflected

light device is that it is effective only when sensing the whole blood of the patient. It cannot be accurately armed during priming, initiation, or rinsing.

Venous Line Clamp

An air detector alarm must activate the venous line clamp (Figure 12.13). The venous line clamp must completely occlude the venous bloodline and withstand an intraluminal pressure of 800 mmHg. The venous line clamp should be constructed as to not damage the bloodlines, and should not restrict the blood tubing when in an open position. The venous line clamp circuitry must interface with and stop the blood pump. Most integrated air-foam detectors meet all of these standards. There are dialysis machines that are unsafe because they include the ability to dialyze with both the air-leak detector and venous line clamp disarmed and only some marginal indication of this disarmed state.

Air-Foam Detector and Venous Line Clamp Monitoring

With an air-foam detector alarm state, identify that the venous line clamp is engaged and that the blood pump is stopped. Visually inspect the entire blood circuit from the venous access backward to the arterial end for the presence of air, foam, or microbubbles. Check the level in the venous drip chamber. It should be 3/4 full. Verify that the venous drip chamber is properly placed in its holder, that the level detector door is closed and latched, and that the mesh in the drip chamber is below the air detector. In addition, verify that the air sensors are clean. Always validate the absence of air before restarting the blood pump and disengaging the venous line clamp. If air is present, disconnect the patient from the extracorporeal circuit.

Before beginning dialysis, make sure that the air-foam detector is turned on and operational, and that the venous blood line is properly placed in the line-clamp holder. Ultrasonic devices are usually activated during priming of the circuit. Reflected light devices cannot be activated until whole blood at full hematocrit is in the venous tubing.

Because each brand of detector varies in its operation, ensure that dialysis personnel are aware of the type of device used in the facility and are in-serviced on its unique features and operation. Unfortunately, when staff pushes the Reset/Restart button in responding to this alarm condition the blood pumps restarts. This

can be a potentially deadly response. Microbubbles that may not be visible to the naked eye can then flow into the patient. The author advises staff to manually turn off the blood pump when responding to an air-in-blood alarm. After all inspections are complete, pushing the Reset button will not automatically start the blood pump. However, if the problem is not corrected the alarm will reoccur with no harm to the patient. Four alarm conditions are outlined here for general information.

- *Alarm condition 1:* Careful inspection reveals that the blood-air level in the venous drip chamber is normal and that there are no microbubbles (foam) in any portion of the line or dialyzer. This is a false alarm. Release the line clamp and reset the detector.
- *Alarm condition 2:* The blood level in the venous drip chamber has fallen. In response, check for upstream bubbles. If none are present, return the blood-air level to normal in the drip chamber with the usual technique, release the line clamp, and reset the alarm.
- *Alarm condition 3:* There are microbubbles (foam) in the venous line. In response, clamp the venous line and the venous access line, directing attention to the patient in the event that emergency management of air embolism is necessary. Another person should remove the line from the air detector clamp, disconnect the patient from the blood circuit, and aseptically join the arterial and venous ends of the blood circuit for recirculation. Remove ultrafiltration and open the saline to remove air from the blood circuit and to collect it in the venous drip chamber. If this measure is successful, place the venous line into the air-detector line clamp and rearm the air-foam detector. If no further alarm is activated, reconnect the blood circuit lines to the patient and reinitiate dialysis.
- *Alarm condition 4:* Gross air and bubbles fill the entire blood circuit, including the dialyzer. In response, clamp the *venous* line and direct attention to the patient for emergency management of air embolism. Dispose of the entire blood circuit, including the dialyzer, and set up a new one to reinitiate dialysis.

Heparin Infusion Pump and Monitoring

The heparin infusion pump is usually located post–blood pump segment. A heparin infusion line attaches to a syringe filled with heparin. This allows for the infusion of heparin

during dialysis. An electric motor drives a piston to move the heparin plunger forward to infuse the heparin. Dialysis personnel must turn the heparin pump on and set the correct hourly infusion rate. No alarms occur if the pump is not turned on or if an incorrect hourly infusion rate is set. Most machines have an audible alarm when the heparin level in the syringe is very low.

Personnel must make sure they are using the correct size of syringe based on the way the heparin pump is calibrated. Make sure the syringe and plunger are placed properly in the holder. Check that the pump is on and that the variable hourly rate is set correctly. Implement hourly checks to ensure the correct infusion of heparin therapy. Newer-model machines allow personnel to program the heparin bolus, infusion rate, and length of time for the infusion.

Blood Flow Rate and Monitoring

The blood flow rate is an important parameter that influences the efficiency of dialyzer clearance. All blood pumps have an on/off switch and an adjustable variable-speed pump. There are no machine alarms if the desired blood flow rate is not set correctly. Double check that the blood flow rate is properly set. A qualified person must calibrate blood pumps to ensure that the actual blood flow is comparable to the blood flow setting. The facility must use appropriate blood tubing size for proper occlusion of the roller pump. Inadequate occlusion causes backflow, foaming, and possibly hemolysis. Overocclusion causes tubing damage, blood leaks, and the potential for hemolysis.

Blood Pump and BloodLines

Narrowed Blood Pump Tubing Segment

In 1998, 30 patients in three different states in the United States developed hemolysis with or without chest pain, shortness of breath, nausea, or abdominal pain while undergoing hemodialysis. Two patients died. All of these catastrophes were due to a manufacturing defect in a small portion of the blood pump segment of the blood tubing. The staff did not notice the defect when inserting the blood pump segment. A marked narrowing of this segment induced massive hemolysis in

these patients, which initially was unexplained and required a formal investigation by the Centers for Disease Control and Prevention.

Kinked Arterial Blood Lines

In a 1-year period, from December 1989 to December 1990, 10 hemolytic reactions occurred in an outpatient hemodialysis unit. Eight patients were hospitalized and one died. All patients developed severe abdominal or back pain an average of 2.5 hours into a 4-hour hemodialysis session using bleach-formaldehyde reprocessed hollow-fiber Cuprophan dialyzers. All had visible hemolysis in a spun hematocrit, seven had a significant decrease in hematocrit, and six developed pancreatitis. Hemolytic reactions continued despite changing to 15-gauge needles, removing bleach from the reuse procedure, and stopping reuse of the dialyzers.

Investigation of each episode failed to find an abnormality in dialysate temperature or tonicity; dialysate or water levels of copper, zinc, nitrates, chloramine, or formaldehyde; or blood pump or venous alarm. On the eighth hemolytic episode, a dialysis staff member noted a kink in the arterial bloodline. Two subsequent hemolytic reactions occurred. In each, kinks were found in the arterial bloodline, either in the excess tubing between the blood pump and drip chamber or in the pre-dialyzer segment. No further hemolytic reactions occurred after changing to a new arterial bloodline without redundant tubing and after securing all lines.

IV Saline Infusion and Monitoring

Access to normal saline (0.9% NaCl) into the extracorporeal circuit occurs via the saline administration line located at the beginning of the arterial blood circuit. Normal saline is used to prime the dialyzer and blood tubing for patient use, to replace volume in the patient during dialysis, and to rinse out RBCs at the conclusion of dialysis. Personnel must make sure an adequate amount of normal saline is available for immediate use during the dialysis treatment. Normal saline drips should be discouraged. Although normal saline comes in collapsible plastic bags, if these accidentally empty during dialysis a few hundred milliliters of air will enter the blood circuit.

Summary

No amount of electronic machinery, fail-safe devices, flashing lights, sirens, dials, or protocols can take the place of an alert and well-trained dialysis staff member. Non-RNs or patient care technicians (PCTs) perform 75% of direct patient care of ESRD patients in the United States. The majority of PCTs have not received the benefits that RN education provides in terms of subject matter, patient assessment, or care of the ill. Many PCTs are only minimally trained to move quickly and to care for many patients with a minimum of nursing observation. No machinery or mechanoelectrical monitoring can take the place of a competent ESRD healthcare person.

Recommended Reading

Anonymous. Multi state outbreak of hemolysis in hemodialysis patients, Nebraska and Maryland, 1998. MMWR Morb Mortal Wkly Rep. 1998;47:483-4.

Bland LA, Arduino MJ, Aguero SM, Favero MS. Recovery of bacteria from reprocessed high flux dialyzers after bacterial contamination of the header spaces and O-rings. ASAIO Trans. 1989;35:314-6.

Curtis, James. Dialysis Technology, A Manual for Dialysis Technicians. 1st Edition. NANT. 1997;1-149.

De Palma JR. Bleach & Murphy's Law. Contemporary Dialysis & Nephrology. 1988 Aug; 9:30-31,39.

De Palma JR. Bicarbonate Dialysis & Water Treatment Contemporary Dialysis & Nephrology. 1988 Mar; 9:20-1,41.

Gutch, CF, Stoner, MH, Corea, AL. Hemodialysis for Nurses and Dialysis Personnel. 6th Edition. Mosby. ISBN: 0-8151-2099-0. 1999;40.

LaForce FM, Nelson M, Air-rinsing after dialysis. A mode of transmission of hepatitis virus. JAMA. 1975;233:331-5.

Lowrie EG, Lew N. The Urea Reduction Ratio (URR); A Simple Method of Evaluating Hemodialysis Treatment. Contemporary Dialysis & Nephrology. 1991;12:11-9.

Medicare Program. Standards for quality of water used in dialysis and revised guidelines on re-use of hemodialysis filters for end-stage renal disease (ESRD) patients HCFA. Final rule. Fed Regist. 1995;60:48039-44.

Nosé, Yukihiro, Manual on Artificial Organs. Volume I. The Artificial Kidney. CV Mosby Company. Saint Louis, Mo. 1969;1-343.

Pittard, JD. Blood & Uremia – 2000. Hemodialysis, Inc. ISBN 1-892265-02-8. 2000. 1-223.

Pittard, JD. Hemodialysis Nursing – Version 7.0. Hemodialysis, Inc. ISBN 1-892265-04-4. 2003.

Pittard, JD, De Palma, JR. Monitors. Hemodialysis, Inc. ISBN 1-892265-05-2. 2004. 1-168.

Pittard, JD, Principles of Dialysis – 2000. Hemodialysis, Inc. ISBN 1-892265-03-6. 2000. 1-120.

Sweet SJ, McCarthy S, Steingart R, Callahan T. Hemolytic reactions mechanically induced by kinked hemodialysis lines. Am J Kidney Dis. 1996;27:262-6.

Utoh J, Harasaki H. Damage to erythrocytes from long-term heat stress. Clin Sci. 1992;82:9-11.

Yu AW, Ing TS, Zabaneh RI, Daugirdas JT. Effect of dialysate temperature on central hemodynamics and urea kinetics. Kidney Int. 1995;48:237-43.

CHAPTER 13

Methods of Hemodialysis Anticoagulation

Patrick H. Pun, MD, and Eugene C. Kovalik, MD

Hemodialysis and continuous renal replacement therapies require extracorporeal blood flow, which exposes blood to surfaces with variable degrees of thrombogenicity. Some form of anticoagulation (usually with heparin) is required to prevent thrombosis, occlusion, and malfunction of the blood circuit. Characteristics of an ideal anticoagulant for use in hemodialysis include efficacy in preventing thrombosis during therapy, no increased risk of intra- and interdialytic bleeding, lack of other adverse effects, simplicity in administration, no or minimal monitoring requirements, and cost effectiveness. These characteristics will be examined for different regimens and modalities under various clinical scenarios in this chapter.

Despite the need for anticoagulation, all hemodialysis patients are at risk of bleeding due to platelet dysfunction related to the uremic milieu of advanced renal failure. Strategies to minimize the risk of bleeding include the use of low-dose heparin or no heparin with rapid blood flow. Regional anticoagulation with citrate, prostacyclin, and heparin-protamine have also been used with varying success. Real-time monitoring of anticoagulation is one way of ensuring the appropriate level of anticoagulation while minimizing bleeding risk.

For therapies using unfractionated heparin (UFH), anticoagulation during hemodialysis can be monitored by the determination of activated clotting times (ACTs), and rapid results can be obtained with point-of-care devices. However, ACTs are used infrequently because of the need to be rigorously standardized, resulting in quality assurance and regulatory issues. In general, most outpatient dialysis units do not routinely measure anticoagulation parameters unless there is an issue with dialyzer clotting or prolonged bleeding following dialysis. Except on rare occasions, we do not regularly monitor anticoagulation levels in the inpatient and outpatient facilities of our institution.

Standard Anticoagulation

Routine anticoagulation protocols typically utilize UFH, and a number of protocols exist to address the competing issues of clotting and postdialysis bleeding from venipuncture sites. A routine repeated bolus regimen usually consists of an initial bolus of UFH (usually about 40 U/kg body weight), followed by a mid-treatment dose of 1000 to 2000 U to maintain suitable anticoagulation.

Alternatively, heparin modeling can be performed using an initial bolus followed by a constant fixed infusion of heparin (usually 10–15 U/kg body weight/h) to maintain an activated clotting time of 200 to 250 seconds (normal = 90 to 140 seconds), which may be terminated prior to the end of treatment to reduce postdialysis venipuncture bleeding. This therapy ensures systemic anticoagulation throughout the dialysis treatment. It is reliable and requires minimal staff intervention after a patient's heparin dose is determined (based on ACT goals). Furthermore, in facilities that practice dialyzer reuse, incorporation of a pharmacodynamic approach to heparin modeling has also been shown to increase dialyzer reuse rate.

Some protocols use higher-bolus heparin doses (i.e., greater than 5000 U) with decreasing infusion rates as the treatment proceeds to minimize postdialysis bleeding. These methods require minimal staff intervention and are standard in most outpatient hemodialysis units. They are, however, unsuitable for patients with significant bleeding risks. The three commonly used standard anticoagulation regimens using UFH are summarized in Table 13.1.

Anticoagulation in Hemodialysis Patients at Risk for Bleeding

Conditions for which patients should be considered at increased risk for bleeding are outlined in Table 13.2. A number of alternative modalities have been used in these at-risk patients.

No-heparin Hemodialysis

No-heparin hemodialysis was developed for use in the patient at high risk of bleeding. Dialyzer and bloodlines are pretreated with 2000 to 5000 U of heparin contained in one liter of normal

Table 13–1

Commonly Used Standard UFH Anticoagulation Regimens

Regimen	Advantages	Disadvantages
Initial bolus 40 U/kg, repeated bolus 1000–2000 U midtreatment	Ease of administration, less postdialysis bleeding	Less effective for longer dialysis times
Initial bolus 40 U/kg, continuous infusion 10–15 U/kg/hr	Steady-state anticoagulation	May require monitoring, prolonged postdialysis bleeding
Initial bolus >70 U/kg, tapered continuous infusion	Steady-state anticoagulation, less postdialysis bleeding	May require monitoring, not suitable for pts with high risk of intradialytic bleeding

Table 13–2

Categorization of Bleeding Risk

Medium Risk	High Risk
Pericarditis	Bleeding diathesis
Recent bleeding <48 h	Clotting factor disorder
Recent placement of tunneled catheter <24 h	Actively bleeding lesion
Minor surgery <72 h	Eye or major surgery <72 h
Eye or major surgery within 3–7 days	Intracranial hemorrhage <7 days

Modified from Saltissi, D. Management of anticoagulation for hemodialysis. In *AR* Nissenson, *RN* Fine (eds.), *Dialysis Therapy*. Philadelphia: Hanley and Belfus 2002.

saline. The heparinized saline is flushed from the extracorporeal lines prior to the start of the dialysis treatment so that heparin is not administered to the patient. Extracorporeal blood flows are rapidly increased to 250 to 500 mL/minute and maintained throughout the treatment.

Twenty-five to 30 mL saline flushes are administered every 15 to 30 minutes into the arterial (pre-dialyzer) limb to minimize hemoconcentration and to wash fibrin strands from the dialyzer into the bubble trap. Of note, the volume of saline administered

must be removed during the dialysis to prevent volume overload. One-to-one nursing is required for administration of saline flushes and careful monitoring of the arterial and venous pressure alarms to detect early extracorporeal circuit clotting.

Using this technique, about 90% of intensive care unit patients with increased risk of bleeding who require hemodialysis can be successfully dialyzed with only a 2% clotting rate in the extracorporeal circuit. No significant loss of clearances has been reported compared to patients on standard anticoagulation. Disadvantages of this technique include the need for close nursing observation and the necessity to convert to minimum-dose heparin or to stop treatment in about 5% of cases. The results of a recent randomized clinical trial in stable HD patients suggested that saline flushes increase the degree of dialyzer circuit clotting and thrombosis compared to control treatments. However, the number of patients was small, and no patient had an increased risk of bleeding. Nevertheless, the advantages and disadvantages of this technique should be weighed carefully.

An additional problem with the no-heparin technique is that blood transfusions cannot usually be given through the dialyzer circuit due to the increased risk of clotting, which may pose difficulty for patients with limited peripheral access who require transfusion. A potential solution that has been successfully used is to utilize a large-bore stopcock to transfuse blood into the venous outflow (post-dialyzer) limb of the circuit.

Minimum-dose Heparin

The use of minimum-dose heparin has been shown to reduce bleeding complications in high-risk patients when compared to regional anticoagulation with heparin and protamine neutralization. The protocol involves boluses of 500 U of heparin every 30 minutes to keep the activated clotting time >150 but <200 seconds. Alternatively, a continuous infusion of heparin with frequent ACT monitoring can be used to achieve the same degree of anticoagulation. The major advantage of this technique is its simplicity. The major disadvantage is that some degree of systemic anticoagulation still occurs, necessitating careful monitoring.

Regional Anticoagulation with Protamine Reversal

The earliest method described to reduce hemodialysis-associated bleeding was regional anticoagulation with protamine reversal.

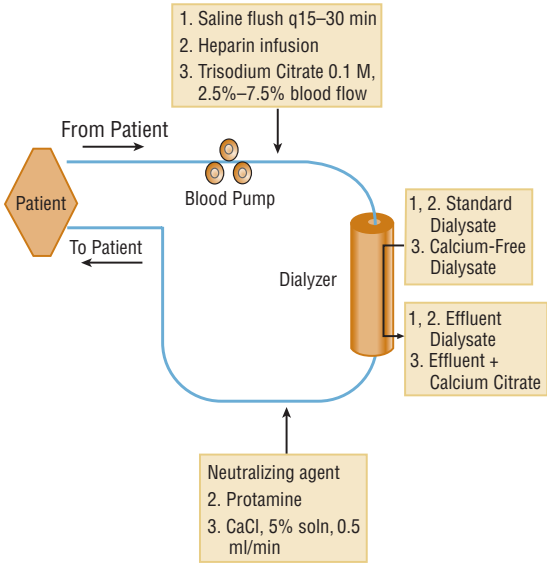


Figure 13–1

Schematic representation of hemodialysis anticoagulation modalities for patients at increased risk of bleeding. The modalities depicted are (1) no-heparin/saline flush, (2) regional heparin anticoagulation with protamine reversal, and (3) reginal citrate anticoagulation.

This procedure involves the constant infusion of heparin into the dialyzer inlet line and the simultaneous constant infusion of the neutralizing agent, protamine, into the venous (post-dialyzer) limb of the circuit to prevent systemic anticoagulation (Figure 13.1). The infusion pump rates are adjusted to keep the whole-blood activated clotting time in the dialyzer circuit at 250 seconds and the blood returning to the patient at its predialysis baseline.

Because of the technical difficulties and the release of free heparin from the protamine-heparin complex back into the general circulation 2 to 4 hours after the termination of dialysis (resulting in rebound bleeding), protamine reversal has been largely abandoned. In addition, simpler regimens consisting of minimum dose and no-dose heparin (as well as citrate regional

anticoagulation) have subsequently been developed that offer a lower incidence of bleeding complications.

Regional Citrate Anticoagulation

The regional citrate regimen that has been adopted in many institutions involves the continuous infusion of isoosmotic trisodium citrate solution (102 mmol/L) into the arterial limb of the dialyzer. The fall in the free plasma calcium concentration induced by binding to citrate is responsible for the anticoagulant activity of this regimen by preventing the progression of the coagulation cascade. A calcium-free dialysate is used, and some of the citrate-calcium complex is then removed across the dialyzer. The citrate infusion rate is adjusted to keep the ACT above 200 seconds in the arterial limb.

Normocalcemia and regional anticoagulation is achieved by the infusion of 5% calcium chloride into the venous return line at a rate of 0.5 mL/minute. This rate is constantly adjusted according to frequent measurements of plasma calcium concentration to prevent hypocalcemia or hypercalcemia. A modification of this technique utilizes hypertonic trisodium citrate (1.6 mmol/L) and dialysate containing 3 meq/L of calcium in an attempt to minimize the amount of replacement calcium needed via venous infusion (Figure 13.1).

Comparative trials have shown a reduced incidence of bleeding with citrate-based regimens compared to standard heparin protocols. Apart from technical complexity and the intensity of monitoring, the major problems with regional citrate anticoagulation are the possibility of hypocalcemia, hypercalcemia, hypernatremia (due to the hypertonic sodium citrate solution), and metabolic alkalosis (due to bicarbonate generated during the metabolism of citrate) that may require treatment with a hydrochloric acid infusion. Patients with liver insufficiency are especially at risk for metabolic complications. Citrate infusion can also affect the function of cellular elements of the blood, including leukocyte activation and platelet function via its hypocalcemic effects. If closely monitored, however, the complication rate is relatively low.

Prostacyclin Regional Anticoagulation

The arachidonic metabolite prostacyclin is a vasodilator and inhibitor of platelet aggregation. Its in vitro half-life is 3 to 5 minutes due to rapid metabolism by endothelial smooth muscle.

Prostacyclin regional anticoagulation involves the infusion of prostacyclin into the dialyzer circuit at 4 to 8 ng/kg per minute. This method is rarely recommended due to its unfavorable side effect profile, including headache, lightheadedness, facial flushing, hypotension due to vasodilation, and expense.

Nafamostat is a prostacyclin analog associated with fewer adverse effects on blood pressure, but it is not yet available in the United States. It may, however, be associated with an unacceptably high incidence of clot formation. In one study using nafamostat, clot formation was observed in up to 36% of dialyzers despite adequate prolongation of the activated partial thromboplastin time (aPTT). In addition, nafamostat cannot be used with polyacrylonitrile membranes due to adsorption onto the membrane surface.

Low-Molecular-Weight Heparin

The type of heparin in current clinical use is a polydispersed unmodified heparin (mean molecular weight ranging from 10,000 to 16,000 daltons). Low-molecular-weight (LMW) derivatives of commercial heparin have been prepared that have a mean molecular weight of 4000 to 5000 daltons. Like unfractionated heparin, LMW heparins inactivate factor Xa. However, they have a lesser effect on thrombin because most of the molecules do not contain enough saccharide units to form the ternary complex in which thrombin and AT III are bound simultaneously. Monitoring of anticoagulation also differs from UFH, in that the aPTT is not accurate with LMH heparin. Heparinoid or antifactor Xa levels must be measured to provide an indication of the degree of anticoagulation.

LMW heparin has been proposed to cause less bleeding and less thrombocytopenia than heparin. Dalteparin, a LMH heparin, is used widely in European countries. Although LMH heparin has been demonstrated to be similarly safe and efficacious compared to UFH, it has generally not been found to be superior to heparin in terms of dialysis-related bleeding, and the increased cost may not justify the preferential use over UFH. It is also important to note that LMW heparin cannot be used as a safe substitute in patients who develop heparin-induced thrombocytopenia (HIT) with UFH, because of the extensive cross-reactivity (>90%) between the LMW heparin and standard heparin in terms of antibody recognition.

One novel use of LMH recently developed is to decrease the thrombogenicity of the extracorporeal circuit itself by covalently

coupling LMH to all surfaces. Preliminary studies have shown that this strategy can be safely used without additional agents, but the clinical and cost effectiveness of this modality to prevent thrombosis and bleeding compared to regional and no-heparin strategies has yet to be examined.

Recombinant Hirudin Anticoagulation

Hirudin inhibits thrombin via the formation of a noncovalent complex. Recombinant hirudin (lepirudin) has been administered either as a single bolus at the start of hemodialysis or as a continuous infusion. Lepirudin is an effective anticoagulant and may result in less prolongation of the ACT than heparin. However, its use has been limited because of a prolonged half-life in hemodialysis patients—possibly leading to bleeding complications with repetitive use. The safety profile of hirudin compounds compared with heparin is currently under investigation.

Continuous Hemodialysis Modalities

Low blood flow rates typically utilized in continuous hemodialysis modalities further increases the risk of circuit thrombosis, making the no-heparin regimen problematic. In addition, continuous therapy increases the likelihood of complications with prostacyclin or protamine. Therefore, minimal-dose heparin is generally the preferred modality in continuous arteriovenous or venovenous hemofiltration or hemodialysis (CAVH/D and CVVH/D). The alternative for patients with increased risk of bleeding is regional citrate anticoagulation.

Heparin

Typically, a bolus dose of 1000 to 2000 U of heparin is given initially—followed by a continuous infusion into the arterial limb of the circuit of between 300 and 400 U heparin/hour. The aim is to maintain the ACT in the venous limb at 1.5 to 2 times control. The heparin dose may be drastically reduced in patients with disseminated intravascular coagulation or thrombocytopenia. Unfortunately, there is some systemic anticoagulation with this technique and it may be contraindicated in patients at high risk of bleeding. The heparin dose and ACT goal can be adjusted downward in patients with increased risk of extracorporeal clotting.

Regional Citrate Anticoagulation

The principles and potential side effects of regional citrate anticoagulation in CAVH/D and CVVH/D are the same as those in standard hemodialysis. Despite heparin being the preferred modality in terms of side effect profile and simplicity, limited evidence from two randomized controlled trials suggests that regional citrate may improve the survival rate of hemofilters and lower bleeding risk compared with heparin in continuous renal replacement therapies.

The possibility of alkalosis may be lessened in part by using an anticoagulant citrate dextrose formula as replacement fluid, which produces less bicarbonate compared with hypertonic trisodium citrate. Further study in a larger number of patients is required to more accurately define the relative benefits and/or risks of heparin versus citrate-based anticoagulation. Although citrate is somewhat more complicated for nursing staff, appropriate protocols should simplify procedures, and citrate may over time become the preferred anticoagulation modality in continuous renal replacement therapy. The protocol we use in our institution is shown in Figure 13.2.

Regional Prostacyclin and Low-Molecular-Weight Heparin Anticoagulation

There are only limited data on the use of these anticoagulants with continuous dialytic techniques. One study found that prostacyclin decreased bleeding episodes in CAVH/D and CVVH/D and was superior to heparin in maintaining circuit integrity during CVVH/D without inducing significant hypotension. Combinations of both prostacyclin and LMW heparin have also been described. However, these favorable outcomes are at odds with studies performed during standard hemodialysis and must be interpreted with caution. Larger clinical trials with these agents are needed to establish their role in continuous renal replacement therapies. Current indications for the use of prostacyclin or LMW heparin are similar to those in standard hemodialysis.

Heparin-induced Thrombocytopenia

The main clinical concern in this disorder is a high incidence of thrombosis, rather than bleeding. The options for patients who have developed HIT include no-heparin hemodialysis, regional citrate hemodialysis, a change to peritoneal dialysis, or the administration of one of the three drugs that appear to be

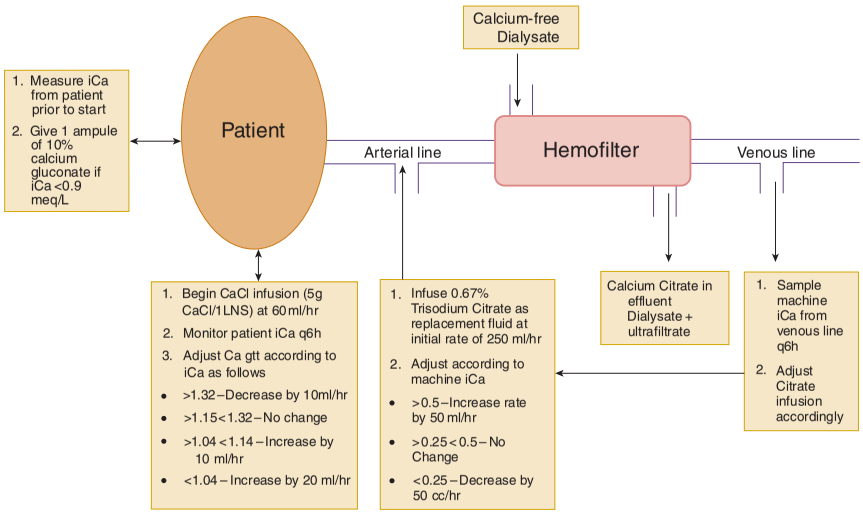


Figure 13–2

Schematic representation of a regional citrate anticoagulation protocol with continuous renal replacement therapy (CRRT). After initial measurement of patient serum ionized calcium (iCa) levels, CRRT is begun with citrate replacement fluid and a calcium infusion via central line. Patient and machine calcium levels are monitored every 6 hours and infusion rates are adjusted accordingly. Calcium infusion rates should be accounted for when targeting net ultrafiltration rates.

Table 13–3

Anticoagulation for Dialysis-Dependent Patients with HIT

Parameter	Danaparoid	Lepirudin	Argatroban[a]	Melagatran
CRRT				
Infusion rate	2500 anti-FXa U bolus, then 600 U/hr x 4 h, then 400 U/hr x 4 h, then 200–600 U/h based on levels[b]	Initiate at 0.005–0.01 mg/kg/h	Initiate at 0.5–1.0 mcg/kg/min and dose adjust to aPTT	ND
Monitoring test	Antifactor Xa level	aPTT	aPTT	aPTT
Target result[c]	0.5–1.0 anti-FXa units	1.5–2.0 x mean of the normal pool	1.5–2.0 x mean of the normal pool	ND
Hemodialysis				
Bolus therapy	3750 anti-FXa U bolus prior to 1st two HD treatments, then dose adjust using levels	0.15 mg/kg bolus prior to HD	0.1 mg/kg bolus prior to HD	Bolus IV dose of 2 mg, add to dialysis fluid for concentration of 0.2 mg/L
Infusion therapy	ND	ND	0.1–0.2 mg/kg/h	ND
Monitoring test	Antifactor Xa level	aPTT	aPTT	aPTT
Target result[c]	0.0–0.4 anti-FXa units pre-HD	2.0–2.5 x mean of the normal pool	1.5–3.0 x mean of the normal pool	ND

Table 13–3

Anticoagulation for Dialysis-Dependent Patients with HIT—Cont'd

Parameter	Danaparoid	Lepirudin	Argatroban[a]	Melagatran
Catheter Lock				
Concentration/volume	750 U in 50 mL saline, then 5–10 mL per port	5 mg/mL per port[d]	ND	ND

a. Argatroban should not be administered without first verifying normal liver function. Dose needs to be adjusted for hepatic insufficiency.
b. Use lower bolus dosing if weight is <50 kg.
c. Target results for the aPTTs are based on individual coagulation laboratory mean values. Do not exceed 100 seconds.
d. Must be aspirated prior to hemodialysis.
ND = No data available at this time, CRRT = continual renal replacement therapy, HD = hemodialysis.
Modified from O'Shea SI, Ortel TL, Kovalik EC. Alternate methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. Semin Dial 2003;16:61.

effective in patients with HIT: danaparoid (which is a heparinoid and not an LMW heparin), recombinant hirudin (lepirudin), and argatroban. Melagatran is a novel long-acting direct thrombin inhibitor currently available only in Europe.

Feasibility studies using these agents have been conducted in hemodialysis patients and they appear to be effective in preventing thrombosis without excess bleeding risk. However, there is no published experience concerning their use in patients with HIT. Overall, the experience with these drugs is limited. Table 13.3 summarizes the recommendations for use of these agents based on currently available data.

Catheter Lock in Patients with Heparin-induced Thrombocytopenia

Hemodialysis catheter lock options in patients with HIT are to pressure-bag the catheters (which is impractical for outpatients) or to instill either tissue plasminogen activator or urokinase. Highly concentrated (47%) citrate has also been used, but is not FDA approved due to issues of accidental systemic injection and arrhythmia. Studies with lower-concentration citrate solution (4 to 7%) are currently underway. A study using a 30% citrate locking solution found no increase in adverse events and also found a decreased risk of catheter-related bacteremia compared to a standard heparin locking solution.

Conclusions

In general, no-heparin dialysis and regional citrate anticoagulation have the most favorable profile for patients at increased risk of bleeding and who require intermittent hemodialysis with the lowest risks of bleeding and dialyzer clotting. Figure 13.1 summarizes the methodology of techniques described in this chapter.

Given overall safety and reasonable ease of use, no-heparin hemodialysis should be the first option among those with HIT. If no-heparin dialysis cannot be performed, the patient should be converted to peritoneal dialysis. The use of danaparoid appears to be a reasonable choice among those in whom no-heparin hemodialysis and peritoneal dialysis are not feasible techniques. Argatroban should not be used in patients with liver disease, given its hepatic mode of elimination.

Recommended Reading

Anticoagulation Strategies to Minimize Bleeding Risk in Intermittent Hemodialysis

Frank R, Muller U, Lanzmich R, et al. Anticoagulant-free Genius hemodialysis using low molecular weight heparin-coated circuits. Nephrol Dial Transplant 2006;21:1013.

Description of a novel anticoagulation modality using LMW heparin covalently bonded to dialyzer circuits.

Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: A meta-analysis of randomized trials. J Am Soc Nephrol 2004;15:3192.

Meta-analysis of 11 clinical trials comparing LMW heparin with other anticoagulant strategies. There was no increased risk of bleeding or circuit thrombosis compared to UFH.

Lohr JW, Schwab SJ. Minimizing hemorrhagic complications in dialysis patients. J Am Soc Nephrol 1991;2:961.

Comprehensive review highlighting the pathogenesis of bleeding risk and treatment of hemorrhage in renal failure patients. Summarizes strategies to prevent bleeding on hemodialysis, including minimal heparin, prostacyclin, regional citrate, and no-heparin anticoagulation.

Sagedal S, Hartmann A, Osnes K, et al. Intermittent saline flushes during hemodialysis do not alleviate coagulation and clot formation in stable patients receiving reduced doses of dalteparin. Nephrol Dial Transplant 2006;21:444.

Randomized trial investigating comparing the efficacy of saline flush no-heparin technique versus control. There were more instances of subclinical and overt circuit thrombosis in the saline-flush technique.

Schwab SJ, Onorato JJ, Sharar LR, Dennis PA. Hemodialysis without anticoagulation: One-year prospective trial in hospitalized patients at risk for bleeding. Am J Med 1987;83:405.

Prospective study of outcomes using the no-heparin technique in 262 inpatient hemodialysis sessions. Less than 2% of the dialysis treatments resulted in clotting in the extracorporeal circuit sufficient to interrupt hemodialysis.

Stamatiadis DN, Helioti H, Mansour M, et al. Hemodialysis for patients bleeding or at risk for bleeding, can be simple, safe and efficient. Clin Nephrol 2004;62:29.

Retrospective and prospective study on the efficacy of the no-heparin technique in 16,954 dialysis sessions, demonstrating that this technique can be adequately and safely performed.

Swartz RD, Port FK. Preventing hemorrhage in high-risk hemodialysis: Regional versus low-dose heparin. Kidney Int 1979;16:513.

Prospective trial comparing bleeding and clotting outcomes in regional heparinization versus the minimal heparin technique in standard hemodialysis. Bleeding risk was significantly increased with regional heparinization.

Von Brecht JH, Flanigan MJ, Freeman RM, et al. Regional anticoagulation-hemodialysis with hypertonic sodium tricitrate. Am J Kidney Dis 1986; 8:196.

Description of the regional citrate anticoagulation technique in standard hemodialysis.

Anticoagulation in the ICU and Continuous Hemodialysis Modalities

Monchi M, Berghmans D, Ledoux D, et al. Citrate versus heparin for anticoagulation in continuous venovenous hemofiltration: A prospective randomized study. Intensive Care Med 2004;30:260.

Prospective randomized trial of 43 CVVHF circuits treated either with regional citrate anticoagulation or low-dose UFH. The median lifetime of hemofilters was increased by 75% in the citrate group, with no increased risk of bleeding.

Ward DM. The approach to anticoagulation in patients treated with extracorporeal therapy in the intensive care unit. Adv Ren Replace Ther 1997;4:160.

Comprehensive review of the practicalities, difficulties, and advantages of low-dose heparin, regional heparin, LMW heparin, no-anticoagulant systems, citrate, and other anticoagulants for both intermittent and continuous modalities. Also discusses the clinical features and complications in individual patients that impact on the selection of the most appropriate method for critically ill patients.

Anticoagulation for Patients with Heparin-induced Thrombocytopenia

O'Shea SI, Ortel TL, Kovalik EC. Alternate methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. Semin Dial 2003;16:61.

Review of the prevalence, diagnosis, and treatment data regarding HIT.

Weijmer MC, Van den Dorpel MA, Van de Ven PG, et al. Randomized, clinical trial comparison of Trisodium citrate 30 percent and heparin as catheter-locking solution in hemodialysis patients. Am J Kidney Dis 2005;2769:2777.

This prospective study found that the use of a trisodium citrate catheter locking solution reduced the incidence of catheter-related bacteremia and was not associated with any untoward metabolic consequences compared to standard heparin lock.

CHAPTER 14

Home Preparation and Installation for Home Hemodialysis

Christopher R. Blagg, MD, and Connie Anderson, RN

Home hemodialysis provides the best patient survival and quality of life of all dialysis modalities and yet today it is infrequently available and is used by less than 0.5% of U.S. dialysis patients. Two recent developments have revived interest in this desirable treatment. First is the steadily increasing interest in the patient benefits of more frequent hemodialysis, both short during the day and overnight while sleeping. The second is the development of new, highly automated hemodialysis machines designed specifically for use in the home and simplified to reduce the burden on patients.

The objective of home preparation is to ensure a safe and comfortable area for hemodialysis and associated tasks. Options are likely to be limited by the individual's home design and size, the needs of others in the home, and cost. For these reasons, the setting usually requires some compromise of the ideal situation (including exceptions to facility standards) related to the physical setting for dialysis. However, many of the activities in the facility addressed by these standards are quite different from those of the home dialysis patient—as the facility must treat an unselected patient population. Nevertheless, patient safety remains paramount in the home and must not be jeopardized.

Patient convenience and satisfaction are only slightly less important and should be addressed as far as resources permit if treatment in the home is to be successful. Certain aspects of the physical setting can only be discussed in a general way here because of the number of home treatment options available and how these may impact on the differing attitudes and lifestyles of patients and their feelings about their dialysis treatment. Accommodation of this diversity is an advantage offered by home treatment and should be viewed positively. With more treatment options available today, it is important that patients be educated about each option and select the one most suitable

to their needs. However, building, electrical, and plumbing codes must not be compromised because these pertain to safety.

The first step is for an experienced staff member to conduct a home survey. This allows discussion with the patient and family of the plans for dialysis in the home and assistance with and facilitation of the necessary home modifications.

Requirements for Home Hemodialysis

Location

A dedicated room for dialysis is not necessary and is not available for many patients. However, space set aside or converted solely for dialysis purposes is likely to offer conveniences that might not be present in a shared space. A cheerful setting the patient finds physically and psychologically comfortable is desirable. Attainment of this goal will vary with the patient's perceptions and values. Many patients may prefer to dialyze in their own bedroom because of its association with a secure place that is comfortable and nonclinical. Others may prefer a family room in order to be involved in family activities during treatment. Whereas most patients leave their dialysis machine in the treatment area permanently, some prefer to store it in a closet between treatments.

The dialysis room is preferably located on the ground level or with an outside exit to grade. Stairs from an upper level or basement can be difficult to negotiate immediately after dialysis, particularly if fluid removal has been rapid or excessive. Grade level is also advantageous for the delivery and installation of equipment and supplies, or should emergency medical assistance be required. More than one exit may be desirable, especially if a basement site is chosen. Other compromises regarding location may be necessary to ensure accessibility of utilities. This is especially true for the waste (drain) line, although water can generally be plumbed to most areas. A room adjacent to a bathroom, laundry, or utility room is frequently chosen for this reason.

Space Requirements

The amount of space needed depends on several factors. These include the use of a bed or reclining chair for treatment; the size and configuration of the hemodialysis system, including the

water-treatment equipment (unless this is not required); preferences for supply storage and the quantities kept; and the individual patient's perceptions regarding space. A comfortable chair should be provided for the dialysis assistant.

Water treatment equipment, storage of most of the supplies, and concentrate mixing (if dry chemicals are used) may be relegated to areas other than the dialysis room itself—provided the area is clean and protected from freezing temperatures. A room with a window that can be opened to the outside is desirable to allow temporary increased ventilation for noxious odors that may be released during equipment disinfection and rinsing with some equipment, or in the event of chemical spills. An open window may also be desirable for patient comfort during treatment if the home or apartment does not have central heating and ventilation. Finally, a window is desirable for outdoor-quality light and for whatever view it may afford to counter any sense of confinement or isolation during the several hours of treatment.

Telephone

A telephone is needed to give access to the physician, supporting facility, and emergency services if assistance is required during dialysis. This telephone should be placed so that it is convenient to the patient when he or she is seated in the dialysis chair or lying in bed during treatment. Important telephone numbers should be entered in or posted on the telephone or on a nearby alarm poster.

Floor

The floor of a dialysis treatment room is subject to spills or drips of saline, dialysis fluid, test solution, cleaning and disinfecting agents, medications, and small amounts of blood. Whereas some patients have chosen to retain carpet in the treatment room in order to preserve the feel of a nonclinical setting, most prefer and are encouraged to replace carpeting with an impervious covering that is easy to clean.

Those who retain their carpet usually place a protective mat of heavy vinyl or other suitable material under the machine and over the surrounding treatment area. If there is suitable wood flooring, the carpet can be removed, the floor refinished, and small area rugs can be used elsewhere in the room to preserve a pleasant home appearance. For practical purposes, however, seamless vinyl

or vinyl tiles provide the best covering for floor protection and ease of cleaning.

Lighting

Lighting is important in the dialysis room, and ideally can be adjusted for a variety of purposes. Bright illumination is required for preparing the dialysis machine and supplies, for cannulation of the blood access, and for clean-up and maintenance after dialysis. More subdued and indirect light should be available for monitoring during treatment and for any use of the space when it is not required for dialysis. These mixed requirements are easily met with a little forethought and planning.

The following points are specific to lighting during dialysis. The lighting should be adequate to safely monitor the equipment and process, but should not produce glare for the patient in the usual treatment position. It must be capable of flooding the room with adequate light in an emergency, is preferably under the control of the patient, and should be convenient to the assistant. Many patients want a separate light for reading during dialysis. This, too, should be under the patient's control—but as with all other electrical equipment within reach of the patient during treatment it must be properly grounded to a low-resistance common ground serving all outlets in the room. Alternatively, it can be double insulated—as this will generally avoid the use of conductive materials in the control knobs, case, or parts handled during routine operation.

Finally, it is most important there be an emergency light that switches on automatically in the event of a power failure—so that dialysis can be terminated safely. Such a light can be maintained in a charged state while connected to power and will come on automatically to provide light for a limited duration during a power failure. Prices range from less than ten dollars to several hundred dollars. The less expensive lights generally provide about the same output as a flashlight and are suitable only as minimal lighting to locate and properly place a battery lantern for terminating treatment.

Those lights capable of providing sufficient light to terminate dialysis are generally more expensive. An emergency generator is not necessary, as regularly performed dialysis is not an emergency and treatment can be postponed for several hours or a day or so. Emergency generators are expensive, and require special connections to avoid feedback to the transmission system and

risks to others. Most also require special installation to avoid hazards associated with storage of fuel.

Electrical Power

Electrical outlets for the dialysis machine and reverse osmosis equipment also require special consideration. Existing outlets in older houses may not meet present electrical code requirements and may not be suitably close to the desired location for the machine. Furthermore, most domestic outlets are only 15-ampere circuits and may be marginal for some dialysis machines—particularly if other outlets on the same circuit are in use for other purposes.

The best approach to standard dialysis equipment is to determine the most appropriate placement of the dialysis machine and have an electrician install an outlet for it with a dedicated circuit to the breaker (fuse box). The wire size and outlet should meet the manufacturer's recommendations for the particular equipment. If an adjacent outlet is available, this can be used for the reverse osmosis equipment—although it will be necessary to convert this if it is not grounded. If no nearby outlet is available, a new dedicated circuit can be installed at the same time as that for the dialysis machine. For reasons of cost, power can be provided to two adjacent outlets by running a single properly sized multiwire cable rather than using two separate cables.

Circuit breakers (20-ampere or as appropriate) are installed at the breaker for each circuit. Most, if not all, dialysis machines have their own integral fuse or breaker—and it is likely that the reverse osmosis equipment will also have one. If not, the capacity of the breakers installed by the electrician should be selected appropriately for the individual machines. If these are different, measures must be taken to prevent use of the wrong outlet for each machine. The facility's technical department or the manufacturer should be able to provide guidance for the electrical needs of the various types of equipment.

Water

Water supply to the water treatment equipment can be from any suitable cold-water line used for potable water. The first essential is to have a water analysis done in order to decide on the water treatment equipment needed to ensure that product water to the machine meets American Association for Medical

Instrumentation (AAMI) standards. It is very important not to use a line that is subject to accidental cross-connection with the hot water service, such as could occur from a faulty mix valve in a faucet or washing machine. The design safety built into the dialysis machine requires more than a single fault to result in harm to the patient, and a hot water cross-connection could cause overheated dialysis fluid in the absence of a dialysis machine alarm if the machine temperature monitor were defective.

Many local authorities now require a back-flow preventer to be installed to eliminate any possibility of contamination of the potable water source from the dialysis machine or reverse osmosis equipment. The cold-water line should end with a boiler drain valve with a 0.75-inch garden hose thread or ball valve with an adapter for the same type of connection. Only plastic lines meeting FDA specifications for transmitting fluids for human consumption (food grade) should be used to carry product water from the water treatment device to the dialysis machine. A sink for hand washing and disposal of fluids (such as saline, dialysis fluid, blood, disinfectants, and residue of chemical testing) should be convenient to the dialysis room, although not necessarily in it.

New Home Hemodialysis Equipment

The foregoing information applies to the installation of conventional hemodialysis equipment in the home. Recently, three small companies have developed new dialysis equipment designed specifically for home hemodialysis and more frequent home hemodialysis. Each has some unique features related to installation.

The first of these to become available, the PHD System (Aksys Ltd.)*, was designed originally for short daily home hemodialysis—although it can be used for nocturnal treatments using an external heparin pump. At this time, home modification is undertaken by the company's technical staff. The electrical requirement is a dedicated 20-ampere circuit using a hospital-grade plug with a ground fault interrupter. The PHD also uses tempered water and thus needs appropriate hot and cold plumbing connections. Water is first routed through a carbon prefilter that occupies about 15 × 15 inches of ground space before entering

*Unfortunately, since this chapter was written, AKsys Ltd. has gone out of business and the PHD System, the most advanced home hemodialysis system to date, is no longer available.

the PHD, where it is further treated to achieve ultrapure water for the dialysate (which is prepared from dry chemicals). A drain is also needed that uses at least 2-inch-diameter tubing.

The System One device (NxStage Medical Inc.) at the time of writing uses 5-L bags of dialysate, similar to those used for continuous ambulatory peritoneal dialysis. Typically, four of these are hung on a stand to provide 20 L of dialysate per treatment. However, use of these bags is in process of being discontinued except for when patients are traveling. Instead, access to tap water will be required for preparation of dialysate in a separate device (NxStage PureFlow SL) that makes "high-purity" dialysate in a 60-L bag for use for three dialyses. This device occupies 20×25 inches of floor space, is described as being the same size as a typical end table, and has a Corian-like top. It plugs into the cycler, which itself plugs into a normal plug.

The device is filled by a simple connection to a cold-water faucet, or a connection under a sink, or to a saddle valve on a copper pipe using tubing similar to that used in a domestic ice maker. The flow is slow and takes about 7 hours to make the dialysate. The device contains two carbon filters and two deionizer tanks. The 60-L bag is contained in a slide-out drawer, and the effluent goes down the drain (as in peritoneal dialysis). Apparently, there is no need to check for contamination because of extensive redundancy—and similarly there are sequential resistivity meters after the redundant deionizer beds.

The Allient Sorbent Hemodialysis System (Renal Solutions, Inc.) was approved by the FDA and introduced in 2006. This requires only a standard power outlet and 6 L of drinking water. No connection to a water supply is needed because dry concentrate is mixed with the drinking water to make the dialysate for one treatment. The sorbent cartridge continuously regenerates and recirculates the small volume of dialysate in the same way as that of the REDY system of the past. At the end of treatment, the dialysate is disposed of down a household drain. Disinfection is not required because all dialysate and blood contact surfaces are disposable.

Waste

With the limitations frequently imposed on location of a waste drain for spent dialysate and reverse osmosis reject water ("brine"), an extension line may need to be spliced onto the drain line from the dialysis machine. If this is done, care must be taken to use lines of equal diameter so as not to increase resistance. An

ideal drain is a standpipe with a minimum diameter of 1.5 inches (similar to that for a washing machine), standing about 30 inches above the floor (the distance recommended may vary, depending on the dialysis machine manufacturer), and connected to a P-trap. This is then joined to the household waste system.

Materials are not critical, and plastic is frequently used because it is easy to work with and less expensive. An alternative is to use a dishwasher tailpiece with a diameter air gap above the P-trap of any convenient sink, with an extension to the top of the counter. It is important with any drain to have a non-siphoning air gap where the machine drain line joins the waste drain plumbing. Plumbing codes vary with locality, and these suggestions should be viewed in light of local codes.

An important consideration in setting up home hemodialysis that is often forgotten is to ensure that the patient knows how to meet local requirements for handling of medical waste, its storage, and disposal. Regulations vary, and the patient must be informed about what is required in their city or county, and the importance of meeting these requirements. Conventional home hemodialysis equipment generates considerable medical waste. Three dialyzers and tubing sets need to be disposed of each week, unless the dialyzers are collected, disinfected, and returned to the patient for reuse.

Even more medical waste is generated with more frequent hemodialysis. The NxStage System One currently uses the four plastic bags of dialysate, a dialyzer, and a tubing set for each dialysis that must be disposed of. With use of the new PureFlow SL there will be fewer bags in the waste but there will still be the dialyzers and tubing sets to dispose of. Similarly, the Allient Home Hemodialysis System sorbent cartridge and tubing set will also be discarded after each treatment. The only equipment that minimizes medical waste is the PHD System. This uses hot water to clean and disinfect the dialyzer and tubing set in situ between treatments for as many as 30 uses, and thus these need to be disposed of only every few weeks.

Summary

Compared to facility treatment, home hemodialysis (and particularly more frequent home hemodialysis) is the best treatment for suitable patients who are willing to do this. It is critical to have technical services support that is knowledgeable about the requirements associated with the various equipment and can help the training staff and the patient make a selection that best meets

their individual needs. Attention to detail in preparing the home setting for hemodialysis can be a lasting investment for both the patient and the facility.

Recommended Reading

Technical Aspects of Establishing Hemodialysis in the Home

Mehrabian S, Morgan D, Schlaeper C, Kortas C, Lindsay RM. Equipment and water treatment considerations for the provision of quotidian home hemodialysis. *Am J Kidney Dis*, 2003, 42 (1 Suppl), 66–70.

Morgan D, Schlaeper C, Lockridge RS. Technical requirements of a home hemodialysis program. Contrib Nephrol 2004;145:21–28.

Curtis J. Taking dialysis from in-center to home: Technical considerations. Nephrol News Issues 2004;18:66, 77.

Piccoli GB, Jeantet A, Burdese M, Mezza E, Segolini GP, Piccoli G. Home dialysis, garbage, and privacy: Nothing is trivial in home hemodialysis. Kidney Int 2005;67:1190.

General Requirements and Technical Aspects of Home Hemodialysis

Anderson C, Blagg CR, Kapikian N, Mailloux LU. Organization and elements of a home hemodialysis program. In BD Rose (ed.), *UpToDate.* Wellesley, MA: [publisher] 2005.

Diaz-Buxo JA, Crawford-Bonadio TL, St. Pierre D, Ingram KM. Establishing a successful home dialysis program. Blood Purif 2006;24:22–27.

General References

Saner E, Nitsch D, Descoeudres C, Frey FJ, Uehlinger DE. Outcome of home haemodialysis patients: A case-cohort study. Nephrol Dial Transplant 2005;20:604–10.

Recent report confirming the better survival of patients treated by home hemodialysis.

Blagg CR. Home haemodialysis: "Home, home, sweet, sweet home!." Nephrology (Carlton) 2005;10:206–14.

A recent review of home hemodialysis.

CHAPTER 15

Peritoneal Dialysis Cyclers and Other Mechanical Devices

José A. Diaz-Buxo, MD, FACP

Peritoneal cyclers are used to automatically deliver multiple exchanges of a prescribed volume of commercial peritoneal dialysis (PD) solution. They were initially created to provide the many and frequent short exchanges of intermittent PD. Following the introduction of continuous cyclic PD (CCPD) and variants, the cycler underwent modifications consistent with these regimens. The utilization of automated PD (APD), now surpassing 50% of all PD in various countries, and advances in computer science has further transformed the cycler into a much more complex and versatile device.

These advances have made possible the incorporation of features to improve the performance, safety, and convenience of modern cyclers. We have moved from an empirical approach to an analytical approach in cycler design. An important step in this direction has been the incorporation of software that allows physicians and nurses to store, analyze, and process medical data in a reliable and simple manner—with the ultimate objective of improving patient outcomes. This development has also connected the patient home to the training center. The ideal characteristics of a modern cycler and the numerous features now available in many of these devices are summarized in Table 15.1.

Mechanical Aspects and Hydraulics

The essential components of a cycler are the control unit, including pumps, occluders, manifolds, electronics, and other mechanical components; the heater cabinet or plate; hardware to process electronic data; and the display screen or control board. Some modern cyclers have eliminated the stand because placement of the cycler in relation to the patient is not critical with the use of active infusion and/or drainage. Others have replaced the valves and occluders with complex disposable flow circuits built into disposable cassettes.

Gravity Infusion and Drainage

This type of cycler uses gravity to deliver the solution from bags, through sterile tubing, via the heater module into the peritoneal cavity (Figure15.1a). Conversely, the bags may rest on a heating tray—with the solution transferred to the distribution module and to the patient. The fluid is heated to body temperature and the prescribed volume of dialysate is measured before infusion. After a prescribed dwell period, the spent dialysate flows by gravity through the patient line into a weigh bag. After completion of the drain, the volume is measured and the dialysate is either collected in a drainage bag or disposed directly into the sewage. The transfer of dialysate into the sewage line can be accomplished by gravity or with the use of a pump.

The control panel monitors and controls temperature, dwell time, drain time, and drainage volume. Most cyclers simply ensure that a predetermined percentage of inflow volume is drained before a new cycle takes place. Most cyclers are capable of precisely monitoring ultrafiltration. Inflow volume is determined and measured by the heating cabinet.

Gravity Infusion and Drainage with Active Solution and Drainage Transfer

The incorporation of active transfer of dialysate from the container to a measuring bag located above the patient level allowed the design of simpler tubing sets and the practical use of larger containers with a potential reduction in cost of therapy (Figures 15.1b and 15.1c). The typical system transfers the dialysate by means of a peristaltic pump. The measuring bag rests on a plate equipped with a heating coil and a weight transducer. During the fill mode, the dialysate will flow into the patient's peritoneal cavity by gravity.

During the drain mode, the inflow lines are occluded and the fluid is passively drained into a weight bag mounted on a second weight transducer. Once drainage is accomplished, the peristaltic pump is energized—simultaneously draining the spent dialysate into a drain bag and refilling the measuring bag. All of these functions are integrated by a control cabinet using microprocessors that allow precise control of inflow volume, ultrafiltration monitoring, dwell time, drain time, and number of cycles. Selection of dialysate osmolality and volume for the diurnal cycle of CCPD (last cycle) is also possible with these devices.

Table 15–1

Characteristics of an Ideal Cycler

Functionality
- Meets the needs of home and acute care setting
- Performs all prescriptions (CCPD, PD Plus, TPD, IPD)
- Delivers high total volume of dialysate (>50 L)
- Delivers large number of cycles before resetting
- Delivers minimum fill volume of 50 mL for infants
- Delivers large fill volumes (≥4 L)
- Delivers dialysis solutions in small increments (10–20 mL)
- Allows fast drainage (≥200 mL/min)
- Ability to pump effluent to either bags or drain
- Records total UF by cycle and at the end of treatment
- Variable alarm volume according to severity of malfunction
- Programmable option for total treatment time with broad limits for fill, dwell, and drain
- Automatic flush-before-fill as part of setup
- Automatic priming of the patient line
- Lock-out option to prevent unauthorized setting changes
- Fast and efficient warming of solutions
- Last bag option
- Appropriate fields for entry of pertinent laboratory parameters in treatment history
- Easy-to-follow step-by-step tutorial

Mechanical
- Ease of portability and custom-made travel case
- Small enough footprint to fit on average nightstand
- Low weight (≤25 lb)
- Capability to hold a broad range of bag sizes (up to 6 L)
- Stability (no tipping while holding up to 30 L of dialysate)
- Noise level ≤30 dBA while running at maximum pumping speed
- 120 and 240 VAC power choices

User Interface
- Easy to read, easy to use, large control panel with variable brightness and color display
- User-friendly menu and graphics

Safety Features
- Device to allow early detection of cloudy effluent
- Locking wheels and nonslip feet to prevent rolling and sliding
- UL/CSA/CE approval
- Constructed of material that is easily disinfected with common agents
- Designed to prevent trapping of foreign matter into corners, seams, and edges
- Sealed outer case to prevent liquids from penetrating unit

Table 15–1

Characteristics of an Ideal Cycler—Cont'd

Reliability
- Able to withstand stresses associated with daily usage and shipment
- Able to withstand extreme temperatures (–25 to 130°F)
- Adequate performance at altitudes of sea level to 7500 ft

Information Technology
- Onboard modem to allow Internet connection
- Two or more USB ports for memory stick, BP monitors, scales, etc.
- Instructions and screens in multiple languages
- Sufficient memory to allow adequate information downloads
- Upgradeable training courses
- Patient data management
- Full-therapy data management
- Administrative module
- Prescription modeling module
- Continuous quality improvement program
- Help feature with online access to service
- Secured data communication

Disposables
- Single-use sterile components
- One-step loading (cassette)
- Advanced connectology with elimination of clamps
- Good visualization of effluent and sample port
- Adequate organizer for operator's use

Other variations on the concept of gravity infusion and drainage with active solution and drainage transfer are available using two pumps (Figure 15.1c). These systems have more complicated disposable tubing sets and hardware.

Active Infusion and Drainage

Various systems have been designed to actively infuse and drain dialysate. The simplest and most economical is the use of two peristaltic or roller pumps (Figure 15.1d). The first actively infuses warmed dialysate into the patient, and the second generates negative pressure to drain the spent dialysate.

A more ingenious alternative is the use of a cassette containing two fluid chambers and a series of channels for solution flow (Figure 15.2). Air pressure is applied to one chamber to

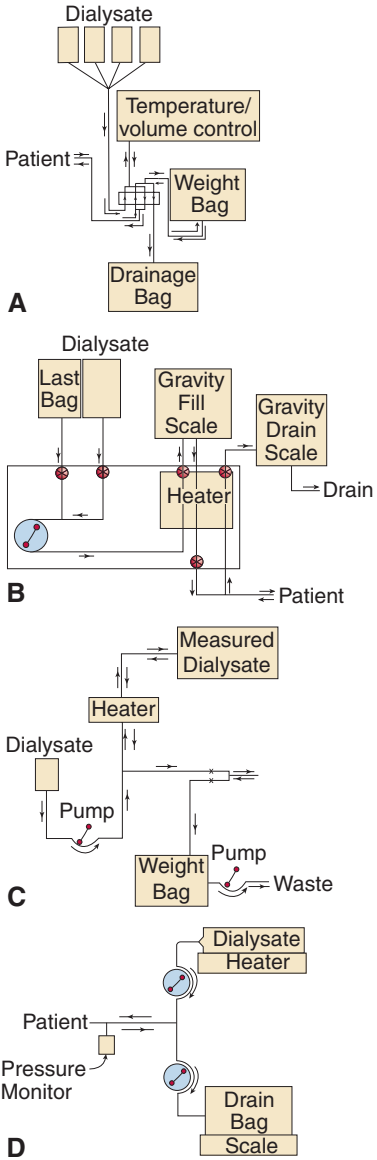


Figure 15–1

Flow diagrams for different types of cyclers. *A*, Gravity infusion and drainage cycler. *B* and *C*, Gravity infusion and drainage cyclers with active solution and drainge transfer (the cycler in panel C incorporates two pumps). *D*, Active infusion and drainage of dialysate.

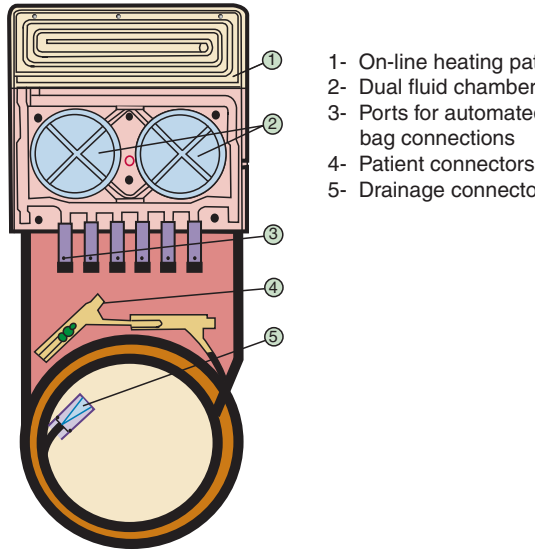


Figure 15–2

Cassette with heating path, dual fluid chambers, ports for automated bag connectors, and drainage lines.

generate positive pressure, thus pressing fluid out of the chamber and into the patient or the drain line—depending on the function (inflow or prime) selected (Figure 15.3). Negative pressure draws fluid in from the patient (during drain) or from the heater bag. The amount of negative pressure applied should approximate the natural gravity pressure observed in continuous ambulatory peritoneal dialysis (CAPD) for the safety and comfort of the patient. Similarly, air can be used to open and close the valves that control flow of solution from various sources and destinations. The measurement of fluid volume flowing through the cassette can also be used for volumetric control.

Connectology

Connectors are required between the cycler tubing set and the patient catheter and solution bags. The use of bags with integrated

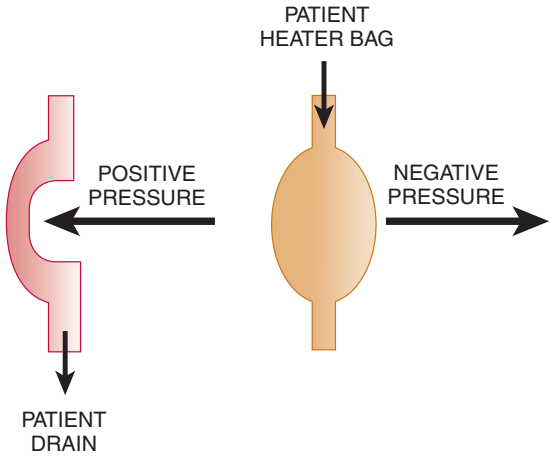
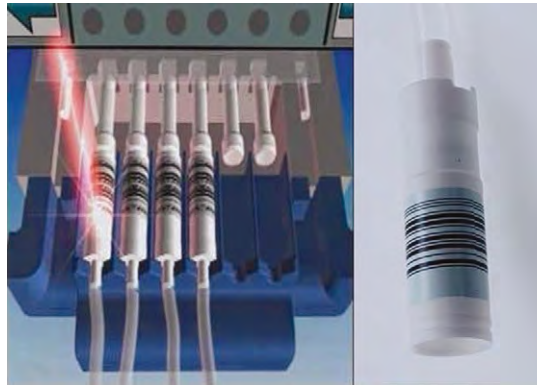


Figure 15–3

Cassette fluid chambers. Left-hand panel shows positive pressure caused by air, resulting in infusion of solution into the patient or into the drain. Right-hand panel shows the effect of negative pressure inside the chamber, causing influx of solution from the patient and into the heating circuit.

lines eliminates a set of connections. Various connectors have been used, including spikes, Luer locks, and threaded male-female connectors with recessed pathways. The connections can be manually performed or facilitated by automated spiking (Figure 15.4a).

Automated connections use a stationary manifold and a moving tray (connection rail) to attach the bag lines to the cassette. This technology simplifies the procedure and reduces the risk of touch contamination by the patient. In addition, the cycler's connecting device may incorporate a bar code scanner to identify the specific solution connected to each port in the manifold by reading the printed bar code on the bag connector (Figure 15.4b). Upon termination of the cycling session, the patient line can be disconnected and capped using sterile technique, external occlusion, or with connectors that automatically occlude the lumen of the tubing with a pin to prevent leakage of dialysate or contamination (Figure 15.5).



A **B**

Figure 15–4

A, Automated connection device showing open tray with four bag lines connected to the cycler and bar code reader. *B*, Bag connector with printed bar code.

Software and Technical Considerations

Cyclers have incorporated new functions as a result of more affordable and sophisticated electronics and computer systems. Some new-generation cyclers have memory cards or USB memory sticks to record treatment data or to download new prescriptions, color touch screens, communication links with central computers in medical centers or dialysis facilities via telephone lines or the Internet, and accessory programs designed to optimize therapy. Significantly larger memory capacity is now possible. This allows extensive data storage and record keeping, automated calculations of various parameters, and transmission to the center or to another computer.

Memory cards and UBS sticks can serve two important purposes: to track and store several months of patient treatment data and to download pertinent patient information and specific prescriptions to the cycler. These memory devices are inserted into the drive of the cycler to track the treatment data over a certain period or to download prescription information from the physician's office. The patient is instructed to bring the memory

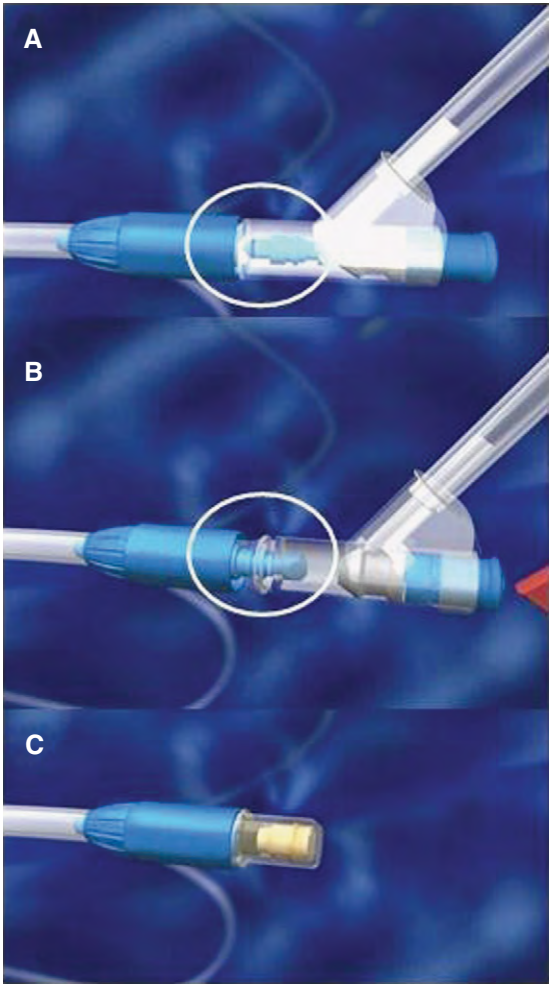


Figure 15–5

PIN technology for APD to effect automatic occlusion of line lumen upon disconnection. *A*, Normal position during treatment. *B*, The pin is inserted into the catheter extension. *C*, Final position with cap.

device to the clinic during routine visits or to periodically transmit the information to the center. At that time, the information is downloaded and analyzed using specific software. Prescription modifications are then entered and dowloaded to the memory device. During the next session, the memory device is reinserted into the cycler driver and the cycler is automatically reprogrammed with the new prescription. Conversely, the communication between the cycler and the medical center can be effected via telephone or the Internet.

Patient information can be downloaded to the cycler. In turn, the cycler will process and analyze the data to formulate the optimal prescription (Table 15.2). The program can provide treatment data from a specific date, or for the entire period of data entry. This information (together with the data produced by the cycler) can then generate treatment monitoring reports, prescription options for optimization of therapy, quality assurance/improvement reports, and review of reports and statistics to check on patient compliance, actual outcomes, trends, and comparison with the center's data or with regional and national average outcomes. These sophisticated analyses can be done at the center using a computer with the special software program or by certain cyclers. The main features of the programs are outlined in Table 15.3.

The user can select a graphic display or a chart summary of the data. The following parameters can be retrieved: the time

Table 15–2

Patient Information That Can Be Downloaded to Cycler

- Demographic data
- Medical status
- Etiology of ESRD
- Co-morbid conditions
- Past medical and surgical history
- Allergies
- Laboratory parameters and adequacy tests
- Residual renal function
- Peritonitis and tunnel infections
- Hospitalization data
- Current medications
- Therapy modality and prescription, including solutions
- Peritoneal access
- Compliance with therapy

Table 15–3

Main Features of Modern Information Systems Used with PD Cyclers

- Management system for patient's personal and medical data
- Adequacy module
- Prescription module
- Advanced module for evaluation and analysis of single-patient treatment data
- Advanced statistical module for analysis of single patient or groups of patients
- Trends
- Distribution histograms
- Cross-correlations
- Data export module
- Graphics and special reports
- Administration module: customizable for the needs of the physician or administration
- Language module allowing immediate translation of downloaded data and cycler-generated data into other languages
- Online help module

of the exchange (fill); length of the exchange (dwell); solution transit (nondialytic) time; drain time; automated exchanges, last fill exchange, or pause exchange; inflow volume; drain volume; net ultrafiltration volume; and time of drain alarms. The data can be displayed as daily therapy, mean of therapy values, or total therapy. With the information available, the renal team can incorporate changes in the prescription and provide feedback to the patient based on his/her compliance record.

The clinic software is also capable of summarizing all data for a particular patient or for all patients in the program for a specific period of time. The data can be transferred to other facilities or to a central data pool via modem. This data collection system can then be used for continuous quality improvement (CQI) and to model delivered therapy to the patient according to patient compliance with the prescription. The information acquired by this system can be used to evaluate specific patient compliance and to compare compliance scores among clinics or geographic regions and by cohorts of patients according to demographic or co-morbid conditions.

Touch screens with familiar and universal symbols to facilitate programming have been developed. The prescription can be

entered using the memory card, directly from the medical center into the cycler by telecommunication or secured Internet (or by the patient using the touch screen and a guided program). Various levels of access to code-protected programs ensure that only scheduled changes can be programmed by authorized operators. The user-friendly screens allow for the selection of regimen (CCPD, IPD, Tidal PD, or any other variations), times, and volumes. In addition, this medical information system can be used for troubleshooting and equipment performance documentation.

The incorporation of bar codes has been used to automatically identify the type of solution employed. This information is transmitted to the cycler memory, compared with the prescription, and accepted or rejected accordingly. This feature ensures correct selection of dialysis solution based on the latest prescription.

Cost Considerations

The many models of cyclers in the market reflect the requirements of different regimens, prescriptions, and availability of funds devoted to renal replacement therapy in different countries. The convenience and safety offered by the state-of-the-art cycler technology is impressive but is not essential to the delivery of adequate care. The use of a cycler necessarily increases the cost of therapy. However, the increase can be minimized or contained by:

- Using fewer but larger containers manufactured with less expensive material and simplified packaging.
- Designing simpler tubing sets. This may also reduce the bioburden resulting from the disposal of plastics.
- Reducing the number of connections and other steps that require additional, often expensive, materials to maintain an aseptic environment.
- Reduction of disposables through reutilization of solution bags as drainage bags and the elimination of drain bags by direct disposal of spent dialysate into the sewage lines.

Conclusions

PD cyclers have evolved into systems that provide much more than automated exchanges for APD. Modern cyclers can monitor, record, store, and analyze data generated from serial treatments. These reports can be accessed or transmitted to the

medical center via protected Internet. Additional programs can suggest optimal prescriptions for specific patients, taking into consideration the combined data downloaded to the cycler and data generated from treatments. Further evolution is likely to occur given the increased utilization of APD and technological progress.

CHAPTER 16

Selecting a Dialyzer: Technical and Clinical Considerations

Nicholas Andrew Hoenich, PhD, CSci, CPhys, MInstP, and Claudio Ronco, MD

Introduction

In patients with chronic kidney disease (CKD), artificial support for the failing kidney is initiated when glomerular filtration rate approaches 15 mL/minute (or earlier if the patient is subject to clinical problems). The most widely utilized artificial support is hemodialysis, a diffusive process in which the blood passes on one side of a semipermeable membrane contained in an artificial kidney or hemodialyzer, the other side of the membrane being bathed by a dilute electrolyte solution (dialysis fluid). The dialyzer is used in conjunction with a proportioning system—sometimes referred to as the artificial kidney machine, whose role is the production of the electrolyte solution, facilitation of blood flow through the extracorporeal circuit, and monitoring of the safety and delivery of treatment.

The concept of dialysis was first described by Thomas Graham in 1861. Its clinical application began in the 1940s, initially for the treatment of acute renal failure. With the availability of a robust method of vascular access in the 1960s, it was extended to the treatment of chronic renal failure.

Currently, two different constructions of dialyzer are in clinical use: the hollow fiber (which uses bundles of fibers for the blood pathway) and the parallel plate, in which the blood passes between pairs of membrane sheets or a membrane tube sandwiched between supporting plates (Figures 16.1 and 16.2). Of these, the most widely used is the hollow fiber type. Within each of the types, further subdivisions in accordance with a variety of criteria may be made (e.g., membrane area, membrane chemical composition, and membrane permeability to water or to middle molecules [generally β_2 microglobulin]). It is not our intention to catalog dialyzer performance but to provide the clinician an overview of the technical and clinical factors required to interpret the dialyzer specification sheet and selection.

Figure 16–1

A modern hollow fiber hemodialyzer utilizing fibers with a three-dimensional microwave structure incorporated into a specifically designed housing generating optimized flow distribution in both the blood and dialysate pathways. *(Photograph courtesy of Fresenius Medical Care, Ag, Bad Homburg, Germany.)*

The Ideal Dialyzer

All current dialyzers may be considered manufacturer interpretations of the ideal device (Table 16.1). Within this specification, many of the parameters are determined by the membrane. Furthermore, some requirements are mutually exclusive or are only partially met by the design solutions offered by manufacturers.

Device Performance and Specification

The hemodialyzer is a simple membrane separation device whose performance characterization by the manufacturer is in accordance with internationally recognized standards (EN 1283 or ISO 8637). Performance is generally presented in a standard format similar to that shown in Figure 16.3. In the clinical setting, the three primary parameters of importance are solute transport characteristics, membrane hydraulic permeability, and

Figure 16–2

A modern multiple-pathway flat plate hemodialyzer. *(Photo courtesy of Gambro Ab, Lund, Sweden.)*

membrane blood contact behavior or biocompatibility. Of these, biocompatibility is the subject of a separate chapter, and subsequent discussion is confined to solute transport and hydraulic permeability characteristics.

Solute Transport

In a dialyzer the transport of molecules across the membrane occurs primarily by diffusion. Other mechanisms of transport (such as convection—a consequence of fluid flux across the membrane—and adsorption to the membrane) also make small contributions, and have been developed as alternate therapies

Table 16–1

Desirable Characteristics of a Dialyzer

- High and consistent clearance of small- and middle-weight uremic toxins, with negligible loss of vital solutes such as LMW proteins and amino acids
- Adequate ultrafiltration with minimal back-filtration at low ultrafiltration rates
- Low blood compartment volume
- Nontoxic and nonthrombogenic materials of construction
- Hemocompatible
- Reusable (if permitted)
- Low cost

Polyflux® H Dialyzer Performance and Specifications

Performance According to EN1283
Clearance in vitro (ml/min) ± 10%
Hemodialysis Q_D 500 ml/min, UF 0 ml/min

	Polyflux 140H			Polyflux 170H			Polyflux 210H		
Q_B	200	300	400	200	300	400	300	400	500
Urea	193	262	309	196	270	321	281	339	378
Creatinine	181	232	266	186	243	281	259	303	334
Phosphate	174	220	250	180	232	266	249	289	317
Vitamin B_{12}	128	149	163	137	162	178	183	203	218
Inulin	91	102	109	100	113	121	131	143	151
KoA	960	1000	1040	1100	1140	1190	1460	1500	1580

Hemodialysis Q_D 700 ml/min, UF 0 ml/min

	Polyflux 140H			Polyflux 170H			Polyflux 210H		
Q_B	200	300	400	200	300	400	300	400	500
Urea	196	275	334	198	283	348	289	362	418
Creatinine	186	246	289	191	259	307	270	326	368
Phosphate	180	234	272	186	248	290	261	311	348
Vitamin B_{12}	134	159	175	145	174	194	192	216	234
Inulin	95	108	116	106	121	131	137	150	160
KoA	–	977	1080	–	1123	1260	1440	1451	1580

	Polyflux 140H	Polyflux 170H	Polyflux 210H
UF Coefficient* (ml/h, mmHg) ± 20%	60	70	85
Priming Volume (ml)	94	115	125
Fluid volume for priming (ml)	≥ 500	≥ 500	≥ 500
Maximum TMP (mmHg)	600	600	600
Recommended Q_B	200–400 ml/min	250–500 ml/min	300–500 ml/min
Recommended Q_D	500–800 ml/min	500–800 ml/min	500–800 ml/min
Specifications			
Effective membrane area (m^2)	1.4	1.7	2.1
Fiber Dimensions (mm)			
Wall Thickness	50	50	50
Inner Diameter	215	215	215
Sieving coefficient**			
Vitamiin B_{12}	1.0		
Inulin	1.0		
B_2-Microglobulin	0.70		
Albumin	<0.01		

*Filtration in vitro measured with bovine blood, hematocrit 32%, protein 60 gl, at 37? C
**Typical values measured with Polyflux 170H, according to EN 1283

Sterilizing Agent	Steam
Sterile Barrier	Medical grade paper

Components		
Membrane	Polyamix™**	(PUR)
Potting material	Polyurethane	(PC)
Housing, Caps	Polycarbonate	(PP)
Protection Caps	Polypropylene	(SIR)
O-rings	Silicon	

**A brand of PAES-PVP-PA

Ordering information

Catalog #	Description	Unit of Sale
Polyflux 140H-A	High Flux Dialyzer	24/case
Polyflux 170H-A	High Flux Dialyzer	24/case
Polyflux 210H-A	High Flux Dialyzer	24/case

Figure 16–3

A typical hemodialyzer specification.

favoring enhanced removal of middle molecules such as hemofiltration and hemodiafiltration.

Solute transport across the membrane is governed by Fick's law, which can be expressed mathematically as

$$J_D = - DAT \frac{dc}{dx}$$

where D is the solute diffusivity, A the area available for transport, T the temperature, and dc/dx the concentration gradient. For molecules with a high diffusivity (i.e., larger molecules), removal is facilitated by flux or by transmembrane fluid movement. Similar to the flux due to diffusion, this can be mathematically expressed as

$$J_C = Q_F C_B S$$

where the convective flux (J_C) is a function of the ultrafiltration—fluid transfer rate across the membrane (Q_F), solute concentration in plasma water (C_B), and sieving coefficient (S)—which under ideal conditions is defined as $(1 - \sigma)$, where σ is the reflection coefficient. The reflection coefficient is a parameter that measures the relative restriction of the membrane to solute compared to the solution. This parameter varies between 0 for a freely permeable molecule and 1 for a completely impermeable solute. When $\sigma = 0$, no solvent drag occurs because no water transport occurs. When $\sigma = 1$, no solvent drag occurs because the solute cannot penetrate the membrane. The clinician generally views solute transport of a dialyzer in terms of clearance, a parameter simply defined as *the amount of solute removed from the blood per unit of time, divided by incoming blood concentration (i.e., the volumetric rate of removal by the device).* This is expressed mathematically as

$$K_B = Q_B \frac{(C_{Bi} - C_{Bo})}{C_{Bi}} + Q_F \frac{C_{Bo}}{C_{Bi}}$$

To account for fluid removal, it is necessary to modify this relationship such that it becomes

$$K_B = Q_{Bin} \frac{(C_{Bi} - C_{Bo})}{C_{Bi}} + Q_F \frac{C_{Bo}}{C_{Bi}} \text{ as } Q_{Bin} - Q_{Bout} = Q_F.$$

It should be noted that this correction does not provide a quantification of solute transport via convection but merely corrects the diffusion equation for differences in the flow rates entering and leaving the dialyzer. For the quantification of

clearance in the presence of convection using hemodialyzers with highly permeable membranes, note that ultrafiltration from blood to dialysate increases solute flow. Therefore, in this case it is possible to represent dialyzer clearance as

$$K = K_0 + TrQ_F,$$

where K_0 is a pure diffusive clearance (no ultrafiltration, equivalent to $Q_{Bi} = Q_{Bo}$), Q_F is the ultrafiltration flow rate, and Tr is the transmittance coefficient. Usually it is assumed that Tr is constant. Experimental studies have indicated that for ultrafiltration rates below 70 mL/minute the clearance is given by

$$K= K_0 + 0.46\ Q_F.$$

Above 70 mL/minute, it is given by

$$K= K_0 + 0.43Q_F + 0.00083Q_F^{\,2}.$$

For any dialyzer, the general relationship between blood flow rate and solute removal follows a similar shape. At low flow rates, the solute removal or clearance cannot exceed the blood flow rate, and at higher flow rates the solute transport is limited by surface area and mass transport characteristics. Classically, the commonly used blood and dialysate flow rates were 200 and 500 mL/minute (respectively). However, with the availability of more efficient devices and reduced treatment times the clinically used blood and dialysate flow rates generally exceed these values. The blood flow rate influences the clearance of small molecules, although there are exceptions to this; for example, phosphate as small molecule (MW 145 daltons) whose removal is influenced both by its behavior within the body (high body mass transfer resistance) and its hydration radius. Because of this, phosphate mass transfer per dialysis session remains inadequate despite the use of high-flux membrane and high-efficiency modalities.

The dialysate flow rate also primarily influences the removal of small molecules. Convective solute transport influences the clearance of middle molecules, whereas surface area plays a role in both the removal of small and middle molecules (Figure 16.4). For optimum small molecular clearance, the dialysate flow rate (Q_D) should be equal to but not exceed twice the blood flow rate (Q_B) because beyond this the gain in solute removal is minimal.

Clearance defines the amount of solute being removed by the device, but it fails to provide any insight into the underlying physical phenomena occurring at the blood membrane and the dialysate membrane interfaces. Mass transfer coefficients are a

convenient way of quantifying the transfer rates in the case of the moving fluid phases, and in the context of small molecules the mass transfer area coefficient (koA) is commonly used. This parameter is the optimum value of small molecular clearance (usually urea) under conditions of infinite blood and dialysate flows (i.e., the maximum clearance possible at infinite blood and dialysate flow rates). The mass transfer coefficient of a dialyzer (koA) is related to the clearance by the mathematical relationship

$$K_B = Q_B \left\{ \frac{\exp\left[\frac{koA}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - 1}{\exp\left[\frac{koA}{Q_B}\left(1 - \frac{Q_B}{Q_D}\right)\right] - \frac{Q_B}{Q_D}} \right\}$$

Dialyzers with koA values less than 500 are generally used only for "soft" or "low-efficiency" dialysis or for small patients. Dialyzers with koA values of 500 to 700 represent moderate-efficiency dialyzers, suitable for routine therapy. Dialyzers with koA values greater than 700 are considered "high-efficiency" dialysis.

By consideration of koA, the clinician may compare different dialyzers or estimate the performance under different flow conditions. However, a couple of caveats apply. This approach does not take into consideration the convective mass transport, and it assumes that the value of koA is constant throughout the different operating conditions. In practice, however, this has been shown not to be the case because increasing the dialysate flow rate results in an alteration of the koA characteristics due to a better flow distribution within the fiber bundle for hollow fiber dialyzers.

The product specification sheets for a dialyzer generally present data for small molecular compounds such as urea (MW 60 daltons), creatinine (MW 113 daltons), and phosphate (MW 145 daltons). In recent years, interest has grown in the removal of other compounds and it has become customary to include the clearance of vitamin B_{12} (MW 1355 daltons) and Inulin (MW 5200 daltons) to represent the removal of "middle-size molecules"—with the clearance data being combined with the sieving coefficient for the membrane.

The data presented and established in accordance with internationally specified standards are laboratory measurements using aqueous solutions containing the solute of interest. These values are generally higher than achieved in vivo. In the range of clinically relevant red cell concentrations, for urea (a small molecule that is highly diffusible) there is an approximately 5%

decrease in clearance that may be compensated for by the use of an increased blood flow rate.

Changing clinical patterns of treatment have meant a shift away from the conventional hemodialysis to the use of both high-flux and high-efficiency dialysis treatments, offering a significant reduction in treatment time without compromising the quantity of the delivered dialysis prescription. Such treatments nevertheless focus on small molecular removal—although high-flux dialysis offers a small enhancement of middle molecular removal. The removal of middle-size or large molecules can only effectively be achieved by the use of con-

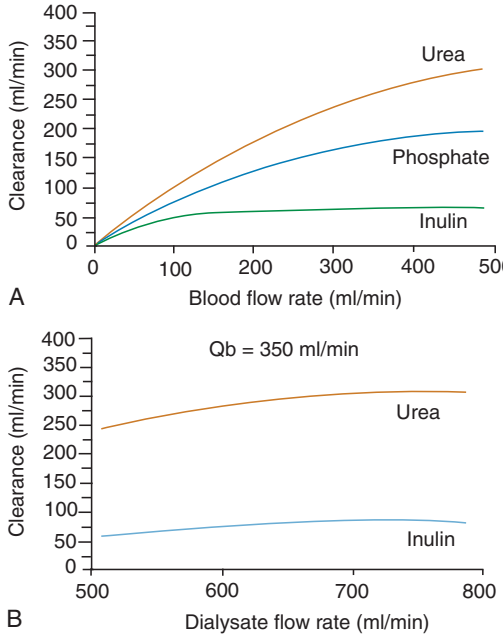


Figure 16–4

The influence of operating parameters on clearance characteristics of a dialyzer. *A*, Influence of blood flow rate at a constant dialysate flow rate on small and large molecular clearance. *B*, Influence of varying the dialysis fluid flow rate on the clearance of small and large molecules.

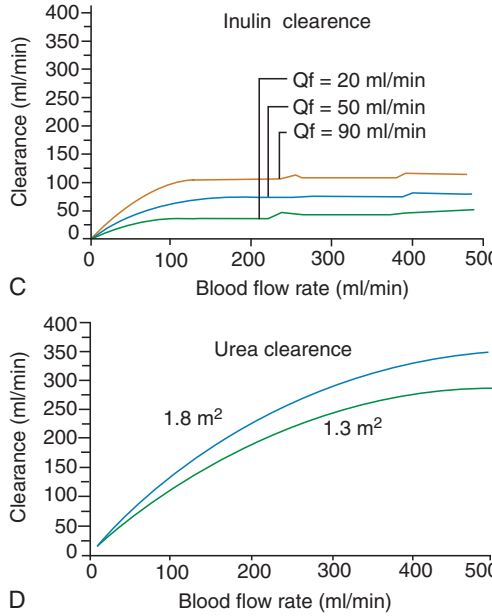


Figure 16–4

Cont'd

C, Influence of flux on the clearance of large molecules. *D*, Influence of surface area on the clearance of small molecules.

vective therapies such as hemofiltration and hemodiafiltration. Hemodiafiltration, being a treatment modality, evolved from the classical hemofiltration therapies of the early 1970s. It combines diffusive and convective transport with convective transport facilitated by the use of increased ultrafiltration and the maintenance of patient fluid balance by the infusion of a pyrogen-free substitution fluid.

Although such therapies are in limited clinical use, and have demonstrated improved solute transport characteristics compared with conventional dialysis, our knowledge of uremic toxins is far from complete. A recent review from the European Uremic Toxin group (EUTox), for example, has identified some 92 compounds with potentially adverse clinical effects.[1]

Further compounding issues are that many compounds are protein bound, making them difficult to remove. In addition, whereas enhancement of membrane permeability or flux results in increased removal current membranes in clinical use are nonselective and increased removal of uremic toxins may be associated with increased removal of amino acids and low-weight proteins. This aspect of membrane performance has to some extent been resolved by the use of manufacturing techniques that utilize "nano"-control of the pores, thereby limiting the loss of macromolecules such as albumin.

Enhancement of Solute Transport

Early developments in dialyzer design were aimed at improving the consistency of performance, followed by emphasis on improving the biocompatibility profile of membrane materials. Today, the focus is on optimization of performance or the achievement of the highest efficiency of solute removal for a given surface area for a specific device. There is, however, no universal agreement as to which method is optimal in achieving this. In the case of hollow fiber devices, a number of approaches have been used. These include the use of flow baffles, spacer yarns, and Moire structured membranes; redesigned blood headers to improve flow distribution in the blood; and dialysis fluid pathways.

Such improvements favor the removal of small molecules. Enhancement of larger-molecule transport has also taken place. This has been achieved by the use of nanocontrolled membranes (optimizing the pore size of the membrane to that of β2 microglobulin) or by the reduction of the inner diameter of the fibers used. This results in an increase of blood compartment flow resistance, which in turn increases transmembrane flux.

Clinical Application of Solute Transport Data

The clinician uses clearance data to establish the small molecular dialysis prescription for the patient to ensure that the minimal targets for dialysis dose defined by guidelines are achieved. In this context, it should be emphasized that whole-body clearance is not equivalent to dialyzer clearance. Furthermore, recent randomized controlled studies showed that increasing the dialysis dose above the currently recommended levels in thrice-weekly hemodialysis does not decrease patient mortality rates.

Targets for adequate removal of middle or large molecules such as β_2 microglobulin have not yet been established despite

the fact that high blood β_2 microglobulin concentrations are an independent and strong indicator of poor outcomes in hemodialysis patients. It has been recognized that convective treatments offer improved removal of such molecules. However, a recent study has indicated that removal is in magnitude similar to the intercompartmental clearance within the body under removal by hemodiafiltration—suggesting that improved removal can be only obtained by alternative strategies such as increased frequency of treatment.

Water Transport

During all renal replacement therapies, plasma water is removed to maintain a euvolemic state in the patient and to minimize the clinical consequences of volume overload. In the case of hemodiafiltration and hemofiltration, this removal provides a simple replacement of the excretory function of the human kidney. The rate of fluid removal is made up of two elements: fluid removal due to a hydraulic pressure differences in the device and removal due to pressure exerted by the presence of proteins (oncotic pressure, approximately 28 mmHg).

Fluid removal by the device in the presence of a pressure gradient is governed by the hydraulic permeabiliy of the membrane and the pressure. In practical terms, the water removal can be expressed in terms of the membrane permeability membrane area and the pressure gradient:

$$Q_F = L_h A\ [P]$$

$$Q_F = L_h A \left[\frac{P_{Bin} + P_{Bout}}{2} + \frac{P_{Din} + P_{Dout}}{2} - P_{osm} \right]$$

Dialyzer specification sheets generally indicate the fluid removal of the device in terms of the ultrafiltration coefficient, a product of hydraulic permeability (L_h) and area (A). The establishment of the dialyzer's ultrafiltration cefficient shown on the product insert is generally established using bovine blood to represent the clinical situation. Such values can differ between batches of dialyzer and during treatment due to protein deposition or membrane fouling by blood components. In plate dialyzers, a further deviation can occur due to the stretching of the membrane over the support structure—leading to a loss of effective area.

Historically, proportioning systems did not incorporate ultrafiltration control mechanisms. However, with the availability of such systems the importance of variability during dialysis or due to interbatch variation has diminished because

the system automatically compensates for any deviation from the set removal rate. As the clinical use of proportioning systems incorporating ultrafiltration control has grown, this has created a special situation in which if the required fluid removal rate during treatment is greater than the minimal ultrafiltration rate of the dialyzer a complex fluid balance within the dialyzer occurs in which the ultrafiltration (i.e., the fluid removal from the patient) is counterbalanced by back-filtration (transfer of fluid from the dialysate pathway).

Such back-filtration has both positive and negative effects for the patient. Although the dialysis membrane represents an effective barrier against bacteria, several studies have demonstrated the potential for bacterial fragments to traverse the membrane and contribute to microinflammation in patients undergoing dialysis. The pore size of the membrane is less important than the membrane structure in this process. Thus, patients treated with low-flux cellulose-based membranes may be at greater risk than patients treated using low-flux synthetic membranes (which have the capacity to adsorb bacterial fragments via interactions of such fragments with the hydrophobic domains in the membrane).

In the presence of ultrafiltration, the clearance of middle molecules is increased (Figure 16.4). By enhancing the internal filtration of the device, further improvements may be achieved. Several methods exist for enhancing internal filtration, including narrowing the inside diameter of the hollow fibers, lengthening the fibers and the module, insertion of an object to narrow the dialysate path, enhancing the permeability of the membrane, and increasing the fiber density ratio. However, each method has some disadvantages. For example, the more the inside diameter of the hollow fiber is narrowed to increase pressure in the blood pathway the greater the possibility of thrombus formation. In addition, the more the fiber density ratio is increased to increase the dialysate pathway pressure drop the less uniform flow becomes in the pathway. Increase of the surface area or alteration of the membrane's porosity generally increases water transport.

Other Considerations when Selecting a Dialyzer

The choice of dialyzer is a complex decision, based not only on the performance of the device but on the factors discussed in the following sections.

Flat Plate or Hollow Fiber?

Industrial data indicates that the most widely used device is the hollow fiber dialyzer. Such dialyzers are compact, easy to handle, and amenable to reprocessing or reuse. Furthermore, their blood compartment volume is fixed. In contrast, flat plate designs make use of molded plates to support the membranes. This approach to manufacture has enabled the size of the devices to be reduced to a size comparable with hollow fiber devices, but the manufacturing process requires high dimensional tolerances during manufacture to ensure that the flow through the multiple pathways is equal and balanced. In contrast to hollow fiber dialyzers, the device priming volume varies with applied pressure and their reprocessing or reuse is difficult. On the other hand, unlike hollow fiber dialyzers the plate dialyzers do not use any potting compound—which can adsorb ethylene oxide (potentially leading to dialyzer-related reactions) or be influenced by irradiation.

Membrane Type

Membranes used in dialyzers are manufactured from cellulose, modified cellulose, or synthetic polymers. World wide there has been a trend toward the use of dialyzers containing membranes manufactured from synthetic polymers. The use of unmodified cellulose such as Cuprophan is declining, and its future production is uncertain. The impact of membranes on clinical outcomes has been the subject of extensive study and considerable uncertainty. In respect of CKD treatment, the published studies have been subject to a meta-analysis by Macleod et al.—who found no evidence of benefit when synthetic membranes were compared with cellulose/modified cellulose membranes in terms of reduced mortality and reduction in dialysis-related adverse symptoms.[2]

Flux

In addition to the increased use of synthetic membranes world wide, there has also been an increased preference toward the use of high-flux dialyzers—possibly reflecting focus on treatment quality and practice outcomes in that a number of observational studies have reported improved survival when using synthetic high-flux biocompatible membranes. Such data based on small cohort studies fails to answer the question whether improved

survival is related to an effect of enhanced biocompatibility or to increased clearance of larger-molecular species. The HEMO study was initiated to address this in a prospective manner. However, the findings of the study have failed to conclusively answer this issue and a second European study is investigating the effects of membrane permeability on clinical outcomes (including mortality, morbidity, vascular access survival, and nutritional status) in a representative European population of incident hemodialysis patients.[3]

Convective therapies such as online hemodiafiltration have the potential to reduce cardiovascular morbidity and mortality due to their better removal of high-molecular-weight uremic toxins, the so-called middle molecules. This aspect is also currently under study by a prospective randomized study comparing online hemodiafiltration with low-flux hemodialysis with respect to cardiovascular morbidity and mortality.[4]

Surface Area

The effective surface area of the dialyzer is the geometric area available for solute transport and ultrafiltration. Thus, it is a parameter that influences both parameters. In the case of dialyzers using unmodified membranes, the surface area is additionally linked to the magnitude of complement activation.

Priming Volume

The priming volume of most of dialyzers is usually between 60 and 120 mL. It is related to the area of the membrane and in general is less than the volume of blood contained in the blood tubing sets. In a typical adult patient, this parameter is not of great clinical importance. However, it could be important in pediatric or small adult patients.

Sterilization

Historically, dialyzers were sterilized by the use of formalin. Today, the three primary methods of sterilization are ethylene oxide gas, steam autoclaving, or γ-irradiation. Reactions arising from the use of ethylene oxide together with environmental health concerns have resulted in a shift away from ethylene oxide in favor of heat and γ-irradiation. Another factor that influences the manufacturer's choice of sterilization is the type of membrane being used, in that some membranes cannot be

sterilized by heat-based methods (e.g., cellulose acetate and polyacrylonitrile). Although the dialyzers produced are sterile, their adequate rinsing prior to use by the patient is a mandatory requirement to ensure that sterilant byproducts and microorganisms destroyed by the sterilization process are removed.

Cost

Historically, dialyzers utilizing synthetic membranes were more expensive than those using cellulose-based membranes. However, today this price difference has diminished. Furthermore, the cost of dialyzers is continually changing and is influenced by local factors such as import duty, tax, and bulk purchase arrangements.

Reuse

Although some hemodialysis providers in the United States have recently embarked on programs to discontinue dialyzer reprocessing, the practice of reuse remains more common in the United States than in many other countries—with hollow fiber devices more commonly reprocessed than plate designs due to ease of cleaning and sterilization using automated systems. Furthermore, the use of strong oxidizing agents to clean the membrane after use favors dialyzers using synthetic membranes. Hemodialyzer reprocessing can be vulnerable to poor implementation and can contribute to morbidity associated with regular dialysis—although a recent analysis indicated that there is no overall survival advantage or disadvantage associated with dialyzer reuse compared to single use in incident hemodialysis patients.[5]

Reprocessing remains a controversial issue because it is impossible to return the dialyzer to its native state after use, thereby compromising its functionality notably in the removal of middle and large molecules and the adsorption of endotoxin fragments that may be present in the dialysis fluid. The long-term clinical effects of denatured proteins that remain on the membrane when reprocessed are at present unknown. The primary justification for reuse has been predominantly financial, although some reuse is geared toward improving blood-membrane biocompatibility. Given the widespread availability of biocompatible membranes, the reduction in the cost of dialyzers, and uncertainties about the quality and safety of reprocessing, it may be timely to reconsider this aspect of dialysis.

References

1. Vanholder R, De Smet R, Glorieux G, Argiles A, Baurmeister U, Brunet P, et al. European Uremic Toxin Work Group (EUTox). Review on uremic toxins: Classification, concentration, and interindividual variability. Kidney Int 2003;63:1934–43.
2. MacLeod A, Daly C, Khan I, Vale L, Campbell M, Wallace S, et al. Comparison of cellulose, modified cellulose and synthetic membranes in the haemodialysis of patients with end-stage renal disease. Cochrane Database Syst Rev 2001;3:CD003234.
3. Locatelli F, Pozzoni P, Di Filippo S. What are we expecting to learn from the MPO study? Contrib Nephrol 2005;149:83–89.
4. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nube MJ, et al. The CONTRAST study group. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients, the Dutch CONvective TRAnsport STudy (CONTRAST): Rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Control Trials Cardiovasc Med 2005;6:8.
5. Robinson BM, Feldman HI. Dialyzer reuse and patient outcomes: What do we know now? Semin Dial 2005;18:175–79.

CHAPTER 17

Biocompatibility of Dialysis Membranes

Nicholas Andrew Hoenich, PhD, CSci, CPhys, MInstP, and Claudio Ronco, MD

Introduction

Dialysis treatment involves the exposure of a patient's blood to nonphysiologic surfaces within the dialyzer and the blood tubing sets. The membrane contained within the dialyzer or related device represents the largest surface for blood contact. This chapter focuses on membrane materials, the interactions that occur when blood comes into contact with such materials, and the influence of such interactions on morbidity and mortality in acute and chronic renal failure.

Definition of Biocompatibility

Classically, biocompatibility was defined as *the ability of a material to perform with an appropriate response in a specific application*. This classical definition is based on the principles that a biomaterial has to perform and not simply exist and that it has to be associated with appropriate responses to ensure satisfactory performance. The main difficulty with this definition is that the applications of materials in the clinical setting are varied and there may be little commonality with the appropriateness of responses. To account for this, the original definition has recently been revised such that the biocompatibility of a material in contact with blood may be considered *the ability to carry out its intended function with minimal interaction between material and blood that adversely affects device performance, and without inducing uncontrolled activation of cellular or plasma protein cascades*.

Membranes Used in Dialysis

Historical human dialysis treatments relied on the use of membranes manufactured from cellulose, and the clinical use of such membranes dominated until the mid 1960s—when synthetic membranes became available. Cellulose membranes

can be produced by a variety of methods, all of which involve the regeneration of cellulose into either a sheet or fiber form. Cuprophan, a membrane widely used in the treatment of renal failure, was manufactured using solutions of copper in ammonia (cuprammonia, or Schweitzer's reagent) for regeneration. Cellulose membranes can also be regenerated using a melt spinning process, a technique developed in the 1960s.

In membranes based on cellulose, the cellulose strands making up the membrane contain gaps—creating tunnels through which molecules can pass. The size of these tunnels favors the passage of low-molecular-weight (LMW) compounds such as urea and creatinine, rather than middle- or larger-molecular-weight uremic toxins. The cellulose strands contain hydroxyl (OH)-groups that upon contact with blood play a pivotal role in determining a material's biocompatibility profile. The fact that this biocompatibility profile is inferior compared to synthetic membranes has resulted in considerable effort placed on the improvement of the biocompatibility by a variety of approaches intended to replace or mask the hydroxyl groups.

Hemophan (Membrana GmbH, Wuppertal, Germany), for example, uses diethylaminoethyl (DEAE). Synthetically modified cellulose (SMC, Membrana GmbH, Wuppertal, Germany) uses benzyl groups. In cellulose di- or triacetate, two or three of the hydroxyl groups are replaced by acetyl groups. The alternative approach to eliminating the interaction between the hydroxyl groups and blood is to mask the groups by grafting a polyethylene glycol layer onto the cellulose, which acts as a buffer between the cellulose and blood to hinder the direct contact of proteins with the surface.

Improvement of biocompatibility can also be achieved by the grafting of polyethylene glycol. This approach is also used by Asahi Kasei in the production of Excebrane, in which vitamin E (d α tocopherol) is added to the core solution during the spinning process. This leads to a covalent bonding to the OH groups of the material. This approach not only offers an improved biocompatibility profile but reduces oxidative stress during treatment by neutralizing oxygen radicals at their site of development. This approach has also extended to synthetic membranes. The classically produced Cuprophan membrane had a low hydraulic permeablility. Cellulose-based membranes in current clinical use are available in a range of permeabilities that permit their use not only in hemodialysis but in alternative therapies (Figure 17.1).

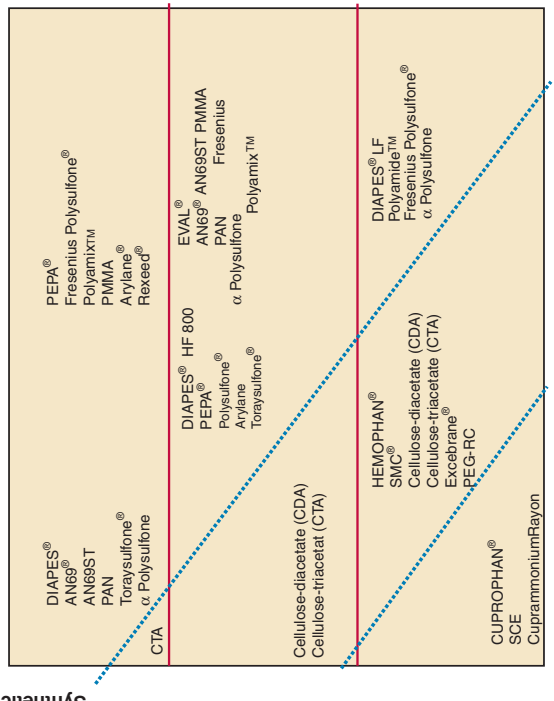


Figure 17–1

Hemodialysis membranes. *(Adapted from data provided by Stefan Breiter, Membrana GmbH, Germany.)*

Synthetic membranes were developed to create a more porous alternative to cellulose membranes that offers improved removal of middle and large molecules. One of the earliest synthetic membranes produced was polyacrylonitrile, which remains in use in a modified form developed to overcome the problems of anaphylactic reactions observed with early variants of this membrane when used by patients taking ace inhibitors for blood pressure control. Synthetic membranes are manufactured from polymers that with the exception of ethylene vinyl alcohol (EVAL) are hydrophobic. To permit their use in blood purification processes, they are blended with a hydrophilic material—generally polyvinylpyrrolidone (PVP).

A number of different synthetic membranes are available for clinical use, including those based on polymethylmethacrylate (PMMA), polycarbonate, and polyamide. Within the synthetic group, by far the most common material is that based on polysulfone. Such membranes are manufactured by different processes, which means that they cannot be treated as a homogenous group.

In terms of their chemistry, most of the currently produced polysulfones differ in their basic polymer. Materials containing isopropyliden groups are termed *polysulfones*, which include Helixone (Fresenius Medical Care, Bad Homburg, Germany), Asahi Polysulfone, Toraysulfone, and α polysulfone (Saxonia Medical, Radeberg, Germany). Polysulfone materials that do not contain isopropyliden groups are termed *polyarylethersulfones* or *polyethersulfones* and include Polyamix (Gambro Sweden), Arylane (Hospal, France), Purema, and Diapes (Membrana, Germany).

Synthetic membranes are also produced in a variety of permeabilities to meet differing clinical requirements. Compared to cellulose, these have a superior biocompatibility profile. However, unlike cellulose membranes they have an asymmetric structure, a consequence of the blending and manufacturing process. Such membranes are characterized by a dense blood contacting surface supported by a more open underlying support structure (Figure 17.2). There are considerable regional and national variations in the membranes used. It is of note, however, that in a recent review two worldwide trends were evident: a decline in the use of cellulose-based membranes in favor of those manufactured from synthetic materials and an increased use of high-flux membranes.[1] The evolution of membranes for renal replacement therapy continues, with new products being introduced into clinical use. Recent and evolving developments

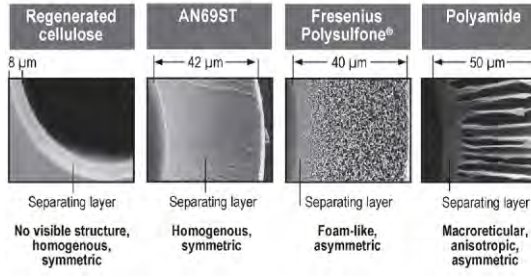


Figure 17–2

Dialysis membrane structures. *(Illustration courtesy of Professor Joerg Vienken, Bioscience Department, Fresenius Medical Care.)*

in membranes may be summarized as developments focusing on the following.

- Increasing the membrane pore size and sharpening the molecular weight cutoff. This permits more effective removal of middle- and larger-molecular-weight uremic toxins but minimizes the loss of albumin.
- The development of a class of membranes that permits the selective passage of LMW proteins and small protein-bound solutes, such as homocyteine and advanced glycation end products (AGEs).[2]
- The development of a membrane with slit-shaped pores that can separately regulate steric and hydrostatic hindrance with a high hydraulic permeability, mimicking the glomerular basement membrane.[3]
- Endothelial cell seeding of the membrane surface to move beyond filtration and add a metabolic component.[4]

Blood/Membrane Interactions

Membranes have traditionally been considered inert barriers between fluid films. However, it is increasingly recognized that interactions occur between the material and blood components (Figure 17.3). The magnitude of interactions is governed by the material's surface rather than by its bulk characteristics. Material-related parameters of importance include hydropho-

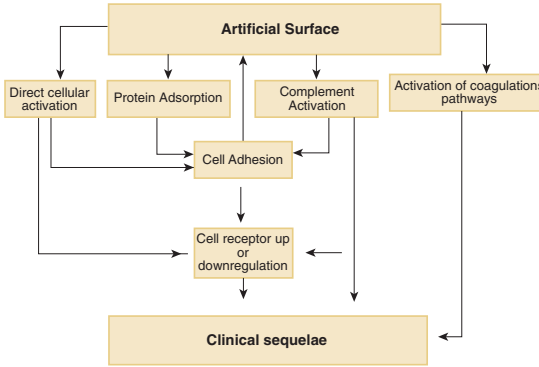


Figure 17–3

Blood/material interactions.

bicity, surface roughness, surface charge, and flow conditions at the time of interaction.

The underlying disease condition and drugs administered may also play a role. Increasingly, it is also being recognized that the membrane's porosity and adsorptive capacity for endotoxin fragments also impact on the biocompatibility of the treatment. Endotoxin fragments may be present in the dialysis fluid and due to their molecular weight distribution, have the potential to cross the membrane and come in contact with blood. This can further stimulate the patients immune system and contribute to micro inflammation associated with hemodialysis.

Contact Activation or Protein Deposition

Generally, the first blood surface contact event is the deposition of proteins onto the material surface. This event is governed by the interfacial properties of the proteins and the material surface. The importance of protein deposition stems from the fact that the deposited proteins exert a strong influence on subsequent cellular interactions with the surface. Adsorbed proteins are the relatively abundant plasma proteins (such as albumin, fibrinogen, immunoglobulin G, and fibronectin) that are replaced by trace proteins, including factor XII (Hageman factor) and high-molecular-weight (HMW) kininogen (HMWK).

This hierarchical adsorption process is called the Vroman effect. The small amount of activated factor XII (XIIa) is the key enzyme in initiating the coagulation, fibrinolysis, and kinin cascades. Activated factor XII and its fragments (XIIf) can potentially induce activation of the classical pathway of the complement system. The adsorption of proteins additionally mediates cellular adhesion. Initially, platelets are involved—due to the presence of receptors on the platelet surface (IIb/IIIa, Ib/IX) that facilitate adhesion. The adsorption of proteins may be considered to provide a degree of bioreactivity to the membrane surface. On the other hand, in the case of porous materials it inevitably modulates the diffusive characteristics of the material.

Activation of the Coagulation System

Activation of the coagulation system occurs as soon as the blood leaves the vessel and comes into contact with a nonphysiologic surface. The initial event of coagulation is platelet adhesion. In parallel with this activation, plasma coagulation proteins are activated that initiate hemostasis. Adhesion is mediated by platelet glycoproteins (GPs) IIb/IIIa and by GPIb and von Willebrand factor (vWF) interactions. Following adhesion, a complex series of reactions is initiated. This involves the release of platelet dense granule adenosine diphosphate ADP, the formation of small amounts of thrombin, and the generation of thromboxane A2. These elements contribute to the recruitment of further platelets into a growing platelet aggregate. Thrombin binds directly to the platelets and contributes to the formation of platelet aggregate formation.

During extracorporeal circulatory procedures, thrombogenecity is governed by three factors: the patient's thrombus generation potential, the membrane material, and the flow conditions within the device. Thrombogenecity can also be influenced by the manufacturing quality and sterilization of the device. The membrane and flow conditions are important because surface contact and shear activate platelets and the coagulation cascade.

All extracorporeal circulatory procedures utilize the anticoagulant heparin, although less commonly LMW heparin may be used to control the activation of the coagulation pathway. However, no anticoagulant can eliminate the hemostatic system activation. The adequacy of anticoagulation during the procedure is generally measured by activated clotting time (ACT), which employs specific agents to trigger the coagulation process.

Such measurement, however, fails to provide a measure of the ability of the material to induce thrombus formation. This ability is a measurement of thrombin-antithrombin (TAT) complex or platelet activation (the release of platelet factor 4 or B thromboglobulin).

Activation of the Immune System

The complement system is a nonspecific defense mechanism that forms part of the immune system. It consists of more than 25 different proteins activated by a variety of agents. The activation of these proteins proceeds in a cascade fashion, leading to lysis. Activation may be via the classical, alternative, or recently discovered lectin pathway—the latter acting via foreign carbohydrates on microbial surfaces.

For membranes, complement activation occurs via the alternative pathway. It is initiated by the deposition of C3b on the material surface, which together with factor B forms C3 and C5 convertases. These enzymes cleave the anaphylatoxins C3a and C5a from C3 and C5 by an autocatalytic process. Once in the circulation, the C-terminal arginine is removed and C3a $_{\text{des Arg}}$ and C5a $_{\text{des Arg}}$ are formed. These fractions are generally measured when membrane-induced complement activation is studied. The cleavage of C5 by C5 convertase results in the production of C5a and C5b, the latter initiating the formation of the membrane attack complex (MAC) and its soluble form SC5b-9 (terminal complement complex). A wide range of clinical sequelae are associated with the generation of C3a, C5a, and C5b-9—and virtually every blood cell type responds either directly via receptors or indirectly via secondary mediators to these complement fractions.

It is well recognized that membranes manufactured from unmodified cellulose are the strongest activators of the complement system. Modified cellulose is intermediate, and membranes manufactured from synthetic polymers are minimal, in activating the complement cascade. The partial replacement or masking of hydroxyl groups in cellulose-based membranes modulates the complement activation but does not completely eliminate it. Furthermore, the degree of substitution does not correlate with the magnitude of improvement—suggesting that other factors are involved. Such factors also play a role in the case of synthetic membranes that activate the complement cascade, albeit minimally in the absence of hydroxyl groups. Activation of the complement system has been reported in all

extracorporeal treatments, and has been shown to occur when blood is exposed to tubing sets.

Cellular Activation

Modification of the physiology or biochemistry of blood cells may occur as a result of direct cell contact with the membrane surface or indirectly as a result of the activation of the coagulation or immune system.

Neutrophils

Following initial contact of the blood and foreign surface, a profound transient neutropenia occurs. The magnitude of leukopenia observed is related to the degree of complement activation. Thus, membranes with a strong complement-activating potential demonstrate the greatest fall in circulating white cells. This dialysis-induced neutropenia is a consequence of the overexpression of receptors (CD11b/CD18 and CD15s) on leukocytes, leading to cell adhesion to the endothelium and to pulmonary sequestration. The measurement of receptor expression [e.g., upregulation of receptors on the polymorphonuclear cell surfaces or the downregulation of L-selectin (CD 62L)] provides a further insight into differences among membranes.

Dialysis enhances oxidative stress and contributes to atherosclerosis, cardiovascular disease, and dialysis-related complications such as amyloidosis. A number of factors in addition to membrane biocompatibility (such as the incomplete correction of uremic toxicity, malnutrition, and the progressive worsening of the clinical condition due to aging and co-morbid conditions) also contribute. Reactive oxygen species production occurs with both cellulose-based and synthetic membranes. However, the magnitude of production is higher with the former. The repeated production of reactive oxygen species has the potential to influence endothelial function. The vitamin E–coated membrane offers a degree of protection against such production at the site of generation. Whether this approach is superior to other treatment—such as the oral prescription of antioxidant therapy (e.g., vitamin C)—remains unresolved at present.

Degranulation of polymorphonuclear leukocytes (PMNs) also occurs during dialysis. In the past, it has been thought that this is a consequence of the activation of the complement system in a time- and membrane-material-dependent manner. Recent

experimental evidence, however, suggests that degranulation does not depend on complement activation but may be influenced by high angiogenin and/or complement factor D levels (which protect against lactoferrin release from PMN during extracorporeal circulation).[5]

Platelets

During dialysis, circulating platelets adhere to proteins deposited on the material surface. Platelet leukocyte co-aggregate formation has been implicated in the pathogenesis of thrombosis and inflammation and is thought to be related to a primary platelet-activating mechanism that involves P-selectin (CD62P)—a marker of activated platelets—and CD15s (the sialyl-Lewis × molecule), a selectin ligand. It is possible that the CD62P/CD15s interaction seen during hemodialysis represents the first stage of leukocyte margination.

Monocytes

Monocytes are activated during blood membrane contact. C5a induces mRNA IL-1β and TNFα transcription and primes the cells for the translation of cytokines following further stimulation. This further stimulation may be endotoxin entering the bloodstream from the dialysis fluid across the membrane, or the direct contact of monocytes with the membrane itself.

Eosinophils

Eosinophils have antihistamine properties and congregate around sites of inflammation. Eosinophilia is known to occur in hemodialysis patients and probably results from allergy to hemodialysis-related material, including the dialyzer membrane.

Erythrocytes

Red cells are remarkably robust. However, they may be subject to increased susceptibility to erythrocyte C5b-9 deposition and complement-mediated lysis in chronic renal failure. Damage may also be induced by mechanical damage arising from the blood pump or by shear stresses from kinked bloodlines. Mechanical damage may occur as a result of extracorporeal circulatory processes arising from the blood pump or as a result of rupture of the cell membrane having come into contact with

granular material. Such lysis results in the release of ADP, which is a potent mediator of platelet aggregation.

Stimulation of Cytokine Generation

Plasma cytokine levels are elevated in dialysis patients, and such elevation is present in early stages of renal failure. Membrane-related factors contributing to this elevation are permeability and the ability to adsorb and/or stimulate cytokines. Not all synthetic membranes have the same adsorptive capacity. Adsorption is most pronounced for polymethylmethacrylate (PMMA) and AN69. Intracellular levels of cytokines are also increased in dialysis patients. This has the potential to contribute to the inflammatory process characterized by increased levels of C-reactive protein and interleukin-6. These elevated levels are not merely a consequence of membrane biocompatibility. Other factors, such as the bacterial contamination of dialysis fluid, play a role (Figure 17.4).

Optimization of Blood Membrane Interactions

The improvement of the biocompatibility profile of a membrane material is generally achieved through alteration of material

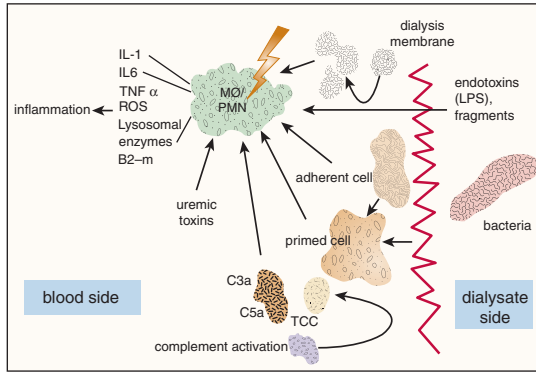


Figure 17–4

Cytokine stimulation and inflammation during hemodialysis.

surface chemistry. Controlled chemical modification leads to the development of predictable biocompatibility profiles. For example, hydrophilic domains on the material surface in polymer blends have a stimulatory effect on the complement activation potential of the material. However, they have little effect on the material's ability to activate platelets. On the other hand, hydrophobic domains show a reduced influence on the activation of the complement system but stimulate platelet adhesion. Although material science has focused on this aspect of membranes, it is clear that the biocompatibility of the material cannot be isolated from the underlying biochemical abnormalities of the patient or from other aspects of the dialytic treatment (such as the microbiologic quality of the dialysis fluid).

Clinical Significance of Biocompatibility

In regard to the clinical effects of membrane biocompatibility, the discussion here is confined to first-use reaction, reuse, effects on patients being treated for acute renal failure, effects on patients undergoing treatment for chronic kidney disease, and membrane selection.

First-Use Reactions

First-use reactions occur shortly following the initiation of dialysis, and rarely later during a dialysis session or even following the completion of treatment. Two main subgroups exist: type A (anaphylactic-type reactions that occur a few minutes following the start of dialysis) and type B, which are not anaphylactoid in nature and usually occur later (20–30 minutes) in the treatment.

Many of these reactions were classically described in regard to cellulose-based membranes. Their cause, however, is multifactorial—including leechables or degradation products (such as ethylene oxide or isopropylmeristrate, a chemical used in the production of hollow fibers) originating from the production process or from prolonged and incorrect dialyzer storage, interactions between the blood and membrane material or the presence of residues associated with inadequate rinsing of the dialyzers.

Reuse

Although dialyzer reuse is declining, it continues to be practiced in the United States and elsewhere. Numerous articles have

been published on the effect of different reprocessing chemicals and techniques on dialyzer biocompatibility. However, there is no single adequately powered prospective randomized clinical trial that provides definitive evidence regarding superiority or equivalence comparing single use and reuse.

Historically, the reprocessing of unmodified cellulose (e.g., Cuprophan) dialyzers—sterilized principally using ethylene oxide—was common and used formaldehyde as the reprocessing chemical. The reuse of such dialyzers was associated with a number of advantages: improved biocompatibility, reduced incidence of "first-use syndrome," and decreased intradialytic symptoms. Adverse reactions, such as immunohemolytic anemia due to anti-N antibody associated with dialyzer reuse, were also reported arising from the incomplete removal of formaldehyde during the rinsing procedure. Skin rashes, rhinorrhea, and asthma-type symptoms were also noted in subjects working in areas where formaldehyde was used. A recent review by Finelli et al.[6] indicates that the use of formaldehyde for reprocessing dialyzers has declined substantially. This, together with other changes in dialysis practice and technology (such as decline in the use of unmodified cellulose dialyzers and the availability of alternatives to ethylene oxide), have eliminated two of the claimed advantages of reprocessing. Thus, today economics is the most important reason for reprocessing.

Acute Renal Failure

Although renal replacement therapy is the mainstay of supportive care in patients with acute renal failure, it can have untoward effects (such as the prolongation of renal failure or impedence of the recovery of renal function). The potential impact of dialyzer membrane biocompatibility on clinical outcomes in acute renal failure has been a subject of ongoing controversy with conflicting data. A recent meta-analysis[7] reviewed all-cause mortality and recovery of renal function by type of dialyzer and dialyzer flux properties (high flux or low flux) and concluded that no demonstrable clinical advantage exists favoring the use of biocompatible versus bioincompatible membranes in the treatment of patients with acute renal failure requiring dialysis.

Chronic Renal Failure

The survival, morbidity, and quality of life of patients undergoing regular hemodialysis treatment is suboptimal. Despite

the proven superiority of biocompatible membranes, we lack definitive evidence that thrice-weekly complement and cell activation over a period of years is detrimental to patients because the results of prospective randomized studies are conflicting. In a recent Cochrane review,[8] the authors found no evidence of benefit when synthetic membranes were compared with cellulose/modified-cellulose membranes in terms of reduced mortality or the reduction in dialysis-related adverse symptoms.

Further large-scale prospective and randomized trials with a long follow-up are needed in order to better clarify the clinical effect of different treatment modalities on the morbidity and mortality of patients on chronic renal replacement therapy. In particular, it must be clarified whether the possible clinical differences in treatment modalities are based on differences in the clearance of middle molecules or on biocompatibility—or, more generally, on the interaction between membrane flux and biocompatibility.

Selection of Membranes

The presently available membranes cover a broad spectrum, from unmodified cellulose low-flux to synthetic high-flux membranes. Unmodified low-flux celluloses have a poor biocompatibility profile (e.g., complement activation), do not prevent the penetration of impurities from the dialysate into the bloodstream, do not remove middle molecules, and have minimal adsorptive capacity. Synthetic membranes are biocompatible, remove middle molecules, and adsorb compounds from both the blood and dialysate pathways. The selection of a membrane for use in treatment of patients is complex and is determined by the performance of the membrane, membrane cost, and philosophy of treatment.

Standards differ in the way they deal with differences among membranes in respect of biocompatibility. On the one hand, the European Best Practice Guidelines[9] recommend that membranes with the lowest degree of complement and leukocyte activation should be used. Membranes that induce strong complement and leukocyte activation, inflammatory reactions, and/or a blunting of the response of leukocytes to stimuli should be avoided. To achieve an improved clinical outcome regarding morbidity and mortality, the use of large-pore/high-flux biocompatible dialyzers should be preferred.

The British Renal Association Standards for dialysis[10] state that “the balance of evidence favours the use of low flux

synthetic and modified cellulose membranes over unmodified cellulose membranes in the majority of patients. The benefits of low flux synthetic and modified cellulose membranes are limited to different aspects of biocompatibility and not patient outcomes. Patients who are likely to remain on dialysis for several years and those with symptoms of dialysis-related amyloidosis should, where possible, receive a dialysis regimen with better clearance of β2 microglobulin such as haemodialysis with high flux synthetic membranes and haemodiafiltration." On the other hand, the Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) excluded membrane biocompatibility, and the Canadian Society of Nephrology makes no recommendation.

References

1. Grassmann A, Gioberge S, Moeller S, Brown G. ESRD patients in 2004: Global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant 2005;20:2587–93.
   This article provides a comprehensive overview of treated ESRD patient numbers for the year 2004, both globally and for various geographical regions (which, together with data available from national and international registries, provide insight into present-day ESRD demographics).
2. Ward RA. Protein-leaking membranes for hemodialysis: A new class of membranes in search of an application? J Am Soc Nephrol 2005;16:2421–30.
3. Humes HD, Fissell WH, Tiranathanagul K. The future of hemodialysis membranes. Kidney Int 2006;69:1115–19.
   This article reviews progress made in improving the biocompatibility of hemodialysis membranes, as well as their hydraulic and permselective properties to remove small solutes and "middle molecules" in compact cartridges. It also discusses future developments aimed at further improving the clearance functions of the kidney to replicate glomerular permselectivity while retaining high rates of hydraulic permeability and utilizing microfluidics and nanofabrication. The extension of membrane technology to biohybrid devices utilizing progenitor and stem cells is also discussed.
4. Humes HD, MacKay SM, Funke AJ, Buffington DA. Tissue engineering of a bioartificial renal tubule assist device: In vitro transport and metabolic characteristics. Kidney Int 1999;55:2502–14.
5. Schmaldienst S, Oberpichler A, Tschesche H, Horl WH. Angiogenin: A novel inhibitor of neutrophil lactoferrin release during extracorporeal circulation. Kidney Blood Press Res 2003;26:107–12.
6. Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. Seminars in Dialysis 2005;18(1):52–61.
7. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure. Cochrane Database Syst Rev 2005;18:CD005283.
   The authors performed a meta-analysis on nine studies with a total of 1062 patients to ascertain whether the use of biocompatible membranes confers an advantage in either survival or recovery of renal function over the use of bioincompatible membranes in adult patients with acute renal failure requiring intermittent hemodialysis according to the flux properties (high flux or low flux) of each of these dialyzers. The pooled relative risk (RR) for

mortality was 0.93 [95% confidence interval (CI), 0.81 to 1.07]. The overall RR for recovery of renal function was 1.09 (95% CI, 0.90 to 1.31). The pooled RR for mortality by dialyzer flux property was 1.03 (95% CI, 0.82 to 1.30). The RR for recovery of renal function by flux property was 0.85 (95% CI, 0.55 to 1.31). A meta-analysis of mortality of kidney transplant recipients was not possible, but the analysis of recovery of renal function in this patient population was 1.09 (95% CI, 0.91to 1.31)—indicating that there is no demonstrable clinical advantage to the use of biocompatible versus bioincompatible membranes in patients with ARF who require intermittent hemodialysis.

8. Macleod AM, Campbell M, Cody JD, Daly C, Donaldson C, Grant A, et al. Cellulose, modified cellulose and synthetic membranes in the haemodialysis of patients with end-stage renal disease. Cochrane Database Syst Rev 2005;20:CD003234.
   The authors performed a meta-analysis of 32 randomized controlled trials (RCTs) or quasi-RCTs comparing different hemodialysis membrane material in patients with end-stage renal disease and found no evidence of benefit when synthetic membranes were compared with cellulose/modified-cellulose membranes in terms of reduced mortality and no reduction in dialysis-related adverse symptoms.
9. European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section III: Biocompatibility. Nephrol Dial Transplant 2002;17(7):32–44.
10. The Renal Association and the Royal College of Physicians of London. *Treatment of Adults and Children with Renal Failure: Standards and Audit Measures*. London: The Lavenham Press 2002.

CHAPTER 18

Urea Kinetic Modeling for Guiding Hemodialysis Therapy in Adults

Frank A. Gotch, MD

This chapter addresses the use of urea kinetic modeling (UKM) in prescribing and monitoring the adequacy of dialysis. Optimal use of UKM requires the use of a computer urea kinetic modeling program because the mathematical routines are too complex for realistic manual or calculator solutions. The purposes of this chapter are to describe UKM, define the role it has had in determining adequacy of dialysis, and indicate some reliable approximation equations for UKM.

Blood Urea Concentration, Normalized Protein Catabolic Rate, and Fractional Clearance

There are only two randomized studies of dialysis dose, and both were guided with UKM (which remains the only generalized dialysis dosing model validated for correlating dose of dialysis with clinical outcome). Although urea is the modeled solute, it has been shown using UKM that uremic toxicity is not directly proportional to blood urea concentration (BUN). However, it has also been shown that the level of uremic toxicity is strongly related to the fractional clearance of urea [dialyzer urea clearance (K) times treatment time (t) divided by urea distribution volume (V), or Kt/V]—which can be used to quantify the dose of dialysis and ensure that it is adequate. These relationships, which were discovered with the National Cooperative Dialysis Study (NCDS), are not intuitively obvious and were not well understood for several years after they were reported.

NCDS Domains of Adequate and Inadequate Dialysis Doses

The NCDS was a National Institutes of Health (NIH)–sponsored multicenter study of outcomes with randomized doses of dialysis.

Its results were plotted on BUN and normalized protein catabolic rate (NPCR) axes, as shown in Figure 18.1a. The urea model was used to prescribe and monitor therapy in the NCDS, which had four treatment arms: groups I and III had low BUN, with long treatment time (t) in I and short t in III; groups II and IV had high BUN, with long t in II and short t in IV. There was not a significant effect of t on outcome, but as seen in Figure 18.1a the therapy failure rate (incidence of clinical uremic complications) was 52% in groups II and IV and 13% in croups I and III. However, there was an unanticipated fifth outcome (group V, shown in Figure 18.1a).

The group V patients all had a low normalized protein catabolic rate (NPCR, gm/kg/day) of 0.60 to 0.80 gm/kg/day. In this group, there was a very high incidence of failure (75%)—irrespective of the BUN. These dichotomous results with respect to BUN were very puzzling. They seemed to imply that with normal protein intake uremic symptoms resulted

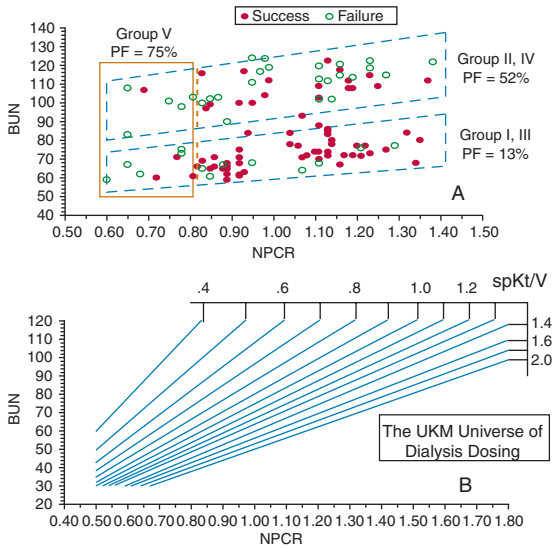


Figure 18–1

A, Results of NCDS. *B*, Solution of urea model.

from underdialysis, whereas the same uremic symptoms were unresponsive to dialysis (expressed only as BUN) with low protein intake. Figure 18.1b shows a generalized solution of the urea model for BUN as a function of NPCR at constant levels of dose expressed as single-pool Kt/V (spKt/V) ranging from 0.4 to 2.0. When Kt/V is constant, BUN increases linearly with urea generation rate (its analog, NPCR)—as plotted in Figure 18.1b. This plot might be considered the "UKM universe of dialysis dosing."

Figure 18.2 depicts superimposition of the urea model solutions (Figure 18.1b) on a map of clinical outcome groups (Figure 18.1a). It is readily apparent in Figure 18.2 that all groups with high failure rates (II, IV, and V) have spKt/V < .8, whereas group I and III patients with low failure rate are all distributed over the spKt/V range of 0.80 to 1.45. Thus, the mechanism common to all of the high-failure groups was a low dose of small solute clearance expressed as the fractional urea clearance (Kt/V). Note that the level of BUN is virtually irrelevant to the definition of an adequate dose because a BUN of 75 can represent low NPCR, and very low spKt/V or can represent high NPCR and high spKt/V. The results shown in Figure 18.2 indicate that uremic symptoms are not proportional to urea concentration, that the generation rate of uremic toxins is not proportional to Gu (group

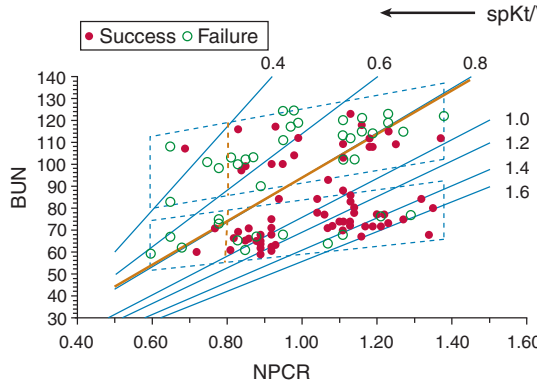


Figure 18–2

NCDS outcome results with superimposed Kt/V grid indicate that outcome failure was virtually eliminated when Kt/V > .80.

V patients had very low NPCR), and that urea serves only as a generic solute for modeling the fractional clearance of low-molecular-weight (LMW) toxins.

The NCDS outcome data in Figure 18.2 are further explored in Figure 18.3. In Figure 18.3a, the domains of inadequate and adequate dialysis defined by that study are depicted on the UKM Dialysis Dosing plot. In Figure 18.3b, the NCDS data are shown as relative risk of failure in all patients stratified as a function of mean spKt/V achieved. Note that RPF was uniformly high in group II and IV patients and uniformly low in group I and III patients. A step function was fitted to the data. This function defines the domains in Figure 18.3a reflecting the randomization of doses in the study (groups II and IV versus groups I and III).

The step function was used to construct the modeling line for adequate dialysis in Figure 18.3, but both the step function and an exponential relationship were reported in the NCDS analysis. Over the subsequent 25 years, these two interpretations of the data were hotly contested. The step function indicated that no outcome benefit would occur with spKt/V > 1.00, whereas the

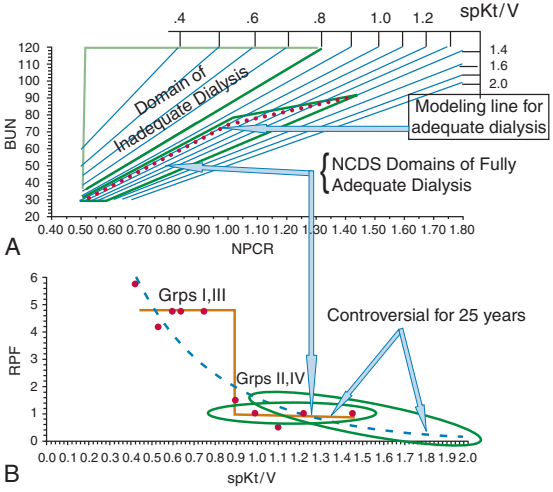


Figure 18–3

Two views of outcome in NCDS.

exponential relationship suggested that an outcome benefit would continuously occur with spKt/V doses as high as 2.00.

The HEMO Study

Because of ongoing controversy and uncertainty about the adequate dialysis dose, the NIH organized a second randomized trial of HD (HEMO) beginning in 1994. The initial design in the pilot study called for a standard dose arm targeted for spKt/V 1.10 to 1.20 (which would overlap the middle of the high-dose arm in NCDS) and for a high-dose arm with spKt/V > 1.45. However, a number of observational studies suggested that the minimal adequate dose of dialysis should be a spKt/V > 1.40. Thus, when the HEMO study started the design was changed to targeted doses to 1.40 and 1.75 in the two arms.

These relationships are shown in Figure 18.4, where it can be seen that the final design of HEMO addressed only the very high-dose part of the NCDS controversy (spKt/V 1.4 to 1.8) but

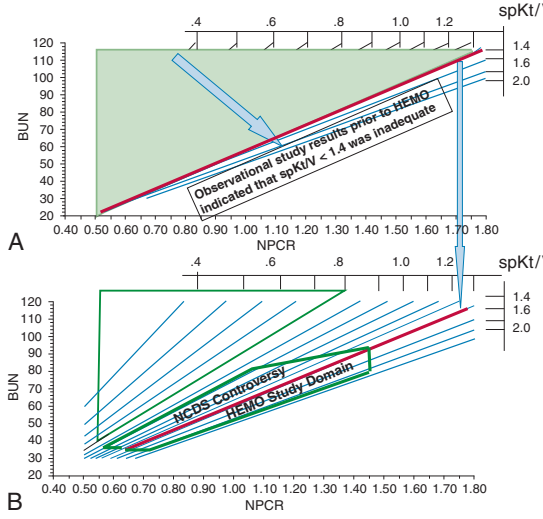


Figure 18–4

The effect of observational study results on design of the HEMO study.

did not address the controversy about adequacy of spKt/V over the range 1.0 to 1.4. HEMO did clearly show that there was no improvement in outcome between spKt/V 1.4 and 1.85 but shed no light on the outcome with spKt/V 1.1 to 1.4.

Observational and Randomized Studies

Figure 18.5 depicts the results of observational studies based on analyses of USRDS and CMS (Center of Medicare and Medicaid Services) data, showing that RRM continues to fall as spKt/V increases to 2.00 (which must be interpreted to indicate that spKt/V less than 2.00 is inadequate therapy). It is quite remarkable, as illustrated in Figure 18.5, that the observational studies indicate that all of the doses studied in both randomized trials (NCDS and HEMO) are inadequate. How can these profoundly different dose responses be reconciled?

The most likely explanation is shown in Figure 18.6b, where the two arms of HEMO are shown individually stratified by quintiles of spKt/V and associated relative risk of mortality (RRM) normalized to the highest dose in each arm. This was

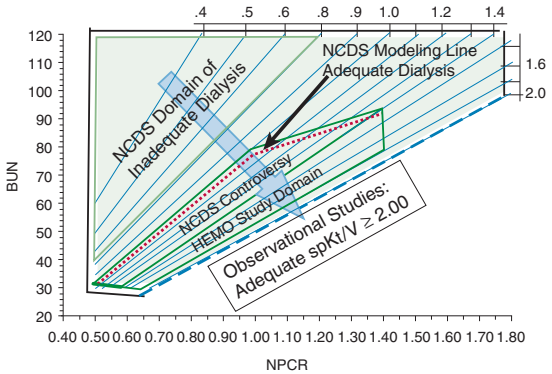


Figure 18–5

Recent obsrational studies have indicated improved outcome with spKt/V = 2.00. If this is true, all of the randomized trial data must be construed to be inadequate dialysis. Is there any way to reconcile these highly contradictory conclusions about an adequate dialysis dose?

originally done in the standard arm because of safety committee concern about patients who might not be reaching the target spKt/V 1.4, judged to be the minimal adequate dose by observational data. The results for the standard arm in Figure 18.6b were very alarming and jeopardized continuation of the study because the data strongly suggested that the lower doses in this arm were inadequate. However, the same analysis was done on the high-dose arm and (as also depicted in Figure 18.6b) the identical relationship was observed over a range of doses that were clearly adequate.

The relationships in Figure 18.6b provide striking examples of dose targeting bias resulting from unrecognized risk factors interfering with achievement of the targeted doses in nonrandomized observational studies. These factors cannot be interpreted as dose responses. Note that the higher the dose range studied the higher the apparently adequate dose becomes. The dose response becomes a self-fulfilling prophesy that seriously compromises the validity of dose-targeted observational studies. The outcomes in both arms of HEMO were

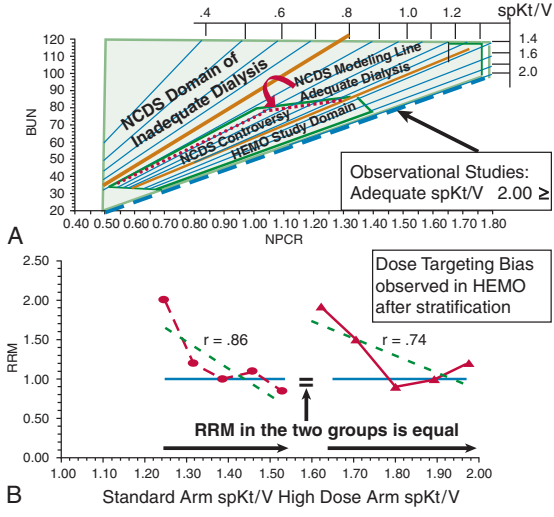


Figure 18–6

Reconciliation of observational studies with randomized trials.

equal, which is also shown in Figure 18.6b (with RRM 1.0). So what can be concluded regarding the adequate dose of dialysis? There is clearly no benefit gained with spKt/V > 1.4, and it remains unknown whether a spKt/V of 1.4 is better than spKt/V = 1.0 due to compromise of the original HEMO study design (as discussed previously).

Volume as an Independent Predictor of Outcome

It has recently been reported that V per se is inversely correlated with RRM in dialysis patients, which adds complexity to analysis of the clinical outcome response to Kt/V. It is unknown why large patients with larger V have lower RRM, but in view of this relationship it is essential to stratify outcome data over a range of constant levels of V when examining RRM as a function of Kt/V (because both Kt/V and V may independently influence outcome).

Cross-sectional observational analyses have suggested that Kt is a better parameter of dosage, but analyses with V held constant have shown the interacting effects of V and Kt/V on RRM (Figure 18.7). The curves in Figure 18.7, where RRM is shown as a function of eKt/V over three tertiles of constant

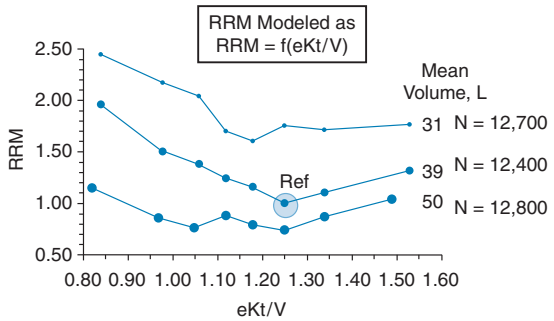


Figure 18–7

RRM in FMC data modeled as a function of eKt/V after stratification for V. A family of nearly parallel curves due to volume effect emerges. It appears by inspection that maximum benefit is reached at eKt/V in the range of 1.20 for three strata of V. There is clearly no improvement at higher levels of eKt/V.

volume, show the strong inverse relationship of RRM to V but also indicate no improvement by increasing Kt/V in any of the groups. Similar relationships were found in the HEMO study. This puzzling relationship requires further research. At present there is no evidence that smaller patients require larger doses of dialysis expressed as Kt/V.

Role of UKM in Dialysis Therapy

A computer modeling program is required for full clinical use of UKM. There are simplified equations now available (Daugirdas and Tattersall references) that are quite reliable for calculation of Kt/V. The approximation equations of Tattersall provide highly reliable estimates of double-pool effects on the single-pool V calculation and are often combined with computer-based UKM analyses. In view of these considerations, it is important to ask what need there is for UKM in clinical dialysis.

There are four major advantages that accrue with the use of UKM. First, the delivered dose of dialysis is more reliably measured with UKM than with the approximation equations (i.e., a higher level of quality assurance is achieved). With UKM, the kinetic equations are solved to calculate V—and any errors in delivery of the dose (recirculation, flow, or time errors) are clearly manifest in errors observed in the calculated V (which should be relatively constant over time). Thus, a high spKt/V may be calculated with an approximation equation in the case of recirculation and faulty sampling technique (not uncommon). However, UKM would show a very small V and clearly indicate technical error.

A second advantage of UKM is that an accurate estimate of PCR (protein catabolic rate, gm/day) is calculated, which is equal to dietary protein intake in relatively stable patients. The PCR is a very useful quantity for the renal dietician, providing her/him with a reliable measure of actual protein intake and month-to-month variability in intake.

It is useful to plot the monthly BUN, NPCR, and Kt/V points on a graph (Figure 18.1b) for each patient. Inspection of the graph over time with the patient can be a valuable educational tool. In patients on protein supplements, the PCR provides a method of evaluating the effect on nitrogen balance. If a plot such as that shown in Figure 18.1b has been used, when protein supplements are seen to simply increase the NPCR and BUN proportional with the amount of supplement probably little has been achieved.

UKM provides for calculation of individualized dialysis prescriptions, which is not possible using approximation equations. An individualized dialysis prescription requires a kinetically determined mean urea distribution volume for the patient (and solution of the dialyzer transport equations over a range of blood and dialysate flows and treatment times) in order to select the best combination of dialyzer, blood and dialysate flows, and treatment time for the patient. UKM computer programs permit archiving of treatment data and as such are also very useful for managing the therapy database for a patient population. Thus, the distributions of spKt/Vs, eKt/Vs, and NPCRs and comparison of delivered versus prescribed Kt/V are valuable analyses readily available with the archived data in UKM programs.

Role of UKM in More Frequent and/or Continuous Hemodialysis Therapy and with Residual Renal Function

There is a strong resurgence of interest in more frequent chronic hemodialysis, including short daytime and long overnight hemodialysis six times per week. In acute renal failure, the spectrum of therapy ranges from continuous to variable-frequency intermittent hemodialysis. There is also interest in starting dialysis at higher levels of residual renal function, and it has been recommended by NKF-K/DOQI that in such cases the combination of CAPD or intermittent dialysis with continuous renal function be quantified with UKM. The most rational approach to these relationships is transformation of intermittent clearance to an equivalent level of continuous clearance. In the steady state with continuous clearance, the relationships among concentration of urea (C), clearance (K), and generation rate (Gu) are given by

$$G = K(C). \tag{18.1}$$

Solution of Equation 18.1 for K gives

$$K = G/C. \tag{18.2}$$

Equation 18.2 can be used to calculate a value for continuous clearance from G and a specified concentration point (C) on the concentration profile resulting with any therapy schedule. The mean pre-dialysis BUN has been used to define an equivalent standard K (stdK) and stdKt/V. The stdKt/V is the only model shown to predict identical adequate doses of both continuous CAPD and thrice-weekly HD (as shown in Figure 18.8, where a

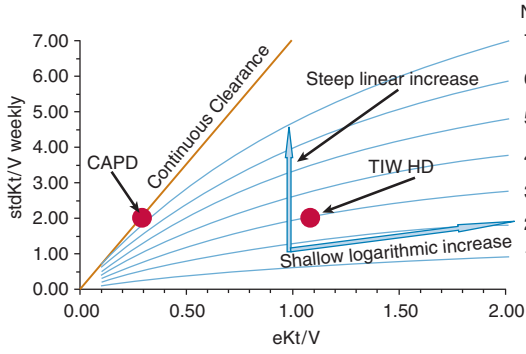


Figure 18–8

Results of solution of stdKt/V model over wide ranges of eKt/V and N. Note that by inspection stdKt/V appears to increase linearly as N increases, and logarithmically with eKt/V. The dose of adequate CAPD and thrice-weekly HD are the same with this model (weekly stdKt/V 2).

generalized solution for weekly stdKt/V as a function of eKt/V delivered each dialysis and the number of dialyses per week are shown). Note the continuous clearance line, which is simply 7 times the values for eKt/V on the abscissa (i.e., each eKt/V is given continuously every day).

The two points on the plot show that a weekly Kt/V for CAPD of 2.0 corresponds well with the stdKt/V of 2.0, which is calculated for thrice-weekly dialysis with eKt/V 1.05 each treatment. The uniform flattening of each of the curves in Figure 18.8 as eKt/V increases is due to the decreasing efficiency of solute removal in each individual dialysis as fractional clearance of body water increases and solute concentration falls to very low levels.

It might be predicted from the shape of the curves in Figure 18.6 that clinical benefits would increase minimally as eKt/V increases beyond 1.05—because of decreasing dialysis efficiency and minimal increase in stdKt/V in this range. The converse is also true. The curves in Figure 18.6 suggest that increasing frequency of dialysis may result in substantial increase in clinical benefit due to the increase in stdKt/V, which can be raised to a new unexplored domain with 6-times-weekly dialysis.

Dosing Recommendations for Adequate HD per CAPD Dosing

Three sets of data are illustrated in Figure 18.9. Set A depicts the recommendations from HEMO for HD and from NKF-K/DOQI for CAPD. These are highly consistent and recommend an adequate stdKt/V = 2.1 for both therapy modalities. Set B shows the recommendations of the ADEMEX study for CAPD and of the NCDS for HD. Note that these two studies are also highly consistent (recommending stdKt/V = 1.75 for both CAPD and HD). Data set C shows the recommended eKt/V = 2.0 for HD from observational studies. This would require a weekly stdKt/V of ≥2.6 for CAPD, which is far higher than any clinical recommendations.

So what can we conclude about dosing in CAPD and a thrice-weekly HD? It would seem clear that the observational studies give false levels of required stdKt/V. The reason for this appears to be dose targeting bias. The ADEMEX findings fit with the NCDS data very well, and both may provide fully adequate doses of dialysis. Because there are some uncertainties in all of these data sets, it would seem safest to use the average

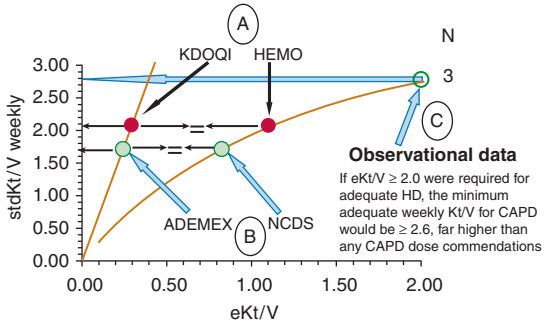


Figure 18–9

Comparison of stdKt/V for CAPD and three sets of HD data. The Ademex study defined adequate stdKt/V = 1.7, which agrees well with the NCDS recommendation for adequate HD. NKF-K/DOQI is based on the HEMO recommendation for spKt/V 1.4, which results in stdKt/V values for both HD and CAPD of about 2.1. The observational studies recommend eKt/V 2.0, which would equate with stdKt/V 2.6 (far higher than recommended for CAPD).

of NKF-K/DOQI and ADEMEX and the average of NCDS and HEMO to model the adequate dose for stdKt/V at about 1.9 and for eKt/V at about 1.05.

Recommended Reading

Gotch F, Keen M. Kinetic modeling in hemodialysis. In Nissenson AR, Fine RA (eds.), *Clinical Dialysis, Fourth Edition.* New York: McGraw-Hill 2005:153–203.

This chapter contains detailed discussions of UKM, eKt/V, and stdKt/V and analysis of NCDS and volume effects on outcome.

Gotch F, Keen M. Kinetic modeling in peritoneal dialysis. In Nissenson AR, Fine RA (eds.), *Clinical Dialysis, Fourth Edition*. New York: McGraw-Hill 2005:385–421.

This chapter contains detailed discussions of CAPD, stdKt/V, combining residual renal function with CAPD or HD, and the kinetic relationships between CAPD and HD.

Greene T, Daugirdas J, Depner T, Allon M, Beck G, Chumlea C, et al. for the Hemodialysis (HEMO) Study Group. Association of achieved eKt/V with mortality in the HEMO study: An example of "dose-targeting bias." J Am Soc Nephrol 2005;11:3371–80.

This article provides a comprehensive analysis of HEMO data stratified by dose and details the problem of dose targeting bias.

Port F, Ashby V, Dhingra RK, Roys E, Wolfe R. Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 2002;4:1061–66.

This is one of many articles from this group on dose response in HD based on observational data.

Daugirdas J. Second generation logarithmic estimates of single pool variable volume Kt/V: An analysis of error. J Am Soc Nephrol 1993;4:1205–13.

This contains the only reliable simplified equation for calculating Kt/V from pre- and post-BUN. The equation approximates quite well the effects of urea generation and ultrafiltration on the Kt/V calculation.

Tattersall J, De Takats D, Chamney P, Greenwood R, Farrington K. The post-hemodialysis rebound: Predicting its effect on Kt/V. Kidney Int 1996;50:2094–2102.

Develops highly reliable simplified equations for correcting single-pool errors in volume calculation and for calculating the equilibrated Kt/V (eKt/V).

CHAPTER 19

Simplified Formulas and Nomograms for Monitoring Hemodialysis Adequacy

Richard A. Sherman, MD, and Robert Hootkins, MD

The most accurate method of determining dialysis delivery to a patient involves the measurement of urea obtained from the dialysate collected over an entire treatment. Unfortunately, this is time consuming and difficult to perform. Consequently, mathematical methods have been devised to model the urea that is lost from the blood side of the dialyzer membrane during treatment.

This approach is referred to as formal urea kinetic modeling (fUKM), which is a mathematical technique for simulating the kinetics of urea mass balance in a dialysis patient using all of the factors that influence urea movement into, out of, and within the patient. However, even UKM has logistic barriers to its routine and widespread adoption. These barriers have led to the development of simplified methods of quantitating dialysis.

Urea Reduction Ratio

The most simplified and widely utilized measure of dialysis dose is the urea reduction ratio (URR) described by Lowrie. The URR is the percentage of reduction in the blood urea nitrogen (BUN) over the course of a single hemodialysis treatment. The extent of the reduction in BUN reflects dialytic urea clearance adjusted for body water (V). The intrinsic "adjustment" for V is apparent by considering that a given dialytic urea clearance produces a slower rate of fall in BUN (i.e., lower URR) in patients with a larger V (urea space). The calculation of the URR is

$$\text{URR}\ (\%) = 100\ [1 - (\text{BUN}_{\text{post}}/\text{BUN}_{\text{pre}})],$$

where BUN_{pre} and BUN_{post} are blood samples obtained immediately before and after dialysis. The use of the URR to monitor dialysis dose ignores the significant urea clearance that results from ultrafiltration, and fails to include (less significantly) urea

generation during the treatment. The BUN_{pre} and BUN_{post} values used for the URR are also the critical inputs into formal urea kinetic modeling programs.

Kt/V

Most published studies of dialysis adequacy have used the Kt/V ratio as popularized by Gotch and Sargent in their reanalysis of the National Cooperative Dialysis Study. The Kt/V is a dimensionless ratio representing the fractional urea clearance. K is the dialyzer blood water urea clearance (mL/minute or L/hour), t is the dialysis treatment length (minutes or hours), and V is the distribution volume of urea (mL or L). For a Kt/V of 1.0, the total volume of blood cleared during the dialysis treatment is equal to the urea distribution volume.

Relationship Between URR and Kt/V

If one considers dialysis of a patient to be from a simple urea space of fixed size to which cleared blood returns to and dilutes, dialysis results in a simple exponential decline of urea concentration during the course of a treatment. The mathematical relationship between Kt/V and URR can be defined as

$$URR = 1 - e^{-Kt/V},$$

where e is a mathematical constant of approximately 2.72. By rearranging and solving for Kt/V, we obtain

$$Kt/V = -\ln (1 - URR),$$

where ln is the natural log. For a Kt/V of 1.0, the URR is 0.63. Actual data from 813 patients showed that URR values of 55, 60, 65, and 70% are associated respectively with median Kt/V values of 0.91, 1.05, 1.23, and 1.41. However, there is a relatively wide range of Kt/V values for any given URR. For example, of the 99 patients with a URR of 67% and a median Kt/V of 1.27, 10% had Kt/V values less than 1.09 and another 10% had values greater than 1.53. In analyzing the Kt/V values in more than 15,000 dialysis patients, Lowrie et al. determined that the equation for best fit of Kt/V with a correlation coefficient (r) of 0.954 was

$$Kt/V = [.024 \times URR] - 0.276.$$

This equation is used by some commercial laboratories to convert the URR to a single-pool (fixed volume) Kt/V. Daugirdas

developed a more complicated but more reliable relationship between URR and Kt/V as

$$Kt/V = -\ln (R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55\ UF/V,$$

where R is the ratio of the postdialysis to predialysis BUN [equal to (1 – URR)], t is the length of the dialysis session in hours, UF is the ultrafiltration volume in liters, and V is the urea distribution volume—which can be determined via anthropometric methods or can be assumed to be 55% of the postdialysis weight (W) in kilograms. Using the latter assumption, the equation becomes

$$Kt/V = -\ln (R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W.$$

The use of logarithms in this formula requires some mathematical adeptness, a barrier that can be bypassed using one of two other approaches. First, the relationship between URR (as well as R) and Kt/V for varying ultrafiltration levels has been published as a nomogram (Figure 19.1)—allowing for an accurate estimation of Kt/V even when one's mathematical skills are limited. A second approach is to use a linear formula rather than a logarithmic one. Because the relationship between Kt/V and URR is logarithmic, a linear formula must pick a tangential line at an arbitrary point in the URR/Kt/V relationship. When the point chosen is a Kt/V of 1.3, the linear formula is

$$Kt/V = 2.2 - 3.3\ (R - 0.03 - UF/W).$$

This equation yields a Kt/V that is very close to a formal single-pool variable-volume UKM value for most clinical settings, has been well validated across the usual range of Kt/V, and yields values within 5% of those derived from urea kinetic modeling.

This "fudged" or derived precision in the relationship between Kt/V and URR has left some nephrologists uneasy with its widespread use. However, other nephrologists argue that complex mathematical manipulations of kinetic data add little clinical value because the URR itself is an excellent tool for predicting mortality in hemodialysis patients. Patients with a URR of 55 to 59% have a 28% increase in mortality compared with patients having URR values of 65 to 69%.

Although the URR is easy to calculate, its accuracy is critically dependent on the accuracy of the two BUN values used in its determination. The predialysis blood samples should be obtained from the arterial line before dialysis has begun, and without any dilution of the blood by saline. The postdialysis sample is often problematic. A common error is to obtain a

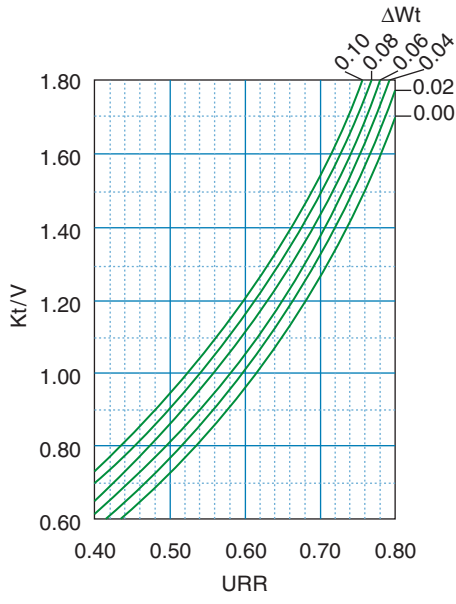


Figure 19–1

Estimated Kt/V from the URR for varying levels of dialytic weight loss. Curves show the URR/Kt/V relationship for weight loss from 0 to 10% of predialysis body weight. *(From Depner TA. Semin Dial 1993;6:242.)* Estimation of Kt/V from the urea reduction ratio for varying levels of dialytic weight loss: A bedside graphic aid.

post*dialyzer* (i.e., venous line) sample rather than a post*dialysis* arterial line sample. This error often accounts for an inexplicably high URR (>90) value.

Because the BUN rebounds almost immediately following dialysis, values for URR will vary if the timing of the postdialysis sample varies. Therefore, it is advisable to devote considerable attention to ensuring that blood-sampling methodology in the dialysis unit is uniform among staff members. A detailed protocol should be provided and followed. The combined goals of simplicity and reliability can be achieved by drawing the postdialysis sample from the arterial bloodline just before termination of the treatment. The blood pump should be stopped exactly 15 seconds after reducing the dialyzer blood flow to

100 mL/minute and the sample should be obtained (stop-flow method). Reducing the blood flow rate to 100 mL/minute eliminates virtually all flow-related access recirculation (except from reversed needles). The 15-second delay is long enough to clear the line of any blood "contaminated" by earlier recirculation but short enough so that urea rebound is not an issue. Use of the BUN obtained with this procedure will yield a URR that can then be used to calculate a single-pool Kt/V.

Equilibrated Corrections to the Kt/V

As a consequence of the way dialysis is performed, multiple types of recirculation (access recirculation and cardiopulmonary recirculation) and disequilibriums (from variations in regional tissue blood flow and the unequal tissue sequestration of urea) occur. The most accurate reflection of the amount of dialysis the patient has received is determined using a postdialysis (equilibrated) urea sample obtained 30 to 60 minutes after dialysis is completed. This value allows an equilibrated Kt/V (eKt/V) to be calculated. An eKt/V is almost identical to a double-pool Kt/V.

Because waiting 1 hour postdialysis to obtain a sample is not practical for most patients and facilities, estimating the eKt/V can be valuable. Because the postdialysis rebound in BUN is proportional to the rate of dialysis (K) divided by a patient's urea distribution volume (V), the eKt/V can be estimated from the single-pool value as

$$eKt/V = spKt/V - (0.6 \times \frac{spKt/V}{t}) + 0.03$$

Thus, a 4-hour treatment yielding a spKt/V of 1.2 is equivalent to a eKt/V of $1.2 - (0.6 \times 1.2/4) + 0.03$, or 1.05. This relationship between the single-pool and the eKt/V has also been published as a nomogram (Figure 19.2). The increasing frequency with which central-vein catheters are utilized for chronic hemodialysis is relevant to dosing assessment. The immediate postdialysis BUN from a venous access is not depressed by cardiopulmonary recirculation. Thus, rebound is reduced and a different equation is used to convert the spKt/V to the equilibrated value:

$$eKt/V = spKt/V - (0.47 \times \frac{spKt/V}{t}) + 0.17$$

The relationship between the single-pool Kt/V for treatments using a venous catheter and the eKt/V has also been published

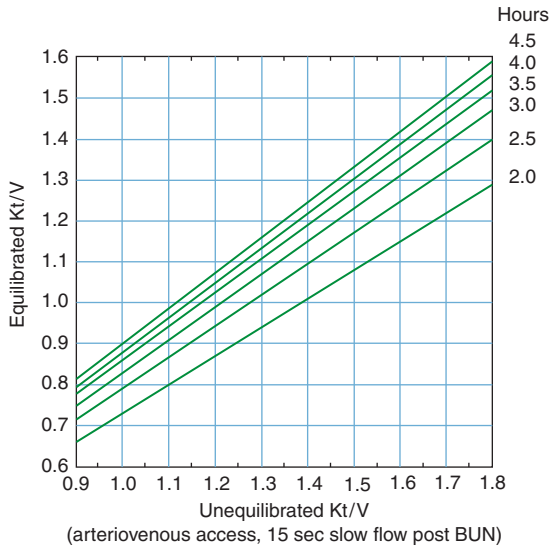


Figure 19–2

Estimation of the eKt/V from the unequilibrated (single-pool) Kt/V for varying treatment times using an A-V access with the postdialysis blood sample obtained from the arterial line 15 seconds after reducing the BFR to about 50 mL/minute. *(From Daugirdas JT. Semin Dial 1995;8:283.)* Estimation of the equilibrated Kt/V using the unequilibrated post dialysis BUN.

as a nomogram (Figure 19.3). This nomogram can also be used in AV access–based dialysis when the BUN_{post} is delayed for 2 minutes.

Novel Forms of Hemodialysis

The use of novel forms of hemodialysis—such as frequent, short and frequent, and long (overnight) dialysis—is becoming more widespread. Assessing the dialysis dose and developing adequacy standards for these treatments is problematic. One approach to the problem is to convert a single-pool Kt/V for an individual treatment into a weekly "standard" (std) Kt/V.

A given stdKt/V results in the same pretreatment BUN regardless of the length or frequency of the dialysis treatment.

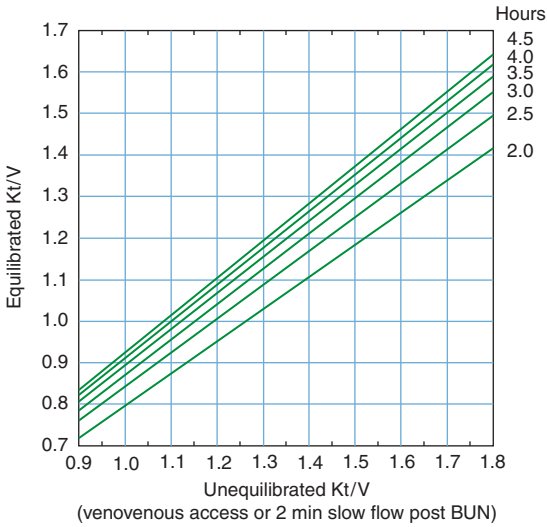


Figure 19–3

Estimation of the eKt/V from the unequilibrated (single-pool) Kt/V for varying treatment times using a central vein access with the postdialysis blood sample obtained from the arterial line 15 seconds after reducing the BFR to about 50 mL/minute. This nomogram can also be used for an A-V access when the postdialysis blood sample is obtained from the arterial line 2 minutes after reducing the BFR to about 50 mL/minute. *(From Daugirdas JT. Semin Dial 1995;8:283.)* Estimation of the equilibrated Kt/V using the unequilibrated post dialysis BUN.

The underlying assumption (unproven) is that differing dialysis modalities providing patients with an equivalent stdKt/V will result in equivalent outcomes. The mathematics for determining the required conversion from a single-pool Kt/V for an individual treatment to a stdKt/V are quite complex. A nomogram approach is far more practical. Figures 19.4a and 19.4b provide nomograms for long (8-hour) and short (2-hour) therapies.

Conclusions

The clinical value of the various mathematical manipulations for URR and Kt/V is currently uncertain and reflects physical/

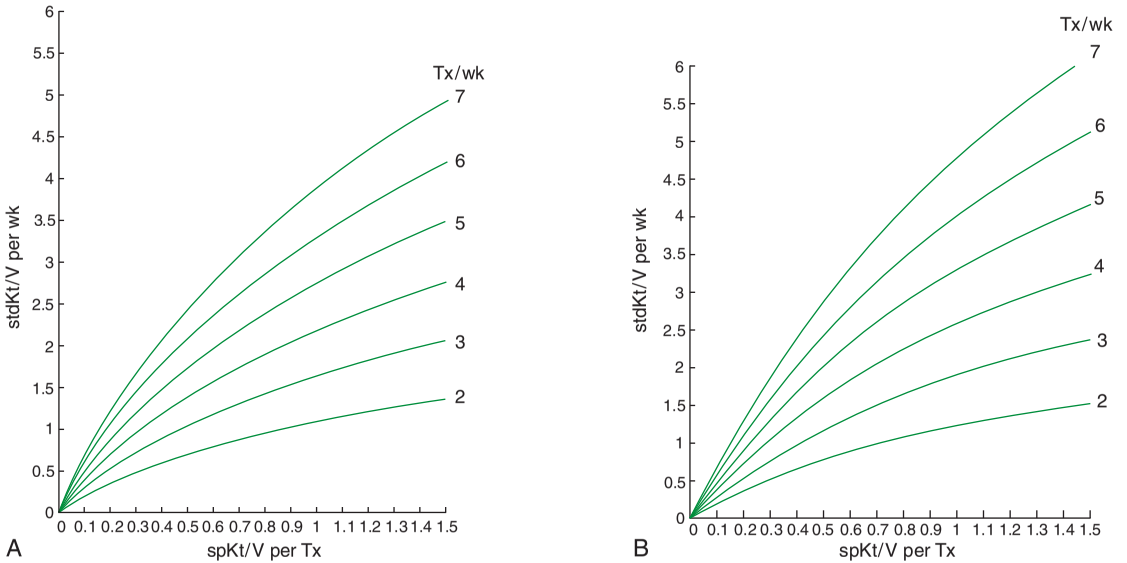


Figure 19–4

Estimation of the weekly stdKt/V from the spKt/V value calculated from one treatment for novel therapies consisting of two to seven treatments weekly of approximately 2 hours *(A)* or approximately 8 hours *(B)*. *(Figures courtesy of John K. Leypoldt.)*

mathematical logic rather than clinical outcome data. Based on simplicity, the simple URR remains a widely used approach. However, its theoretical limitations should be kept in mind. More exact estimates of dialysis doses are easily derived from the URR and from readily accessible clinical data.

The minimum target value for the URR based on National Kidney Foundation–Dialysis Outcomes Quality Initiative and ESRD Network recommendations is at least 65%. The clinical advantages of achieving values in excess of 70% are currently uncertain but may provide a comfort margin that dialysis is not being underprescribed. The mean URR of a dialysis unit is often used as a measure of unit performance in dialysis delivery. However, this approach may obscure the number of at-risk patients with low URR values. Instead, one should examine the percentage of patients not achieving a target URR and use this as a yardstick of performance for individual dialysis facilities.

Recommended Reading

Daugirdas JT. Linear estimates of variable volume, single-pool Kt/V: An analysis of error. Am J Kidney Dis 1993;22:267–70.
This study compares linear formulae Kt/V with the logarithmic formula and with the modeled Kt/V.
Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Study (NCDS). Kidney Int 1985;28:526–34.
This report popularized the use of Kt/V in the reanalysis of NCDS data.
Leypoldt JK, Jaber BL, Zimmerman DL. Predicting treatment dose for novel therapies using urea standard Kt/V. Semin Dial 2004;17:142–45.
An approach to calculating a standardized Kt/V for frequent and longer therapies from single-pool Kt/V estimates for an individual treatment.
Lowrie EG, Lew NL. The urea reduction ratio (URR) a simplified method for evaluating hemodialysis treatment. Contemp Dial Nephrol 1991;12:11–19.
This is the initial publication describing the URR as a new yardstick of dialysis dose.
Sherman RA, Cody RP, Rogers ME, Solanchick JC. Accuracy of the urea reduction ratio in predicting dialysis delivery. Kidney Int 1995;47:319–21.
The range of Kt/V values observed with specific URR values.

CHAPTER 20

Quality, Safety, and Accountability

Jay B. Wish, MD

Introduction

The problems found in end-stage renal disease (ESRD) facilities in the United States mirror fundamental shortcomings in the American health care system in general, as described in the Institute of Medicine (IOM) 2001 report *Crossing the Quality Chasm: A New Health Care System for the 21st Century*. The IOM concludes that "the American health care delivery system is in need of fundamental change." The IOM proposes six key goals for the twenty-first-century health care system. These are summarized in Table 20.1.

The IOM points out that much of the quality "chasm" that currently exists in health care delivery is due to misaligned incentives between health care systems, payers, medical professionals, patients, technology, education, and legal liability. Multiple inter-

Table 20–1

Goals for the Twenty-first-Century Healthcare System

- *Safe:* Avoiding injuries to patients from the care intended to help them.
- *Effective:* Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively).
- *Patient-centered:* Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.
- *Timely:* Reducing waits and sometimes harmful delays for both those who receive and those who give care.
- *Efficient:* Avoiding waste, including waste of equipment, supplies, ideas, and energy.
- *Equitable:* Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.

related dimensions of health care delivery must be addressed, improved, and aligned to improve the quality chasm. Several of these dimensions have immediate relevance to the care of dialysis patients, and include quality, safety, and accountability.

Quality

Quality in health care has taken on increased importance over the past decade as payers, regulators, and patients have all demanded an improved product from health care providers. In the 1980s and early 1990s, the emphasis was on *quality assurance*. However, traditional quality assurance activities were never embraced by physicians because quality assurance departments in hospitals were generally staffed by nurses involved in risk management and utilization review—which fostered the concept that quality assurance was a burdensome and intrusive function with little impact on patient outcome. Although industry had successfully applied the principles of quality improvement for many years because of the opening of worldwide markets that forced manufacturers to focus on quality, American health care providers had been immune from competitive pressures until the increased penetration of capitated payment plans forced health care providers to lower costs and improve quality.

The principles of quality improvement are so intuitive that it is difficult to understand why physicians have been so resistant to embracing them. Table 20.2 summarizes the benefits of quality improvement. Quality improvement is similar to the differential diagnosis of a medical problem. First, one builds a list of possible etiologies ("rule-outs"). Then one initiates testing or therapy to rule out each possibility until the diagnosis is confirmed. Finally, one checks the patient for evidence of improvement to validate that the diagnosis and choice of therapy were correct.

In quality improvement, a multidisciplinary team at the provider level examines an issue in which there is an opportunity for improvement. This might be a structural issue (such as staffing ratios or the water treatment system), a process issue (such as the drawing of postdialysis BUN (blood urea nitrogen) levels or the administration of influenza vaccine), or an outcome issue (such as a high percentage of patients with low Kt/V or with dialysis catheters). The team then brainstorms to list the "differential diagnosis" classified by category, such as procedures, equipment, policies, staff factors, and patient factors. The team votes which one or more of these causes might be responsible for the suboptimal performance, and then develops and implements a

Table 20–2

Benefits of Quality Improvement

Improved Patient Outcomes
- Decreased morbidity and mortality
- Improved quality of life
- Improved satisfaction

Improved Facility Outcomes
- Increased patient census
- Fewer absences for hospitalization
- Decreased mortality
- Increased market share
- Decreased costs
- Increased efficiency
- Improved employee retention and productivity
- Improved risk management
- Fewer regulatory hassles

Improved System-wide Outcomes
- Decreased hospitalization expenses
- More cost-effective care
- Improved rehabilitation
- Contribution to evidence-based literature

change in process to test whether this improves performance. Data collected before and after the process change are compared. If significant improvements in performance occur following the change, the process change is incorporated more widely.

Thus, the fundamental principles underlying quality improvement are: (1) all work can be described as a process, (2) variation exists in every process, (3) the performance of processes can be measured, (4) measurement requires comparison, and (5) the goal is to reduce variation within acceptable limits by testing and validating the processes that will produce the best results. Although the advancement of evidence-based medicine and the proliferation of clinical practice guidelines have begun to clarify which care processes are likely to produce the best clinical outcomes, all providers have unique barriers to process improvement that must be identified at the facility level by those individuals who know the processes best.

Ultimately, "care" represents a linkage of many processes and the success of quality improvement initiatives requires the empowerment of those individuals "in the trenches." An obstacle

to the successful implementation of a quality improvement culture is management failing to relinquish power to its employees and to trust its employees to effectively use the resources that have been put at their disposal to improve processes of care and patient outcomes. Quality improvement has been described as both "bottom up" and "top down." The top-down aspect means that management must commit itself at the highest level (e.g., board of directors, chief executive officer) to a quality improvement culture and to allocate the resources necessary for a quality improvement program to succeed.

This includes the data management infrastructure necessary to track processes and outcomes, education and training of staff in the principles and application of quality improvement techniques, providing employees with the protected time necessary to attend quality improvement meetings and to manage quality improvement data, and individuals in leadership positions emphasizing their commitment to quality improvement through their own actions and words. The bottom-up aspect of quality improvement means that it is ultimately the workers who execute the care processes on a daily basis and who are best qualified to examine which processes of care are most effective—identifying the barriers to improving outcomes and ultimately implementing changes in processes to overcome those barriers and to benefit patients.

Although the IOM has developed a somewhat arcane definition of health care quality ("the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"), many health care providers (including physicians) may find it easier to relate to health care quality as a product delivered by a provider to a customer. This customer could be identified as the patient or the payer. As in other markets, the customer can and should articulate whether or not the product meets expectations.

The expectations of a payer such as Medicare are very clear and are contained in the conditions of coverage for dialysis facilities. However, satisfying these conditions of coverage is merely meeting a minimum standard of care required of all dialysis providers and is quality assurance, not quality improvement. Because the ultimate goal of quality improvement is to improve outcomes for patients, the patient's perspective must be considered—and the use of patient satisfaction and quality-of-life instruments has become increasingly important to identify opportunities for process improvement (especially in the context of the ongoing paradigm shift to a more patient-centered health care delivery environment).

The development of a data management infrastructure is essential to the ability to compare a provider's own performance to others and to itself over time. Data are a cornerstone of quality improvement. An adequate data management infrastructure is essential to repeated measurement of indicators over time, and to inferences made about causality and the improved decision making that is ultimately based on evidence.

Another cornerstone of quality improvement culture is respect for the individual. Quality improvement projects succeed because they are owned and championed at the process level rather than at the executive level. The culture of quality improvement requires a paradigm shift from management to leadership, from control to coaching, from resistance to openness to change, from suspicion to trust, from an internal focus to a customer focus, and to seeing people as resources rather than as commodities.

Physicians have traditionally resisted quality activities as second-guessing by nonexperts, and have almost invariably delegated quality activities to a head nurse or quality assurance coordinator. Quality improvement cannot be delegated. All individuals, especially those in leadership positions, must embrace it for it to succeed. The commitment of the nephrologist is particularly vital for quality improvement to succeed in the dialysis facility because the physician is a respected leader who sets an example by his or her own actions, and because the physician is a central figure for many of the care processes that ultimately impact patient outcomes. The failure of physician buy-in is a common barrier to the successful deployment of quality improvement at the provider level.

Table 20.3 summarizes some of the other barriers. It is easy to become discouraged about quality improvement because it does not always work on the first try. In a differential diagnosis of a medical problem, sometimes many negative tests are performed before a positive test ultimately identifies the nature of the problem. The same is true for quality improvement. Physicians, in particular the medical director of the dialysis facility, must have the patience to champion the quality improvement approach through several unsuccessful cycles until its inevitable success converts the skeptics and is integrated into the facility's culture.

Improvement of physician buy-in to quality improvement can be achieved by giving physicians their own individual data (they are scientists and they love data), by giving physicians comparative data (they are competitive and love to "win"), and by inducing physicians to attend quality improvement meetings by providing refreshments (physicians are busy and most likely to attend meet-

Table 20–3

Barriers to Quality Improvement

- Management does not allocate sufficient resources for data infrastructure, employee training, and protected staff time
- Management behavior is not consistent and sends mixed message to employees
- Management fear of employee empowerment
- Lack of physician buy-in
- Failure to identify and train effective team leaders
- Failure to identify a "champion" for a specific project
- Discouragement or impatience regarding an unsuccessful project
- Assignment of blame

ings if they are concurrent with a meal). The medical director of a dialysis facility should provide leadership for staff physicians by identifying their individual interests and recruiting them as champions of specific quality improvement projects. The medical director is also in the best position to provide liaison among a dialysis facility's management, management staff, and medical staff—providing advocacy leadership for the quality agenda and access to the evidence-based literature that may provide a template for process improvement.

The design and implementation of a quality improvement project (QIP) is relatively straightforward. The leadership of the facility must first make a commitment to adopting a quality improvement culture and providing the data, personnel, and educational resources necessary to its implementation. This could be a clinical outcome such as anemia management, a patient satisfaction issue such as waiting time to begin dialysis, an internal cost effectiveness issue such as low dialyzer reuse, or a regulatory issue such as hepatitis testing. Next, a multidisciplinary team is constituted with interest and expertise in the project. Any literature regarding the issue should be gathered and shared among team members. The team should ascertain whether standards for this issue already exist and whether these can be used as a template for process improvement.

The next step is to determine the scope of the data collection activity, including the sources of data, data collection tools, logistics of data collection, and methods of data analysis. The data are then managed to analyze the processes involved and to identify sources of variation. After the analysis of process has been com-

pleted, causes of process variation are identified and an intervention opportunity is selected. An improvement trial is designed and implemented, and follow-up data are collected and analyzed to determine whether the process change resulted in decreased variation and improved outcomes. Ultimately, the results of the project are reported back to team members—and if the intervention was successful process change is implemented on a wider scale with continued cycles of follow-up for validation.

It is essential that there be no assignment of blame throughout this quality improvement process. When a problem is identified, it should be determined how this system failed the individual rather than how the individual failed the system. Improvements to the system almost invariably lead to improvements in individual performance, and the "ownership" of the process by those responsible for implementing the process improves consistency, employee morale, and employee retention. The key features of quality improvement in health care are summarized in Table 20.4.

Patient Safety

In 2000, the IOM published its landmark report *To Err Is Human: Building a Safer Health System*, which noted that between 44,000 and 98,000 patients in the United States die each year as a result of medical errors. This makes medical errors the eighth leading

Table 20–4

Key Features of Healthcare Quality

Methods
- Internal and external customer driven
- Management by fact
- Respect for people
- Teamwork
- Disciplined problem-solving process

Results
- *Appropriateness:* Balancing benefit and risk
- *Effectiveness:* Ability of intervention to achieve desired outcome in population
- *Efficiency:* Ability to provide effective care at lowest possible cost
- *Safety:* Minimizing adverse effects of interventions
- *Consistency:* Minimize variability of process and outcome
- *Patient satisfaction:* Ability to meet or exceed expectations

cause of death and results in additional national costs of $17 to 29 billion, of which health care costs represent more than 1/2. In addition to economic costs, morbidity, and mortality, medical errors result in a loss of trust by patients in the health care system, loss of morale among health care professionals, loss of worker productivity by employers, and reduced school attendance by children.

The authors note that the decentralized and fragmented nature of the health care delivery system contributes to unsafe conditions for patients, yet licensing and accreditation processes have focused limited attention on the issue. Health care organizations and providers have not focused on patient safety because of issues regarding liability risk exposure when efforts to uncover and learn from errors are successful. Medical errors can be of omission or of commission. The types of medical errors are summarized in Table 20.5.

Table 20–5

Types of Medical Errors

Diagnostic
- Error or delay in diagnosis
- Failure to employ indicated tests
- Use of outmoded tests
- Failure to act on results of tests

Therapeutic
- Error in performance of an operation, procedure, or test
- Error in administering a treatment
- Error in the dose or method of using a drug
- Use of outmoded therapy
- Avoidable delay in treatment or in responding to an abnormal test result
- Inappropriate (not indicated) treatment

Preventive
- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

Other
- Failure of communication
- Equipment failure
- Other system failure

Adapted from Leape L, Brennan AG, Troyen A, et al. Preventing medical injury Qual Rev Bull 1993;19:144.

The IOM report noted that health care services represent a complex and technological industry prone to accidents, especially because many of its components are not well integrated. Nonetheless, much can be done to make systems more reliable and safe—as the failure of large systems is due to multiple faults that occur together. One of the greatest contributions to accidents in any industry (including health care) is human error. Humans commit errors for a variety of known and complicated reasons, but most human errors are induced by system failures. Redesigning the system to prevent human errors is more productive than assigning blame.

Latent areas are more insidious because they are difficult for people working in the system to identify (they may be hidden in computers or layers of management, and people become accustomed to working around the problem). Latent errors can and should be identified long before an active error. These errors pose the greatest threat to safety in a complex system because they lead to operator errors. Current error reporting and response systems tend to focus on active errors, but discovering and fixing latent errors and decreasing their duration is more likely to have a greater effect on building safer systems because this will prevent active errors before they occur. The IOM report made a number of recommendations to federal agencies and health care providers to improve patient safety. These are summarized in Table 20.6.

Following the release of the IOM report on patient safety, the Renal Physicians Association, Forum of ESRD Networks, and National Patient Safety Foundation co-sponsored a consensus conference of stakeholders in ESRD to establish a patient safety agenda for the ESRD community. Representatives from the large dialysis chains were surveyed to determine which safety issues were of greatest concern at their facilities. These are summarized in Table 20.7. This collaborative effort led to the articulation of 47 action options to improve ESRD patient safety, many of which parallel those of the IOM in the "To Err Is Human" report. Many of these action options are national efforts that will require further funding.

At the individual provider level, however, efforts will be required to raise awareness about the magnitude of the patient safety issue and the need for change—along with a change in the culture of the provider to a blameless one in which staff regularly report "near misses" without fear of retribution. Systems must be implemented to track errors and adverse events such that patterns can be identified and systems can be improved. Because medical errors occur at the operator level, it is essential that a dialysis

Table 20–6

Recommendations of the IOM to Improve Patient Safety

- Establish a Center for Patient Safety within the Agency for Healthcare Research and Quality
- Establish a mandatory nationwide reporting system for the most serious medical errors and a voluntary nationwide reporting system for less serious medical errors
- Extend peer review protections to safety data used for improving safety and quality
- Focus greater attention on patient safety by regulators and purchasers of healthcare services
- Improve performance standards and expectations of healthcare professionals regarding patient safety through education and credentialing
- Improve FDA oversight of drug packaging, labeling, and naming to minimize medication errors
- Define executive responsibility for patient safety and institute patient safety programs at the healthcare organization and professional levels
- Implement proven medication safety practices

Adapted from Kohn LT, Corrigan JM, Donaldson Ms (eds.) for the Institute of Medicine. To Err is Human.

unit's staff be trained in the safety sciences and that errors and adverse events are viewed as opportunities for prevention rather than as evidence of individual failure.

Patient safety officers should be designated to stay current with the patient safety literature, which is rapidly expanding, so that proven safety practices can be implemented in the facility without delay. As with quality improvement, the key to success in improving patient safety is the cultural change at the organizational level to promote a blameless environment. Health care providers must receive education in the safety sciences, particularly with regard to the importance of error detection and reporting. In addition, a data collection and reporting infrastructure must be developed to track and eliminate latent errors and near misses before they become active errors and adverse events.

The tensions between the tort system and patient safety demand that the adversarial dispute resolution paradigm in health care be reexamined. Although it is possible that appeals to physicians' ethical commitments to patient welfare and the demonstrated successes of industry-based models of systemic quality improvement may gradually yield buy-in to safety initiatives, the success of this approach is doubtful because the conflicts between the

Table 20–7

Top Dialysis Patient Safety Issues

Patient falls
Medication errors, including:
- Deviation from prescription
- Allergic or other adverse reaction
- Omissions

Access-related events, including:
- Clots
- Infiltrates
- Difficult cannulation
- Poor blood flow

Dialysis errors, including:
- Incorrect dialyzer
- Incorrect line
- Incorrect dialysate
- Dialyzer or dialysis-equipment related sepsis

Excessive blood loss, including:
- Separation of blood lines
- Improper hookup
- Prolonged bleeding from needle sites

Adapted from Forum of End Stage Renal Disease Networks, National Patients Safety Foundation, Renal Physicians Association. *National ESRD Safety Initiative: Phase II Report*. December 2001.

tort system and error reduction programs are fundamental and severe. In addition, physicians' concerns about being sued and losing their liability insurance have escalated considerably in recent years. A tort reform strategy may allay some of these concerns by health care providers, but even though it reduces economic exposure tort reform does not create a more efficient system.

In a no-fault system, an injured patient would only have to demonstrate that a disability was caused by medical management as opposed to the disease process. There would be no need to prove negligence. Such an approach would be better aligned with the blameless philosophy of patient safety and quality improvement, which emphasizes evidence-based analysis of systems of care. A no-fault approach to patient injury would also align incentives for risk reduction, especially if hospitals and their medical staffs are insured by the same entity and all efforts to prevent medical errors are undertaken jointly. Blame and economic punishment for errors that are made by well-intentioned people working in the health care system drives the problem of patient

safety underground and alienates people who are best placed to prevent such problems from recurring.

On the other hand, failure to assign blame when it is due is also undesirable because it erodes trust in the medical profession. Although it is important to meet society's needs to pursue legal justice where appropriate, this should not be a prerequisite for compensation as the current tort system requires. Ultimately, for patient safety efforts to succeed, patients, health care providers, and the legal system must understand the distinction between blame-worthy behavior and the inevitable human errors that result from the systemic factors that underlie most failures in complex systems.

Accountability

Even if an ideal blameless culture for patient safety and quality improvement were achieved, there must be accountability. There is a hierarchy of accountability within each dialysis unit organization, between chain facilities and their corporate parent, and among dialysis providers (including nephrologists), payers, regulators, and patients. Because primarily Medicare funds are used to pay for ESRD services in the United States and these funds are appropriated by Congress, Congress holds the Centers for Medicare and Medicaid Services (CMS) accountable for ensuring that the dialysis services purchased with these funds are of high quality.

The mortality rate for ESRD patients in the United States has consistently been higher than that in Europe, Japan, and Australia—and although some argue that this is caused by differences in case mix data from the United States Renal Data System (USRDS) and from the Dialysis Practice Patterns and Outcomes Study (DOPPS) suggest that this is not entirely the case. The progressive consolidation of dialysis interests in the United States, dominated by the for-profit dialysis chains, has raised concerns that quality of care has been compromised to maximize stockholder returns.

In June of 2000, the Office of the Inspector General (OIG) issued a report that recommended CMS hold individual dialysis facilities more fully accountable for the quality of care delivered to ESRD patients—and that CMS use facility-specific performance measures to encourage facilities to improve the quality of care and ensure that facilities meet minimum standards of operation. The General Accounting Office (GAO) also released a report in June of 2000 that noted that the percentage of surveyed dialysis

facilities with conditions of coverage deficiencies increased from 6% in 1993 to 15% in 1999. The GAO recommended that the frequency of on-sight inspections by state surveys be increased by the allocation of additional Congressional funds for this purpose.

Despite the allocation of those additional funds, the follow-up GAO report in 2003 noted an unacceptably high frequency of a number of deficiencies noted by state surveyors that could adversely affect patient outcomes—including failure to monitor laboratory values and medication supply, failure to administer medication as prescribed, failure to administer dialysis treatments as prescribed, failure to monitor concentration of chemicals in the water system, and failure to involve a transplant surgeon in reviews of the patients' long-term care plans.

The 1997 Balanced Budget Amendment (BBA) enacted by Congress requires the Secretary of Health and Human Services to develop and implement a method of measuring and reporting on the quality of dialysis services provided under Medicare. These clinical performance measures—which address dialysis adequacy, anemia management, vascular issues, and nutrition—are currently applied to random samples of dialysis patients on an annual basis to generate a "snapshot" cross-sectional analysis of regional and national outcomes. These measures are published in the annual reports of the ESRD Clinical Performance Measures Project.

Research has shown that variation in patient outcomes such as dialysis adequacy is largely attributable to factors at the facility (such as its policies governing patient care, associated practice patterns, and attention to individual patient outcomes as opposed to patient-specific causes). Facility-specific hematocrit and urea reduction ratio (URR) data—along with facility-specific standardized ratios for mortality, hospitalization, and transplantation—are compiled each year by the Kidney, Epidemiology and Cost Center (KECC) at the University of Michigan for every dialysis facility under contract with CMS. The facility-specific profiles are sent to the respective ESRD networks for distribution to individual facilities and to state surveyor agencies, and posted in a "consumer-friendly" form on Medicare's Dialysis Facility Compare web site (*www.medicare.gov/Dialysis/Home.asp*).

The KECC facility-specific profiles also provide a standardized hospitalization ratio and standardized transplantation ratio that use a similar methodology to the SMR, adding up patient hospitalization rates and transplantation events for each of the patients in the cohort (corrected for days at risk). The facility-specific hospitalization and transplant data are not currently posted on the

Dialysis Facility Compare web site for consumer consideration, but are distributed to the respective state Departments of Health to trigger survey activities and to the individual facilities to drive internal quality improvement.

The use of the same data for internal quality improvement activities and for external quality oversight and consumer choice raises several concerns. Traditionally, quality data shared between a health care provider and its respective peer-review organization (or specifically between a dialysis facility and its ESRD network) have been confidential and non-discoverable so that there is the highest probability that the data will be valid and free of "gaming." Such data can be used to drive internal quality improvement processes at the facility level and allow the respective ESRD network to target the outlier facilities for confidential and collegial quality improvement intervention activities. As soon as quality data become public (through their release to Medicare state survey and certification agencies, to the Dialysis Facility Compare web site, or to other patient-accessible media), there is inevitably a "gaming" that undermines the effective use of these same data for internal quality improvement activities.

Another major concern regarding the public release of performance data is that of "cherry picking" of the most compliant and healthiest patients to make a facility's performance measure profile appear more favorable, masking process deficiencies and undermining the quality improvement process. Although most of the community recognizes the need for public accountability by health care providers, there is considerable evidence that patients do not use these data consistently to make choices among health care providers and health care plans. Nonetheless, the public reporting quality data has sensitized health care providers to their opportunities for process and outcome improvements and in that sense has improved the overall quality of health care delivery.

The use of physician "report cards" for quality improvement, accountability, and patient choice also is controversial. A randomized controlled trial comparing the use of physician-specific outcome feedback with an identical outcome feedback plus achievable benchmark feedback among 70 community physicians caring for almost 3000 diabetic Medicare patients in Alabama found that the use of achievable benchmarks significantly enhanced the effectiveness of physician performance feedback compared to profiling alone. However, in another study of 232 physicians caring for 3642 patients with type 2 diabetes the use of physician report cards was unable to reliably detect practice differences and was shown to result in the deselection of patients with high prior

costs, poor adherence, or poor response to treatments ("cherry picking").

For performance measures to be successful, they must meet the criteria outlined in Table 20.8. The report *Physician Clinical Performance Assessment: The State of the Art; Issues, Possibilities, and Challenges for the Future* makes the important distinction between the attributes of performance measures used for quality improvement and those used for accountability (credentialing, financial incentives, and selection). As the purpose of quality improvement measures is to improve quality and decrease variation, statistical ability to discriminate among providers, performance level cutoffs, and statistical modeling is unnecessary. On the other hand, these same attributes are absolutely essential if performance measures are to be used for accountability—and a much higher level of statistical robustness and evidence basis is required for quality measures used for accountability versus quality improvement.

Current physician performance measures are not sufficiently robust to be used to assess physician competence, to reward physician outcomes, or to be used by patients and families in the selection process. Current state-of-the-art physician clinical performance assessment is best suited to promote continuous clinical quality improvement within the physician's practice environment. Although measurement of physician clinical performance is possible, use of this information for reporting external to physicians' practice environment for purposes of physician competence assessment, patient choice, and rewarding physician excellence is limited by concerns that most of these performance measures do not meet the criteria outlined in Table 20.8. Premature

Table 20–8

Attributes of Physician Performance Measures

- Evidence basis
- Agreed-on standards for satisfactory performance (benchmarking)
- Standardized specifications
- Adequate sample size for reliable estimate of individual physician performance
- Appropriate adjustment for confounding patient factors (case mix)
- Allow for care to be attributable to the individual physician
- Feasible to collect
- Representative of the activities of the specialty

or inappropriate use of physician performance measures for external accountability or selection may stifle quality improvement activities and lead to manpower shifts and patient access to care issues as opportunity costs for compliance, to data "gaming" (which inaccurately depicts the data quality) and (most unfortunately) to "cherry picking" of patients.

Such concerns notwithstanding, the ESRD program in the United States is under increasing scrutiny by Congress and Medicare as the cost of the ESRD program continues to escalate both in terms of absolute dollars and as a percentage of total Medicare expenditures, and as quality of care issues linger. Another factor is a focus on chronic kidney disease as one of the target areas in the blueprint for the federal government's next decade of health care quality improvement efforts (Healthy People 2010). Specific recommendations within the Healthy People 2010 document with relevance to ESRD include the goal to increase the proportion of new hemodialysis patients who use arteriovenous fistulas as the primary mode of vascular access, to increase the proportion of dialysis patients registered on the waiting list for transplantation, to increase the proportion of patients treated with chronic kidney failure who receive a transplant within 3 years of registration on the waiting list, and to reduce deaths from cardiovascular disease in patients with chronic kidney failure.

To provide more detailed oversight of process and outcome at the dialysis provider level, CMS is developing a "core data set" that will include data elements, standardized data definitions, and specifications for the frequency of data collection. It is anticipated that the core data set will include all of the data elements currently collected by the national ESRD Clinical Performance Measures Project, and will be expanded to include all patients rather than a random sample. It will also include many elements not currently captured by the ESRD Clinical Performance Measures Project. CMS is also developing a data collection infrastructure that will require electronic transmission of patient-specific data from dialysis providers and corporate chains to the ESRD networks and to CMS.

This data collection infrastructure will capture the core data set, and will replace the paper forms currently used by dialysis facilities—such as the Medical Evidence Form (2728), the Death Report (2746), and the Annual Facility Survey (2744). Patient tracking among renal replacement therapy modalities will also be included in this new electronic data system, named CROWN (consolidated renal operations in a web-enabled network) WEB.

Individual dialysis facilities will enter the required data through a secure web site, and large corporate chains will submit data on behalf of all of their facilities through a periodic data dump. Ultimately, the facility and patient-specific data acquired through CROWN WEB and its network to CMS data transmission counterpart SIMS (Standard Information Management System) will be integrated with ESRD data from other sources—including Medicare billing data, USRDS data, United Network for Organ Sharing (UNOS) data, and additional data collected through special studies or other sources.

This integrated data system will be used by CMS and other health care planners in the federal government to formulate policy regarding quality and reimbursement issues. The core data set collected through CROWN WEB will replace the hematocrit and URR data currently collected through the billing process, and provider-specific profiles derived from the core data set will be used by individual networks to target quality improvement activities on a confidential basis. Of more concern is whether facility- or physician-specific profiles derived from the core data set will be used prematurely or inappropriately for public accountability and patient choice. CMS has announced plans to expand the facility-specific data available on the Dialysis Facility Compare web site to include additional quality elements to be derived from the core data set. It is also considering reportage of the results of patient satisfaction surveys.

It should also be noted that the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 contains a section that directs the IOM to conduct an evaluation of leading health care performance measures in the public and private sectors and options for implementing policies that align performance with payment under the Medicare program. The availability of a large set of provider-specific process and outcome measures within the ESRD program makes it likely that the IOM will examine this data set as a potential model for linking performance with payment. The IOM will also view this as a potential model under which ultimately nephrologists and dialysis facilities are financially rewarded or penalized based on their respective performance data. Several demonstration projects with a payment for performance (P4P) component are currently being conducted by CMS.

The availability to CMS of many new domains of provider-specific data through CROWN WEB makes it imperative that performance measures be developed for ESRD that meet the criteria outlined in Table 20.8. As with the structural, process, and outcome issues addressed with internal quality improvement

methodologies, performance measures are classified as structural, process, or outcome. Structural measures refer to the organizational characteristics that provide the resources for quality care. These are the basis for most regulations (such as Medicare's conditions of coverage for dialysis facilities) and are generally the target for survey and certification activities as ensuring minimal capacity for quality.

Although a poor correlation has been found between dialysis facility survey deficiencies (which focus largely on structural measures) and patient outcomes, an internal quality improvement focus on structural measures may be beneficial to patients and the organization. Process measures quantify the delivery of recommended procedures or services correlated with desired outcomes. These form the basis of many of the measurement sets used for public accountability of health plans, such as the Health Plan Employer Data and Information Set (HEDIS). However, the appropriate data collection infrastructure must be in place to adequately capture process measure information.

It has been recommended by physician organizations that payment for performance systems start with process measures because these are the most actionable by providers. Outcome measures are used to capture the effect of an intervention on health status or patients' perceptions of care. Although outcome data are often much easier to capture (through a system such as CROWN WEB) than process data, analysis of outcome data and use of outcome data as performance measures requires much more statistical sophistication (such as case-mix adjustment) than process data.

It must be recognized that health care delivery is not subject to the same specifications and tolerances that would be applied to a supplier of an industrial product. Therefore, given the complexity of health care delivery in general and the variability and unpredictability of patient outcomes in particular it is unrealistic for payers and oversight agencies to set rigid standards of performance by providers—especially when no clear unanimity exists regarding many processes of care. The renal community shares CMS's and Congress's goals to increase dialysis provider accountability and to improve patient outcomes. This includes the GAO goal that every dialysis facility be reviewed at least on a tri-annual basis, with more frequent reviews for facilities with compliance problems.

The renal community supports the continued development and application of validated clinical performance measures derived from evidence-based clinical practice guidelines, such as those

currently being used to assess anemia management, adequacy of dialysis, and vascular access in hemodialysis patients. Nonetheless, many providers fear the advent of "cookbook" medicine in which the training and experience of the practitioner are devalued. Evidence-based clinical practice guidelines, which are designed as clinical decision-making tools, have a misguided tendency to evolve into standards of care. Quality oversight activities then become inappropriately oppressive and cross the line to become the practice of medicine by the regulator.

This is a scenario that ESRD payers, providers, and the patient community must avoid at all costs because it stifles the innovation that leads to quality improvement, returns to the outlier focus of quality assurance, and may ultimately limit access to care as providers begin to cherry-pick patients to avoid the perception of underperformance. The development of a national data infrastructure to allow for provider-specific data collection and provider-specific profiling to drive internal quality improvement activities holds great promise for process and outcome improvement. However, the use of these same data for public accountability carries many concerns that must be addressed because it may undermine the success of the quality improvement partnership between ESRD networks and dialysis providers. A system of public accountability implemented by CMS must include case-mix adjustment strategies to minimize patient selection bias and to encourage facilities to accept high-risk patients without fear that their adverse outcomes may negatively impact on their public facility profiles.

Recommended Reading

Centers for Medicare and Medicaid Services. *2005 Annual Report, ESRD Clinical Performance Measures Project*. Baltimore, MD: Department of Health and Human Services, Centers for Medicare and Medicaid Services, Center for Beneficiary Choices 2005.

A national snapshot of outcomes in ESRD anemia management, dialysis adequacy, nutrition, and vascular access with trends from prior years.

Corrigan JM, Eden J, Smith BM (eds) for the Institute of Medicine. *Leadership by Example: Coordinating Government Roles in Improving Health Care Quality*. Washington, DC: The National Academies Press 2003.

This book by the IOM puts the responsibility for health care reform squarely on the federal government and proposes and national quality enhancement strategy.

Daley J, Vogeli C, Blumenthal D, et al. *Physician Clinical Performance Assessment: The State of the Art; Issues, Possibilities, and Challenges for the Future*. Boston, MA: Institute for Health Policy, Massachusetts General Hospital 2002.

A well-documented call for restraint in the application of clinical performance measures to physician public profiling or payment.

Forum of End Stage Renal Disease Networks, National Patient Safety Foundation, Renal Physicians Association. *National ESRD Patient Safety Initiative: Phase II Report.* December 2001. Accessed at *www.renalmd.org/publications/downloads/ESRDreport2/pdf.*

These two reports are available without charge on the Renal Physicians Association web site and constitute and exhaustive review, taxonomy, and recommendation set for patient safety in dialysis.

Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press 2001.

This landmark book from the IOM calls for a sweeping redesign of the American health care system to improve quality and decrease disparities in processes and outcomes.

Kohn LT, Corrigan JM, Donaldson MS (eds.) for the Institute of Medicine. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press 2000.

This landmark book from the IOM documents the staggering incidence of medical errors and their consequences, and recommends that fundamental system changes be made to ensure patient safety.

Leape L, Brennan AG, Troyen A, et al. Preventing medical injury. Qual Rev Bull 1993;19:144.

One of the seminal articles on patient safety, including a classification system for medical errors.

McClellan WM, Goldman RS. Continuous quality improvement in dialysis units: Basic tools. Advances in Renal Replacement Therapy 2001;8:95.

A detailed description of quality improvement tools and their application to the dialysis setting.

Renal Physicians Association, Forum of ESRD Networks. *Collaborative Leadership for ESRD Patient Safety. Phase 1 Report of the National Patient Safety Consensus for the Community of Stakeholders in End Stage Renal Disease*. January 2001. Accessed at *www.renalmd.org/publications/downloads/ESRDFinalReport/pdf*.

U.S. Department of Health and Human Services. *Healthy People 2010, Second Edition*. Washington, DC: U.S. Government Printing Office 2000.

The "bible" for health care policy development in the United States for the current decade.

U.S. Department of Health and Human Services, Office of the Inspector General. *External Review of Dialysis Facilities: A Call for Greater Accountability*. OEI-01-00050, June 2000.

This government report set off a wave of external and internal review of dialysis patient outcomes in the United States, and provided the impetus for Medicare to redesign its ESRD quality oversight activities.

Wish JB. Quality, safety and accountability in dialysis. In Nissenson AR, Fine RN (eds.), *Clinical Dialysis, Fourth Edition*. New York: McGraw-Hill 2005.

An in-depth review and historical perspective of the issues addressed in this chapter, with emphasis on the regulatory environment.

CHAPTER 21

Initiation of Dialysis Therapy

Scott G. Satko, MD, and John M. Burkart, MD

Historical Criteria for Dialysis Initiation

For patients with acute renal failure, the decision-making process involved in the proper timing of commencement of dialysis is usually fairly straightforward. In these patients, the need for dialysis is heralded by clinical signs and symptoms such as evidence of intractable volume overload or evidence of uremic encephalopathy, pericarditis, gastrointestinal distress, pruritus, or bleeding diathesis. Laboratory data suggestive of an impending need for dialysis in these patients includes metabolic derangements such as intractable hyperkalemia, hyperphosphatemia, metabolic acidosis, and prolonged bleeding time.

This chapter focuses primarily on the indications and process of initiating dialysis in those patients with chronic kidney disease. In these patients, in contrast to those with acute renal failure the decision-making process is not always as straightforward. In those patients with slowly progressive chronic kidney disease, the typical uremic symptoms commonly seen in patients with acute renal failure are often absent. Although subtle signs of uremia (such as anorexia, weight loss, early malnutrition, and decreased energy level) may be present, their onset is often so insidious in nature that the patient "adapts" and either the patient does not relate these problems to the physician or the physician does not recognize their presence. Prior to 1997, when the National Kidney Foundation released its first set of evidence- and opinion-based guidelines on this subject no real consensus existed within the nephrology community regarding the optimal time to initiate dialysis.

Evidence-Based Criteria for Dialysis Initiation

In 1997, the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-K/DOQI) publication outlined the first set of comprehensive guidelines for initiation of dialysis and reviewed the evidence supporting these guidelines. Since that time, these guidelines have undergone several revisions–the latest of which [Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI)

Clinical Practice Guidelines and Recommendations for Peritoneal Dialysis Adequacy and Hemodialysis Adequacy] released in 2006. This chapter provides an in-depth summary of the current recommendations from NKF-K/DOQI.

Preparation for Dialysis

For a chronic kidney disease (CKD) patient to begin dialysis in a timely manner, careful consideration needs to be given to access placement—well in advance of the time at which dialysis is initiated. Patients who have reached CKD stage 4 [defined as glomerular filtration rate (GFR) <30 mL/minute] should receive education regarding the various options available for renal replacement therapy. These options should include renal transplantation (for suitable candidates), hemodialysis (both in-center and home modalities), and peritoneal dialysis. This education is usually best performed in a multidisciplinary fashion. At our center, the educational process begins with an in-depth discussion between the nephrologist and patient about the natural history of chronic kidney disease and the need for timely initiation of renal replacement therapy.

Involvement of family members in this discussion is often beneficial for the patient. The next step in the educational process involves referral to our outpatient dialysis center, where patients and their families are able to meet with other health care providers–including dialysis nurses, renal dieticians, and social workers. Having the opportunity to meet with multiple dialysis-care professionals, tour the dialysis unit, and meet with other chronic kidney disease patients during these pre-dialysis educational sessions usually helps to alleviate some of the fears and concerns patients often have at this point in time. In addition, patients who have received extensive pre-dialysis education are more likely to be able to make an educated decision regarding dialysis modality.

To guide clinicians with the decision-making process, NKF-K/DOQI has developed a classification scheme for stratifying CKD patients based on their level of residual renal function (Table 21.1). Although patients with all stages of CKD should receive education regarding the natural history of their disease and the likelihood that they may eventually progress to end-stage renal disease (ESRD), efforts at education should be greatly intensified once the patient reaches stage 4 (GFR 15–29 mL/minute). It is during this stage the dialysis modality should be chosen, as patients who elect to start hemodialysis will need an appropriate vascular access placed at this time.

Table 21–1

GFR Associated with CKD Stages

CKD Stage	GFR (mL/min/1.73 m^2)
Stage 1	≥90 (with urinary abnormalities; e.g., hematuria, proteinuria)
Stage 2	60–89
Stage 3	30–59
Stage 4	15–29
Stage 5	<15 (or dialysis)

Modified from *http://www.kidney.org/professionals/NKF-K/DOQI/guidelines_ckd/tables.htm*.

Timing of Dialysis Initiation

The 2000 NKF-K/DOQI update recommends that when the level of residual renal function, as measured in units of Kt/V urea, declines to less than 2.0/week initiation of dialysis should be considered when certain criteria are met (Figure 21.1). This threshold is extrapolated from morbidity and mortality data in the peritoneal dialysis patient population. The CANUSA (Canada–U.S.A.) study—a prospective multicenter cohort study of 680 incident peritoneal dialysis patients—gave strong support to the hypothesis that total small-solute clearance [expressed in terms of either weekly Kt/V urea or creatinine clearance (Ccr)] predicted outcomes in this population.

An inverse relationship was found to exist between the level of total small-solute clearance and mortality rate. Over a 2-year period, every 0.1 unit/week increase in total Kt/V was found to correspond to a 6% decrease in the relative risk of death. The total Kt/V value that corresponded to a 78% 2-year survival rate was 2.1/week. Based on this data (as well as on data from other

Kt = urea clearance from 24-hour urine collection (ml/min) x 10.08 to convert to L/wk.

V = urea volume of distribution, or volume of total body water (L)

For women, estimate V as total body weight (kg) x 0.55

For men, estimate V as total body weight (kg) x 0.60

Figure 21–1

Calculation of residual renal Kt/V.

smaller studies), the minimally acceptable total Kt/V target for continuous ambulatory peritoneal dialysis (CAPD) patients was chosen by the 1997 NKF-K/DOQI work group to be 2.0/week.

It is commonly felt that chronic kidney disease patients are similar in many respects to CAPD patients. For example, both groups of patients undergo *continuous* clearance of small-molecular-weight (SMW) solutes, as opposed to the *intermittent* clearance obtained by hemodialysis patients. In addition, metabolism of protein occurs in a similar manner in both patient populations. Nevertheless, it was noted in many studies that the average patient starts dialysis with a residual renal solute clearance in terms of Kt/V urea of 0.7 to 1.2/week.

This finding is at odds with the fact that the recommended minimal target for adequate peritoneal dialysis small solute clearance is significantly higher. For this reason, in the 1997 NKF-K/DOQI guidelines for initiation of dialysis it was decided to use the same urea clearance target for minimally acceptable CAPD (i.e., 2.0/week) as the minimally acceptable lower limit of residual renal function needed to maintain health. It is important to understand, however, that this target is based on theoretical constructs and extrapolation of data from chronic kidney disease patients. This reasoning assumes that one unit of residual renal Kt/V is equivalent to a unit of peritoneal clearance, which is likely not a valid assumption.

The ADEMEX trial randomized Mexican CAPD patients to a standard dialysis prescription (4 daily exchanges of 2 L) or to a modified prescription (adjusted to maintain a target peritoneal clearance of 60 L/week/1.73 m^2). Mean total weekly Kt/V differed between the two groups: 1.80 in the standard group versus 2.27 in the modified prescription group. Surprisingly, the two groups had identical survival after 2 years of follow-up (69.3 versus 68.3%, respectively). In these patients, the level of peritoneal small-solute (urea and creatinine) clearance had very little impact on mortality—suggesting that the level of residual renal function may be a more important prognostic factor. Similar findings were noted in a trial from Hong Kong, in which CAPD patients were randomized to achieve target total weekly Kt/V of 1.5 to 1.7, 1.7 to 2.0, or greater than 2.0. Patients in all three arms of this study had minimal residual renal function, with mean residual renal Kt/V approximately 0.4 to 0.5/week and mean GFR approximately 2.4 to 2.6 mL/minute. All three groups had similar survival rates.

In addition to consideration of the laboratory parameters previously discussed, the NKF-K/DOQI Work Group has also

recommended using other clinical information to help guide the decision regarding timing of initiation of dialysis. If a patient has residual renal function below the Kt/V threshold of 2.0/week but otherwise appears clinically well, it is acceptable under certain circumstances to monitor the patient closely and delay initiation of dialysis. If the patient is free of uremic signs or symptoms, it may be reasonable to delay initiation of renal replacement therapy.

In this situation, it is also necessary to ensure that the patient has evidence of an adequate nutritional state. It is important to ascertain that the patient has stable or increasing edema-free body weight, lean body mass greater than 63%, and stable or increasing serum albumin concentration within the normal range. Another helpful recommended tool is the Subjective Global Assessment (SGA), which evaluates nutritional status based on four criteria: recent weight change, anorexia, subcutaneous tissue, and muscle mass (scored on a 7-point Likert scale). Evidence of malnutrition by any of the previously cited criteria in a patient with residual renal Kt/V less than 2.0/week would suggest the need to initiate dialysis.

The revised 2006 NKF-K/DOQI update recommends evaluating residual renal function in terms of GFR, as this method is generally simpler for clinicians to follow in comparison to calculating residual Kt/V. Residual kidney GFR can be measured (with 24-hour urea and creatinine clearances, taking the average of the two to estimate GFR) or estimated [with the Modification of Diet in Renal Disease (MDRD) equation or with the Cockcroft-Gault equation]). Once the GFR declines to a level <15 mL/minute, the patient should be followed closely for evidence of uremic symptoms, volume overload, intractable acid-base or electrolyte derangements, malnutrition, or other signs that would indicate prompt initiation of dialysis. In most cases, dialysis access should be placed.

Timing of Dialysis Access Placement

An important consideration when planning initiation of dialysis (one unfortunately too often forgotten) is the proper timing of placement of dialysis access. Ideally, this issue should be discussed by the nephrologist as early as possible, even as early as the initial clinic visit—with all patients with chronic renal failure. Much of the apprehension experienced by our patients about dialysis can be alleviated if frank discussions about the need to prepare for the eventuality of dialysis are carried out well in advance of the time it becomes necessary to initiate therapy.

It should never be assumed that a patient will choose one modality of dialysis (i.e., hemodialysis or peritoneal dialysis) over another. Patients in general seem to have an easier time adjusting to the idea of starting dialysis when they are given appropriate education about both major modalities of dialysis, including the risks and benefits of choosing one modality over another. In the absence of any compelling medical indications for selecting a particular modality over another, patients should be allowed to make their own decision regarding modality selection—with appropriate guidance from their nephrologist and multidisciplinary (nursing staff, social worker, dietician, and so on) care team.

For patients who choose to perform hemodialysis, it is of paramount importance to make early arteriovenous fistula placement a high priority. A native arteriovenous fistula should ideally be placed in all suitable patients with chronic kidney disease once their GFR declines to <25 mL/minute, or at the time it is estimated that ESRD will be reached within the next 12 months. The rapidity of decline in residual renal function should be taken into account. A patient who has demonstrated a pattern of maintaining a stable GFR slightly below 25 mL/minute for a period of several years can often be followed closely and undergo access placement at a later point in time.

Early placement of a native arteriovenous fistula should give adequate time for this fistula to fully mature prior to the occurrence of ESRD. Should this fistula not mature within 3 months, early placement should also give ample time to consider either revision of this fistula, placement of a new upper arm fistula, or placement of a polytetrafluoroethylene (PTFE) arteriovenous graft if no suitable veins are found to support a native fistula. For patients deemed not to have suitable vasculature to support a native arteriovenous fistula, the hemodialysis access of second choice would be a PTFE graft. Because these grafts tend to thrombose and/or succumb to infection more often than native fistulas, they should only be considered in patients in whom it is not technically possible to place a native fistula. They should never be considered the hemodialysis access of first choice.

Ideally, a PTFE graft should be placed approximately 3 to 6 weeks prior to the time of initiation of dialysis. If placed too early, there is a high likelihood the graft will thrombose prior to first use. A tunneled cuffed internal jugular catheter should only be considered for dialysis access in patients who have no suitable vascular access for either a native fistula or PTFE graft, patients

who are uremic and in need of dialysis at the time of initial presentation, and possibly in patients who are deemed to have an extremely limited life-span (less than 6 to 12 months).

Tunneled cuffed catheters are recommended over nontunneled cuffed catheters for patients requiring catheter-based vascular access of more than 3 weeks' duration. Due to high risk for infectious complications, it is recommended that an intravascular catheter not be placed until dialysis is initiated. For patients who need urgent dialysis at the time of presentation and initiate dialysis through a catheter, it is important to remember that this catheter should only serve as a "bridge" to a more permanent access. Placement of a more permanent access must be given a high priority, and should be done as soon as the patient is medically stable to undergo this procedure.

For those patients who choose to perform peritoneal dialysis, a Tenckhoff catheter is usually placed between 2 and 4 weeks prior to the time of dialysis initiation. Another approach some are advocating is to bury the external portion of the PD catheter subcutaneously at the time of insertion so that it "matures" in a sterile environment. The distal portion is then exteriorized in a simple outpatient procedure and immediately ready for use. Anecdotal data suggest that it is safe to have these catheters in place 6 to 12 months prior to starting dialysis, so that the patient is ready with a natural access when it is time to start renal replacement therapy. No data exist to show that earlier placement of a curled-tip peritoneal dialysis catheter is associated with increased risk of complications or technique failure.

Writing an Initial Dialysis Prescription: Full Dose versus Incremental

When writing an initial dialysis prescription, it is important to take into account the amount of residual renal function present. For patients who meet the criteria for initiation of dialysis (as outlined previously), dialysis could be initiated with a full-dose prescription—ignoring the residual renal component. Alternatively, this can be done with an incremental prescription in which the dialysis dose is increased as residual renal function decreases—maintaining a total equivalent weekly Kt/V urea >2.0 at all times. For patients with significant residual renal function (weekly Kt/V >1.0), the initial dialysis prescription can be full-dose or incremental. In this group of patients, there are no data to show which of these two methods of prescription management is associated

with a better outcome. For those patients with minimal residual renal function (weekly Kt/V <1.0), a full-dose prescription should be used at the time of initiation of dialysis.

Writing an Initial Dialysis Prescription: Peritoneal Dialysis

Whether dialysis is initiated using a full-dose or incremental prescription, frequent monitoring of the delivered dialysis dose is necessary to ensure adequacy of small-solute clearance. For peritoneal dialysis patients, the NKF-K/DOQI guidelines recommend measuring total solute clearance (as weekly Kt/V) two to three times within the first 6 months of initiating dialysis. If the peritoneal dialysis prescription remains unchanged, it is recommended that both 24-hour dialysate and urine collections for clearance be obtained every 4 months—with urine collections every 2 months until the residual renal weekly Kt/V declines to <0.1.

After the residual renal weekly Kt/V has declined to a negligible level, only 24-hour dialysate collections are necessary—and these should ideally be performed every 4 months in a stable patient. A 24-hour dialysate collection for measurement of peritoneal Kt/V should be performed within 1 month of any change in dialysis prescription, or after any significant change in the patient's clinical status. The dialysis prescription for CAPD patients should then be adjusted with the goal of keeping total (dialysis plus residual renal) solute clearance as measured by Kt/V greater than 1.7/week.

The patient's body size and residual renal function must be taken into account when deciding the initial dialysate exchange volume and number of daily exchanges. For patients with body

Table 21–2

Relationship Between BSA, Residual Renal, and Initial Prescription

	BSA (m^2) <1.8	*BSA (m^2) 1.8–2.0*	*BSA (m^2) >2.0*
Initial No. of Exchanges/ Day	**Residual Renal GFR (mL/min)**		
1	10	11	12
2	7	8	9
4	5	6	7

Modified from Burkart JM, Satko SG. Incremental dialysis: One center's experience over a two-year period. Perit Dial Int 2000;20:418–22.

surface area (BSA) <1.8 m^2, an initial exchange volume of 2000 mL is usually appropriate. For those with BSA 1.8 to 2.0 m^2, an initial volume of 2500 mL can be used. For larger patients, with BSA >2.0 m^2, an exchange volume of 3000 mL can be attempted. For patients in whom an incremental approach to prescription management is taken, our protocol for deciding the appropriate number of exchanges per day is based on the amount of residual renal function at the time of initiation (as indicated in Table 21.2). For example, a patient with BSA 1.9 m^2 and residual renal GFR 8 mL/minute could be placed on a prescription of two daily exchanges of 2500 mL to achieve an adequate total weekly Kt/V.

Writing an Initial Dialysis Prescription: Hemodialysis

As is true for peritoneal dialysis patients, hemodialysis patients can also initiate therapy with a full-dose or incremental dose prescription—based on their level of residual renal function. For a patient with no residual renal function, the goal is to obtain a per-treatment single-pool Kt/V of ≥1.2 for three treatments a week. Patients with a significant amount of residual renal function ($K_rt/V \geq 1.0$) may be able to perform dialysis with a less intense schedule (e.g., once or twice a week initially). As a matter of practicality, however, most hemodialysis patients initiate therapy with a full-dose prescription—as residual renal function is usually lost fairly rapidly once hemodialysis is initiated.

The 1997 NKF-K/DOQI document reviewed the suggested formula for prescription adjustment for those hemodialysis patients undergoing incremental dialysis. Hemodialysis is an intermittent therapy compared to the continuous nature of residual renal function. For this reason, Kt/V from dialysis (K_dt/V) cannot simply be added to K_rt/V to obtain the total weekly Kt/V—as can be done for PD patients. In this case, one should target a weekly total "standardized" Kt/V of >2.0. Figure 21.2 depicts the per-treatment K_dt/V necessary to maintain an "equivalent" total weekly Kt/V of 2.0 in patients with any given level of K_rt/V—performing hemodialysis once, twice, or three times weekly.

When hemodialysis is initiated, the first two or three treatments are often performed at a lower than usual blood flow rate and for a shorter than normal duration. This practice is performed to reduce the risk of "dialysis disequilibrium," which can occur in patients who are severely azotemic prior to being dialyzed. In these patients, the serum urea nitrogen level is a significant com-

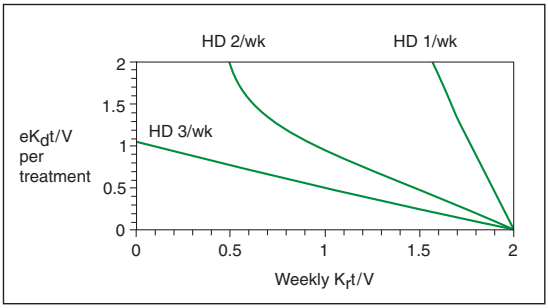


Figure 21–2

eKdt/V = equilibrated double-pool Kt/V per hemodialysis treatment. Krt/V = weekly residual renal Kt/V. (*Modified from National Kidney Foundation*. NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy. *New York: National Kidney Foundation 1997:104*.)

ponent of the total serum osmolality—and overly aggressive dialysis can abruptly decrease the serum osmolality before solute equilibration between the intravascular and extravascular fluid compartments can occur.

This can result in the sudden shift of fluid into the extravascular space, with the most serious side effect being that of cerebral edema. To replace some of the intravascular osmotic load removed with dialysis, it is standard practice at our center to give mannitol 12.5 grams intravenously after the first hour of the first one or two dialysis sessions. A typical hemodialysis prescription for the first treatment session would be 2 hours at a 200-mL/minute blood flow rate, and then 2.5 to 3 hours at a 250- to 300-mL/minute blood flow rate for the second session. Depending on the patient's tolerance of the first two sessions, subsequent sessions are usually performed with a full dialysis prescription (3.5–4 hours at a blood flow rate of at least 300 mL/minute), adjusted so that the total single-pool Kt/V per treatment meets the current recommended guidelines of at least 1.2.

Summary

Considerable changes have occurred in the recommended approach to initiation of dialysis over the past decade. Although a great deal of evidence exists to support these changes, it is important

to remember that much of this evidence is extrapolated from outcome data in dialysis patients rather than derived from randomized controlled studies in pre-ESRD patients. Only time will tell whether the current recommendations will truly improve outcomes in the ESRD population. The subject of initiation of renal replacement therapy is a complex one, involving not only determination of the appropriate timing of this therapy but determination of the most appropriate type of therapy for the individual patient. Only through education of patients early in the course of their renal disease can we hope to attain timely initiation of effective renal replacement therapy.

Recommended Reading

Canada–U.S.A. (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. J Am Soc Nephrol 1996;7:198–207.

A large prospective cohort study of peritoneal dialysis patients, showing the correlation between small-solute clearance and survival.

Lo WK, Ho YW, Li CS, Wong KS, Chan TM, Yu AW, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int 2003;64:649–56.

The second of two important recent large-scale randomized trials suggesting that increasing small-solute clearance has less impact than was previously thought upon improving clinical outcomes in PD patients.

National Kidney Foundation. *NKF-K/DOQI Clinical Practice Guidelines 2000* (2006), *http://www.kidney.org/professionals/NKF-K/DOQI/guidelines.cfm.*

A comprehensive set of guidelines for management of the peritoneal dialysis patient, with rationales for these recommendations and an exhaustive list of supporting references.

Obrador GT, Pereira BJG. Early referral to the nephrologist and timely initiation of renal replacement therapy: A paradigm shift in the management of patients with chronic renal failure. Am J Kidney Dis 1998;31:398–417.

A comprehensive review of the existing guidelines for care of the pre-ESRD patient and initiation of renal replacement therapy.

Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002;13:1307–20.

The first of two important recent large-scale randomized trials suggesting that increasing small-solute clearance has less impact than was previously thought upon improving clinical outcomes in PD patients.

CHAPTER 22

Daily (Quotidian) Hemodialysis

Andreas Pierratos, MD, FRCPC; Christopher T. Chan, MD, FRCPC; and Philip A. McFarlane, MD, FRCPC

The poor dialysis outcomes and the failure of the HEMO and ADEMEX studies to show improvement with increasing dose on both hemodialysis (HD) and peritoneal dialysis led to the increased interest in daily dialysis regimens. Daily hemodialysis is known under its short form (short daily) or the long overnight form (nocturnal hemodialysis). Short daily HD was first described by DePalma in 1969. Daily nocturnal hemodialysis was started by Uldall in 1994.

Method and Technical Aspects

Short, daily hemodialysis is characterized by dialysis performed for 1.5 to 2.5 hours 6 or 7 days per week. High blood and dialysate flows are used, aiming for the highest dialysis dose. Dialysate composition is similar to conventional hemodialysis. Nocturnal hemodialysis is performed nightly during sleep, for 6 to 10 hours 6 to 7 nights a week. Blood flow has been typically 200 to 300 mL/minute (as low as 100 mL/minute in children), whereas a typical dialysate flow is 300 mL/minute. The dialysate contains lower bicarbonate (typically 30 mEq[mmol]/L) and higher calcium concentration (typically 3.0–3.5 mEq/L or 1.5–3.0 mmol/L) than conventional hemodialysis.

In more than 50% of patients, it contains sodium phosphate additive (e.g., Fleet enema 30–120 mL per 4.5 L acid or bicarbonate concentrate)—which gives a final phosphate concentration of 1 to 3 mg/dL (0.3–0.9 mmol/L). Higher phosphate concentration can be used to provide phosphate supplementation in cases of bone repair (e.g., postparathyroidectomy or during pregnancy). Any hemodialysis machine is acceptable for both daily regimens. Several machines have been adapted or created de novo to accommodate the needs of the home dialysis patient on either daily or long regimens. The terms *short daily (quotidian)* and *hemeral hemodialysis* have been used for the short form. *Daily or quotidian (home) nocturnal or nightly hemodialysis* have been used for the longer regimen.

Theory/Kinetics

To explain the comparable patient survival on hemodialysis and peritoneal dialysis despite their unequal dialysis dose (weekly Kt/V 3.2 versus 2.0, respectively), it was proposed that daily or continuous forms of dialysis provide better outcomes than intermittent hemodialysis when providing the same dialysis dose using Kt/V as the dialysis measure. Out of the several universal dialysis dose measures devised to allow an easier comparison of the different dialysis regimens, the most popular is the standard Kt/V (stdKt/V) introduced by Gotch. All dialysis regimens, as well as native kidneys with the same mid-week predialysis BUN (or steady-state BUN in the case of native kidney function), have the same weekly stdKt/V and presumably provide the same clinical outcomes. The latter is speculative. A stdKt/V of 2 corresponds to the minimum NKF-K/DOQI-recommended level of adequacy of Kt/V of 2 for CAPD and single-pool Kt/V of 1.2 for thrice-weekly hemodialysis.

As daily dialysis is associated with lower pre-dialysis BUN and therefore higher stdKt/V than thrice-weekly HD of similar weekly duration, shorter weekly duration is sufficient to deliver a stdKt/V of 2. This would be delivered by daily HD with eKt/V of 0.4 per session, corresponding to a spKt/V of about 0.55. This notion is consistent with the good clinical results described by Buoncristiani in the early 1980s in patients dialyzed with daily Kt/V of 0.23 (1.5–1.7 per week). Maintenance of the same length of weekly dialysis after the conversion to the daily regimen provides a stdKt/V of 2.5 to 3.0. The spKt/V on nocturnal hemodialysis is much higher, at about 1.8 to 2.5 per treatment—whereas the stdKt/V is 4 to 5 for the six-times-a-week regimen.

Nocturnal hemodialysis provides better clearance of both small and especially larger molecules, the removal of which is predominantly time dependent. Thus, in a study the weekly dialysate β_2 microglobulin mass removed increased fourfold from 127 to 585 mg after the conversion from conventional to quotidian nocturnal hemodialysis. Serum predialysis β_2 microglobulin levels decreased from 27.2 to 13.7 mg/dL in 9 months. Similarly, serum β_2 microglobulin levels decreased on short daily hemodiafiltration (which has the added advantage of convective transport).

Advanced glycated end products as well as protein-bound molecules (such as indole-3-acetic acid and indoxyl sulfate) appear to be cleared more efficiently upon quotidian hemodialysis. The impact of these differences on clinical outcomes needs further investigation. Serum homocysteine levels are reported to be lower

on short daily and even lower on quotidian nocturnal hemodialysis patients when compared to conventional hemodialysis.

Vascular Access

Both central venous catheters and peripheral accesses (primarily in the form of AV fistulas, but also grafts) have been used for both daily regimens. Several studies have found that the central venous catheter survival is at least as good or better, and the complications of peripheral accesses are fewer than conventional HD. Controlled studies are missing. The buttonhole technique for AV fistulas—often using non-cutting ("blunt") needles—was popularized for home-based treatments. A single-needle configuration has been used for nocturnal hemodialysis and potentially offers a better safety profile.

Dialyzer Reuse/Remote Monitoring for Home Dialysis

Dialyzer reuse as a cost-saving measure can be implemented for home dialysis. Dialyzer reprocessing can be delayed by 1 week if the dialyzers are refrigerated at home. Several centers practice remote "live" monitoring of patients on nocturnal hemodialysis using either a telephone or an Internet connection. Remote monitoring has not been proven to prevent life-threatening complications yet, but has provided patient reassurance and a tool to monitor compliance and to collect data. It is considered optional. Centralized monitoring of wider areas provides economies of scale.

Patient Selection and Training

In view of the current financial constraints, in most centers the use of in-center daily hemodialysis is restricted to patients with significant comorbidities, refractory hypertension, and significant uremic or dialysis related symptomatology. Any patient who is willing and capable of training is eligible for home daily hemodialysis. Family members or helpers can also be trained. Adequate room for supplies at home and ability to communicate with the home dialysis staff on the phone in case of an emergency are also required. There is no medical contraindication for daily home hemodialysis except for contraindication to systemic anticoagulation for nocturnal hemodialysis.

In view of the improved hemodynamic stability of daily HD regimens, the presence of co-morbidities is an indication rather

than a contraindication to their adoption. The length of training is typically 5 to 6 weeks in previously untrained individuals. Training is usually performed three times a week, concurrent with the patient's dialysis treatments. The patient selection is bimodal, including patients in whom daily hemodialysis represents a "rescue" treatment and patients that select daily hemodialysis for its published advantages and who are generally younger and have lower load of comorbidities.

Health Economics and Quality of Life

Quotidian dialysis is hampered by the increased costs of consumables related to the high frequency of dialysis, and home-based hemodialysis regimens have higher capital costs related to the need of one hemodialysis machine per patient. Potential cost savings are primarily attributable to the modality (such as staffing, consumables, and overhead) or to patient-specific factors (such as medications and hospital admissions).

Several published studies examined the costs of quotidian hemodialysis. Although staffing accounts for between 1/4 and 1/3 of total health care costs for in-center conventional hemodialysis in developed countries, all of these studies confirmed that home dialysis reduces staffing and overhead costs to approximately 1/2 to 1/5 of the cost of in-center hemodialysis. The additional costs of consumables and capital expenditure on quotidian hemodialysis can then be offset by savings in staffing and overhead when dialysis is performed in the home. This benefit does not apply to in-center quotidian dialysis.

Several studies suggested that quotidian hemodialysis is associated with fewer hospital admissions and reduced costs for hospitalization, as well as lower cost of medications [including Epo, cardiovascular medications, and phosphate binders (for nocturnal hemodialysis)]. In all of the studies, the total cost of health care for in-center conventional hemodialysis was higher than for quotidian hemodialysis—with cost savings estimated at between US$5,000 and 10,000 per patient-year. Importantly, home programs were less expensive even when patient-specific savings (such as reductions in hospitalization) were excluded. These results need to be confirmed in randomized controlled studies.

Quality of Life

The quality of life reported for patients performing in-center hemodialysis is among the worst reported for chronic illnesses.

Studies have measured quality of life in hemodialysis patients using utility measures, disease-independent instruments, disease-specific measurements, and instruments unique to hemodialysis.

Utility Scores

Utility scores estimate overall quality of life and are used to calculate quality-adjusted life years (QALYs) in cost-utility studies. Mean utility scores for patients receiving home quotidian nocturnal hemodialysis were significantly higher than those seen in conventional hemodialysis patients, and were on a par with historically reported values following kidney transplant and predicted a better lifetime quality of life.

Disease-Independent Measures

Studies have reported improvements in quality of life scores as measured by the Sickness Impact Profile (SIP), the Beck Depression Index, the RAND-36, and the SF-36 methods. These improvements were driven by improvements in energy, physical functioning, and mental health—and a reduction in depression.

Disease-Dependent and Hemodialysis-Specific Measures

In one study, there was a reduction in the number and severity of dialysis-related symptoms, as well as a dramatic reduction in time to recover from dialysis in quotidian hemodialysis patients. In another study, the KDQOL scores improved with conversion to home short daily hemodialysis in almost every quality of life category.

In summary, it appears that quotidian hemodialysis is cost neutral relative to conventional in-center hemodialysis—and may be cost saving in certain circumstances (especially when the treatments are performed in the home). Quality of life is improved by quotidian dialysis, typically by improving a wide range of symptoms that affect physical and social functioning. Quotidian hemodialysis is the economically "dominant" modality, as it improves outcomes while reducing costs. Future research should help clarify the impact of quotidian hemodialysis on costs for in-center-based therapies, and the effect on costs and quality of life in diverse patient populations.

Cardiovascular Effects

Blood Pressure, Left Ventricular Geometry, and LV Function

Control of blood pressure (BP) with fewer or no medications has been shown with both short and long daily hemodialysis, but the mechanisms may differ. Several groups documented improved BP on daily hemodialysis using less or no medications, as well as regression of left ventricular mass index (LVMI) by 30% over 6 to 12 months on daily hemodialysis. This was associated with decrease in extracellular volume. Nocturnal hemodialysis was similarly associated with excellent BP control on one-only or no medications. Significant decrease in LVMI was also demonstrated within a year after the conversion.

Unlike the reports on short daily hemodialysis, nocturnal hemodialysis was not associated with a decrease in extracellular volume but instead by a decrease in peripheral vascular resistance and a decrease in the circulating levels of norepinephrine. Left ventricular function improved in six patients with left ventricular ejection fraction <40% after conversion to nocturnal hemodialysis, with the ejection fraction increasing from 28 to 41%.

Endothelial Function

Conversion from conventional to quotidian nocturnal hemodialysis was found to be associated with improvement in the endothelial function. The latter was shown by demonstrating improved endothelial-dependent (postischemic vasodilation) and independent vasodilation (response to nitroglycerin). Endothelial progenitor cell number and function, shown to be important for the prevention of cardiovascular disease in the general population and found to be abnormal in dialysis patients, were restored to normal on nocturnal hemodialysis.

Autonomic Nervous System

Conversion from conventional to quotidian nocturnal hemodialysis was found to be associated with partial restoration of the heart rate variability during sleep, closer to control subjects—consistent with decreasing sympathetic activity. This was also consistent with the improved baroreceptor sensitivity and decrease in the circulating levels of norepinephrine shown in other studies. Taken together, these studies suggest that upon

conversion to quotidian nocturnal hemodialysis there is a decrease in sympathetic tone and an amelioration of the abnormally elevated sympathetic to parasympathetic activity ratio.

A review of the first 15 nocturnal hemodialysis patients who underwent renal transplantation added further evidence to this hypothesis by showing a substantial increase in the levels of blood pressure after transplantation in the previously nocturnally dialyzed patients, whereas in patients previously on conventional HD the BP decreased. A decrease in sympathetic activity was also found on short daily hemodialysis—as well as a reduction of the serum levels of brain natriuretic peptide. The serum levels of this neurohormone have been found to correlate with mortality in the ESRD population.

Anemia Control/Erythropoietin Dose

Many studies have shown improved anemia control on quotidian dialysis. These studies involved both short daily and nocturnal hemodialysis. Hematocrit was found to increase, and dose of erythropoietin to decrease (usually by 30%). The variability of the results in these studies may reflect the difference in the length of the follow-up or the selection criteria of the patients. More studies are needed in this area.

Malnutrition-Inflammation Axis

After the conversion to short daily hemodialysis, most patients report an increase in appetite and well-being. Several studies have reported increases in serum albumin, pre-albumin, cholesterol, and body weight. Other studies did not find any changes in serum albumin. Patients on nocturnal hemodialysis are on unrestricted diet, and some patients gain a significant amount of weight after the conversion from conventional HD. Changes in serum albumin are inconsistent in different studies. This may also be related to patient selection criteria and to the length of follow-up. There are early reports of decreased levels of inflammatory markers upon conversion to either form of quotidian hemodialysis, but further studies are needed in this area.

Mineral Metabolism

The current evidence supports increased phosphate removal by short daily hemodialysis. The increased phosphate intake associated with improved appetite while on short daily dialysis

cancels out any significant effect on predialysis serum phosphate. Improvement in phosphate control has been demonstrated only if the duration of daily hemodialysis is more than 2 hours per session.

Quotidian nocturnal hemodialysis doubles phosphate removal, allowing discontinuation of phosphate binders and unrestricted dietary phosphate intake. In more than 50% of patients, intradialytic addition of sodium phosphate is necessary to avoid hypophosphatemia. The calcium-phosphorus product normalizes and an increase in dialysate calcium allows the suppression of PTH levels, often without the use of therapeutic doses of vitamin D analogues. Coronary artery calcification score was stable over 1 year in 14 patients, and extraosseous calcifications resolved in a patient on nocturnal hemodialysis. Patients on quotidian nocturnal hemodialysis need relatively high dialysate calcium (average 3.2 mEq/L to 1.6 mmol/L) to prevent negative calcium balance leading to decreasing bone density. Intermittent measurements of PTH, alkaline phosphatase levels, and bone densitometry are helpful in individualizing dialysate calcium needs.

Sleep

Sleep apnea is present in 50 to 70% of patients in ESRD. Out of 14 patients tested prior to nocturnal hemodialysis training, 8 patients had sleep apnea—and upon conversion to quotidian nocturnal hemodialysis sleep apnea improved significantly. Daytime sleepiness or periodic limb movements were not affected. There are no data on the effect of short daily hemodialysis on sleep disorders.

Patient Survival

Data on patient survival on quotidian hemodialysis are inadequate. Recently, a 68% 5-year and 42% 10-year survival were reported in a cohort of 415 patients on short daily hemodialysis followed in 5 centers up to 23 years. More information on patient survival is expected from the newly formed International Daily Hemodialysis Registry.

Daily Hemofiltration

Hemofiltration and hemodiafiltration provide better middle-molecule removal through convective solute transfer—and evidence has been presented that they offer better hemodynamic

tolerance, quality of life, and possibly lower mortality. The recent wider adoption of inexpensive online production of sterile replacement solution led to increased interest in these regimens. Recently, the use of daily hemo(dia)filtration was described. The studies showed lower predialysis levels of serum β2 microglobulin as well as better phosphate control. The reported regression of cardiac hypertrophy and improved quality of life may be related to the daily regimen rather than to the convective element of the treatment, as these benefits have already been reported on daily hemodialysis.

Pediatric Daily Hemodialysis

Daily treatments have also been used in children. Short daily hemodiafiltration and nocturnal hemodialysis have been reported to improve well-being, nutrition, school attendance, and growth.

Modality Choice

At this point, the main obstacle to adoption of the daily hemodialysis regimens is the unfavorable reimbursement structure in most countries. In jurisdictions where the reimbursement issues have been resolved (Netherlands, British Columbia in Canada, and Australia), the utilization of daily hemodialysis at home has increased rapidly. If daily hemodialysis is not available due to insufficient funding, overnight hemodialysis every other night or three times a week at home or in the dialysis facility should be considered.

Assuming accessibility to quotidian hemodialysis and until the methods are more formally compared, the choice of modality should be based on patient choice, medical indications, and local expertise. Quotidian nocturnal hemodialysis is the closest to the normal renal function, offers better hemodynamic stability and excellent phosphate control, and improves sleep apnea. These advantages are to be weighed against the potential for deficiency syndromes, long exposure to dialysis membranes, and safety concerns at night. Daily convective therapies are also attractive, but more experience is needed before they can be widely adopted.

Summary

Existing studies consistently demonstrated that quotidian hemodialysis in both short and long forms provides improvements in quality of life, BP control, sleep quality, phosphate clearance, and

regression of cardiac hypertrophy. Effects on anemia management and nutrition have been positive, but not as consistent. More rigorous studies in these areas will be needed to establish these benefits. On balance, it seems that more frequent hemodialysis regimens improve a number of important outcomes that are in turn associated with improved patient survival. Future well-designed studies will be needed to confirm this hypothesis. The Frequent Hemodialysis study under the auspices of the NIH and CMS is underway, with results expected in 2009.

Recommended Reading

Gotch FA. The current place of urea kinetic modelling with respect to different dialysis modalities. Nephrol Dial Transplant 1998;13(6):10–14.

There are a few competing methods comparing the dose of dialysis offered by the different dialysis modalities, as well as native kidney function. In this paper, the concept of standard Kt/V is discussed. This dialysis dose measure is based on the mid-week predialysis BUN level. There is an assumption of similarity of clinical outcomes in patients with similar stdKt/V. StdKt/V has been used extensively in the daily hemodialysis literature. Its use has also been extended to other molecules, such as β_2-microglubulin.

Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. Kidney Int 2002;61(6):2235–39.

This is an observational cohort study including 28 patients followed prior to and for more than 2 years after the conversion to nocturnal HD (NHD), as well as a control group of 13 self-care conventional hemodialysis (CHD) patients. The measured parameters included left ventricular mass index (LVMI), BP, hemoglobin, and ECF volume (using bioelectrical impedance). After conversion from CHD to NHD there were significant reductions in systolic, diastolic, and pulse pressure—as well as LVMI. There was also a significant reduction in the number of prescribed antihypertensive medications and an increase in Hb in the NHD cohort. In contrast, there were no changes in any parameters in the CHD cohort.

The significant points of the study are that it offers evidence that nocturnal hemodialysis improves BP control with the use of fewer or no medications and causes regression on LVH in less than 1 year, and that this change is not necessarily related to the decrease in BP. Furthermore, postdialysis ECFV does not decrease after the conversion to nocturnal hemodialysis and therefore the improvement in LVH is not related to the lower postdialysis weight.

Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, Lee S. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: A prospective, controlled study. J Am Soc Nephrol 2005;20(7).

In this nonrandomized prospective controlled study, 26 patients on 3-hour hemodialysis six times a week were compared to 51 matched controls on 4-hour conventional hemodialysis three times a week for 1 year. LVMI decreased on daily hemodialysis, but not in the controls. Other benefits of daily HD included decrease in serum P and lower CRP than the conventional HD group, as well as decreased Epo resistance.

The significant points in this study were the fact that this was a prospective controlled study and that the duration of daily HD at 3 hours was longer than

in other similar studies. This difference likely accounts for the better phosphate control compared to other studies. Another interesting finding was that the percent change in LV mass correlated with the percent change in predialysis serum phosphorus. Although this association may not be causative, it raises the question of the contribution of hyperphoshatemia to the cardiac geometry.

Chan CT, Harvey PJ, Picton P, Pierratos A, Miller JA, Floras JS. Short-term blood pressure, noradrenergic, and vascular effects of nocturnal home hemodialysis. Hypertension 2003;42(5):925–31.

In this study, 18 patients were tested prior to and after conversion to nocturnal hemodialysis. BP, total peripheral resistance, and plasma norepinephrine decreased. Furthermore, endothelium-dependent vasodilatation (which was impaired while on conventional HD) was restored to normal on nocturnal hemodialysis. The brachial artery response to nitroglycerine also improved.

The significance of this study is that it has demonstrated that nocturnal hemodialysis has a significant salutary effect on the endothelial function. Decrease in serum norepinephrine and peripheral vasodilatation were likely related to the improvement in the endothelial function. This is consistent with the improvement in BP control on nocturnal hemodialysis without a significant decrease in the extracellular volume shown in other studies.

Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int 1998;53(5):1399–1404.

In this article, the effect of nocturnal hemodialysis on phosphate metabolism is described in 12 patients. During the "acute" phase of the study, immediately after the conversion from conventional to nocturnal hemodialysis the pre-dialysis phosphate was similar and the postdialysis phosphate only slightly lower when nocturnal compared to conventional HD. The amount of phosphate removed in the dialysate was similar during a single session of both methods. The cumulative weekly phosphate removal was twice as high on nocturnal hemodialysis compared to conventional HD. In the "chronic" phase of the study, pre-dialysis serum phosphate was normal when on nocturnal hemodialysis (without the use of phosphate binders)—whereas the dietetic phosphate intake was higher by 50%.

Phosphate control is one of the main benefits of nocturnal hemodialysis related to the long duration of the treatment. In most patients, there is a need for addition of phosphate into the dialysate to avoid hypophosphatemia. In most patients, serum phosphate before and after a session of nocturnal hemodialysis is normal within a narrow range.

Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. The New England Journal of Medicine 2001;344(2):102–07.

The prevalence of sleep apnea in the ESRD population is higher than 50% of the patients and does not improve on hemodialysis or CAPD. In this study, the 14 first patients enrolled in the nocturnal hemodialysis program in Toronto underwent polysomnography before and after their conversion from conventional to nocturnal hemodialysis. Seven patients had sleep apnea, and the conversion to nocturnal hemodialysis was associated with a reduction in apnea/hypopnea index from 48 to 9 episodes per hour. There was no improvement in periodic limb movements. In another study, there was no improvement in daytime sleepiness after the conversion to nocturnal hemodialysis. The pathogenesis of the uremia-related sleep apnea and the nature of the positive effect of nocturnal hemodialysis are unclear. The minimal dialysis dose, length, and frequency necessary for the improvement are not yet known.

McFarlane PA. Reducing hemodialysis costs: Conventional and quotidian home hemodialysis in Canada. Semin.Dial 2004;17(2):118–24.

The perceived increased cost of providing home daily hemodialysis is a significant obstacle in its adoption. In this article, the author reviewed four costing studies involving patients on conventional, short daily, and nocturnal hemodialysis. Conventional home hemodialysis was the least expensive method. The savings for daily home hemodialysis were significant, but less striking. One study found that nocturnal hemodialysis cost less than in-center hemodialysis [$48,656 versus $59,476 (p = 0.006)] and that costs decreased by $8,046 in those converted from CHD to short daily hemodialysis and by $14,341 in those converted to nocturnal hemodialysis. Another study found that costs increased by $2,521 in those who remained on in-center hemodialysis.

This article provides a good review of several prospective costing studies. The issue of costing can be better addressed in a prospective randomized controlled study such as the ongoing NIH/CMS-sponsored study.

Ronco C. Contributions to nephrology. In Lindsay RM, Buoncristiani U, Lockridge RS, Pierratos A, Ting GO (eds.), *Daily and Nocturnal Hemodialysis*. Basel, Switzerland: Karger 2004.

In this volume of a book series is a compilation of articles addressing issues related to daily and nocturnal hemodialysis. The articles address all the aspects of the modality.

Suri RS, Nesrallah GE, Mainra R, Garg AX, Lindsay RM, Greene T, et al. Daily hemodialysis: A systematic review. *Clinical Journal of the American Society of Nephrology* 2006;1(1):33–42.

There is a significant volume of literature on daily hemodialysis. Many of the studies are patient cohort studies comparing patients to themselves prior to and after the conversion to daily hemodialysis. There are also a small number of prospective controlled studies. There is no prospective randomized controlled study published to this point. This paper is a critical review of the published literature on short daily HD that helps evaluate the quality of the published evidence. It is therefore useful for the planning and design of future studies.

Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. Kidney Int 2005;67(4):1500–08.

This paper is a critical review of the published literature on nocturnal HD that helps evaluate the quality of the published evidence. It is therefore useful for the planning and design of future studies.

CHAPTER 23

NKF-K/DOQI: Key Recommendations

Adeera Levin, MD, and Michael V. Rocco, MD

Over the past four decades, significant variations in the quality and outcome of health care have been documented in most specialities of medical practice. In all aspects of medical care, there has been an increasingly valued recognition that rigorously developed and carefully evaluated clinical practice guidelines (CPGs) may well improve the quality and efficiency of health care. Since 1989, a number of organizations within and outside the United States have established processes and methodologies for the development of evidence-based CPGs. Unfortunately, not all available guidelines are developed according to the same methodologies—leading to some confusion among practitioners.

The variability in methods is most evident across specialties, and occurs across international borders. Nevertheless, clinical decisions in the office or at the bedside, procedures performed in hospitals or day clinics, and health spending by the governments and insurers are now greatly influenced by the existence of CPGs. In the context of nephrology care, concerns about variability in dialysis outcomes led to the development of guidelines—first by the Renal Physicians Association (RPA)[1] and later, building on the initial effort, by the National Kidney Foundation (NKF).[2] In 1995, the Dialysis Outcomes Quality Initiative (NKF-K/DOQI) was launched as an official initiative of the NKF.

The purpose of the initiative was to foster systematic assessment of available literature (initially in the delivery of dialysis care) to develop evidence-based CPGs that would ultimately improve patient care and outcomes. The objectives of NKF-K/DOQI were ambitious: to improve patient survival, to reduce patient morbidity, to ameliorate the quality of life of dialysis patients, and to increase the efficiency of dialysis care. Since the original set of guidelines produced by the NKF-K/DOQI, there have been a number of ongoing initiatives—including the landmark publication of *Guidelines for the Definition, Classification, and Evaluation of Chronic Kidney Disease* in 2002.[3] At that time, the "official" nomenclature of NKF-K/DOQI was changed to NKF-K/DOQI (Kidney Disease Outcomes Quality Initiative) in order to reflect the need for earlier care of all

patients with kidney disease and to widen the scope to include patients prior to dialysis (not just those who had survived to dialysis).

Process and Methodology of NKF, DOQI, and KDOQI Guidelines

The guiding operative principles of NKF-K/DOQI were that guidelines would be developed in an interdisciplinary, evidence-based, scientifically rigorous, and transparent manner. Furthermore, an open review process would ensure input at critical stages prior to publication. Most importantly, the multidisciplinary workgroups charged with developing guidelines have complete independence and ultimate responsibility in the formulation of their recommendations. Selection criteria for guideline development are used so that relevant topics pertinent to patient care and outcomes are addressed in a timely manner.

To ensure the rigor of the process, a systematic and transparent literature review is performed using a highly trained academic evidence review team. Over the last 5 years, the evidence rating system has evolved and methods to ensure consistency in grading have been implemented. In this ever-evolving field (both inside and outside nephrology), consistency and agreement about evidence rating is difficult. In response to recent criticisms that lack of evidence should not lead to the development of weak guideline statements that may be subject to misinterpretation by regulatory agencies, a modified system of guideline statements was developed. Those statements that are truly evidence based will indeed be labeled, and quoted, as guideline statements.

Those statements that have poor evidence in the opinion of the workgroups will be labeled Clinical Practice Recommendations (CPRs), with disclaimers noted in the preamble of the statement. CPRs can serve as a focus for ongoing research agendas and are subject to change as new evidence accumulates. This most recent change in NKF-K/DOQI guideline publication has met with mixed enthusiasm. In this era of ever-increasing governmental regulation, the need to differentiate guidelines (which can be the subject of clinical performance measures) from CPRs (which cannot) was felt to be an important distinction. An ongoing review of the impact of this change in nomenclature for statements will be undertaken.

Research recommendations have been grouped into three categories: critically important, important, and of interest. This reorganization of the research recommendations was made to assist funding agencies in prioritizing the use of research funds in these areas. Finally, pediatric guidelines and clinical practice

recommendations are separated from adult guidelines and recommendations.

Following the development of any initial draft, guidelines are subjected to a multistage review. In the first stage, selected outside experts and an advisory board (expert, multidisciplinary) review the initial draft of the guidelines. In the second stage, a variety of organizations (professional and patient associations, dialysis providers, government agencies, product manufacturers, and managed care companies) are invited to review and comment on a revised second draft of the guidelines. In the final stage, the draft document is open to public review. These comments are then captured and collated in a web-based system, and considered by the workgroups. Where applicable, the comments are incorporated into the final draft of the guidelines and the workgroups review the final document prior to publication.

A principal determinant of successful guidelines is their currency. Unfortunately, any set of guidelines begins to age the moment the obligatory date limit is set on the literature search they will encompass. In fact, once they are published they begin to be outdated exponentially as new data becomes available. It was decided from the outset of the guideline process that each guideline would be maintained as a current and live document, with periodic reviews of the literature and appropriate revision of the guideline accordingly.

Since original publication in 1997, two updates have been published for anemia, vascular access and dialysis adequacy.[4] A number of additional guidelines have been developed: bone and mineral metabolism,[5] treatment of dyslipidemia,[6] cardiovascular disease in dialysis patients,[7] and hypertension.[8] Most recently, the updates on vascular access, peritoneal dialysis, and hemodialysis (HD)[9] have been completed—as has a revamped Anemia guideline[10] and a new endeavour, the Diabetes and CKD management guideline.[11] These updates and new guidelines are an example of the nephrology community's interest in and hunger for updated reviews and broader coverage on other kidney co-morbidities.

The following is a brief summary of the key recommendations of the updated guidelines. The entire text of the five guidelines and their explanatory appendices can be obtained from the National Kidney Foundation (30 East 33rd Street, New York, NY 10016) at *www.kdoqi.org*. It is important to reiterate that the guideline documents are intended for use by professionals trained to understand variations in the practice of medicine, in that the specific needs and response of an individual patient to any intervention will vary among any group of patients. Thus,

the recognition for individualization as an integral component of the delivery of health care is one key to guideline adoption and encourages ongoing research on recommendations where supportive evidence is lacking. As such, no guideline should be used by any official or organization without full consideration of normal biologic variations in the response to an intervention. An appropriate disclaimer to this effect prefaces the published NKF-K/DOQI guideline documents, and the recent division into clinical practice recommendations and guideline statements further clarifies this concept within any one group of statements.

Hemodialysis Adequacy Guidelines

The 2006 HD adequacy guidelines are basically an update and expansion of the 1997[12] and 2000 versions.[4] The new version[9] reorganizes the existing 16 guidelines into 8 major areas addressed by guidelines and/or clinical practice recommendations. Although there is no change in the recommended minimum dose of dialysis, the target dose has been raised from a Kt/V of 1.3 to 1.4 to ensure that the delivered dose of dialysis is greater than 1.2. Guidance is now provided on the recommended minimum dose of dialysis for patients who receive HD on a schedule other than three times per week.

More specific recommendations are also given about how to adjust the HD prescription in patients with significant residual kidney function (RKF) and how to include measures of RKF into adequacy calculations. New areas covered in this clinical practice guideline include the preservation of RKF and the maintenance of euvolemia. The key recommendations of the eight categories in this guideline are summarized in the following sections.

Initiation of Hemodialysis

Patients who reach CKD stage 4 [estimated glomular filtration rate (GFR) <30 mL/minute/1.73 m^2] should receive timely education about kidney failure and options for its treatment, including kidney transplant, peritoneal dialysis, HD in the home or in-center, and conservative treatment. Estimation of GFR, using validated equations such as the MDRD equation for GFR, should guide decision making regarding dialysis initiation. When patients reach stage 5 CKD (estimated GFR <15 mL/minute/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy.

Methods for Measuring and Expressing the Hemodialysis Dose

The dose of HD should be measured at regular intervals and at least monthly. The frequency of treatments should be included in the expression of dose and the dose of HD should be expressed as $(K_{urea} \times T_d)/V_{urea}$ (abbreviated as Kt/V), where K_{urea} is the effective (delivered) dialyzer urea clearance in mL/minute integrated over the entire dialysis, T_d is the time in minutes measured from beginning to end of dialysis, and V_{urea} is the patient's volume of urea distribution in mL. The preferred method for measurement of the delivered dose is formal urea kinetic modeling. Other methods may be used, provided they give similar results and do not significantly overestimate the modeled dose.

Methods for Postdialysis Blood Sampling

Both samples (predialysis and postdialysis) should be drawn during the same treatment session. The postdialysis BUN sample should be obtained by either the slow flow or stop flow methods.

Minimally Adequate Hemodialysis

The minimally adequate dose of HD given three times weekly to patients with Kr <2 mL/minute/1.73 m^2 should be an spKt/V (excluding RKF) of 1.2 per dialysis. For treatment times <5 hours, an alternative minimum dose is a URR (urea reduction ratio) of 65%. The target dose for HD given three times weekly with a Kr <2 mL/minute/1.73 m^2 should be a spKt/V (excluding RKF) of 1.4 per dialysis or a URR of 70%. In the clinical practice recommendation section, opinions are provided regarding the minimal dose of dialysis for patients receiving HD at a frequency other than three times per week. Efforts should be made to monitor and minimize the occurrence of missed or shortened treatments.

Control of Volume and Blood Pressure

The ultrafiltration component of the HD prescription should be optimized with a goal to render the patient euvolemic and normotensive. This includes counseling the patient on sodium and fluid restriction, adequate ultrafiltration, and the use of diuretics in patients with RKF. Daily dietary sodium intake should be restricted to no more than 5 g sodium chloride (2.0 g or 85 mmol sodium). Increasing positive sodium balance by "sodium

profiling" or using a high-dialysate sodium concentration should be avoided.

Preservation of Residual Kidney Function

One should strive to preserve RKF in HD patients. Opinions on how to preserve RKF are provided in the clinical practice recommendations section.

Quality Improvement Programs

For HD adequacy, each dialysis clinic should continue to monitor the processes related to the delivery of dialysis. These include Kt/V, reuse standards, and so on. Consideration should be given to providing resources and training for expanding the assessment of clinical outcomes beyond mortality to include hospitalization rates, QOL (quality of life), patient satisfaction, and transplantation rates—recognizing that without adequate resources and training these outcomes are unlikely to be valid, and the efforts to collect such information may adversely affect patient care. Furthermore, quality improvement programs should include representatives of all disciplines involved in the care of the HD patient.

Pediatric Hemodialysis Prescription and Adequacy

Assessment of nutrition status is an essential component of HD adequacy measurement. The nPCR should be measured monthly, either by formal urea kinetic modeling or by algebraic approximation. For younger pediatric patients, prescription of higher dialysis doses and higher protein intakes at 150% of the recommended nutrient intake for age may be important. Accurate assessment of patient intravascular volume during the HD treatment should be provided to optimize ultrafiltration.

Peritoneal Dialysis Adequacy

Guidelines

This guideline[9] consists of six CPGs and several clinical practice recommendations. Despite new evidence presented in this update, the guideline calls for greater research into peritoneal dialysis adequacy. Several significant changes were made to these guide-

lines. First, the target dose of dialysis (a weekly total Kt/V urea of 2.0) has been replaced by a minimum weekly total Kt/V urea of 1.7.

Second, it is no longer necessary to obtain weekly creatinine clearance values to assess the adequacy of dialysis. The measurement schedule for adequacy determinations has also been simplified. Third, it is recommended that patients with residual renal function be placed on either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (except when contraindicated) to help preserve RKF if the patient's blood pressure permits. Finally, a new section on the importance of and approach to maintenance of euvolemia was added. The key recommendations of the five categories in this guideline are summarized in the sections that follow.

Initiation of Dialysis

These statements are the same as those for the HD guideline on this topic.

Peritoneal Dialysis Solute Clearance Targets and Measurements

For patients with RKF (considered significant when urine volume is >100 mL/day), the minimal *delivered* dose of total small-solute clearance should be a total (peritoneal and kidney) Kt/V_{urea} of at least 1.7 per week. Total solute clearance (residual kidney and peritoneal, in terms of Kt/V_{urea}) should be measured within the first month after initiating dialysis and at least once every 4 months thereafter. If the patient has >100 mL/day of residual kidney volume and residual kidney clearance is being considered as part of the patient's total weekly solute clearance goal, a 24-hour urine collection for urine volume and solute clearance determinations should be obtained at a minimum of every 2 months.

For patients without RKF (considered insignificant when urine volume is =100 mL/day), the minimal *delivered* dose of total small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.7 per week—measured within the first month after starting dialysis and at least once every 4 months thereafter.

Preservation of Residual Kidney Function

It is important to monitor and preserve RKF. In the patient with RKF who needs antihypertensive medication, preference should be given to the use of ACE inhibitors or angiotensin receptor blockers (ARBs). In the normotensive patient with RKF, consideration should be given to the use of ACE inhibitors or

ARBs for kidney protection. Insults to RKF in CKD patients should also be considered insults to RKF in PD patients and should be avoided when possible.

Maintenance of Euvolemia

Each facility should implement a program that monitors and reviews peritoneal dialysate drain volume, RKF, and patient blood pressure on a monthly basis. Among the therapies one should consider in optimizing extracellular water and blood volume are restricting dietary sodium and water intake, use of diuretics in patients with RKF, and optimization of peritoneal ultrafiltration volume and sodium removal.

Quality Improvement Programs

Each home-training unit should establish quality improvement programs with the goal of monitoring clinical outcomes and implementing programs that result in improvements in patient care. Quality improvement programs should include representatives of all disciplines involved in the care of the PD patient, including physicians, nurses, social workers, and dietitians. Suggested domains of clinical activities one should consider monitoring include peritonitis rates, exit site infection rates, technique failure rates, QOL, other catheter-related problems, and catheter survival rates.

Special Needs of Children on Peritoneal Dialysis

The peritoneal equilibration test (PET) is the preferred approach for the clinical assessment of peritoneal membrane transport capacity in pediatric patients and should be performed to aid in the prescription process. The frequent presence of hypertension and associated cardiac abnormalities in children receiving PD requires strict management of blood pressure, including attention to fluid status.

Each home-training unit should establish quality improvement programs with the goal of monitoring clinical outcomes and implementing programs that result in improvements in patient care. In children, growth and school attendance/performance are clinical activities to be monitored in addition to those recommended for adult patients. Quality improvement programs should include representatives of all disciplines involved in the care of the pediatric PD patient, including physicians, nurses, social workers, dietitians, play therapists, psychologists, and teachers. Single-center trends in pediatric clinical outcomes should be compared to national and international data.

Vascular Access Guidelines

In the 2006 NKF-K/DOQI *Guidelines for Vascular Access*,[9] the 38 guidelines from the 2000 update were grouped into 7 major topics for adults, 1 section for children, and a section of clinical outcome goals. Key differences from the 2000 version[4] include a new guideline on the cannulation of the vascular access that includes statements on when a fistula is mature and ready for cannulation. The list of preferred, acceptable, and unacceptable methods for monitoring vascular access dysfunction has been updated and includes a statement that a physical examination of grafts and fistulas should be performed on a monthly basis.

Methods for treating dysfunctional or nonfunctional catheters have also been updated. Finally, goals for autologous fistulas have been revised upward (from 40 to 60%), whereas the avoidance of catheters as permanent access is maintained at 10%. The key recommendations of the nine categories in this guideline are summarized in the sections that follow.

Patient Preparation for Permanent Access

Patients with a GFR of <30 mL/minute/1.73 m^2 should be educated on all modalities of renal replacement therapy options, including transplantation. In patients with CKD stage 4 or 5, forearm and upper-arm veins suitable for placement of vascular access should not be used for venipuncture or for the placement of intravenous catheters, subclavian catheters, or peripherally inserted central catheter lines.

Patients should have a functional permanent access at the initiation of dialysis, with a fistula placed 6 months prior, a graft 3 to 6 weeks prior, and a peritoneal dialysis catheter at least 2 weeks prior to the anticipated start of dialysis. A backup HD access does not need to be placed in most peritoneal dialysis patients.

Selection and Placement of a Permanent Access

The order of preference for placement of fistulae in patients with kidney failure who choose HD as their initial mode of kidney replacement therapy should be (in descending order of preference):

- *Preferred:* In terms of fistulae, a wrist (radial-cephalic) primary fistula, an elbow (brachial-cephalic) primary fistula, and a transposed brachial basilic vein fistula.
- *Acceptable:* AVG of synthetic or biologic material, such as a forearm loop graft (preferable to a straight configuration), an upper-arm graft, a chest wall or "necklace" prosthetic graft,

or a lower-extremity fistula or graft (only when all upper-arm sites are exhausted).
- *Avoid:* If possible, avoid long-term catheters. Long-term catheters or dialysis port catheter systems should be used in conjunction with a plan for permanent access.

Cannulation and Accession of the Access

For all vascular accesses, aseptic technique should be used for all cannulation and catheter accession procedures. Fistulae are more likely to be useable when they meet the rule of 6s characteristics: diameter at least 0.6 cm, no more than 0.6 cm deep, and discernible margins. Fistula hand-arm exercise should be performed to assist with fistula maturation. If a fistula fails to mature by 6 weeks, a fistulogram or other imaging study should be obtained to determine the cause of the problem.

Grafts should generally not be cannulated for at least 2 weeks after placement, and not until swelling has subsided so that palpation of the course of the graft can be performed. The composite polyurethane graft should not be cannulated for at least 24 hours after placement, and not until swelling has receded so that palpation of the course of the graft can be performed. Rotation of cannulation sites is needed to avoid pseudoaneurysm formation.

Detection of Access Dysfunction

Physical examination should be used to detect dysfunction in fistulae and grafts at least monthly by a qualified individual. Techniques (not mutually exclusive) that may be used for surveillance of stenosis in grafts include:
- *Preferred:* Intra-access flow, directly measured or derived static venous dialysis pressure and/or duplex ultrasound
- *Acceptable:* Physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in the graft
- *Unacceptable:* Unstandardized dynamic venous pressures

Techniques (not mutually exclusive) that may be used for surveillance of stenosis in arteriovenous (AV) fistulas include:
- *Preferred:* Direct flow measurements, physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in the outflow vein and duplex ultrasound

- *Acceptable:* Recirculation using a non urea-based dilutional method and static pressures, direct or derived

With all techniques, prospective trend analysis of the test parameter has greater power to detect dysfunction than isolated values alone.

Treatment of Autologous Fistula Complications

Persistent swelling of the hand or arm should be expeditiously evaluated and the underlying pathology corrected. A program should be in place to detect early access dysfunction, particularly delays in maturation, within 6 weeks of access placement. Intervention on a fistula should be performed for the presence of inadequate flow to support the prescribed dialysis blood flow, hemodynamically significant venous stenosis, ischemia in the access arm, and aneurysm formation in a primary fistula. Postaneurysmal stenosis that drives the aneurysm should also be corrected. The aneurysmal segment should not be cannulated. A fistula with >50% stenosis in either the venous outflow or arterial inflow, in conjunction with clinical or physiologic abnormalities, should be treated with PTA or surgical revision.

Treatment of Arteriovenous Graft Complications

Patients with extremity edema that persists beyond 2 weeks following graft placement should undergo an imaging study to evaluate the patency of the central veins. Stenoses that are associated with AVGs should be treated with angioplasty or surgical revision if the lesion causes >50% reduction in the luminal diameter and is associated with clinical and/or physiologic abnormalities. Each institution should determine which procedure, percutaneous thrombectomy with angioplasty or surgical thrombectomy with AVG revision, is preferable based on expediency and physician expertise at that center.

Superficial infection of an AVG should be treated with antibiotics that cover both Gram-negative and Gram-positive microorganisms. Subsequent antibiotic therapy should be based on culture results. Incision and drainage may be beneficial. Extensive infection of an AVG should be treated with appropriate antibiotic therapy and resection of the infected graft material.

Prevention and Treatment of Catheter/Port Complications

Catheters and ports should be evaluated when they become dysfunctional. Dysfunction is defined as failure to attain and main-

tain an extracorporeal blood flow rate of 300 ml/min or greater at a pre-pump arterial pressure more negative than –250 mmHg. Methods that should be used to treat a dysfunctional or nonfunctional catheter or port include repositioning of a malpositioned catheter, thrombolytics (using an intraluminal lytic, intradialytic lock protocol, intracatheter thrombolytic infusion, or interdialytic lock), and catheter exchange with sheath disruption when appropriate.

Treatment of an infected HD catheter or port should be based on the type and extent of infection. All catheter-related infections, except for catheter exit-site infections, should be addressed by initiating parenteral treatment with an antibiotic(s) appropriate for the organism(s) suspected. Definitive antibiotic therapy should be based on the organism(s) isolated. Catheters should be exchanged as soon as possible and within 72 hours of initiating antibiotic therapy in most instances, and such exchange does not require a negative blood culture prior to the exchange. Follow-up cultures are needed 1 week after cessation of antibiotic therapy.

Clinical Outcome Goals

Each center should establish a database and CQI (continuous quality improvement) process to track the types of accesses created and the complication rates for these accesses. The goals for permanent HD access placement should include a prevalent functional AVF placement rate of greater than 65% and a cuffed catheter for permanent dialysis access (e.g., not as a bridge) of less than 10%. Goals for fistula, graft, and catheter complications and patency rates are listed in this guideline.

Vascular Access in Pediatric Patients

Circumstances in which a cuffed vascular catheter may be acceptable for pediatric chronic access include lack of local surgical expertise to place permanent vascular access in small children, patient size too small to support a permanent vascular access, bridging HD for PD training or PD catheter removal for peritonitis, and expectation of expeditious kidney transplantation.

The blood flow rate of an external access should be minimally 3 to 5 mL/kg/minute and should be adequate to deliver the prescribed HD dose. Serious consideration should be given to placing permanent vascular access in children >20 kg in size who are expected to wait more than 1 year for a kidney transplant. If surgical expertise to place permanent access does not exist in the patient's pediatric setting, efforts should be made to consult vascular access expertise among local adult-oriented surgeons.

Anemia of Chronic Kidney Disease Guidelines

Anemia develops in the course of gradual loss of kidney function and afflicts individuals with progressive kidney disease well before the onset of kidney failure and the need for dialysis. The effective treatment of the anemia of kidney disease increases survival, decreases mortality, improves QOL, and in children improves growth and development. From the outset of work on the anemia guidelines, it was evident that its scope must be expanded to cover all patients with CKD, as well as those on dialysis. The current guideline published in 2006[10] and revised in 2007, utilizes the most current information relevant to CKD, dialysis, and transplant populations—and includes pediatric and adult considerations.

This is the first guideline in NKF-K/DOQI to be done with overt involvement of an international guideline development group representation [European Best Practice guidelines (EBPGs)]. The goal was to build on previously done literature reviews by that group, capitalize on current trial data, and critically evaluate key assumptions. The NKF-K/DOQI guidelines from 2006 were subsequently revised in the light of new evidence available after guideline publication. The statements below reflect the final statements of the workgroup, updated as of May 2007. The anemia workgroup defined clinical practice recommendations and guidelines very stringently, and this is reflected in the document very clearly by prefacing each CPR with the statement "In the opinion of the workgroup." The key statements and CPRs include:

- All patients with CKD at any stage should be evaluated for the presence of anemia, defined by gender, as <13.5 in adult males and <12.0 in adult females.
- The initial assessment of anemia in CKD should include a complete blood count, absolute reticulocyte count, serum ferritin to assess iron stores, and serum TSAT *or* content of Hb in reticulocytes (CHr) to assess adequacy of iron for erythropoiesis.
- In the opinion of the work group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13.0 g/dL.
- Patients prescribed ESA should have hemoglobin monitoring at least on a monthly basis. The initial ESA dose and dose adjustments should be determined by the patient's hemoglobin level, the target hemoglobin level, the observed rate of increase

in the level, and clinical circumstances. Additional opinions are provided on how often to administer ESA, how to reduce the dose of ESA, and how to make up for missed ESA doses. It is suggested that patients receive ESA by the subcuteaneous route, except for HD patients (where the risk of pure red blood cell aplasia (PRCA) associated with SC administration, albeit small, has prompted authorities to recommend the IV route). Iron status testing should be monthly during the initial ESA treatment, and then at least every 3 months during stable ESA treatment or in patients not on ESA therapy.

- For HD patients, it is suggested that the serum ferritin level should be maintained >200 ng/m and that either the TSAT is >20% or the CHR is >29 pg/cell. For all other CKD patients, the serum ferritin should be maintained at >100 mg/mL and the TSAT should be >20%. There is insufficient evidence to recommend routine administration of IV iron if the serum ferritin level is greater than 500 ng/mL. There is insufficient evidence to suggest the use of either carnitine or vitamin C in the management of the anemia of CKD. However, androgens should not be used as an adjuvant to ESA treatment.
  The recognition and management of hyporesponsiveness to ESA therapy is also discussed, including pure red cell aplasia.

There are also sections pertaining to special populations, defined as children and those with kidney transplants. A separate document is currently in development that addresses specific research recommendations that will help to shape future research, and ideally ensure that the next set of anemia guidelines can be based on research that has addressed the key unanswered questions regarding clinical care of patients with anemia and CKD.

Diabetes Guidelines

These guidelines published in 2007[11] are unique in that they address the management of a complex group of patients who are often seen and cared for by non-nephrologists. The goal of these guidelines is to clarify with respect to CKD the diagnosis and workup of patients with diabetes, and to inform both nephrology and non-nephrology communities regarding best evidence for treatment and follow-up of CKD in this group of patients. The diabetes guideline were developed by an international group of diabetologists, pediatric and adult nephrologists, dieticians, and internists to ensure that the breadth, depth, and perspective were representative of the various aspects of diabetes care. Key statements in this guideline include:

- All diabetic patients should be screened annually for diabetic kidney disease. Initial screening should commence after 5 years of type 1 diabetes or from the time of diagnosis of type 2 diabetes. Screening should include measurement of urinary albumin-to-creatinine ratio (ACR) in a spot urine sample, measurement of serum creatinine and estimation of glomerular filtration rate.
- An elevated ACR should be confirmed in the absence of urinary tract infection with two additional first-void specimens collected over the next 3 to 6 months.
- The target HbA1C for all people with diabetes should be <7.0%, irrespective of the presence or absence of CKD.
- Hypertensive individuals with diabetes and CKD should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic.
- The target blood pressure in diabetes and CKD should be <130/80 mmHg.
- The target LDL in people with diabetes and CKD stages 1 through 4 should be <100 mg/dL. A level <70 mg/dL is a therapeutic option.
- At all stages of CKD, individuals with diabetes should achieve a dietary protein intake that meets but does not exceed the Recommended Dietary Allowance (RDA) of 0.8 g/kg body weight per day, or 10% of total daily calories.

Special populations addressed include children, adolescents, and the elderly. Note is made in particular of indigenous populations at particularly high risk for developing kidney disease in the presence of diabetes. The issue of managing albuminuria in normotensive diabetic patients and the use of albumin as a surrogate maker was also addressed, as this issue was identified by the workgroup as important. There are separate clinical practice recommendations that describe nutritional and multifaceted approaches to intervention, and approaches to self-management. These recommendations are consistent with current recommendations in the diabetes and general medical literature, as well as recent publications in the nephrology literature.

Overall, the current set of NKF-K/DOQI guidelines and recommendations (most of which were completed on 2006, with the diabetes and revised anemia guidelines completed in 2007) represent a true evolution of process, science, and clinical judgement. The tireless efforts of the volunteers who constitute the workgroups' members and chairs (backed by the professional high-quality evidence review team) have led to a set of well-respected, scholarly, and practical guidelines and practice recommendations

designed to improve the outcomes of people living with kidney disease.

References

1. Renal Physicians Association. Clinical Practice Guidelines 1: Adequacy of Hemodialysis. 1993.
2. Steinberg EP, Eknoyan G, Levin NW, Eschbach JW, Golper TA, Owen WF, et al. Methods used to evaluate the quality of evidence underlying the National Kidney Foundation-Dialysis Outcomes Quality Initiative Clinical Practice Guidelines: Description, findings and implications. Am J Kidney Dis 2000;36:1–11.
3. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 2002;39(2/1):S1–266.
4. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines. Hemodialysis Adequacy, Peritoneal Dialysis Adequacy, Vascular Access, and Anemia of Chronic Kidney Disease: Update 2000. Am J Kidney Dis 2001;37(1/1): S1–S238.
5. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003;42(4/3):S1–201.
6. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. Am J Kidney Dis 2003;41(4/3): S1–91.
7. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis 2005;45(4/3):S1–153.
8. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis 2004;43(5/1):S1–290.
9. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. Am J Kidney Dis 2006;48(1/1):S1–321.
10. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47(5/3):S1–145.
11. National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Disease 49:S1-S180, 2007 (suppl 2).
12. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy, Peritoneal Dialysis Adequacy. Am J Kidney Dis 1997;30(2): S1–136.

CHAPTER 24

Cannulation of Hemodialysis Vascular Access: Science and Art

Lesley C. Dinwiddie, MSN, RN, FNP, CNN

The objective and subjective quality of a hemodialysis treatment using a subcutaneous vascular access can be highly variable based on the cannulation experience. This has become increasingly evident as practitioners, with the urging of the Center for Medicare and Medicare Services, attain percentages of 40% and greater in arteriovenous fistula (AVF) access—the undisputed gold standard for vascular access worldwide. Many reasons have been given to explain the disparate data for achieving and maintaining functional AVFs in the United States, but one that causes a great deal of frustration for practitioners and patients alike is failure to effectively cannulate the outflow vein on a consistent basis. The purpose of this chapter is to provide practical, immediately useable, information on cannulation that will increase the functionality of AVFs and reduce the number of cannulation errors in both AVFs and arteriovenous grafts (AVGs).

The entire vascular access team is responsible, through the continuous quality improvement (CQI) process, for all vascular access outcomes (including those related to cannulation). The seminal act of piercing the skin and threading the needle, usually done by nurses and the patient care technicians under their supervision, is but one step of the cannulation process. All members of the collaborative team should be knowledgeable of the entire procedure.

Steps of the Cannulation Process

Assessment

The predialysis subcutaneous vascular access assessment is both holistic and focused. Flow through the access vessel is the product of cardiac output and mean arterial pressure that will be affected by local anatomical variables such as vessel size,

collaterals, stenoses, and aneurysms. If vital signs are normal for the patient, the cannulator asks about changes in the access and inspects the access limb for absence of swelling and the skin over the vessel for integrity, checks for absence of inflammation, and assesses changes in aneurysms. After inspecting the fingers for color and normal movement, the cannulator should then feel the fingers for temperature (contrasted with the ipsilateral arm) and palpate the distal pulses.

The next action is to feel for the thrill and note the vibratory versus pulsation character. The cannulator should then listen with a clean stethoscope over the entire length of the cannulated portion of the outflow vein or AVG for confirmation of flow (i.e., the bruit) and for evidence of stenosis characterized by a change in amplitude and pitch. Absence of thrill and bruit should be reported immediately. Cannulating to assess for flow is unacceptable and can complicate interventions to lyse thrombus and restore flow.

Once the assessment of flow is complete, the cannulator identifies recent cannulation sites and asks the patient about those cannulation experiences (both positive and negative). If the patient does not have established buttonholes, the cannulator chooses the sites for both the arterial (afferent to the extracorporeal circuit) and venous (efferent) needles. Any area of skin break, with or without exudate, or inflammation should be reported to the nephrologist or APN (Advanced Practice Nurse) prior to cannulation. Site choice involves decision making with regard to rotation of sites; avoidance of stenoses, aneurysms, and pseudoaneurysms; and proximity to anastomoses. Site of entry *and* site of needle tip postcannulation must be considered to ensure successful placement. Accesses bend; steel needles don't.

Needles, both cutting bevel for new sites and noncutting for buttonhole use, currently come in 0.6-inch, 1-inch, and 1.25-inch lengths—and in sizes from 14- to 17-gauge. The arterial needle can be placed either retrograde or antegrade. Retrograde placement of the arterial needle should not position the needle tip in or near the anastomosis. Similarly, the tip for the venous needle (always antegrade) in an AVG placement should not be close to the anastomosis. Recent research at the University of Alabama shows that outflow from the venous needle significantly increases turbulence downstream, which might promote graft pathology such as neointimal hyperplasia. Another consideration is needle placement to avoid recirculation.

Cannulation lore holds that needle tips should be approximately 2 inches apart to prevent recirculation. This rule is some-

what arbitrary because recirculation is primarily related to flow rates in which the extracorporeal flow exceeds intra-access flow. However, in accesses where flow is known or suspected to be less than 600 mL per minute the greater the distance between tips the less risk there is of recirculation.

For the recently created fistula, the assessment is geared toward maturation following the Rule of 6s as stated in the NKF-K/DOQI guidelines (see Table 24.1). This is a hypothetical construct to assist in maturation assessment. Experienced nurses have been shown to correctly predict maturation suitable for cannulation through physical assessment 80% of the time. Whereas DOPPS (Dialysis Outcomes and Practical Patern Study) (international) data have shown that cannulation can be performed successfully at 4 weeks, the revised NKF-K/DOQI guidelines continue to advise longer maturation times of 6 to 8 weeks and early professional assessment. This conservative stance is supported by recent evidence that the two significant variables that lead to a major fistula infiltration are advanced patient age and AVF age of less than 6 months.

Additional assessment is required to determine direction of flow. Normal fistula outflow is anatomically proximal to the central circulation, but exceptions do exist (surgically and by default) regarding retrograde flow through collateral vessel/s when the intended outflow vein is occluded. If any doubt exists regarding the vascular anatomy, an ultrasound mapping should be obtained prior to first cannulation. Ultrasound can also measure the thickness of the vessel wall to determine sufficient strength for cannulation (i.e., maturation).

Cannulation readiness of an AVG is determined not only by the type of graft material but by the condition of the extremity. Generally, the synthetic polytetrofluoroethylene (PTFE) can be cannulated in 14 days or less according to manufacturers' directions. However, swelling and pain in the extremity take

Table 24–1

Rules of 6s for AVF Maturation

- The AVF should be expertly assessed within 6 weeks of creation for maturation.
- Flow through the vessel should exceed 600 mL per minute.
- The vessel should be greater than 6 mm in diameter.
- The vessel should be less than 6 mm from the skin surface.

precedence in the decision to cannulate if a functional catheter is available for access. If these symptoms do not subside within 4 to 6 weeks postoperatively, a potential outflow obstruction may exist that requires intervention prior to cannulation. Biologic grafts are a hybrid of the anatomic features of outflow veins and PTFE and must be assessed accordingly. The assessment method is the same as for any AVG, but the cannulation technique is more like that for a native vein.

Skin and Patient Preparation

Washing of the access site by the patient upon entry to the dialysis unit should be mandatory. Following the assessment, the skin is cleansed with agents per facility protocol—using strict aseptic technique. With the buttonhole technique, the skin is cleaned after stretching the skin away from the buttonhole and/or soaking with a bactericidal solution to loosen the scab. The scab over the entry site is removed with a sterile piece of gauze or a sterile instrument (never the tip of the cannulating needle), and the gloves are changed prior to a second skin cleaning. For all AVF cannulation, regardless of vessel size, a tourniquet is placed proximal to the chosen cannulation sites—sufficient to engorge the vein without occluding flow. The tourniquet not only helps stabilize the vessel but increases the surface tension of the skin—promoting smoother needle entry. Gloves are changed between skin preparation and cannulation.

Cannulation frequently causes the patient anxiety—anticipating both the pain of needle entry and the uncertainty of successful placement. Preparing the patient requires professional reassurance of the cannulator's ability as well as ascertaining the need for local anesthetic. A relaxed and confident patient is easier to cannulate with less pain. Patients who routinely need local anesthetic should be prescribed, and self-administer, a cream containing lidocaine that numbs the skin. Alternatively, ethyl chloride spray or intradermal lidocaine injection can be offered on a limited basis. Local anesthetic should be offered until the patient develops enough trust and scar tissue to safely discontinue it.

An important variable for successful cannulation is patience. The cannulator must take the necessary time to properly set up, assess the patient, prepare skin, and establish confidence. As a patient once asked, "How is it that they have enough time to stick me two or three times when they miss but never enough time to do it right the first time?"

Cannulation

Specific techniques for both rope ladder (a pattern of site rotation that alternates sites from recent punctures while maintaining an effective distance between tips) and buttonhole cannulation are described in detail in the newly revised NKF-K/DOQI guidelines. The rope ladder technique was developed to ensure consistent site rotation, thereby preventing aneurysm formation secondary to weakening of the vessel wall by repeated cannulation in a small area.

The introduction of the buttonhole technique by Twardowski was greeted with much skepticism because it appeared to be directly contradictory to the rotation of sites. However, Twardowski stated that in addition to maintaining the integrity of the vein wall cannulation with the buttonhole or constant-site technique was less painful—in addition to being quick and easy. He added that this method also virtually eliminates infiltrations and reneedling and the infection rate is not significantly higher than multisite cannulation. This is confirmed by the recent literature. Marticorena et al. also demonstrated the salvaging of function in aneurysmal AVFs using the buttonhole technique.

For rope ladder cannulation, anatomic assessment will indicate the appropriate angle of needle entry. The texture of the vessel dictates the degree of force required to penetrate the entry wall while avoiding perforation of the back wall. It is generally thought that AVF cannulation requires a shallower angle of entry than that required for PTFE. When vessel entry is confirmed by the flashback of blood, the cannulator pauses to prevent back wall damage and reorients the needle to follow the angle of the vessel in order to successfully thread the needle in the center of flow. Needles do not need to be rotated 180 degrees (flipped). The back-eye feature of the arterial needle allows for optimal flow of blood into the needle. The venous needle does not require this feature.

Buttonhole cannulation is optimal for the patient who has an AVF, but the outflow vein has limited cannulation sites. This method involves repeated cannulation into the exact same puncture site and a scar tissue tunnel track develops. The scar tissue tunnel tract allows the needle to pass through to the (outflow) vessel of the fistula following the same path each time. Each patient should have two established sets of buttonholes, if possible, created by two different expert cannulators. After at least six sharp entries to establish each buttonhole, the cannulator can then switch to “dull” needles for all future cannulations.

(Ball has recently reported that 6 is not enough and the number required can range anywhere from 8 to 12, with fewer for nondiabetic and more for diabetic.)

The technique needed to find the vein through the tunnel with a dull needle requires needle insertion into the buttonhole, using a twisting motion if necessary to approach the vein. It feels like the tip is bouncing on the vein wall. The cannulator should go 20 degrees forward or back until the needle "drops" into the vein. "When the cannulator goes by feel (not sight) you know they've 'got it.'" Toma et al. confirmed this experience by noting that the angle of the scar tract changed over time, with the entry into the vein becoming more proximal.

This Japanese group also developed a sterile peg device for holding the tunnel open interdialytically for the first 2 weeks to speed up the buttonhole development process. This method has been successfully replicated in Canada. Both groups use angiocaths for the establishment of the buttonholes, and blunt/dull needles when the tunnel is established. In both types of cannulation, proper needle position should be confirmed by the ability to aspirate blood and flush with ease (as well as by the subjective comfort of the patient).

Needle Taping and Beginning Dialysis

Securing the needles to prevent dislodgement while maintaining easy flow is a necessary art. Usually a 1-inch-wide tape across the wings of the needle to anchor and a ½-inch tape chevroned behind and across the wings is sufficient. It is important to be able to see the needle entry site for both needles throughout the dialysis procedure to be able to detect dislodgement or bleeding. Once both needles are secured, the loading dose of heparin can be given and the needles attached to the extracorporeal circuit. The cannulator should set the pump speed to no more than 200 mL per minute and observe both of the needles, the prepump arterial pressure, and the venous pressure while filling the extracorporeal circuit with blood. Ascertaining the patient's comfort and confirming appropriate vital signs precede increasing blood flow to the prescribed level.

Needle Removal

All supplies necessary should be assembled before needle removal. Gentle removal of the tape precedes placing a hemostasis dressing over the needle entry site and the vessel entry site.

The caregiver then gets control of the needle and safety device. The needle should be withdrawn at the same angle it was inserted. Pressure is applied to both the skin and vessel entry site *only* when the needle is *all* of the way out. To do otherwise causes pain and can damage the vessel or buttonhole tunnel. The needle safety device is deployed and both needles are disposed of into a sharps container.

Removing one needle and having the patient hold pressure over the cannulation site is optimal. After hemostasis is achieved, the other needle is similarly removed. However, many elderly or disabled patients are unable to hold their sites. Spring-loaded clamps can be placed over the cannulation sites in those patients, but staff must be vigilant in checking the patient and the clamps frequently and removing them as soon as possible. An appropriate dressing of an adhesive bandage and gauze is applied for discharge. Tape should not be circumferential or tight. Patients and their families should be instructed to remove the gauze upon arriving home, and to remove the adhesive bandage the next morning. Additional instruction on achieving hemostasis, should bleeding recur, is also necessary.

Postdialysis Assessment

Postdialysis assessment should mirror the pre-dialysis assessment for patency and access condition, noting any significant changes from the pre-dialysis assessment. Specifically, the access should be observed for the presence of hematoma or pain, for length of time to hemostasis, and for character of the thrill and bruit.

Special Considerations in Cannulation

First Cannulation

Common practice for cannulation of new fistulae when the patient has a functioning catheter in place is to use one 17-gauge needle for the arterial (or "pull") side, with return to the venous circulation through the catheter. This is sometimes referred to as the "one-and-one" method. Using the needle for the outflow to the dialyzer ensures maturity of the vessel and lessens the risk of a severe infiltration. Attention needs to be directed to the use of heparin in the one-and-one circumstance. A lesser quantity for the loading bolus should be considered, as well as making sure that no heparin is given in the last hour of dialysis.

The lumen of the catheter not used for dialysis should be flushed and locked at the beginning of treatment so that the amount of freshly circulating concentrated heparin is minimized at the end of dialysis. Although it is generally accepted that one needle should be used for three treatments before progressing to using two needles, this decision should be based on the success of cannulation and the confidence of the patient. If an infiltration occurs, subcutaneous bleeding should be quickly controlled and ice applied to the site. The access should not be recannulated until all pain and swelling is resolved. The next attempt to cannulate must be by a very experienced practitioner.

With regard to first cannulation of an AVG, general assessment is as previously described. To confirm direction of flow, especially with a forearm loop configuration, the surgical note should be consulted for the surgically altered anatomy. Assessment to confirm direction of flow can be achieved by gently compressing the mid-graft portion and both listening and feeling for flow dynamics on either side with a pressure increase proximally and decrease distally. Cannulation of a new PTFE AVG should be with both arterial and venous needles of the standard size. A PTFE graft has optimal flow and size when new and does not require the stepwise process commonly employed for patients with catheters and new AVFs.

Who Is the Cannulator?

Venotomy is a basic nursing skill, perfected by experience. However, many staff placing needles in the dialysis unit have limited experience in venotomy when hired to perform patient care in the dialysis unit. Training is "on the job" and the quality of that training is commensurate with the commitment and skill of the trainer. Ideally, all trainees should be subjected to a curriculum that involves detailed anatomy and physiology of the cardiovascular system in order to properly appreciate assessment of the access. Cannulation training tools such as a "training arm" should be used to familiarize the trainee with the feel of the needles as well as the movements necessary to successfully enter the vessel and thread the needle into position. Observing cannulation performed by more experienced staff can inform about technique as well as details of the procedure.

Matching the experience of the cannulator to the degree of difficulty ascribed to the access is also very important. Only those staff members considered expert cannulators should be assigned to cannulate new AVFs and AVGs, as well as accesses

that continue to present cannulation challenges. Newly hired staff must complete competency testing prior to cannulating, even when they claim appropriate experience.

Self-Cannulation

Many patients are capable of cannulating themselves if the vessel is easily accessible. The benefits of self-cannulation are several, but primary is the increased control it gives the patient over the quality of his therapy. This method also reduces staff time requirements and cannulation errors. New patients should be assessed for the ability to self-cannulate, and strongly encouraged to do so if that assessment is positive. Buttonhole cannulation by its very nature lends itself as the technique of choice for the self-cannulator.

Summary

Cannulation of the hemodialysis vascular access is more an art than a science. Many current practices of cannulation need to be scientifically tested, and innovative techniques that will make cannulation easier must be researched for patient safety and satisfaction. The buttonhole technique offers the benefits of pain-free, simplified cannulation in the AVF access, with the potential for long-term benefit in the form of preservation of the vein endothelium. However, the potential for infection with this established tunnel to the bloodstream must not be minimized—and the learning curve for the staff to establish the buttonholes correctly is still quite steep. The vascular access team must keep in mind that although the push is to create AVFs its challenge is to maintain them. The patient-centered CQI process is essential in ensuring appropriate assessment and expert cannulation.

Recommended Reading

Ball L. The buttonhole technique for arteriovenous fistula cannulation. *Nephrology Nursing Journal* 2006;33(3):299–304.

Very thorough recent article. An essential for all facilities teaching the buttonhole technique.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access. A J Kidney Dis 2006;48(1):S176–S307.

Lee T, Barker J, Allon M. Needle infiltration of arteriovenous fistulae in hemodialysis: Risk factors and consequences. Am J Kidney Dis 2006;47(6):1020–26.

New data that support the waiting time of 6 to 8 weeks for cannulation.

Marinella MA, Pierson C, Chenoweth C. The stethoscope: A potential source of nosocomial infection? Arch Intern Med 1997;157(7):786–90.
A study that shows the extent of the problem and gives the solution of frequent cleaning with isopropyl alcohol.
Marticorena RM, Hunter J, Macleod S, Petershofer E, Dacouris N, Donnelly S, et al. The salvage of aneurysmal fistulae utilizing a modified buttonhole technique and multiple cannulators. Hemodialysis International 2006;10:193–200.
Information that broadens the application of the buttonhole technique.
Peterson, P. Fistula cannulation: The buttonhole technique. Nephrology Nursing Journal 2002;29(2):195.
The source for the quotations about the buttonhole technique.
Robbin ML, Chamberlain NE, Lockhart ME, Gallichio MH, Young CJ, Deierhoi MH, et al. Hemodialysis arteriovenous fistula maturity: US evaluation. Radiology 2002;225:59–64.
Information on nurses' ability to assess AVF maturation for cannulation.
Saran R, Dykstra DM, Pisoni RL, Akiba T, Akizawa T, Canaud B, et al. Timing of first cannulation and vascular access failure in haemodialysis: An analysis of practice patterns at dialysis facilities in the DOPPS. Nephrology Dialysis Transplantation 2004;19(9):2334–40.
Toma S**,** Shinzato T**,** Fukui H**,** Nakai S**,** Miwa M**,** Takai I**,** et al**.** A timesaving method to create a fixed puncture route for the buttonhole technique. Nephrol Dial Transplant 2003;18:2118–21.
Information about a product that could help increase the numbers and success of the buttonhole technique both by shortening the time period to establish the buttonholes as well as allowing multiple cannulators.
Twardowski ZJ. Constant site (buttonhole) method of needle insertion for hemodialysis. Dialysis and Transplantation 1995;24(10):559.
A historical reference to explain the "roots" of the buttonhole technique.
Unnikrishnan S, Huynh TN, Brott BC, Ito Y, Cheng CH, Shih AM, et al. Turbulent flow evaluation of the venous needle during hemodialysis. J Bio Eng 2005;127(7):1141–46.
New information on venous anastomosis pathology that impacts needle placement.

CHAPTER 25

Isolated Ultrafiltration

John J. White, MD; Laura L. Mulloy, DO;
Ralph J. Caruana, MD; and Todd S. Ing, MD

Isolated ultrafiltration (UF) has been defined by Robinson and Hawkins as the removal of fluid and molecular substances by convective transport through a semipermeable membrane. The adjective *isolated* was originally included to convey the notion that the process does not take place during hemodialysis, in sharp distinction to intradialytic ultrafiltration (in which ultrafiltration is carried out during hemodialysis).

In the procedure of isolated UF, water and non protein-bound solutes with small molecular weights (such as electrolytes, urea, and creatinine) are removed from the blood in the form of an ultrafiltrate. The concentrations of these solutes in the ultrafiltrate approximate those in the corresponding plasma. Diffusive removal does not occur. Performed with either high-flux or low-flux dialyzer/filter membranes, isolated UF can be carried out for varying lengths of time. Thus, isolated UF can be classified into intermittent isolated ultrafiltration (IIU) and continuous isolated ultrafiltration (CIU).

Intermittent Isolated Ultrafiltration

UF is performed intermittently to remove excess fluid for a period that can extend up to many hours in a single day's session. The procedure can be carried out before or after a dialysis session (or in between two segments of a dialysis session), or without any temporal relationship to a dialysis treatment at all. In intermittent isolated UF, the rate of UF can be fast (e.g., 1 or more L per 1-hour session) or slow (e.g., 1 liter per 4- to 8-hour session).

Should the rate of fluid removal be fast, cardiovascularly unstable patients may not be able to tolerate such a rapid rate. In an attempt to curb the ultrafiltration rate without compromising the total quantity of ultrafiltrate that could be obtained, Canaud et al. succeeded in removing excess fluid satisfactorily (averaging 1.2 L per day) from patients with congestive cardiac failure by performing daily, slow, intermittent IU sessions that lasted from 4 to 8 hours each. In the past, the term *isolated ultrafiltration* was used to signify mainly the relatively fast variety of intermittent ultrafiltration.

Continuous Isolated Ultrafiltration

CIU is also known as slow continuous ultrafiltration (SCUF). UF is carried out continuously, but slowly over a longer period of time (e.g., up to a matter of days in a single sitting) to remove accumulated fluid. The volume of ultrafiltrate obtained can reach several liters per day. Arteriovenous and venovenous variants of continuous isolated UF (AV-SCUF and VV-SCUF) have been described. Because of the slow rate of excess fluid removal, even patients with relatively unstable cardiovascular systems can often respond favorably to continuous isolated UF. Because SCUF also fits into the previous definition of IU, it is included here as being synonymous with CIU.

Physiologic Considerations

The concentration of a solute (such as a plasma electrolyte) in a given ultrafiltrate in the clinical setting of isolated UF is influenced by the plasma concentration of the free (i.e., non–protein-bound) fraction of the solute and by the Gibbs-Donnan effect (in the case of electrolytes). With regard to the Gibbs-Donnan effect, to facilitate discussion assume that there were only diffusible sodium cations and diffusible chloride anions on both sides of the membrane and that nondiffusible protein anions only on the blood side. First, the presence of the non-diffusible protein anions on the blood side hinders (through electrostatic attraction) the free movement of the oppositely charged sodium cations. As a result, the level of sodium becomes slightly higher on the blood side than on the ultrafiltrate side.

Second, in the present example the Gibbs-Donnan effect requires that the product of the diffusible cations (sodium) and the diffusible anion (chloride) on one side of the membrane be equal at equilibrium to the corresponding product on the other side. It then becomes obvious that chloride will be slightly higher on the ultrafiltrate side than on the blood side. In clinical intermittent isolated UF, the ultrafiltrates obtained have been found to have the previously described levels of sodium and chloride when compared to those in the corresponding plasma.

Ultrafiltration removes water and small non–protein-bound solutes from the plasma, but it does not remove the non-ultrafilterable proteins and the protein-bound solutes. As a consequence of the loss of water from the plasma, the plasma concentrations of these non-ultrafilterable solutes will show a small rise following the procedure. Because plasma and its

ultrafiltrate share similar urea and creatinine levels, the post-ultrafiltration plasma levels of these solutes will be similar to those obtained prior to the ultrafiltration session.

The purpose of isolated UF is to remove from the plasma and via the ultrafiltrate excess fluid, along with its accompanying electrolytes. This fluid removal decreases the blood hydrostatic pressure at the capillary level and increases the plasma oncotic pressure (due to a rise in the plasma protein level). The fall in intravascular hydrostatic pressure, the rise in plasma oncotic pressure, and the persistence of an elevated interstitial fluid hydrostatic pressure (should substantial edema persist) combine to facilitate the refilling of the vascular space by fluid from the interstitial space. However, unable to take place instantaneously this refilling process can take a varying length of time.

Hemodynamic Effects

Fluid removal with intermittent isolated UF is better tolerated with regard to cardiovascular stability than comparable removal in the course of intradialytic ultrafiltration performed during conventional bicarbonate-based dialysis. The mechanisms for this observation are not completely understood, but may involve (among other factors) differences between the effects of the two modalities on plasma osmolality and blood temperature.

Conventional hemodialysis is associated with a rapid decrease in plasma osmolality due to falls in the levels of waste products with small molecular weights (such as urea). A reduction in plasma osmolality can facilitate the entry of intravascular fluid into the interstitial and intracellular spaces, thus decreasing the plasma volume and facilitating hypotension. In the case of intermittent isolated UF, however, there is no change in the plasma concentrations of these waste products. Hence, there is no fall in plasma osmolality and no loss of intravascular fluid to the other spaces. As a consequence, blood pressure is likely to be better maintained.

Because the extracorporeal circuit is not ordinarily warmed during intermittent isolated UF, the procedure tends to bring about a small drop in body temperature. It has been noted that the blood returning to the body from the extracorporeal circuit during intermittent isolated UF has a temperature slightly lower than that observed during conventional dialysis carried out at normal body temperature. A lower body core temperature can enhance peripheral vasoconstriction, accounting for a more stable blood pressure.

Fluid removal during intermittent isolated UF carried out at 35ºC (a temperature approximating, if not equal to, that at which the procedure is ordinarily performed) has been found to be associated with a decrease in heart rate. However, despite fluid loss the blood pressure remains relatively stable or can even rise due to a large increase in peripheral vascular resistance and in venous tone. Intermittent isolated UF is more effective in volume removal, partly because of this element of peripheral resistance vessel vasoconstriction and venoconstriction. In contrast, in the case of intradialytic ultrafiltration performed during bicarbonate-based dialysis carried out at 37.5ºC the blood pressure is unchanged, the heart rate tends to increase, the venous tone falls significantly, and the peripheral vascular resistance shows only a small increase.

When the temperature at which the intradialytic ultrafiltration is carried out is lowered to 35ºC, the hemodynamic parameters are improved. However, these improvements still fall short of those superior results obtained by intermittent isolated UF performed at this same low temperature. It is suggested, therefore, that the ability of intermittent isolated UF to maintain cardiovascular stability is more than just the consequence of a lower blood temperature. At present, what causes the previously described vasoconstriction in the course of intermittent isolated UF is still largely unknown.

For fluid-overloaded congestive cardiac failure patients, the acute removal of a large amount of excess fluid by intermittent isolated UF may precipitate cardiovascular instability. In such patients, the use of the continuous isolated UF variety is preferred. With this latter approach, fluid removal proceeds at a slower pace—allowing adequate refilling of the vascular space by the edematous fluid and bringing about satisfactory hemodynamic stability and diuresis restoration.

Acid-Base Effects

No significant changes in blood pH take place during intermittent isolated UF. A mild drop (e.g., by 2 mmoles/L) in the plasma bicarbonate concentration has been found after removing between 1 and 3 L of ultrafiltrate over 1 to 2 hours. This small fall may reflect the slightly enhanced removal of bicarbonate as a result of the Gibbs-Donnan effect. However, respiratory compensation results in an appropriate fall in the P_{CO2}, leaving pH intact.

Hematologic Effects

During intermittent IU, a slight hemoconcentration occurs as a result of fluid removal from the vascular space—with an increase in hematocrit and hemoglobin values. There is no measurable effect on the coagulation system and no clinically significant evidence of hemolysis. Studies have also shown a transient decrease in platelet and leukocyte counts during the first 90 minutes of the procedure in association with the use of cellulosic membranes. These membranes harbor hydroxyl groups that can activate the alternative complement pathway with the liberation into the circulation of anaphylatoxins.

The latter are responsible for the transient leucopenia and thrombocytopenia observed. These hematologic effects are abrogated in isolated UF in the same fashion as in diffusion dialysis when certain synthetic dialyzer membranes are employed instead. These synthetic membranes either activate complement poorly and/or adsorb the anaphylatoxins produced in the course of the procedure.

Clinical Considerations

Hydrostatic UF techniques are standard in modern hemodialysis therapy. Intermittent isolated UF is often performed before a conventional hemodialysis treatment using the same dialysis machine along with the same dialyzer/filter, the same extracorporeal circuit, and the same blood pump. In the case of continuous isolated UF, specially designed machines geared for such use are commercially available. These latter machines can also be used to perform intermittent isolated UF. To obtain an ultrafiltrate from plasma, creating a negative pressure on the ultrafiltrate side is the most favored method of obtaining the driving force for convective fluid transfer (Figure 25.1). The rate of fluid removal in isolated UF is related to:

- Kuf, which is the ultrafiltration coefficient of a dialyzer/filter expressed as mL of ultrafiltrate/hour/mmHg of transmembrane pressure gradient (consequently, Kuf is a function of the water permeability and of the dimension of the dialyzer/filter membrane used).
- Blood flow rate.

The tolerability of volume removal is related to:

- Rate of fluid removal
- Magnitude of volume overload

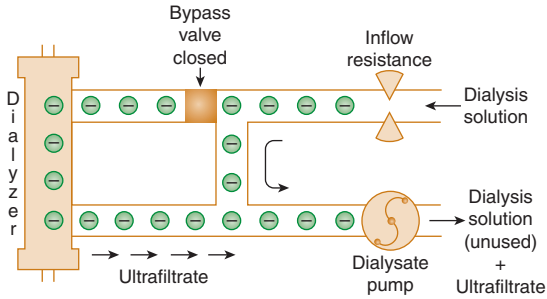


Figure 25–1

Circuit for isolated ultrafiltration. A method using a dialysis machine and a dialysate. Circled dashes depict areas of negative pressure. *(Reproduced with permission from Sigler MH, et al. Slow continuous therapies. In JT Daugirdas et al. (eds.)*, Handbook of Dialysis, Third Edition. *Philadelphia: Lippincott Williams & Wilkins 2001:199–230.)*

- Blood pressure and cardiovascular stability
- Refilling rate of the vascular space from the interstitial space

In edematous patients, by performing the fast variety of intermittent isolated UF it is often feasible to safely remove as much as 2 to 3 L of ultrafiltrate in 3 to 4 hours.

Indications for Isolated Ultrafiltration

The beneficial effects of isolated UF are most evident in patients with severe volume overload, in the absence or presence of renal functional impairment. Edematous patients were treated using intermittent isolated UF as early as 1947 by Alwall. In 1975, Ing et al. demonstrated the efficacy of intermittent isolated UF performed prior to conventional hemodialysis in managing maintenance dialysis patients with chronic overhydration. Large volumes of fluid could be removed without the development of hypotension, and the patients tolerated the procedure well.

In 1976, Bergstrom et al. showed that intermittent isolated UF led to more cardiovascular stability than conventional dialytic ultrafiltration in the course of an acetate-based dialysis. Two

groups of investigators, Kramer et al. in 1977 and Paganini et al. in 1979, championed the notion of continuous and slow isolated UF in the treatment of overhydration. In the past three decades, both the intermittent and continuous forms of isolated UF have proven to be efficacious tools in the disposal of excess fluid in a variety of clinical settings.

Patients with Heart Failure

The heart failure population in the United States is rapidly growing, and heart failure remains a major reason for admission to U.S. hospitals. Outpatient management of this condition is difficult because diuretic therapy is difficult to titrate, partly because of the frequent occurrences of untoward effects such as excessive fluid loss, hypotension, electrolyte/acid-base abnormalities, and/or renal insufficiency. A large number of these patients do not respond to outpatient management and are considered "diuretic resistant." Diuretic therapy is associated with activation of the neurohormonal systems and may result in the upregulation of potentially detrimental hormones such as norepinephrine, renin, and angiotensin. Furthermore, injudicious diuretic use may worsen renal function. Some degree of renal dysfunction is common in the setting of heart failure in the first place. Further deterioration in renal function as a result of diuretic use portends a poorer prognosis.

A variety of small-scale studies have proposed isolated UF as an effective therapeutic tool for the treatment of heart failure. Isolated UF (of both the intermittent and the continuous varieties) can quickly rectify volume overload and improve hemodynamic abnormalities in patients with pulmonary edema or refractory heart failure. As previously mentioned, isolated UF reduces capillary hydrostatic pressure and raises plasma oncotic pressure—thus facilitating the entry of fluid from the interstitial space into the vascular compartment. The resultant increase in intravascular fluid can help improve a patient's responsiveness to diuretic therapy. Isolated UF has many potential advantages over diuretic therapy (Table 25.1). For example, isolated UF results in a greater loss of sodium relative to the loss of water when compared to corresponding losses during diuretic therapy. This is because the sodium concentration in a liter of ultrafiltrate and that in the same volume of plasma are not too far apart, whereas the sodium level in a liter of diuretic-induced urine is usually much lower than that in a liter of plasma.

Table 25–1

Diuretic Therapy Versus Ultrafiltration Effects

Measurements	Diuretics/Isolated	Ultrafiltration
Plasma norepinephrine	Increased	Decreased
Atrial natriuretic peptide	Unchanged or decreased	Increased
Urine output	Increased	Increased
Cardiac output	Variable	Increased or unchanged

Adapted with permission from Sharma A, et al. Clinical benefit and approach of ultrafiltration in acute heart failure. Cardiology 2001;96:144.

Agostoni and co-workers evaluated both the clinical and the neurohormonal markers in chronic cardiac insufficiency patients belonging to New York Heart Association classes II and III, maintained on ACE inhibitor therapy and treated with either intermittent isolated UF or diuretic therapy. Despite a similar degree of fluid removal in both groups, the isolated UF group demonstrated a marked decrease in the serum levels of norepinephrine, aldosterone, and renin activity—and an increase in the serum sodium value. The isolated UF group achieved a clinical improvement that lasted for a period of up to 3 months. These changes were not obtained in the diuretic-treated patients in whom the increase in pulmonary congestion and filling pressure returned within days. It was suggested that following intermittent isolated UF water metabolism was equilibrated at a new set point—so much so that there were lower fluid intake, less diuresis, and absence of weight gain.

The Acute Dialysis Quality Initiative workgroup has addressed the use of isolated UF for the management of heart failure. Despite the purported benefits, the evidence supporting the use of isolated UF is limited to a few small studies. The workgroup has proposed several issues for consideration before the use of isolated UF as a therapy for heart failure is widely recommended. Future studies should address device portability and ease of use, type of venous access, modality and frequency, cost effectiveness, patient outcomes, and the exact role of the cardiologist and of the nephrologist.

Patients with Renal Disease

Patients Who Do Not Require Dialysis Treatments

In patients with the nephrotic syndrome, intermittent isolated UF has been instrumental in alleviating refractory edema that has previously failed to respond to a combination of sodium restriction and diuretic administration. After fluid removal by isolated UF, however, these patients can become more responsive to diuretic therapy—perhaps as a result of the ultrafiltration-induced reduction in renal edema. Occasionally, nonuremic patients with either acute or chronic renal insufficiency develop acute volume expansion. This problem typically occurs in a hospital setting, either postoperatively or as a result of excessive fluid intake in the form of various intravenous infusions (such as those containing vasoconstrictors, antibiotics, electrolytes/glucose, radiocontrast media, total parenteral nutrition compounds, and so on). When diuretic resistance appears, these patients can be treated quite effectively with isolated UF of the intermittent or the continuous variety.

Patients Who Require Dialysis Treatments

In critically ill patients with end-stage renal disease or oliguric acute renal failure, overhydration is also frequently encountered in a manner similar to that described previously for renal patients who do not require dialysis therapy. Currently, there is a host of special means of disposing of excess fluid from these patients. Such means include a more effective approach of intradialytic ultrafiltration involving the augmentation of the procedure by the following maneuvers. The latter comprise the use of a cooler dialysate; the administration of blood or colloid, or the maintenance of a higher hematocrit level (as a result of ongoing erythropoietin therapy); the employment of a higher dialysate sodium level or of dialysate sodium profiling; the use of a dialysate calcium level higher than 1.25 mmoles/L; the use of the alpha-1 adrenergic agonist midocrine; the avoidance of antihypertensive medications prior to dialysis; and the refrainment of food intake a short while before and during dialysis.

Other efficacious methods of removing fluid are available in the form of more frequent and/or more prolonged intratreatment ultrafiltration approaches inherent in the daily regimens (including extended dialysis, short dialysis, long nocturnal

dialysis, and various hemofiltration and hemodiafiltration techniques) and the various continuous renal replacement therapies.

Regular sequential therapy (a short period of intermittent isolated UF followed by a longer period of diffusion dialysis during every treatment), popular some years ago, is seldom employed today. The reasons for its limited popularity are the ready availability of the previously mentioned effective means of excess fluid removal and the small amounts of waste products removed as a result of the isolated ultrafiltration procedure. Because of these scanty waste product returns, a subsequent full diffusion dialysis session is still necessary for proper waste product disposal—thus unfavorably raising the total duration of a treatment session.

Isolated UF can still play a useful role under the following circumstances. First, the procedure is a reasonable alternative if the previously described fluid-removing methods are not readily available. Second, in renal failure patients there are rare occasions in which the blood levels of waste products are not high enough (and the blood electrolyte/acid-base values are not dislocated enough) to warrant a prompt diffusion dialysis treatment. However, the amount of accumulated fluid happens to be gross enough to require its quick removal. At this juncture, the performance of an isolated UF session (of the intermittent or the continuous variety and independent of dialysis) is a convenient option.

Third, an uncommon complication of hemodialysis known as dialysis ascites can occur in certain fluid-filled maintenance hemodialysis patients. Although results are unpredictable, isolated UF, preferably in association with dietary sodium restriction, can be tried if other fluid management techniques applied to ameliorate this complication have failed. Finally, isolated UF (of the intermittent or the continuous category) and intradialytic ultrafiltration are not mutually exclusive but can be practiced in the same patients at various times.

Complications

If removal of fluid by isolated UF is too rapid in rate, hypotension, hypoperfusion, muscle cramping, and even a lactic acidosis can result. Furthermore, the hypotension induced could damage the kidneys further in patients who still possess some measure of renal function. Also, if uncheckable, the resaltant hypotension could lead to cerebro-vascular accidents and mycardial infarction.

Recommended Reading

Agostoni P, Marenzi G, Lauri G, et al. Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: Failure of furosemide to provide the same result. Am J Med 1994;96:191–9.

A randomized trial showing the superiority of isolated ultrafiltration treatments over furosemide therapy.

Bergstrom J, Asaba A, Furst P, et al. Dialysis ultrafiltration and blood pressure. Proc Eur Dial Transplant Assoc 1976;13:293–305.

Makes the case that intermittent isolated ultrafiltration was superior to intradialytic ultrafiltration during acetate-based hemodialysis in terms of blood pressure stability.

Canaud B, Leblanc M, Leray-Moragues H, et al. Slow continuous and daily ultrafiltration for refractory congestive heart failure. Nephrol Dial Transplant 1998;13(Suppl. 4):51–55.

Describes the improvement of fluid overload by intermittent daily isolated ultrafiltration and continuous isolated ultrafiltration techniques in patients with refractory cardiac failure. Also suggests that continuous isolated ultrafiltration and slow continuous ultrafiltration are terms for the same process.

Clark WR, Paganini E, Weinstein D, et al. Extracorporeal ultrafiltration for acute exacerbations of chronic heart failure: Report from the Acute Dialysis Quality Initiative. Int J Artif Organs 2005;28:466–76.

Review and position paper from the Acute Dialysis Quality Initiative addresses important questions regarding the role of isolated ultrafiltration in the management of heart failure.

Davenport A. Ultrafiltration in diuretic-resistant volume overload in nephrotic syndrome and patients with ascites due to chronic liver disease. Cardiology 2001;96:190–95.

Isolated ultrafiltration can restore the ability of nephrotic syndrome patients to respond to diuretic therapy.

Ing TS, Ashbach DL, Kanter A, et al. Removal of fluid with negative-pressure hydrostatic ultrafiltration using a partial vacuum. Nephron 1975;14:451–55.

One of the early descriptions of intermittent pre-dialytic isolated ultrafiltration.

Ing TS, Chen WT, Daugirdas JT, et al. Isolated ultrafiltration and new techniques of ultrafiltration during dialysis. Kidney Int 1980;18:S77–82.

Summaries the early experiences of using intermittent isolated ultrafiltration as a therapeutic tool.

Kooman JP, Gladziwa U, Bocker G, et al. Role of the venous system in hemodynamics during ultrafiltration and bicarbonate dialysis. Kidney Int 1992;42:718–26.

Explores the situation that during intradialytic ultrafiltration (in the course of a bicarbonate-based hemodialysis session) the constriction of veins and resistance vessels is significantly reduced compared to the vascular reaction during an intermittent isolated ultrafiltration treatment.

Kramer P, Wigger W, Rieger L, et al. Arteriovenous haemofiltration: A new and simple method for treatment of over-hydrated patients resistant to diuretics. Klin Wochenschr 1977;55:1121–22.

The very first article describing the use of continuous slow isolated ultrafiltration to treat overhydrated patients resistant to diuretic therapy.

Maggiore Q, Pizzarelli F, Zoccali C, et al. Effect of extracorporeal blood cooling on dialytic arterial hypotension. Proc Eur Dial Transplant Assoc 1981;18:597–602.

Demonstrates that cooling of blood during intermittent isolated ultrafiltration provides superior cardiovascular stability.

Ozkahya M, Ok E, Cirit M, et al. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. Nephrol Dial Transplant 1998;13:1489–93.
In the face of sodium restriction and in the absence of antihypertensive therapy, aggressive intradialytic ultrafiltration along with sessions of intermittent isolated ultrafiltration (when necessary) succeeded in bringing about regression of left ventricular hypertrophy in hypertensive maintenance hemodialysis patients.
Paganini EP, Nakamoto S. Continuous slow ultrafiltration in oliguric acute renal failure. Trans Am Soc Artif Intern Organs 1980;26:201–04.
Describes the use of continuous isolated ultrafiltration to remove excess fluid from patients with acute renal failure, along with the findings of stable hemodynamic parameters.
Robinson BHB, Hawkins JB. Preface. Proc Eur Dial Transplant Assoc 1978; 15: preface pages.
First proper definition of isolated ultrafiltration.
Sharma A, Hermann DD, Mehta RL. Clinical benefit and approach of ultrafiltration in acute heart failure. Cardiology 2001;96:144–54.
Excellent discussion of the potential benefits of isolated ultrafiltration for decompensated heart failure.
Ronco C, Ricci Z, Bellomo R, et al. Extracorporeal ultrafiltration for the treatment of overhydration and congestive heart failure. Cardiology 2001;96:155–68.
Suggests that continuous isolated UF is superior to intermittent isolated UF in the removal of excess fluid from fluid-overloaded heart failure patients. With the former approach, an adequate cardiovascular response and diuresis restoration are common results.
Shin KD, Ing TS, Popli S et al. Isolated ultrafiltration in the treatment of dialysis ascites. Actif Organs 1979;3:120–24.
Although not always readily achievable, hemodialysis ascites has been successfully treated with isolated ultrafiltration in association with dialysis.
van Kuijk WH, Luik AJ, de Leeuw PW, et al. Vascular reactivity during haemodialysis and isolated ultrafiltration: Thermal influences. Nephrol Dial Transplant 1996;11(Suppl. 2):11–15.
Depicts the superior hemodynamic data of intermittent isolated ultrafiltration (carried out at a temperature of 35ºC) when compared to those obtained during intradialytic ultrafiltration performed in the course of bicarbonate-based hemodialysis (carried out at temperatures of 35 and 37.5ºC, respectively).

CHAPTER 26

Common Clinical Problems During Hemodialysis

Peter Kotanko, MD, and Nathan W. Levin, MD

Background

The pattern of intradialytic complications has clearly changed over the last 25 years. The significant progress made in hemodialysis (HD) technology (especially the safety control systems integrated in HD machines), dialysate preparation (improved water standards, more frequent use of bicarbonate dialysate), and membrane biocompatibility (synthetic membranes) have resulted in a reduction of intradialytic complications due to technical problems. Today, cardiovascular complications such as intradialytic hypotension (IDH) and muscle cramps (MCs) prevail.

The reasons for this development are the changing demographics of dialysis populations (increasing age and number of co-morbidities) and shortened dialysis times with higher ultrafiltration rates. Today, close to half of incident patients have diabetes mellitus—and these patients are particularly prone to intradialytic cardiovascular complications.

Intradialytic Hypotension

IDH is the most common intradialytic problem, with an incidence of 5 to 40% of treatments (depending on the definition of IDH, which varies from an asymptomatic percentage fall in systolic blood pressure to symptomatic hypotension requiring active treatment). Hypotensive episodes may result in subclinical myocardial ischemia with detectable ECG ischemia effects, suggesting that attention must be paid to reducing this incidence (which may be 10 to 30% of dialysis sessions). Subclinical myocardial ischemia was implied by the finding of regional wall motion abnormalities detected by serial echocardiography. The wall motion abnormalities were improved by 30 minutes postdialysis.

Females, elderly patients with isolated systolic hypertension, diabetics, and those with documented autonomic neuropathy are at increased risk (Table 26.1). In healthy subjects, as much

Table 26–1

Risk Factors for IDH

- Diabetes mellitus
- Cardiovascular disease: left ventricular hypertrophy, diastolic dysfunction with or without congestive heart failure, left ventricular systolic dysfunction and congestive heart failure, valvular heart disease, pericardial disease (constrictive pericarditis or pericardial effusion)
- Poor nutritional status and hypoalbuminemia
- Uremic neuropathy or autonomic dysfunction
- Severe anemia
- High-volume ultrafiltration due to high IDWG
- Predialysis systolic blood pressure <100 mmHg
- Age 65 years or older
- Female gender
- Unrecognized dehydration especially in patients loosing weight rapidly

as 30% of the blood volume may be removed with maintenance of blood pressure. In the dialysis population, the combination of autonomic dysfunction, ventricular dysfunction and decreased venous return, and increased body temperature impairs the body's ability to cope with the hemodynamic stress caused by UF. Due to the reduced compensatory range, blood pressure falls earlier and eventually IDH may occur.

Major factors determining the hemodynamic response are the ultrafiltration rate (UFR), the plasma refilling rate (PRR), and their instantaneous difference. The UFR is related to ultrafiltration volume (UFV) and the ultrafiltration time (t). Under most circumstances, the weight after the preceding dialysis equals dry weight (DW) and UFV equals intradialytic weight gain (IDWG).

$$UFR = IDWG / t$$

Obviously, prolongation of the procedure to permit slow filtration is possible. However, this is usually impractical. Advantages of longer filtration times have been reported. Increase in frequency of dialysis increases total fluid removal with reported regression of left ventricular mass, but use of this technique has been infrequent. The PRR is the per time unit difference between filtration (Fil) and absorption (Abs) of plasma water in the capillary bed plus the lymphatic flow (Lym).

$$PRR = (Abs + Lym) - Fil$$

Fluid dynamics in the capillary bed can be described by the Starling forces, with the plasma oncotic pressure as a main absorptive factor. The threat of IDH can be reduced by two fundamentally distinct approaches. The first is a reduction of the UFR (by reducing the interdialytic weight gain and thus the UFV, and/or prolongation of UF time, t). The second is by supporting the body's ability to deal with the hemodynamic challenges caused by UF (e.g., by improving vasoconstriction, therapy of CHF (Congestive Heart Failure), or raising serum albumin concentration). Mean arterial blood pressure (MAP) is the product of cardiac output (CO) and total peripheral resistance (TPR):

$$MAP = CO \times TPR.$$

CO is the product of stroke volume (SV) and heart rate (HR).

$$CO = \text{stroke volume (SV)} \times \text{heart rate (HR)}$$

CO and TPR may be affected adversely in a variety of conditions (Table 26.2). During dialysis, UFR exceeds PRR frequently from the extra (and to a lesser extent the intracellular) spaces. This results in a reduction in circulating blood volume. In healthy subjects, this reduction in intravascular volume is compensated for by constriction of peripheral arteries and venous capacitance vessels and in a rise in heart rate. Patients with diastolic dysfunction have particular difficulty in tolerating this hemodynamic stress. Diastolic dysfunction results from impaired myocardial relaxation and reduced distensibility of the left ventricle. This condition can be assumed when heart failure occurs in the presence of normal systolic function (left ventricular ejection fraction = 45%). In patients with diastolic dysfunction, even small reductions in blood volume can reduce end-diastolic filling pressures and thus provoke blood pressure falls.

Systolic dysfunction is in most cases due to myocardial ischemia on the basis of coronary artery disease (CAD). Consequent diagnosis of CAD and appropriate treatment both medically and with vascular interventions (PTCA or bypass surgery) is recommended. Autonomic neuropathy is frequently present in diabetic patients, and adequate metabolic control should be aimed at in the hope of preventing further deterioration. Therapy with drugs interfering with vasoconstriction and other hemodynamic responses to UF should be avoided immediately before or during HD.

Another approach to hypotensive problems has been the use of dialysate sodium increase (ramping, or "modeling") during dialysis, with the objective of maintaining blood volume during ultrafiltration. Undoubtedly, the procedure of increasing the

Table 26–2

IDH Causes and Preventive Strategies

Problem	Cause	Preventive Strategy
Reduction of CO		
Reduced SV	Diastolic dysfunction: ischemic heart disease, ventricular hypertrophy; hypertrophic cardiomyopathy (CMP), valve disease, restrictive CMP, pericardial effusion	Reduction of congestive state, prevention of tachycardia (calcium channel blockers, beta blockers), conversion of atrial fibrillation (AF), antihypertensive drugs, promote regression of LVH (ACEI, ARB)
	Systolic dysfunction: ischemia, dilated CMP, arrhythmia, hypocalcemia due to low dialysate Ca, arrhythmias	Investigate for CAD, drug therapy of CAD, PTCA, bypass surgery, ACEI, ARB, BB, platelet inhibition, avoid negative Ca balance during dialysis, avoid intradialytic hypokalemia
	Reduced venous return: UFR grossly exceeds PRR, blunted constriction of venous capacitance vessels, hypoalbuminemia	Reduction of UFR with prolonged treatment time, improve hypoalbuminemia; avoid mesenterial vasodilatation (no eating during HD), dialysate sodium ≥ plasma sodium, counseling on low sodium intake, avoid warm dialysate, apply isothermic dialysis by BTM
Reduced effective HR	Arrhythmia (AF most common), drugs (BB), autonomic neuropathy (especially in DM), tachycardia	Cardioversion (electrical or medical) with AF, reduction of BB, glucose control in diabetics, achieve adequacy targets

Table 26–2

IDH Causes and Preventive Strategies—Cont'd

Problem	Cause	Preventive Strategy
Reduction of TPR	Autonomic neuropathy, tissue ischemia, food intake (mesenteric vasodilatation), vasodilators, sympathicolytic agents, warm dialysate, anemia, hypoxia	Glucose control, achieve adequacy targets; achieve target Hct, avoid food during HD, pre-dialysis midodrine, avoid warm dialysate, apply isothermic or cool dialysis, improve hemoglobin (erythropoiesis stimulating agents) and oxygen saturation (treatment of concomitant lung disease), oxygen sympathicolytic agents after dialysis
High UFR		
High UFV	High interdialytic weight gain (most important is salt input), wrongly low dry weight	Dietary counseling; avoid intradialytic salt loading; periodic re-evaluation of dry weight
Short treatment time	Organizational time constraints, noncompliance, missed treatments	Prolonging dialysis time, more frequent dialysis, counseling on noncompliance, avoiding missed treatments, recognition of dry weight

dialysate sodium concentration to 150 mmol/L at the beginning of the treatment is effective in reducing episodes and maintaining blood pressure. However, the price paid is an increase in interdialytic weight gain and in blood pressure and in aggravation of the problems of overhydration.

What can be done to reduce interdialytic weight gain that would reduce ultrafiltration needs and make it possible to remove all necessary fluid within a reasonable time? One possibility is a low salt diet of no more than 3 g Na+/day (Figure 26.1). This approach has been successfully shown by the Tassin group for years. With isotonic hyperhydration, a daily sodium chloride intake of 9 g results in an interdialytic weight gain of 1 kg.

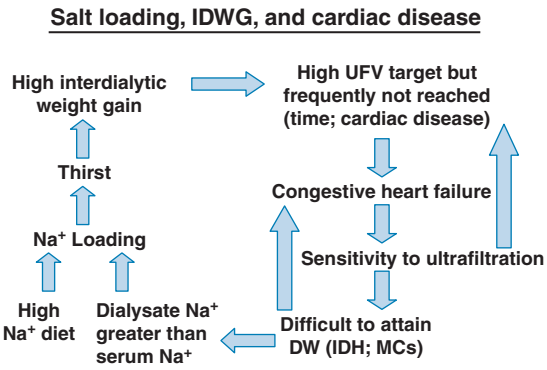


Figure 26–1

The relationship between salt, intradialytic weight gain and cardiac disease. A high dietary Na+ intake and / or Na+ loading during HD may result in post-dialysis thirst and consequent drinking and weight gain. The high ultrafiltration volume (UFV) is frequently difficult to remove. With chronic fluid overload congestive heart failure may ensue. Heart failure increases the patient's sensitivity to ultrafiltration and promotes intradialytic hypotension (IDH) and MCs. These complications in turn are frequently treated by increasing the dialysate Na+ concentration, which completes the circle.

The description of salt as a uremic toxin adds to the value of limiting salt.

Iatrogenic salt loading results from a dialysate sodium concentration exceeding the plasma sodium concentration or from application of IV saline solutions during dialysis. It is helpful to align the dialysate sodium to the patient's own sodium concentration. This proposal relies on the supposition that the serum sodium is constant in an individual and that the use of dialysate sodium higher than the patient's own results in diffusion of sodium into the patient with an increase in sodium body content and in sodium plasma concentration. After the treatment is completed, the patient is thirsty due to the relative hypernatremia and drinks enough fluid to bring the sodium down to the initial set level. A value for plasma sodium concentration should be available soon from the online conductivity clearance software, which will guide therapy.

Monitoring of relative blood volume (BV) changes by BV monitor (BVM) helps to estimate PRR in relationship to UFR. A fall of BV >15% during an HD session sharply increases the risk of IDH. On the other hand, IDH are unusual with a BV fall of <5%. Feedback control of UF has been shown to reduce the frequency of IDH. Maintenance of blood volume during a dialysis treatment suggests overhydration, but marked reduction does not necessarily mean the patient is at dry weight.

Maggiore first reported the biologic effects of cooling dialysate on systematic hypotensive episodes during dialysis. Increase in body core temperature occurs routinely during the dialytic procedures. While initially considered the result of heat retention due to vasoconstriction following fluid removal, this may not be the only major factor involved. Increased core temperature may cause centrally initialed vasodilatation, resulting in blood pressure decrease.

It was concluded from a systematic review of the clinical effects of reducing dialysate fluid temperature that IDH occurred 7.1 times less frequently with cool dialysis and that postdialysis mean arterial pressure was higher with cool-temperature dialysis by 11.3 mmHg. Is there an advantage to maintaining or reducing the core temperature by an automated feedback device (BTM, Fresenius Medical Care) as opposed to arbitrary reductions of dialysate temperature, the effect of which is variable depending on blood flow, ultrafiltration rate, plasma volume, the initial temperature of the patient, and possibly norepinephrine response? One major randomized trial provides evidence of effectiveness of increasing energy loss to maintain core temperature, with the percentage of hypotensive episodes reduced by 50%.

It was concluded that active control of body temperature by BTM can significantly improve intradialytic tolerance in hypotension-prone patients. Cooling dialysate temperature arbitrarily to one level could actually reduce core temperature too much, with consequent shivering and discomfort. The BTM at present provides the ability to change both temperature and energy balance, but the latter is not as clinically useful. The device also permits estimation of access recirculation by automated cooling of dialysate, the effect of which can be expressed as a rate of arterial to venous falls. Overall, the physiologic maintenance of body temperature appears to be a useful tool.

Another approach to the IDH problem is the use of a single dose (5 mg) of midodrine, an alpha-1 agonist drug administered 30 minutes before the dialysis session. This is associated with an improvement in intradialytic blood pressure. Midodrine should

be used cautiously in patients with CHF and in those using beta-blockers, digoxin, and nondihdropyridine calcium channel blockers. A multicenter trial of intravenous L-carnitine therapy at 20 mg/kg into the dialysis venous port with each session of dialysis was associated with reduced frequency of IDH and MCs. Sertraline is a selective serotonin reuptake inhibitor shown to improve hemodynamic parameters in patients with IDH.

Symptomatic IDH should be treated promptly by reduction of UFR and bringing the patient to the Trendelenburg position. If despite this maneuver symptomatic IDH persists, 200 to 500 mL 0.9% NaCl or 100 mL 20% albumin (expensive, but highly efficient) should be given. Most symptomatic episodes can be effectively treated with these interventions. If severe IDH persists, hypovolemia may not be the underlying cause and an extended investigation (including physical exam, ECG, emergency echocardiography, and laboratory studies) is warranted. Arrhythmia, myocardial infarction, pericardial tamponade, hemorrhage, hemolysis, pulmonary embolism, and air embolism should be considered as differential diagnoses. Recent NKF-K/DOQI guidelines on the evaluation and treatment of IDH are available at *http://www.kidney.org/professionals/kdoqi/guidelines_cvd/intradialytic.htm.*

Muscle Cramps

MCs occur during 5 to 20% of HD sessions, frequently concomitant with IDH and low dialysate sodium concentration. MCs result from the constriction of intramuscular arteries in response to depletion of intravascular volume. In the majority of cases they represent potential precursors of IDH. MCs respond well to a single bolus of hypertonic saline (e.g., 10 mL 20% NaCl solution given over 2 to 4 minutes) or glucose (e.g., 20 mL 30% glucose solution given over 2 to 4 minutes). MCs are frequently observed in patients with dry weight targets below their "real" dry weight and thus have relatively high UFR. Preventive measures are similar to those discussed for IDH.

Dialyzer Reactions

There are two distinct types of dialyzer reaction, termed type A and type B. Type A reaction is anaphylactic in nature, and its incidence is 1/20.0 treatments. Ethylene oxide (ETO) has been incriminated in the majority of these cases. In patients taking ACEI and using AN69 membranes concomitantly, similar events have been observed. Allergy to heparin is another cause. Using

ETO-free dialyzers and avoiding AN69 membranes in patients on ACEI are recommended. Type A reaction manifests in the first 20 to 30 minutes. Stopping dialysis immediately without blood return is of paramount importance, and steroids, epinephrine, and H-1 blockers may be needed. Type B reactions, uncommon now with synthetic membranes, are unspecific (with a poorly defined etiology). They are less severe and manifest themselves with back and chest pain. Their treatment is supportive.

Pruritus occurring exclusively during dialysis is most likely caused by an allergy to one or more materials of the extracellular circuit. Chronic itching is often found in the presence of an elevated Ca × P product. Changing the membrane and the bloodline may be helpful. In addition, H-1 blockers are used as a nonspecific treatment. In patients with febrile reactions during dialysis, bacteremia from vascular catheters should be considered as a prime possibility.

Nausea and Vomiting

Nausea and vomiting is associated with IDH, dialyzer reactions, eating during dialysis with gastroparesis, headache, and migraine. Treatment of IDH and antiemetic therapy (e.g., metoclopramide 10 mg IV) attenuate severity of most nausea and vomiting episodes.

Dialysis Disequilibrium Syndrome

Dialysis disequilibrium syndrome (DES) occurs most frequently within the first few dialyses. It is thought to be caused by an acute increase in brain water for osmotic reasons because at the beginning BUN (Blood Urea Nitrogen) may be very high. Common symptoms are headache, nausea, and vomiting. In severe cases seizures and coma may occur. The treatment is supportive, and elevating dialysate glucose concentration to 200 mg/dL (11 mmol/L) is of help. DES can be prevented by keeping dialysis efficiency low (e.g., with a urea reduction ratio below 40%) during the first couple of treatments (low blood and dialysate flow; small dialyzer) and increasing dialysis efficacy slowly over the next 2 to 4 weeks. A dialysate sodium concentration below the serum sodium concentration may worsen DES.

Air Embolism

Air embolism is a rare but potentially fatal complication. The arterial site, improperly connected bloodlines, and disconnected

central venous catheters are potential sources of venous air embolism. In the sitting patient, intravascular air is more likely to cause reduction of cerebral perfusion—resulting in focal neurologic symptoms. In the event of air embolism, the venous line has to be clamped immediately and the patient placed in a recumbent position on the left side. The head should be placed as the lowest point.

Falls

Early postdialysis falls occur frequently. Low blood pressure, orthostatic dysregulation, impaired balance, slippery floors, and unstable footwear are the leading causes. Patients at risk (elderly persons, previous IDH, diabetics) should be accompanied when walking to the scale after treatment. Balance and muscle strength can be improved by specifically tailored physiotherapy programs.

Recommended Reading

Maggiore Q, Pizzarelli F, Santoro A, et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: Results of the European randomized clinical trial. Am J Kidney Dis 2000;40:280–90.

This important paper reports on the largest trial on the effect of thermal control of dialysate on hemodynamic stability in 95 IDH-prone patients selected from 27 centers in 9 European countries. Control of core temperature and regulation of thermal balance were achieved by BTM. Systolic and diastolic blood pressures and heart rate were more stable with BTM control. The results show that active maintenance of body temperature can significantly improve intradialytic tolerance in hypotension-prone patients.

Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant 2006;21:1883–98.

This is an important systematic review on the effects of cool dialysate on IDH. A total of 22 prospective randomized studies comprising 408 patients with standard bicarbonate dialysis were included. The techniques of dialysate temperature adjustment included in the analysis were empirically fixed reduction of dialysate temperature and use of a biofeedback temperature-control device (BTM) to deliver isothermic dialysis or programmed patient cooling. IDH occurred 7.1 times less frequently with cool dialysis. Postdialysis mean arterial pressure was higher with cool-temperature dialysis. There was no reduction in dialysis adequacy as assessed by urea clearance.

Selby NM, Lambie SH, Camici PG, et al. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. Am J Kidney Dis 2006;47:830–41.

This study in eight IDH-prone patients shows that reversible left ventricular wall motion abnormalities develop during dialysis with ultrafiltration. The majority of regional wall motion abnormalities showed improvement in function by 30 minutes postdialysis. Overall mean regional function and ejection fraction were significantly impaired during HD. The authors also show that this phenomenon can be ameliorated by the improved hemodynamic stability of

biofeedback dialysis (acting by temporally decreasing the ultrafiltration rate and increasing the dialysate sodium conductance). Although the number of patients studied is small, this carefully conducted study offers new insights into the pathophysiology of IDH.

Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS. Kidney Int 2006;69:1222–28.

The observational study included 22,000 HD patients from seven countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). A treatment time >240 minutes was independently associated with significantly lower relative risk of mortality. Every 30 minutes longer on HD was associated with a 7% lower relative risk of mortality. These findings were possibly confounded by combining country findings. An ultrafiltration rate >10 mL/hour/kg was associated with higher odds of IDH and a higher risk of mortality. The results of this study strongly support the use of longer treatment times and lower ultrafiltration rates.

Prakash S, Garg AX, Heidenheim AP, et al. Midodrine appears to be safe and effective for dialysis-induced hypotension: A systematic review. Nephrol Dial Transplant 2004;19:2553–58.

This is an excellent systematic review of studies on the safety and effectiveness of the alpha-1 receptor agonist midodrine in HD patients. On average, postdialysis systolic and diastolic blood pressure was higher with midodrine. Six of 10 studies report improvement in symptoms of IDH, and there were no reported serious adverse events ascribed to midodrine. This systematic review is reassuring concerning the use of midodrine as a pharmacologic means of reducing IDH.

Sherman RA. Intradialytic hypotension: An overview of recent, unresolved and overlooked issues. Semin Dial 2002;15:141–43.

This review discusses the etiology and management of IDH. Emphasis is placed on the patient's hemodynamic tolerance to fluid removal, and on the issues of sodium and thermal balance.

CHAPTER 27

Hemodialysis-Associated Seizure Activity

Neenoo Khosla, MD

Among the complications of hemodialysis, seizure activity is one of the most alarming and dramatic. Hemodialysis-associated seizure activity occurs in less than 10% of chronic dialysis patients, but in a substantially larger proportion of acute hemodialysis patients. Children have a higher incidence of seizures compared to adults. In general, seizure activity tends to occur during or shortly after hemodialysis treatment, and preemptive surveillance for 12 to 24 hours after hemodialysis in patients at increased risk is advisable. Furthermore, seizures tend to be generalized and to subside with ongoing stable dialysis therapy. Focal or refractory seizure activity dictates the need to evaluate for localized primary neurologic disease.

In approaching the topic of hemodialysis-associated convulsive activity, it is important to understand that there are predictable characteristics of hemodialysis that can precipitate seizure activity. In addition, particular patients are predisposed to the development of seizures, and certain interventions before and during hemodialysis can reduce the likelihood of this complication.

Precipitating Characteristics of Hemodialysis

Increased frequency of seizures in hemodialysis patients may result from the neuromuscular irritability associated with uremia, as well as from the destabilizing factors associated with hemodialysis itself (Table 27.1). The neuromuscular irritability observed in uremic patients is manifest progressively as tremulousness, muscle cramps, myoclonic activity, arrhythmia, and convulsions. Primary uremic convulsions are thought to occur during severely symptomatic uremia, specifically in cases with very high BUN (Blood Urea Nitrogen) levels and other overt manifestations of uremic toxicity. Seizures associated with uremia are generalized, but partial seizures may rarely be seen. It is important to exclude drug toxicity as a reversible cause of

Table 27–1

Characteristics of Hemodialysis That May Precipitate Seizure Activity

- Uremic encephalopathy
- Dialysis disequilibrium syndrome
- Electrolyte disorders, such as hypercalcemia, hypocalcemia, hypoglycemia, hyperglycemia, hyponatremia, and hypernatremia
- Hypoxemia
- Hemodynamic instability: rapid onset hypotension or hypertension
- Heparinization in the presence of intracranial bleeding
- Rapid transfusion in children
- Drugs, such as those associated with EPO therapy
- Removal of anticonvulsant in patients on such therapy

seizures because a number of drugs are associated with seizures in kidney disease. Seizure activity should abate after adequate dialysis has been established.

Dialysis disequilibrium is an unusual complication of current dialysis practice. It may occur during or after hemodialysis and is postulated to result from an intracellular shift of water in the central nervous system following rapid osmotic solute removal from the intravascular compartment. Minor symptoms of disequilibrium (such as headache, lethargy, and twitching) are common. However, major symptoms of disorientation, seizure, and obtundation occasionally occur. As with primary uremic complications, disequilibrium is more severe when predialysis BUN is very high, when dialysate solute levels are low (Na^+ <140 mmol/L), and when other metabolic aberrations are present. As an example, predialysis hypocalcemia can be exacerbated by the rapid correction of metabolic acidosis.

Hemodynamic instability can also complicate hemodialysis and lead to neuromuscular irritability. For example, hypotension of some degree occurs in up to half of all hemodialysis treatments. It can result from volume removal, osmotic shifts, vasodilatation, autonomic insufficiency, or inadequate cardiac reserve. Severe intradialytic hypertension due to reactive vasoconstriction induced by ultrafiltration occasionally occurs and potentiates seizure activity.

Heparinization can exacerbate preexisting intracranial bleeding, making vigilance for such bleeding essential. Transfusion can also be associated with seizure activity, particularly

in children receiving rapid transfusions. The explanation for such transfusion-related seizures is unclear, but it is postulated to result from the citrate anticoagulant in blood bank products. The advent of injectable erythropoietin (EPO) has reduced the need for transfusions, but has imposed a possible small risk of increased seizure activity during dialysis.

EPO-related seizures are thought to result from a rapid rise in hematocrit, hypertension, increased viscosity, or enhanced platelet activation. Injectable EPO in experimental models has direct vasoactive activity via the release of endothelin (ET-1). However, the association between EPO and seizures remains loose and is not finally established. Initial weekly EPO dosage can be limited to 150 U/kg to minimize the risk of seizures. Some advocate the subcutaneous route of administration rather than IV to decrease any adverse effects of the drug, as well as to increase bioavailability and reduce the cost of treatment.

In patients already on anticonvulsant medications, removal of dialyzable drugs (such as phenobarbital or primidone) may lower the seizure threshold and result in seizure activity. For drugs generally considered less dialyzable, it is also possible that the removal of small amounts of free active drug could precipitate seizures in particularly vulnerable patients. Examples include diphenylhydantoin and carbamazepine.

Several unrelated epileptogenic drugs are particularly problematic in patients with renal failure who are receiving dialysis (Table 27.2). Drugs such as penicillins and quinolones, for which high drug levels are epileptogenic, often require reduced

Table 27–2

Epileptogenic Drugs That Are Problematic in Hemodialysis Patients

- Penicillin and cephalosporin
- Ciprofloxin
- Meperidine (toxic metabolites)
- Ethanol
- Theophylline
- L-Dopa
- Lithium
- Cyclosporine
- Amantidine
- Acyclovir
- Aluminum-containing antacids

dosing in the dialysis patient. Drugs for which accumulated toxic metabolites cause increased neuromuscular irritability and risk of hemodialysis-associated seizure activity (such as meperidine) should be avoided entirely in dialysis patents.

Predisposing Patient Characteristics

Given the destabilizing factors inherent to dialysis, it is also possible to identify patients who will be at increased risk for hemodialysis-related seizure activity (Table 27.3). Obviously, a preexisting epileptic history or underlying central nervous system abnormality predisposes patients to seizure activity. The tendency to hemodialyze children with dialyzers that are large relative to their body size enhances the destabilizing effects of dialysis and the risk of seizures.

Microvascular disease that could affect the central nervous system increases the risk of seizure upon hemodialysis. Uncon-

Table 27–3

Patient Characteristics That Predispose to Hemodialysis-related Seizures

- Demographic and clinical characteristics
- Prior seizure history; known seizure focus
- Primary central nervous system lesion
- Microvascular disease
- Malignant hypertension
- Atheroembolism
- Hemolytic-uremic syndrome
- Myocardial infarction; severe cardiomyopathy
- "Metabolic" encephalopathy
- Severe uremia
- Hepatic encephalopathy
- Severe cardiomyopathy; low cardiac output
- Sepsis
- Drug intoxication
- Laboratory characteristics
- Severe azotemia
- Hypoglycemia
- Hypertonicity or hypotonicity
- Severe acid-base aberrations
- Hypocalcemia or hypomagnesemia
- Hypoxemia or severe anemia

trolled hypertension may predispose patients to erythropoietin-related seizure activity. Myocardial disease, especially acute myocardial infarction or severe cardiomyopathy, also appears to increase the risk of seizure based on reduced cardiac output, hypoxemia, or arrhythmia. Finally, any "metabolic" alteration that manifests as altered mental status or myoclonic activity (e.g., asterixis) increases neuromuscular irritability and predisposes to seizures.

Table 27.3 also lists several clearly defined biochemical changes that in view of the destabilizing influence of hemodialysis previously noted identify patients more vulnerable to seizures. Overall, the appreciation of susceptible patients may help to identify those patients for whom preemptive measures to prevent seizure activity should be considered.

Therapeutic Considerations

Some important therapeutic interventions designed to minimize the risk of hemodialysis-associated seizure activity are listed in Table 27.4.

Table 27–4

Therapeutic Considerations in Hemodialysis-associated Seizure Activity

- Predialysis interventions
- Initiate dialysis earlier for uremic patients
- Identify any intracranial bleeding (reduce heparin)
- Identify myocardial infarction or arrhythmia
- Treat hypocalcemia before correcting severe acidosis
- Consider prophylactic anticonvulsant in high-risk patients
- Consider peritoneal dialysis or continuous venovenous hemofiltration in high-risk patients
- Alterations of hemodialysis
- Limit clearance during initial hemodialysis, especially when BUN very high
- Use bicarbonate dialysate
- Increase dialysate calcium content
- Give sufficient dialysate glucose to avoid hypoglycemia in diabetics
- Avoid rapid or severe reductions in blood pressure
- Administer supplemental oxygen
- Provide several hours of observation after initial seizure
- Hemodialysis

Predialysis Interventions

It is important to initiate hemodialysis before uremia is far advanced; that is, well before the BUN nears 200 mg/dL and before severe encephalopathy occurs. The presence of intracranial bleeding should limit the use of anticoagulation. Myocardial infarction or arrhythmia requires close hemodynamic monitoring. Although current dialysate contains significant ionized calcium, severe predialysis hypocalcemia should be treated before correction of acidosis with dialysis.

Prophylactic anticonvulsants may need to be given before hemodialysis in some patients with reoccurring seizures during the treatment. High-risk patients may also require temporary therapy at the initiation of hemodialysis. Finally, when the risk for seizures is extremely high or refractory to treatment more gradual or continuous therapy (such as continuous venovenous hemofiltration or peritoneal dialysis) may be indicated.

Alterations of the Hemodialysis Procedure

Changes in hemodialysis itself may lower the risk of seizure activity. For example, initial hemodialysis in patients with chronic renal failure (particularly when the BUN is very high) can be altered to limit the total solute clearance achieved. Such limitations for the first treatment or two can be achieved by using a dialyzer with a smaller surface area, by reducing the time on dialysis, or by reducing the rate and reversing the direction of the dialysate flow through the dialyzer. Reduction in blood flow rate is not advised because the reduction can predispose to clotting in the extracorporeal circuit. As chronic treatment progresses, hemodialysis efficiency can be increased.

Transcellular solute and water shifts during hemodialysis can be limited by the use of sufficiently high dialysate sodium content (levels >140 mEq/L) or by the administration of modest amounts of hypertonic NaCl or other osmotic agents (e.g., glucose or mannitol) at intervals during the treatment. Bicarbonate dialysis, as opposed to acetate-containing buffers, improves hemodynamic and neuromuscular stability. Sufficient ionized calcium in the dialysate is important. A level of 3 mEq/L is often advised for vulnerable patients. Finally, sufficient dialysate glucose (approximately 200 mg/dL) not only adds to the total osmotic content of the dialysate but prevents hypoglycemia in insulin-requiring diabetic patients.

Maneuvers to avoid rapid or severe hypotension during dialysis include the use of higher tonicity and bicarbonate in

the dialysate and of synthetic membranes that do not activate internal inflammatory mediators. Additional measures include more gradual fluid removal when possible and volume support with colloid or use of pressors when other methods have failed. In some patients, antihypertensive medications need to be held before hemodialysis. Supplemental oxygen also may be indicated in some patients with underlying cardiac or respiratory disease.

Postseizure Management

Although attention to predisposing factors and therapeutic maneuvers are designed to minimize hemodialysis seizure activity, some patients may require anticonvulsant medications. The dialyzability of anticonvulsant medications is an important consideration in prescribing such therapy in hemodialysis patients (Table 27.5). Specifically, levels of a nondialyzable drug such as diphenylhydantoin will be sustained during treatment. This is in contrast to phenobarbital, which may decrease during treatment. If a dialyzable drug is chosen, an extra dose prior to hemodialysis should be considered. This may also be warranted in particularly vulnerable patients. As noted previously, patients

Table 27–5

Removal of Anticonvulsant Medications by Hemodialysis

- Diphenylhydantoin (little or none)
- Phenobarbitol (significant)
- Benzodiazepines (little or none)
- Carbamazepine (little or none)
- Valproic acid (little or none)
- Trimethadione (partial)
- Primidone (significant)
- Succinimides (partial)
- Paraldehyde (partial)
- Alcohols (significant)
- Gabapentin (significant)
- Topiramate (significant)
- Levetiractem (significant)
- Lamotrigine (partial)
- Vigabatrin (little or none)
- Felbamate (unknown)
- Oxcarbazepine (unknown)

who are extremely seizure-prone (even with optimal treatment) may be better served with alternative dialysis modalities.

Recommended Reading

Beccary M. Seizures in dialysis patients treated with recombinant erythropoietin: Review of the literature and guidelines for prevention. Int J Artif Organs 1994;17:5–13.

In-depth review of seizure activity relative to erythropoietin use.

Bennett W, Aronoff G, Golper T, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, Fourth Edition*. Philadelphia: American College of Physicians 1999.

Comprehensive (and recurrently updated) review of drug prescribing in patients with renal failure. Useful for anticonvulsant drugs in particular and for any class of drugs in general.

Kiley J. Neurologic aspects of dialysis. In Nissenson A, Fine R, Gentile D (eds.), *Clinical Dialysis, Third Edition*. Norwalk CT: Appleton & Lange 1996.

General review of the neurologic complications of dialysis.

Szeto H. Accumulation of normeperidine, an active metabolite of meperidine in patients with renal failure or cancer. Ann Int Med 1977;86:738–40.

Important reference recognizing the danger of meperidine (and its metabolites) in patients with renal failure. Established an important standard for this type of complication.

CHAPTER 28

Arrhythmias in Hemodialysis Patients

Claudio Rigatto, MD, and Patrick S. Parfrey, MD

Cardiac rhythm disturbances are common in dialysis. Multiple studies have shown a high prevalence of ventricular and atrial ectopy and conduction abnormalities in hemodialysis patients, reflecting both the proarrhythmic nature of the hemodialysis process itself and the high burden of structural heart disease in ESRD (end-stage renal disease) populations. The prevalence of chronic or recurrent rhythm disturbances, especially atrial fibrillation (AF), is 50 to 100% higher than in the general population. Treatment of arrhythmias in dialysis patients can be challenging because the pharmacokinetics of many drugs are different, and because in many instances the risk/benefit ratio of many therapies is altered or uncertain.

This chapter summarizes what is known about the etiology and management of rhythm disturbances in hemodialysis. The major emphasis is on chronic management of arrhythmias in dialyzed patients, especially AF. Because the acute management of life-threatening unstable arrhythmias deviates little from current advanced cardiac life support (ACLS) guidelines, only important differences are highlighted. The reader is encouraged to review the latest ACLS guidelines (see Recommended Reading at the end of the chapter). It should be remembered that most of the recommendations in this chapter are based on imperfect or evolving data in nondialysis patients. In the future, direct evidence in hemodialysis populations may help refine the arguments presented here.

Finally, the reader should be aware that a major paradigm shift in the management of chronic arrhythmias (especially AF) has occurred over the past 10 years. Multiple studies have shown that most antiarrhythmic agents (with the exception of beta blockers, calcium blockers, and possibly amiodarone) are associated with poor efficacy, high toxicities (especially sudden cardiac death), and elevated mortality, and are best avoided in most instances. The current paradigm stresses aggressive diagnosis and treatment of underlying structural heart disease.

Etiology and Prognosis

Both patient factors and dialysis factors contribute to arrhythmic risk. Significant underlying cardiac disease (present in the majority of hemodialysis patients) is independently associated with conduction disturbances, atrial and ventricular ectopy, and death. Superimposed on this substrate, changes in volume and extracellular ion composition during dialysis enhance myocardial irritability (Table 28.1). Ventricular and atrial ectopy are more frequent during dialysis than in the interdialytic period. Both atrial (p-wave) and ventricular (t-wave) dispersion increase during dialysis, enhancing the likelihood of reentrant arrhytmias.

Rapid extracellular fluid (ECF) volume fluxes are associated with catecholamine surges and subendocardial ischemia, which are in turn associated with ventricular ectopy. Rapid lowering of potassium, particularly in patients taking cardiac glycosides, is arrhythmogenic—and attenuation of these changes by stepwise ramping of dialysate potassium during dialysis seems to reduce ventricular ectopy. Elevated calcium baths may have a similar impact. Many of the cardiac drugs commonly used in hemodialysis patients (e.g., digitalis preparations) exhibit arrhythmogenic toxicities because of altered pharmacokinetics, end-organ effects, or both.

The prognostic impact of arrhythmias in hemodialysis patients is incompletely defined. Frequent or complex ventricular ectopy is associated with decreased survival, but this effect is not independent of age, hypertension, and underlying heart disease and may simply be a marker of poor cardiac status.

Table 28–1

Factors That May Precipitate Arrhythmias During Hemodialysis

- Digitalis
- Acute volume shifts
- Hypokalemia
- Hypercalcemic dialysate
- Hypomagnesemia
- Myocardial ischemia

Management

General Considerations

Unstable Rhythms

Acute unstable or life-threatening rhythms, defined as heart rhythms associated with chest pain or evidence of circulatory insufficiency (e.g., frank shock, hypotension, impaired mentation), should be managed per current ACLS guidelines. As a general rule, the dialysis procedure should be stopped unless a clear metabolic precipitant correctable by dialysis is present (e.g., hyperkalemia-induced heart block). Intravenous access via the fistula or central line should be maintained. Because a thorough discussion of ACLS procedures is beyond the scope of this chapter, the reader is encouraged to download the latest edition of the ACLS recommendations (see Recommended Reading at the end of the chapter). Any additional considerations in hemodialysis patients are discussed under specific rhythm disturbances.

Preventive Measures

Avoidance of arrhythmogenic stimuli during dialysis may be helpful, particularly in patients in whom dialysis reliably precipitates arrhythmias. Measures such as strict control of interdialytic fluid gain and potassium intake may decrease the need for aggressive ultrafiltration and low potassium dialysate. Substitution of normal instead of the usual elevated calcium bath may be helpful. Discontinuation of arrhythmogenic drugs (e.g., cardiac glycosides) should be seriously considered.

Treatment of Underlying Cardiac Disease

Aggressive medical and surgical therapy of underlying cardiac disease has been shown to prolong life and decrease morbidity in the general population. In contrast, with few exceptions specific antiarrhythmic therapy does not prolong life and may increase mortality in patients with heart disease. In hemodialysis patients with arrhythmias, a search for and aggressive treatment of ischemic heart disease (IHD) and left ventricular dysfunction is probably more important than antiarrhythmic therapy. Appropriate indications for established life-saving therapies such as ASA (aspirin), beta blockers, angiotensin-converting enzyme inhibitors (ACE), and coronary revascularization are discussed elsewhere.

Antiarrhythmic Therapy

Dosing and major indications for cardiac drugs in hemodialysis patients are summarized in Table 28.2. Acute therapy of arrhyth-

Table 28–2

Antiarrhythmic Drugs in Hemodialysis

Total Daily Maintenance Drug	Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Class 1A					
Quinidine 4–14	200 mg po × 3 over 24 h	1200–2400	q8–12 h	2–5 μg/mL	QRS or QTc prolongation >25% may be best index of toxicity. "Extractable" serum levels should be measured.
Procainamide 5–59	12 mg/kg over 20 min IV (max rate 50 mg/min) or 500 mg po q3 h × 3	500–1000	q12–24 h	4–10 μg/ml	Stop if QTc prolongation >25% or hypotension. Combined drug and metabolite (NAPA) level >25 μg/mL is toxic.
Disopyramide 10–18	300 mg po × 1	400–1200	q24–48 h	2–5 μg/ml	Avoid use if possible. May require dose after dialysis.

Table Continued

Table 28–2

Antiarrhythmic Drugs in Hemodialysis—Cont'd

Drug	Total Daily Maintenance Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Class 1B					
Lidocaine 1–3	100 mg IV followed by 50 mg IV 10 min later if required	1–4/min IV	Continuous IV		Not removed by dialysis.
Phenytoin 8	14 mg/kg orally or IV; IV rate not to exceed 50 mg/min	200–400	q8–12 h	5–20 μg/ml	Therapeutic and toxic levels lower in dialysis patients. No significant removal by dialysis.
Mexiletine 10–15	200–300 mg po q8 h	200–900	q8–12 h	0.75–2 μg/mL	No removal by dialysis. Less prolongation of QTc than 1A agents. Less toxicity than tocainide.

Table 28–2

Antiarrhythmic Drugs in Hemodialysis—Cont'd

Total Daily Maintenance Drug	Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Tocainide 17–27	200–400 mg po q8 h	300–1200	q8 h	4–10 μg/mL	Blood levels increased by cimetidine, propranolol, phenytoin; more toxic than mexiletine.
Class 1C					
Encainide unknown	25 mg po od × 7 d	25–200	q24 h	unknown	Not recommended. Significant risk of pro-arrhythmia and death, especially in structural heart disease or post-MI.
Flecainide 9–58	100 mg po od	50–150	q12 h	0.2–1 μg/mL	Same as above.
Class 2					
Propranolol 2.3–3	—	40-–240	q6 h	unknown	Adjust dose by heart rate and AV conduction.

Table Continued

Table 28–2

Antiarrhythmic Drugs in Hemodialysis—Cont'd

Drug	Total Daily Maintenance	Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Metoprolol	2.5–4.5	5 mg IV q5 min × 3 or until desired HR control	50–150	q12 h	unknown	Same as above.
Atenolol	15–42	—	25–50	After each hemodialysis.	unknown	Same as above.
Class 3						
Amiodarone	26–107 d	800–2000 mg po od × 15 d	100–400	q24 h	unknown	No removal by dialysis. Reduce Warfarin or digoxin dose by 50%. Monitor thyroid and hepatic function. Pneumonitis rare at current recommended doses. Despite toxicities, probably the best risk/benefit of any antiarrhythmic in patients with heart disease.

Table 28–2

Antiarrhythmic Drugs in Hemodialysis—Cont'd

Drug	Total Daily Maintenance Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Bretylium 6–32	5 mg/kg IV followed by 10 mg/kg as necessary to max 30 mg/kg	0.2–0.5 mg/min	Continuous IV	unknown	No significant removal by dialysis. Avoid if possible.
Class 4					
Diltiazem 4–6	0.25 mg/kg IV bolus followed by 0.35 mg/kg IV bolus if first dose unsuccessful	120–360	q6–8 h	unknown	Titrate according to HR and AV conduction.
Verapamil 2.4–4	IV 5–10 mg over 2–3 min, repeat in 30 min if needed	60–360	q6–8 h	100–300 ng/ml	Titrate as above. No significant removal by dialysis. Avoid sustained release preparations since metabolites may accumulate.

Table Continued

Table 28–2

Antiarrhythmic Drugs in Hemodialysis—Cont'd

Total Daily Maintenance Drug	Therapeutic Half-life (h)	Acute or Loading Dose	Dose (mg)	Dose Interval	Level
Miscellaneous					
Adenosine Seconds	3–6 mg rapid IV push followed by saline flush repeat with 6–12 mg in 1–2 min if ineffective.	—	—	unknown	No significant removal by dialysis.
Digoxin 80–120	0.75–1.5 mg IV or PO over 24 h measured 12 h post dose	0.125	q24–72 h	1–2 ng/mL	No significant removal by dialysis. Not recommended. Levels increased by quinidine, quinine, esmolol, and verapamil; may require 50% reduction in dose.

mias is summarized in Table 28.3. In general, with the exception of beta blockers and calcium channel blockers chronic use of antiarrhythmic drugs is best avoided. Most Vaughn-Williams classes 1 and 3 drugs are associated with significant risk of sudden death and probably increase mortality. They should be reserved for patients with intractable or life-threatening symptoms.

Specific Rhythm Disturbances

Ventricular Ectopy

Ventricular ectopic beats (also called ventricular premature contractions) are the most common rhythm disturbance in dialysis. They may be precipitated or exacerbated by acute changes in volume and ECF composition. Minimizing these alterations may help. Atrial ectopy rarely requires therapy. Complex ventricular ectopy is usually associated with underlying structural heart disease, which should be aggressively treated. Beta blockers reduce mortality postmyocardial infarction in patients with complex ectopy, and may be beneficial in hemodialysis patients with ectopy and underlying heart disease.

Antiarrhythmic therapy is probably contraindicated in minimally symptomatic patients because chemical suppression of ventricular ectopy in the setting of structural heart disease has been associated with increased, not decreased, mortality. Frequent ventricular ectopy may cause a decrease in the rate of perfused pulses, and may be very distressing to some patients. In highly symptomatic patients in whom cardiac disease is absent or maximally treated, suppression with amiodarone may be the least toxic therapy. Care should be taken to distinguish true ventricular ectopy from ventricular escape rhythms associated with advanced AV (Atrio Ventricular) block, because suppression of ventricular activity in the latter setting is fatal.

Ventricular Tachycardia

A wide QRS complex characterizes ventricular tachycardia (VT). The complexes may be identical (monomorphic) or variable (polymorphic). Polymorphic VT often oscillates between high and low amplitude, as if the electrical axis were twisting (Torsades de pointes). Although a wide complex rhythm can be supraventricular (SVT) in origin, it is ventricular in more than 90% of patients who are older than 65 or who have known structural heart disease. EKG-based criteria have been developed to help distinguish supraventricular from ventricular rhythms, but they are cumbersome to use and have poor predic-

Table 28–3

Emergency Therapy for Selected Arrhythmias in Hemodialysis Patients

Rhythm	Treatment of Choice	Alternative Drugs	Comment
Atrial fibrillation	Cardioversion for hemo-dynamic instability. Rate control or cardioversion for new onset <12 h	Diltiazem, metoprolol, or verapamil for rate control in stable AF	See text. Treat AF with WPW with class 1A agent. AV node slowing may promote VF.
Atrial flutter	Cardioversion for hemo-dynamic instability	Diltiazem, metoprolol, or verapamil for rate control	
Supraventricular tachycardia	Cardioversion for hemo-dynamic instability. Usually self-terminating.	Carotid sinus massage, adenosine, diltiazem, metoprolol, or verapamil	
Ventricular ectopy	No treatment necessary if asymptomatic. Treat underlying cardiac disease.	Beta-blocker	Post-MI, beta-blockers lower mortality.
Sustained VT	Cardioversion for hemo-dynamic instability; lido-caine for stable VT.	ESP-guided anti-arrhythmic therapy, amiodarone, ICD	Empiric amiodarone may be as good as ESP-guided therapy. ICD for drug failure.

Table 28–3

Emergency Therapy for Selected Arrhythmias in Hemodialysis Patients—Cont'd

Rhythm	Treatment of Choice	Alternative Drugs	Comment
Ventricular fibrillation	Defibrillation; lidocaine to prevent recurrence.	ESP-guided anti-arrhythmid therapy, Amiodarone, ICD	Empiric amiodarone may be as good as ESP-guided therapy. ICD for drug failure.
Ventricular arrhythmias due to cardiac glycosides	Lidocaine	Phenytoin or procainamide	Avoid cardioversion unless VF or sustained VT.
Torsades de pointes	Cardioversion; $MgSO_4$	Atrial pacing if $MgSO_4$ not effective; isoproterenol as third line	Stop offending agent. Correct hypokalemia if present. Class 1 and class 3 agents contraindicated.

tive values for SVT given the low pretest probability of SVT in such patients.

Our approach is to treat wide complex tachycardia (WCT) in dialysis patients as ventricular tachycardia unless the patient has known recurrent SVT with aberrancy. Synchronized electrical cardioversion is indicated for hemodynamically unstable individuals or for individuals with chest pain. In stable individuals with new-onset monomorphic VT, lidocaine is the drug of choice for termination of the rhythm. Procainamide is useful in situations in which there is a significant possibility of SVT because, unlike lidocaine, it is also effective in SVT. Recurrent symptomatic monomorphic VT is generally treated with antiarrhythmic therapy guided by electrophysiologic studies (EPS). Refractory cases are best treated with an implantable cardioverter/defibrillator (ICD). In asymptomatic, nonsustained, monomorphic VT, aggressive treatment of underlying cardiac disease is likely the best therapeutic option.

Polymorphic VT (Torsades de Pointes) is associated with QT prolongation, is often recurrent, and may be refractory to cardioversion and lidocaine. Although hereditary long QT syndromes exist, these are extremely rare. Polymorphic VT is most commonly a result of hypomagnesemia or drugs that prolong the QT interval, such as classes 1a and 3 antiarrhythmics (Table 28.2). Hemodialysis patients may be on drugs associated with polymorphic VT, such as quinine and metoclopramide. Diagnosis is critical because management differs considerably. Treatment with class 1a or class 3 agents may be fatal. Magnesium sulfate shortens the QT interval and is the drug of choice to prevent recurrence. Hypokalemia should be corrected. Rapid atrial pacing or isoproterenol-induced tachycardia also shortens the QT interval and may be a useful second-line therapy. Elimination and avoidance of agents or metabolic derangements causing QT prolongation is the best long-term prophylaxis.

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) is usually due to an AV nodal reentrant circuit, and rarely to an auxiliary AV bypass tract [Wolff-Parkinson-White (WPW) syndrome]. Synchronized electrical cardioversion is the treatment of choice for patients with evidence of hemodynamic instability [e.g., systolic blood pressure <90 mmHg, congestive heart failure (CHF), chest pain, or altered mental status]. Termination of stable PSVT can be done with vagal maneuvers (carotid sinus massage) or the use of AV nodal blocking agents, such as adenosine, diltiazem, and

metoprolol (Table 28.2). These agents are also safe in WPW with narrow-complex tachycardia in the absence of AF. Chronic therapy is rarely necessary. In patients with recurrent symptomatic PSVT or WPW, catheter ablation of the reentrant pathway is the therapy of choice.

Atrial Fibrillation

AF is the most common chronic arrhythmia in dialysis patients, having a prevalence between 13 and 27%, depending on the definition of AF (chronic versus paroxysmal) and on the population studied. These figures represent a 50- to 100% increase over the figures reported in the GP. The significance of this rhythm is twofold. First, it is a marker of probable underlying structural heart disease and therefore a marker for increased mortality.

Second, it is associated with a significantly elevated risk of embolic stroke—which in the general population ranges between 5 and 10%. AF may be chronic (i.e., always present), persistent, or paroxysmal. Persistent AF is defined as AF that persists for more than 7 days or that has required cardioversion for termination of the rhythm. Paroxysmal AF is self-terminating, usually within 24 to 48 hours, and is often recurrent. Despite these differences, the risk of stroke appears to be similar in all three forms of AF.

Chronic or Persistent Atrial Fibrillation

The major priorities in the treatment of these forms of AF are rate control and embolic stroke prophylaxis with warfarin.

Rate Control

Calcium blockers and beta blockers are good first-line agents for rate control in most patients. Beta blockers should be avoided in patients with reactive airway disease. Although digoxin is effective at rest, it is less effective than either beta or calcium blockers in controlling the heart rate during exercise. Moreover, toxicity can be a problem in dialysis patients. For these reasons, it is considered a second-line agent. Most guidelines recommend titration of the rate control agent to achieve a resting heart rate of 80 to 90 beats per minute. Chronic heart rates above 130 beats per minute have been associated with cardiomyopathy.

Stroke Prophylaxis

Warfarin is recommended for all patients having at least one of the following risk factors: age >75, valvular heart disease (espe-

cially mitral), hypertension, diabetes, ischemic heart disease, previous ischemic stroke or transient ischemic attack (TIA), congestive heart failure, and thyrotoxicosis. These criteria essentially comprise most hemodialysis patients with AF. The recommended target is an INR of 2 to 3. In clinical trials in the general population, this approach provides relative risk reduction of stroke of 60%.

Even subgroups at high risk for bleeding still appear to benefit. Allowing the INR to fall below 1.7 appears to double the risk of stroke (compared to a therapeutic INR of 2 to 3). Conversely, bleeding risk increases sharply at an INR greater than 3.5. Although the risk/benefit ratio of anticoagulation for AF has not been studied in dialysis, it is probably favorable. ASA may be substituted if warfarin is contraindicated, and is associated with a lesser relative risk reduction of 30%.

Rhythm Control Versus Rate Control

Cardiologists have debated for years whether attempts should be made to maintain sinus rhythm (SR) in nonvalvular AF. Three large randomized controlled trials have recently been published comparing strategies aimed at achieving and maintaining SR (typically electrical or pharmacologic cardioversion followed by maintenance antiarrhythmic drug therapy) with strategies focusing only on rate control. None of the trials showed any benefit of rhythm control. In two of the trials, a disturbing trend to *worse* composite outcomes with rhythm control strategies was observed.

Moreover, all three trials showed that stopping warfarin once SR was achieved resulted in an increased rate of embolism—indicating that warfarin needs to be continued indefinitely even if patients remain in SR once converted. The poor outcome in the rhythm control arms has been attributed to the poor efficacy (less than 50% of patients could maintain SR with maximal therapy) and high toxicity (especially proarrhythmia and sudden death) of current antiarrhythmic drugs. Until better antiarrhythmic strategies can be developed, rhythm control should not be routinely attempted in AF.

Paroxysmal Atrial Fibrillation

The risk of stroke in recurrent or paroxysmal AF is not clearly defined but probably approaches that of chronic AF. Anticoagulation with warfarin, as for chronic AF, is generally recommended. The approach to rate control is similar, although control of the rate during paroxysms may be more difficult. People with very

rare paroxysms who tolerate a fast ventricular response well can probably forego chronic AV nodal-blocking drugs. Digoxin is poorly efficacious in paroxysmal AF, and is not recommended. Beta blockers and nondihydropyridine calcium blockers can successfully control ventricular rates during paroxysmal AF.

Asymptomatic Acute Atrial Fibrillation in the Dialysis Unit

Acute onset of AF during the dialysis procedure is not an uncommon event in the dialysis unit. Some patients will have significant symptoms and require admission for treatment and work-up, whereas a few may be unstable and require ACLS procedures and intensive care unit admission. In our experience, however, many patients remain asymptomatic (other than mild palpitations). In these cases, the diagnosis is typically made when the nurse notes a fast irregular pulse and an EKG is ordered that confirms AF. In our opinion, such cases can usually be managed in an outpatient setting (Figure 28.1)—provided a low clinical probability of ACS, CHF, pulmonary thromboembolism embolism, or sepsis can be established.

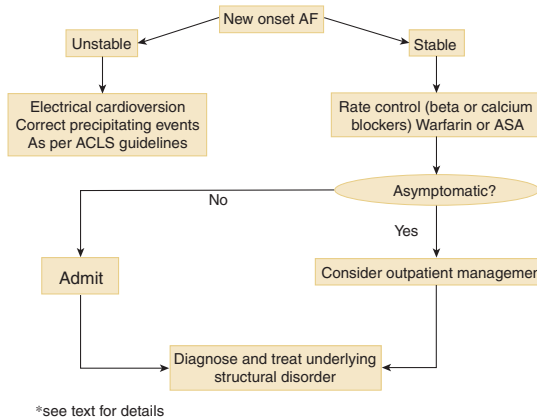


Figure 28–1

Overview of the treatment of acute AF in hemodialysis patients.

Our approach is therefore to obtain a focused cardiovascular history and physical, an EKG, cardiac enzymes, a chest X-ray, a CBC, and an a transcutaneous O_2 saturation before the dialysis treatment is over. If the clinical suspicion of ACS, PTE, or sepsis is low; the ancillary tests cited previously are negative or normal; the ventricular rate is less than 150; and the patient is otherwise relatively high functioning, outpatient management is selected. An oral rate control agent is prescribed and the first dose given in the unit. Warfarin is started, unless there is a contraindication (in which case ASA can be substituted). The dialysis bath, ultrafiltration profile, and patient dry weight are reviewed and altered if possible to make them less arrhythmogenic (see general considerations previously described). The patient is sent home at the end of the treatment, with instructions to return to the emergency room if symptoms or problems arise.

The rate of spontaneous termination of acute AF in nondialysis settings is high: 30% at 3 hours, 60% by 24 hours, and close to 80% by 48 hours. Although data are not available for dialysis, we have observed that most patients will spontaneously convert to SR by the time they present for their next dialysis treatment. Such patients have paroxysmal AF by definition (nonpersistent, self-terminating AF). Because the risk of stroke in paroxysmal AF is similar to that in persistent or chronic AF, and because the majority of dialysis patients will have at least one of the major risk factors for embolic stroke, we usually elect to continue warfarin indefinitely.

In most cases, the rate control agent may be discontinued after spontaneous conversion to SR. Patients with persistent AF should have their warfarin and rate control agent continued indefinitely. At this time, and echocardiogram is requested (to document structural heart disease) and a thyroid function is assessed to exclude occult hypothyroidism. The reader is reminded that the approach previously described is based on opinion and clinical experience, not on randomized controlled trials.

Bradyarrhythmias

Bradycardia is defined as a heart rate <60 BPM. Immediate treatment is indicated for cardiovascular instability [hypotension SBP <90, CHF, acute myocardial infarction (AMI), or chest pain]. Early transthoracic pacing, if available, is preferable to repeated doses of atropine. Reversible causes of bradycardia—such as sinoatrial (SA) or AV node depression with drugs (digoxin, calcium blockers, beta blockers)—should be sought.

Hyperkalemia may manifest as SA arrest or as AV block with a junctional or ventricular escape rhythm in the absence of classical QRST changes. Temporization with intravenous calcium gluconate and insulin/glucose are useful until the patient is dialyzed. Many patients on dialysis may have chronic SA or AV nodal disease secondary to age, CAD, or calcification of the AV valve annuli. In these cases, a permanent pacemaker is required if a superimposed reversible cause is not identified or if there is either third-degree or type 2 second-degree AV block.

Cardiac Arrest

Arrest upon dialysis is, fortunately, a rare event. The usual rhythms associated with a pulseless state are ventricular fibrillation (VF), ventricular tachycardia (VT), asystole, and pulseless electrical activity (PEA). The ACLS guidelines for management of these rhythms are published elsewhere and require little modification. Only special considerations in dialysis patients are discussed in the following.

Asystole in the adult general population is most often an agonal rhythm. However, asystolic arrest in a hemodialysis patient may reflect profound bradyarrhythmia secondary to hyperkalemia. As discussed previously, this phenomenon may supervene in the absence of antecedent classical QRST changes—particularly in patients with underlying SA and AV conduction problems who may not exhibit a junctional or ventricular escape rhythm. It should be suspected in patients arresting with asystole immediately prior to dialysis. Treatment with calcium gluconate and insulin/glucose may be life saving.

Cardiac tamponade in patients with uremic pericarditis is a correctable cause of PEA in hemodialysis patients. Immediate volume infusion to improve cardiac filling and pericardiocentesis to decompress the pericardial sac are necessary for survival. The long-term prognosis of cardiac arrest in hemodialysis patients has not been definitively studied, but may be worse than in nondialysis patients.

Digoxin Toxicity

Digoxin toxicity may manifest as atrial or ventricular ectopy, AF or atrial flutter, high-grade AV block, VT, or VF. Atrial flutter with 4:1 AV block is a classic presentation. Toxicity may result from an inappropriate dosage schedule in light of severely impaired excretion or concomitant use of drugs that increase digoxin levels (e.g., erythromycin, quinidine, verapamil, and amiodarone). Acute lowering of serum potassium concen-

tration during dialysis may further exacerbate toxicity. If suspected, digoxin should be stopped.

Unstable rhythms need to be electrically cardioverted (VT) or defibrillated (VF). Stable ventricular arrhythmias can be treated with lidocaine or procainamide. Cardioversion should be avoided because of the risk of precipitating VF in this setting. In severe cases, consideration should be given to antidigoxin Fab therapy. Often, superior alternatives to digoxin exist for chronic therapy of heart failure or arrhythmias (e.g., ACE inhibitors for CHF)—and consideration should be given to switching to these alternative drugs.

Summary

Arrhythmias are frequent in dialysis patients. They are often a reflection of underlying structural heart disease, which should be aggressively sought and treated. Mitigation of large or rapid alterations in ECF volume and electrolyte composition may minimize exacerbation of arrhythmias during dialysis. Antiarrhythmic drugs should be used sparingly, and only in patients with recurrent severe or life-threatening manifestations.

Recommended Reading

ACLS. *ACLS Guidelines* (Part 7.2, Management of Cardiac Arrest, and Part 7.3, Management of Symptomatic Bradycardia and Tachycardia). Circulation 2005;112(IV):58–77.

The latest version. Useful review of acute arrhythmia therapy and ACLS algorithms.

Bennett WM, Aronoff CR, Colper TA, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, Second Edition*. Philadelphia: American College of Physicians 1991.

de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs. rhythm control in patients with atrial fibrillation: A meta-analysis. Arch Intern Med 2005;165:258–62.

Definitive overview of the evidence.

Nattel S, Opie LH. Controversies in atrial fibrillation. Lancet 2006;367:262–72.

An excellent discussion and critique of the latest evidence, as well as a discussion of promising new therapeutic avenues.

Page RL. Newly diagnosed atrial fibrillation. N Engl J Med 2004;351:2408–16.

A terrific review of the approach to this common arrhythmia.

Snow V, Weiss KB, LeFevre M, McNamara R, Bass E, Green LA., et al., for the Joint AAFP/ACP Panel on Atrial Fibrillation. Management of Newly Detected Atrial Fibrillation: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. Ann Intern Med 2003;139:1009–17.

Excellent summary.

CHAPTER 29

Prevention and Therapeutic Management of Bleeding in Dialysis Patients

Paola Boccardo, Biol Sci D; Miriam Galbusera, Biol Sci D; and Giuseppe Remuzzi, MD

The association between a bleeding tendency and chronic uremia has been demonstrated repeatedly. The clinical manifestations have been well described and vary from ecchymoses, epistaxis, and bleeding from gums and venipuncture sites to overt gastrointestinal bleeding observed in up to a third of uremic patients. However, low-grade gastrointestinal bleeding may be even more common. Although modern dialysis techniques and the use of erythropoietin to correct anemia have reduced its frequency, bleeding is an important complication in dialysis patients and still limits surgery and invasive procedures.

Pathogenesis of Uremic Bleeding

The pathogenesis is multifactorial (Table 29.1). However, platelet-platelet and platelet-vessel wall interactions appear to be of crucial importance. Moderate thrombocytopenia caused by inadequate production or platelet overconsumption is found in the majority of uremic patients. However, thrombocytopenia severe enough to cause bleeding is very rare. In uremia, the mean platelet volume may also be decreased.

Numerous biochemical changes in platelets have been reported, including subnormal dense granule content, impaired release of the platelet α-granule protein, and β-thromboglobulin, reduction in serotonin and ADP (Adenosine Diphosphate), elevation of cyclic AMP (Adenosine Monophosphate), and a reduced ability to generate thromboxane A_2. A functional abnormality of the prostaglandin-forming enzyme cyclooxygenase has been suspected of contributing to the platelet dysfunction of uremia, as an abnormal mobilization of platelet Ca^{2+} content with the consequent impairment of Ca^{2+}-dependent platelet function. Various dialyzable "toxins" (urea, creatinine, phenol, and guanidinosuccinic acid) and high circulating levels of

Table 29–1

Factors Involved in the Pathogenesis of Bleeding Associated with Chronic Renal Failure

Platelet abnormalities
- Subnormal dense granule content
- Reduction in intracellular ADP and serotonin
- Impaired release of the platelet α-granule protein and β-thromboglobulin
- Enhanced intracellular c-AMP
- Abnormal mobilization of platelet Ca^{2+}
- Abnormal platelet arachidonic acid metabolism
- Abnormal ex vivo platelet aggregation in response to different stimuli
- Defective cyclooxygenase activity
- Abnormality of the activation-dependent binding activity of GPIIb-IIIa
- Uremic toxins, especially parathyroid hormone
- Abnormal platelet-vessel wall interactions
- Abnormal platelet adhesion
- Increased formation of vascular PGI_2
- Altered von Willebrand factor

Anemia
- Altered blood rheology
- Erythropoietin deficiency

Abnormal production of nitric oxide

Drug treatment
- β-Lactam antibiotics
- Third-generation cephalosporins
- Nonsteroidal anti-inflammatory drugs

parathyroid hormone have been causally related to uremic platelet dysfunction.

It has been suggested that uremic patients have an abnormal platelet-vessel wall interaction. The decreased binding of both von Willebrand factor (VWF) and fibrinogen to stimulated uremic platelets may account for the defective function of the platelet glycoprotein (GP) IIb-IIIa receptor complex. The reduced binding is caused by a dialyzable toxic substance(s) or is due to GPIIb-IIIa receptor occupancy by fibrinogen fragments present in uremic plasma, because its removal improved the defect.

The impaired GPIIb-IIIa activation in uremia may explain aggregation defects as well as reduced VWF-dependent adhesion and thrombus formation. Although in uremic patients VWF factor quantitative and qualitative abnormalities have not been

consistently observed, a functional defect in the VWF-platelet interaction may indeed play a role. This is because in these patients cryoprecipitate (a plasma derivative rich in VWF) and desmopressin (a synthetic derivative of antidiuretic hormone that releases autologous VWF from storage sites) significantly shorten bleeding time. In addition, molecules [such as prostacyclin (PGI_2) and nitric oxide (NO)] that inhibit platelet function and modulate the vascular tone affecting platelet vessel wall interaction are increased in uremia.

Higher than normal plasma concentrations of the stable NO metabolites, nitrites and nitrates, have been documented in uremic animals. Excessive formation of NO at systemic levels derives from vessels. In addition to its vasoactive properties, NO inhibits platelet aggregation in vitro and platelet adhesion to cultured endothelial cells. The in vivo counterpart of this activity is the prolongation of skin bleeding time observed in healthy volunteers given NO by inhalation. Patients with chronic renal failure have a defective platelet function associated with higher than normal platelet NO synthesis.

Plasma from chronic hemodialysis (HD) patients, unlike normal plasma, potently induces NO synthesis in human umbilical vein endothelial cells (HUVEC). The same results have been obtained in cultured human microvascular endothelial cells exposed to uremic plasma. These findings suggest that substances accumulate in the plasma of uremic patients capable of upregulating vascular NO synthesis. The stimulatory activity is attributable to cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which are potent inducers of the inducible isoform of NO synthase and circulate in increased amounts in the plasma of patients with chronic renal failure who either do not receive dialysis or are on maintenance HD.

Dialysis improves platelet abnormalities and reduces but does not eliminate the risk of hemorrhage. HD can even contribute to the hemostatic abnormalities of these patients because the interaction between blood and artificial surfaces may induce chronic activation of platelets. The consequent release of platelet-derived proteins can induce platelet exhaustion, leading to their dysfunction. Moreover, heparin (used to obtain systemic anticoagulation) can occasionally induce platelet activation and thrombocytopenia. It has also been shown that the hemorrhagic tendency in uremic patients is influenced by the presence of anemia, in that a low hematocrit negatively influences the rheologic component of the platelet-vessel wall interaction.

Clinical and Laboratory Findings

The most common bleeding complications in uremia are petechial hemorrhages, blood blisters, and ecchymoses at the site of fistula access puncture or temporary venous access insertion. Gastrointestinal bleeding is caused by peptic ulcers, hemorrhagic hesophagitis, gastritis, duodenitis, and gastric telangiectasias. Angiodysplasia with gastrointestinal bleeding has been observed in the stomach, duodenum, jejunum, and colon. This abnormality occurs more often in HD patients. Kaposi's sarcoma, cytomegalovirus colitis, and non-Hodgkin's lymphoma may contribute to gastrointestinal bleeding in dialysis patients with HIV nephropathy. Pericarditis is now rare but was frequent in the early days of HD.

Hemorrhagic pericarditis may account for 3 to 5% of deaths among dialysis patients. Another bleeding complication of HD patients is subdural hematoma. Head trauma, hypertension, and systemic anticoagulation are risk factors. A common occurrence in uremic patients is the development of pleural effusions. In patients with fibrinous pleuritis, anticoagulation treatment during dialysis may be a major risk factor in causing bleeding. Spontaneous retroperitoneal bleeding is a rare complication. Other hemorrhagic complications include spontaneous subcapsular hematoma of the liver and intraocular bleeding.

Although the incidence of these severe complications has been lessened recently by better management of chronic renal failure, hemorrhage is still a potentially fatal complication in patients with renal failure who are undergoing major surgery or invasive procedures—including kidney or liver biopsy. To identify patients at risk for hemorrhagic complications, efforts have been aimed at establishing which abnormal laboratory findings in uremia correlate best with an increased likelihood of clinically significant bleeding. The best laboratory hallmark of clinical bleeding caused by uremia is believed to be the cutaneous bleeding time, a test measuring the primary phase of hemostasis; that is, the interaction of the platelet with the blood vessel wall and the formation of the hemostatic plug.

Therapeutic Strategies

Guidelines for the management of hemorrhagic complications of uremia are outlined in Table 29.2.

Table 29–2

Guidelines for the Management of Hemorrhagic Complications of Uremia

- For all patients with hemorrhagic complications or who are undergoing major surgery, the adequacy of dialysis should be appropriately checked.
- It is also advisable to change the dialysis schedule for 1 month in patients who have experienced severe hemorrhages (such as major gastrointestinal bleeding, hemorrhagic pericarditis, or subdural hematomas) or who have undergone recent cardiovascular surgery—so that heparin can be avoided.
- Acute bleeding episodes may be treated with desmopressin acetate at a dose of 0.3 μg/kg intravenously (added to 50 mL of saline over 30 minutes) or subcutaneously. Intranasal administration of this drug at a dose of 3 μg/kg is also effective and is well tolerated. The effect of desmopressin acetate lasts only a few hours, a major limitation to its use in treating severe hemorrhage. Desmopressin appears to lose efficacy when repeatedly administered. Because the favorable effect of cryoprecipitate on bleeding time has not been uniformly observed, we do not recommend its use.
- The ideal treatment of persistent chronic bleeding should have a long-lasting effect. Conjugated estrogen treatment given by intravenous infusion in a cumulative dose of 3 mg/kg as a daily divided dose (i.e., 0.6 mg/kg for 5 consecutive days) is the most appropriate way of achieving long-lasting hemostatic competence.
- Severely anemic patients should receive blood or red blood cell transfusions to improve hematocrit values. Red blood cell transfusion is hemostatically effective only when the hematocrit rises above 30%. Alternatively, bleeding in patients with renal failure and hematocrit less than 30% can be treated successfully with erythropoietin (see Table 29.3).

Dialysis and Systemic Anticoagulation

The prolonged survival of renal failure patients has provided evidence that an effective HD program reduces the incidence of hemorrhagic complications. However, a well-run HD program alone cannot completely avert the risk of bleeding. There are reports of severe spontaneous bleeding episodes in HD patients even when clinical examination and laboratory data had documented good dialytic efficacy.

Thus, the role of HD in the correction of the hemostatic abnormalities of uremia remains controversial. The continuous

platelet activation induced by the interaction between blood and artificial surface, and the release of platelet-derived proteins, can induce platelet exhaustion and consequently favor bleeding in uremic patients. It has been documented that plasma levels of the potent NO inducers TNF-α and IL-lβ rise during dialysis. IL-lβ and TNF-α are generated in vivo by circulating monocytes during HD with complement-activating membranes.

Production of increased cytokines may also be triggered by intact endotoxin, endotoxin fragments, and other bacterial toxins that may cross the dialysis membranes—as well as by acetate-containing dialysate. Because of massive release of cytokines during dialysis, there is an increase in NO synthesis. Uremic patients may occasionally have an increase in plasma levels of NO metabolites during HD. In addition, it was found that plasma collected after HD appears to stimulate NO synthesis by cultured endothelial cells more than does plasma from the same patients before dialysis. Thus, the capacity of the dialysis procedure to remove uremic toxins is negatively counterbalanced by its effects on platelet activation and NO synthesis.

On the other hand, data are also available that NO synthesis does not increase during the course of a dialysis session but rather decreases. This would indicate that under optimal HD conditions (which induce no or minimal cytokine activation) HD corrects the exaggerated NO synthesis, possibly by removing from uremic plasma some dialyzable NO-releasing substances.

Apart from L-arginine, the guanidino compound related to arginine guanidinosuccinate (GSA) accumulates in plasma of uremics and is involved in the generation of NO. GSA's effect of stimulating NO release provides a biologic explanation for the data generated in the early 1970s showing that among uremic toxins GSA was the only one that consistently inhibited platelet function to such a degree that it was defined as the "X" factor in uremic bleeding.

Heparin therapy, used to inhibit clotting in the extracorporeal circuit, can activate platelets and occasionally induces thrombocytopenia by an immunologic mechanism. On the other hand, systemic anticoagulation is associated with a definite additional risk of hemorrhage for HD patients. A number of approaches have been suggested to avoid systemic anticoagulation, at least in those patients at particular risk of bleeding. Some of these approaches are outlined elsewhere in this book. Low-molecular-weight heparin has been proposed as an alternative to unfractionated heparin in patients on chronic HD and hemofiltration who are at high risk of hemorrhage. Simultaneous administration of

low-molecular-weight heparin plus prostacyclin allows safe and effective anticoagulation without affecting HD efficiency.

Dermatan sulfate (DS) has also been proposed as an alternative to heparin, because it causes less bleeding than heparin in animal models. This may be due to its reduced effect on platelet function. It also induces a moderate prolongation of activated partial thromboplastin time. Effective doses ranged from 6 to 10 mg/kg body weight per dialysis session, depending on the type of dialyzer and the duration of the procedure. The DS dose can be given as a single predialysis bolus when the procedure is of short duration (≤4 hours). When the dialysis lasts for a longer period, a combined regimen (bolus plus infusion) is required. A comparative short-term clinical study performed on 10 hemodialyzed patients demonstrated that DS dose can be individually titrated to suppress clot formation during HD as efficiently as does individualized heparin.

Regional citrate anticoagulation is a good alternative to heparin use in HD for patients with increased bleeding risk. However, this method is complex and serious complications due to citrate metabolism have been reported. Patients at high risk of bleeding can also use membranes that do not require systemic anticoagulation with heparin, provided that blood flow is maintained greater than 200 mL/minute. Prostacyclin, a vasodilator and inhibitor of platelet aggregation, showed some promise as a heparin alternative. However, its use has been limited due to vasodilatory effects on the cardiovascular system and other adverse reactions that require careful hemodynamic monitoring. Peritoneal dialysis, when applicable, avoids the risk of bleeding associated with heparin or anticoagulants.

Red Blood Cell Transfusions and Recombinant Human Erythropoietin

The low hematocrit frequently found in uremic patients has a negative influence on the rheologic component of the interaction between platelets and the blood vessel wall. This erythrocyte activity explains the shortening of bleeding time seen in uremic patients after red blood cell transfusions that increase the hematocrit to greater than 30%. Therefore, when uremic patients are given transfusions their hematocrits should be increased to more than 30% (Table 29.2) to improve hemostasis. The beneficial effect is independent of changes in platelet function tests or in VWF-related properties. Many factors contribute to the anemia of uremic patients, including shortened survival of the red cell,

failure of the erythroid marrow, repeated blood loss during dialysis, and (more importantly) defective secretion of erythropoietin.

The cloning of the human erythropoietin (EPO) gene and the production of recombinant human EPO (r-HuEPO) have provided clinicians with a powerful tool for correcting the anemia associated with renal failure (Table 29.3). Clinical trials have provided evidence that r-HuEPO reverses the anemia of uremic patients, eliminating their dependency on transfusions. Increasing doses of recombinant erythropoietin—when given to HD patients with a history of bleeding, severe anemia (hematocrit less than 23%), and a long bleeding time (more than 19 minutes)—induce a progressive increase in hematocrit accompanied by significant shortening of bleeding time. No consistent changes are found in platelet number, platelet aggregation, or platelet thromboxane A_2 formation.

Renal anemia is rapidly corrected by r-HuEPO therapy, but the dose required can vary greatly. Current recommendations are to start with 50 to 100 IU/kg three times per week. With an intravenous dosage of 50 IU/kg three times per week, the rate of hemoglobin rise is approximately 1 g/dL every 4 weeks (with 100 IU/kg three times per week it is 1.5 to 2 g/dL). Higher starting doses are used when there is the need to rapidly increase

Table 29–3

Guidelines for Treatment with Recombinant Human Erythropoietin

- Patients with renal failure and hematocrits less than 30% are candidates for r-HuEPO therapy.
- Before therapy, iron stores should be assessed by a determination of serum ferritin, serum iron, and total iron-binding capacity (TIBC).
- Patients with microcytic anemia and normal iron stores should be evaluated for aluminium toxicity and thalassemia.
- Uncontrolled hypertension is a contraindication to the initiation of r-HuEPO therapy.
- Patients must be urged to adhere to pre-r-HuEPO dietary restrictions.
- The hemoglobin level or hematocrit should be measured each week during induction of therapy and every 2 weeks thereafter.
- Serum iron, TIBC, and serum ferritin should be measured monthly for 3 months and every 2 to 3 months thereafter.

Adapted from Ad Hoc Committee for the National Kidney Foundation. Statement of the clinical use of recombinant erythropoietin in anemia of end-stage renal disease. Am J Kidney Dis 1989;14:163–69.

the level of hemoglobin. However, a rate of hemoglobin rise of more than 3 g/dL in any 4-week period should be avoided because of the possible exacerbation of hypertension.

During the correction phase, the dosage of r-HuEPO must be adjusted monthly until the target is attained. The response to any change of dosage requires 4 weeks to be completely assessed. Each time a dosage needs to be increased, the increment should not exceed 30 IU/kg three times per week. When the target hemoglobin is about to be reached (or in the case of rapid responders), the dosage should be decreased by approximately 25 IU/kg three times per week to avoid overshooting the target. Thereafter, the dose should be titrated down gradually by making adjustments at 8-week intervals.

In the maintenance phase, the minimal dosage of r-HuEPO able to maintain target hemoglobin levels must be sought. It has been suggested that the increased sensitivity to r-HuEPO of the progenitor cells and the gradual expansion of their compartment and that of erythroblasts could result from constant r-HuEPO therapy. In some studies, the subcutaneous administration of r-HuEPO appears more effective and less expensive than the intravenous one—requiring on average a 32% smaller dose to achieve the same target. However, this has not been confirmed by other studies. In continuous ambulatory peritoneal dialysis (CAPD) patients, the intraperitoneal route has been tested and has been found not to be cost effective.

There is waste of drug because the absorption is scanty: the bioavailability of intraperitoneally given r-HuEPO is 1/5 to 1/10 of a subcutaneous dose. In conclusion, both routes (intravenous and subcutaneous) are appropriate for patients on HD—whereas the subcutaneous route is suited for CAPD or predialysis patients.

Hematocrit levels during r-HuEPO treatment should be controlled carefully because a complete correction of renal anemia carries the risk of hypertension, encephalopathy, thrombosis, and hyperkalemia. A controlled study established the minimum level of hematocrit necessary to achieve with r-HuEPO to correct the prolonged bleeding time of uremic patients.

A threshold of hematocrit between 27 and 32% has to be reached for bleeding time to become normal, or nearly normal—indicating that a partial correction of renal anemia is sufficient for this purpose.

In a recent prospective controlled study, no significant changes were documented in fistula function tests or in heparin requirements in patients given r-HuEPO or placebo. Similarly, the incidence of graft thrombosis in HD patients on r-HuEPO was not increased.

Cryoprecipitate and Desmopressin Acetate

Cryoprecipitate enriched with factor VIII/VWF, obtained when plasma is frozen and thawed, has been found to shorten bleeding time and to reduce bleeding in uremic patients undergoing major surgery. The effect of cryoprecipitate is apparent 1 hour after infusion, but maximal effects on bleeding time are obtained 4 to 12 hours (average: 8 hours) after the infusion. By 24 to 36 hours, the effect of cryoprecipitate is no longer detected. As much as 50% of patients fail to respond. Because this therapy carries the risk of transmission of infectious agents, it has been largely replaced by other approaches.

A possible therapeutic alternative to cryoprecipitate is desmopressin acetate (DDAVP), a synthetic derivative of antidiuretic hormone. DDAVP induces the release of autologous VWF from storage sites into plasma, and avoids the risk of transmitting serum hepatitis or other blood-borne diseases through the administration of blood products. In two randomized double-blind crossover trials, DDAVP was effective in shortening bleeding time of uremic patients at a dose of 0.3 μg/kg given IV (added to 50 mL of saline) or at the same dose given subcutaneously. Peak responses are achieved after a 30- to 90-minute delay when the subcutaneous route is employed. The shortening of bleeding time is significant in most patients 1 hour after the administration, and the duration of the effect averages 6 to 8 hours. Bleeding time subsequently returns to basal values. In some patients, DDAVP loses efficacy after repeated administrations, probably due to a progressive depletion of the storage sites from which VWF is released by the drug.

DDAVP can also be given by the intranasal route, which is well tolerated and quite safe. At 10 to 20 times the intravenous dose (3 μg/kg), intranasal DDAVP shortens bleeding time and decreases clinical bleeding. Adverse effects include facial flushing, mild transient headache, nausea, abdominal cramps, and mild tachycardia. Rarely, thrombotic events occur following DDAVP administration—particularly in patients with underlying advanced cardiovascular disease.

Conjugated Estrogens

Patients with gastrointestinal or intracranial bleeding, or those undergoing major surgery who require long-lasting hemostatic competence, may benefit from the use of a mixture of conjugated equine estrogens. Estrogens were first proposed to treat uremic bleeding based on the observation that abnormal bleeding in

women with von Willebrand's disease is corrected by pregnancy, when the blood estrogen levels rise. One oral dose of 25 mg of conjugated estrogen normalizes bleeding time for 3 to 10 days, with no apparent ill effects. A controlled study showed that conjugated estrogens, given intravenously at the cumulative dose of 3 mg/kg divided over 5 consecutive days, produced a long-lasting reduction in bleeding time in uremic patients.

The effect becomes manifest only after several hours, but lasts 14 days. Apparently, it cannot be ascribed to an effect on the multimeric structure of von Willebrand factor, platelet aggregation, or platelet thromboxane production. A subsequent dose-response study showed that at least 0.6 mg/kg estrogen was needed to reduce bleeding time, and that four or five infusions spaced 24 hours apart were needed to reduce bleeding time at least 50%. Low-dose transdermal estrogen (estradiol 50–100 micro G/24 hours) applied as a patch twice weekly was found to reduce recurrent gastrointestinal bleeding, with parallel improvement in bleeding time and no side effects.

Additional studies have shown that the shortening effect of conjugated estrogens on bleeding time in uremic rats is antagonized by giving the animals the nitric-oxide precursor L-arginine, which suggests that conjugated estrogens exert their hemostatic effect by interfering with the nitric oxide synthetic pathway. In the same model, estrogens almost completely return plasma nitrate to normal—further confirming a direct involvement of nitric oxide in the hemostatic effect of these molecules. Thus, estrogens may be a reasonable alternative to cryoprecipitate or DDAVP in the treatment of uremic bleeding—especially when a long-lasting effect is required.

Tranexamic Acid

Tranexamic acid (TXA), an inhibitor of the fibrinolytic system, stabilizes hemostatic clots by preventing the binding of plasminogen to fibrin and the activation of plasminogen to plasmin. It has been shown that TXA rapidly decreases bleeding time in uremia. Case reports showed that TXA was effective in controlling chronic bleeding from colonic angiodysplasias and spontaneous subdural and cerebral hematoma in dialysis patients. In a pilot study, at the dosage of 20 mg intravenously followed by 10mg/kg/48 hours orally for the next 4 weeks, TXA was found to be beneficial as adjunctive therapy in treating major upper gastrointestinal bleeding in dialysis patients.

Recommended Reading

Ad Hoc Committee for the National Kidney Foundation: Statement on the clinical use of R-HuEPO in anemia of end stage renal disease. Am J Kidney Dis 14:163–69, 1989.

A summary and a guideline on the use of recombinant human erythropoietin in renal disease.

Boccardo P., Remuzzi G., Galbusera M.: Platelet Dysfunction in Renal failure. Semin Thromb Hemost 30:579–589, 2004.

Kim YG.: Anticoagulation during haemodialysis in patients at high-risk of bleeding. Nephrology 8:S23–S27, 2003.

A review on anticoagulation during dialysis.

Noris M., Remuzzi G.: Uremic Bleeding: Closing the Circle After 30 Years of Controversies? Blood 94:2569–2574, 1999.

Details of the pathogenesis of uremic bleeding.

CHAPTER 30

Hemolysis During Hemodialysis

Ramin Sam, MD; Leila Haghighat; Carl M. Kjellstrand, MD, PhD; and Todd S. Ing, MD

Introduction

Low-grade chronic hemolysis is common in uremia, as red blood cell life span is clearly decreased with reduced renal function. Using isotope red cell tagging, it has been shown that red cell life span averages about 1/2 to 1/3 of normal in uremia. In addition, uremic erythrocytes have been found to be less deformable and osmotically more fragile when compared to their normal counterparts. Transfusion of uremic erythrocytes into an individual with normal renal function will restore the life span of those cells to normal. On the other hand, normal erythrocytes transfused into a uremic individual will have shortened survival. In the past, chronic hemolysis in maintenance dialysis patients may have manifested as increased blood transfusion requirements. However, these days such hemolysis probably more often presents itself as erythropoietin resistance (larger erythropoietin doses being required for a given therapeutic response). A variety of abnormalities (such as impairment of red cell enzymatic activities and reduced synthesis of Na^+ - K^+ pump units by uremic reticulocytes) have been suggested to be the causes for the heightened predisposition of uremic erythrocytes to hemolysis.

Uncommonly, patients on dialysis can have severe (at times life-threatening) hemolysis. These patients fit into either of two categories, depending on whether hemolysis involves all or the majority of the patients being dialyzed under similar circumstances in a given dialysis center or whether the hemolysis is patient specific. Hemolysis in the former is often the result of water-borne toxins, centralized dialysis equipment failure, or blood tubing defects—whereas in the latter it results from medication or possibly inadequate dialytic therapy. Use of constricted blood tubing systems and of hypo-osmolal or abnormally warm dialysate results in intravascular hemolysis, whereas drug-induced hemolysis is usually extravascular.

Signs and Symptoms of Hemolysis

The signs and symptoms of hemolysis are largely nonspecific, but certain findings are suggestive. Blood undergoing intravascular hemolysis can show color changes from cherry red to port wine. A sudden deepening of skin pigmentation during or shortly after dialysis can also be a consequence of severe intravascular hemolysis. It is highly likely that these blood and skin color changes are all related to the release of hemoglobin and methemoglobin from erythrocytes, as well as the generation of methemalbumin and a complex containing hemopexin and heme. In slowly developing hemolysis, the patient may not notice any symptoms at all.

In severe acute or subacute hemolysis, the most common presenting symptoms are anorexia, nausea, vomiting, abdominal pain, diarrhea, and back pain. Patients with hemolysis can also present with headache, lethargy, malaise, chills, diaphoresis, hypotension, hypertension, dyspnea, chest pain, palpitation, leg cramps, cyanosis, dark urine (and death can be associated). Pancreatitis can also occur. Laboratory findings include a low hemoglobin concentration, an elevated serum bilirubin level, reticulocytosis, the presence of Heinz bodies, the presence of methemalbumin in the serum, and an elevated serum lactic dehydrogenase value.

Other laboratory evidences of hemolysis comprise low haptoglobin levels, a reduced Cr^{15} erythrocyte survival with splenic sequestration, and an abnormal Coomb's test. The onset of clinical manifestations varies, depending on the cause of hemolysis. Occurrence of symptoms within 2 hours of starting dialysis (e.g., hemolysis due to defective blood tubing) and 8 to 24 hours after the onset of dialysis (e.g., copper-induced hemolysis) has been reported.

Causes of Hemolysis

Refer to Table 30.1 in regard to this section.

Water Supply or Dialysate Problem

Chloramine

Chlorine is the most commonly used antiseptic agent for water supplies in the United States. Unfortunately, chlorine can react with other compounds in water to form undesirable byproducts (such as trihalomethanes). A growing practice is to combine chlorine and ammonia to form chloramine (a compound con-

Table 30–1

Causes of Hemolysis

A Water supply or other toxins
- Chloramine
- Copper
- Zinc
- Nitrites and nitrates
- Formaldehyde
- Combination of acetic acid, peracetic acid, and hydrogen peroxide
- Glutaraldehyde
- Sodium hypochlorite

B Hydrogen peroxide

C Hypo-osmolal dialysate and hemodilution

D Dialysate temperature >42ºC
- Dialysis equipment or other dialysis problems
- Faulty blood tubing (e.g., abnormal narrowing)
- Kinking of blood tubing
- Small-bored cannula or needle
- Very high blood flows
- Abutting of "arterial" needle against wall of vascular access
- Malocclusion of blood pump
- Thrombosis of vascular catheter
- Dialyzer blood port clots
- Traumatic arteriovenous fistula

E Patient-specific factors
- Uremia (e.g., insufficient dialysis)
- Infection
- Lack of erythropoietin
- Certain medications
- Underlying systemic illness (e.g., SLE)
- Hypersplenism
- Hypophosphatemia

taining NCl groups and produced by the attachment of chlorine to nitrogen) and to use this chemical as an alternative bactericidal compound. Despite being much less reactive than chlorine, chloramine has been found to cause hemolysis outbreaks among dialysis patients in various parts of the world. Most recently, in a dialysis unit in Brazil 16 patients who developed hemolysis after having been exposed to high concentrations of chlorine and chloramine in product water were described.

Deionization tanks can only remove undesirable ions in exchange for hydrogen or hydroxyl ones but cannot remove nonionic substances such as chloramine. Similarly, reverse osmosis

removes 99% of ionic contaminants, 100% of colloidal material, and 100% of microorganisms—but cannot remove chloramine. Chloramine is ordinarily removed by passage through carbon filters. Often such passage is adequate to prevent chloramine-induced hemolysis. However, if the chloramine-contaminated water is pumped through a carbon filter too forcefully the elevated water pressure generated can create artificial channels within the device—thus allowing the passage of chloramine-contaminated water into the dialysate. In addition, traditional carbon filters may not have enough capacity to prevent hemolysis when tap water chloramine concentrations are inordinately high—as in the case of drought. An alternative method of removing chloramine from dialysate is to enrich the latter with ascorbic acid. However, serum ascorbic acid levels should be monitored to prevent hypervitaminosis C and secondary hyperoxalosis. This ascorbic acid approach has not been widely adopted.

Chloramine concentrations are determined indirectly by subtracting free chlorine levels from total chloramine values. The Association for the Advancement of Medical Instrumentation (AAMI) has set a level of 0.1 mg/L as the maximum concentration of chloramine allowed in a dialysate. Chloramine levels as low as 0.25 mg/L have been reported to bring about shortened erythrocyte life span, manifested by an increased erythropoietin requirement. Chloramine-induced hemolysis can present as methemoglobinemia, Heinz body anemia, or acute intravascular hemolysis (if chloramine levels are markedly elevated).

Metals

In the early days of hemodialysis, an often-reported cause of hemolysis was copper poisoning. The leakage of copper from copper-containing dialysis equipments leads to hemolysis, especially in the face of exhausted deionizers whose effective ion-binding sites are too depleted to be able to remove the metal adequately. More recently, the use of copper in dialysis equipment has dramatically lessened. Less frequently, zinc-contaminated dialysate has been reported to induce hemolysis in dialysis patients.

Nitrates and Nitrites

These compounds have engendered hemolysis in home hemodialysis patients who used nitrate- and nitrite-rich well water as their water supply to generate a dialysate.

Disinfectants

Formaldehyde is used as a sterilant for reprocessing used dialyzers and for the disinfection of the dialysate circuit of certain dialysis machines. The chemical has also been found in the filters used in a water filtration system. If faulty rinsing procedures are employed or formaldehyde-tainted water filtration filters are used, formaldehyde can inadvertently be introduced into the blood. Formaldehyde in the blood may lead to the development of auto-antibodies against erythrocytes in the form of anti-N-like antibodies that can result in hemolysis. These anti-N-like antibodies are cold agglutinins and show a preference for agglutinating erythrocytes with the NN blood type.

In addition to its other myriad detrimental effects on the body, formaldehyde is a reducing agent and capable of converting NAD to NADH—thus bringing about an inhibition of glycolysis at the level of glyceraldehyde 3-phosphate dehydrogenase and a resultant decline in ATP stores. This reduction in ATP availability (as well as the sterilant's other harmful effects) can foster hemolysis. Other sterilizing agents that have been implicated in inducing hemolysis are glutaraldehyde, sodium hypochlorite, and a mixture of acetic acid, peracetic acid, and hydrogen peroxide. A recent report describes an outbreak of hemolysis in 19 children in a pediatric dialysis unit as a result of disinfecting the water treatment system with a concentrated solution of hydrogen peroxide. There was a mean reduction in hemoglobin levels of 12%.

Hemodilution

A reduction of serum osmolality to 260 mmoles/kg does not seem to affect erythrocyte mechanical fragility. However, if osmolality is lowered further a significant degree of hemolysis may occur. Hemodilution can be caused by misadventures such as administering hypo-osmolal plasma expanders. It can also result from dialyzing against hypo-osmolal dialysates, as a result of using a faulty conductivity-measuring device. For instance, in 1994 (in a dialysis center) human error caused a central dialysate delivery machine to be switched to the "rinse and water" mode instead of being directed to the "dialysate" mode. As a consequence, several patients were inadvertently dialyzed with a hypo-osmolal dialysate. The afflicted patients developed symptoms within only 3 minutes of initiating dialysis. One of these patients died as a result.

Dialysate Temperature

A dialysate temperature in excess of 42ºC has been associated with hemolysis that may last for days or even weeks.

Problems with Dialysis Equipment or Procedure

When blood is forced to flow through a narrow orifice or channel, the formed elements are subjected to substantial turbulence and immense shearing strain. As a result, red blood cells can become damaged and fragmented—a phenomenon known as the red cell fragmentation syndrome. Such damaged cells, often shaped like triangles or helmets (for example), are very susceptible to lysis. In 1998, an outbreak of hemolysis took place in three different states—affecting a total of 30 patients. The hemolysis was attributed to the use of defective blood tubing sets containing abnormally narrow apertures.

Of the 25 patients affected in Nebraska and Maryland alone, more than 90% required hospitalization. Of the admitted patients, 32% required intensive unit care—and 36% had to be given blood transfusions. Other causes of obstruction in the vascular circuit that can foster hemolysis include partial occlusion of a vascular catheter (e.g., at its tip, by a thrombus, development of a thrombus at a dialyzer blood port, wide disproportion between the caliber of a dialysis needle or of a cannula (both being too small) and the blood flow rate (being too high), malocclusion of a roller pump with its consequent constricting effect on the blood path within the pump segment of an "arterial" blood tubing, impingement of the bevel of an "arterial" needle against the wall of a vascular access, and kinking of a blood tubing.

The abutting of an "arterial" needle against the wall of a vascular access can obstruct the needle's bevel and reduce the caliber of the blood path. If the blood pump now keeps on pumping at the original speed, a vacuum can be created that can lead to "arterial" tubing collapse as well as a highly turbulent and often to-and-fro movement of the blood within that tubing. This scenario most often occurs when the delivery of blood through the "arterial" needle is inadequate, as in the case of access stenosis. Kinking can be the result of the improper manner in which blood tubing is routed over a hard and narrow support, especially if easily collapsible tubing is used. Hemolysis associated with blood path problems is mainly intravascular in nature. However, milder stimuli may lead to less significant damage to red blood cells—causing them to be removed subsequently by the reticuloendothelial system (extravascular hemolysis).

It has been found that the smaller the diameter of a hemodialysis blood cannula the higher the hemolytic effect. Moreover, the position of the apical and lateral holes of a cannula determines

the magnitude of blood damage. Even with catheters that are available commercially today, if the blood flow is 500 mL/min or higher there is a higher risk of erythrocyte damage. Thus, when high blood flows are required larger-size cannulas should be used. Single-needle dialysis is also a risk factor for hemolysis.

Whether a high ultrafiltraion rate can foster hemolysis is controversial. Dialysis with a negative arterial chamber pressure greater than –350 mmHg, has been found to cause a mild hemolysis. The latter is not severe enough to lead to an increased requirement for erythropoietin dosage. However, one study found that during ultrafiltration even at negative pressures as high as –710 mmHg on the blood side of the ultrafiltering membrane no measurable hemolysis was discerned. A recent report describes a patient with mechanical hemolysis secondary to a traumatic carotid-jugular arteriovenous fistula that manifested as hyporesponsiveness to erythropoietin therapy. The hemolysis resolved after surgical correction of the fistula. Most commonly, low-grade hemolysis is seen with prosthetic or calcified cardiac valves.

Uremia and Hemolysis

Patients on hemodialysis are more prone to develop hemolysis than patients with normal renal function when exposed to the same offending agents. In one study, the combination of uremia and bacteremia led to significantly more hemolysis than either uremia or bacteremia alone. It has been suggested that there may be an increased susceptibility of uremic erythrocytes to lysis as a result of the presence of noxious agents or of oxidative stress. Lipid peroxidation of the red blood cell membrane (caused by increased free radical formation that occurs in uremia alone and by exposure of polymorphonuclear leucocytes to artificial materials in the extracorporeal circuit during hemodialysis), along with the consequent lack of cell deformability and the presence of splenic sequestration, may be an underlying mechanism.

Whether antioxidants that reduce free radical production can prevent red blood cell damage in uremic patients is at present unknown. Many trials have evaluated the effectiveness of vitamin E-coating of the dialyzer membrane and glutathione and vitamin C infusion on both oxidative damage to red blood cells and hemolysis. Although most studies have found a benefit, the findings were not yet extensive enough to warrant universal implementation. Recently, the use of electrolyzed-reduced water that contains active hydrogen and possesses a lower redox potential (to prepare dialysates for hemodialysis) has been

suggested to reduce hemodialysis-enhanced production of reactive oxygen species and proinflammatory cytokines, peroxidation of erythrocytes, and hemolysis.

The beneficial effects on erythrocytes (including that of the reduction of erythropoietin dosage because of the amelioration of hemolysis) are believed to be related to the scavenging of reactive oxygen species by the electrolyzed-reduced water used to prepare the dialysate. Electrolyzed-reduced water is generated by passing compressed water into a compartment of electrolysis through a solenoid valve. Treatment with erythropoietin may not only augment red cell generation but reduce hemolysis in patients with uremia. Withdrawal of erythropoietin has been found to lead to neocytolysis (selective hemolysis of the youngest red cells).

Insufficient dialysis may also lead to hemolysis, as revealed by the U.S. National Cooperative Dialysis Study. In this study, the hematocrit value in the group with a mid-week blood urea nitrogen (BUN) level of 105 to 115 mg/dL was significantly lower than the value in the group with a corresponding BUN value of 76 mg/dL. Although this difference in hematocrit may partly be due to reduced red cell production or more occult bleeding, some investigators have observed an inverse relationship between BUN concentrations and red cell life span. Others have shown that the osmotic resistance of the red cells to hemolysis is impaired with uremia and is improved after dialysis.

Patient-specific Factors

Other causes of hemolysis include medications, co-existing illnesses, and electrolyte abnormalities. Medications are a well-known cause of hemolysis in dialysis patients, especially in those with glucose-6-dehydrogenase deficiency. Some common offending agents include aspirin, penicillins, cephalosporins (especially cefotetan), sulfonamides, sulfones, nitrofurantoin, phenacetin, primaquine, quinidine, hydralazine and some vitamin K derivatives. One case report describes massive hemolysis after intramuscular injection of diclofenac. Another report reviewed a patient with severe acute respiratory syndrome on long-term dialysis who developed hemolysis after being treated with ribavirin.

Systemic disease states such as systemic lupus erythematosus, scleroderma, periarteritis nodosa, thrombotic thrombocytopenic purpura, the hemolytic uremic syndrome, malignant hypertension, and certain malignant tumors all predispose to the occurrence of microangiopathic hemolytic anemia. Hyperslenism

due to causes such as chronic hepatitis, transfusion hemosiderosis, marrow fibrosis, and silicone deposition is well documented to cause hemolytic anemia. A low serum phosphorus concentration from any cause may lead to a predisposition to hemolysis.

Consequences and Treatment of Hemolysis

With severe hemolysis, a profound anemia may occur that may require blood transfusions. However, the more immediate danger in end-stage renal disease patients is that of hyperkalemia. This problem is exacerbated if hemolysis occurs after blood has passed through the dialyzer.

After the diagnosis of hemolysis is confirmed, one needs to find and then remove the cause. Obviously, discontinuation of dialysis is important if intradialytic acute hemolysis is suspected. The blood present in the dialyzer and in the blood tubing should not be returned to the patient, as this blood may contain excessive amounts of potassium. In addition, it is imperative to monitor the electrocardiogram frequently in these patients so that hyperkalemia can be detected promptly. Further management should follow available guidelines intended for the treatment of hyperkalemia (if present) and for that of severe anemia.

Recommended Reading

Calderaro RVV, Heller L. Outbreak of hemolytic reactions associated with chlorine and chloramines residuals in hemodialysis water. Rev Saude Publica 2001;35:481–86.

Chlorine and chloramines can cause hemolysis.

Centers for Disease Control and Prevention. Multistate outbreak of hemolysis in hemodialysis patients. JAMA 1998;280:1299–1300.

Narrow orifices in blood tubing can lead to hemolysis.

Davidovits M, Barak A, Cleper R, et al. Methaemoglobinaemia and haemolysis associated with hydrogen peroxide in a paediatric haemodialysis centre: A warning note. Nephrol Dial Transplant 2003;18:2354–58.

Exposure to hydrogen peroxide can bring about hemolysis.

Evers J. Cardiac hemolysis and anemia refractory to erythropoietin: On anemia in dialysis patients. Nephron 1995;71:108.

A dialysis patient developed hemolysis after aortic and mitral valve replacement.

FDA. FDA notifies health care professionals of problem with the Baxter Healthcare's Meridian hemodialysis instrument: Kinks in device tubing can pose serious risk to patients. FDA News P05-100, December 16, 2005.

Kinking of blood tubing can result in hemolysis.

Francos GC, Burke JF Jr., Besarab A, et al. An unexpected cause of acute hemolysis during hemodialysis. Trans Am Soc Artif Intern Organs 1983;29:140–44.

Hemodialysis patients developed hemolysis because of application of shearing stress onto their erythrocytes during the latter's passage through the bevels of "arterial" needles that had butted against the walls of vascular accesses.

Huang KC, Yang CC, Hsu SP, et al. Electrolyzed-reduced water reduced hemodialysis-induced erythrocyte impairment in end-stage renal disease patients. Kidney Int 2006;70:391–8.
Hemolysis in maintenance hemodialysis patients is reduced along with a rise in hematocrit when electrolyzed-reduced water is used to prepare dialysates.
Nand S, Bansal VK, Kozeny G, et al. Red cell fragmentation syndrome with the use of subclavian hemodialysis catheters. Arch Inter Med 1985;145:1421–23.
Red blood cells can be damaged by forcing blood through some catheters.
Orringer EP, Mattern WD. Formaldehyde-induced hemolysis during chronic hemodialysis. N Engl J Med 1976;294:1416–20.
Formaldehyde released from filters of a water filtration system contaminated product water.
Rice L, Alfrey CP, Driscoll T, et al. Neocytolysis contributes to the anemia of renal disease. Am J Kidney Dis 1999;33:59–62.
Erythropoietin therapy withdrawal can lead to hemolysis of young red blood cells.
Seukeran D, Fletcher S, Sellars L, et al. Sudden deepening of pigmentation during haemodialysis due to severe haemolysis. Br J Dermatol 1997;137:997–99.
Color of skin becomes darker after the occurrence of hemolysis.
Shaldon S, Chevallet M, Maraoui M, et al. Dialysis associated auto-antibodies. Proc Eur Dial Transplant Assoc 1976;13:339–47.
Ant-N-like antibodies were detected in patients exposed to formaldehyde-reprocessed dialyzers.
Twardowski ZJ, Haynie JD, Moore HL. Blood flow negative pressure and hemolysis during hemodialysis. Home Hemodial Int 1999;3:45–50.
A high negative pressure greater than –350 mmHg causes a slightly higher hemolysis than dialysis with less negative arterial chamber pressure.
Ward RA, McLeish KD. Polymorphonuclear leukocytes oxidative burst is enhanced in patients with chronic renal insufficiency. J Am Soc Nephrol 1995;5:1697–1702.
Polymorphonuclears in patients with chronic renal insufficiency produce more reactive oxygen species with a given stimulus than corresponding cells from normal subjects.
Yasuda T, Shimokasu K, Funakudo A, et al. An investigation of blood flow behavior and hemolysis in artificial organs. ASAIO J 2000;46:527–31.
Forcing blood through a narrow path can cause turbulence and impose shearing strain on formed elements.

CHAPTER 31

Methods and Complications of Dialyzer Reuse

John Kenneth Leypoldt, PhD

Background and Rationale

Dialyzer reprocessing or reuse is a technique employed in many dialysis centers in the United States to decrease hemodialysis (HD) treatment costs. Historically, various medical reasons have been championed over the years to justify dialyzer reprocessing, but few of these have relevance today. For example, reuse of dialyzers containing unmodified cellulosic (e.g., cuprophane) membranes was shown in the late 1970s and 1980s to decrease the activation of complement proteins in patient blood during extracorporeal circulation—thereby improving the biocompatibility of such membranes.

It was also often argued that the incidence of so-called first-use syndrome, which may be caused by either complement activation or release of residual ethylene oxide sterilant, was believed to be less frequent in centers practicing dialyzer reuse. Such medical justifications are no longer applicable because the landscape of dialyzers and dialysis membranes has changed significantly over the past few decades. Clearly, unmodified cellulosic membranes are rarely used today in the United States. Further, current dialyzers contain biocompatible (low complement activation) dialysis membranes made from synthetic polymers (e.g., polysulfone and polyethersulfone)—which can be sterilized using a number of new methods, rather than using ethylene oxide. Thus, the historical medical and scientific arguments that dialyzer reprocessing improves patient outcomes no longer have validity.

Current Status of Dialyzer Reuse in the United States

The methods and frequency of dialyzer reuse have changed continuously over the past three decades. In 1976, 18% of dialysis centers in the United States reused dialyzers—and those centers used exclusively formaldehyde as the disinfectant or germicide and bleach as a cleaning agent. At that time, dialyzer reprocessing

was largely performed manually (i.e., without the use of an automated reprocessing machine). Between the early 1980s and the end of the twentieth century, dialyzer reuse increased in popularity (it peaked at more than 80% of all dialysis centers in the late 1990s). During that time period, peracetic acid (actually a mixture of peroxyacetic acid, acetic acid, and hydrogen peroxide) was increasingly used as a germicide and automated reprocessing machines were also more common.

There was also a substantial change in the composition of dialysis membranes during this time, from the use of predominantly unmodified cellulosic membranes to a predominance of synthetic dialysis membranes today. Therefore, it has been difficult to make a simple comparison of the relative advantages and disadvantages of using reused and single-use dialyzers because these entities have changed over the past decades (and continue to change).

The most current report describing dialyzer reuse in the United States used data from December of 2002. In that annual survey from the Centers for Disease Control and Prevention, 63% of all dialysis centers reused dialyzers—with 20% using formaldehyde as the germicide, 76% using peracetic acid as germicide, and 4% using other methods of disinfection. These statistics are not, however, reflective of the current state of dialyzer reprocessing in the United States because certain providers of HD have made wholesale changes in their policy toward dialyzer reuse during early years of the twenty-first century.

A recent publication by Lacson and Lazarus estimated that 61% of all HD patients in 2005 were treated with single-use dialyzers. Based on that number, the author estimates that more than 90% of HD patients who are being treated with reused dialyzers are using peracetic acid as the germicide and automated reprocessing machines. These are estimates only, but reflect the remarkable changes in the practice of dialyzer reuse that have occurred recently in the United States.

Reuse Method

The exact procedures used in the reprocessing of dialyzers depend on several factors. However, the basic essential steps are similar. A schematic diagram describing these steps is shown in Figure 31.1. It has been recommended by NKF-K/DOQI guidelines that each new dialyzer be pre-processed to obtain an accurate estimate of the total cell (or fiber bundle) volume of a given dialyzer before first use. Although this is not a routine practice at all dialyzer centers, it is felt to be more reliable than trusting manufacturers'

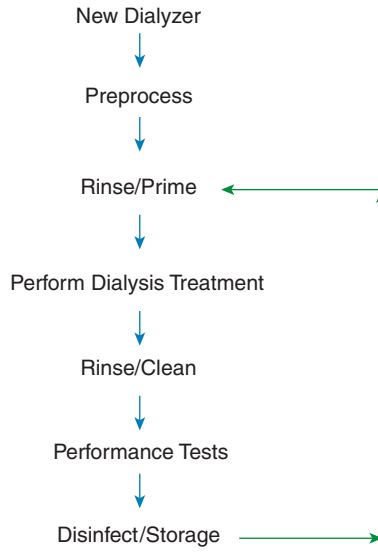


Figure 31–1

Essential steps in dialyzer reprocessing.

reported average volume or an average volume from a given batch of dialyzers—as there may be lot-to-lot variability in the total cell volume of dialyzers.

After pre-processing, the dialyzer is rinsed and primed. The important element in this step with respect to dialyzer reprocessing is that residual germicide be completely removed from the dialyzer. The dialyzer can then be connected to the patient and the HD treatment performed. Several technical factors that may cause thrombosis during or immediately after completion of the HD treatment can affect the number of times a dialyzer is reused. These include the dose of heparin, presence of air within the dialysis circuit, the blood level within the drip chambers, and appropriate placement of dialysis needles. After the end of the HD treatment, the dialyzer is rinsed and transported to the reuse room—where it is extensively rinsed. This rinsing and cleaning process may involve the use of a chemical agent, such as bleach or hydrogen peroxide.

The next step is to test the dialyzer to ensure that its performance is similar to that for a new dialyzer. The main performance test is to measure the total cell volume. If the total cell volume is between 80 and 120% of its initial value, small solute (e.g., urea and sodium chloride) clearances for this dialyzer are likely between 90 and 110% of their initial values. It should be noted that this test of dialyzer total cell volume does not evaluate other performance criteria, such as middle-molecule clearances (see material following).

A pressure/leak test is also performed at this stage to ensure that the integrity of the dialyzer is intact. If the dialyzer does not pass the required tests, it is discarded. Otherwise, the dialyzer is filled with germicide and stored until the next use. The most common germicides are peracetic acid (concentration of 3–4%), formaldehyde or formalin (concentration of 1–4%), glutaraldehyde (concentration of 0.8%), and heated water containing citric acid (concentration of 1.5%). After a specified time period, depending on the germicide used the dialyzer is ready to be rinsed and primed before the next use.

Effects of Reprocessing on Dialyzer Performance

Dialyzer reprocessing can affect dialyzer performance by altering dialysis membrane permeability. According to Association for the Advancement of Medical Instruments (AAMI) standards and recommended practices, it is commonly assumed that dialyzer performance is not altered when reprocessing is performed. However, this is not always correct. The available data suggest that dialyzer reprocessing has little effect on dialyzers clearances for small solutes. However, middle-molecule and large-solute removal by high-flux dialyzers may be substantially altered—with dialyzer performance changes varying as a function of both the dialysis membrane and the reprocessing germicide.

Reprocessing Using Bleach

Reprocessing of high-flux dialyzers containing polysulfone membranes using formaldehyde and bleach has been shown to increase the removal of middle molecules and other large-molecular-weight substances as the number of reuses increases. One possible mechanism for altered dialysis membrane permeability is that bleach may lead to a loss of polyvinylpyrrolidone (PVP) from the dialysis membrane. PVP, a wetting agent used as a copolymer

in the production of some synthetic dialysis membranes, imparts hydrophilicity to the membrane and constrains pore dimensions.

Loss of PVP (e.g., when using bleach) potentially results in a more hydrophobic membrane with larger pores. The clearance of β_2-microglobulin (MW = 11.8 kilodaltons) increases approximately twofold after 10 bleach reuses of a high-flux polysulfone dialyzer compared to first use. Early studies also demonstrated that as the number of bleach reuses of a dialyzer containing high-flux polysulfone membranes exceeds a certain number (approximate 10 reuses) membrane pore size becomes so large that substances as large as albumin (MW = 66 kilodaltons) appear in the dialysate (up to 20 g of albumin lost per HD treatment). It is no longer recommended that the dialyzers containing high-flux polysulfone membranes studied in those early studies be reprocessed using bleach.

Subsequently, Fresensius Medical Care North America (FMC-NA) manufactured two different high-flux dialyzers for repeated use in the United States: the F80B dialyzer for reprocessing with bleach and the F80A dialyzer for reprocessing with other germicides. Similar different versions of more recent dialyzers (Optiflux 200B and 200A) are also available. Depending on the conditions during reprocessing, it is theoretically possible for dialytic albumin loss to occur. However, recent findings indicate that this is no longer a significant clinical concern. The specific disinfectant used in conjunction with bleach significantly influences the permeability changes for a high-flux dialyzer. Data from the HEMO Study indicate that the membrane permeability increase occurring during successive bleach and formaldehyde reprocessing is similar when using bleach and peracetic acid as the germicide, but not when using bleach and glutaraldehyde.

Reprocessing Using Peracetic Acid

Reprocessing using peracetic acid (without bleach) causes a decrease in the removal of middle molecules by high-flux dialyzers as the number of reuses increases. However, this effect is dependent on the type of dialysis membrane. For example, the decrease in clearances of β_2-microglobulin during the HEMO Study was approximately 50% after four reuses for dialyzers containing high-flux cellulose triacetate membranes but insignificant for those containing polysulfone membranes. This is thought to be related to the failure of peracetic acid to remove proteins that have adsorbed to dialysis membranes during contact with blood during the HD treatment. Proteins that adsorb to the membrane after

each blood contact are fixed and can continuously accumulate within the membrane pore structure to increase the resistance to transmembrane transport of middle molecules.

The protein accumulation also decreases the water or hydraulic permeability of the dialysis membrane, but has little impact on small-solute clearances—suggesting that the adsorbed proteins foul or clog the pore structure but do not make the dialysis membrane appreciably thicker. The resultant effect of protein adsorption, therefore, is a decrease in the removal of middle molecules. The effect of peracetic acid reprocessing on β_2-microglobulin clearances has been carefully studied in the HEMO Study because middle-molecule removal was one of the primary interventions during that study.

Reprocessing Using Heat

The potential pitfalls encountered with chemical reprocessing of dialyzers have prompted the use of alternative modalities of reuse. Albeit used in only a small portion of dialysis centers, reprocessing with heated water merits mention. To date, only dialyzers containing polysulfone membranes have been used in published studies using heat reprocessing. The first studies using heat alone (i.e., 105ºC for 20 hours) yielded concern for dialyzer integrity (e.g., casing and resin leaks) at these high temperatures. The specific mechanisms for these findings are not known, although it is thought to involve the direct effects of heat on the casing and potting compounds of the dialyzer.

To better maintain membrane integrity, more recent studies have used modified heat reprocessing techniques—specifically, 1.5% citric acid in water heated to 95ºC for 20 hours. Early studies concluded that heated citric acid reprocessing of dialyzers containing high-flux polysulfone membranes results in a modest increase in membrane permeability—giving enhanced removal of β_2-microglobulin without a corresponding increase in albumin loss. These findings were corroborated in the HEMO Study. A limitation of heat reprocessing is that the maximum number of reuses seems limited to approximately 15 reuses—well below the typical values for other chemical-based technologies. Consequently, the overall impact of heat reprocessing on dialyzer performance may also be less.

In summary, dialyzer reprocessing can alter dialyzer performance. Alterations in the clearance of small solutes as a result of dialyzer reprocessing are minor. Alterations in the clearance of middle molecules as a result of dialyzer reprocessing can be

substantial. However, the clinical significance of these changes remains unclear.

Reuse Versus Single-Use Comparisons

Comparisons among clinical outcomes for patients using single-use dialyzers with those using reused dialyzers have been performed by numerous investigators over the past 15 years. Early comparisons in the late 1980s suggested that HD patient mortality was higher in patients who reused dialyzers with some germicides but not with others. Additional studies in the early 1990s, however, could not always reproduce these findings. Further, later studies in the 1990s suggested that mortality was reduced in patients who reused dialyzers using bleach during reprocessing. These studies are not directly comparable because of differences in dialyzer reprocessing procedures and germicides, as well as differences in dialysis membranes—which have occurred over this time period.

Two recent comparisons of reused and single-use dialyzers have reached distinctly different conclusions. One analysis using the FMC-NA database suggested that patient mortality was lower in patients treated by single-use dialyzers. This analysis was confined to prevalent patients treated using one type of dialyzer containing polysulfone membranes and another reprocessed primarily using formaldehyde and bleach. In contrast, an alternative analysis using data from the Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention showed that patient mortality was not different in patients treated using reused or single-use dialyzers. The latter was a study of national incident patients for all dialyzer types and reprocessing methods.

The differences in patient survival between reused and single-use dialyzers reported in these studies are very small (less than 10%), and statistical significance was not achieved in all analyses. Such observational cross-sectional studies are not ideal for resolving small differences that can be easily obscured by methodology biases and confounding factors. Such analyses will be repeated in future years, and any differences in patient survival between reused and single-use dialyzers should only be considered definitive when similar conclusions are reached using various analytical methodologies over a period of several years.

Noneconomic differences between reused and single-use dialyzers that remain current concerns are listed in Table 31.1. First, there is a concern over potential acute systemic toxicity

Table 31–1

Noneconomic Difference Between Dialyzer Reuse and Single Use

Concern	Reuse	Single Use
Acute systemic toxicity	Residual germicide	Leachable toxic substances
Dialyzer sterility/ disinfection	Dialysis provider	Dialyzer manufacturer
Environmental disposal	Germicide waste	Plastic medical waste

of the infusion of chemicals into the patient. Reuse of dialyzers potentially exposes patients to residual amounts of germicides during each HD treatment, but single-use of dialyzers potentially exposes patients to very small quantities of leachable organic compounds that may not be completely removed by rinsing the dialyzer. These risks are small, and are difficult to quantify because they will only likely become apparent after repeated exposure and there is little published data on long-term consequences.

Second is the concern over the reliability of dialyzer sterility. The integrity of the reused dialyzer is the responsibility of the dialysis provider, but the integrity of the single-use dialyzer is ensured by the manufacturer. Third, environmental waste concerns differ for reused and single-use dialyzers. Using dialyzers only a single time creates considerable amounts of plastic medical waste, but dialyzer reprocessing frequently employs chemicals that cannot be readily environmentally degraded. These costs to the environment are difficult to compare.

Summary and Conclusions

Reuse of dialyzers remains an essential method in many dialysis centers throughout the United States to decrease HD treatment costs. Changes in dialyzer performance as a result of dialyzer reprocessing have been clearly identified. Routine measurement and maintenance of dialyzer total cell volume ensures adequate small-solute clearances with dialyzer reuse. In contrast, such measurements do not ensure constant membrane permeability to middle molecules. Consequently, changes in middle-molecule and large-solute removal may go undetected clinically.

Near-future developments in dialyzer reprocessing would permit more complete cleaning of the dialysis membrane (to maintain

its permeability with only minimal exposure to bleach) and the development of simple tests for detecting changes in dialysis membrane permeability during dialyzer reprocessing to ensure the reliability and safety of dialyzer reprocessing. Dialysis providers, physicians, and patients should continuously update their knowledge of the economics and reliability of dialyzer reuse.

Recommended Reading

American National Standards Institute. Association for the Advancement of Medical Instrumentation: Reuse of Hemodialyzers. Washington, DC, ANSI/AAMI RD47, 2002.

Standards for reuse of hemodialyzers.

Cheung AK, Agodoa LY, Daugirdas JT, Depner TA, Gotch FA, Greene T, et al. for the HEMO Study Group. Effects of hemodialyzer reuse on clearances of urea and β_2-microglobulin. J Am Soc Nephrol 1999;10:117–27.

Large data set regarding the effect of reuse on dialyzer performance for various dialyzers and reuse methods.

Fan Q, Liu J, Ebben JP, Collins AJ. Reuse-associated mortality in incident hemodialysis patients in the United States, 2000 to 2001. Am J Kidney Dis 2005;46:661–68.

Recent comparison of patient mortality when using reused and single-use dialyzers. The data is from the Center for Medicare and Medicaid Services and the Centers for Disease Control and Prevention.

Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial 2005; 18:52–61.

Most recent published data from the Centers for Disease Control and Prevention regarding dialyzer reuse statistics.

Lacson E Jr, Lazarus JM. Dialyzer best practice: Single use or reuse? Semin Dial 2006;19:120–28.

Recent discussion of the medical and economic issues regarding dialyzer reuse.

Lowrie EG, Li Z, Ofsthun N, Lazarus JM. Reprocessing dialysers for multiple uses: Recent analysis of death risks for patients. Nephrol Dial Transplant 2004;19:2823–30.

Recent comparison of patient mortality when using reused and single-use dialyzers (data from Fresenius Medical Care North America).

Twardowski TJ. Dialyzer reuse. Part 1: Historical perspective. Semin Dial 2006;19:41–53.

Recent extensive historical review of dialyzer reuse.

Twardowski TJ. Dialyzer reuse. Part 2: Advantages and disadvantages. Semin Dial 2006;19:217–26.

Recent extensive discussion of dialyzer reuse methods.

CHAPTER 32

Clinical Application of High-Efficiency Hemodialysis

Gerald Schulman, MD

The fundamental goals of hemodialysis are to remove uremic toxins and to maintain fluid balance. The chronicle of changes that have occurred in our understanding of the pathogenesis of the uremic syndrome and in the technical limitations of therapy over the past five decades serves as the palimpsest for documenting whether those goals have been satisfactorily accomplished. Thus, when the goal was to prevent neurologic complications and the available artificial kidneys were inefficient 7- to 10-hour dialysis treatments were necessary.

In 1983, the results of the National Cooperative Dialysis Study (NCDS), a prospective and randomized trial that examined the impact of urea clearance on patient morbidity, validated urea as at least one type of surrogate marker of dialysis adequacy in patients undergoing thrice-weekly hemodialysis treatments. At the same time, membrane technology had advanced with respect to allowing the efficient clearance of both low- and high-molecular-weight substances. This intersection of events has permitted support for shortened dialysis times whether or not one believes that clearance of low-molecular-weight substances or middle molecules are important. A national trend toward shortened dialysis times has occurred.

Whereas the narrow definition of high-efficiency or high-flux dialysis has nothing to do with dialysis time, short dialysis is often inextricably linked to these two types of dialyzers in clinical practice: the use of high-efficiency and high-flux dialyzers permits short high-efficiency hemodialysis to be accomplished. Coincident with this trend toward short dialysis times using high-efficiency and high-flux dialyzers, the conclusions of the HEMO Study have been reported. It is noteworthy that the HEMO Study remains the only other randomized prospective trial, after the NCDS, to have examined hemodialysis dose along with dialyzer flux more than three decades after Medicare (CMS) provided the entitlement of the ESRD Program.

Dialyzer Definitions

Dialyzers are classified as conventional, high-efficiency, or high-flux. There is some imprecision surrounding these definitions. The blood flow and the length of treatment employed when using these dialyzers should not be part of the definition. Nor should urea clearance be used in the definition because clearance or dialysance varies with blood flow (Figure 32.1). Instead, the dialyzer is defined by the KoA_{urea} (urea mass transfer coefficient) of its membrane, its ultrafiltration coefficient, and its degree of hydrophobicity/hydrophilicity (Table 32.1). The latter parameter governs the permeability of the membrane to high-molecular-weight substances, its degree of biocompatibility, and its ability to adsorb plasma proteins and peptides to its surface.

The conventional dialyzer has a homogenous membrane that permits effective small-solute clearance, but its clearance of medium solute is relatively low. Urea clearance at a blood flow

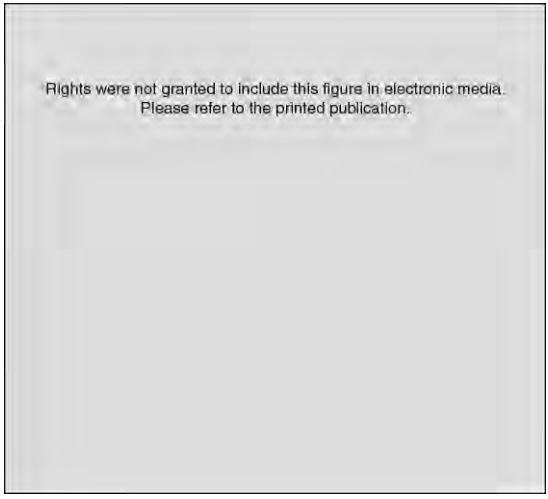


Figure 32–1

The relationship between the clearance of low-molecular-weight substances such as urea and blood flow. (*From Barth R. Pros and cons of short, high-efficiency, and high-flux dialysis. In C Jacobs, C Kjellstrand, K Koch, JF Winchester (eds.)*, Replacement of Renal Function by Dialysis. *Kluwer Academic Press 1996*.)

Table 32–1

Comparison of Dialyzers

Dialyzer	KoA_{urea}	Ultrafiltration (ml/min)	Hydrophobic/ Coefficient	Hydrophilic	Membrane
Conventional		<450	<10 mL/mmHg/h	Hydrophilic	Symmetric
High-efficiency		>450	10–19 mL/mmHg/h	Intermediate	Intermediate
High-flux		>450	>15 mL/mmHg/h	Hydrophobic	Asymmetric

of 300 mL/minute is less than 200 mL/minute (Figure 32.1). The relatively low hydraulic permeability of the membrane usually permits treatment with a dialysis machine that does not have an ultrafiltration controller. These membranes are cellulose based and contain nucleophilic groups that permit complement activation unless they have been chemically modified. The blood flow and membrane structural limitations on urea mass transfer preclude their use in high-efficiency hemodialysis.

Both high-efficiency and high-flux dialyzers have membranes with a KoA_{urea} greater than 450 mL/minute. Under standard operating conditions of a blood flow of 400 mL/minute, the urea clearance is more than 250 mL/minute (Figure 32.1). The high-flux membranes are semisynthetic or synthetic thermoplastics that permit some passage of molecules exceeding 10,000 daltons or more, with a clearance as high as 40 mL/minute. In addition, significant adsorption of protein and peptides from the blood onto the membrane may occur with these membranes. When the high-flux membrane is chemically modified such that the hydraulic permeability and the permeability to high-molecular-weight substances is reduced, a high-efficiency membrane is created. Thus, with respect to these low-molecular-weight substances high-flux and high-efficiency dialyzers have similar performance characteristics. They differ in their respective clearance rates of high-molecular substances.

Use of High-Efficiency Dialyzers

There are several reasons to use high-efficiency and high-flux dialyzers (Table 32.2). Each of these dialyzer types has a low-molecular-weight solute clearance rate far greater than that of

Table 32–2

Reasons to Use High-efficiency Dialyzers

- Low-molecular-weight solute clearance
- Ensure adequate dialysis in large patients
- High-molecular-weight solute clearance
- Clearance of high-molecular-weight substances such as β_2-microglobulin (Hi-Flux)
- Biocompatibility
- Reduced complement activation; less morbidity and mortality
- Short dialysis
- Improved lifestyle while receiving adequate therapy

conventional dialyzers. They are useful in large patients with high urea volumes to ensure delivery of an adequate level of therapy. In addition, the high-flux dialyzers also clear higher-molecular-weight substances—including substances proven to produce toxicity [such as β_2-microglobulin (MW 11,800 daltons)]. The surfaces of these membranes are more biocompatible, and cause less activation of complement and less neutropenia and immune cell dysfunction during dialysis. Several studies have suggested that biocompatible membranes have a favorable impact on morbidity and mortality of hemodialysis patients. However, the primary motivation behind the use of the efficient dialyzers is often the facilitation of shorter dialysis times.

Short Dialysis

The Hemodialysis Prescription

The goal is to reduce dialysis time to the greatest extent possible while safely delivering an adequate level of therapy. Dialysis time will vary and depends mainly on the size of the patient, the blood flow that can be achieved by the access, and the ultrafiltration rate required to maintain fluid balance. Typical dialysis times range between 150 and 210 minutes. Blood flows range between 350 and 500 mL/minute, with 400 mL/minute being the most common.

It is important to note that unless blood flow is increased to at least 350 to 400 mL/minute the potential benefit of substantially increased clearance of low-molecular-weight substances is not realized. Thus, an adequately functioning access is an absolute requirement for short dialysis (Figure 32.1). Dialysate flow rate should also be maximized. Increasing dialysate flow from 500 to 800 mL/minute can increase clearance by as much as 10% at any given blood flow. Ultrafiltration rate remains a major limitation to safely delivered short dialysis. The frequency of symptomatic hypotension increases as the ultrafiltration rate rises. A safe rate of net fluid removal is one that does not exceed 1 L/hour.

The target for the dialysis prescription remains a single-pool Kt/V of =1.3 based on the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-K/DOQI) guidelines. Quantification of the hemodialysis treatment is especially important during short dialysis for several reasons. Shortened time may increase urea rebound, particularly in patients with a low urea volume. When an immediate postdialysis BUN is measured for urea kinetics in this situation, the single-pool Kt/V may be greatly

overestimated. Indeed, the single-pool Kt/V may overestimate the true equilibrated Kt/V by more than 0.2. In addition, short dialysis is much less forgiving of any errors or delays encountered during the treatment. Constant vigilance is required to ensure adequacy.

The clearance of low- and high-molecular-weight substances is affected by the parameters of the dialysis prescription (Table 32.3). The potential adverse effects on small-molecule clearance of decreasing time is countered by increased dialyzer surface area and increased blood and dialysate flow. Decreased time imposes a major limitation on the clearance of high-molecular-weight substances even when high-flux dialyzers are used to perform short dialysis.

An example illustrates the current limitations of shortened treatment. Assuming a dialyzer clearance of 250 mL/minute and a treatment time of 180 minutes, the largest patient who can reach a Kt/V of 1.2 is one who weighs 65 kg (Kt/1.2 = V; 45/1.2 = 37.5 L; weight = V/0.58). Thus, even with the best current technology for many patients short dialysis can safely be done with only a modest saving of time if a thrice-weekly regimen is maintained.

Precautions Required for Short Dialysis

There are drawbacks associated with the technique of short dialysis itself, as well as with the use of the membranes. There is a risk of underdelivery of dialysis, of increased intradialytic symptoms, and of hypertension. There is also preliminary evidence emerging that extended and more frequent dialysis treatments

Table 32–3

Factors Influencing Clearance

	Low Molecule Weight	High Molecule Weight
Increases in:	***Clearance***	***Clearance***
Blood flow	++++	±
Dialysate flow	++	0
Membrane surface area	++	++++
Time	+++	++++
Ultrafiltration rate	+	+
Hydraulic permeability	++	+++

may have significant advantages. This is contrary to the current trend of shortening treatments.

The postdialysis rebound that follows high-efficiency hemodialysis leads to an overestimate of delivered Kt/V unless newer formulas based on an estimate of double-pool kinetics are used to calculate an equilibrated Kt/V, or unless the target Kt/V is purposely set at a higher level. The functional status of the hemodialysis access must be routinely assessed and ideally able to provide blood flow greater than 400 mL/minute without recirculation. The machines must be maintained to ensure that the roller pumps are delivering the stated blood flows. The patients must receive the full treatment without interruption. Short dialysis requires nearly perfect delivery, or there is a danger of inadequate therapy.

Fear that more intradialytic symptoms would occur with short dialysis has, fortunately, not been borne out. This is most likely due to the use of dialysate with a higher sodium concentration, improved dialysate delivery systems capable of altering the sodium during the treatment, and ultrafiltration control. Dialysis disequilibrium has not been a major problem in patients receiving short dialysis. However, in patients with small urea volumes (or in those with excessive weight gains leading to symptomatic hypotension) short dialysis may be precluded because adequate ultrafiltration cannot be achieved in the shortened dialysis time.

Hypertension may be more of a problem in short dialysis. The majority of patients on dialysis require antihypertensive medication. An unacceptable number of patients are frankly hypertensive during part of the interdialytic period. There have been reports of a greater requirement for antihypertensive medication and a higher prevalence of left ventricular hypertrophy in patients dialyzed for shorter times. In contrast, in centers that use regimens with very long dialysis times the vast majority of patients do not require any antihypertensive medications. A similar early experience is now being reported with centers using daily (i.e., 5–6 times per week) nocturnal dialysis.

The centers that employ long thrice-weekly or daily nocturnal hemodialysis are also reporting much improved calcium and phosphorus control. With conventional and short dialysis, phosphate binders must usually be used. Over many years, calcium and phosphorus might be deposited in soft tissues (including the vasculature) and might promote atherosclerosis and medial calcification of arteries. Hyperphosphatemia and elevated calcium X phosphorus product have been shown in multiple observational studies to be associated with increased mortality in dialysis patients.

Although it is currently only a speculation, the remarkably improved control of blood pressure and phosphorus seen with very long treatments may eventually be shown to prevent the morbidity and mortality associated with elevated phosphorus levels and hypertension. At present, most studies looking at the adverse effects of shortened dialysis time on morbidity and mortality are confounded by other variables—such as skewed patient demographics, the use of bioincompatible membranes, and the delivery of inadequate dialysis. Nevertheless, it is possible that longer times will eventually be shown to be beneficial and allow the beneficial effects of flux to be manifest. Clearly, more investigation along these lines is required. For now, careful monitoring of patients undergoing short dialysis is mandatory. With this caveat, short dialysis can currently be regarded as an acceptable regimen for the delivery of hemodialysis.

High-Efficiency Dialyzers

Role of High-Efficiency Dialyzers

Another important role for these dialyzers is to ensure an adequate dose of dialysis irrespective of time. High-efficiency and high-flux dialyzers have a much greater urea clearance than do conventional dialyzers. High-flux dialyzers have similar small-molecule clearance and clear larger substances as well. These attributes are increasingly being exploited to deliver adequate levels of dialysis. The membranes found in these dialyzers may also have a beneficial impact on morbidity and mortality (Table 32.4). Thus, based on data from the USRDS the relative risk of mortality is reduced in patients who are dialyzed against semisynthetic or synthetic membranes compared to those who are dialyzed against cellulosic membranes. This data was controlled for the dialysis dose received by the patients.

An extensively studied feature is the biocompatibilty of these membranes and the clinical sequelae triggered by blood-membrane interactions. They cause less complement activation compared to cellulosic membranes. The latter membranes lead to the generation of the anaphylatoxins C3a and C5a. These anaphylatoxins are capable of serving as potent chemotactic agents, producing vascular smooth muscle contraction and inducing symptoms similar to anaphylaxis. The reactions induced by the anaphylatoxins can be dramatic, resulting in acute elevations in pulmonary artery pressure, hypotension, and even death. In addition, symptoms such as chest

Table 32–4

Beneficial Effects of High-efficiency Dialyzers

- High urea clearance
- Reduced complement activation
- Decreased inflammation
- Decreased protein catabolism
- Reduced hypersensitivity reactions to dialyzer
- Improved neutrophil and lymphocyte function
- Reduced infection
- Decreased hospitalization
- Reduced β_2-microglobulin generation; high β_2-microglobulin clearance (high-flux); decreased β_2-microglobulin amyloid deposits
- Improved nutrition
- Reduced hypertriglyceridemia (high-flux)
- Improve neuropathy
- Decreased atherosclerosis

pain, back pain, and shortness of breath are seen with increased frequency when new cellulosic membranes are used.

There is a small group of patients who consistently develops symptoms ranging from chest or back pain to full anaphylactoid reactions within 15 to 20 minutes following the initiation of hemodialysis with new (nonreused) cellulosic membranes. This constellation of symptoms has been termed the *first-use syndrome*. Individuals who suffer from this phenomenon activate the complement system more vigorously than do patients who do not experience these reactions. When a cellulosic membrane is reused with formaldehyde as the sterilant, anaphylatoxin generation is attenuated and the frequency of symptoms is markedly reduced–presumably due to fixation of plasma proteins to the membrane as a result of the reuse procedure.

As dramatic as the foregoing reactions may be, the chronic effects of repeated complement activation are also important. Hemodialysis against cellulosic membranes leads to generation of reactive oxygen species. The neutrophils activated by the dialysis membrane find their way to circulatory beds such as the lungs, and out of the circulation into tissues where the generated free radicals can induce injury to the endothelial and parenchymal cells.

Reactive oxygen species have also been shown to induce strand breaks in DNA, which may be implicated in the increased

incidence of malignancies in patients on dialysis. Furthermore, the production of nitric oxide during hemodialysis with cellulosic membranes has been reported to be greater than during hemodialysis with more biocompatible (noncomplement-activating) membranes. Following activation by complement, neutrophils exhibit increased adherence. This increased adherence can lead to aggregation of neutrophils, and rarely to embolic phenomena, reduction in peak expiratory flow, and hypoxia.

Multiple lines of evidence suggest that chronic blood-membrane interactions are responsible for the development of osteodystrophy due to β_2-microglobulin-associated amyloidosis. β_2-microglobulin deposits lead to symptoms such as carpal tunnel syndrome, painful lesions in long bones, and arthropathy in patients who have been on hemodialysis for more than 5 years. By 15 years of maintenance hemodialysis, many patients are affected by this disorder.

The incidence of β_2-microglobulin is greater in patients undergoing dialysis with complement-activating cellulosic membranes. The release of this substance from mononuclear cells following contact with cellulosic membranes is greater than the release following contact with more biocompatible membranes. In a prospective study examining β_2-microglobulin levels over a period of 18 months, a cohort of hemodialysis patients was dialyzed with either complement-activating membranes or with the biocompatible synthetic polymethylmethacrylate membrane.

The levels of β_2-microglobulin in the group dialyzed with the cellulosic membrane were significantly higher at the conclusion of the study. The finding that the polymerization of β_2-microglobulin is enhanced in the presence of activated neutrophils suggests a pathogenic mechanism relating the higher levels and the increased incidence of arthropathy in patients dialyzed with complement-activating membranes.

Although overt acute reactions to blood-membrane interaction are relatively uncommon, a number of studies suggest that repetitive activation of granulocytes can lead to decreases in their phagocytic activity. A clinical correlate of this defect is suggested by studies that demonstrate a higher incidence of infection in patients using complement-activating membranes compared to patients using biocompatible membranes. Cellular immunity is also adversely affected in patients dialyzed with complement-activating membranes.

Reduced expression of IL-2 receptors in T cells harvested from patients dialyzed with cellulosic membranes is restored to normal levels when these patients are switched to more biocompatible membranes. Natural killer cell cytolytic activity is also

reduced in patients undergoing dialysis with cellulosic membranes. Lymphocytes obtained from patients dialyzed with bioincompatible membranes show less reaction to mitogen stimulation, depressed mixed lymphocyte reaction, and a decreased proliferative response.

Several studies suggest that a consequence of the attenuated inflammatory response following contact of blood with a biocompatible membrane is a decrease in protein catabolism. A possible clinical correlate of this phenomenon is an improved nutritional status following the use of biocompatible membranes. The improved nutritional status is further supported by the observation that patients switched from cellulosic dialyzers to synthetic dialyzers increase their protein intake.

The high-flux membranes, by virtue of their permeability to high-molecular-weight substances, may provide additional clinical benefits. The impact on the generation of β_2-microglobulin was discussed previously. High-flux membranes can also adsorb and remove this substance. These membranes can also remove advanced glycosylation end products implicated in atherosclerosis and possibly in promoting the polymerization of β_2-microglobulin. A number of reports suggest that triglycerides are lowered and neuropathy is improved during high-flux dialysis.

The surfaces of the high-flux and high-efficiency dialyzers are similar. Thus, the blood-membrane interactions are similar—as are their small molecule clearances. The permeability to high-molecular-weight substances is a major distinguishing characteristic between the two types of dialyzers. Whether this difference confers an advantage to the high-flux dialyzers over high-efficiency dialyzers awaited the completion of the NIH-sponsored HEMO Study. In this study, the influence of high- and low-flux dialyzers and standard or high hemodialysis dose on mortality was compared in a multimember prospective randomized trial.

The Hemo Study

Although multiple lines of evidence have suggested that kinetic modeling is an important index of dialysis adequacy and that the degree of removal of low-molecular-weight substances correlates with survival, these relationships have only been examined prospectively in two studies: the NCDS and the HEMO Study. Thus, it is important to integrate the conclusions of these prospective studies with the observational studies that have suggested that high doses of dialysis with high-flux membranes have a favorable impact on patient outcome.

The requirements and efforts for the implementation of high-dose/high-flux hemodialysis are not trivial. The time, effort, and costs associated with providing high doses and high-flux dialysis are substantial. The NKF-K/DOQI guidelines have already made recommendations regarding a dose of dialysis below which poor patient outcomes are likely to occur. What had been completely lacking was prospective data regarding any potential beneficial effects upon outcome of increasing Kt/V to very high levels. Consequently, the National Institutes of Health instituted a second multicenter prospective randomized trial to assess the impact of the dialysis prescription on morbidity and mortality of hemodialysis patients: the HEMO Study.

The study design consists of a two-by-two factorial design that assessed the effect of hemodialysis dose and membrane flux on outcome. In this study, an equilibrated Kt/V of 1.05 was compared to an equilibrated Kt/V of 1.45–comparable on average to single-pool Kt/V of 1.25 and 1.65, respectively. In addition, the effect on mortality and morbidity of high-flux versus low-flux dialyzers was compared. All-cause mortality is the primary outcome. Morbidity assessed from hospitalization, time to hospitalization for cardiovascular and infectious causes, and time to a decline in serum albumin concentration are secondary outcome measures. The design called for a concurrent sample size of 900 patients from 15 clinical centers, with replacement of those participants who died, were transplanted, or dropped out.

In the group of control subjects randomized to a normal hemodialysis dose arm, the achieved single-pool Kt/V was 1.32+/-0.09 and the achieved equilibrated Kt/V was 1.16+/-0.08. In the subjects randomized to the high-dose arm, the achieved values were 1.71+/-0.11 and 1.53+/-0.09 (respectively). Dialyzer flux, based on the clearance of $beta_2$-microglobulin clearance, was 3+/- 7 mL/minute in the low-flux group and 34+/-11 mL/minute in the high-flux group. The primary outcome, death from any cause, was influenced neither by the dialysis dose nor the dialyzer flux assignment. The relative risk of death in the high-dose group compared to the usual-dose group was 0.96 (95% confidence interval, 0.84 to 1.10; P = 0.53), and the relative risk of death in the high-flux group compared to the low-flux group was 0.92 (95% confidence interval, 0.81 to 1.06; P = 0.23). The main secondary outcomes (including first hospitalization for cardiac causes, infection, or all-cause mortality; decline in albumin or all-cause mortality; and all hospitalization not related to vascular access problems) also did not differ between the dose and flux groups.

The effects of hemodialysis dose and flux intervention were also adjusted for a series of pre-specified baseline factors of age, gender, race, years on dialysis, presence or absence of diabetes, score for coexisting conditions excluding diabetes, and albumin level. For the entire study population of 1846 randomized patients, all of the pre-specified covariates were independent predictors of death. Thus, older age (per 10-year increment), male gender, white race, presence of diabetes, longer time on dialysis (per 1-year increment), higher baseline Index of Coexisting Disease, and lower baseline albumin level were associated with higher mortality in all patients independently of their randomization.

When subgroup analysis was performed based on these pre-specified baseline factors, interactions with the primary treatment interventions were detected. Females randomized to the high-dose hemodialysis group had a lower risk of mortality. Subjects with a longer length of time on hemodialysis *at entry into the study* had a lower mortality rate if they were allocated to the high-flux arm of the study. The reasons for these subgroup outcomes are not completely clear. For instance, lower body weight versus dose does not explain the improved outcome among female subjects. When length of time in the study is added to the baseline length of time on dialysis, the benefit of flux disappears.

Although the data from the subgroup analyses are interesting and suggest further avenues for inquiry, the primary results indicate that within the conventional schedule of thrice-weekly hemodialysis neither an increased dose of dialysis nor the use of a high-flux membrane improves survival, reduces the hospitalization rate, or maintains a higher serum albumin level compared to a standard hemodialysis dose and the use of high-flux membranes.

The results from the HEMO Study should be reassuring to nephrologists that if the current NKF-K/DOQI guidelines are achieved adequate therapy is being delivered to their patients receiving thrice-weekly therapy. However, the study should not be interpreted as sanctioning a minimal dose of hemodialysis. It is prudent to provide a margin above a minimal dose to protect the patient from receiving less dialysis than intended due to factors that result in lower than intended blood flows, poor blood pump calibration, poor access function, or premature treatment termination. In particular, the HEMO Study should not be used as a justification to reduce hemodialysis time. Time was not an independent intervention in this study. Dialysis time itself is an important factor in blood pressure control and in avoiding hypotension in patients. Thus, one cannot conclude from the HEMO Study that minimizing time while maintaining an “acceptable” Kt/V is justified.

It should also be noted that the potential benefits of high flux are not ruled out by the HEMO Study. The elements of the hemodialysis prescription that have the most important impact on the removal of high-molecular-weight solutes are membrane surface area and dialysis time (Table 32.3). The conclusions of the HEMO Study are only valid for relatively narrow thrice-weekly treatment regimens lasting between 3 and 5 hours. Flux may have resulted in greater differences in the removal of high-molecular-weight substances during longer treatment times (e.g., 6–8 hours) or during more frequent treatment sessions (6–7/week). In the latter situation, it may be that flux will be shown to have an impact on mortality and morbidity.

It is also apparent from the HEMO Study that the 22% gross mortality rate currently experienced by hemodialysis patients in the United States will not be impacted by changing the dose of thrice-weekly treatments. It is becoming increasingly evident that nondialytic therapies will have to be directed against processes such as inflammation and accelerated cardiovascular disease that lead to the mortality seen in the ESRD population. In addition, the processes that result in cardiovascular disease (the leading cause of mortality in dialysis patients) originate long before the patient is started on dialysis. Therapeutic interventions must begin when the patient is identified with early chronic kidney disease.

Precautions Required for High-Efficiency Dialysis

The higher hydraulic permeability to high-molecular-weight substances of high-flux dialyzers requires that several precautions be employed in delivering safe therapy. The high rate of transfer of small molecules mandates the use of bicarbonate-buffered dialysate. In the past decade, virtually all dialysis units in the United States have converted to bicarbonate-buffered dialysate. Water and dialysate must be of high quality (with low bacterial content) to prevent endotoxin-associated pyrogenic reactions—with water having a bacterial colony-forming units count of <200 CFU/mL.

Dialyzer reuse requires special comment. Most of the clinically important pyrogenic reactions have been in association with reuse. The standards of the Association for the Advancement of Medical Instrumentation (AAMI) for reuse should be adhered to in minimizing these reactions. It should also be realized that reuse may change the fundamental characteristics of the

dialyzer membrane. Repeated exposure to formaldehyde may increase the permeability of high-flux membranes to substances as large as albumin. Conversely, peracetic acid-hydrogen peroxide (Renalin) reduces permeability to large substances. Thus, as few as five reuses with peracetic acid-hydrogen peroxide and cellulose triacetate membranes markedly attenuate the clearance of β_2-microglobulin.

In this context, a hypersensitivity reaction associated with dialyzers containing AN-69 (a high-flux, polyacrylonitrile-based membrane) deserves mention. In the last decade, anaphylactoid reactions were observed in patients dialyzed against PAN membranes while receiving angiotensin-converting enzyme (ACE) inhibitors. The preponderance of evidence suggests that bradykinin generated by the membrane is responsible for the reactions. AN-69 is a strong activator of bradykinin, and the ACE inhibitor (itself a kinase inhibitor) interferes with bradykinin degradation. This combination may lead to persistently elevated levels of bradykinin in susceptible individuals—producing bronchospasm, hypotension, and (rarely) death.

A disturbing report from the Centers for Disease Control further extends information concerning the effects of dialyzer reprocessing on this phenomenon. The report described 12 anaphylactoid reactions in 10 patients from a single dialysis unit. The reuse sterilant was peracetic acid–hydrogen peroxide delivered by an automated system. The membrane used in the dialysis unit was polysulfone rather than AN-69. Seventy percent of patients with an adverse reaction were using ACE inhibitors, whereas only 9% of patients with adverse reactions were not. All 12 reactions occurred with reprocessed dialyzers.

No further reactions occurred in that dialysis unit when reuse was terminated. It is surprising that more reports of adverse reactions under these conditions have not been forthcoming, given the number of dialysis units that reprocess polysulfone and use peracetic acid–hydrogen peroxide. The relative contribution of the membrane, the reuse procedure, or the reuse agent cannot be determined from this single report. In patients taking ACE inhibitors who experience hypersensitivity reactions, particularly when dialyzed against AN-69 or reused high-flux dialyzers, the ACE inhibitors should be discontinued.

The safety of dialyzer reuse has been questioned. More than 80% of hemodialysis units in the United States were practicing reuse by the year 2000, but this practice has been less popular in Europe. Indeed, it had been suggested that reuse accounted

for the higher mortality rates seen in hemodialysis patients in the United States. However, data from the United States suggesting that reuse (when properly carried out according to AAMI recommendations) leads to excessive mortality had not been forthcoming until recently. In a recent important study, 25% of 71,000 patients treated by a large dialysis organization were switched from reuse to single use. Although the selection of patients who switched from reuse to single use was not randomized, analysis of the data supported a survival advantage among patients treated with single dialyzers. The practice of dialyzer reuse has declined over the past five years in the United States to less than 50%.

Conclusions

High-efficiency dialyzers are in common use worldwide. Due to their high urea clearance, they permit the safe and effective application of short dialysis in properly selected patients. Perhaps more importantly, their use (along with a properly functioning access and sufficient time) allows the nephrologist to readily deliver an adequate level of therapy to hemodialysis patients. The features of the membranes in these dialyzers may offer other benefits to those patients undergoing hemodialysis.

Already, unprecedented reductions in phosphorus levels are achievable when high-flux membranes are used in conjunction with nocturnal hemodialysis. Nevertheless, the full potential of using high-flux membranes has yet to be determined. The HEMO Study did not provide the ultimate answer to whether the use of high-flux dialyzers results in a beneficial impact on mortality and morbidity. Dialysis time was not an independent variable in the HEMO Study, and the dialysis time range of 3 to 5 hours during thrice-weekly treatment may have been insufficient to examine the impact of flux.

The impact of daily nocturnal dialysis may finally allow the importance of the removal of high-molecular-weight substances to be determined. Water treatment and microbiologic surveillance must be carefully performed when using these dialyzers. The practice of reuse may defray the cost of using the more expensive membranes. However, dialyzer reuse is declining because of safety concerns and because the potential benefits of high-flux and high-efficiency dialyzers has led to their widespread use irrespective of cost. High-efficiency and high-flux dialyzers are replacing conventional dialyzers and will be the main dialyzers utilized in the future.

Recommended Reading

Charra B, Calemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. Kidney Int 1992;41:1286–91.

This is an excellent study demonstrating the benefits of long, slow dialysis that is designed to deliver a very high dose of dialysis. This paper serves as a counterpoint to high-efficiency dialysis.

Dumler F, Stall K, Moline R, Seesaw G, Leaven NM. Clinical experience with short-time dialysis. Am J Kidney Dis 1992;19:49–56.

This is an early study of the feasibility of high-efficiency dialysis.

Hornberger JC, Chernew M, Petersen J, Garber AM. A multivariate analysis of mortality and hospital admissions with high-flux dialysis. J Am Soc Nephrol 1992;3:1227–34.

A study that describes a beneficial effect of high-flux dialysis.

Schulman G, Levin NW. Membranes for hemodialyzers. Semin Dial 1994; 7:252–56.

This is a review of biocompatibility and other features of dialysis membranes.

U.S. Renal Data System. *USRDS 2006 Annual Data Report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2006.

This is the United States dialysis registry and has a wealth of information regarding the current treatment modalities and survival statistics of dialysis patients.

Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. for the HEMO Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002;347:2010–19.

This randomized prospective study is the only major trial examining the impact of dialyzer flux on patient survival performed since the ESRD program was established in 1972.

Lacson E Jr, Lazarus JM. Dialyzer best practice: Single use or reuse? Semin Dial 2006;19:120–28.

An excellent review of the evidence, both pro and con, for dialyzer reuse.

CHAPTER 33

Continuous Renal Replacement Therapies

André A. Kaplan, MD, FACP, FASN

It has been close to 30 years since Peter Kramer first proposed a blood pressure (BP)–powered filtration system designed for rapid fluid removal in patients resistant to diuretics. His technique, known as CAVH (continuous arteriovenous hemofiltration) was very efficient for simple filtration but was soon found to be inadequate for removing the large amounts of nitrogenous wastes associated with the hypercatabolic patient. In an attempt to deal with this inadequacy, several technical modifications were developed—including the addition of a diffusive component for solute removal, CAVHD (continuous arteriovenous hemodialysis), and the development of procedures employing continuous blood-pumped filtration or dialysis [including CVVH (continuous venovenous hemofiltration), CVVHD (continuous venovenous hemodialysis), and CVVHDF (continuous venovenous hemodiafiltration)]. All of these techniques are most often applied in the intensive care unit and are grouped and known as continuous renal replacement therapy (CRRT).

The most obvious advantage of these continuous treatments is that they allow for a constant readjustment of fluid and electrolyte therapy and for the administration of large amounts of parenteral nutrition and medication without the risk of interdialytic volume overload. A further advantage, at least for the hemofiltration-based treatments (CAVH, CVVH, CVVHDF), are their convective mode of solute transport—known to increase middle-molecule clearance when compared to diffusion-based dialytic techniques.

When compared to peritoneal dialysis, CRRT is not problematic in patients with abdominal surgery and offers isovolumetric fluid removal without the risk of peritonitis. Application of CRRT requires consideration of when to start the treatment, the amount of solute clearance desired, the type of replacement fluid or dialysate, the anticoagulation, the concomitant nutrition (including nutrients lost in the filtrate or dialysate), and drug dosing.

Definitions

Most CRRT systems employed in the United States are pump-driven systems. Nonetheless, BP-driven systems employing arterial catheters can still provide a simple and immediately available means of renal replacement and fluid removal. As such, and to allow the reader to appreciate terms found in the literature, the following definitions are provided.

Continuous Arteriovenous Hemofiltration

The standard CAVH circuit is depicted in Figure 33.1a. Arterial access allows blood to flow through a tubing circuit to a low-resistance hemofilter and back to a venous access. Filtrate, which is relatively protein free (Table 33.1), is produced at a rate of several hundred mL/hour and is collected into a bag connected to the ultrafiltrate port of the filter. In the postdilution mode, the replacement fluid is infused into the venous tubing. In the pre-dilution mode, the replacement fluid is infused into the arterial tubing (Figure 33.1b). Continuous anticoagulation is administered through a prefilter tubing connection.

Pre-dilution

The infusion of replacement fluid into the prefilter tubing segment of the circuit promotes the transfer of intraerythrocytic urea into the plasma compartment, where it becomes available for removal in the filtrate. The predilution technique also limits the hemoconcentration that can result from aggressive filtration rates. Disadvantages of pre-dilution include the increased cost of replacement fluid (approximately 20% more than with post-dilution) and a dilution of the filtrate chemistries compared to plasma levels.

Slow Continuous Ultrafiltration

BP-driven filtration without replacement fluid designed to provide continuous iso-osmotic fluid removal for aid in the management of oliguric patients is known as slow continuous ultrafiltration (SCUF). Intermittent hemodialysis is likely to be required for adequate solute removal. SCUF is useful as a means of maintaining fluid balance in patients intolerant of aggressive fluid removal.

Table 33–1

Relation of Ultrafiltrate to Plasma with Continuous Arteriovenous Hemofiltration

	Ultrafiltrate (UF)	Plasma (P)	UF/P Ratio
Sodium (mEq/L)	135.3 ± 11.2	136.2 ± 10.37	0.993 ± 0.023
Potassium (mEq/L)	4.05 ± 0.71	4.11 ± 0.66	0.985 ± 0.055
Chloride (mEq/L)	103.7 ± 9.55	99.3 ± 10.8	1.046 ± 0.037
Carbon dioxide (mEq/L)	22.13 ± 5.08	19.78 ± 4.69	1.124 ± 0.085
Blood urea nitrogen (mg/dL)	82.9 ± 38.4	79.1 ± 36.1	1.048 ± 0.024
Serum creatinine (mg/dL)	6.63 ± 4.00	6.5 ± 3.86	1.020 ± 0.074
Uric acid (mg/dL)	7.54 ± 3.33	7.35 ± 3.00	1.016 ± 0.081
Phosphorus (mg/dL)	4.15 ± 1.29	3.94 ± 1.13	1.044 ± 0.078
Glucose (mg/dL)	173 ± 84.5	164.5 ± 76.6	1.043 ± 0.055
Total proteins (g/dL)	0.13 ± 0.13	6.21 ± 0.32	0.021 ± 0.021
Albumin (g/dL)	0.02 ± 0.04	2.65 ± 0.46	0.008 ± 0.016
Calcium (mg/dL)	5.12 ± 0.42	8.08 ± 0.61	0.637 ± 0.071
Total bilirubin (mg/dL)	0.44 ± 0.55	12.1 ± 9.52	0.030 ± 0.029
Direct bilirubin (mg/dL)	0.26 ± 0.31	7.35 ± 5.89	0.030 ± 0.019

All values are expressed as means ± SD; n = 10 samples.
Modified from Kaplan AA, Longnecker RE, Folkert VW. Continuous arteriovenous hemofiltration: A report of six months' experience. Ann Intern Med 1984;100:358–67.

Continuous Arteriovenous Hemodialysis

With CAVHD, a diffusive component is added in order to enhance solute clearance. The circuit is the same as that for CAVH, with the addition of a constant infusion of dialysate passing through the filtrate compartment of the filter (Figure 33.1c). Clearance rates increase linearly, with dialysate flow rates up to 33.3 mL/minute (2 L/hour). Further increases in dialysate flow result in less efficient clearance/dialysate ratios. With a doubling of dialysate flow of up to 4 L/hour, urea clearance increases only 50%—to approximately 50 mL/minute.

Continuous Venovenous Hemofiltration

The CVVH circuit requires a blood pump and an air detector, and is often equipped with arterial and venous pressure monitors (Figure 33.1d). This technique has the clear advantage of avoiding the potential complications of arterial access and is capable of providing a substantial amount of convection-based clearance. Blood flow rates between 100 and 250 mL/minute decrease the tendency for filter clotting and may limit the dosage requirements for anticoagulants.

Continuous Venovenous Hemodialysis

The CVVHD circuit resembles that of CVVH but employs a variable amount of dialysate to flow past the filtrate compartment of the filter (Figure 33.1e). Solute clearance is by diffusion. The machines used are similar to those employed for CVVH.

Continuous Venovenous Hemodiafiltration

A combination of CVVH and CVVHD with variable amounts of dialysate and replacement fluid is known as continuous venovenous hemodiafiltration (Figure 33.1f).

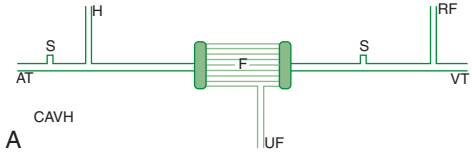
Pumped Systems for Continuous Therapies

There are several units designed specifically for CRRT. These devices use pumped systems to propel the blood past the filter/dialyzer. Pumped control is also provided for reinfusion of the replacement fluid and/or the dialysate. The appropriate pressure monitors and air detectors are also employed. Filtrate/dialysate outputs can be controlled and measured, thus decreasing nursing duties involved in measuring ultrafiltration rates. In some units, the filters and tubing are provided fully assembled in a cartridge format allowing for a “plug-in” setup of the system.

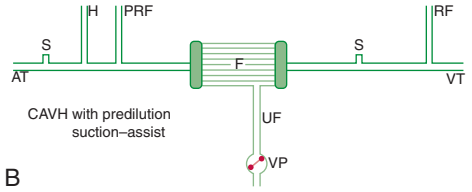
System Components

Hemoaccess

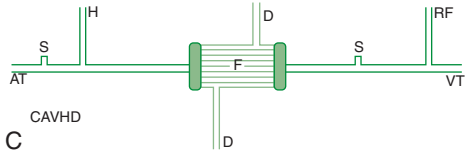
For the BP-driven circuits (CAVH, CAVHD), the ideal vascular access has the largest internal diameter and shortest length. For pump-driven circuits (CVVH, CVVHD, CVVHDF), standard double-lumen catheters are commonly used.


H
RF
S
S
F
AT
VT
CAVH
UF

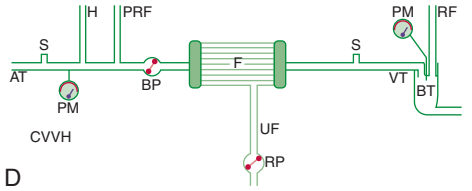
A


H
PRF
RF
S
S
F
AT
VT
CAVH with predilution
suction–assist
UF
VP

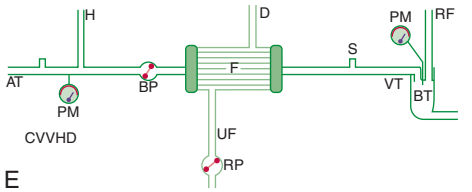
B


H
D
RF
S
S
F
AT
VT
CAVHD
D

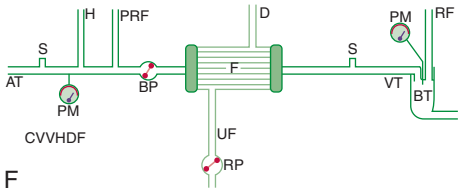
C


H
PRF
PM
RF
S
S
F
AT
VT
BP
BT
PM
CVVH
UF
RP

D


H
D
PM
RF
S
F
AT
VT
BP
BT
PM
CVVHD
UF
RP

E


H
PRF
D
PM
RF
S
S
F
AT
VT
BP
BT
PM
CVVHDF
UF
RP

F

Figure 33–1

Circuit diagrams: *A*, CAVH with postdilution infusion of replacement fluid. *B*, CAVH with the pre-dilution mode for replacement fluid administration. *C*, CAVHD. *D*, CVVH. *E*, CVVHD. *F*, CVVHDF. (AT = arterial tubing, S = sampling port, H = heparin line, F = filter, UF = ultrafiltration fluid, RF = replacement fluid, VT = venous tubing, PRF = predilution replacement fluid, VP = vacuum pump, D = dialysate, PM = pressure monitor, BP = blood pump, RP = roller pump, BT = bubble trap.) *(Modified and updated from Kaplan AA. Continuous arteriovenous hemofiltration and related therapies. In C Jacobs, CM Kjellstrand, KM Koch, JF Winchester (eds.),* Replacement of Renal Function by Dialysis, Fourth Edition. *Dordrecht, The Netherlands: Kluwer Academic Press 1996:390–417.)*

Filters

Ideal filters are those that provide high water permeability with low resistance and a minimal tendency to clot. Most of these are of a hollow fiber configuration manufactured from synthetic membranes. CAVHD is strongly dependent on diffusion and may be efficiently performed with a plate dialyzer. The pumped systems are no longer dependent on the potentially marginal pressures and flows inherent in the arterially driven circuits and can be successfully operated with a wider variety of filters, such as those used for standard pump-driven hemodialysis.

Biocompatibility

Filters offered for use with CRRT circuits are considered biocompatible, but biocompatibility may be relative—and polyacrylonitrile (PAN) is considered biocompatible in regard to complement activation but can inhibit kinin catabolism [resulting in severe anaphylactic-like reactions in patients taking angiotensin-converting enzyme (ACE) inhibitors].

Tubing

Because resistance increases linearly with the length of the component, shortening the blood tubing provides a relatively simple way of decreasing system resistance. This is only a significant issue in the arterially driven circuits, and is relatively irrelevant in a pumped system.

Replacement Fluid

Considering that the fluid infused with hemofiltration-based CRRT systems can result in the quasi-replacement of the patient's salt and water content (2–3 L per hour = 48 to 72 L/day), solutions should be formulated to provide a near-normal electrolyte mix. Several manufacturers have offered prefabricated fluid in large-volume bags to limit the need for frequent bag replacement. These prefabricated solutions are available in a variety of formulations that give the clinician a choice of buffer and potassium content. If filtration rates are high, magnesium and phosphorus must be monitored and replaced accordingly.

For more modest replacement protocols and for rapid bedside preparation, a near-normal electrolyte balance can be attained by alternating two different solutions: 1 L of normal saline (to which is added two 10 mL ampules of calcium gluconate) and 1 L of half-normal saline, to which is added 50 mEq of sodium bicarbonate (Table 33.2). Three to 4 mEq/L of potassium can be added to each liter to maintain normokalemia. Ringer's lactate offers a readily

Table 33–2

Bedside Preparation of Replacement Fluid Used in Continuous Arteriovenous Hemofiltration

	Solution 1[a]	Solution 2[b]	Combined Concentration[c]
Sodium	154	127	140.5
Chloride	154	77	115.5
Calcium	8	—	4
Bicarbonate	—	50	25
Gluconate	8	—	4

a. Solution 1 is composed of 1 L of normal saline and 2 ampules of (10%) calcium gluconate.
b. Solution 2 is composed of 1 L of half-normal saline and 50 mEq of sodium bicarbonate.
c. There may be small differences in the combined concentrations of both solutions due to dilution with additives (bicarbonate, calcium, etc.).
Note: Requirements for calcium replacement may vary due to concomitant administration of calcium via alternative means (i.e., enteral or parenteral nutrition). Minimum ongoing filtrate/dialysate losses of calcium will be in the range of 1 to 3 mEq/L (0.5–1.5 mmol/L). Daily monitoring of ionized calcium levels is recommended.
Modified from Kaplan AA, Longnecker RE, Folkert VW. Continuous arteriovenous hemofiltration: A report of six months' experience. Ann Intern Med 1984;100:358–67.

available solution, but hepatic conversion of lactate to bicarbonate may be hampered under conditions of severe hemodynamic compromise or liver failure.

Of note is that all dextrose-containing solutions can result in a massive infusion of calories, which is only partially offset by the glucose concentration of the filtration fluid. Adequate assessment of the infusion and removal of these calories is necessary to fully account for the nutritional consequence of the treatment (see material following on protein and amino acid losses).

Dialysate

CRRT techniques based on diffusion (CAVHD, CVVHD, CVVHDF) require a dialysate. The same solutions used for hemofiltration replacement can be used as a dialysate. Infusion rates of 1 to 2 L per hour are commonly employed. Some clinicians use standard peritoneal dialysis solution, but the dextrose content can result in a substantial amount of infused glucose. The addition of 3 to 4 mEq of potassium per liter may be necessary to avoid hypokalemia.

Anticoagulation

At present, there is a considerable choice of anticoagulant strategies that have been applied to the continuous therapies (Table 33.3). An ideal anticoagulant regimen provides at least 1 to 2 days of adequate filter patency, minimal systemic effect, easy monitoring, a means of rapid reversibility, and minimal secondary effects.

Clinical Management

Nitrogen Balance and Treatment Prescription

Early studies regarding the prophylactic initiation of dialytic therapy suggested that initiating dialysis when blood urea nitrogen (BUN) is between 90 and 100 mg/dL improves survival in acute renal failure. More recent data would support initiating therapy at even lower levels (<70 mg/dL). Once initiated, enhanced urea clearance may also improve survival. In one study, hemofiltration rates of >35 mL/kg/hour were associated with improved outcome compared with rates of 20/mL/kg/hour. However, a follow-up study could not confirm these results. Table 33.4 lists the urea clearance capabilities of the available renal replacement tech-

Table 33–3

Anticoagulation for the Continuous Therapies

Method	Loading Dose	Maintenance Dose	Comments
Saline flush			Least hemorrhagic risk; short filter patency; most successful with low platelets, short tubing, and predilution
Heparin	1000–2000 U heparin	5–10 U/kg/h	Standard technique; easy Reversibility with protamine; risk of thrombocytopenia
Regional	1000–2000 U heparin Heparinization protamine at 5-20 mg/h	5–20 U/kg/h	Reduced risk of bleeding, variable requirements for protamine; frequent readjustments of heparin/ protamine ratio
LMW heparin	40 mg	10–40 mg/h	Decreased risk of bleeding; prolonged half-life; incomplete reversal with protamine; specialize monitoring
Regional citrate	100–180 ml/h 4% trisodium citrate		Decreased risk of bleeding, excellent filter patency; most protocols require diffusive component to system (CAVHD, CVVHD); extensive monitoring required
Prostacyclin	4–8 ng/kg/min Heparin at 2–4 U/kg		Excellent filter patency; often used with heparin; difficult to monitor; risk of hypotension; prolonged action; no reversibility

Modified from Kaplan AA. Continuous arteriovenous hemofiltration and related therapies. In C Jacobs, CM Kjellstrand, KM Koch, JF Winchester (eds.), *Replacement of Renal Function by Dialysis, Fourth Edition*. Dordrecht, The Netherlands: Kluwer Academic Press 1996:390–417.

Table 33–4

Time-Averaged Urea Clearance for Renal Replacement Therapies

Urea Clearance Technique	Prescription	(mL/min)	L/d	L/wk
Hemodialysis[a]	3 × 4 h/wk	17.9	25.7	180
	7 × 4 h/wk	41.7	60	420
Peritoneal dialysis	2 L/h	16.7	24	168
CAVH	14 L/h	6.9	10	70
CAVHD[b]	1–2 L/h[c]	19–35	27–51	189–357
CVVH	1–3 L/h	17–50	24–72	168–504
CVVHD[c]	1–3 L/h[c]	19–53	27–77	189–536

a. Assumes urea clearance of 250 mL/min.
b. Assumes 3 L/d net filtrate.
c. Infused dialysate.
Modified and updated from Kaplan AA. Extracorporeal blood purification in the treatment of acute renal failure with multi-organ involvement. Blood Purif 1996;14:86–93.

niques. Remember that the values listed are those achievable under ideal conditions.

Nutrition

The impressive fluid removal capabilities of the continuous therapies allow for voluminous nutritional support without the fluid balance oscillations inherent to the intermittent techniques. If dextrose-containing solutions are employed, the continuous techniques can also provide significant caloric infusion as a result of the replacement fluid or dialysate. Nonetheless, the glucose content of the filtration fluid or spent dialysate must also be accounted for. In contrast, replacement fluid or dialysate does not normally contain amino acids—and the loss of these nutrients is directly related to the net solute clearance provided by a given therapy. In general, amino acid losses will be approximately 250 to 500 mg/L of filtrate or dialysate (a considerable amount when using rates of 2 to 3 L/hour).

Drug Clearances

An increasing number of medications have been studied concerning their drug kinetics during CRRT. For those medications

that have not undergone this type of analysis, there are four major factors that must be considered: molecular weight, the degree of protein binding, the drug's volume of distribution, and the drug's endogenous clearance. Aside from these factors, the clinician must consider the efficiency of the system being employed.

If a drug is removable by a continuous filtration technique, the net clearance provided must be ascertained. Clearly, the amount of a filterable drug removed by 10 L of filtrate from a CAVH circuit is not equal to the amount removed by 50 L of filtrate provided by CVVH. The great inter-patient variability in drug metabolism renders periodically obtained blood levels invaluable when dealing with medications of narrow therapeutic index.

Complications

Complications seen with the continuous therapies can be subdivided into three major categories: technique related, circuit related, and access related. Of those related directly to the technique, anticoagulation-associated hemorrhage is the most common. Patients treated with these techniques are also those most likely to develop endogenous coagulopathies. Hypotension can result if large filtrate outputs are not properly matched with sufficient replacement fluid. Improper fluid balance can also occur as a result of inaccurate monitoring or as a result of minor, but repeated, inaccuracies in the measurements of the collection apparatus. An apparently minor 5% error in the accuracy of the output measurement can easily translate into a 2- to 3-L error in daily balance.

Hyponatremia has been reported as a result of combining hyponatric dialysate (132 mEq/L) and a hyponatric parenteral nutrition. Large volumes of dextrose-containing replacement fluid or dialysate may lead to hyperglycemia requiring supplemental insulin. Hyperlactemia or metabolic acidosis may result if the patient cannot properly metabolize large amounts of lactate or acetate.

When large volumes are exchanged rapidly (1–3 L/hour), there is a risk of systemic hypothermia—and gentle warming of the solutions is advisable. Continued removal without adequate supplementation may result in hypokalemia, hypocalcemia, hypophosphatemia, or hypomagnesemia—especially when the patient is maintained with parenteral nutrition devoid of these electrolytes.

Accidental disconnection from the hemoaccess or filter and filter blood leaks are less likely now that component improve-

ments have been made. Air embolism is always a risk when employing a blood pump. As with any pumped system, a bubble detector is an absolute requirement.

Percutaneous cannulation of the femoral vessels presents the possibility of local or retroperitoneal hemorrhage, arteriovenous fistula, and nerve damage. Prolonged vessel cannulation can lead to thrombosis, cellulitis, sepsis, and embolization—including pulmonary embolus. Arterial cannulation presents the possibility of ischemia and necrosis of sites distal to the access. Quinton-Scribner shunts can result in repeated clotting, infection, and distal ischemia.

Special Indications

Neonates/Pediatric Patients

Abdominal surgeries, abdominal wall malformations, and peritoneal infections may render peritoneal dialysis impossible. CRRT is an alternative therapy that can provide continuous fluid and electrolyte management, with filtration rates as low as 40 mL/hour. An ultrasmall minifilter can operate with minimal blood flows.

Multiple Organ Failure and Cytokine Removal

Several investigators have attempted to demonstrate the possible advantages of the continuous therapies in the removal of inflammatory mediators. The most convincing data was produced with high-volume hemofiltration (50–100 L/day) and frequent filter changes (twice daily) to maintain an efficient amount of filter adsorption. This aggressive protocol did result in the lowering of serum levels of cytokines, but the associated receptor antagonists were also removed such that the net affect on the patient's physiology remains in doubt. Thus, despite the fact that inflammatory mediators can be found in the filtrate or dialysate of CRRT systems it remains to be demonstrated that this removal results in a clinically useful improvement in the inflammatory response.

Nonrenal Uses for CRRT

The well-tolerated fluid removal capabilities of the continuous therapies have prompted their use in the management of patients with congestive heart failure who are resistant to conventional therapy. Using continuous hemofiltration, anecdotal and preliminary reports document the salutary hemodynamic effects of slow continuous fluid removal, demonstrating improvement in cardiac

index and a decrease in peripheral resistance. Fluid removal sessions on a biweekly or monthly schedule have been used as a "bridge" to cardiac transplantation.

Hepatic Failure

In a treatment trial of patients with fulminant hepatic failure, those receiving CAVH had a more stable course with a decrease in intracranial pressure. In another study, CVVH was capable of removing middle-molecular-weight toxins and improving the level of consciousness.

Intoxications

CRRT can be useful in the treatment of intoxications by drugs with a tendency to "rebound" when removed by more rapid intermittent techniques. N-acetyl procainamide and lithium toxicity can be successfully treated with CRRT.

Lactic Acidosis

Because continuous therapies allow for the massive infusion of bicarbonate without the risk of hypernatremia or fluid overload, these techniques can be used for the management of lactic acidosis.

Continuous Therapies Versus Conventional Dialytic Techniques

Several studies have attempted to compare the survival of patients treated with the continuous therapies with the survival of patients

Table 33–5

Mortality Studies Comparing CRRT to IHD

Authors	Year	Prospective	Survival Rate (%)	
			CRRT	*IHD*
Bartlett et al.	1986	Yes	28	12 ns
Bellomo et al.	1992	No	41	30 ns
Kruczynski et al.	1993	No	75	18[a]
van Bommel et al.	1995	No	43	59 ns
Swartz et al.	1999	No	—[b]	—
Mehta et al.	2001	Yes	40	58 ns
Augustine et al.	2004	Yes	33	30 ns

a. $p < 0.05$, but patients receiving CAVH had a lower mean age (45 versus 61).
b. Odds of death with CRRT were 2.03 without correction for comorbid factors ($P < 0.05$) and 1.09 with correction (P = NS).

treated with conventional dialytic techniques (Table 33.5). Despite substantial effort, the sum of these studies provides no conclusive evidence to support the contention that the continuous therapies provide an improved outcome for patients with acute renal failure. It is perhaps more useful to consider the advantages the continuous therapies offer in terms of a smooth and well-tolerated means of fluid removal, the ability to provide substantial nutritional support, and the continuous maintenance of acid-base and electrolyte homeostasis.

Recommended Reading

Kaplan AA. Continuous renal replacement therapies in the intensive care unit. J Inten Care Med 1998;13:85–105.

In-depth review of CRRT techniques. Extensively referenced.

Palevsky PM. Dialysis modality and dosing strategy in acute renal failure. Seminars in Dialysis 2006;19:165.

Evdence-based recommendations regarding dosing guidelines, initiation of therapy, and choice of renal replacement therapy in patients with acute renal failure.

Tolwani AJ, Prendergast MB, Speer RR, et al. A practical citrate anticoagulation continuous venovenous protocol for metabolic control and high solute clearance. Clin J Am Soc Nephrol 2006;1:79–87.

Exhaustive review of the available protocols for citrate anticoagulation in CRRT.

CHAPTER 34

The Allient Sorbent Hemodialysis System

Warren B. Shapiro, MD

The Allient Sorbent Hemodialysis system—manufactured by Renal Solutions, Inc. (Warrendale, P.A.)—is the only truly transportable hemodialysis machine available today and to date the only FDA-approved use of sorbents for the treatment of renal failure. Unlike other hemodialysis machines, the Allient system can be brought to the patient in any location. Because spent dialysate is purified by a sorbent cartridge (see material following) and recirculated rather than discarded, a connected water supply and drainage are not needed and only a small volume of dialysate is necessary—allowing for a readily transportable unit. Should the water for the preparation of dialysate be impure, the dialysate is purified by first passing it through the sorbent cartridge before the treatment begins.

The Allient system consists of two components: a dialysis machine and a sorbent cartridge (Figure 34.1). The dialysis machine has a disposable dialysate reservoir, a dialysate pump that pumps the spent dialysate through the sorbent cartridge (200–400 mL/minute), and an infusate pump for returning an infusate consisting of calcium, magnesium, and potassium salts to the dialysate to replace the ions removed by the sorbent cartridge. The blood pump is a pressure-regulated two-chamber system (the chambers are separated by a flexible diaphragm) in which blood—propelled by alternating positive and negative pressure—flows through the chambers.

This system allows for the use of single- or double-needle (or catheter) vascular access. The blood flow is directly measured by two ultrasonic flow monitors. In addition, the machine contains alarms to warn of abnormalities in dialysate and infusate flow, dialysate volume, temperature, and pressure. It also incorporates a blood leak detector and ammonium detector. Because the dialysate is recirculated, any ultrafiltrate removed from the patient will remain within the dialysate reservoir and thus can be measured as an increase in dialysate volume or weight. The sorbent cartridge is the heart of the Allient system (Figure 34.2). The cartridge consists of four layers through which the used dialysate passes.

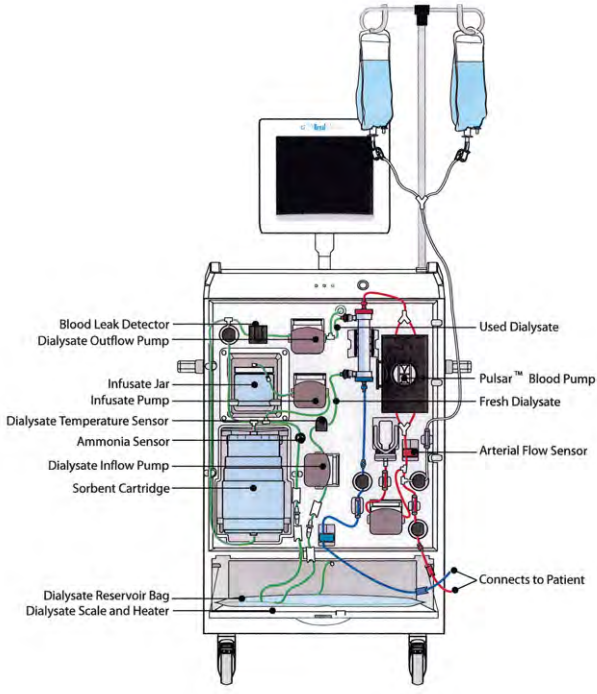


Figure 34–1

Components of the Allient Hemodialysis Sorbent system.

- Activated carbon (adsorbent layer)
- An enzyme layer (urease)
- A cation exchanger [zirconium phosphate (ZP)]
- An anion exchanger layer [hydrated zirconium oxide (ZO) and zirconium carbonate (ZC)]

The dialysate first passes though the activated carbon layer, which removes traces of heavy metals, chlorine, chloramine, and hypochlorite—as well as creatinine, uric acid, and other organics able to cross the dialysis membrane. Glucose is adsorbed, but quickly saturates the activated carbon—after which equilibrium

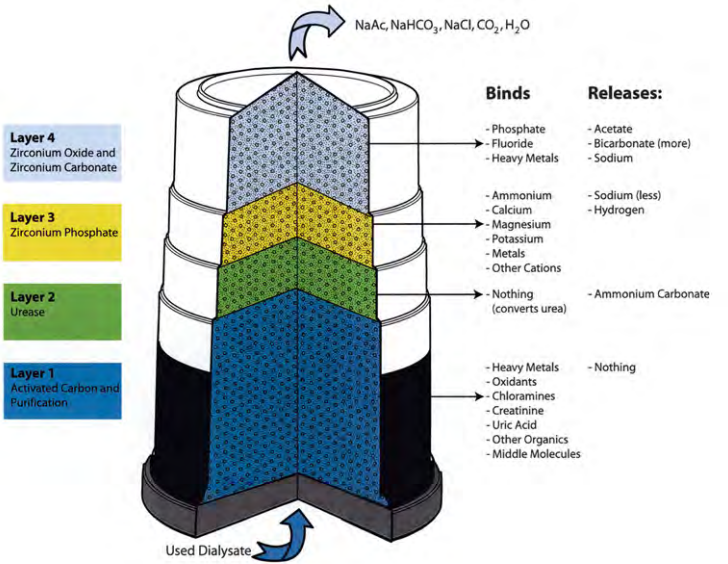


Figure 34–2

The sorbent cartridge and its functions.

is established across the dialyzer among carbon, dialysate, and plasma glucose.

Spent dialysate next contacts the urease layer, where urea is converted by the urease into ammonium carbonate. The ammonium ion is exchanged in the ZP layer for hydrogen and sodium. The hydrogen combines with carbonate to form bicarbonate and carbonic acid, the latter breaking down into water and carbon dioxide. The release of sodium from the ZP layer results in a steady increase in dialysate sodium throughout treatment. This increase in dialysate sodium is compensated for by sodium-hydrogen exchange in the ZP layer early in the treatment, which results in a lowering of dialysate sodium. Later in the treatment, the ZP layer donates sodium so that the mean dialysate sodium is between 135 and 140 mEq/L. In addition to ammonium ions, ZP also exchanges calcium, magnesium, and potassium for sodium.

In the ZO-ZC layer, other phosphate anions (for example, in the water used to make the initial dialysate) are exchanged for acetate and carbonate (the carbonate becomes bicarbonate). This layer also binds iron, aluminum, lead, and mercury. As noted, the sorbent cartridge removes calcium, magnesium, and potassium from the dialysate and these ions must be replaced. This is accomplished by a continuous infusion of the acetate salts of the previously cited ions into the dialysate reservoir. The composition of the infusate can be varied to treat hyper- or hypokalemia or calcemia. The specifications of the Allient system are provided in Table 34.1. The exact amount of acetate, bicarbonate, and sodium added to the dialysate and eventually to the patient depends on the amount of urea, calcium, magnesium, and potassium exchanged in the cartridge (see material following).

User Guidelines

It is important to remember the both sodium and bicarbonate generation by the cartridge are linked to urea removal. Therefore, if the urea load is low (as with a small patient)—with the BUN less than 50 mg/dL or with a short dialysis time—both hyponatremia and metabolic acidosis may ensue because there is insufficient urea available for the sorbent cartridge to generate both bicarbonate and sodium. These potential problems can be avoided in patients with low urea by adding extra sodium (as sodium chloride or sodium bicarbonate) to the dialysate or intravenously to the patient during the treatment. A therapy calculator

Table 34–1

Parameters of the Allient System

General Parameters
- Dialysate capacity: 6 L at the start
- Dialysate flow rate: 200–400 mL/min
- Blood flow rate: 150–400 mL/min

Urea Removal
- Sorb+ (3–6 h): 9.5–23.5 g
- Hisorb+ (3–6 h): 23.5–35.0 g
- Sorb HD (6–8 h): 12.5–20.0 g
- HiSorb HD (6–8 h): 15.0–30.0 g

Creatinine Removal Minimum Capacity
- Sorb+: 2.8 g
- Hisorb+: 4.0 g
- Sorb HD: 2.7 g
- HiSorb HD: 3.8 g

Phosphorus Removal Minimum Capacity
- Sorb+: 1.9 g
- Hisorb+: 2.8 g
- Sorb HD: 1.5 g
- HiSorb HD: 2.2 g

Uric Acid Removal Minimum Capacity
- Sorb+: 2.0 g
- HiSorb+: 3.0 g
- Sorb HD: 2.0 g
- HiSorb HD: 3.0 g

Sodium Added to the Dialysate During a 4-hour Treatment
The amount of sodium added to the dialysate and thus potentially to the patient is related to the starting dialysate sodium concentration, the patient's total body water, the baseline urea level and, the dialyzer characteristics. The Therapy Calculator (TC) is a computer program designed to assist the physician in prescribing sorbent dialysis so that the recommended dialysate/cartridge combination will result in a postdialysis serum Na within ± 2 mEq/L of the prescribed postdialysis value. Note: during dialysis, serum sodium may vary by as much as ± 5 mEq/L. This should be considered if early termination is contemplated. Clinical trials on normonatremic ESRD patients have validated the TC sodium dynamics thus far.

is available to the clinician (from Renal Solutions) to assist in formulating the dialysis prescription.

The Allient System requires only 6 L of dialysate compared to 120 to 190 L for standard single-pass dialysis (dialysate flow

rate 500–800 mL/minute). Thus, for a 70-kg patient with 42 L of total body water the ratio between dialysate and total body water is 1:7 using the Allient system. This means that an increase in dialysate sodium of 7 mEq/L results in an increase in body water sodium of only 1 mEq/L. This relationship between dialysate and total body water protects the patient from the effects of the large change in dialysate composition that occurs during sorbent dialysis. It also means that to effect a substantial change in plasma electrolytes the dialysate electrolyte composition must be altered by a factor of 7, which may require that the dialysate electrolyte (sodium) concentration be adjusted during a treatment.

In the original sorbent (REDY) cartridge, aluminum oxide (alumina) was used as a space filler in the ZP and HZO layers—and as a binder for urease—because it was thought that alumina was nontoxic. Subsequent studies showed that when this original sorbent cartridge (no longer manufactured) was used with bicarbonate dialysate the aluminum was rendered soluble, resulting in elevated dialysate and eventually plasma aluminum levels in chronically treated patients. The manufacturer subsequently removed all of the aluminum from the REDY cartridge with the exception of that used to bind urease.

This modified cartridge has been extensively tested for the release of aluminum, and studies have shown that the cartridge does not release aluminum and that it can actually remove aluminum from the water used to prepare dialysate. Llach et al. showed in vitro and in vivo that the REDY sorbent cartridge could remove aluminum from water in which the level of aluminum is as high as 470 μgm/L as indicated by a post-cartridge aluminum of less than 10 μg/L. In vivo, when the REDY sorbent system was compared to single-pass dialysis it was shown that there was no difference in the pre- and post-treatment plasma aluminum concentrations between the two types of dialysis treatment and that dialysate aluminum remained below 4 μg/L at all times with both treatments. Based on this and other studies, one can infer that the "aluminum problem" can be laid to rest. If the dialysate aluminum is known to be above 30 μg/L due to high water aluminum content, it should be purified by a single-pass flow through the sorbent cartridge prior to use.

It has been reported that the use of citrate as an anticoagulant during sorbent dialysis may lead to a loss of the integrity of the sorbent cartridge, resulting in the release of urease and aluminum. Therefore, the manufacturer warns against its use during sorbent dialysis.

Serum Electrolyte and Acid-Base Adjustments

Adjustment of Serum Sodium

Depending on the patient's pre-dialysis serum sodium level, an adjustment of the initial sodium concentration of the dialysate may be required—which is easily carried out by varying the amount of concentrate used to make the dialysate and/or by adding water or hypertonic saline as needed during treatment. To decrease the serum sodium, water should be added to the dialysate until the desired dialysate sodium (as indicated by conductivity) is reached. Dialysate is removed periodically (500 to 1000 mL at a time) and replaced with water to maintain the desired sodium as indicated by conductivity. To increase the serum sodium, a concentrated solution of sodium chloride (3%) is added to the dialysate until the desired dialysate sodium (conductivity) is reached. Because rapid changes in serum sodium can be dangerous and result in permanent brain damage, both hyper- and hyponatremia should be corrected slowly.

Adjustment of Serum Potassium

By adjusting the infusate to alter the dialysate potassium concentration, serum potassium can be increased or decreased depending on the clinical condition. The dialysate potassium is changed by altering the potassium concentration in the infusate. For the patient with hypokalemia, a dialysate potassium concentration of 3 to 4 mEq/L can be used. For the patient with hyperkalemia, a dialysate potassium of 1 to 2 mEq/L may be necessary to lower serum potassium.

Adjustment of Serum Calcium

Hypo- or hypercalcemia can be corrected by altering the dialysate calcium concentration. Normally, the dialysate calcium is kept at 3.0 mEq/L to maintain the serum calcium level in patients treated with calcium containing phosphorus binders. With the Allient system, dialysate calcium concentration can be altered by changing the calcium content of the infusate.

Treatment of Metabolic Acidosis

Metabolic acidosis can be treated using the Allient system. The sorbent cartridge and infusate add acetate and bicarbonate to

the dialysate and the patient. The amount of bicarbonate added to the dialysate is directly related to the amount of urea nitrogen removed by the cartridge and to a smaller extent to the amount of phosphorus and other anions exchanged in the ZO-ZC layer.

It must be remembered that during dialysis only the plasma bicarbonate is altered. However, changes in the plasma bicarbonate alone may not result in the desired normalization of pH if there is a concomitant respiratory disturbance. In patients with mixed acid-base disturbances, it is imperative to determine the blood gasses at frequent intervals during the dialysis—especially at the point when dialysate and plasma equilibrate (2–3 hours)—to assess the degree of correction obtained.

Potential Uses of the Allient System

Home Hemodialysis

Recently, slow nocturnal hemodialysis has been increasing in popularity as an alternative to rapid thrice-weekly hemodialysis. The Allient system would be ideal for this application due to the fact that no changes to the water and sewage system are necessary and the system can be plugged into any standard outlet. A new line of sorbent cartridges has been specifically developed to enable use at low dialysate flow rates (200–300 mL/minute) for treatment times as long as 8 hours.

Continuous Renal Replacement Therapy

The Allient system can be used in the SLED (slow low-efficiency dialysis) mode, using the cartridges discussed previously, to provide low-flow 6- to 8-hour treatments to unstable acute patients. Once the dialysis nurse sets up and initiates treatment, the patient is monitored by the intensive care unit (ICU) nurse. The Allient automatically terminates treatment and rinses the blood back into the patient at the pre-programmed time. SLED procedures are generally initiated late in the day and terminated in the very early morning hours, to enable the ICU patient to be available for other procedures during the busy daylight hours.

Conclusions

Although there have been many attempts at using sorbents for the treatment of patients with renal failure (and hepatic failure), at present the Allient system is the only commercially available

device for regenerating dialysate. The Allient system offers a unique method of providing hemodialysis in situations where the use of ordinary dialysis machines would be difficult—such as locations where potable water and waste lines may not be available. In addition, the upgraded technology of the Allient system facilitates the treatment of patients with SLED in an ICU setting and possibly patients desiring home treatment. As for any device, the user of the Allient system must be familiar with the chemistry of the sorbents in order to gain the maximum efficiency from the system with the fewest complications.

Recommended Reading

Ash S. The Allient dialysis system. Seminars in Dialysis 2004;17:164–66.
Describes the Allient system in detail and outlines potential uses of the machine.
Hansen S. Advances in sorbent dialysis. Dial Transplant 2005;34:9:648–52.
Reviews sorbent regenerated dialysis and new advances, including the Allient system.
Shapiro WS. Sorbent dialysis. In Nissenson AR, Fine RN (eds.), *Clinical Dialysis*. New York: McGraw-Hill 2005:982–89.
An in-depth review of sorbent dialysis.

CHAPTER 35

Convective Renal Replacement Therapies for Acute Renal Failure and End-Stage Renal Disease

Jeffrey J. Letteri, BS; Claudio Ronco, MD; Zhongping Huang, PhD; Dayong Gao, PhD; and William R. Clark, MD

Introduction

Hemodialysis (HD) remains the primary treatment modality for the management of patients with both acute renal failure (ARF) and end-stage renal disease (ESRD). Although the removal of low-molecular-weight (LMW) nitrogenous waste products is very effective with HD, clearance of larger molecules is limited due to their primarily diffusive nature. In clinical practice, chronic dialysis therapy prescription is driven largely by factors influencing urea clearance. The widespread use of urea-based dosing of chronic HD therapy can be traced to studies from approximately 25 years ago.

These studies, performed with dialyzers having very limited middle-molecule clearance capabilities, suggested that patient survival was more dependent on changes in small-solute clearance than on middle-molecule clearance. Studies over the subsequent 15 years suggested a direct relationship between delivered urea-based HD dose and patient outcome. A similar clinical relationship was suggested by studies involving patients treated with chronic peritoneal dialysis (PD). These studies led to the development of specific urea-based dosing guidelines for both therapies.

However, the general approach of small-solute-based dosing of chronic dialysis has been called into question by recent outcome data. Indeed, both the HEMO Study and the ADEMEX Study failed to confirm a survival benefit for increasing dose delivery in a clinically relevant respective dose ranges for HD and PD. Because these studies suggest that conventional diffusion-based therapies may be limited in their ability to influence outcome, they indicate the need for alternative chronic dialysis approaches—an example of which is convective therapies.

In an analogous manner, a reassessment of the dialytic management of critically ill patients with ARF has also occurred recently. Preliminary research aimed at laying the groundwork for quantifying prescribed and delivered dialysis dose in this setting has been done over the past decade. With this foundation, three recent studies establishing a relationship between delivered treatment dose and outcome with daily HD and convection-based continuous renal replacement therapy (CRRT) have clearly changed clinical practice. In one CRRT study, Ronco and colleagues reported a direct relationship between daily ultrafiltrate volume and survival in critically ill ARF patients treated with postdilution CVVH (continuous veno-venous hemofiltration).

A normalized ultrafiltration rate of 35 mL/kg/hour or more (on average) was associated with a 30-day mortality of approximately 45%, whereas a more standard ultrafiltrate rate (mean, 20 mL/kg/hour) was associated with a 30-day mortality of approximately 65%. Likewise, Saudan et al. reported significantly better outcomes in ARF patients receiving a mean normalized effluent rate of 42 versus 25 mL/kg/hour in CVVHDF (continous veno-venous homodiafiltration) (30-day survival 70 versus 50%, respectively). Moreover, results of several recent studies indicate that relatively early application of convection-based CRRT also improves survival in critically ill patients with ARF and/or septic shock.

These recent findings suggest that the utilization of convective therapies in both ARF and ESRD will increase in the future. This chapter provides a review of convective therapies, with a discussion initially of the determinants of convective solute removal. This is followed by an overview of the manner in which hemofiltration (HF) and hemodiafiltration (HDF) are applied clinically.

Convective Solute Removal

The determinants of convective solute removal differ significantly from those of diffusion, which is primarily a concentration-gradient-driven process. On the other hand, convective solute removal is determined primarily by the sieving properties of the membrane used and the ultrafiltration rate. The mechanism by which convection occurs is termed *solvent drag*. If the molecular dimensions of a solute are such that transmembrane passage to some extent occurs, the solute is swept (“dragged”) across the membrane in association with ultrafiltered plasma water. Thus, the rate of convective solute removal can be modified either by changes in the rate of solvent (plasma water) flow or by changes

in the mean effective pore size of the membrane. As discussed in material following, the blood concentration of a particular solute is an important determinant of its convective removal rate.

Both the water and solute permeability of an ultrafiltration membrane are influenced by the phenomena of secondary membrane formation and concentration polarization. The exposure of an artificial surface to plasma results in the nonspecific instantaneous adsorption of a layer of proteins, the composition of which generally reflects that of the plasma itself. This layer of proteins, by serving as an additional resistance to mass transfer, effectively reduces both the water and solute permeability of an extracorporeal membrane. Evidence of this is found in comparisons of solute sieving coefficients determined before and after exposure of a membrane to plasma or other protein-containing solution.

Although concentration polarization primarily pertains to plasma proteins, it is distinct from secondary membrane formation. Concentration polarization specifically relates to ultrafiltration-based processes and applies to the kinetic behavior of an individual solute. Accumulation of a solute that is predominantly or completely rejected by a membrane used for ultrafiltration of plasma occurs at the blood compartment membrane surface. This surface accumulation causes the solute concentration just adjacent to the membrane surface (i.e., the submembranous concentration) to be higher than the bulk (plasma) concentration. By definition, concentration polarization is applicable in clinical situations in which relatively high ultrafiltration rates are used. Conditions that promote the process are high ultrafiltration rate (high rate of convective transport), low blood flow rate (low shear rate or membrane "sweeping" effect), and the use of postdilution (rather than pre-dilution) replacement fluids (increased local solute concentrations).

Convective Renal Replacement Therapies: Dilution Point Considerations

Postdilution Hemofiltration

The location of replacement fluid delivery in the extracorporeal circuit during HF has a significant impact on solute removal and therapy requirements. Replacement fluid can be delivered to the arterial blood line prior to the hemofilter (pre-dilution mode) or to the venous line after the hemofilter (postdilution mode). In postdilution HF, the relationship between solute clearance and

ultrafiltration rate is relatively straightforward. In this situation, solute clearance is determined primarily by and related directly to the solute's sieving coefficient and the ultrafiltration rate. (Sieving coefficient is defined as the ratio of the solute concentration in the filtrate to the simultaneous plasma concentration.)

For a given solute, the extent to which it partitions from the plasma water into the red blood cell mass and the rate at which it is transported across red blood cell membranes also influence clearance. For example, the volume of distribution of both urea and creatinine includes the red blood cell water. However, whereas urea movement across red blood cell membranes is very fast the movement of creatinine is significantly less rapid. Furthermore, red blood cell membranes are completely impermeable to many uremic toxins. A prominent example of this is the LMW protein toxin class, for which the volume of distribution is the extracellular fluid. These observations lead to the obvious conclusion that hematocrit also influences solute clearance in HF. Finally, through its effect on secondary membrane formation and concentration polarization (see previous discussion) plasma total protein concentration is also a determinant of solute clearance in HF.

For a given volume of replacement fluid over the entire molecular weight (MW) spectrum of uremic toxins, postdilution HF provides higher solute clearance than does pre-dilution HF. As discussed in material following, the relative inefficiency of the latter mode is related to the dilution-related reduction in solute concentrations—which decreases the driving force for convective mass transfer. Despite its superior efficiency with respect to replacement fluid utilization, postdilution HF is limited inherently by the attainable blood flow rate. More specifically, the ratio of the ultrafiltration rate to the plasma flow rate delivered to the filter (termed the *filtration fraction*) is the limiting factor. In general, a maximal filtration fraction of approximately 25 and 50% usually guides prescription in postdilution HF in the acute and chronic realms, respectively. At filtration fractions beyond these values, concentration polarization and secondary membrane effects become prominent and may impair hemofilter performance.

In chronic HF, the technology of online production by sequential ultrafiltration of dialysate provides essentially unlimited volumes of replacement fluid to be used. This ready availability of replacement fluid and the resultant capability to employ ultrafiltration rates as high as 400 mL/minute permits attainment of clearances in pre-dilution that far surpass the filtration fraction-

limited maximal clearances in postdilution HF. Thus, as discussed in material following, the predominant mode used in contemporary chronic HF is pre-dilution.

For acute HF (usually delivered continuously as CVVH), the blood flow limitations imposed by the use of temporary cathethers accentuates the filtration fraction-related constraints on maximally attainable ultrafiltration rate in the postdilution mode. Therefore, the ultrafiltrate volumes shown by Ronco and colleagues to improve survival can usually be achieved only in the pre-dilution mode. This is the case even though an essentially unlimited supply of replacement fluid is not usually available, as the source is typically from bags rather than an online generation system in acute HF. Thus, as discussed in material following, efficient utilization of replacement fluid in acute pre-dilution HF is an important consideration.

Pre-dilution Hemofiltration

From a mass transfer perspective, the use of pre-dilution has several potential advantages over postdilution. First, both hematocrit and blood total protein concentration are reduced significantly prior to the entry of blood into the hemofilter. This effective reduction in the red cell and protein content of the blood attenuates the secondary membrane and concentration polarization phenomena described previously, resulting in improved mass transfer. Pre-dilution also favorably impacts mass transfer due to augmented flow in the blood compartment, because prefilter mixing of blood and replacement fluid occurs. This achieves a relatively high membrane shear rate, which also reduces solute-membrane interactions. Finally, pre-dilution may also enhance mass transfer for some compounds by creating concentration gradients that induce solute movement out of red blood cells.

The previoulsy cited mass transfer benefits must be weighed against the predictable dilution-induced reduction in plasma solute concentrations, one of the driving forces for convective solute removal. The extent to which this reduction occurs is determined mainly by the ratio of the replacement fluid rate to the blood flow rate, which may be as high as unity in contemporary chronic online HF. However, the ultrafiltration rate afforded by such a high replacement fluid rate allows the dilution-related loss of efficiency to be overcome.

A frequently overlooked consideration is the important influence of blood flow rate on solute clearance, particularly in

acute HF. For small solutes, which are distributed in the blood water (BW) component within the blood passing through the hemofilter, the operative clearance equation in pre-dilution HF is:

$$K = Q_F \times S \times [Q_{BW} / (Q_{BW} + Q_S)], \quad (35.1)$$

where K is solute clearance, Q_{BW} is blood water flow rate, Q_F is ultrafiltration rate, S is the sieving coefficient, and Q_S is the substitution (replacement) fluid rate. At a given Q_F value, pre-dilution CVVH is always less efficient than postdilution CVVH with respect to fluid utilization (as discussed previously). A sieving coefficient of 1.0 implies equivalence of blood water and ultrafiltrate concentrations, resulting in small-solute clearances effectively equal to Q_F in postdilution CVVH. As Equation 35.1 indicates, the larger Q_S is relative to Q_{BW} the smaller is the entire fraction represented by the third term on the right-hand side. In turn, the smaller is this term the greater is the loss of efficiency (relative to postdilution) due to dilution.

Because employing a relatively low Q_S is not an option in high-dose CVVH due to the direct relationship that exists between Q_F and Q_S, attention needs to be focused on achieving blood flow rates that are significantly higher than those used traditionally in CRRT (i.e., 150 mL/minute or less). In fact, widespread attainment of doses consistent with the intermediate and high-dose arms in the study performed by Ronco and colleagues (35–45 mL/hour/kg) cannot occur unless blood flow rates of approximately 250 mL/minute or greater become routine in pre-dilution CVVH.

Evidence supporting the critical importance of Q_B in pre-dilution CVVH appears in Figure 35.1. For this single-pool modeling analysis, a dose equivalent to 35 mL/hour/kg in postdilution is targeted. In addition, a filter operation of 20 hours per day is assumed to account for differences in prescribed versus delivered therapy time. For patients of varying body weight, the substitution fluid requirements to attain this dose are shown as a function of Q_B. For low blood flow rates (=150 mL/minute), these data suggest that substitution fluid rates required to achieve this dose are impractically high in the majority of patients (>70 kg) due to a "chasing-the-tail" phenomenon.

To achieve the dose target, a high ultrafiltration rate is required. However, the concomitant requirement of a similarly high substitution fluid rate has a relatively substantial dilutive effect on solute concentrations at low Q_B. On the other hand, for Q_B values greater than 250 mL/minute the dilutive effect of the substitution

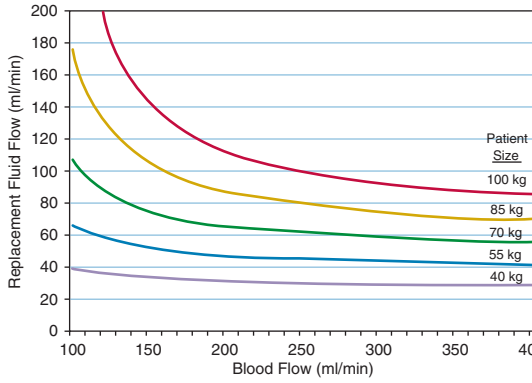


Figure 35–1

Substitution fluid requirements as a function of blood flow rate in pre-dilution CVVH. *(Reprinted with permission from Clark WR, Turk JE, Kraus MA, Gao D. Dose determinants in continuous renal replacement therapy. Artif Organs 2003;27:815–20.)*

fluid is attenuated significantly. With the resultant improvement in fluid efficiency, the target dose can be delivered practically to a broad range of patients.

Hemodiafiltration

Although considerable enthusiasm for chronic HF existed in the late 1970s and early 1980s, its popularity waned subsequently for several reasons. As online technology was not available at the advent of chronic HF, replacement fluid volumes were limited to approximately 20 L or less per treatment and the postdilution mode was employed. Nevertheless, urea clearances obtained with such volumes were substantially less than those achieved with HD. The increasing focus on urea-based quantification of dialysis therapy in the 1980s only served to accentuate the relatively low urea clearances in HF.

A solution to this problem was reported in 1978 by Leber et al., who described a system employing simultaneous HF and HD with a polyacrylonitrile (RP6) dialyzer. The operating parameters included a blood flow rate of 200 mL/minute, a dialysate flow rate range of 200 to 900 mL/minute, and an ultrafiltration rate

range of approximately 40 to 60 mL/minute. The replacement fluid was lactate based and administered postfilter from bags, whereas the dialysate was acetate based. Relative to pure HF at an ultrafiltration rate of 55 to 60 mL/minute, diffusive removal provided by a dialysate flow rate of 900 mL/minute increased urea and creatinine clearance approximately threefold.

As was the case for HF, the introduction of online technology broadened significantly the capabilities of HDF. As HDF therapy has evolved, ultrafiltration rates and exchange volumes have increased and are now approximately 100 mL/minute and 20 to 25 L/session, respectively. However, the general approach of using ultrafiltration to generate ultrapure dialysate and replacement fluid sequentially (a process termed *cold sterilization*) remains intact. In chronic online HDF, solute clearances are typically higher when replacement fluid is delivered postfilter. However, the progressive rise in hematocrits over the past few years imposes filtration fraction-related restrictions with this mode in some patients. Consequently, HDF devices with the capability of delivering replacement fluid both prefilter and postfilter have been developed recently. Use of the "mixed mode" avoids high transmembrane pressures, which are typically associated with high filtration fraction and membrane fouling (*vide infra*).

The same principle of augmenting total clearance by combining diffusion and convection applies to acute HDF. However, due to the different flow rate regimes used the effect of this combination on the total removal of a specific solute differs between acute and chronic HDF. In chronic HDF, diffusion and convection "interact" in such a manner that total solute removal is significantly less than that expected if the individual components are simply combined. This phenomenon is explained in the following way. Diffusive removal results in a decrease in solute concentration in the blood compartment along the axial length (i.e., from blood inlet to blood outlet) of the hemodialyzer/hemofilter. As convective solute removal is directly proportional to the blood compartment concentration, convective solute removal decreases as a function of this axial concentration gradient.

On the other hand, hemoconcentration resulting from ultrafiltration of plasma water causes a progressive increase in plasma protein concentration and hematocrit along the axial length of the filter. This hemoconcentration and resultant hyperviscosity causes an increase in diffusive mass transfer resistance and a decrease in solute transport by this mechanism. Moreover, convective solute removal also lowers blood compartment solute

concentrations—thus reducing diffusive transmembrane concentration gradients. The effect of this interaction on overall solute removal in conventional HD and chronic HDF has been analyzed rigorously by numerous investigators. The most useful quantification is:

$$Kt = Kd + Qf \times Tr. \quad (35.2)$$

In this equation, Kt is total solute clearance, Kd is diffusive clearance under conditions of no ultrafiltration, and the final term is the convective component of clearance. The latter term is a function of the ultrafiltration rate (Qf) and an experimentally derived transmittance coefficient (Tr), such that

$$Tr = S\,(1 - Kd/Qb), \quad (35.3)$$

where S is solute sieving coefficient. Thus, Tr for a particular solute is dependent on the efficiency of diffusive removal. At very low values of Kd/Qb, diffusion has a very small impact on blood compartment concentrations and the convective component of clearance closely approximates the quantity S×Qf. However, with increasing efficiency of diffusive removal (i.e., increasing Kd/Qb), blood compartment concentrations are significantly influenced. The result is a decrease in Tr, and consequently a decrease in the convective contribution to total clearance.

A schematic representation of these considerations appears in Figure 35.2. In this diagram, the effect of an increasing ultrafiltration rate on the diffusive, convective, and total clearance of solutes with varying molecular weight is demonstrated. For urea, relative to the baseline of zero net ultrafiltration an increase in ultrafiltration rate to 100 mL/minute has a marginal effect on total clearance. As the figure demonstrates, diffusive clearance actually decreases (for the reasons described previously). On the other hand, the net effect on total clearance of vitamin B_{12} and inulin (having molecular weights of approximately 1300 and 5200, respectively) is significantly larger. This is consistent with the tenet that in contradistinction to diffusion the relative impact of convective solute removal increases with solute molecular weight. However, it is important to note that the incremental gain in convective clearance with increasing ultrafiltration rate is not on a one-to-one mL/minute basis.

The situation is much different for the acute continuous therapies employing both diffusion and convection. Due to the relatively low flow rates used for these therapies, changes in solute concentrations within the filter are also relatively small. This allows total solute clearance to be estimated by simply adding the diffusive

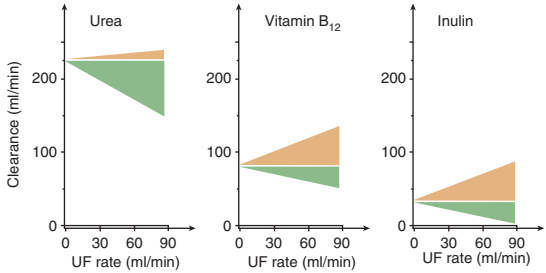


Figure 35–2

Effect of increasing ultrafiltration on diffusive, convective, and total clearance of solutes with varying molecular weight. *(Reprinted with permission from Ledebo I. Principles and practice of hemofiltration and hemodiafiltration. Artif Organs 1998;22:20–25.)*

and convective components. In other words, no interaction between the two mass transfer processes occurs.

Convective Renal Replacement Therapies: Practical Considerations and New Trends

Chronic Therapies

The early clinical application of HF for ESRD in the late 1970s and early 1980s was constrained by the general lack of availability of online generation systems for replacement fluid. Although the technique of cold sterilization was developed by Henderson and colleagues in the early 1970s, commercially viable online fluid production systems were not available for clinical use until almost a decade later. In the interim, replacement fluids for chronic HF were delivered from bags of fluid sterilized by the usual technique of terminal sterilization. However, the necessity of providing replacement fluid in this manner was a practical limitation for total treatment volume exchanges. Furthermore, this limitation mandated the use of the postdilution mode so as to allow the attainment of maximal small clearances for a given exchange volume. At the same time, based primarily on the results of the National Cooperative Dialysis Study (NCDS), clinicians increasingly became convinced of the

importance of small-solute clearance in chronic uremia. In this context, the popularity of chronic HF waned in the early to mid 1980s.

Once online fluid generation systems became available as part of standard HD machines, the conundrum of inadequate solute clearance by convective modalities was essentially solved. As noted previously, one advancement allowing this was online HDF. However, the essentially unlimited availability of replacement fluid permitted the use of ultrafiltration rates that could also attain clinically acceptable small-solute clearances in pure pre-dilution HF.

In an elegant review, Ledebo very clearly demonstrated the manner in which this can be achieved clinically in pre-dilution HF and careful study of her analysis (Table 35.1) is very instructive. First, the inability of postdilution HF to achieve adequate solute clearance is clearly demonstrated. Because of filtration fraction constraints, replacement fluid volume is generally limited to about 30% of blood flow rate in postdilution HF. (Based on an assumed hematocrit of 32%, this corresponds to a maximum filtration fraction of approximately 44%.) For a "standard"-size patient with a urea distribution volume of 40 L, the table clearly shows the degree to which urea Kt/V falls short of currently accepted guidelines.

Table 35–1

Representative Treatment Parameters in Online Hemofiltration

	Postdilution HF		Pre-dilution HF	
Blood flow rate (mL/min)	300	400	300	400
UF rate (mL/min)	90	120	300	400
Infusion rate (mL/min)	80	110	290	390
Weight loss (mL/min)	10	10	10	10
Urea clearance, K (mL/min)	90	120	150	200
For t = 4 h:				
UF volume (L)	21.6	28.8	72.0	96.0
Infusion volume (L)	19.2	26.4	69.6	93.6
Weight loss (L)	2.4	2.4	2.4	2.4
Total urea clearance K×t (L)	21.6	28.8	36.0	48.0
For V = 40 L: Kt/V	0.54	0.72	0.90	1.20

Reprinted with permission from Ledebo I. Principles and practice of hemofiltration and hemodiafiltration. Artif Organs 1998;22:20–25.

On the other hand, clinically acceptable urea Kt/V values can be achieved with pre-dilution HF by taking full advantage of the large replacement fluid volumes capable of being delivered by an online system. Because the replacement fluid rate is essentially matched to the blood flow rate, an increase in blood flow rate provides a higher replacement fluid volume and therefore a higher urea Kt/V. Note that to achieve a urea Kt/V of 1.2 in a "standard"-size patient over a 4-hour treatment a blood flow rate of 400 mL/minute is required. Therefore, for a given treatment time the same Kt/V target in a larger patient or a higher Kt/V target requires a higher blood flow rate.

Whereas chronic HF is now exclusively performed in the pre-dilution mode, replacement fluids in chronic HDF have typically been delivered postfilter to achieve maximal small-solute clearance. However, in some patients with relatively high hematocrits high filtration fractions and transmembrane pressures may limit therapy efficacy in postdilution HDF. For a patient with a hematocrit of 35%, a typical 24-L replacement fluid exchange volume results in an acceptable filtration fraction of approximately 38% if a blood flow rate of 400 mL/minute can be obtained. However, at a blood flow rate of 300 mL/minute the filtration fraction is greater than 50%—likely resulting in high transmembrane pressures and potentially impaired filter performance.

For this and other clinical scenarios, online HDF systems now have the capability of delivering simultaneous prefilter and postfilter replacement fluids. In a study performed by Pedrini and colleagues, a filter was first operated at a certain maximum TMP in postdilution mode. This resulted in a specific ultrafiltration rate in postdilution for a given patient, and clearances were obtained at this ultrafiltration rate. In mixed and pre-dilution modes, the same ultrafiltration rate was used and TMP and clearances were measured. No solute clearance was significantly different in the postdilution and mixed-dilution modes. However, small-solute clearances (urea and creatinine) were significantly lower in pre-dilution compared to both mixed mode and postdilution.

On the other hand, phosphate and B2M (β-2 micro-globulin) clearances did not differ significantly among the three modes. The results demonstrate certain clearance benefits for mixed dilution over pre-dilution and suggest comparability between postdilution and mixed dilution. Moreover, as a function of treatment time TMP in mixed dilution remained constant (at approximately 200 mmHg).

On the other hand, TMP progressively increased in postdilution—reaching a value greater than 400 mmHg by 180 minutes.

Continuous Therapies for Acute Renal Failure

At least until recently, the ultrafiltration rate (Q_f) in CVVH has typically been in the 1- to 2-L/hour range. However, in response to recent outcome data published by Ronco and colleagues prescription of significantly higher Q_f values is occurring. In postdilution HF, the mode employed in the Ronco study, the relationship between solute clearance and Q_f is quite straightforward. In this situation, solute clearance is determined primarily by and related directly to the solute's sieving coefficient (SC) and the Q_f. For reasons described previously, the relationship between clearance and Q_f may not be as predictable in pre-dilution relative to the case of postdilution. Consequently, the claim that Q_f is a dose surrogate in pre-dilution HF needs to be demonstrated.

To this end, Huang and colleagues have investigated the effect of Q_f on solute removal parameters in pre-dilution CVVH for a blood flow rate of 200 mL/minute and removal parameters at Q_f values of 20, 40, and 60 mL/minute (corresponding respectively to 17, 34, and 51 mL/hour/kg) for a 70-kg patient. These parameters are measured for solutes of varying MW. The relationship between solute clearance and Q_f for urea, creatinine, vancomycin, and inulin appears in Figure 35.3. Overall, these data are consistent with a convective therapy for two reasons. First, for each solute the clearance/Q_f relationship is linear—confirming a direct relationship between these two parameters. Second, for a given Q_f over the solute MW range investigated clearance is not strongly dependent on MW—at least in comparison to HD. Specifically, very little difference in clearance is observed between the two small solutes and between the two middle-molecule surrogates as a function of Q_f.

On the other hand, reflecting its diffusive basis HD is associated with much larger differences in clearance over the same MW range. The authors concluded that because an orderly relationship exists between Q_f and solute clearance Q_f is a reasonable dose surrogate in pre-dilution CVVH—as has been suggested for postdilution CVVH and CVVHDF. Overall, these data seem to validate the use of effluent-based dosing—which is being employed in two ongoing international trials evaluating the relationship between CRRT dose and outcome.

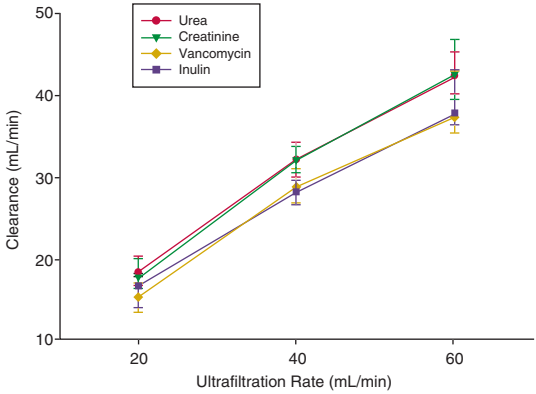


Figure 35–3

Solute clearance (mL/minute) as a function of ultrafiltration rate (mL/minute) in pre-dilution CVVH. *(Reprinted with permission from Huang ZP, Letteri JJ, Clark WR, Zhang W, Gao D, Ronco C. Ultrafiltration rate as a dose surrogate in pre-dilution hemofiltration. Int J Artif Organs [in press].)*

Summary

Recently performed outcome studies suggest that alternative dialytic approaches are needed to improve survival in both ARF and ESRD patients. One approach that may influence survival favorably in both settings is broader application of convective therapies. This chapter has provided a review of convective therapies used in both the acute and chronic dialysis settings. It is expected that these therapies will assume increasing importance in the future.

Recommended Reading

Clark WR, Gao D. Low-molecular weight proteins in end-stage renal disease: Potential toxicity and dialytic removal mechanisms. J Am Soc Nephrol 2002;13:S41–47.

Review article in which the phenomena influencing convective solute removal (such as ultrafiltration, membrane sieving properties, and concentration polarization) are discussed.

Clark WR, Winchester JW. Middle molecules and small molecular weight proteins in

ESRD: Properties and strategies for their removal. Adv Renal Replace Ther 2003;10:270–78.
Review article in which the toxicity of relatively larger sized uremic toxins is discussed, along with dialytic removal mechanisms.
Clark WR, Turk JE, Kraus MA, Gao D. Dose determinants in continuous renal replacement therapy. Artif Organs 2003;27:815–20.
Review article in which the fundamental importance of blood flow rate in both pre-dilution and postdilution CVVH is emphasized.
Colton CK, Henderson LW, Ford C, Lysaght MJ. Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. J Lab Clin Med 1975;85:355–71.
Seminal paper describing the technical considerations in hemofiltration. (Note: the original name for hemofiltration was hemodiafiltration.)
Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002;347:2010–19.
HEMO Study primary paper reporting insignificant effect of either dose or membrane flux on chronic HD patient survival.
Henderson LW. Pre vs post dilution hemofiltration. Clin Nephrol 1979;11:120–24.
A succinct and clear differentiation of pre-dilution and postdilution HF from the perspective of solute removal.
Henderson LW, Beans E. Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int 1978;14:522–25.
Classic initial description of the use of membrane filtration for the preparation of replacement fluid in HF.
Huang ZP, Letteri JJ, Clark WR, Zhang W, Gao D, Ronco C. Ultrafiltration rate as a dose surrogate in pre-dilution hemofiltration. Int J Artif Organs (in press).
Laboratory study in which the effects of ultrafiltration and solute MW on clearance are assessed.
Leber HW, Wizemann V, Goubeaud G, et al. Simultaneous hemofiltration/hemodialysis: An effective alterantive to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clin Nephrol 1978;9:115–21.
Original clinical description of chronic hemodiafiltration.
Ledebo I. Principles and practice of hemofiltration and hemodiafiltration. Artif Organs 1998;22:20–25.
Very thorough review of the major clinical factors influencing the delivery of online convective therapies.
Paniagua R, Amato D, Vonesh EF, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002;13:1307–20.
ADEMEX Study primary paper reporting insignificant effect of CAPD (continuous ambulatory peritoneal dialysis) dose on peritoneal dialysis patient survival.
Pedrini LA, de Christofaro V, Pagliari B, Sama F. Mixed predilution and post-dilution online hemodiafiltration compared with traditional infusion modes. Kidney Int 2000;58:2155–65.
Clinical study assessing the effect of different dilution points on solute clearance and operational parameters.
Ronco C, Bellomo R, Hommel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous hemofiltration on outcomes in acute renal failure: A prospective, randomized trial. Lancet 2000;355:26–30.
Seminal paper describing a relationship between CRRT dose and patient outcome in a randomized controlled trial.
Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006;70:1312–17.

Second randomized controlled trial establishing a relationship between CRRT dose and patient survival.

Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Eng J Med 2002;346:305–10.

Single-center German study indicating that patient survival and recovery of renal function are improved by relatively frequent application of conventional HD.

CHAPTER 36

Determination of Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis Prescriptions

Scott G. Satko, MD, and John M. Burkart, MD

According to the United States Renal Data System (USRDS) 2005 Annual Report, approximately 9% of the prevalent end-stage renal disease (ESRD) patients in the United States are currently performing peritoneal dialysis (PD). PD can be performed manually (continuous ambulatory PD, CAPD) or with the assistance of a cycler (automated PD, APD). Selection of appropriate patients for either of these two modalities is mainly based on lifestyle considerations, but also on the patients' physical characteristics and transporter status of the peritoneal membrane.

Rationale for Current Clearance Guidelines

When a patient initiates PD, it is important for the clinician to take into account the amount of residual renal function present. The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative publications from 2000 and 2006 recommend that unless certain conditions are met initiation of renal replacement therapy should be considered when the residual renal Kt/V urea falls to less than 2.0/week or when glomerular filtration rate (GFR) declines to less than 15 mL/minute (see the chapter on initiation of dialysis therapy for further details). Once PD is initiated, the updated NKF-K/DOQI document recommends that a total weekly Kt/V of at least 1.7 be the minimum small-solute clearance goal for patients on PD.

Historical univariate and multivariate analyses of retrospective data obtained on prevalent PD patients have suggested that those patients with weekly Kt/V <1.89 to 1.96 were more likely to have lower 5-year survival rates. However, due to limited sample size, limited patient follow-up, and retrospective study designs the true effect of small-solute clearance on morbidity and mortality was still not entirely certain from the conclusions of these

studies. The CANUSA (Canada–U.S.A.) Study—a prospective multicenter cohort study of 680 incident PD patients—however, suggested that total small-solute clearance did predict outcome. The investigators in this study followed 78 patients for a length of 2 years. In this population, every 0.1 unit/week increase in total Kt/V was associated with a 6% decrease in the relative risk of death over 2 years of follow-up. Every 5 L/1.73 m^2/week increase in total Ccr was associated with a 7% decrease in the relative risk of death. The total weekly Kt/V and total weekly Ccr values associated with a 78% 2-year survival rate were 2.1 and 70 L/1.73 m^2, respectively. These data were analyzed using two assumptions: total solute clearance did not change over time (in fact, it did) and the predicted benefit from 1 unit of residual renal Kt/V was equal to that of 1 unit of peritoneal Kt/V (not proven). Reexamination of the CANUSA data, however, has suggested that much of the change in mortality rate may be due more to the level of residual renal function than to actual changes in peritoneal clearance.

Two recent randomized controlled trials have suggested that peritoneal clearance may play much less of a role in affecting overall mortality than other factors, such as residual kidney clearance. The first such trial to show this was ADEMEX, in which Mexican CAPD patients were randomized to a standard dialysis prescription (four daily exchanges of 2 L) or to a modified prescription (adjusted to maintain a target peritoneal clearance of 60 L/week/1.73 m^2). As expected, mean total weekly Kt/V was lower in the control arm (1.80 versus 2.27 in the intervention arm). Surprisingly, the two groups had identical survival after 2 years of follow-up (69.3% in the standard group versus 68.3% in the modified prescription group).

In these patients, the level of peritoneal small-solute (urea or creatinine) clearance had very little impact on mortality, suggesting that the level of residual renal function may be a more important prognostic factor. Similar findings were noted in a trial in Hong Kong, in which CAPD patients were randomized to three treatment arms with varied solute clearance goals (target total weekly Kt/Vs of 1.5–1.7, 1.7–2.0, or >2.0). Patients in all three arms of this study had minimal residual renal function, with mean residual renal Kt/V of approximately 0.4 to 0.5/week and mean GFR of approximately 2.4 to 2.6 mL/minute. As in the ADEMEX trial, all three groups had similar survival rates. These data suggest that to optimize 2-year survival a minimal total small-solute clearance goal for CAPD would be a Kt/V of >1.7/week.

Discrepancy between Kt/V and Creatinine Clearance

In a relatively high percentage of patients, total weekly Kt/V and Ccr are positively correlated. In others, these two measurements of small-solute clearance are discordant. There are multiple reasons for this discrepancy, including length of time on dialysis, amount of residual renal function, peritoneal membrane transport type, body size, and dialysis prescription. Kt/V and Ccr values also differ significantly when calculations of V (urea volume of distribution) and BSA (body surface area) are normalized using desired rather than actual body weights. Total small-solute clearance is an important determinant of morbidity and mortality in PD patients, but mainly due to the residual renal component.

There are no data to support which of the two major indicators of adequacy (Kt/V or Ccr) is better. The randomized trials suggest that one can use Kt/V as the "dose" surrogate measurement and that there is no additional benefit to using creatinine clearance in an Asian or Mexican PD population. In actual clinical practice, nephrologists are frequently faced with a situation in which only one of these values is above target. Unfortunately, there are no rigorous outcome data to help us decide what to do clinically in this situation. In our experience, this discrepancy between Kt/V and Ccr occurs from 23 to 25% of the time, depending on whether actual or ideal body weight is used in the calculation of V and BSA for normalization of these parameters. The 2006 revised NKF-K/DOQI guidelines recommend targeting dose using Kt/V.

To understand why the two clearance measurements are often discordant, it is important to remember how creatinine and urea are handled by the nephron and the peritoneum. Renal clearance of creatinine occurs by both glomerular filtration and tubular secretion. With advanced degrees of renal insufficiency, the renal creatinine clearance overestimates the true GFR. Renal clearance of urea also occurs by glomerular filtration, but urea can be reabsorbed by the renal tubules. For this reason, renal urea clearance is usually an underestimation of the true GFR. When calculating total weekly creatinine clearance for PD patients, it is recommended that an estimation of GFR be used for the residual renal clearance.

This is most commonly estimated as the mean of the residual renal urea and creatinine clearances. Even when the estimated GFR is used for creatinine clearance, the residual renal Ccr tends to be relatively higher than the residual renal urea clearance. For this reason, residual renal function tends to contribute relatively more Ccr/1.73 m^2 than Kt/V to total weekly solute clearance.

On the other hand, small-solute clearance by the peritoneum is mainly dependent on diffusion. Urea undergoes more rapid diffusion through the peritoneal membrane than does creatinine because of its smaller molecular weight.

The typical CAPD dwell time is 4 to 6 hours. During this time, dialysate urea usually becomes equilibrated with blood in patients of all transport types. On the other hand, because creatinine is transported relatively more slowly, equilibration of creatinine between blood and dialysate is likely to occur only in rapid transporters during the typical dwell times used for CAPD. Given these diffusive characteristics of the peritoneal membrane, anuric patients will typically have a relatively higher Kt/V than Ccr. This finding becomes most apparent in low transporters, especially those patients using either APD or CAPD with unusually short dwell times.

Previous guidelines have suggested that one should attempt to change the dialysis prescription so that both Kt/V and Ccr are at target. If only one of these values can be at or above target, the nephrologist should aim to have that parameter be the weekly Kt/V. As mentioned, the updated 2006 NKF-K/DOQI guidelines recommend only measuring solute clearance in terms of Kt/V (and not measuring peritoneal creatinine clearance) to avoid the inconsistencies previously discussed. Furthermore, measuring creatinine clearance in addition to urea clearance provides little additional data useful to the prediction of short-term (2-year) clinical outcome.

It is acknowledged that small solutes are not the only uremic toxins. "Adequacy" of dialysis entails more than just removal of small solutes. It is known that to optimize outcomes one must control blood pressure, blood volume, acid-base status, and other metabolic issues related to kidney failure. It is also acknowledged that recent randomized trials only evaluated short-term risk of death related to small-solute clearance. They did not evaluate long-term outcomes, risk of death related to middle-molecular-weight solute clearance, or "dose" of dialysis related to metabolic control of other solutes such as phosphate.

Epidemiologic data suggests that relative risk of death is related to serum phosphate levels and calcium/phosphate metabolism. Phosphate control may be predictive of long-term outcome. Phosphate removal on PD parallels that of creatinine removal. If one were to lower total weekly Kt/V in PD, one might also lower phosphate removal. Further studies are needed to see if the lower total small solute clearance targets for PD have an adverse effect

on long-term outcomes in PD patients with a higher protein/phosphate intake than patients in Mexico and Hong Kong.

Peritoneal Transport Characteristics

When an initial PD prescription is selected, the transporter characteristics of the peritoneal membrane are not known. For this reason, the initial prescription empirically assumes that the patient is an "average" transporter. Peritoneal equilibration testing (PET) should be performed within 1 month of initiation of PD (and then at least semiannually) to determine the patient's transporter status (Figure 36.1).

Patients who are high (or "rapid") peritoneal transporters [4-hour dialysate/plasma (D/P) creatinine >0.81] will usually have excellent peritoneal clearance while on a standard CAPD regimen but frequently encounter difficulty with ultrafiltration. This is due to excessive reabsorption of glucose, which diminishes the osmotic gradient necessary for ultrafiltration to occur. These patients often do better when given a dialysis prescription with short dwell times. APD is often the optimal modality for these patients. With APD, one could prescribe multiple short dwells overnight, and at times a "dry day" avoiding the "long" nighttime dwell of CAPD. In these patients (high and high-average transporters), if a daytime dwell is used daytime dwell is appropriately shortened either by the performance of a midday manual exchange or midday drainage of fluid with the remainder of the day "dry."

On the other hand, patients who are low (or "slow") peritoneal transporters (4-hour D/P creatinine <0.50) will often experience underdialysis when given short dwell times. For these patients, the

4-hour Dialysate / Plasma (D/P) Creatinine Ratio	Transporter Status
≤ 0.50	Low
0.51–0.65	Low-average
0.66–0.81	High-average
> 0.81	High

Figure 36–1

Peritoneal transport characteristics.

long dwells used in CAPD (e.g., three 5-hour daytime dwells and a single 9-hour nighttime dwell) are optimal. To reach clearance targets, anuric patients who are low transporters usually need to perform a "continuous" modality of dialysis—with each 24-hour day divided evenly into dwell periods. When performing CAPD, this is most effectively done by using a nighttime exchange device (NXD) to divide the long nighttime dwell. Similarly, when performing APD this is most effectively done by performing a midday manual exchange.

Many patients, especially those who are rapid transporters or have diabetes with suboptimal glycemic control, may have difficulty achieving adequate ultrafiltration. This problem is often associated with rapid uptake of dextrose-containing peritoneal dialysate through the peritoneal membrane, with associated diminution of the osmotic gradient for ultrafiltration. These patients often respond better to the use of 7.5% icodextrin during the longest daily dwell, in place of dextrose-containing dialysate. Icodextrin is a glucose polymer produced via hydrolysis of starch, which is not significantly metabolized or transported through the peritoneal membrane.

Icodextrin solution uses a colloid osmotic gradient for ultrafiltration, resulting in slow but sustained ultrafiltration rates not influenced by peritoneal transport characteristics. The ultrafiltration profile for a 15-hour icodextrin dwell would typically exceed that of a 2.5% dextrose dwell and equal or exceed that of a 4.25% dextrose dwell in most patients. Compared to dextrose-containing dialysate, icodextrin appears to be more biocompatible and is associated with a lower rate of formation of advanced glycation end products. Although in theory icodextrin should be associated with a lower long-term risk of peritoneal damage, it is important to note that no long-term mortality data yet exist proving better outcomes in patients using icodextrin.

Calculation of Prescribed Kt/V for Peritoneal Dialysis

In a patient who is an average transporter (i.e., with 4-hour D/P creatinine of 0.50–0.81), dialysate and plasma are nearly 100% equilibrated with urea during the typical dwell time used in CAPD. Four-hour D/P urea values are usually 80 to 100% in this population. For this reason, it can be assumed that K (urea clearance, in L/day) is roughly equivalent to the 24-hour dialysate drain volume. Estimated weekly Kt would then be equal to (24-

hour drain volume in L/day) × (7 days). V (volume of distribution of urea, in liters) is equivalent to the volume of total body water. This value can be estimated using the Watson formulae.

- *For men:* V (liters) = 2.447 + [0.3362 × body weight (kg)] + [0.1074 × height (cm)] – [0.09516 × age (years)]
- *For women:* V (liters) = –2.097 + [0.2466 × body weight (kg)] + [0.1069 × height (cm)]

Alternatively, V can be more roughly approximated by multiplying body weight (in kg) by a factor of 0.55 for women and 0.60 for men. Estimations using equations such as the Watson formulae are recommended, however. For example, consider the situation in which an anuric 75-kg man is performing CAPD using four exchanges of 2 L per day. Assume his drain volume is 2.3 L/exchange, giving him a daily ultrafiltration volume of 1.2 L. It then follows that:

$$\text{Kt} = (2.3\ \text{L} \times 4/\text{day}) \times (7\ \text{days/week}) = 64.4\ \text{L/week}$$

$$\text{V} = (75\ \text{kg}) \times (0.60\ \text{L/kg}) = 45\ \text{L}$$

$$\text{Kt/V} = (64.4\ \text{L/wk}) \div (45\ \text{L}) = 1.43/\text{week}$$

This calculation illustrates that a "typical" CAPD regimen of 4 × 2.0 L would not provide acceptable small-solute clearance for an anuric 75-kg male. Suppose this patient increased the number of exchanges per day to 6 × 2.0 L, in an attempt to provide better clearance. If he is an average transporter and is performing 3-hour dwells during the daytime in order to accommodate six daily exchanges, it is likely that urea may not become fully equilibrated between dialysate and plasma during the short dwells. During these short dwells, assume that urea is only 80% equilibrated between dialysate and plasma (see PET curve for urea in Figure 36.1). Assuming that the daily ultrafiltration volume is unchanged, the patient's clearance is now as follows.

$$\text{Kt} = (2.2\ \text{L} \times 6/\text{day}) \times (7\ \text{days/week}) \times (3\text{-hour D/P urea } 80\%) = 73.9\ \text{L/week}$$

$$\text{V} = (75\ \text{kg}) \times (0.60\ \text{L/kg}) = 45\ \text{L}$$

$$\text{Kt/V} = (73.9\ \text{L/week}) \div (45\ \text{L}) = 1.64/\text{week}$$

Although this patient's clearance has now improved, he still does not meet recommended guidelines for dialysis adequacy. Suppose, however, that instead of increasing the number of daily exchanges this patient increases his exchange volume from 2 to 3 L. If he performs four daily exchanges, his total daily exchange

volume will be 12 L—the same as in the previous scenario. However, with the longer dwell time urea will now become more fully equilibrated between dialysate and plasma—leading to an increase in clearance. Assuming that his daily ultrafiltration volume is the same as before, his clearance is now as follows.

$$Kt = (3.3\ L \times 4/day) \times (7\ days/week) = 92.4\ L/week$$

$$V = (75\ kg) \times (0.60\ L/kg) = 45\ L$$

$$Kt/V = (92.4\ L/week) \div (45\ L) = 2.05/week$$

This case illustrates the point clearly that for the average CAPD patient increasing exchange volume has a substantially greater effect on improving peritoneal small-solute clearance than does increasing the number of exchanges. Although the effect of changing exchange volume and dwell time can be predicted using kinetic modeling, in clinical practice it is necessary to perform a 24-hour dialysate collection after each change in order to verify the actual effect of these changes in any individual patient.

A recent study by Perez et al. examined the effect of increasing the number of nightly APD exchanges on urea and creatinine clearances, net ultrafiltration, and monetary cost. Using 9 × 2 L nightly exchanges (compared to 5 × 2 L nightly exchanges) provided peritoneal urea and creatinine clearances of 21 and 25% higher, respectively, and 47% more ultrafiltration volume. These increases, however, were obtained at the expense of using 80% more dialysate fluid (18 L versus 10 L) and a 54% greater monetary cost. As the number of nightly exchanges increases, a proportionally greater amount of time is spent filling and draining compared to dwelling. This leads to less efficient use of dialysate because much less small-solute clearance occurs during the filling and draining periods than during the dwelling periods.

To perform PD most efficiently, it is important to optimize dialysate dwell time. As illustrated in the case previously cited, if it is necessary to adjust a patient's prescription to improve clearance the first step should be to attempt to increase the exchange volume. In situations in which the exchange volume is already maximized (i.e., 3 L) or the patient is unable to tolerate such an increase, the next step should be to increase the number of daily exchanges. From a practical standpoint, it is rather difficult for a CAPD patient to perform more than four manual exchanges a day. If these patients require more than four daily exchanges and wish to continue CAPD, the best solution is to add an extra automated exchange with an NXD. Similarly, CCPD patients who require extra exchanges often benefit from

performing one or two daytime manual exchanges in order to optimize clearance.

By optimizing dwell times through the manipulations described previously, it is possible to use the patient's time and peritoneal dialysate most efficiently. In this era in which cost-containment issues are of paramount importance, it is especially prudent to prescribe PD in the most efficient way possible.

Summary

A number of factors must be taken into consideration when selecting an appropriate PD prescription for a patient. First, the patient's lifestyle considerations must be taken into account—assuming that no compelling medical indications for selecting one modality over another exist. Next, it is important to consider the patient's body size, transporter status, and level of residual renal function. For patients with significant amounts of residual renal function, it is important to measure residual renal function periodically so that the dialysis prescription can be adjusted appropriately.

Recommended Reading

Amici G, Thomaseth K. Role of drain and fill profile in automated peritoneal dialysis. Contrib Nephrol 1999;129:44–53.

A discussion of urea and creatinine kinetics during the filling and draining phases of APD.

Burkart JM, Schreiber M, Korbet SM, Churchill DN, Hamburger RJ, Moran J, et al. Solute clearance approach to adequacy of peritoneal dialysis. Perit Dial Int 1996;16:457–70.

A discussion of the rationale for the current recommended small-solute clearance guidelines for peritoneal dialysis.

Canada-U.S.A. (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. J Am Soc Nephrol 1996;7:198–207.

A large prospective cohort study of peritoneal dialysis patients, showing the correlation between small-solute clearance and survival.

NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines. National Kidney Foundation, 2000 (2006 update in press), *http://www.kidney.org/professionals/NKF-K/DOQI/guidelines.cfm*.

A comprehensive set of guidelines for management of the peritoneal dialysis patient, with rationales for these recommendations and an exhaustive list of supporting references.

Lo WK, Ho YW, Li CS, Wong KS, Chan TM, Yu AW, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int 2003;64:649–56.

The second of two important recent large-scale randomized trials suggesting that increasing small-solute clearance has less impact on improving clinical outcomes in PD patients than was previously thought.

Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002;13:1307–20.

The first of two important recent large-scale randomized trials suggesting that increasing small-solute clearance has less impact on improving clinical outcomes in PD patients than was previously thought.

Perez RA, Blake PG, McMurray S, Mupas L, Oreopoulos DG. What is the optimal frequency of cycling in automated peritoneal dialysis (APD)? Perit Dial Int 2000;20:548–56.

An examination of the effect of increasing the number of nightly APD exchanges on urea and creatinine clearances, net ultrafiltration, and monetary cost.

Satko SG, Burkart JM, Bleyer AJ, Jordan JR, Manning T. Frequency and causes of discrepancy between Kt/V and creatinine clearance. Perit Dial Int 1999;19:31–37.

A retrospective analysis of the frequency of discordance between the two commonly used measurements of small-solute clearance, with a discussion of possible reasons for this discrepancy.

Teehan BP, Schleifer CR, Brown JM, Sigler MH, Raimondo J. Urea kinetic analysis and clinical outcome on CAPD: A five-year longitudinal study. Adv Perit Dial 1990;6:181–85.

A long-term outcome study of peritoneal dialysis patients, showing the correlation between urea kinetics and morbidity and mortality.

2005 USRDS Annual Data Report Atlas. *http://www.usrds.org/atlas.htm.*

CHAPTER 37

Tidal Peritoneal Dialysis

Zbylut J. Twardowski, MD, PhD

Continuous ambulatory peritoneal dialysis (CAPD) is the most commonly used form of peritoneal dialysis at present. However, automated peritoneal dialysis (APD) has become the fastest growing modality for renal replacement therapy. Patients either start on APD or transfer from CAPD because of medical and sociopsychological problems. Typical medical complications leading to transfers are related to high intra-abdominal pressure, inadequate ultrafiltration, and inadequate dialysis.

Many of these patients can continue peritoneal dialysis therapy on nightly peritoneal dialysis (NPD). NPD evolved from older regimens (intermittent peritoneal dialysis and CAPD), incorporating their advantages and eliminating some of their disadvantages.

Terminology

There is a difference between continuous and intermittent peritoneal dialysis regimens and techniques. "Regimen" refers to the overall systematic plan of dialysis. Intermittent peritoneal dialysis means that the dialysis sessions are performed several times per week, with periods without dialysis. A continuous regimen means that the dialysis solution is present in the peritoneal cavity continuously, with the exception of short insignificant periods between exchanges. "Technique" refers to the method of dialysis solution flow during a single dialysis session. The continuous-flow technique uses dual-lumen catheterization (i.e., two catheters, one for inflow and the other for outflow). The intermittent-flow technique uses one catheter for inflow and outflow. Flow is interrupted after both inflow and outflow during an exchange, and hence the term *intermittent*.

Comparison of Continuous and Intermittent Techniques

Major advantages of the continuous-flow technique are constant contact of the dialysate with the peritoneal membrane and the delivery of fresh dialysis solution, maintaining a high solute gradient between the plasma and dialysate. A major disadvantage

is fluid channeling between the two catheter lumens at high fluid flow rates. This phenomenon causes a low-solute gradient near the peritoneal membrane, which negates the advantage of high fluid flow. In the past, another disadvantage was the difficulty of continuously maintaining near-identical inflow and outflow rates to preserve constant intraperitoneal fluid volume. This made the continuous-flow technique very demanding, tedious, time consuming, and expensive.

The intermittent-flow technique has fewer mechanical problems, which is the main reason this technique succeeded against the continuous-flow technique and replaced it in the late 1950s. A major disadvantage lies in its inability to increase the efficiency of dialysis with an increase of dialysis solution doses above approximately 3 L/hour. It has been shown that urea and creatinine clearances in rapid-fluid-exchange peritoneal dialysis are higher with a dialysis solution dose of 3 L/hour than with 4 L/hour. This phenomenon is related to an inherent feature of the technique in which the dialysate of each exchange is drained as completely as possible. With high doses of dialysis solution, a high plasma/dialysate concentration gradient is maintained during the dwell time. However, at the beginning of inflow and at the end of outflow the area of contact between the peritoneal membrane and dialysate is not complete—hampering the solute diffusion.

Figure 37.1 illustrates this phenomenon. In the figure, mid-dialysis intraperitoneal fluid volumes longer than 1 hour with three types of intermittent-flow techniques are shown. The top panel shows a classic intermittent-flow peritoneal dialysis technique with 2-L volume, 10-minute inflow, 30-minute dwell, and 20-minute outflow time. Some undrainable amount of fluid (residual volume) is always present in the peritoneal cavity during a dialysis session. Shaded areas under the volume lines portray periods of diminished dialysis efficiency due to the incompletely filled peritoneal cavity. It may be assumed that during the initial 5 minutes of inflow time and the last 15 minutes of outflow time the average efficiency is only 50% of that during the dwell. This is because the dialysis solution is not in contact with the entire peritoneal membrane area. Consequently, approximately 10 minutes (17%) of the 60-minute total exchange time is lost for dialysis.

The middle panel in Figure 37.1 presents a rapid intermittent-flow peritoneal dialysis with no dwell time. The drainage starts immediately after infusion. Dialysate flow is doubled, markedly increasing the concentration gradient between plasma and

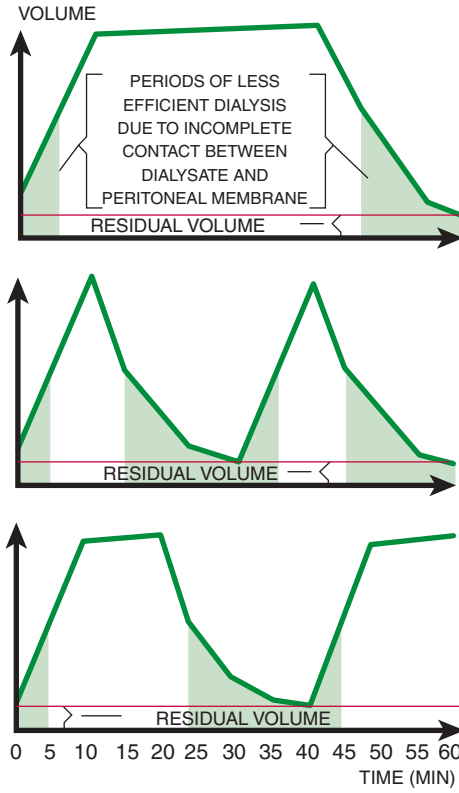


Figure 37–1

Intermittent-flow peritoneal dialysis technique. Shaded areas represent periods of diminished dialysis efficiency because dialysate is not in contact with the entire peritoneal membrane surface.

dialysate, but the efficient dialysis time is decreased by 20 minutes (34%) per hour. The bottom panel portrays an intermittent flow with short dwell time. Dialysate flow is 3 L/hour. The efficient dialysis time is decreased by 12 minutes (20%). Because of less wasted time compared to the technique without dwell time, the efficiency of dialysis is higher despite a lower dose of dialysis.

Nightly Intermittent Peritoneal Dialysis

Nightly intermittent peritoneal dialysis (NIPD) is a form of intermittent peritoneal dialysis performed every night. This method is attractive to patients with contraindications to CAPD or CCPD (Table 37.1). For adequate dialysis, up to 12 hours of total dialysis time may be required. This method would be even more attractive if, by increasing the efficiency of dialysis, the time of dialysis could be limited to a usual resting time of 8 to 9 hours.

Tidal Peritoneal Dialysis

The tidal peritoneal dialysis (TPD) technique was developed to overcome the problem of decreased peritoneal membrane contact with dialysate while maintaining a high dose of dialysis. This technique is a hybrid of continuous- and intermittent-flow peritoneal dialysis techniques, combining their advantages and eliminating disadvantages.

The TPD technique is based on previous observations that maintaining a fluid reservoir in the peritoneal cavity throughout the dialysis and rapidly exchanging a part of the fluid increase the efficiency of dialysis. In TPD, a bolus of fluid is infused into the peritoneal cavity at the beginning of treatment. However, unlike a typical complete-volume-drainage technique only part of the fluid is drained—leaving a reserve volume, on top of which a tidal volume of fresh solution is cycled.

Mechanism of Effect

Figure 37.2 depicts the TPD principle. The upper panel shows a single TPD session. There is some undrainable amount of fluid

Table 37–1

Advantages of NIPD (TPD) Compared with CAPD and CCPD

- Overcomes medical complications associated with CAPD/CCPD (i.e., high intra-abdominal pressure and changed posture, hernias, abdominal dialysate leaks, peritoneal-pleural leak, hemorrhoids, bladder prolapse, low back pain, high peritoneal solute transport, high glucose absorption, poor ultrafiltration, psychosocial advantages)
- No distorted body image due to protruding abdomen
- Convenient treatment time for employed and school-attending patients
- Convenient dialysis schedule for helpers

(100–300 mL) always present in the peritoneal cavity (residual volume). The residual volume is usually higher in the supine position than in the upright position. At the beginning of a TPD session, the peritoneal cavity is filled with dialysis solution (initial fill). After a dwell time, a portion of dialysate is drained. Immediately after tidal drain the dialysate is replaced with fresh dialysis solution and cycles are repeated until the end of a dialysis session, when the fluid is drained as completely as possible (final drain). Only at the beginning and end of a dialysis session is there no full contact between the peritoneal membrane and dialysate. Thus, the "wasted time" is minimal.

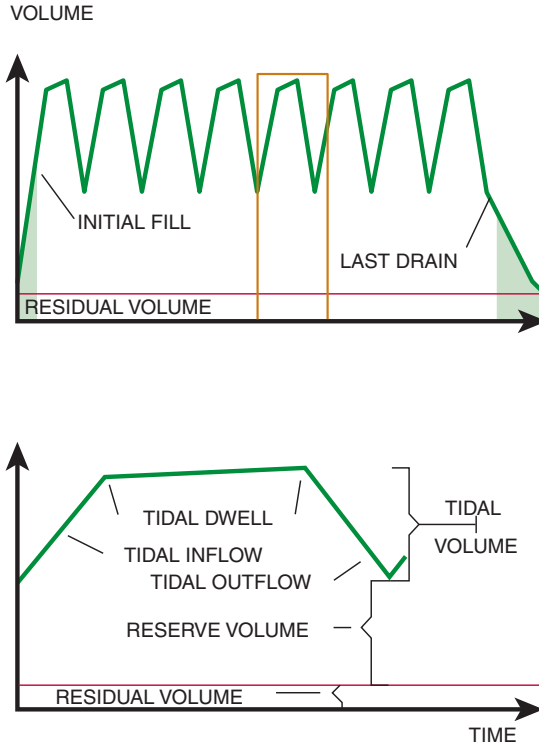


Figure 37–2

Tidal peritoneal dialysis principle and terminology.

The lower panel of Figure 37.2, which is an enlarged view of the upper panel, shows mid-dialysis TPD volume and time terms. Tidal inflow is followed by tidal drain and tidal outflow. Tidal drain volumes are higher than tidal fill volumes by the volume of ultrafiltration generated during the dwell times. Tidal volume is the mean of tidal inflow and outflow volumes. Reserve volume ensures constant contact between the peritoneal membrane and dialysate.

TPD efficiency depends on the maintenance of a sufficient reserve volume to ensure adequate contact of dialysate with the peritoneal membrane, a suitable tidal volume to ensure adequate mixing of dialysate with fresh dialysis solution, and a high dose of dialysis solution to provide a high concentration gradient between plasma and dialysate. In our studies, the highest efficiency occurred when tidal and reserve volumes constituted 50% of the total intraperitoneal volumes of 2 to 3 L in adults. The gain in dialysis efficiency depends on the dose of dialysis solution. The higher the dose the greater the gain.

At low doses of dialysis solution (<1 L/hour), the efficiency is lower; at medium doses (2 L/hour), the gain in efficiency is unnoticeable; and at higher doses (>3 L/hour) the gain in efficiency is significant. In our studies using 27 L/8 hours (3.4 L/hour) we found a gain in creatinine and urea clearances of about 20% compared to intermittent-flow peritoneal dialysis at a similar dose of dialysis solution (26 L/8 hours, 3.3 L/hour). Eight-hour TPD provided urea and creatinine clearances equal to 24-hour CAPD in patients with higher-than-average peritoneal transport rates.

For patients with lower-than-average peritoneal transport rates, 9 to 10 hours of dialysis was needed to match 24-hour CAPD efficiency for small solutes. For phosphate removal, tidal peritoneal dialysis performed over 8 to 10 hours is about 20% less efficient than 24-hour CAPD but more efficient than intermittent peritoneal dialysis (IPD). Protein losses in TPD are only slightly lower than in CAPD. It should be realized that the protein transport from the blood to the peritoneal cavity is almost constant, whether or not there is fluid in the peritoneal cavity. After starting TPD, in the first few exchanges this protein is removed—adding to the protein transported during TPD.

Several studies showed higher clearances with TPD compared to IPD at higher dialysate flow rates but lower clearances with lower dialysate flow rates. Some studies did not show significant clearance differences between TPD and IPD at higher dialysate flow rates. However, it is almost impossible to use a very high

flow rate with IPD because the outflow rate decreases at the end of drainage. Therefore, the residual volume increases and ultimately IPD becomes TPD. In reality, these studies compared TPD to TPD.

A major disadvantage of TPD is the cost of solutions if high-dose high-efficiency treatment is implemented. The cost could be decreased with the availability of a fully automated peritoneal dialysis machine based on the reverse osmosis proportioning system. Such a machine is not available at present.

An interesting concept of hybrid dialysis was evaluated by Raj and colleagues in 2000. In this system, a fixed quantity of peritoneal dialysis fluid was infused into and removed from the peritoneal cavity in a tidal mode. This fluid was dialyzed against the secondary dialysate in the hemodialysis system. Ultimately, the peritoneal fluid contained electrolyte concentrations similar to those of the secondary dialysate with bicarbonate instead of lactate. After 8-hour dialysis the fluid with accumulated large molecules was discarded. Clearances of urea, creatinine, and phosphate were markedly better compared to 8-hour IPD. Protein losses were similar.

TPD has other advantages that do not require high doses of dialysis solution. The fluid flow mechanics are better than with a complete-drain intermittent-flow technique. Because in TPD there is always some sump volume in the peritoneal cavity, dialysate flow is fast throughout the tidal exchange. Cycler alarms are less frequent than with the intermittent-flow techniques. Another advantage is that some patients experience less infusion and outflow pain. This pain is felt usually at the beginning of inflow and at the end of outflow with an intermittent technique. The presence of a reserve volume eliminates the periods when the pain is present. The author has used a tidal mode instead of an intermittent mode more frequently for these last two purposes, because they are attainable with doses of dialysis below 2 L/hour.

Clinical Application

For TPD, a cycler with a tidal mode is needed (Table 37.2). For low-dose TPD, the total dose of dialysis solution and the time of the dialysis session are the same as for NIPD (usually 15–20 L of dialysis solution for 8–12 hours)—depending on the peritoneal solute transport rates (the higher the transport the lower the dose and time). Inflow and outflow times depend on inflow and outflow rates, which have to be measured with the height of a bed

Table 37–2

Comparison of NIPD and NTPD

Parameter	High Dialysate Dose (>3 L/h)	Low Dialysate Dose (<2 L/h)
Efficiency	NTPD > NIPD	NTPD ≤ NIPD
Ultrafiltration	NTPD < NIPD	NTPD ≤ NIPD
Cost	NTPD = NIPD	NTPD = NIPD
Fluid flow mechanics	Better with NTPD	Better with NTPD
Inflow and outflow pain	Less with NTPD	Less with NTPD

NIPD = nightly intermittent peritoneal dialysis, NTPD = nightly tidal peritoneal dialysis.

similar to that used at home. Usual flow rates range between 150 and 250 mL/minute with most currently used catheters. Dwell times depend on the total dialysis session time.

Prediction of ultrafiltration is important to ensure that the reserve volume remains unchanged. If ultrafiltration volumes were overestimated, the reserve volume would be gradually depleted. If ultrafiltration volumes were underestimated, the reserve volume would gradually increase—leading to abdominal discomfort. The ultrafiltration volume per exchange is calculated by dividing the total ultrafiltration volume per session (as found on NIPD for a particular dextrose concentration) by the number of tidal exchanges. The ultrafiltration volume is slightly lower with TPD compared to IPD, as glucose absorption is slightly higher. Appropriate adjustments of tidal ultrafiltration volumes (as well as inflow, outflow, and dwell times) have to be made during several initial home TPD sessions.

The necessity for later changes in machine settings is rare. Peritoneal dialysis solute and water transport remain remarkably constant for a long time. The author's three long-term TPD patients have required only minimal adjustments in machine settings for up to 5 years. These adjustments have been needed due to changes in ambient temperature, residual urine output, and diet—rather than because of peritoneal transport characteristics. If daytime exchanges are also used (CCPD with TPD at night), a gradual increase in peritoneal solute transport characteristics is more likely over the years, glucose absorption is increased, and ultrafiltration is gradually decreased.

Recommended Reading

Kathuria P, Twardowski ZJ. Automated peritoneal dialysis. In R Gokal, R Khanna, Krediet RT, Nolph KD (eds.), *The Textbook of Peritoneal Dialysis, Second Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2000:435–63.

Comprehensive review of automated peritoneal dialysis, including tidal peritoneal dialysis.

Raj DSC, Self M, Work J. Hybrid dialysis: Recirculation peritoneal dialysis revisited. Am J Kidney Dis 2000;36(1):58–67.

A new approach to a hybrid of peritoneal dialysis and hemodialysis.

Twardowski ZJ. New approaches to intermittent peritoneal dialysis therapies. In Nolph KD (ed.), *Peritoneal Dialysis, Third Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 1989:133–51.

Historical review of various peritoneal dialysis techniques.

Twardowski ZJ, Ksiazek A, Majdan M, Janicka L, Bochenska-Nowacka E, Sokolowska G, et al. Kinetics of continuous ambulatory peritoneal dialysis (CAPD) with four exchanges per day. Clin Nephrol 1981;15:118–30.

Thorough review of PD kinetics, including discussion on protein transport.

Twardowski ZJ, Nolph KD, Khanna R, Gluck Z, Prowant BF, Ryan LP. Daily clearances with continuous ambulatory peritoneal dialysis and nightly peritoneal dialysis. Trans Am Soc Artif Intern Organs 1986;32:575–80.

In-depth explanation why protein losses in 8- to 10-hour NIPD are similar to 24-hour CAPD.

CHAPTER 38

Peritoneal Dialysis Solutions

Declan de Freitas, MRCPI, and Alastair J. Hutchison, FRCP

The basis of peritoneal dialysis (PD) is the removal of various solutes and fluid from the patient. These processes can be independently altered by variations to the type of dialysis solution used. Solute removal is achieved by diffusion (down a concentration gradient) and convection, which transports solutes across the membrane in the ultrafiltrate. The electrolyte composition of the dialysis solution can be modified such that certain solutes are either not removed or diffuse into the patient. Fluid balance can be altered by varying the osmolality of the solution used, with fluid either absorbed or removed. Thus, the ability to appropriately prescribe differing PD solutions is a key factor in achieving electrolyte homeostasis, acid-base neutrality, fluid balance, and a nonuremic state.

Early PD solutions (such as 0.8% saline, 5% dextrose, and Ringer's lactate) were associated with pulmonary edema and with electrolyte and acid-base disturbances. Subsequent research led to the realization that the composition needed to be similar to interstitial fluid and hypertonic to plasma in order to achieve fluid removal (ultrafiltration, UF). Several osmotic agents were evaluated, with glucose found to be inexpensive, safe, and effective. It has become the standard osmotic agent for PD solutions, and little has changed since the 1950s. However, better understanding of peritoneal anatomy and physiology has led to the development of newer PD solutions with better biocompatibility (at least in vitro). This has paved the way for better treatment of PD patients, with improved survival and fewer complications.

There are a number of PD solutions in use today, with their general composition shown in Table 38.1. These vary little between manufacturers and it can be seen that PD solutions are made up of three essential components.

- Electrolytes
- Osmotic agents
- Acid-base buffers

Electrolytes

Electrolyte disturbance is obviously a common feature of end-stage renal failure. To maintain homeostasis, solutions must contain

Table 38–1

Composition of Standard PD Solutions

• Sodium	132–134 mmol/L
• Potassium	0–2 mmol/L
• Calcium	0–1.75 mmol/L
• Magnesium	0.25–0.75 mmol/L
• Chloride	95–107 mmol/L
• Lactate	35–40 mmol/L
• Glucose	1.5–4.25 g/dL
• pH	5.2–5.5
• Osmolality	358–511 mOsm

sodium, potassium, calcium, and magnesium as major cations (with lactate/bicarbonate and chloride) to maintain electrical neutrality.

Sodium

The concentration of sodium in PD solutions is between 130 and 137 mmol/L, with the most commonly used being between 132 and 134 mmol/L. Clinical studies have not reported any specific side effects related to these concentrations, but nomograms are available to predict net sodium removal—adjusted for the glucose concentration of the solution. Interestingly, studies in CAPD patients have shown that varying the sodium concentration from 132 to 141 mmol/L has little effect on the serum sodium concentration.

The net removal of sodium per liter of ultrafiltrate (about 70 mmol) is much less than one would expect from the extracellular fluid concentration. This is due to the low sodium-sieving coefficient of the peritoneal membrane and the Donnan equilibrium. However, in symptomatic hypotensive patients higher sodium concentrations in PD fluids (137–142 mmol/L) have been used with benefit. Conversely, "very-low-sodium" concentrations (100–120 mmol/L) have been tried in a limited way (with some success) in managing hypertension and fluid overload. These solutions are not currently commercially available.

Of note, residual renal function (when present) plays a significant role in sodium homeostasis, which may account for the limited effects of small variations in PD fluid sodium concentration. Hypernatremia may occasionally occur, especially in rapid-cycling APD. UF and the phenomenon of sodium sieving result in water losses that are proportionately greater than sodium losses.

Potassium

Hyperkalemia is a common and life-threatening problem in end-stage renal failure. Potassium homeostasis in the PD patient is dependent on numerous factors, including reduced dietary intake, increased intestinal excretion, residual renal function, serum potassium levels, insulin bioavailability, cell membrane Na/K ATPase activity, dialysate potassium concentration, and acid-base balance.

The potassium concentration in commercially available solutions varies between 0 and 2 mmol/L. Most physicians use solutions without potassium to maximize potassium removal, which occurs predominantly by diffusion rather than solute drag due to its low concentration in extracellular fluid. With these solutions, hypokalemia occurs in between 10 and 36% of patients, which can be corrected by relaxing dietary restrictions, by oral potassium supplementation, or (less easily) by adding 1 to 4 meq/L of potassium to the dialysate as required. Again, nomograms are available to predict potassium removal.

Calcium

Calcium homeostasis is dependent on the direction of the diffusive gradient and the UF rate. Transfer from dialysate to patient is negatively correlated with the degree of UF. Calcium homeostasis is also related to oral calcium intake, vitamin D prescription, parathyroid hormone, and phosphate levels. Whereas the normal serum ionized calcium level varies from 1.15 to 1.29 mmol/L, the calcium concentration of dialysate (in which all of the calcium is ionized) can vary from 0 to 1.75 mmol/L. In the 1980s, solutions using 1.75 mmol/L were commonly used and were associated with an increased incidence of hypercalcemia.

Currently, the optimal dialysate calcium concentration is not known. However, it clearly may vary from one patient to the next—depending on their serum levels. The majority of physicians are prescribing a more physiological calcium concentration (1.25–1.55 mmol/L) because of concern relating to calcium "overload" and vascular mineralization. However, the current controversy regarding the maximum advisable calcium intake has tended to focus on oral intake from calcium-containing phosphate binders, and dialysate calcium has been to some extent neglected.

Several studies have shown that a PD solution calcium level of 1.0 to 1.25 mmol/L can lead to adequate calcium balance and phosphate control with oral calcium binders, and reduces the risk of hypercalcemia. However, hypocalcemia may occur—especially if compliance with vitamin D analogues or calcium containing

phosphate binders is incomplete. Lower dialysate calcium levels are available (0.6–1.0 mmol/L) and are used by some centers in PD patients with severe hyperparathyroidism who need increasingly high doses of calcitriol—although the introduction of cinacalcet will probably render this approach obsolete. The earlier formulations containing 1.75 mmol/L are still used in hypocalcemic patients, or in those patients who are noncompliant with calcium or calcitriol supplements.

Better understanding of calcium homeostasis should allow the dialysate calcium prescription to be tailored in accordance with the serum calcium level and phosphate binder prescription. However, very little is known of peritoneal calcium balance in automated PD and this undoubtedly needs further study.

Magnesium

The normal serum value for magnesium is between 0.60 and 1.00 mmol/L, depending on the laboratory reference range. In PD patients, the serum level is largely dependent on both dietary intake and the concentration of magnesium in the dialysate. In addition, the duration of the dwell, degree of UF, and peritoneal permeability can affect peritoneal transport. However, as with calcium very little is known of magnesium balance in APD.

Currently available PD solutions contain ionized magnesium at concentrations between 0.25 and 0.75 mmol/L. In most studies, the use of 0.75 mmol/L has resulted in elevated serum magnesium levels in many patients. However, there are no reported side effects from this. Some authors have suggested that hypermagnesemia may inhibit bone remodeling, whereas others believe it may have a protective effect on soft tissue calcification but no sizeable prospective studies exist. Experience with a dialysate magnesium concentration of 0.25 mmol/L has shown a normalization of serum magnesium with no hypomagnesemia. A zero dialysate magnesium concentration has also been tested to allow the use of oral magnesium salt as an additional phosphate binder, but this approach is limited due to magnesium's laxative effect and the additional need to monitor serum magnesium routinely.

Osmotic Agents

Glucose

Until the late 1990s, glucose was the only osmotic agent available for PD. It has the advantages of being inexpensive, readily avail-

able, not directly toxic, and effective. In North America, solutions contain 1.5%, 2.5%, and 4.25% dextrose monohydrate and are labeled as such. In Europe, solutions are labeled 1.36%, 2.27%, and 3.86%—denoting the anhydrous dextrose or glucose concentration. PD fluid contains very high glucose concentrations in order to achieve effective UF, with unused solutions having a glucose concentration varying from 75 mmol/L (1.36%) to 215 mmol/L (3.86%).

UF is greatest at the beginning of an exchange but dissipates as the glucose is absorbed, mainly through the lymphatic system. In patients who have a high transporter status, rapid absorption can result in UF failure and net fluid gain despite large glucose concentrations. This absorption can contribute up to 20% of the patient's caloric intake per day. Hyperglycemia and hyperinsulinemia have been observed in nondiabetic patients undergoing PD, due to the large amount of glucose absorbed. This may therefore precipitate or exacerbate diabetes mellitus. Obesity due to the caloric load has also been observed, as well as hypertriglyceridemia and abnormal serum lipoprotein levels. All of these metabolic abnormalities can increase the cardiovascular burden associated with ESRF (end stage renal failure).

It is perhaps not surprising that glucose has been associated with peritoneal membrane changes in long-term PD patients. Therefore, although it has been considered nontoxic it is clearly not devoid of significant side effects. With long-term PD, morphologic changes occur in the peritoneum—resulting in derangements in membrane function. There are several mechanisms by which these progressive changes in the peritoneal membrane occur. The mesothelium is constantly exposed to glucose concentrations well beyond the diabetic range, and such high concentrations have been shown in vitro and in vivo to be toxic. They are also implicated in peritoneal neoangiogenesis. This process is associated with increased vascular endothelial growth factor (VEGF) levels, and an increase in the peritoneal vasculature surface area—resulting in more rapid dissipation of the osmotic gradient generated by such a low-molecular-weight osmotic agent.

Glucose also activates the polyol pathway (also called the sorbitol/aldose reductase pathway), causing the secretion of TGF-β1, MCP-1, and fibronectin in cultured mesothelial cells. Excessive activation of the polyol pathway leads to increased levels of sorbitol and reactive oxygen molecules and decreased levels of nitric oxide and glutathione. This also places osmotic stresses on the cell membrane. Any one of these elements alone can promote cell damage within the peritoneum.

Glucose has the potential to bind nonenzymatically to free amino groups on proteins or to lipids, resulting in the formation of advanced glycosylation end products (AGE). AGE formation is accelerated when ambient glucose levels are elevated or when the prevailing oxidant stress is high, as in uremia. The peritoneal cavity of PD patients thus provides good conditions for accelerated AGE formation and accumulation—and AGE have been detected immunocytochemically in the mesothelium, submesothelial stroma, and vascular wall of PD patients. AGE can induce VEGF expression in diverse cell types and therefore may have the potential to promote peritoneal neoangiogenesis.

The presence of glucose degradation products (GDPs) generated during steam sterilization and storage of dialysis solutions is associated with direct cytotoxicity and acceleration of the process of AGE formation. The formation of GDPs can be reduced by sterilizing high-glucose concentrations at a low pH, using a double-chambered dialysis bag to separate the glucose and solution buffer.

Although glucose-based PD fluids have enabled PD to become an established therapy for thousands of patients who might otherwise not have received dialysis, it is clear that important goals for the clinician today are to reduce patient exposure to glucose, minimize the total amount of glucose absorbed, and avoid the hyperosmolar stress, high glucose, and GDP exposure of the peritoneum. Non glucose-based PD solutions, as well as lower GDP-containing solutions, are now available and offer a positive way forward.

Icodextrin

Icodextrin at 7.5% is a polyglucose preparation used as a primary osmotic agent. It employs colloidal rather than crystalline osmotic pressure to effect a sustained UF profile that is beneficial for long dwells. Due to its colloidal properties, a 7.5% icodextrin solution exerts an osmotic pressure of only 282 mOsm compared with glucose 1.36, 2.27, and 3.86% PD solutions (which exert osmotic pressures of 358, 401, and 511 mOsm, respectively). However, it is three to five times more efficacious than 1.36% glucose for UF and equivalent to the 3.86% glucose over long dwells. Furthermore, the GDP content of icodextrin is very low compared to that of glucose-containing solutions. Its beneficial effects on fluid removal are explained by its large molecular size and slow absorption from the peritoneum, sustaining the osmotic effect and resulting in an almost linear increase in UF during a long dwell. Increased UF also results in improved solute clearances.

Other potential benefits include a reduction in glucose-induced lipid abnormalities and improved phagocytosis by polymorphonuclear lymphocytes and monocytes. It is recommended as a once-daily replacement for a single glucose exchange during the long nocturnal dwell in CAPD and the long daytime dwell in APD. The indications for use of icodextrin are summarized in Table 38.2 and Table 38.3.

The European Automated Peritoneal Dialysis Outcomes Study (EAPOS) looked at how peritoneal function was affected by exposure to glucose and by the use of icodextrin for the long dwell. At baseline, patients using icodextrin had significantly higher solute transport and lower UF capacity (poorer membrane function) compared to those using glucose only. Despite this, UF capacity remained unchanged in the icodextrin group but decreased significantly in the patients not using icodextrin. In addition, solute transport remained unchanged at 12 months and decreased significantly at 24 months—compared to the non-icodextrin group (for which it increased significantly at 12 and 24 months). These differences were independent of age, time on dialysis, and peritonitis episodes.

Icodextrin's use is associated with nonphysiologic blood maltose (the end product of icodextrin metabolism by amylase) levels, which have no associated toxicity but can interfere with the GDH-PQQ (glucose dehydrogenase pyrrolquinoline quinone) method of glucose determination on finger prick glucose monitors—indicating falsely high levels even in hypoglycemic patients. No accumulation of the glucose polymers occurs with once-daily usage.

Table 38–2

Indication for Using Icodextrin

- Long dwell dialysis
- Overnight to replace 3.86% glucose
- Daytime dwell in APD
- Loss of UF
- Hyperpermeability
- Presence of a large vascular surface area
- Loss of aquaporins
- During peritonitis
- In diabetic patients to reduce glucose load

Table 38–3

Newer PD Solutions and Their Characteristics

7.5% Icodextrin
- Reduced glucose exposure
- Better/longer ultrafiltration
- Low GDP levels
- Once daily for long dwell
- May interfere with BM monitoring

1.1% Amino Acids
- Reduced glucose exposure
- Similar UF profile to 1.36% glucose
- Low GDP levels
- Prevent or help manage malnutrition
- May increase urea and acidosis

Bicarbonate/Lactate Buffered Solution
- Standard glucose exposure
- Standard UF profile
- Low GDP levels
- Normal pH
- Less peritonitis
- Less inflow pain

Amino Acids

Amino-acid-based solutions are used as a substitute for glucose-based solutions and as a nutritional supplement. Albumin losses in PD constitute up to 63% of the total protein lost in the dialysate. Amino-acid-based solutions have been shown to replace amino acids lost during PD and possibly to correct protein malnutrition. A 1.1% amino-acid-based solution, containing 87 mmol/L amino acids, is available as Nutrineal (Baxter Healthcare Corporation)—with an osmolality of 365 mOms/kg of water. With an absorption rate of 70 to 80% over 4 to 6 hours, a single exchange coinciding with a major meal can contribute up to 25% of the target daily protein intake in an average adult. This is achieved without the phosphate loading associated with dietary protein supplementation. This may be beneficial in severely malnourished patients, but the clinical results of treatment with amino acid PD fluids are disappointing.

Although amino-acid-based solutions are effective osmotic agents, their use is associated with increased acidosis and urea generation—leading to increased alkali and dialysis prescription.

Thus, they are primarily used to replace a single glucose exchange to serve as nutritional supplementation in severe malnutrition and in hypercatabolic states such as peritonitis, and to reduce membrane exposure to glucose and GDP. There is no evidence that they prevent malnutrition.

Glycerol

Glycerol, a low-molecular-weight sugar alcohol, has been been the subject of trials primarily in PD patients with diabetes. It produces more UF initially than equivalent glucose concentrations, but due to its low molecular weight is absorbed rapidly—resulting in a lower total net UF than glucose. A higher pH makes it more biocompatible, and despite higher calorie loads glucose homeostasis and insulin requirements are better than in PD patients with diabetes treated with a standard glucose dialysate. The risk of hyperosmolar symptoms and raised triglycerides has limited its use and it is not commercially available.

Fructose, Xylitol, and Sorbitol

These have been the subject of trials in patients with diabetes on PD, but they have failed to show any advantage over glucose-based solutions (or were limited by their side effect profile).

Acid-Base Buffers

Metabolic acidosis is a common complication of end-stage renal disease. Patients on PD tend to have better control of metabolic acidosis, as reflected by normal mean bicarbonate levels. This correction is predominantly achieved by continuous supplementation with alkali as part of PD solutions. The buffer composition of available PD solutions can be divided into three categories.

- Nonbicarbonate buffers
- Bicarbonate/lactate combination buffers
- Bicarbonate buffers

Nonbicarbonate Buffers

Nonbicarbonate buffers (including lactate, acetate, and pyruvate) are naturally occurring compounds with established metabolic fates, such as the glycolytic pathway. Acetate is no longer used due to an association with peritoneal membrane injury. Pyruvate buffers are not commercially available. Lactate is used either alone

or in combination with bicarbonate. It is a naturally occurring molecule that is metabolized in the glycolytic pathway, is stable, and has a long safety history with Ringer's lactate solution. In the liver, it is metabolized back to pyruvate, which is then converted back to CO_2 and H_2O (80%) or to glucose (20%). Either of the following processes results in the generation of bicarbonate.

$$\text{Lactate}^- + 3O_2 \forall HCO_3^- + 2CO_2 + 2H_20$$

$$2\ \text{Lactate}^- + 2H_20 + 2CO_2 \forall 2HCO_3^- + \text{glucose}$$

The load of lactate absorbed from PD solutions is small compared to the rate of lactate production in vivo, with no elevations in serum lactate occurring as a result. Problems with lactate solutions include pain upon infusion, peritoneal macrophage and mesothelial cell toxicity, enhanced glucose-mediated peritoneal toxicity, and peritoneal fibrosis through TGF-β1 and BCP-1 production.

Bicarbonate/Lactate Combination Buffers

In an attempt to improve biocompatibility, a glucose-based solution buffered with a combination of lactate (15 mmol/L) and bicarbonate (25 mmol/L) has been produced (Physioneal, Baxter Healthcare Corporation). This solution has an osmolality similar to that of a standard glucose-based solution, with a pH of 7.4 as opposed to the standard pH of 5.5. The bag is double chambered, with the glucose separate from the sodium bicarbonate and sodium lactate.

The development of novel gas-tight plastic bag materials has made it possible to store bicarbonate-based solutions for extended periods. This allows the glucose portion to be heat sterilized at a lower pH, resulting in less GDP production and thus improving its biocompatibility. Compared with lactate-buffered solutions, this solution is associated with lower peritonitis rates, improved function of macrophages and neutrophils, and less peritoneal membrane damage—as measured by lower effluent IL-6, hyaluronan, and VEGF levels and higher CA 125 levels. The long-term outcome of this biocompatible solution is still under study.

Bicarbonate Buffers

Recent advances in manufacturing technology have provided the option of separate alkaline and acidic fluid compartments. This permits the sterilization of glucose at very low pH, with greatly reduced glucose-degradation product formation. With the use of

lactate and/or bicarbonate as a buffer, this sterilization produces neutral-pH final dialysis solutions. A pure bicarbonate-buffered CAPD solution with 34 mmol/L of bicarbonate buffer is commercially available (Fresenius Medical Care).

Advantages suggested for such solutions include better patient acceptance (due to reduced pain during the fluid infusion) and a significant increase in serum bicarbonate concentration. A higher bicarbonate concentration of 39 mmol/L has also been examined and may provide additional acid-base correction in patients who remain mildly acidotic with 34 mmol/L solution. Whether bicarbonate fluids or bicarbonate/lactate fluids have specific advantages over each other under long-term use conditions in clinical practice remains unknown.

Recommended Reading

Coles G. Biocompatibility and new fluids. Perit Dial Int 1999;19(2):S267–70.
A comprehensive review of the biocompatibility issues in PD solutions in the late 1990s with both in vivo and in vitro analysis.
Davies SJ, et al. Longitudinal membrane function in functionally anuric patients treated with APD: Data from EAPOS on the effects of glucose and Icodextrin prescription. Kidney Int 2005;67:1609ô15.
A study showing the dangers of hypertonic solutions and the benefits of icodextrin 7.5% solution.
Hutchison AJ, Gokal R. Towards tailored dialysis fluids in CAPD: The role of reduced calcium and magnesium in dialysis fluids. Perit Dial Int 1992;12:75–76.
A review of the calcium and magnesium balance on CAPD and the rationale of reduced concentrations of these ions in PD solutions.
Leypoldt JK, Charney DI, Cheung AK, et al. Ultrafiltration and solute kinetics using low-sodium peritoneal dialysate. Kidney Int 1995;48:1959–66.
The rationale behind the increased UF and solute kinetics using low-sodium PD solutions.
Martis L, Topley N, Holmes CJ. Conventional and newer peritoneal dialysis solutions. In Owen WF, Pereira JG, Sayegh MH (eds.), *Dialysis and Transplantation: A Companion to Brenner and Rector's* The Kidney. Philadelphia: W.B. Saunders 2000:179–98.
A comprehensive review of PD solutions covering the in vitro effects and their clinical relevance.
Vardhan A, Zweers M, Gokal R, Krediet R. A solutions portfolio approach in peritoneal dialysis. Kidney Int. 2003;64(88):S114–24.
A comprehensive review of available PD solutions.

CHAPTER 39

Lymphatics, Peritoneal Fluid Losses, and Peritoneal Dialysis

Ramesh Khanna, MD

Introduction

Following intraperitoneal infusion of hypertonic or iso-osmotic solution in humans, a considerable capacity for fluid absorption has been observed and an absorption rate up to 300 mL per hour has been reported. Similarly, a continuous absorption of fluid (regardless of the tonicity of the dialysis solution) significantly reduces the measured net ultrafiltration during a dwell time in CAPD (continuous ambulatory peritoneal dialysis) patients. Indeed, a century ago intraperitoneal blood transfusions were used to correct anemia in neonates and fetuses.

There are two pathways through which fluid absorption may occur from the peritoneal cavity: by absorption across the capillary wall in response to osmotic and/or hydrostatic pressure gradients or by absorption by convection into the lymphatics located both in the subdiaphragmatic area and the interstitium of the abdominal wall. The exact route through which the intraperitoneal fluid is absorbed from the peritoneal cavity in peritoneal dialysis patients has been a topic of controversy and subject of debate between physiologists and clinicians. The terms *lymphatic flow rate*, *effective lymphatic absorption rate*, *true lymphatic flow*, and so on have further confused clinicians.

Researchers in mid-1900s assumed that all fluid absorbed from the peritoneal cavity along with proteins passed through lymphatics and that the rate of absorption was directly proportional to intraperitoneal hydrostatic pressure. The issue has been made difficult due to lack of a single lymphatic vessel that drains the peritoneal cavity. Therefore, it has not been possible to directly measure lymph flow from the peritoneal cavity. A number of studies have pointed out a marked discrepancy between the observed rate of fluid absorption from the peritoneal cavity and the appearance in the plasma of the protein equivalent fluid. Studies indicate that the plasma appearance rate of fluid is less than 25% of the total fluid absorbed from the peritoneal cavity.

The specialized end lymphatics (stomata) were first observed in 1863, and were recently reconfirmed as allowing entry of intraperi-

toneal fluid, solutes, particles, and cells by extracellular pathways. A negative pressure created by diaphragmatic movement during inspiration aided by the intraperitoneal positive hydrostatic pressure causes absorption of fluid through lymphatics. Nearly 80% of the peritoneal lymphatic drainage enters the venous circulation via the right lymph duct. Estimations of peritoneal lymphatic absorption in patients with hepatic ascites have ranged from 24 to 225 mL/hour, whereas in patients with malignant ascites the range is from 1 to 63 mL/hour.

Rate of Fluid Loss from the Peritoneal Cavity during Peritoneal Dialysis Exchanges

In hypertonic peritoneal dialysis, the net transcapillary ultrafiltration rate is highest during the exchange at time zero and decreases exponentially as the dialysate glucose concentration is dissipated by a combination of dilution by the ultrafiltrate and transperitoneal glucose absorption. The peak intraperitoneal fluid volume is observed much before the cessation of ultrafiltration and osmotic equilibration.

After the peak, the intraperitoneal volume begins to decrease—indicating that the net fluid absorption occurs much before net transcapillary ultrafiltration is complete. In addition, osmolar equilibrium is reached before osmotic pressure and glucose equilibrium. The dialysis solution becomes iso-osmolar with the plasma before glucose equilibrium because of solute sieving. That the dialysis solution becomes hypo-osmolar to the plasma toward the end of the dwell time further suggests that net transcapillary ultrafiltration continues after osmolar equilibrium. Consequently, the reduction in intraperitoneal volume after attaining a peak really represents absorption through lymphatics and not into the microcirculatory capillaries.

Direct measurements of drain volumes after sequential dwell times suggest that the rate of decrease in the intraperitoneal volume averages 39 mL/hour. The net absorption rate is not significantly different irrespective of whether 2-L volumes of 1.5, 2.5, or 4.25% dextrose dialysis solution are instilled. Irrespective of the initial solution tonicity and infusion volumes, a near constancy of absorption rate reflects a nonosmotic- or nonhydrostatic-driven absorption of an isosmotic fluid—presumably through lymphatic channels.

Direct measurement of lymphatic drainage (thoracic duct and caudal mediastinal lymph duct) of the peritoneal cavity in anesthetized sheep after administration of 50-mL/kg volumes

of 1.5% dialysis solution estimated a total rate of lymph flow of 0.454 mL/hour/kg over a 6-hour period. The direct estimation of lymph flow rate in this study is likely a gross underestimation of the true rate because of the use of anesthesia. Anesthetic agents may depress active lymphatic pumping. The estimation of lymph flow response to excess intraperitoneal fluid in five awake sheep following cannulation of the caudal mediastinal node efferent lymphatic vessel showed a sevenfold increase in the flow rate from that of the baseline. In the caudal mediastinal lymph vessel alone, the rate of lymph flow was 0.5 mL/minute.

In conclusion, by extrapolation from previous studies of drain volumes after infusion of isotonic and hypertonic solutions (by analogy with ascites, and by direct estimation of lymph flow rates in response to dialysis solution in awake sheep) the average fluid loss from the peritoneal cavity is about four- to fivefold larger than plasma appearance of fluid—measured directly or indirectly.

Clinical Implications

Net ultrafiltration volumes are significantly decreased by cumulative intraperiotneal loss of fluid after long dwell exchanges in CAPD patients. Nevertheless, this loss produces a relatively greater reduction in net ultrafiltration in adults with high peritoneal solute transport characteristics. Loss of such fluid also contributes to reduced solute clearances because it depends on solute removal and ultrafiltration volume. Accordingly, it is not surprising that the efficiency of the peritoneum as a dialyzing membrane is greater than recognized.

Reductions in ultrafiltration and solute clearances due to back-absorption may therefore provide an opportunity for alternative means of increasing net ultrafiltration and solute removal without increasing the glucose load. Preliminary studies in animal models and human subjects suggest potential exists for decreasing such back-absorption fluid through pharmacologic action of certain drugs or through measures that reduce intraperitoneal hydrostatic pressure. None of the studies reported so far has provided a clinical tool to enhance ultrafiltration solute clearances in human subjects as yet.

Summary

Despite the continued controversy and debate over the term *lymphatic flow*, the following facts are undisputed and accepted by all. Loss rates of fluid from the peritoneal cavity during peritoneal

dialysis exchanges are significant and are usually of the order of greater than 1.0 mL/minute in most patients and have a major impact on the kinetics of ultrafiltration in long-dwell exchanges. Such fluid losses reduce both net ultrafiltration volumes and solute clearances each day by approximately 50% and 15%, respectively, each day. Nevertheless, currently available dialysis solutions allow sufficient net ultrafiltration to achieve adequate daily fluid balance and small-solute clearances in the majority of CAPD patients. These losses contribute significantly to fluid balance in those patients with loss of ultrafiltration. Future research should attempt to reduce such fluid losses through chemical or physical methods.

Recommended Reading

Flessner MF. Effective lymphatic absorption rate is not a useful or accurate term to use in the physiology of peritoneal dialysis. Peritoneal Dialysis International 2006;24:309–13.

An excellent discussion and review of peritoneal physiology that provides evidence to support the view that effective lymphatic absorption rate *is an imprecise and misleading term in describing the physiology of water transport during peritoneal dialysis.*

Flessner MF. Net ultrafiltration in peritoneal dialysis: Role of direct fluid absorption into peritoneal tissue. Blood Purification 1992;10:136–47.

An excellent review article that reviews the physiology of peritoneal fluid losses and its impact on ultrafiltration.

Krediet RT. The effective lymphatic absorption rate is an accurate and useful concept in the physiology of peritoneal dialysis. Peritoneal Dialysis International 2006;24:309–13.

An excellent discussion and review of peritoneal physiology that provides evidence to support the effective lymphatic absorption rate is an accurate and useful concept in the physiology of peritoneal dialysis.

Krediet RT, Koomen GCM, Koopman MG, Hoek FJ, Struijk DG, Boeschoten EW, et al. The peritoneal transport of serum proteins and neutral dextran in CAPD patients. Kidney Int 1989;35:1064–72.

Peritoneal interstitium is probably a third compartment between blood and dialysate in which equilibrium with blood and dialysate is present for serum proteins but not for dextran.

Mactier RA, Khanna R. Peritoneal lymphatics. In Gokal R, Khanna R, Krediet R, KD Nolph (eds.), *The Textbook of Peritoneal Dialysis, Second Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2000:173–92.

An exhaustive review of the current knowledge of peritoneal cavity lymphatics.

CHAPTER 40

Abnormalities of Host Defense Mechanisms During Peritoneal Dialysis

Clifford J. Holmes, PhD

The widespread use of peritoneal dialysis (PD) solution delivery systems designed to minimize the probability of touch contamination in both CAPD and APD (automated PD)—combined with overall improvements in catheter placement and exit-site care protocols, continuous quality systems, patient training, and so on—has made significant improvements in the last two decades on the incidence of peritonitis. The 2005 ISPD recommendations on PD–related infections identify the achievement of selected centers around the world in attaining peritonitis rates as low as one episode in every 50 patient-months.

Clearly, the prevention of peritoneal microbial contamination is the primary consideration in the prevention of peritonitis. Nevertheless, evidence exists from longitudinal studies using effluent culture techniques that the peritoneum is contaminated without subsequent peritonitis in as much as 7% of exchanges. Peritoneal host defense mechanisms must therefore be operative, despite the process large-volume intraperitoneal dialysis afforded by modern PD techniques.

Peritoneal macrophages and opsonins were first characterized in the dialysis effluent of CAPD patients in 1983. Since then, much research has led to the understanding of the important role the peritoneal membrane (especially the mesothelial cell lining) has in peritoneal host defense. In addition, the presence of granulocyte inhibitors in dialysis effluent and the effect of dialysis solution on host defense mechanisms have been the subject of much research. This chapter provides a brief review of peritoneal host defense mechanisms in PD patients, followed by a description of current and future therapeutic interventions aimed at augmenting identified deficiencies.

Host Defense Mechanisms of the Peritoneal Cavity

Relative to the normal peritoneum, the chronically dialyzed peritoneal cavity is considered an immunocompromised site. Factors that are important in this respect include inefficient lymphatic removal of contaminating microorganisms; critically reduced levels of antibody, complement, and leukocytes; the presence of granulocyte inhibitors; and the use of bioincompatible dialysis solutions. Lymphatic removal, particularly via the subdiaphragmatic lacunae, is believed to play an insignificant role in the prevention of CAPD peritonitis. It is proposed that the large volume of dialysate impairs convection of bacteria and phagocytosed cells to the lymphatics (hence, the rare observation of clinical septicemia associated with peritonitis). Furthermore, the concentrations of two important opsonins (immunoglobulin G and C3) are on average approximately 1/30 to 1/70 that of normal peritoneal fluid—and the leukocyte count is reduced to 10^3 to 10^4 cells/mL from a normal range of 10^6 to 10^7/mL.

Despite these general observations, the peritoneal macrophage (the predominant cell in dialysis effluent) has been proposed as the first line of cellular defense against bacterial invasion. Overwhelming of this phagocyte by microbial pathogens is believed to lead to clinical infection—with the classic associated polymorphonuclear leukocyte response, seen as a cloudy bag by the patient. Effective functioning of the peritoneal macrophage within the peritoneum is assumed to be initially dependent on effective opsonization of the invading pathogen by IgG, by C3b, and perhaps to a lesser extent by fibronectin.

Microorganisms are engulfed by macrophages by a process termed *receptor-mediated phagocytosis*. Intracellular killing of the microbe by macrophages then ensues via oxidative and nonoxidative mechanisms. Generation of chemotactic factors such as leukotriene B_4 may attract more phagocytes to the site of microbial invasion, thereby assisting in the immune response. Neutrophils will be recruited, potentially in very large numbers, to the site of inflammation in a classic amplification manner. In this respect, it is now thought that mesothelial cells play a pivotal role. In recent years, human peritoneal mesothelial cells have been reported to secrete cytokines, chemokines, and growth factors, and to express several important adhesion molecules—suggesting that these cells are critically involved in the orchestration of the inflammatory response to injury.

Ongoing research into peritoneal host defense continues to illustrate its complexity (Figure 40.1). For instance, it has been

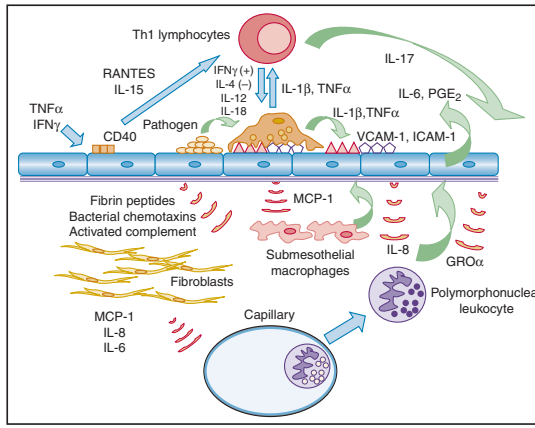


Figure 40–1

Cells and mediators involved in the host defense of PD patients. This diagram represents some of the better-described cells and mediators putatively involved in peritoneal host defense in PD patients.

reported that defensins (small antimicrobial peptides established as important contributors of innate immunity) are expressed by peritoneal leukocytes from CAPD patients—and are expressed by the peritoneal membrane and cultured mesothelial cells. It is now recognized that observations of elevated levels of γ interferon, TNF α, IL-12, and IL-18 during peritonitis represent a bias toward a Th1 immune response; that is, a response that activates cell-mediated immunity rather than humoral (antibody) immunity.

Detailed analyses of peritoneal leukocyte subpopulations continue to dissect the nature and function of this diverse population, as exemplified by recent observations of CD14+ cells that differentiate into macrophages or dendritic cells. Within this pool is an additional subset of cells (described as myeloid dendritic precursor cells) that is likely pivotal to the Th1 response in peritonitis. Finally, significant insights into the molecular regulation of the immune response, both in the amplification and the resolution phases of peritonitis, have been made in recent years. For example, it is now known that it is IL-6 signaling via its soluble IL-6 receptor that coordinates the transition from

neutrophil to mononuclear cell infiltration during the course of peritonitis.

Is Opsonic Activity of Peritoneal Dialysate Important?

The most compelling evidence that effective intraperitoneal opsonization of potential pathogens is important in the prevention of peritonitis is the finding that there is an inverse relationship between the opsonic activity and/or IgG concentration of effluent and the frequency of peritonitis. Several groups have reported this finding. However, an almost equal number of studies have found no such correlation within their patient populations. Reasons for disagreement among studies are unclear but may include inadequate sample sizes and differences in methodologies, such as dwell times used or the assays employed for determination of opsonic activity.

Serum IgG levels have been reported to be low in pediatric CAPD patients, with no selective absence of any subclass. In contrast, total serum IgG levels were reported to be normal in a Dutch adult CAPD population—with a selective decrease in IgG_2 and IgG_4 caused by decreased synthesis. In neither study was a correlation with peritonitis identified.

Phagocytosis and Intracellular Killing

The in vitro phagocytic capability of peritoneal macrophages of most CAPD patients appears to be comparable to that of peritoneal macrophages obtained from women undergoing laparoscopy and of peripheral blood monocytes. In fact, not only is phagocytic function unhindered in most patients but such dialysate-elicited macrophages appear to resemble stimulated or activated cells as described by a variety of functional and phenotypic characteristics. Studies that have included peritoneal macrophages from laparoscopy patients for comparison have found that CAPD peritoneal macrophages also exhibit some characteristics of immature cells. Together, these observations suggest that the peritoneal macrophage population of CAPD patients consists of young inflammatory cells.

Some reports have identified specific functional defects or changes in peritoneal macrophage function associated with PD. In patients with frequent episodes of peritonitis (e.g., 2/patient-year) there appears to be an impairment in intracellular killing of bacteria by macrophages associated with enhanced prostaglandin

E_2 production and decreased interleukin-1 production, Fc receptor expression, and respiratory burst activity. Due to the cross-sectional design of these latter studies, it is impossible to determine cause or effect. A single-center longitudinal study of PD patients has identified a transient decrease in the phagocytic capacity of macrophages in the few days before peritonitis. To date, two reports have identified changes in macrophage-receptor expression and in cytokine synthesis that occur with time on PD—although no specific relationship to peritonitis was reported.

Impaired phagocytosis and intracellular killing by both peripheral blood and peritoneal polymorphonuclear leukocytes have been reported in CAPD patients. In a follow-up clinical study, a trend toward higher peritonitis rates and catheter removals in patients with proven defective intracellular killing by peripheral blood PMN (polymorpho-nuclear neutrophils) was reported—which did not, however, reach statistical significance.

Can Cytokine Responses Predict the Clinical Course of Peritonitis?

Recent research suggests that the cytokine response profile to peritonitis correlates with the clinical course of infection. In patients with a rapid response to antibiotic therapy, effluent levels of the proinflammatory cytokines IL-12, IL-18, and γ interferon were significantly more elevated than those of patients with a protracted response. Furthermore, two distinct patterns of peritoneal T-cell gene expression of γ interferon and two important transcription factors involved in T-cell differentiation were seen between the rapid and protracted response to treatment groups. These differences could not be explained by baseline characteristics.

Peritoneal Dialysis Solution Biocompatibility

In addition to the previously described immunologic alterations within the population with a high peritonitis incidence, it is now well established that several aspects of conventional PD solution formulations can impair in vitro peritoneal leukocyte, mesothelial, and fibroblast function. The acidic pH of commercially available dialysis fluids, in combination with their high lactate concentration, can inhibit phagocytosis and oxidative metabolism of peritoneal phagocytes—as well as the ability of mesothelial cells to secrete cytokines. Hypertonicity, especially of the highest glucose concentrations employed (4.25% wt/vol),

can diminish phagocytic function and respiratory burst activity. Similarly, the concentrations of glucose degradation products (again, especially in the highest glucose levels) can suppress cell function in vitro. Several animal models have also shown an improvement in peritoneal membrane function with more biocompatible solutions. In terms of clinical evidence, despite the ability to demonstrate that peritoneal cell function can be improved with biocompatible solutions there is only limited evidence from uncontrolled studies that infection rates may be reduced with this new generation of solutions. The effect of biocompatible solutions on the course of peritonitis and on the overall inflammatory insult remains unknown.

Granulocyte Inhibitory Proteins

There is a growing list of both low- and high-molecular-weight compounds isolated from both PD effluent and from plasma ultrafiltrates from high-flux hemodialysis patients that are inhibitors of granulocyte function. It is likely that these compounds are not produced locally but are being removed by dialysis. The specific role of these compounds in the pathogenesis of peritonitis is not well understood.

Therapeutic Approaches

Immunologically based therapeutic interventions designed to prevent peritonitis in CAPD patients have focused on enhancing opsonic activity of effluent or on correcting leukocyte defects in patients at high risk for peritonitis. Unfortunately, neither of these strategies was originally derived from prospective studies—and immunoprophylaxis for PD patients has not yet been proven either safe or effective in the long term. In the following sections, both historical and current approaches to the therapeutic enhancement of peritoneal host defenses of PD patients are discussed. They are summarized in Table 40.1.

Strategies to Enhance Opsonization

Passive immunization by chronic intraperitoneal instillation of intravenous-quality IgG and active immunization with commercially available staphylococcal vaccines have been used to enhance opsonization. Clinically, several uncontrolled studies have reported some benefit to intraperitoneal IgG therapy in patients with a

Table 40–1

Therapeutic Strategies to Enhance Peritoneal Host Defense Mechanisms

Not Possible/Practical Today	Clear Benefit Not Established
1. Enhance lymphatic uptake 2. Selectively remove dialysate inhibitors of granulocyte function	1. *S. aureus* vaccination 2. Immunomodulation with IP α-IF, 1,25-dihydroxy vitamin D_3, GM-CSF, or SC administration of G-CSF
Limited Benefit Identified	**Potential Future Benefit?**
– Intraperitoneal IgG – Peritoneal resting with continued antibiotic therapy for uncomplicated and mild cases of peritonitis	– Biocompatible PD solutions

IgG = immunoglobulin, P = intraperitoneal, SC = subcutaneous, PD = peritoneal dialysis, G-CSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte macrophage colony-stimulating factor.

high incidence of peritonitis. However, due to the inability to accurately identify patients at high risk for peritonitis by measurement of effluent IgG in a prospective manner and in the absence of controlled randomized studies contemporary experience with intraperitoneal instillation of IgG appears to be restricted to the treatment of refractory peritonitis in conjunction with antibiotic therapy in a small number of selected centers.

An *S. aureus* vaccine consisting of a conjugate between *S. aureus* capsular polysaccharides 5 and 8 (conferring specificity) and detoxified *Pseudomonas aeruginosa* exotoxin (conferring T-cell-dependent memory) failed to confer protection against *S. aureus* peritonitis and exit-site infection.

Strategies to Enhance Cell Function

Until recently, experience in enhancing cell function was limited to a few uncontrolled studies of either intraperitoneal α-interferon or calcitriol (1,25-dihydroxy vitamin D_3). The rationale for exogenous α-interferon was simply to supply this mediator of immune function to correct for decreased production of lymphocyte interferon. Calcitriol enhances the antimicrobial function of macrophages

by improving superoxide production and intracellular killing. However, reports describing a significant reduction in peritonitis rates using these agents are limited and small in study size.

Several groups have suggested that granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be of use in patients presenting with recurrent peritonitis or who have proven impaired PMN killing. The colony-stimulating factors have shown clinical benefit in many studies of patients with pathologic states associated with abnormal phagocytic cell function and increased risk of infection (e.g., HIV, hematopoietic malignancy, and cirrhosis). Despite the demonstration of transient changes in peritoneal cell numbers, phagocytic index, cell-receptor expression, and dialysate cytokine levels observed after a 3-day course of intraperitoneal GM-CSF, the usefulness of GM-CSF as an adjunctive treatment of recurrent or refractory peritonitis has not been reported.

Long Dwells and Peritoneal Membrane Resting

Longer dwell periods associated with some forms of APD permit a transient and intermittently enhanced opsonic activity and leukocyte function. Recent clinical trials on peritonitis rates comparing CAPD with APD have been conflicting in their conclusions, but there seems to be a trend toward a lower peritonitis incidence with APD. The practice of "resting" the peritoneum during treatment for recurring or relapsing peritonitis by temporarily discontinuing PD with continuation of antibiotic therapy is occasionally used by some clinicians, although its role appears to be limited to uncomplicated and clinically mild cases. This approach is based on the logic that enhanced opsonic activity, leukocyte function, and possibly lymphatic removal will ensue—thereby allowing either less aggressive antibiotic therapy or reduced potential for relapse. Unfortunately, no controlled studies have been published on such approaches.

Summary

Today there exists a relatively large body of published research characterizing the host defense system of PD patients. Abnormalities of local peritoneal immunity include dilutional and bioincompatible effects of the dialysis solution itself, specific leukocyte functional defects, and the presence of functional inhibitory uremic molecules. Despite growing insight into the

pathobiology of PD-related peritonitis, there has been limited translation of this knowledge as yet into practical clinical measures for enhancing peritoneal host defense.

Recommended Reading

Brunkhorst RR. Host defenses in APD. Seminars in Dialysis 2002;15(6):414–17.
A review of differences between APD and CAPD on peritoneal host defense status and its clinical implications.

Dursin B, Tuncer M, Felek R, et al. Benefits of low dose immunoglobulin in the treatment of refractory CAPD peritonitis and longevity of technical survival on CAPD. International Urology and Nephrology 2005;37:565–69.
A single center's experience in using IP IgG as an adjunctive treatment for refractory peritonitis.

McCully ML, Chau TA, Luke P, et al. Characterization of human peritoneal dendritic cell precursors and their involvement in peritonitis.
A recent example of the continuing phenotypic and functional characterization of peritoneal leukocyte populations.

McLoughlin R, Hurst SM, Nowell MA, et al. Differential regulation of neutrophil activating chemokines by IL-6 and its soluble receptor isoforms. Journal of Immunology 2004;172:5676–83.
A seminal research study describing pivotal cellular and molecular mechanisms behind the regulatory role of neutrophils during peritonitis.

Mortier S, Lameire NH, De Vriese AS. The effects of peritoneal dialysis solutions on peritoneal host defense. Peritoneal Dialysis International 2004;24(2):123–38.
A comprehensive review of peritoneal host defense mechanisms and the effects of peritoneal dialysis solutions and its components on peritoneal host defense.

Wang HH, Lin CY. Interleukin 12 and 18 levels in peritoneal dialysis effluent correlate with the outcome of peritonitis of patients undergoing peritoneal dialysis: Implications for the type I/type II T cell immune response. American Journal of Kidney Disease 2005;46:328–38.
A recent study that identifies biochemical indices of peritoneal immunity that appear to be predictive of the outcome of peritonitis.

C H A P T E R 4 1

Peritoneal Catheter Exit-Site and Tunnel Infections

Zbylut J. Twardowski, MD, PhD

Infection Prevention

There are three fundamental prerequisites for exit-site infection prevention: catheter design, implantation technique, and post-implantation care.

Catheter Design

Silicon rubber tubing with double polyester cuffs is still the best design for preventing infection. A permanent bend between cuffs seems to have an edge over other catheter designs because it allows implantation of the catheter in an unstressed condition in an arcuate tunnel with both internal and external exits directed downward.

Implantation Technique

Prior to implantation—depending on the size and shape of the abdomen, the presence of previous scars, and the patient's preference—the exit site should be selected and marked in such a way that the catheter will not be subjected to excessive motion with patient activity and no pressure will be exerted on the tunnel by a belt or tight garment or when the patient bends forward. Prophylactic antibiotics for catheter placement, preferably cephalosporins (1.0 g IV 1 hour preoperatively and repeated 12 hours postoperatively), provide an adequate antibiotic level in the coagulum and will decrease the bacterial load in the wound.

General anesthesia should be avoided, if possible, because it predisposes to vomiting and constipation and requires voluntary coughing during the postoperative period as part of pulmonary atelectasis prevention. Coughing, vomiting, and straining markedly increase intra-abdominal pressure and predispose the catheter to abdominal leaks. Pericatheter dialysate leaks interfere with fibrous tissue ingrowth into the cuff and should be avoided. For

presternal catheter implantation, general anesthesia is preferable because of the need to create a long tunnel.

A meticulously sterile surgical technique during implantation is mandatory. Perfect hemostasis, preferably using cauterization, is required because in our experience a wound hematoma frequently leads to early exit-site infection. After implantation, the catheter is covered with several layers of gauze and is anchored with air-permeable tape. The dressing is left in place for a week.

Peritoneal dialysis exchanges are performed to check the patency of the catheter and to remove residual blood from the peritoneal cavity, if present. The exchanges are continued until the dialysate is clear. Ambulatory peritoneal dialysis is delayed for at least 10 days after the implantation, but peritoneal dialysis in the strict supine position (while the fluid is in the peritoneal cavity) may be started immediately after in-and-out exchanges are completed. A 1-L volume of dialysis solution is used for the initial supine peritoneal dialysis exchanges.

Early Postimplantation Care

To delay bacterial colonization of the exit site and to minimize trauma, the dressing should not be changed too frequently. To delay bacterial colonization, we use a systemic antibiotic against Gram-positive bacteria (usually cephalothin or trimethoprim-sulfamethoxazole) for 2 weeks after implantation and a local antibiotic (usually mupirocin ointment or cream) for at least 6 weeks. Postoperative dressing changes should be restricted to specially trained staff. We do weekly dressing changes for the first 2 weeks postcatheter implantation if drainage is not excessive. More frequent dressing changes are indicated after 2 weeks because the exit has already become colonized and thus the major rationale for infrequent dressing changes (avoidance of exit colonization) no longer exists. Moreover, more frequent cleansing of the exit will decrease the number of bacteria at the exit.

Aseptic technique, including both masking and wearing sterile gloves, should be used for postoperative dressing changes. Nonionic surfactant (e.g., Poloxamer 188) is used to help gauze removal if the gauze is attached to the scab. If the scab is forcibly removed and the epidermal layer is broken, a new scab has to form and the epidermization is prolonged. Care is taken to avoid catheter pulling or twisting. The exit and skin surrounding the catheter are cleansed with nonionic surfactant, patted dry with

sterile gauze, covered with several layers of gauze dressings, and secured with air-permeable tape.

The exit and visible sinus should be evaluated for quality of healing at each dressing change throughout the 6-week healing period. If healing does not progress, or if there are signs of deterioration or infection, a culture of the exudate should be taken and an appropriate systemic antibiotic should be given.

We recommend that our patients do not shower or take tub baths post catheter implantation to avoid colonization with water-borne organisms and to prevent skin maceration. Once more frequent dressing changes are started (after approximately 2 weeks), the patient may take a shower—but only before the dressing change. Otherwise, sponge baths should be used and patients should avoid exit-site wetting.

Protecting the catheter from mechanical stress seems to be extremely important, especially during break-in. Catheters should be anchored in such a way that the patient's movements are only minimally transmitted to the exit. The method of catheter immobilization is individualized, depending on exit location and the shape of the abdomen. We believe that better exit protection prevents infections in most patients.

Late Postimplantation Care

Late care, after the healing process is completed, is simpler. Cleaning with soap and water is the least expensive care method and tends to prevent infections better than povidone-iodine painting and hydrogen peroxide cleaning. The cleansing agent should decrease the number of bacteria and be harmless to the body defenses. Povidone-iodine in bactericidal concentrations is cytotoxic to mammalian cells and is harmful to granulation tissue if it enters the sinus. It is also harmful to catheter material, both polyurethane and silicone rubber. Thus, if strong oxidants of this type are used they should be applied only around the exit site and should be prevented from entering the sinus and from soaking the catheter itself.

A dressing cover should be used for at least 6 to 12 months after implantation. One year after implantation, patients can use or not use dressing covers—but the catheter still has to be protected from trauma. The author recommends that his patients only use showers and avoid submersion in water (particularly in a Jacuzzi, hot tub, or public swimming pool) unless watertight exit-site protection can be implemented. Prolonged submersion

in water containing high concentrations of bacteria frequently leads to severe infection with consequent loss of the catheter. Swimming in the ocean and in well-sterilized private pools is less hazardous to the patient. Exit-site care must be performed immediately after a shower or water submersion, with particular attention paid to obtaining a well-dried exit site.

Excellent results observed with mupirocin ointment in healing exits, in prevention of infections in *S. aureus* nasal carriers, and in the treatment of equivocal exits and recurrent exit-site infections (see material following) inclined the author to extend indefinitely the use of mupirocin ointment on the exit site. Patients report that the epidermis around the exit site is less dry and chafed as the catheter "glides" better over the sinus epidermis. It is possible that the good results of mupirocin and other ointments applied on the exit sites are, at least partly, related to the moisturizing/lubricating action of the ointment base. Continuous mupirocin use has been reported to decrease exit infections in peritoneal and intravenous catheters.

Diagnosis of Exit-Site Infection

There is no difficulty in the diagnosis of peritonitis: the dialysate contains either a small number of cells when uninfected or a large number of cells, mostly granulocytes, when infected. Normal dialysate does not contain microorganisms, but a correctly performed culture is usually positive in peritonitis. Bacterial peritonitis cannot be cured without antibiotics. Attempts to classify exit-site appearance into two categories (infected and not infected) are difficult, if not impossible, because infected and uninfected exit-site appearances overlap.

This overlap is due to the peculiarity of the tissue reaction to the foreign body penetrating the skin and stems from the delicate balance between bacteria in the sinus and the host defenses. The presence of a small amount of exudate causing crust formation does not indicate infection, but if the bacterial attack is more severe the amount of exudate increases, granulation tissue proliferates and becomes more vascularized, the epithelium regresses, and the signs of infection become obvious. Low-grade exit-site infection may abate without systemic antibiotics.

For 8 years we evaluated exit-site appearance in the immediate postimplantation period and after the exit site healed. The classification we developed is based on the cardinal signs of inflam-

mation: heat, redness, swelling, and pain. Additional features—specific for an exit site of any skin-penetrating foreign body—are drainage, regression of epidermis, and exuberance (profuse overgrowth) of granulation tissue ("proud flesh"). Granulation tissue is defined as exuberant if it is significantly elevated above the epidermis. Culture results do not influence the exit-site classification. Positive cultures in exit sites that are not inflamed indicate colonization, not infection. Cultures are commonly negative from infected exit sites when patients are on antibiotic therapy. However, inflammation in almost all cases is caused by infection—regardless of culture results. Inflammatory responses to the tubing itself or to local irritants are rare.

Improvement or deterioration of inflammation is associated with respective decreases or increases of pain, induration, drainage, and/or exuberant granulation tissue, and/or regression or progression of epithelium in the sinus. An increase in lightness (pink, pale pink) or darkness (deep black, brown) and a decrease in color diameter indicate improvement. An increase in red color saturation and an increase in diameter indicate deterioration. Ultimately, a new classification with five distinct categories of exit-site appearances was established: acute infection, chronic infection, equivocal, good, and perfect. Finally, two special categories were identified: external cuff infection and traumatized exit. Trauma may result in various appearances. Cuff infection may not be associated with exit infection. The classification categories of exit-site infections are outlined in Table 41.1.

Treatment Recommendations

The use of the classification system presented in Table 41.1 facilitates early diagnosis of exit-site problems and enables treatment to be more specific.

Acute Exit-Site Infection

A culture of exit-site exudate or, if there is swelling/erythema without expressible exudate, a smear culture of the skin surrounding the exit site should be taken as soon as a clinical diagnosis of an acute exit-site infection is made. Systemic antibiotics should be started before culture results are available. Gram-positive organisms are frequently the cause of exit-site infections. Accordingly, oral cephalosporin or trimethoprim-sulfamethoxazole may be selected as the initial antibiotic. The

Table 41–1

Classification Categories of Exit-Site Infections

Category	Description
Acute catheter exit-site infection	Purulent and/or bloody drainage from the exit site (spontaneous or after pressure on the sinus) and/or swelling and/or erythema with diameter ≥13 mm from border to border, and regression of epithelium in the sinus. Acute catheter inflammation lasts <4 weeks and may be accompanied by pain, exuberant granulation tissue around the exit site or in the sinus, and the presence of a scab or crust. The exit-site culture may be negative in patients receiving antibiotics.
Chronic catheter exit-site infection	Purulent and/or bloody drainage from the exit site (spontaneous or after pressure on the sinus) and/or exuberant granulation tissue around the exit site and/or in the sinus; and regression of epithelium in the sinus. Chronic infection persists for >4 weeks and crust or scab is frequently present. Swelling, erythema, and/or pain indicate exacerbation. Otherwise, they are absent. The exit-site culture may be negative in patients receiving antibiotics.
Equivocally infected catheter exit site	Purulent and/or bloody drainage that cannot be expressed outside the sinus, accompanied by regression of the epithelium and the occurrence of slightly exuberant granulation tissue around the exit site and/or in the sinus. Erythema with a diameter <13 mm from border to border may be present, but pain, swelling, and external drainage are absent. The exit-site culture may be negative in patients receiving antibiotics.
Good catheter exit site	The exit-site color is natural, pale pink, purplish, or dark, and there is no purulent or bloody drainage. Clear or thick exudate may be visible in the sinus. Mature epithelium covers only part of the sinus; the rest is covered by fragile epithelium or plain granulation tissue. Pain, swelling, and erythema are absent. A positive periexit-site smear culture, if present, indicates colonization (not infection).

Table Continued

Table 41–1

Classification Categories of Exit-Site Infections—Cont'd

Category	Description
Perfect catheter exit site	The perfect catheter exit site is at least 6 months old and its entire visible length of sinus tract is covered with keratinized (mature) epithelium. Exit-site color is natural or dark, and there is no drainage. A small, easily detachable crust may be present in the sinus or around the exit. A positive periexit-site smear culture, if present, indicates colonization (not infection).
External cuff infection without exit-site infection	Intermittent or chronic, purulent, bloody or gooey drainage (spontaneous or after pressure on the cuff) and induration of the tissue around the cuff. Exuberant granulation tissue may be seen deep in the sinus. The sinus epithelium may be chronically or intermittently macerated. The exit site may look normal upon external examination. Ultrasound may show a fluid collection around the cuff, but a negative ultrasound does not rule out cuff infection. The exit culture may be negative in patients receiving antibiotics.
Traumatized exit site	The features of a traumatized exit site depend on the intensity of the trauma and on the time interval until examination. Common features of trauma are pain, bleeding, scab, and deterioration of exit-site appearance (e.g., a perfect exit site transforms to a good or to an equivocal or to an acutely infected exit site).

antibiotic prescription should be adjusted after the organism(s) is identified and the antibiotic sensitivity results are available.

The antibiotic is initially prescribed for a period of 7 to 10 days, the time required for an uncomplicated acute infection to heal (achieve a good appearance). If there is no improvement after this period, another appropriate antibiotic is substituted or a second synergistic antibiotic is added. Rifampin is frequently used as a second antibiotic for Staphylococcal infections. Antibiotic therapy is continued for 7 days after achieving the

healthy appearance of an exit. Conditions that delay healing or that make therapy ineffective are cuff and/or tunnel infection, infection due to a resistant organism or virulent pathogens (such as *Staphylococcus aureus*, *Pseudomonas sp*., or *Candida*), and patient noncompliance.

Exuberant granulation tissue (proud flesh) is cauterized with a silver nitrate stick. No more than one or two applications may be necessary in acute infection. This procedure speeds the healing process and facilitates epithelialization. Cauterization should be restricted to granulation tissue only. Touching of the adjacent epithelium should be avoided. Use of a magnifying glass aids in precise cauterization. This can be done safely by a physician or nurse. Patients should not cauterize granulation tissue themselves.

Recommendations for the care of infected exit sites are based on sound surgical practices and on anecdotal experiences. Increasing the frequency of dressing changes to one or two times a day helps the healing process, especially in those with copious drainage. Nonirritating solution (e.g., nonionic surfactant) is our preferred cleanser to remove drainage and to reduce the number of microorganisms. An infected exit site should be covered with a sterile dressing to absorb drainage, to protect against trauma, and to shield against superinfection.

Topical treatments include application of soaks to the exit site two to four times daily, as well as the application of dry heat to the exit site. Soaking solutions include normal saline, hypertonic saline, sodium hypochlorite, dilute hydrogen peroxide, povidone-iodine, and 70% alcohol. Local application of povidone-iodine ointment, mupirocin, and Neosporin cream, ointment, or ophthalmic solutions have been recommended. In the author's opinion, strong oxidants and other irritating solutions should not be used. It is the author's belief that topical antibiotics are of limited value in treating acute or chronic infection with copious drainage because of the inability to achieve high enough local concentrations. However, topical antibiotics are helpful once drainage diminishes.

Catheter immobilization is a sound practice. Immobilizing a catheter protects it from accidental trauma. Trauma leads to bleeding, and blood is a good medium for the multiplication of microorganisms. Catheter immobilization should be continued during the acute infection stage, or implemented then if it is not already in practice.

Most acute infections respond favorably to therapy. An exit site with an acute infection in association with proud flesh and bleeding requires prolonged antibiotic therapy. An association with a positive nasal culture has no influence on the outcome.

Recurrent infections that progress to chronic infection and/or cuff infection are associated with a poor prognosis. Catheter removal is indicated when acute exit-site infection leads to tunnel infection and peritonitis.

Chronically Infected Exit Site

The workup leading to the proper diagnosis of a chronically infected exit site is similar to that performed to diagnose acute infection. An antibiotic is started immediately after diagnosis, if the patient has not already been on an antibiotic. Once the culture and antibiotic sensitivity results are available, an appropriate antibiotic is chosen. A combination of synergistic antibiotics is preferred to a single agent to avoid emergence of resistant organisms, in that the therapy is given over a prolonged period. In chronic infection, the bacterial flora or the antibiotic sensitivity may change during the course of treatment. Therefore, an unresponsive exit site may have to be cultured repeatedly for a timely diagnosis. The response to treatment is usually slow. The features of a chronic infection change very slowly to those of an equivocal exit site, and then eventually to those of a good exit site.

The antibiotic therapy and local care of the exit site are continued until the desired features of a good exit site are achieved. In some cases, exit-site features change to equivocal and remain as such for a long time. In such cases, the systemic antibiotic may be discontinued and replaced with a topical antibiotic (see material following). Chronic infection requires repeated cauterization of exuberant granulation tissue.

Typically, weekly cauterization for several weeks is necessary. The cauterization is continued as long as the proud flesh persists. The cauterization will discolor the proud flesh from red to gray. Some cases of chronic infection may require long-term suppressive doses of a systemic antibiotic. Typically, these cases show reinfection upon discontinuing the systemic antibiotic. It is likely that such cases represent undiagnosed cuff infection and require appropriate treatment (see material following). Local care is similar to that used in treating acute infection. After achieving the features of an equivocal exit site, the frequency of local care may be reduced to once a day.

Equivocal Exit Site

The equivocal exit site is a subclinical form of infection. If left untreated, most equivocal exit sites progress to acute infection.

Therefore, aggressive management of equivocal exit sites assumes great importance. Aggressive local care with a topical antibiotic may cure most equivocal exit sites. Exit sites with external slightly exuberant granulation tissue, which usually progress to acute infection, require systemic antibiotics.

Cauterization of the slightly exuberant granulation tissue in the sinus may be necessary. An acute infection may acquire equivocal features during the recovery phase. Such an exit site warrants less aggressive therapy compared to an exit site with acute infection. Discontinuation of the systemic antibiotic and daily local care is continued in such a situation.

Local therapy with topical antibiotics is the mainstay of treatment for an equivocal exit site. A topical antibiotic is chosen based on the exit-site swab culture results. The topical antibiotics we have successfully used include mupirocin, Neosporin, gentamicin, chloramphenicol, and tobramycin in bacterial infections and ketoconazole 2% cream in fungal infections. The effectiveness of this approach is due to the absence of copious drainage from the sinus tract. Systemic antibiotics may be used in cases unresponsive to topical therapy. The response to therapy is excellent, with a cure occurring in almost all cases.

Good and Perfect Exit Sites

Catheter immobilization, protection from trauma, use of liquid soap and water for daily care, and use of Shur-Clens to remove large irritating crust are appropriate measures to prevent infection. In the author's experience, a perfect exit site is unlikely to become infected unless severely traumatized or grossly contaminated after submersion in water loaded with bacteria.

Traumatized Exit Site

Bleeding is a common sequela of trauma. Extravasated blood is a good medium for bacterial growth. Bacteria that have colonized the exit site multiply rapidly in the presence of decomposing blood and infect the disrupted tissue. Infection may occur as early as 24 to 48 hours after trauma. The prompt administration of an antibiotic, chosen based on the history of skin colonization, may prevent acute infection. In the absence of information about previous skin colonies, an antimicrobial agent effective against Gram-positive organisms (such as a cephalosporin or a quinolone) may be chosen. Therapy may have to be continued for 7 days after achieving a good appearance. Aggressive treatment is necessary

in every instance of trauma reported by the patient. Local care requires gentle cleansing of all blood from the exit site.

External Cuff Infection with or without Exit-Site Infection

Ultrasound examination of the tunnel is a valuable tool in the diagnosis of cuff infection. Although positive findings with ultrasound examination help to establish a diagnosis of tunnel infection, a negative examination does not rule out the existence of an infection. Cuff infection responds to therapy slowly, if at all, and a complete cure is unlikely. De-roofing the sinus tract and cuff shaving have been practiced with some success. In the author's experience, cuff shaving prolongs catheter life for approximately 6 to 12 months. These temporary measures may be suitable for patients who are expected to stay on therapy for a short period (e.g., patients awaiting transplant). However, cuff infection is a strong indicator for catheter removal in long-term peritoneal dialysis patients. If there is no active peritonitis, catheter replacement and removal are now being done in one procedure.

Anecdotal reports suggest that cuff shaving may provide better results in presternal catheters. This may be related to the presence of three cuffs and a long tunnel in the presternal catheter. Shaving of the subcutaneous cuff leaves two cuffs as a double barrier against periluminal bacterial penetration.

Local and Systemic Use of Antibiotics for Prophylaxis and Treatment of Exit-Site Infection

There is no evidence to support the use of prophylactic antibiotics to reduce the incidence or frequency of infections in healed exit sites and tunnels. Healthy exit sites usually do not become infected unless traumatized. Therefore, a prophylactic antibiotic is not recommended for good or perfect exit sites in the absence of trauma. A prophylactic antibiotic is indicated for the management of accidentally traumatized exits. In most cases of trauma, this may be considered a treatment and not a prophylaxis because in most reported trauma cases the exit site deteriorates to equivocal—which is a subclinical form of exit-site infection. The other indication for prophylaxis is the chronic infection in which discontinuation of systemic antibiotics results in reappearance of the infection. In such a case, long-term prophylaxis with a suppressive dose of an antibiotic is useful. As mentioned

previously, these are probably cases of undiagnosed low-grade external cuff infection.

In nasal carriers of *Staphylococcus aureus*, randomized trials showed decreased infectious complications in patients treated with prophylactic systemic trimethoprim-sulfamethoxazole or rifampin. Topical intranasal application of antibiotics against *Staphylococcus aureus* is less likely to prevent exit-site infection, unless there is a high probability of microorganism transfer from the nares to the exit site by the fingers or by other means. As mentioned previously, in our studies the strains are usually different in the nares and at the exit site. Even if the strains were the same, it seems preferable to use topical antimicrobial agents on the exit site (where the bacteria are harmful) instead of using it in nares.

Topical antibiotics in acute or chronic infection are of little value because they cannot achieve sufficient local concentrations before being washed away with large drainage. Antibiotics administered systemically can provide therapeutic concentrations locally by being excreted into the drainage. Local antibiotics can achieve high concentrations in the sinus in equivocal, good, or perfect exit sites but are most useful for equivocal exit sites. Many patients use local ointments (mostly mupirocin) indefinitely to moisturize, to lubricate, and to decrease or eradicate bacterial colonization of the sinus and exit site. The author has not observed any change in physical properties, such as color or texture, of silicone rubber catheters in patients using ointments for up to 8 years. Caution is advised if topical treatment is used with polyurethane catheters, as they are prone to damage with any topical therapy.

Recommended Reading

Twardowski ZJ (ed.). Peritoneal catheter exit-site morphology and pathology: Prevention, diagnosis, and treatment of exit-site infections. Perit Dial Int 1996;16(3):1–117.

Detailed descriptions of the various exit-site appearances illustrated by over 200 color photographs.

Twardowski ZJ, Nichols WK. Peritoneal dialysis access and exit site care including surgical aspects. In Gokal R, Khanna R, Krediet RT, Nolph KD (eds.), *The Textbook of Peritoneal Dialysis, Second Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2000:307–61.

Comprehensive review of peritoneal dialysis catheter history, theory, and practice.

Twardowski ZJ, Prowant BF. Current approach to exit site infections in patients on peritoneal dialysis. Nephrol Dial Transplant 1997;12(6):1284–95.

CHAPTER 42

Peritonitis in Peritoneal Dialysis Patients

Philip Kam-Tao Li, MD, FRCP, FACP;
Chi-Bon Leung, MB, FRCP; Cheuk-Chun Szeto, MD, FRCP

Introduction

Peritoneal dialysis (PD) is now a standard therapeutic modality of end-stage renal disease (ESRD) and accounts for about 15% of the dialysis population worldwide. About 80% of ESRD patients in Hong Kong are treated by continuous ambulatory PD (CAPD). Peritonitis in PD remains a major cause of technique failure and morbidity. It accounts for 15 to 35% of hospital admissions and contributes significantly to mortality. Prevention and treatment of peritonitis in PD patients remain important and challenging for nephrologists. As the lead author has participated in drafting the 2005 update to the recommendations of the ISPD Ad Hoc Advisory Committee on PD-related infections, this chapter references those findings—as well as those of our own center's experience.

Diagnosis of Peritonitis in Peritoneal Dialysis Patients

Peritonitis is defined by the presence of cloudy PD effluent with 100 white blood cells/mm^3 and at least 50% polymorphonuclear cells. Abdominal pain and fever are usually associated with the development of peritonitis, but do not in isolation indicate a diagnosis of peritonitis. There are other causes of cloudy peritoneal effluent, which include chemical peritonitis, eosinophilia of the effluent, hemoperitoneum, and rarely malignancy and chylous effluent.

Peritonitis Rate in Pritoneal Dialysis Patients

Peritonitis rates can be calculated using months of PD at risk divided by number of episodes, and expressed as an interval in months between episodes. It can also be expressed as the number of infections in a given time period divided by dialysis-years at

risk, and expressed as episodes per year. In 1976, Popovich and Moncrief first employed PD using two 1-L glass bottles with a long disposable transfer set. At this time, the peritonitis rate was 1 in 2.5 patient-months. In 1978, when Oreopoulos used a plastic collapsible dialysate bag for PD, the peritonitis rate was 1 in 10.5 patient-months. Throughout the years of development of the connectology using the technique of "flush before fill" in Y-set disconnect systems and later with the double-bag disconnect system, the peritonitis rate has significantly improved. A peritonitis rate of one episode per 25 patient-months to 46.8 patient-months has been achieved.

The International Society for Peritoneal Dialysis (ISPD) 2005 updated guidelines for PD-related infections suggested that peritonitis rate should be no more than 1 episode every 18 months (0.67 per year at risk), although the rate achieved will depend to some extent on the patient population.

Organisms Involved in Peritonitis

Several routes leading to peritonitis in PD are known: intraluminal (mainly through touch contamination), periluminal (through exit-site or tunnel infections), intestinal, systemic (through the bloodstream), and rarely ascending (through the vagina). In the 1980s (when the standard straight set spike system was the most common method for CAPD), Gram-positive organisms accounted for about 60% of all peritonitis infections (*Staphylococcus aureus* 10%, *Staphylococcus epidermidis* 40%, *Streptococcus* species 10%) and Gram-negative enteric organisms for about 20%. Our recent data showed that Gram-positive and Gram-negative organisms accounted respectively for about 39.6% and 32.4% of all peritonitis episodes (Table 42.1). This is mainly a result of the use of "flush before fill" and the double-bag disconnect system leading to a marked reduction in the Gram-positive organisms—especially the coagulase-negative staphylococcus.

Among all Gram-negative organisms, *Pseudomonas* and those from the family *Enterobacteriaceae* were the most common causes. *Enterobacteriaceae* are often labeled "enteric bacteria"—with a number of major human intestinal pathogens (e.g., *Shigella*, *Salmonella*). Several others are normal colonizers of the human gastrointestinal tract (e.g., *Escherichia*, *Klebsiella*). Peritonitis caused by *Enterobacteriaceae* may be due to touch contamination, exit-site infection, or possibly a bowel source (such as constipation, colitis, or transmural migration), but the etiology is often unclear.

Table 42–1

Microorganisms Causing Peritonitis in Prince of Wales Hospital in Year 2005

Causative Organisms	Percentage
Gram-positive organisms	**39.6%**
• Coagulase-negative staphylococcus	13.7%
• *Staphylococcus aureus*	12.2%
• *Streptococcus* species	10.1%
• Diphtheroid species	0.7%
• *Corynebacterium* species	0.7%
• Miscellaneous	2.2%
Gram-negative organisms	**32.4%**
• *Escherichia coli*	13.7%
• *Pseudomonas* species	8.6%
• *Klebsiella* species	3.6%
• *Acinetobacter* species	2.9%
• *Serratia* species	0.7%
• Miscellaneous	2.9%
Polymicrobial	**9.3%**
Culture-negative peritonitis	**15.1%**
Fungi	**2.9%**
Mycobacterium tuberculosis	**0.7%**

Figure 42.1 shows the trend from 1994 to 2003 in our hospital, including the actual incidence of different organisms causing peritonitis in PD patients. The figure indicates a significant drop in absolute number of peritonitis episodes per patient-year of PD. Notable is the drop in Gram-positive organisms, which is much more significant than the other categories. This is mainly related to improvements in connectolgy and in CAPD exchange techniques.

Collection of Peritoneal Dialysis Effluent for Microbiological Culture and Sensitivity Testing

The diagnosis of peritonitis and its subsequent management depends on good specimen collection. Proper collection of the PD effluent for analysis (including cell count and culture) is required. A sample of peritoneal fluid (preferably the first bag of PD fluid) should be collected before the addition of antibiotics. It is sent

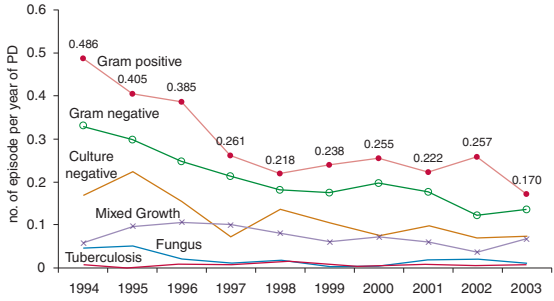


Figure 42–1

The actual incidence of the different types of organisms causing peritonitis in PD patients from 1994 to 2003 in the Prince of Wales Hospital.

immediately to the laboratory for absolute cell count and differential counts—as well as for culture. If the collection is done after flush-out cycles, the result may be altered.

Cell count is important because it can differentiate cellular elements of the peritonitis from those that are acellular (such as fibrin and chyle). The white cell count should exceed 100/mm^3 before the diagnosis of peritonitis is made. The majority of the cell count in an untreated effluent sample of suspected infective peritonitis should be comprised of neutrophils or lymphocytes. Abundance of eosinophil indicates a diagnosis of chemical peritonitis, in which chemicals causing irritation to the peritoneum render an eosinophilic response. A high level of lymphocytes or macrophages should raise the suspicion of tuberculosis peritonitis. Most laboratories will make a smear with direct differential cell counting after staining, with or without dilution. Cell lysis, however, can occur after 24 to 48 hours of specimen collection—which will render cell morphology unidentifiable.

The specimen for culture can be collected in universal sterile bottles and sent to laboratory for prompt processing. The specimen is centrifuged and the bottom portion of the fluid is used for direct Gram stain and plate culture. The Gram stain result is used to guide further use of antibiotics. Prompt collection and handling of the specimen is important. Otherwise, there may be a high probability the organism may not be recovered.

Another widely used collection method for culture is the direct inoculation of peritoneal effluent—such as blood culture (both the aerobic and anaerobic)—into the BacTec system. Factors and nutrients inside this system will enhance growth of the organism. If there is evidence of pH changes (via Gram stain and antibiotic susceptibility assessment) suggesting signs of life within the system, a portion of the fluid is aspirated for subculture identification of the organism. This method provides reliable microbiologic data due to the growth enhancement effect and decrease the culture negative rate.

Impact of Peritonitis

The risk of dying during an episode of peritonitis in the 1980s and 1990s in different series was in the range of 0.8 to 2.5%. An analysis of causes of mortality among 296 PD patients in the Prince of Wales Hospital recently indicated that peritonitis accounts for 16.6% of all deaths. Our own data showed that the 2-year technique survival of CAPD patients was 88% without peritonitis, which would decrease to 70% when the patient had peritonitis.

Long-term success of PD depends on the preservation of adequate peritoneal membrane function. Peritoneal permeability characteristics have prognostic implications for technique assessment and patient survival. We found that peritoneal transport increases after severe peritonitis, defined as episodes requiring Tenckhoff catheter removal or antibiotic therapy of more than 3 weeks. In our patients, severe peritonitis resulted in a lasting rise in D/P (Dialysate to plasma ratio of creatinine) and loss of ultrafiltration—whereas the number of peritonitis episodes did not have any long-term impact on peritoneal transport. Improvements in connectology can reduce the less aggressive organisms (such as coagulase-negative staphylococcus), but proportionately an increase of more severe peritonitis by other organisms would surface.

We previously reviewed the clinical course of patients with severe peritonitis. Tenckhoff catheters were removed and then reinsertion was attempted at least 4 weeks later. In about half of the patients, reinsertion failed and the patient was put on long-term hemodialysis. For patients who could be resumed on PD, there was a significant decline in net ultrafiltration volume. Of these patients returned to PD, almost 90% required additional dialysis exchanges or hypertonic dialysate to compensate for the loss of solute clearance or ultrafiltration. There was no significant change in dialysis adequacy or nutritional status.

Risk Factors for Peritonitis

Information about specific risk factors associated with heightened incidence of peritonitis in CAPD is important in the reduction of this common dialysis-related complication. Table 42.2 summarizes patient-related, technique-related, and environment-related risk factors for peritonitis.

Patient age has been found to be a risk factor. Patients younger than 20 are having a much higher risk compared with older. In the study by Oxton in 1994, each year of increase in age is associated with a reduction in risk of peritonitis. Socioeconomic status of patients has also been shown to be associated with peritonitis risk. Education level significantly influences the peritonitis rate, with data showing that patients with less than 9 years of education have almost double the peritonitis rate of patients with more than 12 years of education.

Table 42–2

Risk Factors for Peritonitis

Patient Related

Demographics

- Age (younger patient higher risk)
- Race (African American higher risk)
- Education level (lower education higher risk)
- Socioeconomic status (patient on Social Security higher risk)
- Depression score (depressed patient higher risk)
- Duration of follow-up (shorter duration higher risk)

Physical Conditions

- Diabetic status (diabetic patient higher risk)
- Serum albumin level (lower albumin higher risk)
- Exit site and tunnel tract conditions (infected exit site higher risk)
- Nasal carriage (*Staphylococcus aureus* carrier higher risk)

Technique Related

Center Effect

- Training method (enhanced training lower risk)

Connectology

- Straight set versus Y set disconnect versus double bag (double bag lowest risk)
- Prophylactic topical antibiotics for nasal carriage and exit-site care (application lower risk)

Environment Related

- Climate (hot and humid higher risk)

Our recent data show that patients receiving Social Security assistance and those younger than 40 years fared worse than others in terms of their risk of peritonitis. Mean peritonitis-free time for subjects on Social Security assistance was 2.7 months, and 16.4 months for those who were not. Dependence on Social Security assistance prior to PD was associated with a greater than twofold increased likelihood of peritonitis. Depression, as indicated by a Beck Depression Inventory (BDI) score, was shown by a center to be associated with the development of peritonitis after controlling for age greater than 65 years, ethnicity, diabetes mellitus, and coronary artery disease.

CAPD patients with diabetes mellitus are at particular high risk for peritonitis. There are data showing the increase in both staphylococcus infection as well as Gram-negative organisms. This can possibly be attributed to the adverse effect of diabetes on peritoneal defense mechanisms by interfering with the migration of phagocytic cells into the peritoneum. Formation of advanced glycation end products might further suppress the phagocytic activity of resident peritoneal macrophages in diabetes. Decreased intestinal motility or slower colonic transit time among diabetic subjects favor bacterial overgrowth, with increased risk of peritonitis secondary to enteric organisms.

Two large series, one from United States and one from our own center, confirmed the independent predictive value of baseline low serum albumin regarding subsequent risk of CAPD peritonitis. In the U.S. study, every 10 g/L decrease of serum albumin concentration at the start of dialysis conferred a 74% higher risk for developing peritonitis. We found a similar magnitude of peritonitis susceptibility (a 67% greater risk for every 10 g/L decrease in serum albumin level) among our cohort of Chinese CAPD subjects.

Patients with *Staphylococcus aureus* nasal carriage are at higher risk for *Staphylococcus aureus* infections. The rate of such infections may be reduced with prophylactic antibiotics. Intranasal mupirocin is preferred, and repetitive courses are needed because recolonization is frequent. Caution must be taken due to the potential for the development of resistance with long-term prophylaxis.

Climate may also play a role in the predisposition to peritonitis. Our recent study showed that there was a substantial seasonal variation in the incidence of dialysis-related peritonitis, with peak incidence in the months that are hot and humid. We also found a significant seasonal variation in the rate of peritonitis caused by Gram-negative bacteria (with the exception of *Pseudomonas*). Gram-negative peritonitis was common during the summer months.

Transmural migration of bacteria may be responsible for this because of the more diarrheal nature of the disease. A similar but not significant trend of seasonal variation was also observed in Gram-positive peritonitis. Keeping a cool and dry living environment may help to reduce peritonitis in PD patients in tropical countries.

Prevention of Peritonitis

Strategies to prevent peritonitis include better patient selection, better patient training, improved exit-site care, treatment of *Staphylococcus aureus* nasal carriage, antibiotic prophylaxis, better systems of CAPD, and possibly improved peritoneal immune response using biocompatible solutions.

Better training methods would improve the peritonitis risk of patients, and there is evidence indicating the effectiveness of training and retraining to reduce peritonitis rates. Careful selection of patients will also help to diminish the rate of peritonitis secondary to contamination. Patients must be taught aseptic technique, with emphasis on proper hand-washing procedures. Continued monitoring of peritonitis rate is necessary in a dialysis program so that intervention can be made if peritonitis rates are high. Peritonitis rates should be less than 1 episode per 18 patient-months, as recommended by the ISPD 2005 guidelines. A higher rate of peritonitis should be followed by a critical appraisal of the pathogenetic organisms and the training program, with appropriate intervention taken.

In terms of catheter placement, the silicon Tenckhoff catheter is a standard. There is no evidence to show that any other particular catheter is better for the prevention of peritonitis. The double-cuff catheter is preferred because it has a better survival compared with the single-cuff catheter and is less likely to result in catheter removal for exit-site infection. Downward-pointing exit-site locations, suggested as a method of reducing exit-site infections, may decrease the risk of catheter-related peritonitis. It is recommended that prophylactic antibiotics administered at the time of insertion decrease infection risk. A single dose of intravenous first-generation cephalosporin is most frequently used. Intravenous vancomycin as a 1-g single dose is an effective alternative, but the potential benefit versus the risk of vancomycin in hastening resistant organisms has to be considered.

Good exit-site care would help to prevent catheter infections and thus peritonitis. Catheter immobilization, proper location of the exit site, sterile wound care immediately after placement of the

catheter, and avoidance of trauma are useful preventive measures. For routine exit-site care, use of antibacterial soap and water are recommended by many centers. Use of an antiseptic such as povidone-iodine or chlorhexidine to clean the exit site is also a good measure.

Nasal carriage of *Staphylococcus aureus* has been associated with an increased risk of exit-site infection, tunnel infections, peritonitis, and possible catheter loss. The rate of such infections may be reduced with prophylactic antibiotics. Topical application is preferred to oral antibiotics in prevention. Antibiotic prophylaxis with mupirocin applied at the exit site, intranasally, or with oral rifampin reduces the risk of *Staphylococcus aureus* catheter infection. The ISPD 2005 peritonitis treatment guidelines suggest the use of intranasal mupirocin twice per day for 5 to 7 days every month once a patient is identified as a nasal carrier. Another option is to apply mupirocin only in response to a positive culture. Exit-site mupirocin can be used in response to a positive culture for *Staphylococcus aureus* for preventing exit-site infections. Recently, gentamicin cream applied daily to the peritoneal catheter exit site was shown to reduce *Pseudomonas aeruginosa* and other Gram-negative catheter infections. It also reduced peritonitis. It was also shown to be as effective as mupirocin in preventing *Staphylococcus aureus* infections. However, the potential for developing resistance with long-term prophylaxis should be noted.

Improved connection systems have the benefit of reduction in the incidence of peritonitis. Results from the Y-set disconnect systems consistently give a lower peritonitis rate than standard spike set. The technique of "flush before fill" is used. The double-bag system is a completely sterilized disposable integrated system that contains an empty bag and a fresh dialysate-containing bag, both secured to Y connecting tubing. This superiority of double-bag disconnect systems over Y-set disconnect systems has been demonstrated by our group and other centers.

Management of Peritonitis

PD patients presenting with cloudy effluent should be presumed to have peritonitis. In addition to truly culture-positive infectious peritonitis, cloudy effluent can also be due to infectious peritonitis with sterile cultures, chemical peritonitis, eosinophilia of the effluent, hemoperitoneum, or even specimen taken from "dry" abdomen. Rarely, it can result from malignancy or chylous effluent.

Assessment of the patient should include history taking of possible touch contamination, compliance in sterile dialysis technique,

recent procedures that may have led to peritonitis, and change in bowel habits (either diarrhea or constipation). Careful physical examination, including vital signs, should be performed—especially to look for septicemia as a result of peritonitis, as this may affect the route of administration of the antibiotics. One must also carefully assess the exit site and tunnel for edema, erythema, tenderness, and discharge to look for evidence of associated exit-site infection—which may be the cause of the peritonitis. After the initial assessment of the patient, effluent cell counts, differential, and culture should be obtained (as described previously).

Antibiotic therapy should be initiated as soon as cloudy effluent is seen, without waiting for confirmation from the laboratory of the cell count so as to prevent delay in treatment. Empiric antibiotics must cover both Gram-positive and Gram-negative organisms. The ISPD 2005 updated guidelines recommend center-specific selection of empiric therapy, dependent on the history of sensitivities of organisms causing peritonitis. The guidelines also suggest that Gram-positive organisms may be treated with vancomycin or a cephalosporin, and Gram-negative organisms with a third-generation cephalosporin or aminoglycoside.

Figure 42.2 shows the initial management of PD-related peritonitis. We recommend cefazolin (a first-generation cephalosporin) rather than vancomycin because of the potential of the emergence

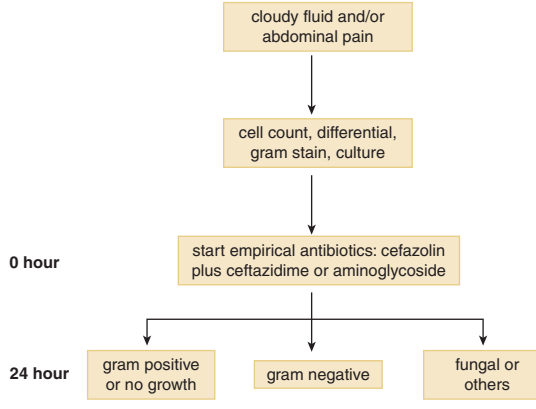


Figure 42–2

Initial management of PD-related peritonitis.

of vancomycin-resistant organisms. Another antibiotic is added to cover Gram-negative organisms, and our center typically uses ceftazidime until culture results are known. In the 2000 update of the ISPD Advisory Committee on Peritonitis, due to some evidence suggesting a more rapid loss of residual renal function in patients receiving aminoglycosides, routine use of aminoglycosides in PD patients with residual renal function is not recommended. However, recent randomized trials failed to demonstrate a significant effect of short-term usage of aminoglycosides on residual renal function. The ISPD 2005 updated guideline thus recommends that short-term aminoglycoside use appears to be safe and inexpensive and provides good Gram-negative coverage. Caution needs to be taken with an extended course of aminoglycoside therapy, which may increase the risk for both vestibular and ototoxicity.

Antibiotics Administration

If the patient suffers from septicemia or appears toxic as a result of the peritonitis, antibiotics should be administered intravenously in addition to other resuscitative measures. Otherwise, intraperitoneal antibiotics are the preferred route of administration and can be given in each exchange as continuous dosing or once daily as intermittent dosing. In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption of the antibiotic into the systemic circulation. Once-daily therapy has the advantage of ease of use by patient and staff, both in hospital and at home.

Evidence supports good efficacy of intermittent dosing of aminoglycosides and vancomycin in CAPD. Once-daily dosing (40 mg IP in 2 L) is as effective as dosing in each exchange (10 mg/2 L IP in four exchanges per day) for CAPD peritonitis. There are theoretical advantages of administering aminoglycosides as a single dose in a long-dwell exchange, which may result in less ototoxicity and nephrotoxicity. Intraperitoneal vancomycin is well absorbed when given in a long dwell and subsequently crosses again from the blood into the dialysate with fresh exchanges. Intermittent doses of vancomycin can be given as a loading dose of 30 mg/kg IP in long dwell, with repeat dosing of 15 mg/kg IP in long dwell every 3 to 5 days (following levels). Data in support of intermittent dosage of the first-generation cephalosporin is less complete. We would prefer using continuous administration of the first-generation cephalosporin. Table 42.3 summarizes the intraperitoneal antibiotic dosing recommendations for CAPD patients from the ISPD 2005 updated guidelines.

Table 42–3

Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients[a]

	Intermittent (per exchange, once daily)	Continuous (mg per L, all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin	15 mg/kg	LD 500, MD 125
Cefepime	1 g	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Ceftazidime	1000–1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Ampicillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	MD 125
Amoxicillin	ND	LD 250–500, MD 50
Penicillin G	ND	LD 50,000 units, MD 25,000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Vancomycin	15–30 mg/kg Q5–7d	LD 1000, MD 25
Aztreonam	ND	LD 1000, MD 250
Antifungals		
Amphotericin	NA	1.5
Combinations		
Ampicillin/sulbactam	2 g Q 12 h	LD 1000, MD 100
Imipenem/cilistatin	1 g BID	LD 500, MD 200
Quinopristin/dalfopristin	25 mg/L in alternate bags[b]	

a. Dosing of drugs with renal clearance in patients with residual renal function (defined as more than 100 mL/day urine output) dose should be empirically increased by 25%.
b. Given in conjunction with 500 mg IV twice daily.
LD = loading dose in mg, MD = maintenance dose in mg, NA = not applicable, ND = no data.
Adapted with permission from Piraino B, et al. for ISPD Ad Hoc Advisory Committee. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int 2005;25:107–31.

With effective treatment, the patient should begin to improve clinically within 12 to 48 hours, and the total cell count and percentage of neutrophils in the peritoneal fluid should begin to decrease. Often visual inspection of the effluent will suffice, but if there is no improvement within 48 hours repeat cell count and culture are necessary. Isolation of causative bacteria and determination of their antimicrobial sensitivity can generally be performed within 2 to 3 days. When the culture of the organisms comes back, appropriate adjustment of the antibiotics is necessary—taking into consideration the clinical response.

Treatment of Specific Organisms

Gram-Positive Organism Cultures

In terms of the following discussion, see Figure 42.3. If *S. aureus*, *S. epidermidis*, or a *Streptococcus* species is identified, continued therapy with cefazolin is recommended. Many *S. epidermidis*-like

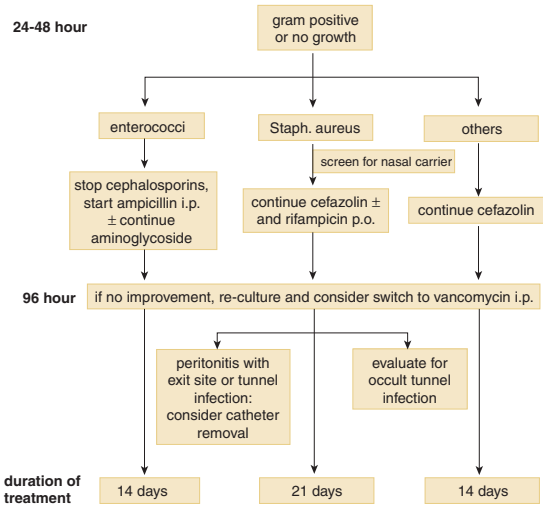


Figure 42–3

Management of peritonitis caused by Gram-positive organisms.

organisms reported to be resistant to first-generation cephalosporins are sensitive to the levels achieved in the peritoneal cavity. As a result, if the patient is clinically responding to treatment there is usually no need to change the antibiotic regimen. If an *Enterococcus* species is cultured, ampicillin or vancomycin with or without an aminoglycoside is generally employed. If the improvement is prompt, antimicrobial therapy should be continued for a total of 14 days. However, *S. aureus* peritonitis requires antimicrobials for 3 weeks. Patients with *S. aureus* peritonitis also require screening as possible nasal carriers.

Culture-Negative Peritonitis

In regard to the following discussion, see Figure 42.3. If the culture results are negative at 24 hours, the most likely explanation is that a bacterial infection was present but that the responsible organisms failed to grow in the culture sample. Management depends on whether the patient is improving clinically. Most authorities recommend continuing cefazolin alone for 2 weeks if the patient is improving. On the other hand, patients with culture-negative peritonitis who do not improve should be recultured to look for unusual organisms such as fungi and mycobacteria.

Gram-Negative Organism Cultures

In regard to the following discussion, see Figure 42.4. If a single non-*Pseudomonas* species is recovered, the peritonitis can usually be treated by continuation of the initial IP third-generation cephalosporin or aminoglycoside alone—or by another single appropriate antibiotic. Treatment should be continued for 14 days. If a *Pseudomonas* species or *Stenotrophomonas maltophilia* is recovered, two anti-*Pseudomonas* antibiotics are needed. Suitable choices include aminoglycoside, third-generation cephalosporin, semisynthetic penicillin with anti-*Pseudomonas* activity (e.g., piperacillin), fluroquinolone, aztreonam, imipenem, and trimethoprim-sulfamethoxazole. It should be noted that semisynthetic penicillins can inactivate aminoglycosides in vitro and thus should not be coadministered intraperitoneally. *Pseudomonas* peritonitis often requires catheter removal. The duration of therapy should be 21 days. If the peritoneal catheter is removed, appropriate antipseudomonal antibiotics should be continued for another 2 weeks.

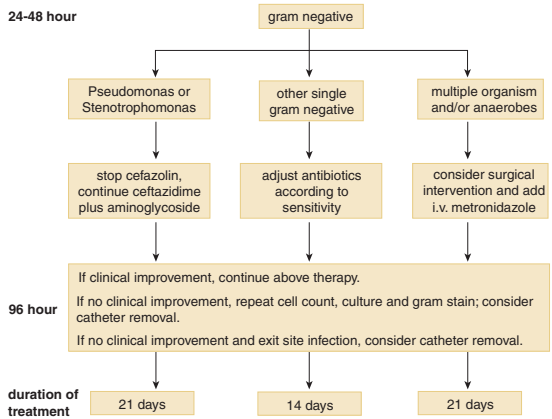


Figure 42–4

Management of peritonitis caused by Gram-negative organisms.

Polymicrobial Peritonitis

In general, peritonitis due to multiple Gram-positive organisms will respond to antibiotic therapy. Most of these infections can be resolved without catheter removal. Surgical evaluation is not routinely required. However, if one of the organisms recovered is Gram-negative or is an anaerobe, an intra-abdominal abscess or a perforated abdominal viscus should be suspected. Management should be individualized.

Tuberculous Peritonitis

Standard antituberculous chemotherapy is needed. Streptomycin and ethambutol are generally not recommended in dialysis patients. Catheter removal is often required but is not mandatory provided prompt therapy is carried out.

Fungal Peritonitis

Candida is the most prevalent species. Prompt removal of the catheter as soon as fungi are identified, together with treatment for at least 10 days after its removal with antifungal agents, is

generally recommended (such as by the ISPD 2005 guideline). The patient is then maintained on hemodialysis. In some patients, a new catheter can be inserted 4 to 6 weeks later.

Indications for Catheter Removal

Catheter removal should generally be undertaken when peritonitis fails to resolve after treatment with appropriate antibiotics for 4 to 7 days. After catheter removal, systemic antibiotics should be continued for another 2 weeks. A new catheter can be reinserted after 4 weeks. Resumption of PD is possible in approximately half of patients, but a problem with ultrafiltration is common.

Relapsing Peritonitis

Relapsing peritonitis is defined as peritonitis with the same organism within 4 weeks of stopping antimicrobial therapy. In the case of relapsing Gram-negative peritonitis, catheter removal should be strongly considered—especially in patients with *Pseudomonas* infection. With less serious infections, it may be possible to insert a new catheter simultaneously with removal of the old catheter after the infection is cleared.

Special Considerations in Automated Peritoneal Dialysis

The choice of first-line antibiotics in CAPD applies also to APD. The recommendations for antibiotic treatment are based mainly on data obtained using CAPD and on limited experience in APD. In many centers, during peritonitis APD patients are changed to a CAPD schedule because it is then easier to evaluate the clinical course. If patients stay on APD, once-daily administration of aminoglycosides is recommended. There are few data concerning efficacy of first-generation cephalosporins given intermittently for peritonitis, particularly for the patient on a cycler. In contrast, it would be a safe approach to add a first-generation cephalosporin to each exchange.

Predictors of Treatment Failure in Peritonitis

Our recent data showed that number of years on PD, diabetes mellitus, Gram-negative organisms, *Pseudomonas*, and fungal or *Mycobacterium* species were independent risk factors predictive of treatment failure. In addition, the peritoneal dialysate total

white blood cell count on day 3 of peritonitis predicted treatment failure independent of standard risk factors. Using a peritoneal dialysate white count cut-point of 1090 per cubic millimeter on day 3, the sensitivity was 75% and the specificity was 74% for the prediction of treatment failure (defined as catheter loss or peritonitis-related death).

Conclusions

It is 30 years since Popovich and Moncrief first introduced PD. However, PD-related peritonitis remains a difficult complication with significant impact on patient well-being and survival. Improvements in the peritonitis rates remain to be achieved. This is achievable through more research into areas that include an even better CAPD system, means of reduction of peritonitis from endogenous and periluminal infections, improvements in catheter design, and a more biocompatible peritoneal dialysate for improved peritoneal defense against infection.

Recommended Reading

CARI (Caring for Australians with Renal Impairment). Evidence for peritonitis treatment and prophylaxis: Treatment of peritoneal dialysis-associated peritonitis in adults. Nephrology 2004;9(3):S91–106.

Review documenting the currently available data related to evidence-based treatment of PD-associated peritonitis.

Chow KM, Szeto CC, Cheung KK, Leung CB, Wong SS, Law MC, et al. Predictive value of dialysate cell counts in peritonitis complicating peritoneal dialysis. Clin J Am Soc Nephrol 2006;1:768–73.

This study demonstrates and cross-validates the superiority of peritoneal dialysate white cell count on day 3 to predict outcomes of dialysis-related peritonitis.

Chow KM, Szeto CC, Leung CB, Kwan BC, Law MC, Li PKT. A risk analysis of continuous ambulatory peritoneal dialysis-related peritonitis. Perit Dial Int 2005;25:374–79.

This study shows the trend of change of organisms in our center and confirms the susceptibility of diabetic CAPD and hypoalbuminemic patients to peritonitis.

Leung CB, Szeto CC, Chow KM, Kwan BC, Wang AY, Lui SF, et al. Cefazolin plus ceftazidime versus imipenem/cilastatin monotherapy for treatment of CAPD peritonitis: A randomized controlled trial. Perit Dial Int 2004;24(5):440–46.

This study shows that monotherapy of imipenem/cilastatin has similar efficacy compared to the two standard regimens of cefazolin plus ceftazidime or netilmicin in the treatment of PD peritonitis.

Li PKT, Law MC, Chow KM, Chan WK, Szeto CC, Cheng YL, et al. Comparison of clinical outcome and ease of handling in two double-bag systems in continuous ambulatory peritoneal dialysis: A prospective randomized controlled multi-center study. Am J Kidney Dis 2002;40:373–80.

This study shows that the two double-bag systems have similar incidences of peritonitis and exit-site infection with comparably good clinical outcome.

Lui SL, Cheng SW, Ng F, Ng SY, Wan KM, Yip T, et al. Cefazolin plus netilmicin versus cefazolin plus ceftazidime for treating CAPD peritonitis: Effect on residual renal function. Kidney Int 2005;68(5):2375–80.

This prospective randomized controlled trial indicates no difference on the effects of IP. cefazolin plus netilmicin or i.p. cefazolin plus ceftazidime on residual renal function in CAPD patients with peritonitis..

Piraino B, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, et al. for the ISPD Ad Hoc Advisory Committee. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int 2005;25:107–31.

The most updated ISPD recommendations on peritonitis, focusing on evidence-based guidelines and on prevention.

Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Antimicrobial agents to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. Am J Kidney Dis 2004;44:591–603.

The meta-analysis suggested a lack of adequately powered randomized trials to address the issues on using antimicrobial agents to prevent peritonitis in peritoneal dialysis.

Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Catheter-related interventions to prevent peritonitis in peritoneal dialysis: A systematic review of randomized, controlled trials. J Am Soc Nephrol 2004;15:2735–46.

This systematic review demonstrated that of all catheter-related interventions designed to prevent peritonitis in PD only disconnect (twin-bag and Y-set) systems have been proved to be effective (compared with conventional spike systems).

Szeto CC, Chow KM, Wong TY, Leung CB, Wang AY, Lui SF, et al. Feasibility of resuming peritoneal dialysis after severe peritonitis and Tenckhoff catheter removal. J Am Soc Nephrol 2002;13:1040–45.

An analysis of severe peritonitis that suggests that an early assessment of peritoneal function after Tenckhoff catheter reinsertion might be valuable.

Szeto CC, Chow VC, Chow KM, Lai RW, Chung KY, Leung CB, et al. Enterobacteriaceae peritonitis complicating peritoneal dialysis: A review of 210 consecutive cases. Kidney Int 2006;69:1245–52.

This study shows that Enterobacteriaceae *peritonitis is a serious complication of PD and that treatment with two antibiotics may reduce the risk of relapse and recurrence.*

Szeto CC, Leung CB, Chow KM, Kwan BC, Law MC, Wang AY, et al. Change in bacterial aetiology of peritoneal-dialysis-related peritonitis over ten years: Experience from a center in South-East Asia. Clin Microbiol Infect 2005;11:837–39.

This study reviews 1787 episodes of PD-related peritonitis in 544 patients between 1994 and 2003.

Wong TYH, Szeto CC, Lai KB, Lai KN, Li PKT. Longitudinal study of peritoneal membrane function in CAPD: Relationship with peritonitis and fibrosing factors. Perit Dial Int 2000;20:679–85.

The study examines peritoneal transport changes after severe peritonitis.

CHAPTER 43

Apparently Inadequate Peritoneal Membrane Function for Solute Removal

Zbylut J. Twardowski, MD, PhD

Adequacy of Dialysis

There are no universally accepted objective criteria for *adequacy* of dialysis, although it is a frequently used term. Most nephrologists agree that an adequately dialyzed patient feels well and looks good, has a good appetite, is well nourished, has no symptoms or signs of uremia, is rehabilitated to the degree possible considering concomitant conditions, and exhibits well-controlled blood pressure. Morbidity and mortality should be low. However, it has not been determined what the rates should be. It seems impossible, at present, to achieve morbidity and mortality rates similar to those of the population without renal failure. The degree of RRF (residual renal function), protein catabolic rate, dialysis efficiency, and sufficient ultrafiltration are the four major determinants of the adequacy of dialysis.

Residual Renal Function

In most dialyzed patients, RRF gradually deteriorates over time. The rate of renal functional decline varies among patients even when they have similar kidney disorders. However, after 5 years of dialysis urine output becomes negligible in almost every patient (Figure 43.1). This deterioration is reflected by gradual increases in serum creatinine and BUN levels despite unaltered dialysis efficiency (Figure 43.2).

Protein Catabolic Rate

Creatinine generation in the body is proportional to the total muscle mass. Gradual body weight gain by a dialysis patient is caused mainly by the combination of fat deposition and, to a lesser extent, to an increase in total body muscle mass. Although increased muscle mass may account for some of the observed

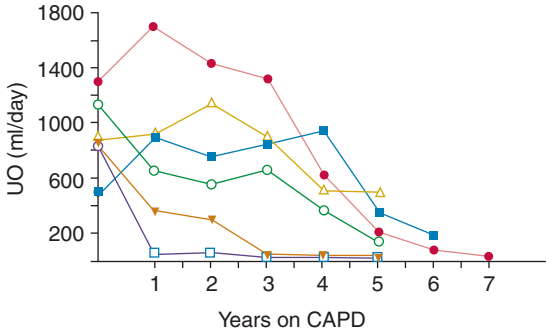


Figure 43–1

Decline of urine output over time in 6 long-term peritoneal dialysis patients.

increase in serum creatinine level, most of the increase results from a reduction of nephron mass. The concomitant increase in BUN level is less dramatic than that of serum creatinine because BUN generation is dependent on protein intake as well as on clearance during dialysis.

A patient whose renal function deteriorates loses appetite, particularly for high-protein foods, and decreases protein intake—thus decreasing BUN generation and blunting the increase in BUN level despite the reduction of renal clearance. Renal function is mostly needed to excrete waste products of protein metabolism, such as urea and nonvolatile acids (including phosphates and ingested electrolytes). It is a known phenomenon that hibernating bears, metabolizing their accumulated fat, maintain internal milieu with normal BUN levels without producing urine. Their BUN, serum electrolytes, and blood pH remain stable.

Loss of appetite with decreased protein intake is the most salient feature of inadequate dialysis, which is similar to the situation before the start of dialysis when renal function deteriorates. This feature is a body defense mechanism against intoxication with waste products of protein metabolism. Although a decrease in protein intake blunts the occurrence of uremic symptoms, long-term low-protein intake leads to malnutrition and must be avoided.

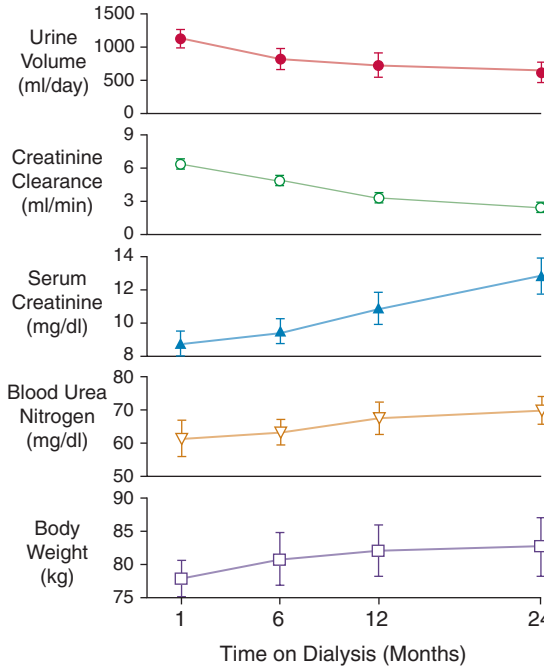


Figure 43–2

Changes over time in urine volumes, renal creatinine clearances, serum creatinine levels, blood urea nitrogen concentrations, and body weights of 10 peritoneal dialysis patients using unaltered doses of dialysis for 24 months (mean ± sem).

Dialysis Efficiency

Peritoneal dialysis clearance usually remains stable for at least several years. Increased clearance observed during a peritonitis episode returns to the pre-peritonitis value after the infection has resolved. However, some patients have changes in membrane permeability over time. The nature of these changes cannot always be ascertained. Usually, the peritoneal transport rates increase gradually with time on peritoneal dialysis. Ultrafiltration capacity deteriorates with time, but this is a subject of another chapter.

Peritoneal solute transport rate may be assessed with a standardized peritoneal equilibration test. Following complete drainage of the long-dwell overnight exchange, 2 L of 2.5% dextrose solution are instilled into the peritoneal cavity. Immediately after infusion, a 200-mL volume of dialysate is drained into an empty bag and mixed—and a 20-mL aliquot is collected through an injection port. The remaining fluid (180 mL) is reinfused. Sample collection is repeated at 30 minutes, 1 hour, 2 hours, and 3 hours dwell time. After 4 hours, the exchange is drained as completely as possible. Blood samples for urea nitrogen, creatinine, glucose, sodium, and protein determinations are taken at the beginning and at the end of the exchange. Dialysate samples are obtained for urea nitrogen, creatinine, glucose, sodium, and protein determinations. Dialysate glucose concentrations and dialysate-to-plasma ratios of creatinine obtained from 103 patients are shown in Figure 43.3.

Creatinine concentrations must be corrected for glucose interference. Patients with solute-transport rates below the mean value are likely to develop symptoms of inadequate dialysis when RRF becomes negligible. On the other hand, the patients with high solute transport rates, including rapid glucose absorption, have poor ultrafiltration in CAPD (continuous ambulatory peritoneal dialysis) and tend to become fluid overloaded after losing RRF.

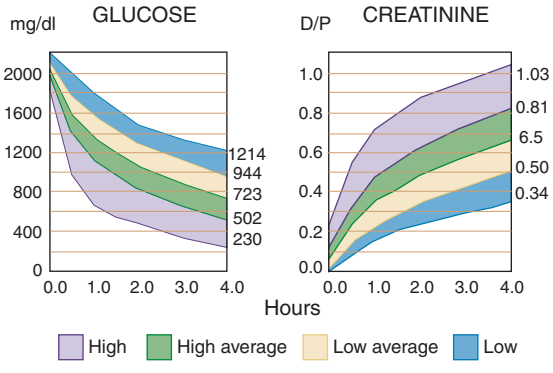


Figure 43–3

Peritoneal equilibration test results from 103 evaluations.

Sodium sieving is higher in patients with low peritoneal transport for glucose and other solutes.

Adequacy of Peritoneal Dialysis by NKF-K/DOQI Guidelines

Adequacy of dialysis is judged based on a total dialysis dose, which in controlled studies provides acceptable morbidity and mortality. The recommendations for peritoneal dialysis dose are based on the CANUSA study, which was a prospective cohort study involving 680 patients from 14 enters in Canada and the United States. Of the patients, 97.9% were treated with CAPD and 2.1% with CCPD (continuous cycling peritoneal dialysis). During the study, peritoneal clearances were not increased to offset declines in renal function. Because the RRF decreased over time and the dialysis dose did not change, RRF (but not peritoneal solute clearance) was an important predictor of outcome.

The CANUSA study showed that mortality decreased as the total (renal plus dialysis) clearance increased. "No leveling off of the mortality was observed, although an independent effect of dialysis dose with survival was not demonstrated," according to the study. The peritoneal dialysis component remained the same (Kt/V of 1.67 to 1.7 per week). Thus, variations in clearances were related mainly to RRF—which decreased from a beginning weekly Kt/V of 0.71 to a weekly Kt/V of 0.28 at 24 months. Therefore, the mortality was correlated with RRF rather than with the dialysis prescription. If we accept that mortality was mostly related to the RRF, it is logical that with better renal function mortality would be lower (although there would be a leveling off at some unknown point).

Based on these observations, the CANUSA authors accepted as a reasonable target a weekly Kt/V of 2.1 and a creatinine clearance of 70 L/1.73 m^2 of body surface area (BSA). At these values, the survival rate at 2 years was 78%. The Dialysis Outcomes Quality Initiative (DOQI) Committee of the National Kidney Foundation (NKF) accepted slightly lower values as more reasonable. Table 43.1 outlines NKF-K/DOQI–recommended doses of Kt/V and creatinine clearance.

These recommendations are not based on evidence, but on opinion. There are several problems associated with them. There is no proof of equivalency between renal and dialysis clearances, and it is not known whether creatinine clearance or Kt/V_{urea} is more helpful in clinical practice. In the CANUSA study, the renal contribution to creatinine clearance was calculated as the mean

Table 43–1

NKF-K/DOQI Recommended Doses for Peritoneal Dialysis

Weekly Creatinine Clearance Modality	Weekly Kt/V_{urea}	(L/1.73 m^2 BSA)
CAPD	>2.0	>60
CCPD	>2.1	>63
NIPD, NTPD	>2.2	>66

These recommendations are based on total clearance (peritoneal and renal) assuming that renal creatinine clearance is the sum average of renal urea and creatinine clearances. CAPD = continuous ambulatory peritoneal dialysis, CCPD = continuous cyclic peritoneal dialysis, NIPD = nightly intermittent peritoneal dialysis, NTPD = nightly tidal peritoneal dialysis.

of creatinine clearance and urea clearance to estimate creatinine clearance by glomerular filtration only (and to exclude tubular secretion). Renal creatinine clearance by glomerular filtration is much higher than renal urea clearance (due to urea reabsorption) in healthy and diseased kidneys. Thus, if a patient loses RRF the combined (peritoneal and renal) creatinine clearance decreases proportionally more than does the Kt/V_{urea} and the ratio of combined creatinine clearance to Kt/V_{urea} decreases.

In peritoneal dialysis, urea—with a molecular weight (MW) of 60 daltons—equilibrates much faster than creatinine (MW 113). The ratios of D/P creatinine, D/P urea, and D/P creatinine to D/P urea differ in various transport categories. The ratios of D/P creatinine to D/P urea are lower with short-dwell exchanges and higher with long-dwell exchanges in all transport categories, but the ratios are always higher in higher transporters. The ratios reach unity at very-long dwell times (4–12 hours), depending on peritoneal solute transport characteristics.

Table 43.2 outlines ratios of weekly creatinine clearance to Kt/V in NIPD (nightly intermittent peritoneal dialysis) and CAPD patients without RRF. After RRF is lost, only in patients with high peritoneal transport is it possible to achieve NKF-K/DOQI guideline recommended target Kt/V_{urea} and creatinine clearance values. In other patients, the creatinine clearance is below the target, even if Kt/V_{urea} is above 2.0 and 2.2 for CAPD and NIPD, respectively. A prospective randomized study in a large Mexican peritoneal dialysis population (ADEMEX) showed that in the anuric patients

Table 43–2

Creatinine Clearance (L) at a Kt/V of 2.2 in NIPD and 2.0 in CAPD

Transport	NIPD		CAPD	
Category	Females	Males	Females	Males
Minimal value	32.90	38.80	30.70	36.30
Low transporters	33.70	39.80	35.70	41.60
Mean ± SD	34.30	40.50	39.40	46.50
Low average transporters	40.00	47.20	43.20	51.00
Mean	44.70	52.70	46.70	55.10
High average transporters	48.00	56.60	50.10	59.10
Mean ± SD	50.80	59.90	53.20	**62.80**
High transporters	55.60	65.60	58.10	**68.50**
Maximal value	59.40	**70.00**	**62.70**	**73.90**

Values in boldface are above the NKF-K/DOQI guidelines for creatinine clearance at recommended Kt/V. Assumptions: Total body water in males = 41.7 L, total body water in females = 32.1 L, body surface area in males = 1.92 m^2, body surface area in females = 1.74 m^2. NIPD = nocturnal intermittent peritoneal dialysis (hourly 2-L exchanges), CAPD = continuous ambulatory peritoneal dialysis (five 2-L exchanges).
From Twardowski ZJ. Relationships between creatinine clearances and Kt/V in peritoneal dialysis patients: A critique of the NKF-K/DOQI document. Perit Dial Int 1998;18:252–55, with permission.

an increase in Kt/V and creatinine clearances to reach NKF-K/DOQI guidelines did not decrease mortality.

Achieving the Adequacy Guidelines

For some patients, achieving the recommended clearance guidelines may require a substantial increase in the dialysis prescription by increasing dialysate volume, the number of exchanges, or both. This raises the concern that the targets are achievable only with an unacceptable increase in the cost of dialysis and/or deterioration in the patient's quality of life. The benefits of increasing clearance must be balanced with the risks for some patients associated with larger fill volumes. The increase in intra-abdominal pressure associated with large intraperitoneal volume may lead to hernias in predisposed individuals and may lead to increased fluid absorption and less net ultrafiltration. Increased glucose absorption associated with larger fill volumes is another important consideration. In patients who have lost RRF, it may be

impossible to achieve the NKF-K/DOQI guidelines for both creatinine and Kt/V_{urea}.

This is particularly common in patients with less than high solute-transport rates (Table 43.2). The results of the ADEMEX study incline nephrologists to rely more on the clinical symptoms than on rigid numbers. They are less inclined to slavishly follow NKF-K/DOQI targets if patients are doing well clinically. The results of the ADEMEX study and the reanalysis of the CANUSA study strongly suggest that Kt/V values above 1.7 do not improve outcomes. It is expected that the next NKF-K/DOQI guidelines will accept this number.

Incremental Peritoneal Dialysis

Until recently, the decision to initiate dialysis was based on the development of uremic symptoms or complications. Current recommendations adopted by the Working Group of the NKF-K/DOQI suggest that dialysis should be initiated once the renal Kt/V_{urea} falls below 2.0 or once the normalized protein nitrogen appearance spontaneously declines below 0.8 g/kg/day. A renal Kt/V_{urea} of 2.0 corresponds to a urea clearance of 7.0 mL/minute and a creatinine clearance between 9 and 14 mL/minute/1.73 m^2 BSA. The rationale behind early or "healthy start" is to avoid malnutrition and uremic complications. The results of the NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis-2) Study Group did not show benefits for patients who started PD according to NKF-K/DOQI recommendations compared to those who started later.

Comparisons of early and later starts are associated with "lead-time bias" (i.e., inappropriate comparison from the start of dialysis instead of the comparison from the time of the same renal function). The early start of peritoneal dialysis is associated with some risks, including infection and the possibility that increasing the length of time on peritoneal dialysis may contribute to eventual patient "burn-out." The reduced interference with daily routine and lower work burden with automated peritoneal dialysis (APD) make this a preferable procedure in some patients for the early start. Again, clinical assessment (not numbers) should guide the decision when to start. For those who prefer to rely on numbers instead of clinical assessment, Kt/V of 1.7 and creatinine clearance below 8 mL/minute (80 L/week) are reasonable limits below which dialysis should be started. However, in patients with uremic symptoms at higher Kt/V and creatinine clearance values dialysis should be started.

Patients who have urine output >1 L/day may achieve clinically adequate dialysis on CAPD with a smaller dialysis dose (e.g., three 2-L exchanges per day). The patient should be warned that the dose of dialysis must be appropriately increased as RRF deteriorates. APD also offers an option for incremental peritoneal dialysis. Patients with significant RRF may initially be started on 8-hour NIPD. With a decline in RRF, switching to high-dose or longer NIPD or to CCPD may augment clearances.

Summary of Recommendations

Peritoneal dialysis should be started at the occurrence of the first uremic symptoms, before malnutrition develops; that is, when Kt/V_{urea} falls below 1.7 or the normalized protein nitrogen appearance spontaneously declines below 0.8 g/kg/day. A renal Kt/V_{urea} of 1.7 corresponds to a urea clearance of 6.0 mL/minute and a creatinine clearance between 8 and 12 mL/minute/1.73 m^2 BSA. The final decision should be made on clinical grounds after discussion with the patient. With substantial residual function, the volume and number of exchanges may be reduced. However, the patient has to be warned that the dose of dialysis needs to be increased with failing RRF. RRF deteriorates in all patients over months or years of peritoneal dialysis. Therefore, incremental peritoneal dialysis should be used in all patients. As RRF deteriorates:

- Increase the number of exchanges
- Increase the volume of some or all exchanges
- Increase the time of nightly peritoneal dialysis
- Combine nightly and daily exchanges in patients who lost RRF
- Peritoneal clearances should be carefully followed.
- Peritoneal dialysis might be sufficient in small persons with high peritoneal transport characteristics.
- NKF-K/DOQI–recommended targets for creatinine clearance cannot be achieved in a majority of patients. It is easier to achieve recommended Kt/V_{urea} in these patients. If patients are clinically doing well, do not have any uremic symptoms, and have a Kt/V of greater than 1.7, no change of dialysis prescription is needed.

If Kt/V_{urea} targets cannot be achieved—or if a patient decreases protein intake in spite of recommended Kt/V_{urea} and subtle uremic symptoms (sleep disturbances, anorexia, dysgeusia, pruritus, restless leg syndrome, and so on) still occur and quality of life is deteriorating—the patient should be switched to hemodialysis or

receive a kidney transplant. However, the role of transplantation in the management of such patients is rather limited. The patient who is eligible for transplantation usually receives a transplant while RRF is well preserved. In some patients who initially refuse transplant, inadequate dialysis and the necessity of using other than the regular CAPD or NIPD regimen may constitute an incentive to contemplate transplantation as an alternative.

In a patient with a previously unsuccessful renal transplant, RRF is often markedly reduced—and these patients usually do better on hemodialysis while awaiting a subsequent transplant. The combination of peritoneal dialysis and hemodialysis can be tried, but is usually impractical. Many patients who fail peritoneal dialysis prefer home hemodialysis (HHD) over in-center hemodialysis. As new machines for home hemodialysis are being developed, the transfer from PD to HHD may be more common. The author's personal experience indicates that small patients may continue peritoneal dialysis for more than 10 years even without RRF. However, larger patients usually require transfer to hemodialysis a few years after losing RRF.

Recommended Reading

Kathuria P, Twardowski ZJ. Automated peritoneal dialysis. In Gokal R, Khanna R, Krediet RT, Nolph KD (eds.), *Peritoneal Dialysis, Second Edition*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2000:435–63.

Comprehensive review of various peritoneal dialysis regimens and techniques.

Twardowski ZJ. Relationship between creatinine clearance and Kt/V in peritoneal dialysis: A response to the defense of the NKF-K/DOQI document. Perit Dial Int 1999;19:199–203.

Comprehensive analysis of the NKF-K/DOQI recommendations of Kt/V and creatinine clearance targets for CAPD, CCPD, and NIPD.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy, 2000. Am J Kidney Dis 2001;37(1):S65–136.

Peritoneal dialysis adequacy guidelines and a rationale for them.

Nelson RA. Protein and fat metabolism in hibernating bears. Fed Proc 1980;39(12):2955–58.

A review of the metabolism in hibernating bears enabling them to survive several months without excreting urine.

Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002;13:1307–20.

A prospective randomized study showing that increasing Kt/V to greater than 1.7 does not improve survival.

Bargman JM, Thorpe KE, Churchill DN, and the CANUSA Peritoneal Dialysis Study Group. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: A Reanalysis of the CANUSA study. J Am Soc Nephrol 2001;12:2158–62.

This reanalysis of the CANUSA study indicates that the mortality in this study depended on the residual renal function and not on the efficiency of dialysis.

Korevaar JC, Jansen MA, Dekker FW, Boeschoten EW, Bossuyt PM, Krediet RT for the NECOSAD Study Group. Netherlands Cooperative Study on the Adequacy of Dialysis-2. Evaluation of NKF-K/DOQI guidelines: early start of dialysis treatment is not associated with better health-related quality of life. National Kidney Foundation-Dialysis Outcomes Quality Initiative. Am J Kidney Dis 2002;39(1):108–15.

This report, based on a large Dutch prospective multicenter study, showed that early start of peritoneal dialysis according to NKF-K/DOQI recommendations is not associated with benefits for patients.

CHAPTER 44

Ultrafiltration Failure and Encapsulating Peritoneal Sclerosis

Dana Negoi, MD, and Ramesh Khanna, MD

Ultrafiltration Failure

Lately, management of fluid status is becoming the focus of peritoneal dialysis (PD) prescription, especially after multiple studies indicating that both fluid and sodium removal are independent predictors of survival in PD. In the early days of PD, it was assumed that this dialytic modality would permit optimal fluid management because PD is a continuous procedure that allows smooth daily removal of salt and fluid intake. In fact, this is a myth. In general, CAPD (continuous ambulatory PD) patients are in a state of continuous fluid overload and as a consequence their cardiovascular morbidity and mortality are higher.

Management of fluid balance becomes difficult after the initial years on CAPD, especially after the residual renal function is lost and fluid and sodium removal are almost entirely dependent on the peritoneal membrane function. The term *ultrafiltration failure* should be reserved for those cases where euvolemia or dry weight cannot be achieved primarily due to the peritoneal membrane failure to generate enough ultrafiltration (UF) despite the use of an appropriate PD prescription. At the end of a PD exchange, net UF or net fluid removal is the difference between the volume of transcapillary UF (TCUF) and the volume peritoneal fluid lost from the peritoneal cavity due to tissue and lymphatic reabsorbtion.

$$\text{Net UF} = \text{TCUF} - (\text{tissue} + \text{lymphatic absorption})$$

According to the three-pore model, in PD using dextrose-based solutions TCUF involves water movement across the peritoneum through small and ultrasmall pores—probably in equal amounts. The large pores are present in very small number and their contribution to fluid removal is minimal. The driving force for water movement from the peritoneal capillary in the peritoneal cavity is created by the crystalloid-osmotic gradient generated by the presence of glucose in high concentrations in the PD fluid. The

higher the gradient the higher the TCUF. This is why the highest UF is generated at the beginning of the dwell. As the glucose concentration decreases in the PD fluid due to absorption, the driving force for TCUF decreases. Water movement through the small pores drags small solutes (including sodium) along with it. In contrast, ultrasmall pores (which are now known to be aquaporin 1) allow only free water transport into the peritoneal cavity.

Definition of Ultrafiltration Failure

Clinically, UF failure has been defined as the presence of volume overload despite the use of three or more 4.25% glucose-based dialysis exchanges per day. This definition is imprecise, because it does not specifically address the issue of peritoneal membrane function. An abnormal UF response of the peritoneal membrane to an appropriate osmotic stimulus needs to be demonstrated in order to make a diagnosis of true UF failure. This can best be accomplished by testing the peritoneal membrane UF function using the modified PET (peritoneal equilibration test; described later in the chapter), introduced by Krediet and his group in mid 1990s.

This test measures the volume of UF obtained when the peritoneal membrane is challenged with hyperosmolar 4.25% dextrose solutions. It is the test recommended by the ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis for evaluation of the peritoneal membrane function. UF failure is present when net UF is less than 400 mL after a 4-hour dwell with 2 L of 4.25% dextrose dialysis solution.

Apparent Ultrafiltration Failure

In clinically volume-overloaded PD patients, apparent UF failure (attributable to nonmembrane causes for fluid overload) is more common than true peritoneal membrane UF dysfunction. These nonmembrane-related causes are usually reversible and need to be investigated and eliminated first when evaluating a patient for possible UF failure. The reversible causes may be patient or prescription related, or mechanical problems related to catheter drainage or dialysis solution leaks (Table 44.1). Patient-related problems can be caused by noncompliance with PD prescription. This may come from failure to comprehend a complex therapeutic regimen, inadequate teaching, burn-out, or a defiant patient who has difficulty in accepting the illness.

A high salt and fluid intake is frequently a cause for volume expansion, particularly in that most patients are not appropriately

Table 44–1

Reversible Causes of Fluid Retention

- Patient related
- Deficient education/training
- Complex therapy
- Burn-out
- Noncompliant patient
- Inappropriate prescription
- Mismatch of prescription and membrane type
- Improper choice of dialysis solution
- Mechanical problems
- Dialysis solution leaks
- Catheter obstruction
- Omental entrapment
- Malposition

instructed to limit the intake. Persistent hyperglycemia in diabetics will cause lower UF due to diminished osmotic gradient between the blood and PD fluid. Prescription-related problems arise from the failure to tailor dialysis prescriptions to a given type of membrane, especially one with no residual renal function. Prescription mismatch causes fluid retention, especially in patients who are high transporters. High peritoneal transport may result transiently from acute bacterial or chemical peritonitis. Alternatively, some patients have an inherently high transporting peritoneum. In either case, an appropriate prescription consists of short dwell exchanges lasting no more than 2 to 3 hours—so that the maximal UF is captured before late reabsorbtion of fluid decreases net UF during the exchange.

Such short dwell exchanges are usually achieved through the aid of a cycler machine, preferably during the night. Use of polyglucose (icodextrin) during peritonitis for better UF is also an accepted approach. We do not advocate frequent use of 4.25% dextrose solutions to avoid long-term membrane effects due to high glucose exposure. In some cases, long dwells generate low or negative UF and there is need to avoid excessive hypertonic exchanges. In these situations, shortening the duration of the long dwell can be achieved using a midday exchange in APD or a nighttime exchange device in CAPD. In addition, icodextrin can be used in long dwell to enhance UF. Mechanical problems include catheter obstruction, entrapment, and malposition. They cause inadequate draining with increased residual volume, which

will dilute the incoming dialysate and decrease the osmotic gradient—hence decreasing the TCUF.

Catheter function may be tested as an outpatient procedure by performing a quick "in-and-out" exchange. A perfectly functioning catheter should fill 2 L of fluid in approximately 10 minutes and drain in about 15 to 20 minutes. Migration of the catheter tip to a position outside the pelvis may result in poor drainage. Such malposition can be recognized on a plain radiograph of the abdomen. Once recognized as the cause of poor catheter function, treatment consists of administering laxatives or enemas to evacuate the colon. If malpositioning persists, surgical repositioning of the catheter tip into the pelvis may be required. Poor drainage may also result from omental wrapping of the catheter tip. This usually results in prolonged drainage time. Surgical correction with omentectomy is required in such situations. Of note, these complications tend to be seen frequently during the early months after catheter insertion. Late occurrence is usually related to severe peritonitis.

In the case of dialysate leaks, seepage of the dialysis solution from the peritoneal cavity will cause a decrease in the intraperitoneal volume of dialysate and thus a decrease in the total amount of glucose present in the peritoneal cavity during a dwell. This will result in more rapid dissipation of the osmotic gradient, with resultant impaired UF. Dialysate leaks that occur externally are easy to recognize. However, internal leaks can only be diagnosed with certainty with peritoneal computed tomography with contrast. The disruption of parietal peritoneum usually requires surgical correction and a period of 3 to 6 weeks of hemodialysis. Supine PD with low fill volumes may be an alternative therapy if a patient wants to avoid hemodialysis or if vascular access is difficult to obtain.

True Ultrafiltration Failure

After reversible causes of volume expansion have been excluded, peritoneal membrane function should be tested by a modified peritoneal equilibration test using 4.25% dextrose glucose solution. By definition, a net UF of less that 400 mL at 4 hours is classified as UF failure. The membrane-related causes of UF failure are outlined in Table 44.2. The steps of the test are as follows.

1. On the evening before the test, the patient performs a standard CAPD exchange with an 8- to 12- hour dwell overnight.
2. The overnight dwelling fluid is completely drained with the patient upright.

Table 44–2

Membrane-Related Causes of Fluid Retention

- Low drain volume and high transporter
- Inherent
- Acquired
- Peritonitis
- Long-term PD
- Low drain volume and low transporter
- Adhesions following severe peritonitis
- Advanced cases of sclerosing peritonitis
- Low drain volume and average transporter
- Mechanical problems
- Excessive lymphatic reabsorption
- Internal dialysis solution leak
- Aquaporin deficiency

3. With the patient in the supine position, 2 L of 4.25% dialysis solution is infused over 10 minutes. The patient should roll from side to side after each 400 mL of solution is infused.
4. The time the infusion is completed is noted. This is the zero dwell time.
5. At 0- and 2-hour dwell times, 200 mL of dialysis solution is drained into the drain bag and a 10-mL dialysate sample is drawn using a syringe. This is transferred to a red-topped tube. Fluid is analyzed for glucose, sodium, and creatinine concentrations.
6. The remaining withdrawn solution is reinfused back into the peritoneal cavity.
7. At the 2-hour dwell time, a blood sample is drawn for creatinine, sodium, and glucose.
8. At the 4-hour dwell time, the abdomen is completely drained and the total drain volume is measured.
9. A 10-mL sample of drained fluid is placed into a red-topped tube, and glucose, sodium, and creatinine concentrations are measured.
10. D/P creatinine and sodium and D/D_0 glucose are calculated as follows: D/P = dialysate creatinine or sodium concentration at 0, 2, and 4 hours divided by the serum creatinine or sodium. D/D_0 = dialysate glucose concentration at 0, 2, and 4 hours divided by the blood glucose at time 0.

11. The three points obtained for creatinine and sodium D/P values at 0, 2, and 4 hours are plotted on the creatinine and sodium graph (Figures 44.1 and 44.2). Glucose D/D_0 values at 2 and 4 hours are plotted on the glucose graph (Figure 44.1). Patients are classified according to membrane type as follows.
    - *High transport (D/D_0 < 0.3 and D/P Cr = 0.81–1.0):* Patients characterized as high solute transporters tend to have good urea and creatinine clearance but poor UF due to rapid absorption of glucose and dissipation of the osmotic gradient.
    - *Normal (average) transport (D/D_0 = 0.3–0.5 and D/P Cr = 0.5–0.81):* Failure to ultrafilter in the face of normal transport characteristics implies fluid leak, catheter malfunction, and excessive lymphatic reabsorbtion of ultrafiltrate or aquaporin deficiency.
    - *Low transport (D/D_0 > 0.5 and D/P Cr = 0.34–0.5):* Patients with low solute transport tend to have poor urea and creatinine clearances and do not transport glucose rapidly across the peritoneal membrane. If poor UF occurs despite maintenance of an adequate osmotic gradient,

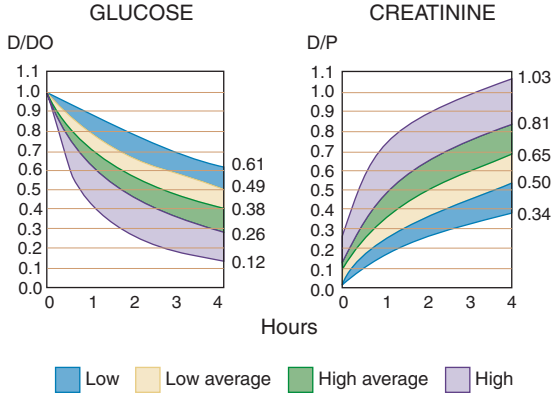


Figure 44–1

Glucose D/D0 and creatinine D/P ratios during the modified PET are plotted against baseline values to characterize solute transport characteristic of patients presenting with fluid retention.

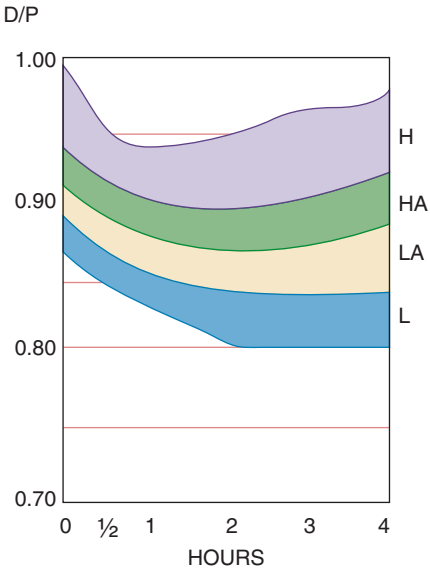


Figure 44–2

Sodium D/P ratios during dwell time plotted against baseline values during the modified PET.

it must be only due to the reduction in peritoneal surface area because of adhesions or peritoneal sclerosis. Peritoneography may be helpful in diagnosis, and it can show PD trapped in small cavities delineated by adhesions. Surgical lysis of the adhesions may help in restoring the normal or near-normal anatomy of the peritoneal cavity and facilitate continuation of PD without the need for transfer to hemodialysis. Low drain volume and low small-solute transport are also seen in advanced stages of sclerosing peritonitis.

The prevalence of UF failure in long-term PD patients has been found in as high a level as 36% of the patients who were on PD for more than 4 years and who had a modified PET test compatible with UF failure. The causes of UF failure are large vascular surface area in 65% of the patients, rapid effective lymphatic reabsorbtion in 35%, and impaired free water transport or

decreased maximum dip in D/P sodium in 65 % of the patients. Most patients typically have a combination of etiologic factors, and the most frequent combination is large vascular area and impaired free water transport.

High transport status of the peritoneal membrane may be an inherent condition at initiation of dialysis in about 15% of patients, or acquired later at some stage in the course of dialysis. It occurs transiently during acute peritonitis as a result of vasodilatation and an increase in the number of perfused peritoneal capillaries caused by inflammation. This condition resolves gradually 2 to 3 months after the resolution of the acute episode of peritonitis. However, the persistent condition is frequently seen in long-term PD patients due to an increase in vascular surface area attributable to neoangiogenesis. This is now recognized to occur due to prolonged membrane exposure to glucose, advanced glycosylation end products, and frequent episodes of peritonitis.

Aquaporin deficiency cases are now being recognized and reported. This condition is relatively rare. Aquaporins are ultra-small pores that permit solute-free water transport by way of crystalloid osmosis. It is assumed that 40 to 50% of osmotic-induced UF is mediated by aquaporins. Because free water (without sodium) is transported through these pores, a drop in dialysate Na concentration is expected to occur during the initial 60 to 90 minutes of the dwell. This phenomenon is known as "sodium sieving." A D/PNa ratio of >0.88 correlates with aquaporin deficiency at 60 minutes during the modified PET.

Another indirect indication of aquaporin deficiency is the small difference in UF volumes between 1.5 and 4.5% glucose solution because aquaporin UF is primarily due to crystalloid pressure. High transporters also have a less-than-anticipated drop in D/P sodium during the early hours of an exchange. This is believed to be caused by rapid absorption of glucose and a decrease in osmotic pressure. Increased lymphatic transport is a diagnosis of exclusion: D/P creatinine ratio is unchanged, D/PNa at 1 hour is normal, and no mechanical causes for low drain volume can be identified. It can be demonstrated from the high clearance of macromolecule (albumin, Dextran 70) from the peritoneal cavity. This is difficult to perform in clinical practice and remains only a research tool.

Management of Ultrafiltration Failure

Patients who are high transporters are best managed with automated PD, using a cycler that delivers short dwell exchanges at night. These patients should not receive more than 5 cycles during

a 9- to 10-hour session per night. Increasing the cycle number and frequency will cause an increase in the dead time spent on filling and draining, and will decrease the efficiency of dialysis. Management of the long dwell requires particular attention because these patients will have neutral or even negative UF at the end of this dwell. The use of icodextrin is encouraged in these patients. Alternatively, the long dwell can be shortened by introducing a midday exchange.

A particular problem in APD is the lower total daily sodium removal compared to CAPD, which uses longer dwell times. Due to short dwell exchanges during APD, the sodium sieving (explained previously) results in more free water and less sodium removal per exchange compared to CAPD. Sodium removal can be enhanced during APD by prescribing short dwells of least 2 hours, by not eliminating the longer day dwell, or by using icodextrin for the long dwell and by introducing a midday exchange if possible.

Using dialysis solutions with lower Na concentration has been shown to increase sodium removal. However, such low-sodium dialysis solutions are not commercially available. Peritoneal rest has been shown to help with management of UF failure. Four-week temporary transfer to hemodialysis can help restore peritoneal membrane UF function. Patients who require more than one episode of peritoneal rest tend to have a poorer response to subsequent peritoneal rest. It is more effective if performed early in the course of CAPD.

In cases of increased lymphatic reabsorbtion, management should be directed toward increasing TCUF (as in increased transport status). In aquaporin deficiency, peritoneal rest can also help. Icodextrin is highly recommended in these situations because it causes sustained UF by means of colloid osmosis and does not involve the function of aquaporins but only that of the small pores.

Changes in Peritoneal Membrane Structure with Peritoneal Dialysis

The peritoneal, mesothelium, and underlying stroma undergo morphologic changes in response to injury induced by bacterial or chemical toxins introduced into the PD fluid. These changes range from peritoneal opacification with unknown clinical significance to catastrophic encapsulating peritoneal sclerosis (EPS) with devastating clinical outcome. Peritoneal membrane structural changes have been noted by Dobie for the Peritoneal Biopsy Registry and the facts discussed in the following section have emerged.

Uremic Peritoneum in Nondialyzed Uremic Patients

The peritoneal membrane shows ultrastructural abnormalities in 35% of uremic patients before starting PD. These charges have been described as electron-dense rods, initially located in the rough endoplasmic reticulum, which upon accumulation may burst from their confines to fill the cytoplasm—leading to mesothelial desquamation. These abnormalities regress after correction of the uremic state with PD.

Tanned Peritoneum

Patients on long-term CAPD may display drying, wrinkling, and brownish discoloration of the visceral and parietal peritoneum. Histologically, the outer portion of the peritoneum shows replacement by an acellular band of hyalinized collagen (with absence of mesothelium) and a sparse mononuclear cell infiltrate in the underlying tissues.

Mural Fibrosis

Mural fibrosis reflects the pathologic progression of the tanned peritoneum syndrome. Macroscopically, in addition to peritoneal tanning there is thickening and stiffness of the bowel wall. The clinical sequelae resemble those of EPS, with patients presenting with symptoms related to bowel obstruction due to invasion of the bowel muscle layer and mesenteric nerve plexus by the hyperplastic fibrous tissue. An encapsulating membrane, however, is not seen. Radiologically, bowel distention may be absent in the presence of intestinal obstruction because the stiffened bowel fails to distend.

Encapsulating Peritoneal Sclerosis

EPS is the end stage of intra-abdominal inflammatory processes resulting in sheets of fibrous tissue that envelope various viscera. This is the most serious and fatal complication of PD. A mortality of nearly 50% has been noted in some series of case reports. Histological examination of sclerotic tissue reveals dense fibrous tissue permeated with a chronic inflammatory infiltrate of variable density. The clinical manifestations of this disorder are related to bowel obstruction and poor UF despite maintenance of a high D/D_0 ratio seen with the PET.

Evidence for possible etiologic agents was obtained from epidemiologic studies conducted as part of a cooperative inter-

national study on EPS (Table 44.3). The study noted a higher incidence of peritonitis (1 episode in 5.5 patient-months) for patients with the disorder compared to the global frequency of 1 episode in 10 patient-months. The affected patient population was noted to have a high frequency of fungal and pseudomonal infections and association with the use of dialysate containing acetate. Subsequent studies incriminated chlorhexidine, used as a sterilant in the connecting procedure, as an etiologic agent. Experiments showed that chlorhexidine creates mesothelial tight-junction disruption with deposition of chlorhexidine magnesium crystals in the underlying stroma.

Treatment of Encapsulating Peritoneal Sclerosis

No uniform successful treatment exists at this time for EPS. Based on anecdotal experiences, a variety of treatments have been suggested. Delayed diagnosis of the condition limits successful outcome. Surgical and/or medical management has been suggested. PD in any form must be discontinued. Medical management is indicated for early stages of the condition, where no bowel obstruction has yet occurred, and consists of the use of steroids and/or immunosuppressants. Total parenteral nutrition for prolonged periods may be necessary. Good results have been reported by this approach, including resolution of symptoms and new membrane formation. When there is a cocoon formation, surgical intervention becomes inevitable either to relieve or prevent intestinal obstruction.

Total intestinal electrolysis has been done with encouraging outcome. Attempts to free the bowel from the constricting fibrous tissue are frequently associated with bowel perforation, severe peritonitis, and high mortality. Overall prognosis following surgical intervention is poor. Lack of precise knowledge of the process

Table 44–3

Etiologies of Sclerosing Encapsulating Peritonitis

- Microbial peritonitis
- Fungal
- Pseudomonal
- Acetate
- Chlorhexidine

limits our ability to plan a preventive strategy. Early recognition and diagnosis of the condition in the long-term PD patient should be the goal. There are no telltale indicators except for being aware of the condition in long-term patients.

Recommended Reading

Honda K, Nitta K, Horita S, Tsukada M, Itabashi M, Nihei H, et al. Histological criteria for diagnosing encapsulating peritoneal sclerosis in CAPD. Advances in Peritoneal Dialysis 2003;19:169–75, 2003.

A very descriptive and graphic presentation on establishing criteria for diagnosis of EPS.

Kawaguchi Y, Kawanishi H, Mujais S, et al. Encapsulating peritoneal sclerosis: Definition, etiology, diagnosis and treatment. Perit Dial Int 2000;20(S4):43.

Excellent review presenting a detailed discussion of the clinical syndrome of sclerosing peritonitis, including extensive review of the literature.

Kawanishi H. Surgical treatment for encapsulating peritoneal sclerosis. Advanves in Peritoneal Dialysis 2002;18:139–43.

This article makes a compelling argument in favor of medical and surgical management of EPS.

Krediet RT, Lindholm B, Rippe B. Pathophysiology of peritoneal membrane failure. Perit Dial Int 2000;20(S4):22.

This comprehensive and applied discussion of the pathophysiology of peritoneal membrane failure also offers a brief discussion of fluid and solute transport across the peritoneal membrane, adequately covering the concept of aquaporin and its role in PD.

Nolph K, Gokal R, Mujais S. ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int 2000;20(S4):3.

A comprehensive discussion of the problem of ultrafiltration failure and very practical clinical recommendations.

Mujais S, Nolph K, Gokal R, et al. Evaluation and management of ultrafiltration problems in peritoneal dialysis. Perit Dial Int 2000;20(S4):5.

A detailed report on the problem of ultrafiltration, including a practical discussion of workup, diagnosis, and treatment. A highly recommended and very useful clinical review.

CHAPTER 45

Hypotension in Peritoneal Dialysis Patients

Ramesh Khanna, MD

Introduction

The excellent blood pressure control seen in patients on CAPD (continuous ambulatory peritoneal dialysis) is attributed to continuous and sustained ultrafiltration and sodium removal, which help maintain patient euvolemic levels at their dry body weight. The reduction in blood pressure is most marked during the initial weeks of therapy, when patients are on a severely salt-restricted diet. However, additional gradual decreases occur over the next few months.

The blood pressure response to CAPD correlates well with reduction in fluid body weight, emphasizing the importance of fluid volume in the pathogenesis of hypertension in end-stage renal disease. In fact, hypertension can often be controlled without drug therapy—even when plasma renin and aldosterone levels are observed to increase.

Continuous Ambulatory Peritoneal Dialysis

During CAPD exchanges, net water and sodium are removed. CAPD patients lose approximately 1 to 1.5 L/day of ultrafiltrate (with a sodium concentration of approximately 132 mEq/L) because the dialysate equilibrates with serum sodium during a 4- to 6-hour exchange. The total sodium loss during a day can be readily calculated as

$$\text{Daily sodium loss with dialysis} = (\text{drain volume} \times \text{drained dialysate sodium concentration}) - (\text{infusion volume} \times \text{infused dialysate sodium concentration}).$$

Thus, a typical CAPD patient could easily lose 132 to 198 mEq/day of sodium through the ultrafiltrate. A patient accustomed to restricted sodium intake during the course of chronic renal failure continues to consume a low-sodium diet during early periods of CAPD therapy. Consequently, CAPD patients become sodium depleted over the course of therapy due to a combination

of dialysate sodium loss and restricted sodium intake. Initially, such sodium depletion is beneficial in controlling hypertension. Most CAPD patients require multiple antihypertensive agents for control of hypertension before starting CAPD, but gradually need fewer drugs and eventually discontinue needing drugs. This is the time to increase salt intake to minimize salt losses.

If dietary sodium intake is not increased, severe sodium depletion can lead to hypotension—especially in very compliant patients and with primary cardiac disease. Total body sodium depletion results in decreased vascular response to infusions of vasoconstrictor agents such as norepinephrine. Salt repletion in such patients results in restoration of the vascular pressor response, extracellular fluid volume, and blood pressure.

In certain CAPD patients, such as those with severe cardiac dysfunction, hypotension may occur readily after initiating CAPD. Surprisingly, many patients are asymptomatic despite a severe degree of hypotension. This degree of hypotension is possibly due to the lack of renin response from the native kidneys because most patients are functionally anephric.

In contrast, during peritoneal dialysis therapies (automated peritoneal dialysis, APD) with short-dwell exchanges of 1 to 2 hours, such as intermittent peritoneal dialysis (IPD), the dialysate sodium concentration decreases due to solute sieving and hypotonic ultrafiltration. This considerably diminishes sodium loss during the PD therapy. Consequently, hypertension control in patients on intermittent dialysis therapies is not as readily achieved. Most patients require continued fluid and dietary salt restriction, and many patients need severe salt restriction and medications to lower blood pressure. Hypotension, if it occurs, is generally transient as a result of rapid ultrafiltration during a dialysis session. The algorithm shown in Figure 45.1 depicts a systematic approach to a CAPD patient with hypotension.

Management

Acute hypotension due to intravascular volume depletion is managed by fluid repletion until the blood pressure is restored. The patient is advised to avoid using hypertonic dialysis solutions. Dialysis is continued with 1.5% dextrose dialysis solution until the desired blood pressure is reached. The dwell time may be prolonged beyond the usual period so that a significant amount of dialysis solution is reabsorbed from the peritoneal cavity. Blood-pressure-lowering agents are temporarily withheld. In extreme cases of hypovolemia, intravenous fluid replacement may be necessary.

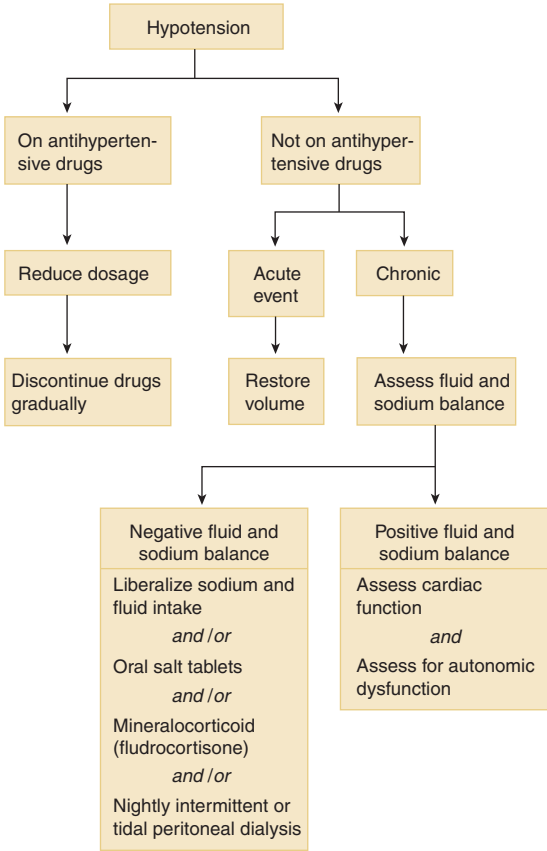


Figure 45–1

A systematic approach to assessment of hypotension in the CAPD patient.

The response to treatment is immediate, and the blood pressure returns to normal levels quickly. During follow-up visits, careful attention should be given to training the patient in adjusting the dry body weight. It is not unusual for a CAPD patient to initially gain significant fluid-free body weight due to amelioration of

uremic symptoms. Management of chronic hypotension during CAPD is complex and requires close monitoring of the patient's fluid and sodium balance. If upon assessment the patient is found to be in negative sodium balance the following steps may be taken alone or in combination.

- Liberalize dietary sodium intake.
- If the patient is unable to consume the desired amount of salt through dietary means, oral salt tablets may be given.
- Fludrocortisone, a mineralocorticoid, may help in some cases—especially in patients with significant residual renal function. Although the exact site and mechanism of action of fludrocortisone in a patient with nonfunctioning kidneys are uncertain, use of this drug improves blood pressure significantly. Even though no evidence suggests that there is an effect at the peritoneal level, such a hypothesis is very attractive. It is important to monitor the patient carefully during the administration of salt and mineralocorticoid, especially with regard to weight gain. The goal during such therapies is to raise the blood pressure without a significant increase in body weight.
- Refractory hypotension unresponsive to the preceding measure is managed by changing the PD prescription. Instead of continuous long-dwell exchange therapies, such as CAPD or CCPD (continuous cycling peritoneal dialysis), patients are managed on short-dwell exchange therapies such as nightly IPD. Because of the positive sodium balance during intermittent therapy exchanges, hypotension is gradually reversed. In some patients, restoration of normal blood pressure occurs while the body weight is actually decreasing.

Patients with an underlying primary cardiac disease are particularly sensitive to fluid and salt removal and may become hypotensive with minimal fluid shifts despite being in positive fluid and sodium balance. Appropriate cardiac management is mandatory in such cases.

Diabetic patients with autonomic neuropathy pose a unique problem during dialysis. Ultrafiltration during dialysis aggravates orthostatic symptoms and some diabetics may have syncopal attacks. To minimize orthostatic symptoms, a certain degree of fluid is retained. Inevitably this leads to supine hypertension. The approaches previously listed may be tried in various combinations to achieve a satisfactory result. Prescribed caffeine, an adenosine receptor blocker that causes vasoconstriction in a 250-mg dose, or two cups of coffee prior to meals may improve orthostatic or postprandial hypotension.

Midodrine, a selective alpha-1-adrenergic receptor agonist, was recently approved by the FDA for orthostatic hypotension and appears to be a promising agent. It causes both arterial and venous constriction. It is a pro-drug that is converted to desglymidodrine, an active metabolite that does not cross the blood-brain barrier and that is therefore free of the central nervous system side effects seen when other sympathomimetics are used. It has a bioavailability of 93% after oral intake, even in patients with gastroparesis. It is a short-acting drug with a 4-hour duration of action. The most common side effects associated with it are piloerection, pruritus, and urinary retention. Supine hypertension is a common troublesome side effect with higher doses. Midodrine 10 mg used orally three times a day is effective and safe in the treatment of neurogenic orthostatic hypotension.

Recommended Reading

Agrawal A, Saran R, Khanna R. Management of orthostatic hypotension from autonomic dysfunction in diabetics on peritoneal dialysis. Perit Dial Int 1999;19:415–17.

A detailed review of pathogenesis and management of hypotension in diabetic patients.

Leenen, FHH, Shah P, Boer WH, et al. Hypotension in CAPD: An approach to treatment. Perit Dial Bull 1983;3:23–25.

A treatment plan based on a pathophysiologic mechanism of hypotension in CAPD.

CHAPTER 46

Abdominal Catastrophes, Peritoneal Eosinophilia, and Other Unusual Events in Peritoneal Dialysis

Rajnish Mehrotra, MD, and Pranay Kathuria, MD

Repeated instillation and drainage of dialysate during the course of chronic peritoneal dialysis (CPD) therapy is a unique clinical situation that infrequently draws attention to primary intra-abdominal events. These events are often unrelated to the CPD treatment itself but are brought to attention because of an abnormal appearance of drained dialysate, with and without abdominal pain. They are important for two reasons. First, some conditions (such as visceral perforation) present with peritonitis. Thus, unless a nephrologist considers the diagnosis of primary intra-abdominal events definitive intervention may be delayed. Second, some conditions (such as hemoperitoneum) are very alarming but often require only reassurance of the patient. In this chapter, we discuss several such primary intra-abdominal events. Complications of CPD therapy such as peritoneal sclerosis and sclerosing encapsulating peritonitis are discussed elsewhere in this volume.

Abdominal Catastrophe

In CPD patients, the term *abdominal catastrophe* refers to the signs and symptoms associated with severe visceral inflammation or perforation. Invariably, these patients present with bacterial peritonitis. Occasionally, however, crampy abdominal pain with clear peritoneal dialysis effluent may be present. Enteric peritoneal contamination may occur as a result of perforated diverticulitis, appendicitis, incarcerated hernia, ischemic colitis, nonocculusive meseneteric ischemia, gangrenous cholecystitis, or perforated gastric or duodenal ulcer. It has been suggested that CPD patients present with abdominal catastrophes more frequently than the general population and more frequently than patients undergoing hemodialysis. However, these data are based on small single-center studies and no definitive conclusions can be made in this regard.

Rarely, erosion of the Tenckhoff catheter into the ileum or colon may be the primary event leading to visceral perforation. This is often limited to patients with a dormant indwelling access not being used for CPD therapy.

Notwithstanding the early reports, patients with autosomal dominant polycystic kidney disease do not appear to be at a higher risk for diverticular disease or enteric peritonitis when compared to other groups of CPD patients. Furthermore, the relationship of presence of colonic diverticula to the occurrence of enteric peritonitis or abdominal catastrophe remains unclear. It appears that patients with large number (≥10) or size (≥10 mm) of diverticuli or nonsigmoid location may be predisposed to a higher incidence of enteric peritonitis. However, most patients with diverticular disease never develop enteric peritonitis or visceral perforation. Thus, the presence of diverticulosis should not be considered a contraindication to CPD therapy.

The initial clinical presentation of peritonitis associated with abdominal catastrophes is indistinguishable from CPD peritonitis from other causes. The presence of fecal or biliary material in the peritoneal effluent, although highly suggestive, is rare. The peritoneal white blood cell count associated with abdominal catastrophe is usually higher than in other causes of peritonitis. However, data are not sufficient to recommend a reliable cut-off value for the peritoneal cell count. Pneumoperitoneum can be present in asymptomatic CPD patients (see material following) and does not help in diagnosing visceral perforation. Other imaging studies, such as computed tomography, are often unrevealing as well.

There is an increasing body of data that allows us to challenge the conventional wisdom associating polymicrobial peritonitis with abdmominal catastrophes. Less than 20% of patients with abdominal catastrophes have polymicrobial peritonitis. Cultures of peritoneal effluents usually demonstrate a single Gram-negative (or, rarely, an anaerobic) organism. Conversely, less than 10% of cases of polymicrobial peritonitis have an underlying surgical cause (Table 46.1). Thus, the routine use of laprotomy in patients diagnosed per peritoneal fluid culture with more than one organism is probably inappropriate. The concentration of amylase in the peritoneal effluent appears to be promising. Levels that exceed 500 IU/L seem to be highly suggestive of visceral perforation.

Given the previously cited data, the diagnosis of abdominal catastrophes in CPD patients is often delayed—and this in turn leads to a greater probability of an adverse outcome. Thus, a high index of clinical suspicion is required in the diagnosis of episodes of peritonitis associated with abdominal catatstrophes. However,

Table 46–1

Relationship of Polymicrobial Peritonitis and Surgical Causes

	Episodes of Polymicrobial Peritonitis	Catheter Removal	Death	Surgical Causes
Pittsburgh	39	17	1	3
New Haven	80	12	4	6
Chicago	43	14	1	3
Hong Kong	140	45	9	4
Total	302	88 (29%)	15 (5%)	16 (5%)

Adapted from Szeto CC, Chow KM, Wong TYH, Leung CB, Li PKT. Conservative management of polymicrobial peritonitis complicating peritoneal dialysis: A series of 140 consecutive cases. Am J Med 2002;113:728–33.

evidence suggests that the condition should be considered in patients with enteric peritonitis that respond inadequately or incompletely to conventional therapy. Large perforations, such as those associated with gastric or duodenal ulcers or ischemic colitis, are often fatal. Smaller perforations (such as those associated with appendicitis or diverticulitis), however, have a slightly better prognosis.

Pneumoperitoneum

In the general population, the presence of air under the diaphragm is considered diagnostic of visceral perforation and is a trigger for surgical intervention. However, cross-sectional studies have demonstrated that up to 1/3 of CPD patients have demonstrable pneumoperitoneum on plain radiography. A larger proportion has intraperitoneal air as assessed by computed tomography.

Pneumoperitoneum is particularly common after the placement of a CPD catheter, after manipulation or intervention involving the peritoneal access, or following gastrointestinal endoscopic procedures. On the other hand, if used correctly the disconnect systems for CPD therapy preclude the introduction of free air into the peritoneal cavity. However, pneumoperitoneum has been reported to occur under conditions such as the use of a cycler and when the patient eliminates the step of flushing the line before filling the peritoneal cavity.

Some patients present with sharp abdominal pain that may radiate to the shoulder, with the inadvertent introduction of air into the peritoneal cavity. However, most cases are diagnosed incidentally—and in an asymptomatic CPD patient with an unremarkable abdominal examination pneumoperitoneum is of little consequence. It only requires retraining the patient to ensure that the CPD exchange occurs in a closed system.

In the setting of peritonitis, the presence of pneumoperitoneum has a somewhat higher probability of being associated with underlying visceral perforation and requires aggressive radiologic workup. Contrary to earlier reports, the size of pneumoperitoneum has little predictive value for the diagnosis of visceral perforation. Furthermore, diagnostic laprotomy should still be used only when the clinical suspicion is high and other corroborative evidence (such as high peritoneal effluent amylase levels or other radiologic studies) presents a strong possibility for visceral perforation.

Iatrogenic Complications of Gastrointestinal or Gynecologic Procedures in CPD Patients

Gastrointestinal and gynecologic procedures and interventions are performed frequently in all populations, including CPD patients. There have been several case reports that have documented episodes of peritonitis following sigmoidoscopy or colonoscopy (particularly if it involves polypectomy or argon photocoagulation), gastroscopy (particularly if it involves sclerotherapy or heat coagulation), hysteroscopy, endometrial biopsy, and the placement of intrauterine devices. The nature of published reports does not allow one to estimate the incidence of peritonitis following endoscopic procedures or interventions. Furthermore, it is unlikely that a randomized controlled trial will be conducted to test the benefit of routine antibiotic prophylaxis of CPD patients undergoing gastrointestinal or gynecologic procedures. In light of these considerations, it is recommended that prophylactic antibiotics that provide coverage against enteric Gram-negative and anaerobic bacteria be routinely administered prior to such procedures in CPD patients.

Percutaneous endoscopic gastrostomy (PEG) tubes are used to provide enteral nutrition. The presence of a well-healed PEG tube is not a contraindication to the start of CPD therapy. However, the PEG tube and CPD catheter should be clearly marked because inadvertent administration of enteral nutrition feeds into the peritoneal cavity can lead to severe (and often fatal) chemical peritonitis. On the other hand, placement of a new PEG tube in a patient

undergoing CPD therapy carries a high risk of infection—particularly of fungal peritonitis. Thus, if a CPD patient requires the placement of a PEG tube peritoneal dialysis should be interrupted for 2 to 6 weeks and the patient should undergo temporary hemodialysis if needed.

Pancreatitis

Several single-center studies suggest that among patients undergoing CPD the incidence of pancreatitis may be up to threefold higher when compared to patients undergoing maintenance hemodialysis. The pathophysiologic basis for the increased incidence is unclear, but systemic abnormalities such as hypertriglyceridemia and hypercalcemia (or local events, such as irritation of pancreas from the retroperitoneal diffusion of peritoneal dialysate) have been proposed as possible culprits.

The clinical presentation of acute pancreatitis in CPD patients is often the same as that observed among patients without end-stage renal disease. The peritoneal dialysate is often clear, but may demonstrate increased total white blood cell count with or without positive effluent cultures. Hemoperitoneum or chyloperitoneum may be seen occasionally. Rarely, in patients with hemorragic pancreatitis the dialysate may be brownish-black due to the presence of methhemalbumin. Although serum amylase levels may be helpful, dialysate amylase (>100 IU/L) provides greater diagnostic information. However, serum and dialysate amylase are up to sixfold lower among CPD patients treated with icodextrin-based dialysate. Serum and dialysate lipase are more reliable under those circumstances. If radiologic testing is pursued to either diagnose pancreatitis or any of the complications, it is prudent to completely drain all peritoneal dialysis fluid before imaging is performed to provide a better and complete visualization of the pancreas.

The data on the prognosis of CPD patients with pancreatitis is inconsistent. Some centers have reported a higher morbidity and mortality when compared to patients without end-stage renal disease. Thus, early diagnosis and careful management are critical to ensure optimal outcomes.

Peritoneal Eosinophilia

Among the differential diagnosis of cloudy bags upon peritoneal dialysis is peritoneal fluid eosinophilia—a condition with eosinophils constituting greater than 10% of the total peritoneal white blood cell count and the eosinophil count exceeding 100 cells per cubic

milliliter of peritoneal effluent. Peritoneal eosinophilia can be seen in the presence of CPD-related peritonitis. However, many cases occur in the absence of peritonitis. In the past, the leading cause was hypersensitivity to peritoneal dialysis material (possibly the plasticizers or sterilants). Introduction of air or blood into the peritoneum has also been associated with peritoneal fluid eosinophilia. Icodextrin (and dialysate additives such as antibiotics, heparin, and povidone-iodine) may also induce this condition. A rare cause is sclerosing encapsulating peritonitis.

Most episodes of peritoneal eosinophilia develop in the first 3 months after initiating peritoneal dialysis, with an occasional patient presenting years after starting peritoneal dialysis. Prior reports put the incidence between 5 and 61%, but the incidence has significantly receded in recent years due to improvements in the quality of peritoneal dialysis materials. Patients typically present with cloudy bags, and some may have abdominal pain or fever. An elevated blood eosinophil count and elevated IgE levels are found in less than half of patients. While awaiting cell counts and cultures, it is common to initiate antimicrobial therapy for presumed bacterial peritonitis.

With a confirmed diagnosis of noninfective peritoneal eosinophilia, it is appropriate to follow a course of watchful expectancy because most cases will resolve spontaneously. Steroids (intraperitoneal or oral) are indicated for patients with a protracted course or frequent recurrences. Steroids may also be used to maintain catheter patency in patients with severe abdominal pain or very turbid fluid. Other successful treatment options reported in the literature include antihistamines, ketotifen (a mast cell stabilizer), and glycyrrhizin (an extract of licorice with anti-inflammatory properties).

Hepatic Subcapsular Steatosis

Subcapsular steatosis or fat accumulation in the liver appears to occur exclusively among diabetic patients undergoing CPD therapy and receiving intraperitoneal insulin. This condition is clinically asymptomatic, is not associated with any liver function test abnormalities, and appears to be without clinical consequence. However, the recognition of this entity by a nephrologist is important to avoid misinterpreting hepatic subcapsular steatosis as a more serious lesion (such as metastatic malignancy).

Increasing body weight, higher intraperitoneal insulin dose or serum triglycerides, and higher peritoneal transport rate appear to increase the likelihood for the development of hepatic sub-

capsular steatosis. Recent studies also suggest that it is the intraperitoneal administration of insulin rather than the glucose load that leads to the steatosis. It has been proposed that insulin is absorbed from the liver surface into the subcapsular hepatocytes, where it suppresses the oxidation of fatty acids. This leads to the esterifiication of the fatty acids to form triglycerides, which accumulate and result in hepatic subcapsular steatosis.

On ultrasonography, the steatosis appears as a bright echogenic rim or as discrete echogenic subcapsular nodules—best seen in the subdiaphragmatic segments of the liver. On computed tomography, it is seen as discrete nodular low-attenuation subcapsular or thin rind-like lesions. On magnetic resonance imaging, hepatic subcapsular steatosis is identified as hyperintense lesions (and chemical shift imaging demonstrates the presence of fat in the liver). Serial imaging has shown the lesions to be reversible upon discontinuation of intraperitoneal insulin. However, it may take several months for complete resolution.

Hemoperitoneum

Hemoperitoneum is not an uncommon complication of peritoneal dialysis. The presence of even minimal amounts of blood can color the peritoneal fluid pink or red. Performance of the dialysis procedure by CPD patients often brings cases to light, which would have been otherwise clinically silent.

The various causes of hemoperitoneum are categorized in Table 46.2. Hemoperitoneum is more common among premenopausal women—with causes related to gynecological conditions such as retrograde menstruation, ovulation, cyst rupture, and endometriosis. Hemoperitoneum with retrograde menstruation or endometriosis usually presents prior to the onset of vaginal bleeding. These patients are most likely to have recurrent hemoperitoneum. In a number of patients, no definite etiology can be determined. It has been suggested that hemoperitoneum may have been a result of minor tears of the omental vessels. Occasionally, a peritoneal catheter has been reported to have eroded into the major mesenteric vessels—leading to hemoperitoneum.

Most cases of hemoperitoneum are benign. Uncommonly, hemoperitoneum is a sign of underlying intraperitoneal pathology. In these patients, bleeding often persists beyond 36 hours. Fewer than 25% of cases have major hemorrhage and need transfusion or surgical intervention. An initial assessment includes a good history, including details of menstruation, recent trauma, and use of anticoagulant or antiplatelet drugs. The patient should undergo

Table 46–2

Causes of Hemoperitoneum

Gynecologic Disorders
- Ovulation (mid-cycle)
- Retrograde menstruation (with periods)
- Ruptured ovarian cyst
- Endometriosis (with periods)
- Ectopic pregnancy

Associated with Acute Abdomen
- Acute hemorrhagic pancreatitis
- Acute cholecystitis
- Splenic rupture or infarction
- Peritonitis

Peritoneal Membrane Abnormalities
- Sclerosing peritonitis
- Peritoneal carcinomatosis
- Peritoneal calcification
- Radiation injury

Miscellaneous
- Trauma
- Exercise
- Postcolonoscopy
- Bleeding disorders
- Rupture of hepatic or renal cysts
- Kidney or liver tumors
- Retroperitoneal hematoma
- IgA nephropathy
- Idiopathic

assessment of the hemodynamic status, and be evaluated for signs of an abdominal catastrophe. Subsequent evaluation is often dictated by this initial assessment.

The management of hemoperitoneum is often expectant, and if necessary is directed at the primary cause. To prevent the occlusion of the peritoneal dialysis catheter, the addition of 500 to 1000 units of heparin to each bag of dialysate is often recommended. Instillation of unwarmed dialysate at room temperature has also been proposed as a means of inducing vasoconstriction of the peritoneal circulation (by the cooler dialysate) to slow the bleeding. However, care should be exercised to avoid hypothermia during the winter months in cold locales. Desmopressin and unconjugated estrogens can ameliorate uremic bleeding.

Chyloperitoneum

Chyloperitoneum results from the leakage of chyle into the peritoneal cavity. Patients present with turbid or typical milky dialysate. The diagnosis is confirmed if chylomicrons are detected or if dialysate triglyceride levels are higher than the plasma level. Patients on peritoneal dialysis can loose substantial amounts of protein and lymphocytes with repeated exchanges, leading to malnutrition and immunosuppression. Excessive fluid loss causing dehydration can also be an issue.

The underlying causes are related to interruption or obstruction of the lymphatic system. Malignancies, especially lymphomas, are reported as the most common cause of chyloperitoneum. Trauma (either at the time of insertion of the peritoneal catheter, or from repeated catheter movement), acute and chronic pancreatitis, cirrhosis, amyloidosis, superior vena cava syndrome, and tuberculous peritonitis are other causes of chyloperitoneum. Elevations of peritoneal triglycerides have also been associated with the use of dihydropyridine calcium channel blockers.

Evaluation of patients should include a detailed history and examination—along with computerized tomographic scans, magnetic resonance imaging, or lymphoscintigraphy as indicated. Strategies on the treatment of chylous ascites focus on decreasing the production of chyle and treatment of the underlying cause. Most patients can be continued on peritoneal dialysis. Long-chain fatty acids are absorbed from the bowel directly into the lymphatic system and contribute to chyle flow, whereas medium-chain triglycerides are absorbed directly into the bloodstream and decrease the chyle flow. Thus, high-protein low-fat diets containing medium-chain triglycerides can be employed–and over several months have been shown to be effective. Bowel rest with total parenteral nutrition is an alternative. Octreotide, a somatostatin analogue, has been reported to be effective in anecdotal reports.

Recommended Reading

Fontan MP, Rodriguez-Carmona A, Galed I, Iglesias P, Villaverde P, Garcia-Ureta E. Incidence and significance of peritoneal eosinophilia during peritoneal dialysis-related peritonitis. Perit Dial Int 2003;23:460–64.

Single-center retrospective observational study with brief review of etiology, diagnosis, and management of peritoneal eosinophilia.

Greenberg A, Bernardini J, Piraino BM, Johnston JR, Perlmutter JA. Hemoperitoneum complicating chronic peritoneal dialysis: Single-center experience and literature review. Am J Kidney Dis 1992;19:252–56.

Single-center case series of hemoperitoneum among CPD patients and a review of the literature.

Kern EO, Newman LN, Cacho CP, Schulak JA, Weiss MF. Abdominal catastrophe revisited: The risk and outcome of enteric peritoneal contamination. Perit Dial Int 2002;22:323–34.

A systematic analysis of 63 episodes of abdominal catastrophes in 41 patients undergoing chronic peritoneal dialysis at a single center in the United States.

Szeto CC, Chow KM, Wong TYH, Leung CB, Li PKT. Conservative management of polymicrobial peritonitis complicating peritoneal dialysis: A series of 140 consecutive cases. Am J Med 2002;113:728–33.

Case series of 140 episodes of polymicrobial peritonitis from Hong Kong and a comprehensive review of the literature comprising a total of 302 published cases.

Torun D, Oguzkurt L, Sezer S, Zumrutdal A, Singan M, Adam FU, et al. Hepatic subcapsular steatosis as a complication associated with intraperitoneal insulin treatment in diabetic peritoneal dialysis patients. Perit Dial Int 2005;25:596–600.

Clinical and radiologic correlates of hepatic subcapsular steatotosis in CPD patients and a review of the literature.

C H A P T E R 4 7

Abdominal Hernias in Continuous Ambulatory Peritoneal Dialysis

Michael H. Schwenk, PharmD; Bruce S. Spinowitz, MD; and Chaim Charytan, MD

Access-related complications contribute significantly to the morbidity and mortality of end-stage renal disease (ESRD) patients on hemodialysis and peritoneal dialysis. Peritonitis, catheter malfunction, exit-site leaks, and infections all occur in both continuous [CAPD (continuous ambulatory peritoneal dialysis) and CCPD (continuous cycling peritoneal dialysis)] and intermittent peritoneal dialysis (IPD)—although some of these complications occur with greater frequency in the CAPD population. More serious complications (such as catheter erosion into bowel, bladder, or vagina) are related to the physical presence of a catheter irrespective of the form of peritoneal dialysis used. Since the introduction and widespread application of CAPD, the problem of abdominal hernias and their attendant morbidity has been recognized as a consequence of chronic peritoneal dialysis.

Prevalence

Hernias are relatively uncommon in IPD and CCPD, presumably because of the lower intra-abdominal pressure during recumbency—as opposed to the ambulatory state of patients undergoing CAPD. The problem of hernias in relation to CAPD was acknowledged shortly after the development of this modality, with the recommendation that patients with existing hernias be excluded from this therapeutic approach. Subsequently, several investigators reported a variable but significant incidence of this complication. This incidence tends to increase with greater use of CAPD.

In our experience, 44 of 157 CAPD patients developed 81 hernias in 215 patient-months of follow-up. Overall, hernias tend to occur in about 20% of the CAPD population—with a range of 9 to 28% reported. Although an equal percentage, approximately 28% of male and female patients in our series developed hernias. Women tended to have a greater number of recurrent hernias

and accounted for 52 of 81 hernias (64%). Parous females are substantially more susceptible to this complication. The occurrence of hernia is generally independent of age, although some authors have noted an increased frequency in older men.

There is no correlation between the etiology of renal disease and hernia formation, with the exception of polycystic kidney disease. In our series, 6 of 13 patients (46.2%) with polycystic kidney disease developed abdominal hernias—whereas 38 of 144 patients (26.4%) with other etiologies of ESRD developed abdominal hernias. This relationship may be related to a suspected collagen defect associated with polycystic kidney disease.

Patient activity prior to or during dialysis, steroid therapy, albumin levels, and nutritional status have no demonstrable effect on hernia development. No correlation has been found with the type of catheter used or with type of incision (midline versus paramedian transrectus), although a paramedian transrectus incision has been suggested as a means of decreasing the incidence of incisional hernias (see material following). Previous surgical history does not influence the development of hernia except in those patients who have undergone prior hernia repair. In our series, 12 of 26 patients with prior hernia surgery developed recurrent abdominal hernias while on CAPD.

A variety of types and locations of hernias can occur. The common types include incisional, umbilical, ventral, inguinal, and femoral. They may contain subcutaneous fat or include bowel or peritoneal fluid. In our series, there were 30% incisional, 38% umbilical, 17% inguinal, and 15% ventral hernias. Unusual hernias have been reported as well, including diaphragmatic and cystocele or uterine prolapse occurring only after the initiation of CAPD. Diagnostic procedures employed to locate occult abdominal hernias include peritoneal scintigraphy and computed tomography with dialysate containing radiocontrast. One series of 59 patients examined with peritoneal scintigraphy at the initiation of peritoneal dialysis revealed an asymptomatic abdominal hernia incidence rate of 17%, most of which remained asymptomatic at 8 months of follow-up.

Prophylactic and Therapeutic Measures

Oreopoulos reported that there were no incisional hernias when catheters were implanted using a paramedian transrectus incision rather than a median approach, although others have not confirmed this. Prosthetic mesh reinforcement overlying the abdominal wall has been reported to be an effective procedure when repairing

hernias to prevent further recurrences. In a small retrospective analysis of CAPD patients with large or multiple abdominal hernias who were not candidates for hemodialysis, placement of a polypropylene mesh at the time of hernia repair was reported to prevent hernia recurrence. In addition, there was a lower incidence of peritonitis after mesh placement compared to before mesh placement.

Hernia development has both medical and practical consequences. The potential for incarceration exists and has been reported. This complication in 15 of 81 hernias in our series led to emergency surgery in those patients. Early in their development, hernias may be difficult to recognize or are ignored by the patient. Thus, it is common for them to present with acute incarceration requiring emergent surgery. Even when hernias are recognized early, their correction requires hospitalization and interruption of CAPD therapy—contributing to morbidity, cost, and patient inconvenience. The development of hernias, particularly recurrent hernias, is therefore a significant factor contributing to patient dropout from CAPD therapy. In our series, recurrent hernias contributed 3% to the dropout rate from CAPD to hemodialysis.

Increased intra-abdominal pressure with a change from the supine to the upright position could explain the difference in the incidence of hernia development among the various peritoneal dialysis modalities. In IPD, the patient remains supine throughout the treatment and the incidence of hernias is lowest and minimal. In CCPD, patients maintain a full volume in their abdominal cavity throughout the day but the bulk of their treatment occurs in the recumbent position and they too have a relatively low frequency of hernias. However, recently a survey of 75 randomly selected dialysis units in the USA and Canada involving 1864 peritoneal dialysis patients found no difference in hernia incidence among the various peritoneal dialysis modalities (CAPD, automated PD, and nocturnal IPD).

Clearly, other factors may play a role. The relationship to polycystic disease may relate to a genetic collagen defect, which has been postulated to explain the renal and liver cysts that develop in these patients—as well as the increased incidence of diverticulosis, valvular defects, and aneurysms. Acquired focal weakening of the abdominal wall is a predisposing factor for hernias, as evidenced by the incidence of hernia development in parous women, patients with pre-CAPD hernia history, and the high frequency of incisional hernia development.

Although a direct relationship of dialysate volume and the likelihood of hernias was previously suspected, recent reports have

cast doubt on this possibility. The use of larger exchange volumes has become more widely employed in an attempt to meet National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-K/DOQI) clearance guidelines in large patients and/or in those patients who progressively lose residual renal function. In a retrospective analysis of patients who received continuous dialysis over a 15-year period, 79 of 656 patients (12%) developed abdominal hernias—at an overall rate of 0.06 hernias per dialysis-year. While 11% of patients who used exchange volumes of 2 L or less developed hernias, compared to 14% of patients who at some point used more than 2 L (2.5 or 3 L) exchanges at some point, this difference was not statistically significant.

A retrospective case-control study of 244 peritoneal dialysis patients over 5 years revealed similar exchange volumes (2.2 ± 0.3 L), weight, and body surface areas in patients with or without hernia development. Overall, 14% of patients developed abdominal hernias—including 3 patients with 1.5 L exchanges—whereas there were no hernias in the 11 patients with 3 L exchanges. Recently it has been reported that a weekly Kt/V of greater than 2 was associated with a lower rate of hernia development than that when weekly Kt/V was less than 2.

Further prophylactic and therapeutic approaches to this problem are difficult and have not been established. Patients with preexisting hernias can have them repaired before the initiation of CAPD. This may be done simultaneously with catheter insertion. The experience of some authors suggests that a paramedian transrectus incision might decrease the incidence of incisional hernias at the site of catheter insertion. Administration of antitussives and laxatives when indicated may be useful. A reinforcing prosthetic polypropylene mesh may prevent local recurrences.

The temporary interruption of CAPD and the support of these patients by hemodialysis in the period following hernia repair or other intra-abdominal surgery may decrease the likelihood of hernia recurrence. If hemodialysis cannot be performed, low-volume PD or nighttime continuous cycling PD should be used for at least 2 to 4 weeks following major abdominal surgery for hernia repair. There is no evidence that abdominal binding or the wearing of a corset will in any way decrease the incidence of hernia development. On occasion, we have placed patients with recurrent hernia development on CCPD. Preliminary indications seem to show that switching to this modality may slow recurrent hernia formation. The data do not support the opinion that polycystic kidney disease is an absolute contraindication to peritoneal dialysis.

Recommended Reading

Canivet E, Lavaud S, Wampach H, et al. Detection of subclinical abdominal hernia by peritoneal scintigraphy. Adv Perit Dial 2000;16:104–07.
Incident asymptomatic abdominal hernias in peritoneal dialysis patients.
Mettang T, Stoeltzing H, Alscher DM, et al. Sustaining continuous ambulatory peritoneal dialysis after herniotomy. Adv Perit Dial 2001;17:84–87.
A case series describing surgical repair of abdominal hernias with polypropylene mesh and subsequent resumption of peritoneal dialysis.
Van Dijk CMA, Ledesma S, Teitelbaum I. Patient characteristics associated with defects of the peritoneal cavity boundary. Perit Dial Int 2005;25:367–73.
A large survey of risk factors for abdominal hernias in peritoneal dialysis patients.

CHAPTER 48

Dialysate Leaks

Michael H. Schwenk, PharmD; Chaim Charytan, MD;
and Bruce S. Spinowitz, MD

Leaks of dialysate around the peritoneal dialysis catheter are a significant mechanical complication in patients on continuous ambulatory peritoneal dialysis (CAPD) or intermittent peritoneal dialysis (IPD). The incidence reported in the literature is quite variable. In a recent survey in our own CAPD unit, 1/3 of 50 patients (chosen at random) had an exit-site leak at some time during treatment with CAPD. This rate may be somewhat higher than at other centers, because of our definition of a leak—which is the development of any moisture around the catheter that has a high glucose level as tested by a Dipstix (excluding the possibly of serous drainage). Icodextrin solutions may test positive for glucose if a glucose dehydrogenase pyrroloquinolinequinone method is used. Most patients experience a single leak, which in the majority of instances occurs within 1 month of placement of the peritoneal catheter (early leak). Leaks occurring after 30 days of catheter placement are referred to as late leaks.

The incidence of this complication may be decreased by allowing a minimum 2-week healing period after catheter insertion, before initiation of CAPD. If peritoneal dialysis is an absolute necessity prior to 2 weeks, it is best to have the patient treated by IPD, nightly automated PD, or CCPD (continuous cycling peritoneal dialysis) in the recumbent position at night rather than by CAPD. The latter increases intra-abdominal pressure and will increase the risk of an exit-site leak, at least in the perioperative period. Leaks are associated with steroid therapy, previous placement of a catheter through the same site, a midline approach to catheter placement as opposed to paramedian insertion, previous abdominal surgery, obesity, and improper cuff implantation—but not with age >60 years, antecedent exit-site infection, or peritonitis.

In addition to exit-site leaks, any dialysate loss from the peritoneal cavity other than through the lumen of the catheter is considered a dialysate leak. Leakage may occur through the diaphragm (see the chapter on hydrothorax and peritoneal dialysis), into hernias, into the subcutaneous tissue (recognized as pitting edema of the abdomen or scrotal or labial swelling), through the vagina, or into a patent processus vaginalis. Leaks can occur immediately

after catheter implantation, shortly thereafter, or months to years afterward. Diagnosis and evaluation of dialysate leaks can be made by nuclear scintigraphy or by computerized tomography (CT) peritoneography, which uses a mixture of contrast material (1 mL/kg nonionic contrast) and dialysate (30 mL/kg) instilled after drainage of the peritoneal cavity. CT can then be performed, and may be repeated at 1 and 4 hours. After the procedure is completed, the mixture is drained. To avoid the use of iodinated radiocontrast material, magnetic resonance peritoneography can be employed. Recently, video-assisted laparoscopy has been reported to be useful in the diagnosis of non–exit-site leaks.

Dialysate leaks compromise dialysis efficacy. Leaks at the exit site are significant in their association with two major problems. First, these patients require the discontinuation of CAPD and transfer to in-center hemodialysis until the leak abates. This interferes with the smooth management of the dialysis patient and may create significant disruption in their lifestyle. Second, in our series 50% of all leaks led to some infectious complication—either peritonitis or an exit-site infection requiring antibiotic therapy. Prophylactic antibiotic administration is controversial. In very rare cases, leaks may ultimately require removal of the catheter.

For these reasons, exit-site leaks must be dealt with promptly. Fortunately, most leaks respond to simple discontinuation of peritoneal dialysis. We discontinue dialysis for a minimum of 2 weeks. It is our impression that when dialysis is restarted after only 1 week the frequency of recurrence of these leaks is much greater. When restarting CAPD, we also prefer to start with lower volumes of dialysate. During this reinstitution of therapy, the patient may be required to perform additional exchanges—but we believe that this is best in the long term. Usually within 7 to 10 days of resuming peritoneal dialysis, the patient may again return to 2-L exchanges. By following this regimen, it is an extremely rare patient whose leak does not resolve and who requires replacement of the peritoneal catheter.

Dialysate leaks, other than those associated with the catheter exit site, should be corrected surgically when possible (e.g., patent process processus vaginalis). In the case of subcutaneous anterior abdominal wall dialysate leakage, an exercise program should be instituted to strengthen the abdominal muscles. Similar to the treatment of exit-site leaks, temporary transfer to hemodialysis or the employment of lower dialysate exchange volumes performed at night should be effected.

Prevention of dialysate leaks may be accomplished, or the incidence diminished, by the following measures. Avoidance of catheter

insertion through a previous site is suggested. In addition, care should be taken to ensure proper implantation of the deep Dacron cuff of the catheter into the rectus muscle and sheath. The use of abdominal isometric contraction exercises to strengthen weak abdominal muscles may be useful in preventing dialysate leaks.

Although most clinicians continue to advocate a delay in starting peritoneal dialysis until wound healing has occurred, a recent study has reported similar rates of early and late dialysate leaks (about 10%) after catheter insertion irrespective of whether there was a 2-week period of gradual increase in exchange volume or an immediate use of 2-L exchange volume. Employing 3 purse-string sutures to anchor the catheter and inner cuff has also been advocated to allow peritoneal dialysis to start immediately after catheter placement—with an early leak incidence of 1% reported. These sutures are placed at the peritoneal membrane–cuff junction, the inner rectus fascia–cuff junction, and the outer rectus fascia–catheter junction.

The use of fibrin glue applied to the peritoneal cuff suture during catheter implantation has been reported to prevent early leakage in children undergoing chronic peritoneal dialysis. The incidence of leakage with fibrin glue application when dialysis was started within 5 days of catheter implantation was less than the rate seen in a control group, which did not utilize fibrin glue during catheter placement. In both children and adults, fibrin glue has been successful when used to treat peritoneal dialysis catheter leakage.

Recommended Reading

Joffe P. Peritoneal dialysis catheter leakage treated with fibrin glue. Nephrol Dial Transplant 1993;8:474–76.
The use of fibrin glue in the prevention and treatment of peritoneal dialysis catheter leakage.
Leblanc M, Ouimet D, Pichette. Dialysate leaks in peritoneal dialysis. Semin Dial 2001;14:50–54.
General review of dialysis leaks.
Rusthoven E, van de Kar NA, Monnens LA, et al. Fibrin glue used successfully in peritoneal dialysis catheter leakage in children. Perit Dial Int 2004;24:287–89.
A surgical technique to allow immediate start of peritoneal dialysate leaks.
Sojo ET, Grosman MD, Monteverde ML, et al. Fibrin glue is useful in preventing early dialysate leakage in children on chronic peritoneal dialysis. Perit Dial Int 2004;24:186–90.
The use of fibrin glue in the treatment of peritoneal dialysis catheter leakage in adults.
Song JH, Kim GA, Lee SW, et al. Clinical outcomes of immediate full-volume exchange one year after peritoneal catheter implantation for CAPD. Perit Dial Int 2000;20:194–99.
Immediate dialysis after catheter implantation.
Stegmayr BG. Three purse-string sutures allow immediate start of peritoneal dialysis with a low incidence of leakage. Semin Dial 2003;16:346–48.
The use of fibrin glue in prevention of peritoneal dialysis catheter leakage in children.

CHAPTER 49

Hydrothorax and Peritoneal Dialysis

Michael H. Schwenk, PharmD; Bruce S. Spinowitz, MD; and Chaim Charytan, MD

The presence of hydrothorax (pleural effusion) indicates an abnormal pathophysiologic state secondary to a dysequilibrium between the formation and removal of pleural fluid. Various mechanisms may be responsible for the accumulation of an abnormal volume of pleural fluid in peritoneal dialysis patients. Hydrothorax, the accumulation of abnormal fluid in the pleural space, may be associated with movement of fluid from the peritoneal to the pleural space.

Any condition leading to ascites may result in a pleural effusion by the passage of fluid through either diaphragmatic lymphatics or diaphragmatic defects. Due to the existence of a pressure gradient across the diaphragm, fluid may migrate at a rapid rate from the peritoneal space—exceeding the exit rate via pleural lymphatics. With the advent and widespread use of continuous ambulatory peritoneal dialysis (CAPD) and other forms of chronic maintenance peritoneal dialysis, acute and chronic hydrothorax complicating peritoneal dialysis has been reported in adults as well as in children.

Clinical Manifestations and Prevalence

The clinical characteristics most commonly seen are dyspnea, chest pain, and hypotension. Atrial fibrillation is rarely seen. The clinical onset of acute hydrothorax following the initiation of a peritoneal dialysis session varies between 4 and 48 hours, with most being discovered within 24 hours. The accumulated pleural fluid is undoubtedly dialysate, based on its rapid accumulation after the onset of peritoneal dialysis, its generally rapid disappearance upon discontinuation of peritoneal dialysis, and its chemical characteristics. Patients develop dyspnea shortly after beginning peritoneal dialysis, which progressively worsens as the dialysis is continued despite efficient ultrafiltration. In most cases, the observation that pleural fluid glucose markedly exceeds blood glucose concentration (together with low fluid protein content) is evidence that the fluid is peritoneal dialysate.

A delayed-onset large hydrothorax, although uncommon, is a serious complication reported in chronic peritoneal dialysis patients. A multicenter study reported a 2.9% prevalence of pleural effusion in CAPD patients. Permanent discontinuation of peritoneal dialysis was necessary in 34% of these patients. One study reported a 5% incidence of hydrothorax in its CAPD population. Acute as well as delayed-onset hydrothorax associated with peritoneal dialysis most commonly affects older females, is rare in children, and is predominantly right-sided.

Pathogenesis

The occurrence of these large pleural effusions during peritoneal dialysis may be due to a variety of mechanisms. A role for diaphragmatic lymphatics has been suggested in the development of the smaller pleural effusions seen in patients on peritoneal dialysis. This mechanism is supported by the predominance of right-sided pleural effusion that would correlate with the presence of more numerous lymphatics in the right hemidiaphragm. A more likely mechanism is fluid leakage through diaphragmatic defects such as right-sided vena caval foramen, esophageal hiatus in the right diaphragmatic crus, an aortic hiatus, and other nonorgan-related diaphragmatic defects. These defects, coupled with negative intrathoracic pressure and positive intra-abdominal pressure, favor the movement of dialysate from peritoneal to pleural cavities.

Diagnosis

The diagnosis should be suspected in a peritoneal dialysis patient presenting with poor dialysate drainage and/or poor ultrafiltration volume, and who has symptoms of dyspnea and tachypnea, physical findings of decreased breath sounds, and radiologic evidence of pleural effusion. All causes of hydrothorax—such as uremic pleuritis, congestive heart failure, fluid overload, hypoalbuminemia, systemic inflammatory conditions (e.g., systemic lupus erythematosus, bacterial, tubercular, or viral etiology), and procedure-related hydrothorax secondary to peritoneal dialysis itself—should be considered.

Various procedures may be used to demonstrate the dialytic origin of the pleural effusion. Thoracentesis and pleural fluid analysis reveal pleural fluid resembling dialysate. The total protein is usually <1 g/dL, with a leukocyte count of <100/mm^3 (predominantly mononuclear cells), a glucose concentration of 300 to 400 mg/dL or greater, and lactate dehydrogenase <100 IU/L.

A simultaneous measurement of glucose, protein, and lactate dehydrogenase in the serum should be made.

Intraperitoneal instillation and thoracic retrieval of methylene blue dye may demonstrate movement of fluid from peritoneal space to pleural cavities. Although the procedure is relatively simple and inexpensive, the patient is subjected to a risk of chemical peritonitis, allergic reactions, and repetitive thoracenteses. This test may be unreliable because dye is diluted in the dialysis solution, and thus we do not recommend this procedure.

The transdiaphragmatic pleural fluid leaks during peritoneal dialysis may also be demonstrated by radionuclide scanning, using ^{99m}Tc-labeled macroaggregated albumin. Scintigraphy may be performed using 10 mCi of ^{99m}Tc-albumin colloid, instilled intraperitoneally through the dialysis catheter, followed by 2 L of dialysis solution. Scintigraphic views may be obtained using a large-field scintillation camera centered in the diaphragmatic region. Studies in anterior, lateral, or posterior positions may demonstrate the appearance of radioactivity above the diaphragm. The test is usually performed at the start of the infusion and a dynamic series of 1 to 15 minutes followed by 30 minutes, 1 hour, and 6 hours is used.

The radionuclide procedure offers distinct advantages over simple dyes. It is noninvasive, although some authors have drained pleural fluid samples for accurate isotope counting. ^{99m}Tc has a 6-hour half-life. In addition, even assuming no excretion at all radiation exposure to the patient is very small (about 10 mrad). Thus, ^{99m}Tc can be used safely even in the absence of renal function—and the same study may be repeated at intervals to assess the success of measures taken to correct the leaks. Additional diagnostic procedures utilized to confirm hydrothorax include peritoneography utilizing radiocontrast and computed tomography, as well as magnetic resonance imaging.

Management

The goals of management are the resolution of hydrothorax and the prevention of its recurrence so that CAPD may be continued. Small effusions require monitoring only. However, if there is a massive hydrothorax further peritoneal dialysis should be discontinued and a prolonged drainage via the peritoneal catheter should be allowed while the patient is in a semirecumbent position. This may result in pleural space drainage as well. If a patient has severe dyspnea or cardiovascular instability, therapeutic thoracentesis should be performed. The effusion usually resolves completely with discontinuation of peritoneal dialysis.

Massive hydrothorax is an indication for temporary transfer to hemodialysis, which may permit spontaneous closure of a diaphragmatic defect. However, there are reports of CAPD patients who were successfully transferred to nighttime cycling peritoneal dialysis in the recumbent position. The spontaneous closure of diaphragmatic defects is facilitated due to a decreased intraperitoneal pressure with the performance of peritoneal dialysis with small volumes of dialysate. The volume of dialysate may then be progressively increased.

If a conservative approach to treatment fails, a correction of a pleuroperitoneal communication or diaphragmatic defect can also be achieved by pleurodesis—most commonly using tetracycline, asbestos-free talc, fibrin glue, or autologous blood instillation. Of the various agents used for pleurodesis, tetracycline and asbestos-free talc are used most frequently—although tetracycline injection is no longer commercially available. The procedure involves placement of a chest tube with complete drainage of the effusion, followed by the instillation of a slurry of 2 to 5 g sterile talc in 50 mL of normal saline. The chest tube is clamped for an hour, the patient rotated, and the tube then unclamped with maintenance of –20 cm H_2O suction. The patient may experience chest pain and fever, which might require analgesics/antipyretics. The use of autologous blood for pleurodesis is said to be free of the side effects of talc and tetracycline.

Pleurodesis may not be effective in all patients—with a 48% success rate reported in a recent review (although talc is recognized as being the most effective agent)—and may need to be repeated several times before it is successful. A theoretical complication is passage of the slurry into the abdomen, where it might induce membrane injury and fibrosis. The small volume of instilled solution and supine position of the patient minimize the effect of gravity and this potential risk. In addition, pleural adhesions resulting from pleurodesis may preclude subsequent thoracoscopy. Diaphragmatic defects can be closed with surgical repair by direct suturing.

The defect may or may not require reinforcement with Teflon felt patches. Surgical intervention has the advantage that the communication may be directly located, inspected, and closed with a predictable result and with the least possibility of recurrence. Recently there have been reports on the use of videothoracoscopic surgery (preferable to thoracotomy), with or without talc pleurodesis or poudrage, for the diagnosis and correction of hydrothorax for which no macroscopic pleuroperitoneal communication can be found. CAPD should be interrupted for 10 to 28 days to allow

spontaneous closure of the defect (or to allow for permanent fibrosis after pleurodesis) and resolution of the effusion, although in pediatrics a 1- to 2-day waiting period has been reported.

Spontaneous closure of the peritoneal communication after 2 to 6 weeks will occur in about 50% of cases. If hydrothorax recurs following reinstitution of peritoneal dialysis or initial pleurodesis, repetition of pleural sclerosis or surgical intervention may be considered. Alternatively, the patient may be permanently transferred to nighttime cycling peritoneal dialysis or hemodialysis. Resumption of peritoneal dialysis after these therapeutic maneuvers has been reported to range from 60 to 100% in the most recently reported case series.

Recommended Reading

Chow KM, Szeto CC, Li PK. Management options for hydrothorax complicating peritoneal dialsysis. Semin Dial 2003;16:389–94.
An update reviewing the treatment of hydrothorax in peritoneal dialysis, emphasizing video-associated thoracoscopy.
Szeto CC, Chow KM. Pathogenesis and management of hydrothorax complicating peritoneal dialysis. Curr Opin Pulm Med 2004;10:315–19.
A review of recent literature pertaining to the pathogenesis, diagnosis, and treatment of hydrothorax during peritoneal dialysis.
Tang S, Chui WH, Tang AWC, et al. Video-assisted thorascopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. Nephrol Dial Transplant 2003;18:804–08.
A case series describing the treatment of video-assisted thoracoscopy and talc pleurodesis for acute hydrothorax in peritoneal dialysis.

CHAPTER 50

Acid-Base Homeostasis in Dialysis

F. John Gennari, MD

When renal replacement therapy is initiated, regulation of acid-base balance by the kidneys is replaced by a new homeostatic process responding to the physical principles of diffusion and convection rather than to the pH of the body fluids. Balance is achieved by alkali addition during dialysis, not by regulated acid excretion. Consequently, serum [HCO_3^-] in the steady state is dependent in large part on the kinetics of HCO_3^- diffusion across the dialysis membrane—which in turn is highly dependent on the characteristics of the dialysis treatment used. Despite the lack of a pH-dependent regulatory system, a new steady state is achieved in which day-to-day HCO_3^- consumption by endogenous acid production is matched by HCO_3^- addition during the dialysis treatment.

Although dialysis therapy creates a new steady state, it is much less able to adapt to day-to-day changes in acid production or to superimposed disorders of acid-base equilibrium. This chapter reviews the nature of this unique regulatory process and the tools for identifying disturbances of acid-base homeostasis in dialysis-dependent patients. Throughout the chapter, the term *serum [total CO_2]* refers to the routinely measured variable that correlates closely with serum [HCO_3^-] and the term *[HCO_3^-]* itself refers to the value calculated from measurements of PCO_2 and pH in blood—or to the concentration of bicarbonate in the bath solution.

Determinants of Serum [total CO_2] in Dialysis Patients

The amount of alkali added during hemodialysis or peritoneal dialysis is related to the dialysance of the alkali source used (HCO_3^- or lactate) and to the transmembrane concentration gradient (Figure 50.1). Because dialysance (a function of membrane permeability and surface area) and bath [HCO_3^-] are fixed by the dialysis prescription, serum [HCO_3^-] is the variable that determines the amount of alkali added. The lower the serum value the more alkali added. Consequently, a new equilibrium is achieved in the steady state in which the alkali consumed in buffering endogenous acid produc-

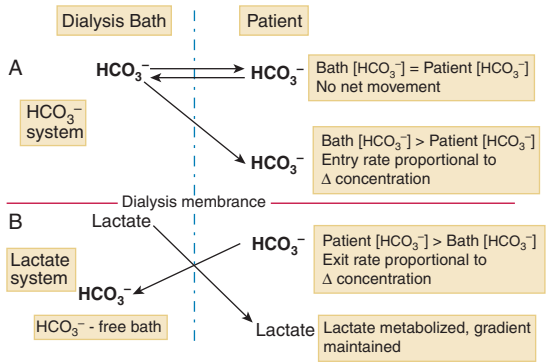


Figure 50–1

A, Role of patient's serum [HCO_3^-] in determining rate of [HCO_3^-] movement across the dialysis membrane. *B*, Dynamics of lactate entry and [HCO_3^-] loss across a dialysis membrane using a lactate-based bath. Note that the same principles (although in the opposite direction) govern [HCO_3^-] movement across the membrane.

tion (a process that reduces serum [HCO_3^-]) is matched by the alkali added during treatment. The final value achieved in a given patient, assessed by measurement of serum [total CO_2], is determined by the factors outlined in the following section.

Hemodialysis

In patients receiving hemodialysis, pre-dialysis serum [total CO_2] in the steady state is determined by the dialysis and patient characteristics outlined in Table 50.1. The dialysis prescription is fixed, and unless blood flow rate is compromised should not be a source of great variation in pre-dialysis serum [total CO_2]. Of the patient characteristics outlined in the table, the first two have the major impact on pre-dialysis serum [total CO_2]. Renal generation and loss of HCO_3^- are usually trivial, and organic acid production (which influences the net retention of alkali during dialysis) has little impact unless it is unusually large (see discussion of metabolic acidosis later in the chapter).

The effects of variations in endogenous acid production and fluid retention between treatments are outlined in Table 50.2.

Table 50–1

Determinants of Pre-dialysis or Steady-State Serum [total CO_2] in Patients Receiving Dialysis Therapy

Hemodialysis Prescription
Bath [HCO_3^-] (or [Lactate], used in some forms of daily hemodialysis)
Permeability and surface area of dialysis membrane
Blood and dialysate flow rates
Duration and frequency of dialysis treatments
Peritoneal Dialysis Prescription
Bath [Lactate] (or [HCO_3^-])
Volume and dwell time of exchanges
Permeability and surface area of peritoneal membrane
Patient Characteristics
Endogenous acid production
Fluid retention[a]
Renal HCO_3^- generation or loss (in patients with residual renal function)
Organic acid production during dialysis treatments

[a] Fluid retention affects the space of distribution and therefore the concentration of HCO_3^- in the extracellular fluid.

In this table, pre-dialysis serum [total CO_2] has been calculated using some simple assumptions to illustrate the magnitude of these effects.

These estimates have been substantiated by experimental and clinical observations. Variations in acid production over a reasonable range can change pre-dialysis serum [total CO_2] from normal to frankly acidotic values. Endogenous acid production varies directly with dietary intake of sulfur-containing proteins. Thus, patients with limited intake of animal protein will have a higher pre-dialysis serum [total CO_2] than will patients eating a diet high in animal proteins. Variations in fluid retention have a smaller, but still significant, effect. As Table 50.2 indicates, dialysis against a bath with a [HCO_3^-] of 35 mEq/L three times weekly does not restore pre-dialysis serum [total CO_2] to 24 mEq/L unless endogenous acid production is quite low.

It is important to emphasize that pre-dialysis [total CO_2] is a nadir value. Serum [total CO_2] rises to 28 to 32 mEq/L just after each hemodialysis treatment and then gradually falls to the pre-dialysis level over the interval between treatments. Nonetheless, maneuvers to increase this value to 24 mEq/L have beneficial

Table 50–2

Effect of Endogenous Acid Production and Fluid Retention on Pre-dialysis Serum [total CO_2] in Patients Receiving Hemodialysis with a Bath [HCO_3^-] = 35 mEq/L

Daily Endogenous Acid Production (mEq)[a]	Pre-dialysis Serum [total CO_2] (mEq/L)[b]
30	24.2
60	21.9
90	19.6
120	17.3
Fluid Retention (L)[c]	
0	23.1
2	21.9
4	20.8
6	19.8

[a] Assuming 2 L fluid retention between treatments.
[b] After long interval between treatments (68 hrs).
[c] Assuming 60 mEq/day endogenous acid production.
Other assumptions: Weight 70 Kg, post-dialysis serum [total CO_2] = 28 mEq/L, HCO_3^- buffer space = 0.5 × body weight.

effects on both muscle and bone metabolism. There appear to be no deleterious effects when bath [HCO_3^-] is increased, and some dialysis programs have either increased bath [HCO_3^-] to 37 to 39 mEq/L in all patients or are individualizing the concentration based on pre-dialysis serum [total CO_2]. Another approach to increasing serum [total CO_2] is to reduce the interval between treatments. Patients receiving daily hemodialysis have higher serum [total CO_2] values without any change in bath [HCO_3^-], and bath [HCO_3^-] usually must be decreased to avoid frank alkalemia. Whether maneuvers to restore pre-dialysis [total CO_2] completely to normal will decrease morbidity and mortality remains to be determined.

Peritoneal Dialysis

In patients receiving peritoneal dialysis, steady-state serum [total CO_2] is also determined by the dialysis and patient characteristics outlined in Table 50.1. Bath lactate concentration has been set at 40 mEq/L—a value that maintains serum [total CO_2] in the normal range in most patients. In some centers in Europe, peri-

toneal dialysis with a HCO_3^--containing bath solution (mixed just before instillation) has improved acid-base status further. The higher exchange volumes and shorter dwell times now routinely used in continuous cycling peritoneal dialysis have had little impact on serum [total CO_2].

Normal Values

The range of "normal" values for pre-dialysis serum [total CO_2]—and for arterial blood pH, PCO_2, and [HCO_3^-]—in patients receiving conventional hemodialysis or peritoneal dialysis are shown in Table 50.3. In patients receiving hemodialysis, average serum [total CO_2] has risen by 1 to 2 mEq/L in the last decade without any change in dialysis prescription—possibly reflecting a lower protein intake in the older population now receiving this treatment. There are only a few measurements of PCO_2, pH, and [HCO_3^-]—obtained more than 20 years ago—indicating a mild acidosis with an appropriate secondary respiratory response. Patients receiving peritoneal dialysis have average values for serum [total CO_2] in the normal range, but arterial acid-base measurements in these patients also show a very mild acidosis.

Table 50–3

Steady-State Acid-Base Values in Stable Dialysis Patients

	Conventional Hemodialysis	Peritoneal Dialysis
[total CO_2] mEq/L	22.4 ± 2.9 (249)[a]	26.4 ± 3.0 (109)[b]
[HCO_3^-] mEq/L	19.7 ± 1.9 (36)[c]	21.5 ± 2.4 (33)[d]
pH	7.38 ± 0.5 (36)	7.38 ± 0.04 (33)
PCO_2 mmHg	34 ± 1.9 (36)	37 ± 5.1 (33)

Means ± S.D., numbers in parentheses = number of patients

[a] Gennari FJ, 2006. Personal observations measured either in venous, graft or fistula blood samples pre-dialysis after long interval between treatments. Hemodialysis bath [HCO_3^-] = 35 mEq/L

[b] venous blood measurements. Data from Gennari FJ, Feriani M. Acid base problems in hemodialysis and peritoneal dialysis. In N Lameire, RL Mehta (eds). *Complications of Dialysis*. New York: Marcel Dekker 2000:361–376.

[c] [HCO_3^-], pH and PCO_2 values in hemodialysis patients obtained pre-dialysis from arterial blood. Hemodialysis bath [HCO_3^-] = 35 or 36 mEq/L. Data from Gennari FJ, Feriani M. Acid base problems in hemodialysis and peritoneal dialysis. In N Lameire, RL Mehta (eds). *Complications of Dialysis*. New York: Marcel Dekker 2000:361–376.

[d] [HCO_3^-], pH and PCO_2 values in peritoneal dialysis patients obtained from arterial blood. Peritoneal bath [Lactate] = 40 mM. Data from Feriani M. Use of different buffers in peritoneal dialysis. Seminars in Dialysis 2000;13:256–260.

Diagnosis and Management of Acid-Base Disorders

The nephrologist caring for patients receiving dialysis therapy has two tasks with regard to their acid-base status. The first task is to identify patients with persistently low values for serum [total CO_2] (less than 20 mEq/L) and to determine whether treatment modification can improve this situation. The second task is to uncover superimposed acid-base disturbances. In making either assessment, serum samples for total CO_2 must be processed and run in a timely fashion. Shipment of blood samples to a distant laboratory and delay in analysis may spuriously reduce the value by as much as 5 mEq/L.

The Patient with a Persistently Low Serum [total CO_2] Level

Dialysis patients with pre-dialysis or steady-state serum [total CO_2] values less than 20 mEq/L are at increased risk for muscle catabolism and for worsening renal osteodystrophy. Those with pre-dialysis values less than 16 mEq/L have higher mortality. All such patients should be assessed to determine reversible causes for the low values. One should assess treatment issues, such as adequacy of dialysis, but in most cases the cause is one of the patient characteristics cited in Table 50-1. Nutritional assessment of protein and fluid intake should be undertaken, and appropriate modifications recommended. If these measures fail, increasing bath [HCO_3^-] by 1 to 4 mEq/L will increase pre-dialysis serum [total CO_2] in most patients. Management is more difficult in patients receiving peritoneal dialysis. If nutritional measures fail, the only option is to switch back to hemodialysis or to a bicarbonate-containing peritoneal dialysis solution.

In patients receiving hemodialysis, measurement of serum [total CO_2] pre- and postdialysis can assess adequacy of treatment and (more importantly) organic acid production during the procedure. In a small minority of patients, typically those with severe hypotension during the procedure, organic acid (presumably lactic acid) production can consume virtually all of the added HCO_3^-—with the organic anions produced lost into the bath solution. Consequently, alkali stores remain low despite adequate HCO_3^- delivery during the procedure. Treatment options are limited for such patients to switching to a slower form of hemodialysis or to peritoneal dialysis.

Superimposed Acid-Base Disorders

The presence of a superimposed metabolic acid-base disorder in a patient receiving dialysis therapy can be brought to one's attention by a change or new abnormality in serum [total CO_2] (Figure 50.2). By contrast, respiratory disorders can only be suspected from clinical signs and symptoms. Serum [total CO_2] varies widely among dialysis patients. Fortunately, this parameter is usually measured on a regular basis—allowing a baseline for comparison in an individual patient. Assessment of a suspected new acid-base disorder involves the same three steps as in patients with functioning kidneys.

1. Identification of the primary disorder (i.e., metabolic acidosis or alkalosis; respiratory acidosis or alkalosis).
2. Assessment of the secondary response, in order to determine whether the disorder is simple or mixed (simultaneous presence of two or more acid-base disorders).
3. Determination of the cause. For this analysis, assessment of whether the anion gap has changed is useful.

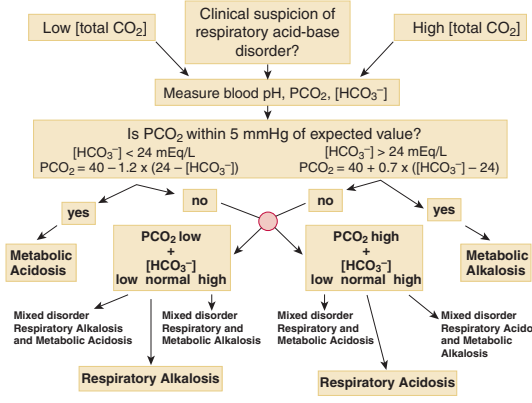


Figure 50–2

Approach to the diagnosis and characterization of acid-base disorders in dialysis patients. See text for definitions of high and low serum [total CO2]. *(Adapted from Gennari FJ. Acid-base considerations in end-stage renal disease. In WL Henrich (ed.),* Principles and Practice of Dialysis. *Baltimore: Lippincott, Williams & Wilkins 2005:402.)*

Steps 1 and 2 require measurement of arterial PCO_2, pH, and $[HCO_3^-]$. In patients with functioning fistulas or synthetic grafts, a separate arterial puncture is not required for this measurement. Blood from fistulas or grafts is equivalent to arterial blood.

Rules for identification of the Primary Disturbance in Dialysis Patients

- *Metabolic acidosis:* Serum [total CO_2] lower than the usual value by 3 mEq/L or more.
- *Metabolic alkalosis:* Serum [total CO_2] higher than the usual value by 3 mEq/L or more.
- *Respiratory acidosis:* Arterial PCO_2 higher than predicted for the prevailing serum $[HCO_3^-]$ by 5 mmHg or more (see equations following).
- *Respiratory alkalosis:* Arterial PCO_2 lower than predicted for the prevailing serum $[HCO_3^-]$ by 5 mmHg or more (see equations following).

Evaluation of the Secondary Response

Arterial PCO_2 responds to changes in serum $[HCO_3^-]$ in dialysis patients in the same fashion as in individuals with normal renal function. Thus, the rules of thumb are the same.

- *For serum $[HCO_3^-]$ <24 mEq/L:* Arterial PCO_2 (mmHg) = $40 - 1.2 \times (24 - \text{serum } [HCO_3^-])$
- *For serum $[HCO_3^-]$ >24 mEq/L:* Arterial PCO_2 (mmHg) = $40 + 0.7 \times (\text{serum } [HCO_3^-] - 24)$

In contrast to patients with functioning kidneys, serum $[HCO_3^-]$ does not change in response to changes in PCO_2. As discussed previously, it is fixed primarily by the dialysis prescription and by endogenous acid production. Thus, there is no "adaptive" secondary change in serum $[HCO_3^-]$ in response to hypocapnia or hypercapnia.

Causes of Acid-Base Disorders

Metabolic Acidosis

Although many patients receiving dialysis therapy have a chronic stable mild metabolic acidosis, a key management issue is to recognize the development of a new and more severe metabolic acidosis; that is, a further reduction in serum [total CO_2] (see

previous rules for recognition). The causes of metabolic acidosis are outlined in Table 50.4.

Virtually all of the causes of metabolic acidosis in patients receiving dialysis therapy produce an increase in the anion gap. The most common cause is diabetic ketoacidosis. In contrast to patients with functioning kidneys, fluid and alkali replacement are unnecessary for treatment. In the absence of kidney function, no fluid or ketoanion losses occur. Insulin therapy rapidly leads to metabolism of the retained ketoanions, regenerating the HCO_3^- consumed, and quickly restores serum [HCO_3^-] to the premorbid level. With other organic acidoses, dialysis removes the offending toxins and replenishes alkali stores quickly.

If the anion gap is not increased, only two causes need to be considered. The first cause is gastrointestinal alkali loss. Such losses are straightforward to diagnose and can be replaced rapidly by dialysis at the same time losses are curtailed by therapeutic intervention. The second cause is excessive fluid volume expansion with salt and water. As outlined in Table 50.2, pre-dialysis serum [total CO_2] is inversely related to fluid retention between treatments. The effect is usually only a mild reduction in serum [total CO_2]. Iatrogenic volume expansion in these patients will produce the same effect.

Table 50–4

Causes of Metabolic Acidosis in Dialysis Patients

Increased Anion Gap
Endogenous causes
Diabetic ketoacidosis
Lactic acidosis
Alcoholic ketoacidosis
Increased endogenous acid production (catabolic state)
Toxin ingestions
Methyl alcohol
Ethylene glycol
Salicylates
Paraldehyde
No Increase in Anion Gap
Gastrointestinal alkali loss
Expansion acidosis

Metabolic Alkalosis

A new metabolic alkalosis may be missed in patients receiving dialysis treatment because serum [total CO_2] may still be in the normal range for patients with functioning kidneys. For example, in a dialysis patient with a steady-state serum [total CO_2] of 21 mEq/L a sudden increase to 26 mEq/L indicates the development of a metabolic alkalosis. Hypokalemia, a characteristic feature of metabolic alkalosis in patients with functioning kidneys, does not occur. Moreover, dialysis patients have no way to excrete excess alkali added to the body. Once metabolic alkalosis is induced, it is sustained by the dialysis procedure itself—which does not remove HCO_3^- unless serum [HCO_3^-] is greater than 35 mEq/L.

None of the primary renal causes of metabolic alkalosis (e.g., aldosterone adenoma, Bartter syndrome) can produce this disorder in patients without renal function. Metabolic alkalosis has only two causes in dialysis patients: gastrointestinal HCl loss and excess alkali administration (including that caused by daily hemodialysis). The most common cause of metabolic alkalosis is vomiting or nasogastric suction. An increase in serum [total CO_2] may be the key to identifying the presence of bulimia in a dialysis patient. Steps aimed at reducing or eliminating the gastrointestinal acid loss will correct the disorder over time.

A sometimes-overlooked cause is exogenous alkali administration. In addition to sodium bicarbonate ingestion (e.g., Alka-Seltzer, baking soda), a common source is organic anion administration. Citrate, lactate, acetate, and other organic anions given in various parenteral solutions can all increase serum [total CO_2]. Unless metabolic alkalosis is severe (serum [total CO_2] greater than 33 mEq/L), it can usually be ignored if these anions are a necessary part of therapy. Discontinuation or a reduction in the amount given will correct or ameliorate the disorder. Metabolic alkalosis in the intensive care unit is often caused by daily hemodialysis in patients with low rates of endogenous acid production, or by excess HCO_3^- or lactate replacement in patients receiving continuous renal replacement therapy. The combination of sodium polystyrene sulfonate (Kayexalate, Sterling Drug) and aluminum hydroxide can cause metabolic alkalosis by acting together to bind H^+ in the stomach.

Rapid reduction in serum [total CO_2] is rarely required. Hemodialysis limits the increase to about 35 mEq/L unless H^+ losses are very large. If rapid removal is necessary, bath [HCO_3^-] can be reduced to facilitate alkali loss during hemodialysis. Alternatively, one can institute continuous venovenous hemofiltration and use only saline for replacement fluid.

Respiratory Acidosis

Detection of respiratory acidosis requires clinical suspicion, and measurement of arterial pH and PCO_2 is necessary to confirm the diagnosis (Figure 50.2). Serum [total CO_2] does not increase in response to hypercapnia in patients receiving dialysis therapy. Even the small increase normally engendered by the buffer response to acute hypercapnia may be modified by the dialysis treatment.

With the exception of the patient on a ventilator with fixed-minute ventilation in whom an increase in CO_2 generation can increase arterial PCO_2, respiratory acidosis is caused by pulmonary insufficiency. Thus, the first approach to management should always be an attempt to improve ventilation. If ventilation cannot be improved, increasing serum [HCO_3^-] can mitigate the acidemia. To achieve this goal, bath [HCO_3^-] can be increased or the patient switched to peritoneal dialysis.

Respiratory Alkalosis

Hypocapnia induces severe alkalemia in patients receiving dialysis therapy because there is no secondary renal response, and the body buffer response is reversed by alkali addition during treatment. Diagnosis requires clinical suspicion and measurement of arterial pH and PCO_2.

Respiratory alkalosis has multiple causes, including hypoxemia, anxiety, central nervous system disease, pulmonary disease, and hepatic failure. Correction of the cause of the hypocapnia, if possible, is the first approach to treatment. If the alkalemia is severe (pH >7.65), arterial PCO_2 should be increased acutely using a rebreathing device. Sustained hypocapnia is more difficult to manage. The only option is to dialyze the patient against a bath with a low [HCO_3^-].

Mixed Acid-Base Disorders

Two or more acid-base disorders can coexist in patients receiving dialysis therapy, but the occurrence of such mixed disorders is rare. Mixed disorders are diagnosed by demonstrating that the secondary response to a given acid-base disorder is either less than or greater than that predicted by the rules presented previously (Figure 50.2). Table 50.5 lists the possible mixed disorders in dialysis patients. The importance of detecting the presence of more than one disorder lies in the approach to management. For example, the presence of metabolic acidosis (low serum [HCO_3^-]) and respiratory acidosis (arterial PCO_2 not appropriately reduced)

Table 50–5

Mixed Acid-Base Disorders in Dialysis Patients

Mixed Metabolic and Respiratory Acid-Base Disorders
Metabolic acidosis [HCO_3^-] ↓
+ respiratory acidosis PCO_2 ↑ 5 mmHg or more above expected value[a]
+ respiratory alkalosis PCO_2 ↓ 5 mmHg or more below expected value
Metabolic alkalosis [HCO_3^-] ↑
+ respiratory acidosis PCO_2 ↑ 5 mmHg or more above expected value
+ respiratory alkalosis PCO_2 ↓ 5 mmHg or more below expected value
Mixed Metabolic Acidosis and Alkalosis
Anion gap ↑ without equivalent ↓ in serum [HCO_3^-]

a. See Figure 50.2 for formulas defining appropriate PCO_2 for any given serum [HCO_3^-].

requires that attention be directed to the patient's ventilatory status—as well as correcting the metabolic acidosis.

Recommended Reading

Feriani M. Use of different buffers in peritoneal dialysis. Seminars in Dialysis 2000;13:256–60.

Acid-base measurements in patients receiving peritoneal dialysis, using either lactate or bicarbonate in the bath solution.

Gennari FJ. Effect of renal replacement therapy on acid-base homeostasis, and acid-base disorders in dialysis patients. In Gennari FJ, Adrogué HJ, JH Galla, NE Madias (eds.), *Acid-base Disorders and Their Treatment*. New York: Taylor & Francis 2005:697–730.

Complete discussion, fully referenced, of acid-base balance in both peritoneal and hemodialysis (and of acid-base disorders) in patients receiving dialysis therapy.

Uribarri J, Zia M, Mahmood J, et al. Acid production in hemodialysis patients. J Am Soc Nephrol 1998;9:114–20.

Acid balance measurements in patients receiving conventional hemodialysis.

Wu DY, Shinaberger CS, Regidor DL, et al. Association between serum bicarbonate and death in hemodialysis patients: Is it better to be acidotic or alkalotic? Clin J Am Soc Nephrol 2006;1:70–78.

Large cohort study demonstrating the inverse relationship between protein catabolic rate and pre-dialysis serum [HCO3-] in patients receiving conventional hemodialysis, and showing that mortality risk at varying pre-dialysis values is due largely to malnutrition and inflammation rather than to the presence of acidosis or alkalosis.

CHAPTER 51

Nutritional Therapy in Maintenance Hemodialysis

Kamyar Kalantar-Zadeh, MD, PhD, MPH

Introduction

At least one out of every five individuals who undergo maintenance dialysis treatment dies each year in the United States. Almost half of all these deaths are attributed to cardiovascular diseases. It was once believed that the traditional cardiovascular risk factors such as obesity and hypercholesterolemia are the main causes of poor clinical outcome. However, recent randomized controlled trials have failed to show an improvement of mortality by lowering serum cholesterol (the 4D Trial).

Evidence suggests that conditions other than the traditional cardiovascular risk factors must be related to the enormous cardiovascular epidemic and high death rate in this population. Protein-energy malnutrition continues to be at the top of the list among the potential candidates for the poor clinical outcomes in maintenance dialysis patients. Epidemiologic studies have repeatedly and consistently shown a strong association between survival and measures of nutritional status in maintenance dialysis patients.

Malnutrition in Dialysis Patients

Protein-energy malnutrition is the state of decreased body pools of protein with or without fat depletion, or a state of diminished functional capacity caused at least in part by inadequate nutrient intake relative to nutrient demand. Hence, protein-energy malnutrition can be improved by nutritional repletion in dialysis patients for chronic kidney disease (CKD). Malnutrition is engendered when the body's need for protein or energy fuels or both cannot be satisfied by the current dietary intake. Although micronutrients (including minerals and vitamins) may present adequately to excessively in the setting of renal insufficiency and decreased renal clearance, many protein-energy malnourished dialysis patients may also have a relative deficiency in vitamins and trace elements. Up to 75% of dialysis patients may have signs or symptoms of malnutrition.

Table 51.1 and Figure 51.1 show potential contributors of malnutrition in maintenance dialysis patients. Malnutrition appears to develop prior to the development of renal replacement therapy, most likely during CKD stage 3 or even earlier. Observational studies have indicated a progressively worsening nutritional state

Table 51–1

Possible Effectors of Protein-Energy Malnutrition in Maintenance Dialysis Patients

Inadequate Nutrient Intake
Diminished appetite (anorexia):
- Uremic toxicity
- Impaired gastric emptying (e.g., in diabetes mellitus)
- Inflammation with or without co-morbid conditions
- Emotional and/or psychological disorders

Problems with diet and food intake:
- Prescribed restrictions: low-potassium/low-phosphate regimens
- Social constraints: poverty, inadequate dietary support
- Physical incapacity: inability to acquire or prepare food or to eat

Nutrient Losses During Dialysis
- Loss through hemodialysis membrane into hemodialysate
- Adherence to hemodialysis membrane or tubing
- Loss into peritoneal dialysate

Hypercatabolism Due to Co-morbid Illnesses
- Cardiovascular diseases, cardiac cachexia in chronic heart failure
- Diabetic complications (gastroparesis, recurrent infection)
- Infection and/or sepsis (e.g., dialysis access related)
- Other co-morbid conditions (e.g., systemic disorders with cachexia)

Hypercatabolism Associated with Dialysis Treatment
- Negative protein balance as a result of dialysis treatment
- Negative energy balance

Endocrine Disorders of Uremia and Other Metabolic Disorders
- Resistance to insulin
- Resistance to growth hormone and/or IGF-1
- Increased serum level of or sensitivity to glucagons
- Hyperparathyroidism
- Other endocrine disorders
- Chronic inflammation
- Oxidative stress

Acidemia with Metabolic Acidosis
Concurrent Nutrient Loss with Frequent Blood Losses

Abbreviation: IGF-1 = insulin-like growth factor 1.

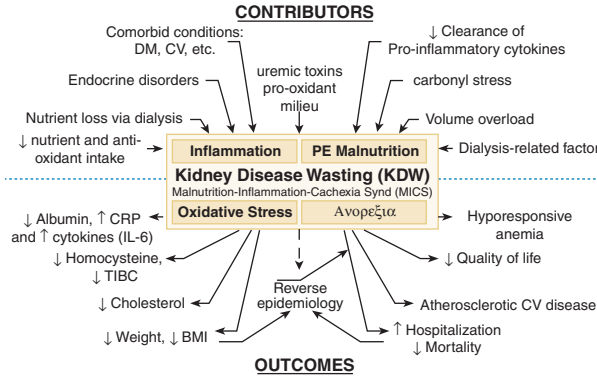


Figure 51–1

Schematic representation of the causes and consequences of MICS (PE = protein-energy, DM = diabetes mellitus, CV = cardiovascular, KDW = kidney disease wasting, CRP = C-reactive protein, TIBC = total iron binding capacity (also known as transferrin), BMI = body mass index).

as the glomerular filtration rate (GFR) falls below 60 mg/minute. Diminished appetite and anorexia are main causes of malnutrition. Anorexia may be related to uremic toxins and elevated circulating cytokines, or may be engendered via signaling through the central melanocortin system. Hemodialysis patients with a poor appetite have higher levels of inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), and an almost twofold increased risk of death.

Dietary restrictions imposed by nephrologists and dietitians to prevent hyperphosphatema or hyperkalemia may also lead to low protein intake. Many protein-rich foods are considered major sources of dietary phosphorus. Moreover, many fresh fruits and vegetables are highly rich in potassium, and their avoidance to control hyperkalemia may not only lead to deficiency in important antioxidant vitamins and trace elements but may leave an atherogenic diet as the main source of food for hemodialysis patients. Hemodialysis treatment can contribute to the development of malnutrition. Nutrient loss may happen through hemodialysis membrane, although the degree of contribution of this condition to hemodialysis-associated malnutrition may not be substantial.

High prevalence of co-morbid conditions and metabolic disorders (including insulin resistance and acidosis) may also lead to hypercatabolism and/or wasting. A higher-than-normal resting energy expenditure is also reported in dialysis patients independent of co-morbidity (Table 51.1).

Chronic Inflammation and Kidney Disease Wasting

Under normal conditions, inflammation is as a protective response triggered by injury that serves to destroy, dilute, or sequester both the injurious agent and the injured tissue. This important defense mechanism is inherently *acute* and usually subsides whenever the injury is resolved. However, inflammation may become harmful to the organism if it becomes *chronic*. Evidence suggests that hemodialysis patients with signs of malnutrition are more likely to have abnormally high circulatory levels of inflammatory markers and proinflammatory cytokines such as CRP and IL-6, both known to be strong predictors of poor outcome. It is not clear why chronic inflammation occurs commonly in dialysis patients but potential causes are outlined in Table 51.2.

Inflammation may be associated with anorexia in hemodialysis patients. Chronic inflammation may also lead to increased rate of protein depletion in skeletal muscle and other tissues, muscle and fat wasting, hypoalbuminemia, and hypercatabolism—leading to kidney disease wasting (KDW). Because protein-energy malnutrition and inflammation are usually concurrent, act in the same direction on laboratory markers and body proteins, and are associated with KDW and atherosclerotic cardiovascular disease in dialysis patients, a so-called "malnutrition-inflammation complex (or cachexia) syndrome" (MICS) has been defined to underscore the close link between these two conditions (Figure 51.1). However, there is currently no conclusive consensus regarding the nature or direction of the association between malnutrition and inflammation and their common pathophysiologic link with KDW and survival.

Assessment of Nutritional Status

Methods and tools to assess protein-energy malnutrition in dialysis patients are classically divided into four major categories: assessment of appetite and dietary intake, biochemical and laboratory assessment, body composition measures, and nutritional scoring systems (Table 51.3). A normal appetite is essential to maintain

Table 51–2

Effectors of Chronic Inflammation in Maintenance Dialysis Patients

Chronic Inflammation in the Setting of Decreased GFR
- Decreased clearance of proinflammatory cytokines (IL-6, TNF-α, IL-1β)
- Endotoxinemia in the setting of volume overload leaky gut
- Volume overload induced inflammation (similar to chronic heart failure)
- Oxidative stress in pro-oxidant milieu or because of deficient antioxidant intake
- Carbonyl stress (e.g., increased advanced glycation end products)
- Decreased levels of antioxidants (e.g., vitamin E, vitamin C, carotenoids, selenium, glutathione)
- Protein-energy malnutrition

Co-morbid Conditions
- Systemic disease states (e.g., lupus erthematosus or HIV disease)
- Conditions that may lead to increased inflammation (e.g., CVD, DM, advanced age)
- Higher incidence of infection due to immune system attenuation of uremia
- Remnant allograft from a previous solid organ transplantation

Inflammatory Conditions Related to Dialysis Therapy

Hemodialysis therapy:
- Exposure to dialysis tubing
- Dialysis membranes with decreased biocompatiblility
- Impurities in dialysis water and/or dialysate
- Back-filtration or back-diffusion of contaminants
- Foreign bodies (such as PTFE) in dialysis access grafts
- Intravenous catheter

Peritoneal dialysis therapy:
- Episodes of overt or latent peritonitis
- PD catheter as a foreign body and its related infections
- Constant exposure to PD solution

Abbreviations: CKD = chronic kidney disease, IL-6 = interleukin-6, TNF-α = tumor necrosis factor alpha, IL-1β = interleukin-1 beta, GFR = glomerular filtration rate, SLE = systemic lupus erythematosus, HIV = human immune deficiency virus, CVD = cardiovascular disease, DM = diabetes mellitus.

adequate food intake and to avoid undernourishment. Even though poor appetite and anorexia are early signs of uremia and may be a cause of malnutrition in dialysis patients, there is currently no uniformly accepted quantitative assessment for appetite because

Table 51–3

Assessment Tools for Evaluation of Malnutrition in Maintenance Dialysis Patients

Nutritional Intake and Appetite
- Appetite assessment questionnaires
- Direct dietary assessment: diet recalls and diaries, food frequency questionnaires
- Indirect assessment [e.g., urea nitrogen appearance: nPNA (nPCR)]

Body Composition
- Weight based measures: weight-for-height, BMI, edema-free fat-free weight
- Skin and muscle anthropometry via caliper: skinfolds, extremity muscle mass
- Total body elements: total body potassium, total body nitrogen
- Energy-beam-based methods: DEXA, BIA, NIR
- Other methods: underwater weighing

Laboratory Measures
- Visceral proteins (negative acute phase reactants): albumin, prealbumin, transferrin
- Somatic proteins and nitrogen surrogates: creatinine, SUN
- Lipids: cholesterol, triglycerides, other lipids and lipoproteins
- Growth factors: IGF-1, leptin
- Peripheral blood cell count: lymphocyte count or percentage

Nutritional Scoring Systems
- Conventional SGA and its modifications (e.g., DMS, MIS, CANUSA)
- Other scores: HD-PNI, others (e.g., Wolfson, Merkus, Merckman)

Abbreviations: nPNA = normalized protein nitrogen appearance, nPCR = normalized protein catabolic rate, BMI = body mass index, DEXA = dual-energy X-ray absoptiometry, BIA = bioelectrical impedance analysis, NIR = near infrared interactance, SGA = subjective global assessment of nutritional status, DMS = dialysis malnutrition score, MIS = malnutrition inflammation score, CANUSA = Canada-USA study based modification of the SGA, HD-PNI = hemodialysis prognostic nutritional index, SUN = serum urea nitrogen, IGF-1 = insulin-like growth factor 1, CRP = C-reactive protein, IL = interleukin (e.g., IL1 and IL6), TNF-α = tumor necrosis factor alpha, SAA = serum amyloid A.

appetite is inherently subjective. It has been argued that chronic inflammation is a cause of poor appetite in hemodialysis patients. If this hypothesis is true, inflammation may be causally linked to malnutrition by engendering anorexia in dialysis patients.

Dietary assessment is a traditional nutritional evaluation, because both the quality and quantity of the ingested nutrients

can be assessed with a high degree of reproducibility. However, dietary assessment methods (including the 24-hour recall, 3-day diary with interview, and food frequency questionnaires) are currently rarely employed in dialysis patients. A more routinely used and readily available method is the calculation of the weight-normalized protein equivalent of total nitrogen appearance (nPNA), also known as the normalized protein catabolic rate (nPCR)—which is derived from the rate of urea generation between the two subsequent dialysis treatment sessions. This urea-kinetic estimate of the protein intake is associated with survival in hemodialysis patients (Figure 51.2). Among limitations of nPNA are its mathematical correlation with Kt/V and the required assumption for the closed and stable system (i.e., no residual renal function and no negative or positive nitrogen balance).

Anthropometry and body composition measures are used as conventional indicators of nutritional status in dialysis patients. Weight-for-height and body mass index (BMI = weight/height^2) can be conveniently calculated and are also known to predict outcomes in dialysis patients. However, the reliability of these measures to represent the true body composition is questionable—

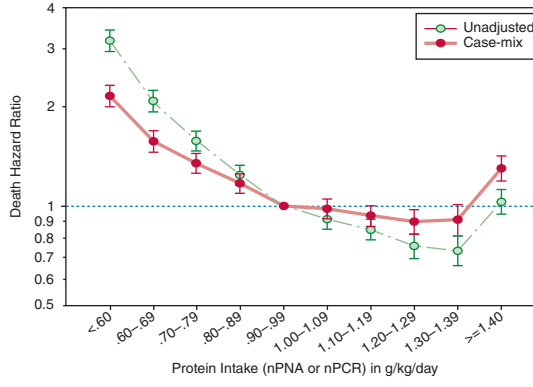


Figure 51–2

Association between urea kinetic measured protein intake (3-month averaged nPCR or nPNA) and 2-year mortality in 53,933 maintenance hemodialysis patients. Case-mix associations are adjusted for demographic and clinical confounders.

particularly because a high BMI can occur with both high total body fat and very high muscle mass. Furthermore, there is a paradoxical association between higher BMI and better survival in hemodialysis patients (Figure 51.3). This consistently observed counterintuitive association, also known as obesity paradox, underscores the important role of nutrition in the survival of hemodialysis patients.

Caliper anthropometry, including mid-arm muscle mass and skin-fold thickness, has poor reproducibility. More reliable methods (such as underwater weighing and total nitrogen or potassium measurements) are costly and rarely used in dialysis patients, although they are considered gold standards. Energy-beam methods may provide more pragmatic alternatives. Portable devices such as those based on bioelectrical impedance analysis (BIA) or near-infrared interactance (NIR) technology are evaluator and patient friendly, whereas dual-energy X-ray absorbsiometry (DEXA) is a more elaborate and costly method that requires both resources and expertise.

Serum concentrations of albumin, prealbumin (transthyretin), transferrin (total iron binding capacity, TIBC), cholesterol, urea

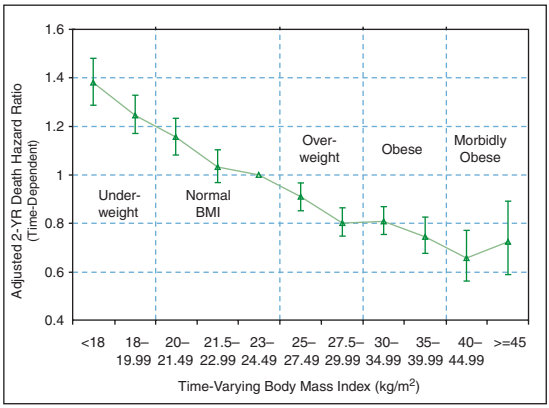


Figure 51–3

Association between the averaged body mass index (based on 3-month averaged posthemodialysis dry weight) and 2-year mortality in 54,535 maintenance hemodialysis patients—adjusted for demographic, clinical, and laboratory confounders.

nitrogen, and creatinine can be evaluated as markers of nutritional status and outcome predictors in dialysis patients. However, these laboratory values may significantly be confounded by such non-nutrition factors as inflammation, oxidative stress, iron stores, liver disease, and residual renal function. Serum albumin is one of the most sensitive mortality predictors in hemodialysis patients (Figure 51.4). A fall in serum albumin concentration to as low as 0.6 g/dL from baseline over a 6-month interval is associated with a doubling of the death risk in these patients.

Several scoring systems have recently been developed to assess the overall nutritional aspects of dialysis patients. The Subjective Global Assessment (SGA) is probably the most well-known scoring tool, which has also been recommended by the NKF-K/DOQI Nutrition guidelines for the periodic assessment of dialysis patients. Among the limitations of the SGA are the inherently "subjective" characteristics of its assessment components and its semiquantities scoring. Fully quantitative versions of the SGA that have been developed for dialysis patients, including the Dialysis Malnutrition Score (DMS) and the Malnutrition-Inflammation Score (MIS). The reproducibility and objectivity

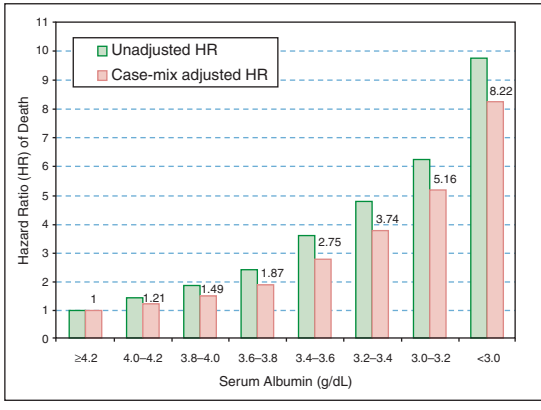


Figure 51–4

Association between serum albumin levels (averaged over 3-month intervals) and subsequent 2-year death risk in 58,058 maintenance hemodialysis patients from 2001 to 2003.

of the DMS and especially of the MIS may be superior to the conventional SGA for hemodialysis patients.

Consequences of Protein-Energy Malnutrition

In addition to anorexia, hypoalbuminemia, and KDW, malnutrition may have other clinically important consequences in dialysis patients. These consequences are discussed in the sections that follow.

Refractory Anemia

Anemia appears to be more common in those dialysis patients who also suffer from malnutrition and/or inflammation. A blunted response to erythropoiesis-stimulating agents (ESAs) is usually associated with increased levels of proinflammatory cytokines such as IL-6. In a meta-analysis, L-carnitine administration used to improve nutritional state was associated with improved hemoglobin and decreased ESA dose requirement in anemic dialysis patients. In the pre-ESA era, anabolic steroids were used successfully to improve both nutritional status and anemia in dialysis patients.

Atherosclerotic Cardiovascular Disease

Dialysis patients with coronary heart disease often have hypoalbuminemia and elevated levels of inflammatory markers. Emerging data in both the general population and dialysis patients indicate that indicators of inflammation such as increased serum CRP level are stronger predictors of cardiovascular events than LDL-hypercholesterolemia. The association between elements of MICS and atherosclerosis in dialysis patients has been underscored by some investigators who have chosen the term *malnutrition-inflammation-atherosclerosis* (MIA) *syndrome* for this entity. Chronic inflammation may be the missing link that causally ties protein-energy malnutrition to poor outcome and high death rate in these individuals.

Reverse Epidemiology

In highly industrialized and affluent countries, protein-energy malnutrition is an uncommon cause of poor outcome in the

general population—whereas overnutrition is associated with a greater risk of cardiovascular disease and shortened survival. In contrast, in maintenance hemodialysis patients "undernutrition is one of the most common risk factors for adverse cardiovascular events. Similarly, certain markers that predict a low likelihood of cardiovascular events and an improved survival in the general population, such as decreased BMI (Figure 51.3) and lower serum cholesterol levels, are risk factors for increased cardiovascular morbidity and death in dialysis patients. Hence, obesity, hypercholesterolemia, and hypertension appear paradoxically to be protective features associated with a greater survival among dialysis patients.

The association between undernutrition and adverse cardiovascular outcome in dialysis patients, which stands in sharp contrast to that seen in the general population, has been referred to as "reverse epidemiology." Possible causes of reverse epidemiology include survival selection during the progression of CKD and time discrepancy between competitive risk factors (i.e., the short-term killer undernutrition versus the long-term killer overnutrition). The emergence of the reverse epidemiology hypothesis may have a bearing on the management of dialysis patients. It is possible that new standards or goals for traditional risk factors such as body mass, serum cholesterol, and blood pressure be considered for these dialysis patients—especially if they suffer from protein-energy malnutrition.

Recommended Dietary Intake for Hemodialysis Patients

Table 51.4 outlines recommended dietary requirements for adult hemodialysis patients. The NKF-K/DOQI guidelines recommend 1.2 g per kg body weight per day of dietary protein intake (DPI) for clinically stable hemodialysis patients. At least 50% of the dietary protein should be of high biologic value. According to an observational study, a 3-month averaged nPNA (nPCR) between 1.2 and 1.4 g/kg/day was associated with the greatest 2-year survival in more than 50,000 hemodialysis patients (Figure 51.2).

The NKF-K/DOQI recommended protein intake is 30 to 35 kcal/kg/day. The NKF-K/DOQI guidelines currently do not have any specific recommendation with regard to lipids and most micronutrients—with the exception of calcium and phosphorus intake in the NKF-K/DOQI guidelines for bone disease. The recommendations in Table 51.4 are from the author and are based on literature

Table 51–4

Recommended Dietary Nutrient Intake for Adult Patients Undergoing Maintenance Hemodialysis

Macronutrients and Fiber	
Dietary protein intake (DPI)[a]	• 1.2 g/kg/d for clinically stable patients (at least 50% should be of high biological value) • ≥1.2–1.3 g/kg/d for acutely ill patients
Daily energy intake (DEI)[a]	• 35 kcal/kg/d if <60 years • 30–35 kcal/kg/d if 60 years or older
Total fat	25–35% of total energy intake
Saturated fat	<7% of total energy intake
Polyunsaturated fatty acids	Up to 10% of total calories
Monounsaturated fatty acids	Up to 20% of total calories
Carbohydrate	Rest of calories (complex carbohydrates preferred)
Total fiber	>20–25 g/d
Minerals and Water (Range of Intake)	
Sodium	750–2000 mg/d
Potassium	<80 mEq/d
Phosphorus[b]	10–15 mg/kg/d
Calcium[b]	≤1000 mg/d
Magnesium	200–300 mg/d
Iron	See chapter on anemia
Zinc	15 mg/d
Water	Usually 750–1500 mL/d
Vitamins (Including Dietary Supplements)	
Vitamin B1 (thiamin)	1.1–1.2 mg/d
Vitamin B2 (riboflavin)	1.1–1.3 mg/d
Pantothenic acid	5 mg/d
Biotin	30 μg/d
Niacin	14–16 mg/d
Vitamin B6 (pyridoxine)	10 mg/d
Vitamin B	2.4 μg/d
Vitamin C	75–90 mg/d
Folic Acid	1–5 mg/d
Vitamin A	See chapter on bone disease
Vitamin D	See text
Vitamin E	400–800 IU (optional; see text)
Vitamin K	No consensus

a. According to the NKF-K/DOQI guidelines for nutrition in dialysis patients.
b. See chapter on bone disease.

partially related to nondialysis populations. Indeed, in some areas (such as vitamin A and folic acid) there are conflicting observations.

Management of Malnutrition

Because malnutrition and inflammation are powerful predictors of death risk in dialysis patients, it is possible that nutritional and anti-inflammatory interventions improve poor outcome. Evidence suggests that maintaining an adequate nutritional intake in patients with a number of acute or chronic catabolic illnesses

Table 51–5

Overview of Nutritional and Anti-inflammatory Interventions for Dialysis Patients with Protein-Energy Malnutrition

Oral Interventions
- Increasing macronutrients with food intake
- Oral dietary supplements (in addition to routine diet)

Enteral interventions
- Tube feeding (NG tube, PEG)

Parenteral Interventions
- Intradialytic parenteral nutrition
- Other parenteral interventions (e.g., TPN)

Hormonal Interventions
- Androgens
- Growth factors/hormones

Nonhormonal Medications
- Anti-inflammatory agents (e.g., borage oil, pentoxiphylline)
- Antioxidants (e.g., vitamin E, acetylcysteine)
- Appetite stimulators (e.g., megesterol)
- Carnitine
- Others (e.g., fish oil)

Dietary Counseling
- In-center supervision/counseling
- Other indirect dietary interventions (e.g., psychotherapy)

Dialysis Treatment Related
- Increasing dialysis dose and frequency (daily or nocturnal)
- Membrane compatibility modification

Abbreviations: NG tube = nasogastric tube, PEG = percutaneous esophagogastrostomy, TPN = total parenteral nutrition.

may improve their nutritional status irrespective of the etiology. Whether nutritional treatment may improve morbidity and mortality in dialysis patients is currently not clear. There are no large-scale randomized controlled trials that have examined these questions. Observational data analyses have shown association between higher-than-usual protein intake (1.2 to 1.4 g/kg body weight per day) and greatest survival in hemodialysis patients (Figure 51.2).

Table 51.5 outlines selected nutritional interventions that have been tried or recommended in hemodialysis patients. Enhancing food intake by either dietary counseling or positive reinforcement may be helpful, especially if dialysis facility dietitians take a proactive role to this end. Many nephrologists and dietitians advocate oral supplementations as an adjunct therapy. However, it is important to appreciate that simultaneously imposed dietary restrictions to control potassium, phosphorus, and/or calcium intake or to manage diabetes mellitus or dyslipidemia may interfere with or even contradict the foregoing efforts to increase protein and energy intake. This unresolved dilemma has been an ongoing matter of confusion for both dialysis patients and health care providers.

Table 51–6

Anti-inflammatory and Antioxidant Agents for Dialysis Patients with Signs of MICS (Including Hypoalbuminemia)

- Antioxidant vitamins
- Vitamin E
- Vitamin C
- Vitamin A and carotenoid
- Other antioxidants
- Eicosanoids (fish oil)
- γ-linolenic (borage oil)
- Megestrol acetate
- Pentoxifylline
- Steroids/ACTH
- NSAID
- Anti–TNF-α agents
- Thalidomide
- Statins
- ACE inhibitors and ARB
- Beta blockers
- N-acetylcysteine

Table 51–7

Appetite Stimulants for Use in Maintenance Dialysis Patients with Anorexia and Malnutrition or Kidney Disease Wasting

- Megestrol acetate
- Medroxyprogesterone
- Pentoxifylline
- Dronabinol
- Cyproheptadine
- Melanocortin blocker
- Anabolic steroids
- Other corticosterioids

Tube feeding and parenteral interventions may reinforce protein and energy intake even among anorectic patients. Recent metabolic studies demonstrated that intradialytic parenteral nutrition (IDPN) promoted a large increase in whole-body protein synthesis and a significant decrease in proteolysis in noninflamed but malnourished hemodialysis patients. However, other studies on IDPN have failed to show improvement in nutritional status or clinical outcome in dialysis patients.

Hormonal or pharmacologic interventions may be associated with many side effects that mitigate the enthusiasm of using them, although emerging data suggests that dietary supplements with anti-inflammatory interventions (Table 51.6)—especially if associated with simultaneous appetite-stimulating properties such as megesterol acetate or pentoxiphylline (Table 51.7)—may improve nutritional status and outcomes in dialysis patients. A number of other techniques have been employed or recommended for the prevention or treatment of protein-energy malnutrition before the onset of dialysis therapy, maintenance of an adequate dose of dialysis, avoidance of acidemia, and aggressive treatment of superimposed catabolic illness.

Recommended Reading

Hurot JM, Cucherat M, Haugh M, Fouque D. Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. J Am Soc Nephrol 2002;13:708–14.

An interesting meta-analysis of the effect of L-carnitine on improving anemia treatment in hemodialysis patients.

Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients. J Am Soc Nephrol 1996;7:2646–53.

This study advances the hypothesis that energy expenditure is increased in the setting of maintenance hemodialysis treatment.

Kalantar-Zadeh K, Kopple J. *Nutritional management of hemodialysis patients. In Kopple J, Massry S (eds.), Nutritional Management of Renal Disease, Second Edition*. Philadelphia: Lippincott, Williams & Wilkins 2004:433–66.

More comprehensive details about nutritional management of hemodialysis patients.

Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis 2003;42:864–81.

An inclusive review about the causes and consequences of MICS.

Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2001;38:1251–63.

The creation of a fully quantitative nutritional scoring system based on SGA, which is currently used annually in more than 100,000 hemodialysis patients across the USA.

Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD study. Kidney Int 2000;57:1688–1703.

Nutritional analysis of the classic MDRD data and the impact of nutritional markers on the progression of CKD toward ESRD.

National Kidney Foundation. Part I, Kidney Disease-Dialysis Outcome Quality Initiative: NKF-K/DOQI Clinical Practice Guidelines for nutrition in chronic renal failure. Am J Kidney Dis 2000;35:S1–140.

Recommended guidelines by the National Kidney Foundation NKF-K/DOQI Work Group on the management of malnutrition in dialysis patients.

Shinaberger CS, Kilpatrick RD, Regidor DL, McAllister CJ, Greenland S, Kopple JD, et al. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. Am J Kidney Dis 2006;48:37–49.

Epidemiologic analyses of national data dissecting the associations between protein intake and survival in hemodialysis patients.

CHAPTER 52

Nutritional Management in Peritoneal Dialysis

Robert McGregor Lindsay, MD, FRCPC, FRCP (Edin), FACP, FRCP (Glasg), and Evelyn Spanner, MSc,R

Patients with progressive loss of kidney function often suffer a decline in their nutritional status. This was especially evident during the early days of dialysis, when predialysis therapy consisted of maintaining patients for prolonged periods of time with very-low-protein diets and allowing them to have advanced uremia before dialysis was instituted.

Current recommendations emphasize the need for earlier dialysis initiation to maintain a better nutritional state. The commencement of dialysis should lead to an improvement in nutritional status following correction of the uremic state. However, dialysis therapy—whether by hemodialysis or peritoneal dialysis (PD)—imposes its own set of nutritional problems. Thus, despite major improvements in dialytic techniques malnutrition continues to be a concern in patients on dialysis. This chapter specifically addresses those aspects that pertain to PD.

Nutritional Requirements in Peritoneal Dialysis

The daily nutrition requirements for PD are listed in Table 52.1, which highlights the attention that must be paid to daily energy intake (DEI) and protein, mineral, and vitamin intake.

Daily Energy Intake

For these patients, energy requirements are greatly facilitated by the significant quantity of glucose absorbed from the dialysate. However, in some patients oral energy intake may need to be decreased to prevent excess weight gain and obesity. The recommended level of energy intake is 145 kJ/kg/day. Total DEI should be the sum of the kilojoules from absorbed dialysate glucose plus the kilojoules that accrue from the diet. Because older age may be associated with reduced physical activity, it is recommended that DEI be reduced to 125 to 145 kJ/kg/day for older patients with

Table 52–1

Daily Dietary Requirements for PD Patients

Protein	Ideal: 1.2–1.3 g/kg standard body wt (50% high biological value) Minimum: 0.8 g/kg
Energy	145 kJ/kg ideal body wt[a] (35 kcal/kg) if <60 years; 125–145 (oral + dialysate) kJ/kg if ≥60 years
Carbohydrate	Remainder of energy supply
Fat	30% of total energy supply
Calcium	≤2000 mg/d inclusive of calcium from calcium-based phosphate binders
Phosphorus	≤1000 mg/d (50% of dietary phosphorus is absorbed, so phosphate binders are usually necessary to control serum phosphorus)
Magnesium	200–300 mg
Potassium	Individualize level for maintenance of normal serum levels
Sodium/water	Individualize prescription for volume/blood pressure status; usually 130–175 mmol/d
Vitamin Supplements:	
Thiamin	1.5 mg
Riboflavin	1.8 mg
Pantothenic acid	5 mg
Niacin	20 mg
Pyridoxine HCl	10 mg
Bitamin B12	3 μg
Vitamin C	60 mg
Folic acid	1 mg
Vitamin A	No addition
Vitamin D	Individualize
Vitamin E	15 IU
Vitamin K	None[b]

a. Ideal body weight for normal persons of same age, sex, and height (not "dry" weight for the patient).
b. Addition may be needed for patients who are not eating and who receive antibiotics.

sedentary lifestyles. Absorption of glucose from the dialysate constitutes approximately 20 to 30% of a patient's required energy intake. The following formula can be used to predict the grams of glucose absorbed.

$$(1 - D/D_0)x_i$$

Here, D/D_0 is the ratio of remaining dialysate dextrose at 4 hours to the initial dextrose in the dialysate at zero hours, and x_i is the

initial grams of glucose instilled. Alternatively, glucose absorption from dialysate can be measured (rather than estimated)—when the 24-hour collection is being done—by subtracting the quantity of glucose in the daily dialysate effluent from the total quantity of glucose instilled that day. This large glucose uptake may, in a negative sense, suppress the patient's overall intake—particularly as the patient may experience abdominal discomfort and fullness.

Protein

The attainment of energy needs affects protein requirements because energy has a protein-sparing effect. The primary concern, however, rests with the ability of a chronic PD patient to maintain an adequate protein intake. A daily protein intake of 1.2 to 1.3 g/kg/day is recommended for stable PD patients. This figure has been derived from nitrogen balance studies in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Some experts suggest that the observations so made define the lower limit of protein required to maintain positive nitrogen balance and that many PD patients could be in nitrogen equilibrium with lower protein intakes. Protein needs may vary depending on stress or metabolic needs. In our opinion, the minimum dietary protein intake for the PD population should be 0.8 g/kg/day. Any patient with a protein intake ≤0.8 should be reassessed by the registered dietitian to decrease the risk of protein malnutrition.

Allowing for essential amino acid requirements, at least 50% of the daily protein intake should be of high biologic value. As the amount of protein secreted into the peritoneal fluid ranges from 5 to 15 g/day (60–80% as albumin), with occasional patients secreting <5 or as much as 20 g/day, the diet should be sufficient in protein to compensate for these losses. Several factors make maintaining an adequate level of protein nutriture difficult: intercurrent illnesses and peritonitis by causing increased protein requirement, early satiety related to glucose influx, altered taste sensation, and a particular loss of appetite for high-protein food sources.

Some general suggestions to assist patients in increasing their protein intake include ingestion of protein foods before others, frequent meals with high protein sources, and educating patients as to the use of oral enteral supplements (especially those high in protein and/or energy). Adequacy of protein intake can be assessed by evaluating the normalized protein equivalent of nitrogen

appearance (nPNA, previously normalized protein catabolic rate or nPCR) by utilizing the following equations (Bergstrom formula).

$$\text{nPNA} = 13 + 0.204\ \text{UNA (mmol/day)} + \text{dialysate protein losses (g/day)}$$

$$\text{nPNA} = 19 + 0.213\ \text{UNA (mmol/day)}$$

UNA (urea nitrogen appearance) is the total urea in the daily dialysate plus urine measured in mmol/day. The results are then corrected to standard body weight.

Minerals

The balance between limiting phosphorus and achieving adequate protein intake is a major nutritional concern in PD. These patients are limited to ≤1000 mg/day from their food intake, of which 50% is absorbed. A lower ratio of phosphorus-to-protein intake should be emphasized. Phosphate binders are also required to control serum phosphate levels. Patients should be advised to redistribute their binders concomitantly with their food intake, particularly if these patients are consuming more frequent meals to boost their protein intake. Calcium intake should be ≤2000 mg/day from both food sources and calcium-based phosphate binders. In light of the evidence that aluminum toxicity is a major cause of osteomalacia and other low-turnover bone abnormalities, in addition to its adversely affecting red blood cells and the brain the use of aluminum-based phosphorus binders poses a risk. They may be prescribed for short time periods in cases of hypercalcemia.

Other non calcium-based phosphate binders may be needed in PD patients with hypercalcemia or a high calcium phosphate product that limits calcium-based binders, concerns with low serum parathroid hormone, or with severe vascular or soft tissue calcification. It will be recalled that when the use of aluminum-based phosphate binders was widespread the recommended dialysate calcium concentration was 3.25 mEq/L (1.62 mmol/L). The advent of calcium-based binders led to the reduction of the dialysate calcium concentration to prevent non-aluminum low-turnover bone disease. A change back to non–calcium-based binders may require a reevaluation of the dialysate calcium concentration.

Sodium intake should be individualized based on blood pressure and weights, with the suggested sodium intake being approximately 130 to 175 mmol/day. If fluid retention problems occur, sodium and fluid intake should be altered to control any

undesirable weight gain and to alleviate the need for higher glucose concentration exchanges. Recent studies have shown that subclinical volume expansion is common in PD patients, particularly once residual renal function is lost. Controlling daily sodium ingestion may therefore be important with declining residual function. This is also important in APD patients, in whom sodium removal has been shown to be significantly lower than in CAPD patients. Potassium intake is generally unrestricted with PD unless the serum level is increased or decreased. Patients receiving PD may be at risk for hypokalemia, especially when their nutritional intake is poor. Some patients may require potassium supplementation.

Vitamins

Reduced serum and tissue vitamin levels may occur in PD patients with anorexia and poor nutritional intake or with altered metabolism and dialysate losses of water-soluble vitamins. Therefore, it is prudent to routinely supplement their oral intake (Table 52.1).

Nutritional Problems in Peritoneal Dialysis

The major problem in the PD population is that of protein malnutrition. Recent investigations have assessed the incidence of protein-energy malnutrition and have found that approximately 40% of PD patients were at least mild to moderately malnourished, and that 4 to 8% were severely malnourished. Further studies have shown that 25 to 60% of PD patients were ingesting <0.8 g of protein/kg/day when this is assessed by either a 3-day food intake record or by calculation of the nPNA. The nPNA is a reliable tool for estimating the dietary protein intake when it is routinely assessed by qualified registered dieticians.

Although plasma albumin can undoubtedly be influenced by factors other than nutrition (e.g., volume expansion due to decreased ultrafiltration, increased transperitoneal protein loss, inflammation, and co-morbidity), it is clear that a serum albumin will change with protein malnutrition. High peritoneal membrane transport among PD patients may result in lower serum albumin concentrations, particularly from higher protein losses without increased protein intakes. PD patients may also show a decrease in anthropometric values and nitrogen balance during frequently recurring episodes of peritonitis. Conversely, following aggressive treatment of peritonitis protein intake will increase, nitrogen balance will become

positive, and anthropometric values will improve. In such patients, there is a direct linear correlation between nitrogen intake and nitrogen balance. In addition, serum albumin is a good marker of such changes.

Influence of Protein Malnutrition on Outcome

The National Cooperative Dialysis Study (NCDS) indicates that for hemodialysis patients outcome is dependent on the dose of dialysis as modeled by the removal of urea. The more recent HEMO Study defined the upper limits of that dependency. The ADEMEX trial showed that mortality was not improved by increasing peritoneal small-solute clearance. However, significant increases in death due to uremia and fluid overload occurred in the control group. In the NCDS, nutrition was also shown to be important in outcomes because patients with a low nPNA (g/kg/day) had a high morbidity rate.

In the ADEMEX trial, patients with nPNA values greater than 0.8 g/kg/day had a significantly better survival compared with patients whose nPNA values were less than 0.8 g/kg/day. More recent studies confirm the importance of nutrition. Patients with a low plasma urea, low cholesterol, and low albumin have an increased risk of death compared to "standard" hemodialysis patients. Likewise, there is definite evidence that a low serum albumin in the PD population is associated with increased morbidity and mortality. In the CANUSA study of the adequacy of PD, the relative risk of either technique failure or death decreased by 3% for each 1 g/L increase in serum albumin—and 21% for each 1 unit increase in the subjective global assessment (SGA) score (see material following for an explanation).

The ADEMEX trial also showed a significant survival effect with higher serum albumin levels. There is enough data to support the contention that many PD patients do not ingest the daily protein requirement to maintain nitrogen balance and that malnutrition is a common outcome. Dietary protein and energy intake (as well as other non-nutritional factors) can influence plasma albumin, and a falling albumin will influence outcome.

Relationships among Malnutrition, Inflammation, and Atherosclerosis

Recent evidence suggests that inflammation alone or in combination with a low protein intake and transperitoneal albumin

losses plays a significant role in the resulting hypoalbuminemia in PD patients. Serum albumin and C-reactive protein (CRP) participate reciprocally in the acute-phase process. In nonrenal subjects, elevated CRP levels predict cardiovascular morbidity. Similarly, increased CRP is a strong risk factor for both total and cardiovascular mortality in hemodialysis and PD patients.

It is suggested that there is a syndrome of malnutrition, inflammation, and atherosclerosis (MIA) that carries a high mortality rate in dialysis patients. The malnutrition associated with MIA is now referred to as type 2 malnutrition. Type 1 malnutrition, on the other hand, is associated with the uremic syndrome per se or with factors related to uremia and its treatment (e.g., underdialysis, physical inactivity, food intake, and depression). The spectrum of altered nutritional status seen in dialysis patients may, however, entail a continuous overlap between both types of malnutrition and hence may evolve into a mixed type of malnutrition.

Influence of Adequacy of Dialysis on Nutritional Status

Inadequate dialysis is a potentially reversible cause of protein malnutrition in dialysis patients, whether on PD or hemodialysis. The current NKF-K/DOQI guidelines recommend a minimum weekly peritoneal Kt/V urea of at least 1.7. The ADEMEX trial results indicated no improvement in 2-year survival when peritoneal clearance of small solutes was increased to a weekly Kt/V = 2.27. A trial of increasing Kt/V should, however, be considered in patients with evidence of uremic symptoms that could be resulting in anorexia, nausea, and poor nutritional status. It may even be justified considering a change to hemodialysis in some patients. Likely, manipulations of dialysis dose will only influence those patients with type 1 protein malnutrition.

Assessment of Nutritional Status

Optimal measures for comprehensively assessing nutritional status are not well established in the PD population. In nonuremic individuals, muscle mass is usually estimated from measurements of mid–upper-arm circumference and is felt to be representative of total body protein. The standard values in renal failure patients and in the PD population have not been established. Likewise, the same criticism can be applied to the use of anthropometric measurements—including skin-fold thickness to assess body fat

and hence to calculate lean body mass. These measurements are useful but must be obtained serially by a trained individual to be of any value.

Energy intake is best estimated by a food intake record and from changes in the physical examination (actual weight, percentage of usual post-drain weight, percentage of standard body weight, muscle weakness, volume status, and so on). In addition, we have found regular measurement of dietary energy and protein intake, nPNA, serum albumin, and serum creatinine levels particularly useful. These should be performed at least every 3 months on all PD patients. SGA should also be done every 6 months. SGA was initially developed to determine the nutritional status of patients undergoing surgery and has subsequently been validated in the PD patient population. This technique, which combines medical history (weight loss, anorexia, and GI symptoms) and physical examination (loss of subcutaneous fat and muscle mass), is a potent predictor of survival. The CANUSA study showed that a higher SGA score was associated with a lower relative risk of death and fewer hospitalized days per year.

Management of Nutritional Problems

Protein Malnutrition

The most common problem in the PD population is that of protein malnutrition. A scheme for the assessment and management of this is shown in Figure 52.1. This scheme shows that early on the physician must determine whether dialysis is adequate. Thus, we have found it very useful to perform regular assessment of creatinine clearance and urea kinetics (Kt/V_{urea} and nPNA, and where necessary a peritoneal equilibration test). Details of how to perform these assessments and tests, as well as target values, are provided elsewhere in this book.

If dialysis is inadequate, clearly it has to be made adequate. Usually, this can be done by a change in the PD prescription. A few patients, however, simply cannot receive adequate treatment by any form of PD (very large size, limited residual function, inadequate peritoneal transport)—and these patients should be considered for hemodialysis. A change to hemodialysis may even be considered as a temporary measure in the occasionally very malnourished PD patient while either enteral or parenteral nutrition is given. Once a new, good steady state of nutrition is obtained a return to PD can be made.

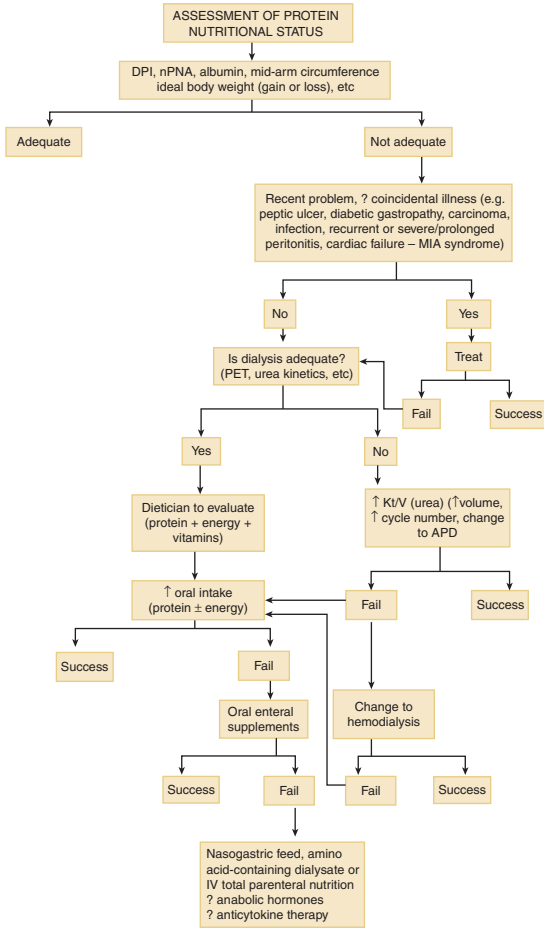


Figure 52–1

Assessment and management of protein/energy malnutrition in PD patients (DPI = dietary protein intake, PET = protein equilibration test).

A positive response to an increased dialytic dose is likely only in type 1 malnourished patients who may also show some benefit from anabolic hormones. Small short-term studies in PD patients on the use of agents such as recombinant insulin-like growth factor (rh IGF-1) and growth hormone (rh GH) have shown them to improve nitrogen balance. However, high costs and potential side effects have limited their clinical use. The effectiveness of rh IGF-1 and rh GH in hemodialysis patients is blunted if inflammation is present.

In the PD patient with type 2 malnutrition, the approach must be to identify and treat (if possible) the co-morbidity causing the inflammatory response. It may be of benefit to obtain a C-reactive protein level to distinguish these patients. In the future, it is possible that anticytokine therapy (e.g., 1L-1 receptor antagonists, anti-TNFa antibodies, thalidomide, and so on) may have a role.

A nephrology RD is important in any dialysis unit. This professional is best able to assess the patient's overall nutritional state (inclusive of protein, energy, and vitamin status) and individual requirements, and to advise the patient how best to manage his or her nutrition plan. If a patient cannot ingest the necessary protein plus energy requirement, oral enteral supplements should be tried first—using the commercially available preparations that will give protein with or without energy. Should the use of oral enteral supplements not meet with success, either nasogastric tube feeding or the use of amino–acid–containing dialysis solutions must be considered. Intraperitoneal amino acids (IPAAs) appear to increase protein balance in type 1 malnourished PD patients who have low protein intakes. However, a limiting factor is that adequate quantities of energy and vitamins cannot be provided by IPAA. As a last resort, total intravenous parenteral nutrition may be used.

Glucose Malabsorption

Energy intake may need to be modified for PD patients because of their absorption of glucose from dialysate. Higher levels of glucose absorption have been associated with increased transport rates. As mentioned previously, the dialysate glucose may provide as much as 30% of the patient's total daily energy intake. Unfortunately, considerable variability is seen in glucose absorption.

Nutrition-related problems may be created or worsened by absorption of glucose from dialysate: weight gain with increase in abdominal fat, high triacylglycerol levels, and increased risk of hyperglycemia. If weight gain is a major problem, the only

options are to limit dietary calories, decrease sugars and fats, and increase exercise. The patient should also be instructed to limit sodium and fluid intake sufficiently to permit a decrease in the glucose concentration of dialysate as necessary for adequate ultrafiltration. IPAA can be utilized to reduce the number of glucose-containing exchanges and to increase protein balance. These solutions can result in approximately 80% peritoneal uptake of amino acids, depending on dwell time. A polyglucose-based solution (such as icodextrin) can also be considered—to increase ultrafiltration volumes in the longer-duration dwells, leading to reduced extracellular fluid volumes without increasing the use of hypertonic glucose solutions. In the PD population, hypertriglyceridemia occurs because of conversion of excess glucose to triacylglycerols by the liver. Its management should be the same as that for weight gain. Some patients may benefit from supplementation with omega-3 fatty acids or lipid-lowering agents. The excess glucose load presents an additional problem for the diabetic, who may have to adjust their diet, oral hypoglycemic drugs, and insulin dose—or who may require insulin for the first time to achieve optimal glycemic control.

Summary

PD is an excellent form of renal replacement therapy, but it does impose a set of unique and challenging nutritional requirements for the patient. Adequate protein and oral calories adjusted for those absorbed from the dialysate, and levels of mineral and vitamins, have to be considered in achieving the nutritional needs of the individual PD patient. Malnutrition, especially protein malnutrition, is a major cause of morbidity and mortality in this population. Hence, regular monitoring of nutritional status by an experienced nephrology RD is essential.

Recommended Reading

Nutritional Management in Peritoneal Dialysis

Heimburger O, Stenvinkel P, Lindholm B. Nutritional effects and nutritional management of chronic peritoneal dialysis. In Kopple JD, Massry SG (eds.), *Nutritional Management of Renal Disease*. Philadelphia: Lippincott, Williams & Wilkins 2004:477–512.

Kopple JD, Hirschberg R. Nutritional and peritoneal dialysis. In WE Mitch, S Klahr (eds.), *Nutrition and the Kidney*. Boston: Little, Brown 1993:290–313.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice. Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy, Vasular Access. Am J Kidney Dis, 48:S1–S322, 2006 (Suppl 1).

General Review

Jones MR, Burkart JM, Hamburger RJ, et al. Replacement of amino acid and protein losses with 1.1% amino acid peritoneal dialysis solution. Perit Dial Int 1998;18:210–16.

Jones MR, Hagen T, Algrim-Boyle C, et al. Treatment of malnutrition with 1.1% amino acid peritoneal dialysis solution: Results of a multicenter outpatient study. Am J Kidney Dis 1998;32:761–69.

Kopple JD, Bernard D, Messana J, et al. Treatment of malnourished CAPD patients with an amino acid-based dialysate. Kidney Int 1995;47:1148–57.

CHAPTER 53

Parenteral Nutrition in Patients Undergoing Maintenance Dialysis

Denis Fouque, MD, PhD, and Raymond Vanholder, MD

Introduction

There are many speculative reasons why, in general, intravenous nutrition may improve the nutritional status of patients treated by maintenance dialysis. Patients are referred three times weekly, with a vascular access allowing nutrient infusion without need for additional maneuvers to create vascular access—which simplifies applicability, delivery, and compliance for a limited extra cost. On the other hand, time to exposure for nutritional support is in fact rather short (approximately 10–15 hours weekly) compared to total parenteral nutritional support used in intensive care units or at home for patients with intestinal failure. Hence, nonrenal nutritionists often question the efficacy of intradialytic parenteral nutrition (IDPN).

In addition, IDPN is more expensive than any oral or enteral nutrition. Thus, the key questions are whether patients have a large enough spontaneous intake (e.g., greater than 20 kcal and 0.8 g protein/kg IBW/day) to benefit sufficiently from the limited supplement related to the intermittent pattern of intradialytic infusion and in what way does IDPN interfere with spontaneous food intake function in terms of metabolic and appetite alterations.

A number of retrospective analyses, prospective trials, and reviews have addressed the various aspects of IDPN. From a metabolic point of view, each hemodialysis session dramatically decreases plasma amino acid levels—and as a consequence blunts intracellular protein synthesis, mainly in muscle. In addition, in response to the rapid plasma amino acid decrease at the start of the hemodialysis session muscle proteolysis occurs in order to maintain an adequate plasma and cellular amino acid concentration.

These events result in a clearly catabolic balance at the end of the dialysis session. Feeding patients by parenteral route during the dialysis session has been shown to revert this acute catabolic state by raising plasma amino acid concentration toward normal

values. In addition, exercise may improve nutritional efficiency of IDPN. Recently, Pupim et al. reported that a brief 15-minute cycling exercise at the beginning of the dialysis session dramatically improved the anabolic effect of the IDPN supplement.

However, it is less clear if these beneficial effects are associated with long-term improvement in nutritional status and morbidity and mortality. Indeed, protein metabolism may also be modified during the nondialysis days, and to some extent compensate for the dialysis-induced acute catabolic state. In more prolonged surveys, improvements in serum albumin and spontaneous food intake have been reported—but few studies were adequately designed and to date evidence only reaches a low grade. Thus, long-term randomized studies should address the potential effect of IDPN on nutritional status and morbidity/mortality of maintenance (MHD) patients. The ongoing FineS study (the largest prospective randomized controlled trial addressing the efficacy of oral and intradialytic nutritional support in malnourished MHD patients) may provide more useful information about indications and limits of nutritional support in these patients.

Indications for Intradialytic Parenteral Nutrition

The current available guidelines issued from the wave II European Best Practice work group recommend the following steps.

1. Oral and/or enteral feeding [nasogastric or percutaneous gastrostomy (PEG)] should be applied first, rather than any intravenous nutrition in a malnourished MHD patient.
2. When intensive dietary support, oral supplements, and enteral nutrition have failed to improve intake (and if nutritional status remains impaired), a course of IDPN may be proposed if spontaneous intake is greater than 20 kcal/kg IBW and 0.8 g protein/kg IBW per day.
3. IDPN (Ideal Body Weight) should not be proposed if the patient's spontaneous intake is lower than 20 kcal/kg IBW and 0.8 g protein/kg IBW per day. In that case, total parenteral nutrition infused over the entire day should be counseled.

Administration of Intradialytic Parenteral Nutrition

A typical solution for IDPN consists of a 1-L solution to be infused during the session. Usually, 250 mL of a 20% lipid emulsion (450 kcal), 500 mL of a 10% amino acid solution

(200 kcal), and 250 mL of 50% dextrose (450 kcal) are mixed. Recently, these solutions have been proposed in a three-in-one plastic bag ready to be mixed before the session and placed on the venous line of the hemodialysis circuit. A pump should be used to fine-tune the rate of infusion during the entire session to avoid hyperosmolarity and hypertriglyceridemia.

During the first week of IDPN treatment, the infusion rate might be set at 125 mL/hour—to be increased subsequently up to 250 mL/hour according to the patient's tolerance. The rate of infusion should not exceed 250 mL/hour so that serum lipid clearance is not saturated and symptoms such as nausea and vomiting due to hyertriglyceridemia are avoided. During the FineS study, decreasing the infusion rate to 125 mL/hour during 2 weeks in case of symptoms allowed their disappearance in most patients—after which the infusion rate of 250 mL/hour could be restored without subsequent reappearance of symptoms. An equivoluminous degree of ultrafiltration should be added to the regular ultrafiltration rate to maintain fluid balance. Because these solutions are usually poor in ions, sodium chloride can be added in an order of magnitude of 1 g/250 mL of solution—which corresponds to 1 g NaCl per hour.

Monitoring and Side Effects of Intradialytic Parenteral Nutrition

Nausea and vomiting were observed in 15 to 25% of patients of the randomized controlled FineS study. Usually, decreasing the infusion rate and reducing the total IDPN by half for 1 to 2 weeks allows to prescribe the previous infusion rate without return of symptoms. Intradialytic cramping may occur in rare cases of low plasma osmolality if sodium profiling is not used or available during the hemodialysis session. As already mentioned, sodium chloride should be added to the IDPN solution at 1 g NaCl per hour of infusion.

Glucose metabolism should be regularly checked during and at the end of the first session, and then weekly thereafter. Hyperglycemia (>300 mg/dL) can occur in response to the high glucose infusion rate, particularly in insulin-resistant patients. To prevent this, low doses of short-acting insulin should be administered (2 to 6 units)—which may in addition induce an anabolic response. On the contrary, some patients may experience postinfusion-reactive hypoglycemia in response to the lag action of endogenous insulin. In this particular case, IDPN should be stopped between 30 to 60 minutes before the end of the session.

Hypertriglyceridemia may occur when the IDPN solution contains lipids and the infusion rate is too high. In already dyslipidemic patients, this side effect may temporarily contraindicate the start of IDPN until pharmacologic treatment has corrected the lipid abnormality. Alternatively, IDPN not containing lipids may be used. Serum lipids and liver enzymes should be monitored monthly during the IDPN exposure. Monitoring of serum potassium and phosphate is required weekly at the start and during the first month (and then monthly) to prevent a plasma decrease in response to an anabolic state inducing a greater need of these compounds for cell synthesis.

Indications for Total Parenteral Nutrition

It is the authors' view that if a patient does not have a spontaneous intake greater than 20 kcal/kg or 0.8 g/kg per day an IDPN prescription would not fulfill his/her requirements and may even impair his/her care by falsely reassuring the dialysis staff. Thus, a PEG with continuous enteral support (or if this is not possible, a daily total parenteral nutrition (TPN)] should be prescribed. When a TPN is prescribed, the nutrient amounts should be increased to reach the patient's total daily requirements (see Chapter 17). In addition to IDPN, a continuous parenteral administration should cautiously include sodium, potassium, and magnesium (depending on the body's previous stores and demand)—as well as hydrosoluble vitamins and trace elements.

Recommended Reading

Bohe J, Rennie M. Muscle protein metabolism during haemodialysis. J Renal Nutr 2006;16:3–16.

This up-to-date review explores the regulation in protein metabolism and its specific alterations observed during maintenance hemodialysis, which potentially explain muscle wasting.

Chertow GM, Ling J, Lew NL, Lazarus JM, Lowrie EG. The association of intradialytic parenteral nutrition administration with survival in hemodialysis patients. Am J Kidney Dis 1994;24:912.

This study reports a retrospective analysis of the charts of 1600 National Medical Care hemodialysis patients who received IDPN, indicating that patients with low serum albumin (≥3.3 g/dL) had an improved survival.

Czekalski S, Hozejowski R. Intradialytic amino acids supplementation in hemodialysis patients with malnutrition: Results of a multicenter cohort study. J Ren Nutr 2004;14:82–88.

This prospective study reports the effects of a 6-month IDPN administration in 97 hemodialysis patients. The study showed an improvement in serum albumin, subjective global assessment, and anthropometry—with a dose-response trend.

Foulks CJ. An evidence-based evaluation of intradialytic parenteral nutrition. Am J Kidney Dis 1999;33:186–92.

This systematic review evaluates 24 clinical IDPN studies and calculates a "number needed to treat" and cost effectiveness of intradialytic parenteral nutrition. No firm recommendation for use could be done.

Hiroshige K, Iwamoto M, Kabashima N, Mutoh Y, Yuu K, Ohtani A. Prolonged use of intradialysis parenteral nutrition in elderly malnourished chronic haemodialysis patients. Nephrol Dial Transplant 1998;13:2081–87.

This study reports a prospective nonrandomized trial in 28 hemodialysis patients receiving IDPN for one year. The study showed improved body composition and nutritional biochemical parameters.

Mortelmans AK, Duym P, Vandenbroucke J, et al. Intradialytic parenteral nutrition in malnourished hemodialysis patients: A prospective long-term study. JPEN 1999;23:90–95.

This prospective study analyzes the impact of a 9-month IDPN treatment in 26 hemodialysis patients. The study showed an increase in body weight, fat mass, serum transferrin, and prealbumin. There were 10 drop-outs for intolerance when no sodium was added to the IDPN solution.

Navarro JF, Mora C, Leon C, et al. Amino acid losses during hemodialysis with polyacrylonitrile membranes: Effect of intradialytic amino acid supplementation on plasma amino acid concentrations and nutritional variables in nondiabetic patients. Am J Clin Nutr 2000;71:765.

This randomized study analyzes the effects of IDPN for 3 months in 17 hemodialysis patients and shows an improvement in plasma amino acids and serum albumin without improvement in nutritional status.

Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. J Clin Invest 2002;110:483–92.

This acute metabolic study shows in 7 patients that an intradialytic parenteral infusion of nutrients during the hemodialysis session strongly induces an anabolic response by increasing protein synthesis and decreasing protein degradation at local tissue and systemic levels.

Pupim LB, Flakoll PJ, Levenhagen DK, Ikizler TA. Exercise augments the acute anabolic effects of intradialytic parenteral nutrition in chronic hemodialysis patients. Am J Physiol Endocrinol Metab 2004;286:E589–97.

This acute metabolic study shows in 6 patients that a short pedaling exercise at the beginning of the hemodialysis session strongly improves the anabolic effect of an intradialytic parenteral infusion of nutrients.

Schulman G, Wingard RL, Hutchison RL, Lawrence P, Hakim RM. The effects of recombinant human growth hormone and intradialytic parenteral nutrition in malnourished hemodialysis patients. Am J Kidney Dis 1993;21:527–34.

This acute metabolic study shows an additional anabolic effect of a 6-week treatment with recombinant growth hormone to a 6-week intradialytic parenteral treatment in 7 malnourished hemodialysis patients.

Smolle KH, Kaufmann P, Holzer H, Druml W. Intradialytic parenteral nutrition in malnourished patients on chronic haemodialysis therapy. Nephrol Dial Transplant 1995;10:1411–16.

This prospective noncontrolled study reports the effects of an intradialytic amino acid infusion in 16 hemodialysis patients for 4 months, including improved biochemical nutritional parameters but no change in clinical parameters.

CHAPTER 54

Liver Disease in Dialysis Patients

Fabrizio Fabrizi, MD; Suphamai Bunnapradist, MD; and Paul Martin, MD

A variety of acute and chronic diseases of the liver (most notably viral hepatitis) may occur in patients on maintenance dialysis due to end-stage renal disease (ESRD) (Table 54.1). The most important causes of hepatitis in this population are chronic hepatitis B and C infection. The majority of dialysis literature on hepatitis refers to hemodialysis (HD) patients. Individuals on peritoneal dialysis (PD) are less prone to acquiring blood-borne infections for several reasons: there is no extracorporeal blood manipulation, patients on PD have had typically a lesser need for blood products, and PD takes place in the home (avoiding exposure to other patients).

Although the U.S. Renal Data System (USRDS) and the Lombardy Dialysis and Transplant Registry (RLDT) do not frequently list cirrhosis as a co-morbid condition (2%, USRDS; 1.5%, RLDT), the death rate for ESRD patients with cirrhosis is about 35% higher than the death rate for ESRD patients without (P = 0.03). It is probable that the time to recognition of major complications related to hepatitis B virus (HBV) and hepatitis C virus (HCV)—such as cirrhosis and hepatocellular carcinoma (HCC)—exceeds the life expectancy of the typical dialysis patient. However, as dialysis techniques and overall survival improve, the cumulative burden due to chronic viral hepatitis may become more apparent in this population. The most important cause of death in patients on maintenance dialysis remains cardiovascular. However, the overall risk of cancer is increased in dialysis when compared to the general population—and the higher frequency of HCC observed in dialysis patients may reflect the higher prevalence of chronic HCV and HBV infection.

Hepatitis B

HBV is a partially double-stranded compact DNA virus. HBV is spread by intimate and nonintimate contact as well as parenterally. It can be recovered from most body fluids and is relatively

Table 54–1

Liver Disease in Dialysis Patients

- Acute viral hepatitis (HAV, HBV, HCV, HEV)
- Chronic viral hepatitis (HBV, HCV)
- Steatohepatitis
- Drug hepatotoxicity
- Iron overload
- Congestive heart failure

hardy—permitting its survival outside the body and increasing its infectivity. Sexual contact and intravenous drug use are the most commonly identified modes of transmission in the adult population, whereas maternal-to-infant transmission helps perpetuate HBV infection in endemic areas such as Asia and sub-Saharan Africa. Acute HBV infection occurring in dialysis units implies lapses in precautions to avoid transmission.

Interpretation of Diagnostic Tests

Hepatitis B surface antigen (HBsAg) is the first HBV marker detectable in serum in acute infection. By the time clinical and biochemical hepatitis is present after an incubation period of up to 140 days, other serologic markers of HBV infection appear—including antibody to HBV core antigen (anti-HBc). Hepatitis B core antigen, a marker of viral replication found in infected hepatocytes, does not circulate in serum. However, its corresponding antibody (anti-HBc) does. Documented HBsAg positivity in serum for 6 or more months suggests chronic HBV with a low likelihood of subsequent spontaneous resolution. Chronic HBV is diagnosed by the absence of IgM anti-HBc.

IgM anti-HBc is a marker of acute or recent acute hepatitis B, and is detectable for 6 months after infection—whereas IgG anti-HBc is lifelong. If acute HBV resolves, neutralizing antibody against HBsAg (anti-HBs) develops. If HBV infection becomes chronic, other HBV markers—including HBV DNA and hepatitis e antigen (HBeAg)—should be sought. Both of these markers imply viral replication and thus greater infectivity, although any patient who is HBsAg positive is potentially infectious.

Natural History of HBV Infection in Dialysis Patients

HBV infection in dialysis patients is usually low grade, without marked elevation of serum aminotransferase activity. However, dialysis patients with acute HBV show a marked propensity to become chronically infected because of a relatively defective immune response due to chronic uremia. Impairment of cell-mediated immunity despite a normal number of T cells and an increased CD4:CD8 ratio has been recognized in this population. No significant difference in morbidity and mortality between HBsAg-positive and HBsAg-negative patients undergoing HD in the United States has been reported.

In contrast to renal transplant recipients with chronic HBV infection, there is no evidence of accelerated progression to decompensated cirrhosis or HCC. It is possible that a reluctance to perform liver biopsies in dialysis patients may underestimate the severity of liver disease due to HBV, particularly as serum aminotransferase elevation in chronic dialysis patients may be absent even in the face of significant histologic abnormality.

HBV in Dialysis Units

By the late 1960s, viral hepatitis had been recognized as an important issue in HD units. A significant decline in HBV incidence among HD patients and staff in North America and Europe was reported during the period 1974 to 1995, which was mostly attributable to implementation of the 1977 Centers for Disease Control and Prevention (CDC) isolation guidelines—as well as to screening blood products for HBsAg and anti-HBc. In addition, there was a decline in blood product requirements for dialysis patients because of the introduction of erythropoietin. Importantly, the major decline in HBV incidence and prevalence in the dialysis population occurred prior to the introduction of the HBV vaccine—highlighting the effectiveness of the CDC recommendations.

In 1985, the CDC also recommended (updated, 1988) adoption of standard barrier techniques; that is, universal precautions. Currently, both universal precautions and the following specific measures are recommended: monthly testing of patients for HBsAg; dedicated rooms, machines, instruments, medications, and supplies for HBV-infected patients; routine cleaning and disinfection procedures that include separate areas for clean and contaminated items; handling of blood specimens with gloved hands; and storage of specimens in areas removed from medication prep-

aration or central supply areas. The Dialysis Center Precautions may also prevent transmission to other pathogens, such as HCV and HIV.

Dialysate should be treated as infectious material and disposed of appropriately. Only staff with anti-HBs antibody, either naturally acquired or vaccine induced, should be assigned to HBsAg-positive patients. Those who lack anti-HBs should be assigned to HBsAg-negative individuals and should be strongly encouraged to receive vaccination. If the HBV antigen-antibody status of a patient is not yet established, the patient should be dialyzed in areas separate from other patients. Floors should be covered with surfaces that enable adequate cleaning. Smoking and eating within HD units should be prohibited. Machinery, floors, and utensils should be disinfected with formalin or with a solution containing bleach or glutaraldehyde. Staff should wear gowns and change them frequently, with a fresh pair of gloves used for each patient.

HBV Epidemiology in Dialysis Units

Current Status

The National Surveillance of Dialysis Associated Diseases in The United States, conducted by the CDC in 2002, reported a 1.0% mean prevalence of HBsAg seropositivity in dialysis patients—a figure that has not changed substantially during the past decade. Similarly, the incidence of HBV infection in patients also has not changed substantially during the past decade (and in 2002 was 0.12%). However, despite the marked decline in HBV incidence during the last three decades HBV outbreaks in HD units continue to be reported.

These outbreaks typically reflect a failure to perform and review HBsAg screening, as well as a lack of appropriate isolation of HBsAg-positive patients. Although ultimately vaccination programs offer the promise of eliminating HBV infection from North America and Western Europe, emigration from areas of the world where HBV remains highly prevalent will result in infected patients who develop ESRD entering the dialysis pool.

Treatment of HBV Infection

Two forms of antiviral therapy are currently available: the interferons and the oral nucleosides. Accepted indications for therapy are evidence of persistent viral replication with HBeAg positivity and elevated ALT levels in patients with chronic HBsAg carriage. Successful treatment may abort progression of liver disease. Particularly with interferon (INF) therapy, clearance of HBeAg

may be ultimately followed by loss of HBsAg—indicating complete resolution of HBV infection. INF has a less favorable side-effect profile and has had a diminished role in the treatment of HBV since the advent of the nucleoside analogues, which are potent inhibitors of viral replication with few side effects.

The more recent introduction of the pegylated interferons, which have greater potency and allow weekly administration, has rekindled interest in the use of INF in the ESRD population—at least for HCV. Recently, small and uncontrolled prospective clinical trials have demonstrated efficacy and safety with lamivudine therapy for HBV in dialysis patients—with ALT normalization and HBV DNA suppression in treated patients. A major limitation of lamivudine is a high rate of viral resistance. Several other oral agents have or will be licensed for the treatment of HBV, with differing potency and resistance profiles. Combination regimens of nucleoside analogues will be used in the future to enhance antiviral potency and to limit resistance. The preliminary nature of these data precludes definitive conclusions.

HBV Vaccination

Safe and effective vaccines that contain HBsAg, either plasma derived (since 1982) or manufactured by recombinant DNA technology (since 1986), are available. HBV vaccination is recommended for all susceptible dialysis patients. However, the major decline in HBV infection in HD units between 1976 and 1980 antedated availability of the vaccine. Chronic dialysis patients have a suboptimal response to vaccination compared to the general population. The rate of patients mounting anti-HBs titers with protective concentration (i.e., responders) is lower, anti-HBs antibody titers in responders are low and decline logarithmically over time. No significant difference has been found in the response rate between HD and PD patients.

In addition, a 2002 survey by the CDC indicates that the rate of dialysis patients who completed vaccination against HBV infection was only about 50%. A variety of approaches have been tried to enhance the response rate of HBV vaccination in dialysis patients, including administration of double or multiple doses, intradermal HBV vaccine, and use of adjuvants. It is reasonable to consider HBV vaccination in patients with chronic kidney disease (CKD) before they become dialysis dependent, given that the response rate is probably higher. Four doses (40 mcg each) of recombinant HBV vaccine administered by intramuscular route at months 0, 1, 2, and 6 are currently recommended in dialysis patients.

Hepatitis D

Hepatitis D virus (HDV), an RNA virus, requires HBV to complete its replicative cycle and does not occur in its absence. HDV infection may occur simultaneously with acute HBV infection (coinfection) or may be acquired later in the course of chronic HBV infection (superinfection). The clinical significance of HDV is an increased severity of clinical liver disease than that due to HBV infection alone. Unlike HBV, HDV is almost invariably associated with clinically important liver dysfunction.

Routine serologic diagnosis of HDV infection is currently based on the detection of circulating antibody to HDV antigen (anti-HDV). HDV is not a major problem in dialysis patients, although occasional cases have been reported. HDV infection should be mainly considered in any HBV-infected patient with rapidly deteriorating liver function. INF therapy is efficacious in at least some cases of delta hepatitis. The nucleoside analogues are not.

Hepatitis C

HCV is a single-stranded RNA virus. It is typically spread by parenteral routes and is significantly less infectious than HBV. Nonparenteral transmission of HCV is inefficient, and the important modes of transmission in the general population are transfusion and intravenous drug use. As will be discussed, there is also compelling evidence of HCV spread within HD units.

Interpretation of Diagnostic Tests

Diagnostic testing has evolved rapidly in the decade since identification of HCV, although concern remains about the lack of sensitivity of anti-HCV enzyme-linked immunosorbent assay (ELISA) serologic testing in ESRD patients. The recombinant immunoblot assay (RIBA), which has been used to improve specificity in anti-HCV-positive individuals, has been of most utility in low-risk populations such as blood donors. Direct detection of HCV RNA by polymerase chain reaction (PCR) may be necessary to confidently exclude HCV infection in ESRD patients.

A variety of PCR tests for HCV are available, varying in sensitivity and their ability to quantitate viral load. Improper collection, handling, and storage of samples may also impact test results. Quantitative PCR tests measure viral load, whereas the more sensitive qualitative tests can detect even low-level viremia. It is important to know whether the PCR test was quantitative or qualitative when interpreting the results obtained. Detection of

HCV RNA in a small but significant minority of ESRD patients, negative by routine serologic testing, implies that PCR testing should be obtained if there is concern about HCV infection despite negative serologies.

Aminotransferase elevations, which are typical of chronic HCV, are frequently absent in ESRD patients—which further confounds evaluation of possible HCV infection in this population. Thus, the absence of ALT elevation does not exclude HCV viremia. Chronic HCV infection has a typically indolent progression to cirrhosis, and most patients (even in the normal renal function population) die due of cirrhosis rather than of HCV-related liver disease. As the natural history of HCV evolves over decades rather than years, the adverse consequences of chronic HCV infection may not be apparent in a population with ESRD who have a high attrition rate from nonhepatic diseases.

HCV Epidemiology in the Dialysis Population

A large number of studies in dialysis patients have confirmed a high prevalence of HCV infection. The major risk factors for HCV acquisition have been cumulative time on dialysis and the number of blood transfusions. Anti-HCV screening of blood products has virtually eliminated the latter risk of HCV acquisition. Furthermore, erythropoietin use has lowered blood product requirements in ESRD patients. After the initial decline of HCV incidence in HD patients related to blood transfusions, the subsequent reduction in HCV spread in some but not all units likely reflects the implementation of infection control procedures within HD units.

Clinical Course of HCV Infection

HCV infection is frequently subclinical, with fluctuating serum aminotransferases—although more marked ALT elevations may occur at the time of initial HCV acquisition. ALT levels are abnormally low in most patients on dialysis, and chronic HCV infection may not be associated with biochemical dysfunction—although histologic injury may be present. However, HCV plays an important role in the pathogenesis of liver disease in dialysis patients. Liver biopsy is still the only reliable method of assessing the severity of liver disease in most dialysis patients with HCV. This is because even cirrhosis may be present with minimal biochemical dysfunction. Serum markers of fibrosis are currently undergoing evaluation but have not replaced liver biopsy.

Strategies to Control HCV Transmission in Dialysis Units

Unlike HBV, the CDC has not recommended to date rigorous segregation for HCV-infected HD patients—reflecting in part the lower infectivity of HCV. HCV is present in minute quantities in circulating blood and is rapidly degraded outside the body. Inoculation of an HCV-infected patient with a different or even the same strain of virus results in a fresh bout of hepatitis. The latter observation suggests that use of dedicated machines for HCV-infected patients should not be a cornerstone of limiting spread.

The CDC currently recommends monthly monitoring of serum aminotransferase activity. Quarterly monitoring of transaminase values in PD patients has been suggested. Routine anti-HCV screening of HD patients is indicated only for epidemiologic purposes after a baseline antibody test is obtained. Strict adherence to universal precautions and sterilization of dialysis machines is recommended for preventing HCV spread in HD units and appears to eliminate spread of HCV in these circumstances.

Therapy

IFN is the mainstay of treatment for HCV. It exhibits a variety of antiviral, immunomodulatory, and antiproliferative activities. Tolerance to initial monotherapy with standard IFN appears to be lower in dialysis than nonuremic patients with chronic HCV infection. However, more than 1/3 of dialysis patients with HCV have been successfully treated with IFN with sustained clearance of circulating HCV RNA. Ribavirin is a synthetic guanosine analogue with activity against many viruses. It enhances a sustained IFN response rate in HCV therapy.

There has been an understandable reluctance to use ribavirin in dialysis patients because of concern about its major side effect (hemolytic anemia) in this population with baseline anemia—particularly as ribavirin and its metabolites are not removed by dialysis. Preliminary small-scale studies, however, suggest that with marked dose reduction and careful monitoring of the hematocrit it may be feasible to use ribavirin in CKD to enhance response rates to INF regimens. As noted previously, the pegylated interferons have now entered clinical practice—although they have not yet been widely studied in the CKD population.

The decision to treat a patient with chronic HCV infection in the absence of CKD is generally based on histologic determination of disease severity and viral factors such as genotype. Patient age, co-morbidities, likely tolerance to side effects, and similar criteria

are also appropriate considerations in the patient with and without renal insufficiency. Effective therapy for hepatitis C in CKD patients is an important goal—made more important by the poor prospect for an effective vaccine against HCV.

Nonviral Hepatitis-Related Hepatic Dysfunction

Almost any drug has the potential for hepatoxicity. In general, there is no evidence that chronic dialysis patients are more prone to hepatoxicity than normal individuals. However, drug interactions may play a role in the pathogenesis of drug-induced liver disease in this population because patients on maintenance dialysis usually receive multiple medications. The widely used nonsteroidal anti-inflammatory drugs infrequently cause hepatic injury. Allopurinol and anabolic steroids may be hepatotoxic in patients with renal failure.

Numerous antibiotics can produce hepatic dysfunction. Some cardiovascular medications are hepatotoxic, including amiodarone. Monitoring of aminotransferase activity using HMG-CoA reductase inhibitors is recommended during treatment of hypercholesterolemia. Body aluminium overload due to prolonged exposure to aluminium containing medications such as aluminium hydroxide can be associated with hepatic dysfunction. The diagnosis of drug-induced hepatotoxicity is one of exclusion. Other potential causes of obscure hepatic dysfunction in this population include hepatic congestion due to heart failure and steatosis due to poorly controlled diabetes mellitus, obesity, and hyperlipidemia. In addition, given the widespread availability of herbs and other nonprescription products to patients who may fail to report their use, a careful medical history is crucial.

In HD patients, iron overload due to multiple transfusions has been reported. Its frequency has probably decreased with the advent of erythropoietin treatment (Table 54.2). Before the intro-

Table 54–2

Approach to Hepatic Dysfunction

- Exclude viral hepatitis (anti-HCV, HBsAg, HAV IgM, HEV IgM)
- Review medication use (including herbal products)
- Evaluate for cardiac dysfunction
- Obtain iron indices
- Consider liver biopsy

duction of erythropoietin, hepatic iron overload occurred in multiply transfused patients with CKD. Although iron overload in this circumstance does not typically cause clinical liver disease, it does require differentiation from primary hemochromatosis by genetic testing hepatic iron quantification.

Conclusions

Liver disease remains an important cause of morbidity and mortality in patients on chronic dialysis. The most common cause of dialysis-associated liver disease is viral hepatitis, which is more frequent in HD than PD patients. As life expectancy in chronic dialysis patients increases, the cumulative burden due to chronic viral hepatitis may be more apparent in this population. Already there is evidence that patients with chronic HCV, as well as HBV, have a poorer prognosis following renal transplantation due to accelerated progression of liver disease. Although control measures have significantly limited HBV spread within HD units, HCV remains frequent in this population. Strict adherence to the spread of blood-borne pathogens is necessary to limit HCV's spread.

Recommended Reading

Bruchfeld A, Lindahl K, Reichard O, Carlsson T, Schvarcz R. Pegylated interferon and ribavirin C in haemodialysis patients. Nephrol Dial Transplant 2006;doi:10.1093/ndt/gfl072.

The first report on combination therapy (pegylated-IFN plus ribavirin) in haemodialysis patients.

Fabrizi F, Dulai G, Dixit D, Martin P. Meta-analysis: Interferon for the treatment of chronic hepatitis C in dialysis patients. Aliment Pharmacol Ther 2003;18:1071–81.

Systematic review of efficacy and safety of initial monotherapy with standard IFN for chronic hepatitis C in the dialysis population.

Jadoul M, Cornu C, van Ypersele de Strihou C for the Universitaires Cliniques St-Luc (UCL) Collaborative Group. Universal precautions prevent hepatitis C virus transmission: A 54-month follow-up of the Belgian Multicenter Study. Kidney Int 1998;53:1022–25.

Emphasizes the importance of measures to prevent hepatitis C transmission within hemodialysis units.

Kalantar-Zadeh K, McAllister CJ, Miller LG. Clinical characteristics and mortality in hepatitis C-positive haemodialysis patients: A population based study. Nephrol Dial Transplant 2005;20:1662–69.

Describes impact of hepatitis C on survival in chronic hemodialysis patients.

Kellerman S, Alter MJ. Preventing hepatitis B and hepatitis C virus infections in end-stage renal disease patients: Back to basics [editorial comment]. Hepatology 1999;29:257–63.

A succinct overview of control of hepatitis in dialysis units.

Marcelli D, Stanhard D, Conte F, et al. ESRD patient mortality with adjustment for comorbid conditions in Lombardy (Italy) versus the United States. Kidney Int 1996;50:1013–18.
Reports on the epidemiology and clinical impact of cirrhosis in dialysis population.
Martin P, Carter D, Fabrizi F, et al. Histopathological features of hepatitis C in renal transplant candidates. Transplantation 2000;69:1479–84.
Highlights the role of liver biopsy in the evaluation of hepatitis C in renal transplant candidates.
Russo MW, Ghalib R, Sigal S, et al. Randomized trial of pegylated interferon alpha-2b monotherapy in haemodialysis patients with chronic hepatitis C. Nephrol Dial Transplant 2006;21:437–43.
Reports a poor safety profile of pegylated IFN in the dialysis population.

CHAPTER 55

Ascites in Dialysis Patients

Alf M. Tannenberg, MD

The incidence of ascites in chronic hemodialysis patients, sometimes referred to as nephrogenic ascites, is probably <5% and appears to be declining. Over the last decade, better volume control has been achieved in chronic hemodialysis patients—perhaps due to several factors, including better overall nutrition, more biocompatible dialysis membranes, and better volumetric control of ultrafiltration. However, when the problem occurs it presents both a diagnostic and therapeutic challenge.

Chronic hemodialysis patients with ascites may be divided into two groups based on the underlying causes of the ascites (Table 55.1). In one group of patients, a known cause of ascites irrespective of the renal functional status can be identified. The other group has idiopathic dialysis ascites uniquely related to end-stage renal disease (ESRD) or to chronic hemodialysis. Although etiologic factors cannot be identified in idiopathic ascites, pathophysiologic factors associated with it include uremic syndrome, chronic hyperparathyroidism, fluid overload states, compartmentalization (osmotic dysequilibrium) syndrome, and hypoproteinemic syndrome.

The pathophysiology of ascites formation is not discussed here. However, note that the peritoneal membrane vasculature and lymphatics normally constitute an efficient and complex solute delivery and removal system. In particular, the peritoneal lymphatics serve a very important function by acting as a one-way convective drainage system out of the peritoneal cavity for fluid, cells, and macromolecules. This lymphatic system is normally the primary avenue for removing excess intraperitoneal fluid and returning it to the systemic circulation.

Diagnostic Evaluation

In chronic hemodialysis patients with ascites, the cause of the ascites may be found in up to 15% of cases. To determine the possible etiology of the ascites, evaluation of the ascitic fluid through paracentesis or at laparoscopy is essential (Figure 55.1). The initial differentiation between ascitic fluid transudates and exudates is of the utmost importance. This differentiation is made by comparing the levels of serum and ascites albumin and total protein

Table 55–1

Causes of Ascites in Dialysis Patients

Nonrenal
- Cirrhosis with portal hypertension
- Budd-Chiari syndrome
- Inferior vena cava compression
- Congestive heart failure
- Tricuspid insufficiency
- Constrictive pericarditis
- Nephrotic syndrome
- Hypothyroidism
- Pancreatitis
- Tuberculous peritonitis
- Peritoneal malignancy

Renal
- Idiopathic dialysis ascites

obtained at approximately the same time by venipuncture and paracentesis or at laparoscopy. In addition, diagnostic paracentesis or laparoscopy allows for cultures (tubercular, fungi, predominant organisms), cytologic studies for malignancy, biochemical determinations (amylase, lipase, lactic dehydrogenase), and cell counts.

Typically, the ascitic fluid is straw colored and shows exudative characteristics. Useful physiologic measures suggestive of exudative ascites are noted in Table 55.2. Establishing the exudative characteristics of the ascites narrows the etiologic possibilities to tuberculous peritonitis, pancreatitis, malignancy, and idiopathic dialysis ascites.

To determine the role of dialysis osmotic disequilibrium in dialysis ascites formation, the diagnostic paracentesis is made immediately before the start of a hemodialysis session. An 18-gauge plastic catheter is placed in the peritoneal cavity through a paracentesis needle. This catheter is left in place until postdialysis ascitic fluid sampling has been completed. The catheter is then removed. In this way, ascitic fluid may be sampled immediately before and after hemodialysis. By measuring the osmolality at these times in the serum and ascitic fluid, one can determine whether osmotic disequilibrium is a factor in ascites formation. The characteristic finding in this type of disequilibrium is an ascitic fluid–serum osmotic gradient difference of at least 12 mOsm/kg at the end of 4 hours of hemodialysis.

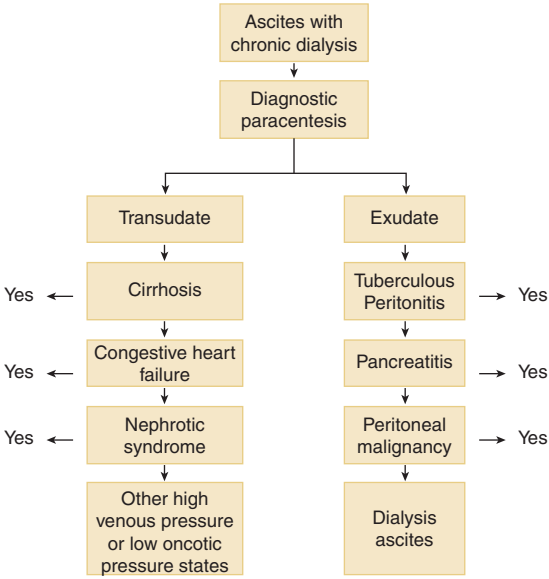


Figure 55–1

Diagnostic algorithim for ascites.

Table 55–2

Ascite Exudative Characteristics

- Ascites total protein ≥ 3 g/dL
- Serum albumin – ascetic albumin ≤ 0.9 g/dL
- Ascites total protein – serum total protein ≥ 0.72

If the ascitic fluid is a transudate, the etiologies listed in Table 55.3 must be considered. Along with the usual diagnostic methods, ultrasound and computed tomography are helpful imaging tools for many of the known causes of ascites. When available, laparoscopy (peritoneoscopy) is invaluable in the evaluation of chronic hemodialysis ascites—especially in the diagnosis of cirrhosis, tuberculous peritonitis, peritoneal malignancies, and pancreatitis. As

Table 55–3

Etiology of Ascitic Transudates

	Low Oncotic Pressure	High Venous Pressure
Cirrhosis	X	X
Budd-Chiari Syndrome		X
Inferior vena caval compression		X
Congestive Heart Failure		X
Constrictive pericarditis		X
Tricuspid insufficiency		X
Nephrotic syndrome	X	

the algorithm in Figure 56.1 illustrates, the diagnosis of idiopathic dialysis ascites is a diagnosis of exclusion when exudative ascites has been established.

Treatment of Dialysis Ascites

If a specific etiology has been determined for the chronic dialysis ascites, treating or eliminating that cause will likewise treat the ascites. For idiopathic dialysis ascites, various treatment modalities may be tried (Table 55.4). Ascitic fluid reinfusion and peritoneal-venous shunting are two approaches that have been used successfully to control ascites formation. Their virtue is the conservation of ascitic fluid proteins. Because reinfusion techniques are technically cumbersome, they are used only sporadically. Peritoneal-venous shunting techniques provide continuous reinfusion of ascites directly into the venous circulation by way of a one-way valve.

Examples of this type of approach are the LeVeen, Denver, and Minnesota shunts. Shunting techniques are best used at institutions that are experienced in their use so that the side effects associated with shunts can be minimized. Other therapeutic modalities that have been tried for the treatment of chronic dialysis ascites include intraperitoneal steroids, bilateral nephrectomy, laparotomy, and intermittent paracentesis. Overall results, however, have been so disappointing with these treatments that they are rarely used. From a practical viewpoint, there are three possible approaches to therapy for idiopathic dialysis ascites. These are discussed in the sections that follow.

Table 55–4

Treatment Modalities for Idiopathic Dialysis Ascites

Treatment Modality	Response
Fluid restriction with intensive Hemodialysis and ultrafiltration	Fair
Ascitic fluid reinfusion	Variable
Peritoneal-venous shunts	Variable
Peritoneal dialysis	Good
Renal transplantation	Excellent

Aggressive Fluid Management with Frequent Hemodialysis and Ultrafiltration

The first approach is aggressive fluid management with sodium and water restriction, coupled with frequent hemodialysis and isolated ultrafiltration—with up to five or six treatments per week for several weeks. Peripheral fluid overload is much more easily corrected by this method than by standard hemodialysis, although hypotension is a frequent limiting factor. When technically possible, this approach may be coupled with ascitic fluid reinfusion techniques or with peritoneal-venous shunts.

Peritoneal Dialysis

If the first approach is unsuccessful, the next approach is some form of peritoneal dialysis. Peritoneal dialysis usually successfully mobilizes ascitic fluid. Peritoneal dialysis may be used either temporarily or as a permanent dialytic modality instead of hemodialysis. It must be remembered, however, that if hypoalbuminemia is present peritonaeal dialysis may aggravate this condition. When using peritoneal dialysis to remove and eliminate ascitic fluid, the focus should be on gradual elimination of ascites irrespective of the mode of peritoneal dialysis used. Thus, each peritoneal dialysis cycle should drain only 500 to 1000 mL more fluid than was infused. This eliminates the possibility of hypotension secondary to sudden complete drainage of ascitic fluid. In addition, at the end of the procedure an abdominal binder should be placed for about a week.

The type of peritoneal dialysis employed is not critical. An acute peritoneal dialysis catheter may be placed intermittently on a weekly basis for 2 or 3 weeks if it is planned to continue with

chronic hemodialysis thereafter. If acute intermittent peritoneal dialysis is used, the one caveat is to ensure that all the ascites is drained and that all excess fluid in the form of edema is removed—using hypertonic dialysate if necessary to accomplish this end. If the patient is to be permanently placed on peritoneal dialysis, any of the chronic peritoneal dialysis modalities (such as intermittent peritoneal dialysis, continuous cycling peritoneal dialysis, and continuous ambulatory peritoneal dialysis) may be used successfully to permanently control ascites.

Transplantation

Renal transplantation is the most effective form of therapy for chronic idiopathic dialysis ascites, with a success rate approaching 100%. However, not all patients with dialysis ascites are willing to accept a kidney transplant—and in some cases there may be medical contraindications to transplantation. Initially, the appearance of ascites in chronic hemodialysis patients was believed to indicate an extremely poor prognosis. Today, however, the prognosis with the various treatment modalities available is certainly much better than was reported in the early 1970s and 1980s.

Recommended Reading

Liver Disease in Dialysis Patients

Caramelo C, Albalate M, Bermejillo T, et al. Relationships between plasma ferritin and aminotransferase profile in hemodialysis patients with hepatitis C virus. Nephrol Dial Transplant 1996;11:1792–96.

Highlights altered iron indices in patients with hepatitis C on hemodialysis.

Jadoul M, Cornu C, van ypersele de Strihou C for the Universitaires Cliniques St-Luc (UCL) Collaborative Group. Universal precautions prevent hepatitis C virus transmission: A 54-month follow-up of the Belgian Multicenter Study. Kidney Int 1998;53:1022–25.

Emphasizes the importance of measures to prevent hepatitis C transmission within hemodialysis units.

Kellerman S, Alter MJ. Preventing hepatitis B and hepatitis C virus infections in end-stage renal disease patients: Back to basics [editorial comment]. Hepatology 1999;29:257–63.

A succinct overview of control of hepatitis in dialysis units.

Martin P, Carter D, Fabrizi F, et al. Histopathological features of hepatitis C in renal transplant candidates. Transplantation 2000;69:1236–37.

Highlights the role of liver biopsy in the evaluation of hepatitis C prior to renal transplantation.

Stehman-Breen CO, Emerson S, Gretch D, Johnson RJ. Risk of death among chronic dialysis patients infected with hepatitis C virus. Am J Kidney Dis 1998;32:629–34.

Describes the impact of hepatitis C in chronic hemodialysis patients.

Ascites in Dialysis Patients

Gluck Z, Nolph KD. Ascites associated with end-stage renal disease. Am J Kidney Dis 1987;10:9–18.
A broad-based review of the subject.
Han SH, Reynolds TB, Fong TL. Nephrogenic ascites. Medicine 1998;77:233–45.
Recent review of 16 cases with literature review.
Mauk PM, Schwartz JT, Lowe JE, et al. Diagnosis and course of nephrogenic ascites. Arch Intern Med 1998;148:1577–79.
Emphasizes the role of peritoneoscopy as a diagnostic tool in dialysis ascites.
Tannenberg AM. Ascites in chronic hemodialysis. Semin Dial 1990;3:240–44.
An in-depth review of the subject.

CHAPTER 56

Care of the HIV-Infected Dialysis Patient

Rudolph A. Rodriguez, MD

Between 1995 and 2000 the number of prevalent cases of end-stage renal disease (ESRD) in patients with HIV infection doubled in the United States. This increase in prevalence was mainly due to an increase in survival among ESRD patients with HIV infection. The incidence of ESRD in patients with HIV infection remained largely unchanged during this period. With African Americans comprising 87% of the patients with ESRD and HIV infection, the incidence of ESRD among this population is not likely to fall given that HIV infection rates are rising in the African American community. HIV-associated nephropathy (HIVAN) has become the third leading cause of ESRD among African Americans aged 20 to 64.

The HIV-infected ESRD patient provides specific medical and logistic challenges to dialysis care providers. Hemodialysis, peritoneal dialysis, and transplantation are options for these patients—and each modality has advantages and disadvantages, with no treatment showing a survival advantage in HIV-infected patients. In addition, some facilities with less familiarity with HIV-infected ESRD patients may fear the risks to dialysis personnel. Guidelines for the management of chronic kidney disease in HIV-infected patients and recommendations of the HIV Medicine Association of the Infectious Diseases Society of America have now been published in *Clinical Infectious Diseases* to help with the management of these complicated patients (see Recommended Reading section).

Improved Survival of the HIV-Infected ESRD Patient

Early data from the 1980s showed that newly diagnosed patients with ESRD and AIDS were dying on average 1 to 3 months after starting hemodialysis. Based on this observation, some nephrologists argued that dialysis should be restricted in this population. However, these early studies predominantly included patients late in the course of the HIV disease and with advanced opportunistic infections. Present-day early detection, treatment, and prophylaxis

of HIV infection and opportunistic infections have led to improvements in the survival in HIV patients. The survival for ESRD patients with HIV infection has also improved, with a median survival of approximately 2 years.

Data from the United States Renal Data System has shown a steady increase in survival among ESRD patients with HIV infection since the advent of the highly active antiretroviral therapy (HAART) in the mid to late 1990s. Both CD4 count and serum albumin at the initiation of chronic dialysis seem to be strong determinants of survival in these patients. Currently there is no reason to withhold renal replacement therapy solely on the basis of HIV infection.

Hemodialysis Issues

Dialysis Vascular Access

The most common renal replacement modality used in HIV-infected patients is hemodialysis. The potential disadvantages of hemodialysis include the risk of infections from temporary catheters and grafts, and the potential risk of blood exposure and needle-stick injuries to dialysis providers. Patency rates for prosthetic grafts are lower in HIV-infected ESRD patients compared to HIV-negative patients, whereas patency rates are not different for native arteriovenous fistulas in these two groups of patients. Not surprisingly, infection rates are seen at a higher rate in HIV infected patients with prosthetic grafts than with native arteriovenous fistulas.

Because the progression of HIVAN to ESRD is typically quite rapid, HIV-infected patients with chronic kidney disease should be referred to a nephrologist early—and all possible efforts should be made for early surgical placement of a native arteriovenous fistula. Although HIV-infected patients do appear to be at increased risk for Gram-negative catheter infections, they do not appear to have a higher overall risk of infection from tunneled dialysis catheters compared to other ESRD patients. Therefore, native arteriovenous fistulas should be placed despite the need for a tunnel dialysis catheter.

Infection Control in Hemodialysis

The Centers for Disease Control guidelines for providing dialysis treatments to HIV-infected individuals emphasize careful adherence to universal body substance precautions, which is the only required

safeguard that must be followed by dialysis providers treating HIV-infected ESRD patients. Unlike hepatitis B virus-infected ESRD patients, HIV-infected ESRD patients do not require special isolation procedures during dialysis—and dialyzer-reuse programs may include HIV-infected patients. Although it is unlikely that HIV infection could be transmitted by the use of a reused dialyzer from an HIV-infected individual used mistakenly on a non HIV-positive patient, a policy of nonreuse among HIV-infected patients could eliminate this remote possibility. Routine infection-control precautions such as blood precautions, routine sodium hypochlorite cleaning of dialysis equipment and surfaces that are frequently touched, and restriction of nondisposable supplies to individual patients are sufficient in HIV-infected patients on hemodialysis. Unnecessary precautions such as isolation of HIV-infected patients from other patients could violate the medical confidentiality of the patient.

Providing hemodialysis to HIV-infected patients carries the potential risk of exposure to contaminated blood or needles to dialysis personnel and other patients. A tragic incident occurred in Columbia, South America, where nine hemodialysis patients were infected with HIV. Improperly reprocessed patient care equipment was the likely mode of transmission. This incident highlights the fact that strict guidelines to universal precautions and common sense must be enforced in all dialysis units due to HIV and other blood-borne pathogens. To date there have not been cases reported of HIV transmission among ESRD patients in the United States.

All dialysis care personnel should take precautions against needle-stick injuries, including barrier precautions such as wearing gloves. Such injuries constitute the major potential risk for HIV transmission to personnel. The current regulations of the Division of Occupational Safety and Health (OSHA) state that needleless systems should be in place. This regulation requires needleless systems for withdrawal of blood once venous access is established and for administration of medications and fluids. If needleless systems are not used, needles with injury-protection devices should be used.

Dialysis staff that receive a needle stick or are exposed to HIV-contaminated blood or other body fluids should be immediately referred to a hotline or a medical provider experienced in dealing with blood-borne pathogen exposure. The size of the HIV particle is much larger than most dialyzer membrane pore sizes, making it unlikely to cross the dialyzer membrane into the dialysate or ultrafiltrate. Despite noting a small decrease in plasma HIV RNA levels pre- versus posthemodialysis, one study could not measure

HIV RNA in the ultrafiltrate of 10 HIV-infected hemodialysis patients. However, there are few data on the presence of HIV in dialysate—especially in regard to reused dialyzers. Despite this lack of evidence, dialysate should be treated as potentially contaminated body fluid.

Peritoneal Dialysis

There are advantages and disadvantages to offering peritoneal dialysis to HIV-infected patients. The potential exposure by contaminated blood or needles to dialysis personnel is obviously not present with peritoneal dialysis. On the other hand, peritoneal protein losses in malnourished HIV patients and severe peritonitis are potential concerns in this population. The incidence and spectrum of peritonitis has been reported in several small series of HIV-infected patients.

One study of 39 HIV-infected ESRD patients on CAPD confirmed that HIV-infected patients have a higher overall risk of peritonitis and are more likely to have peritonitis attributed to *Pseudomonas sp.* and fungi than other ESRD patients. However, it is likely that the higher peritonitis rate is not due to HIV infection itself but to confounding variables such as low socioeconomic status and intravenous drug use. These studies suggest that peritoneal dialysis compares favorably with hemodialysis in HIV-infected patients, with comparable patient survival and very few reports of peritoneal dialysis technique failure.

HIV has been identified in peritoneal dialysate fluid and it should be handled as contaminated body fluid. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet, and to dispose of dialysate bags and lines by placing and tying them in plastic bags and disposing of the plastic bags into conventional home trash systems.

Transplantation

Kidney transplantation is available for HIV-infected ESRD patients through a National Institute of Allergy and Infectious Diseases sponsored clinical trial or as part of routine care at several transplant centers in the United States (*http://www.clinicaltrials.gov/ct/show/NCT00074386*). Transplantation was once thought to be risky in this population due to the potential risks of immunosuppression in the context of HIV infection. However, as mentioned previously HAART has led to improved survival in ESRD patients with HIV infection—and interestingly some immunosup-

pressive agents commonly used in transplantation may have a beneficial impact on patients with HIV infection.

Preliminary evidence from several kidney transplant centers suggest that patient and graft survival in HIV-infected ESRD patients are similar to other high-risk populations, and immunosuppression has not led to rapid progression of HIV infection or to unexpected reductions in CD4 counts. In addition, one study reviewed data from the United Network for Organ Sharing kidney transplant data between 1997 and 2004 and compared graft and patient survival of 38 HIV patients to 38 non HIV-infected recipients who had received a graft from the same donor. Graft and patient survival was not statistically different among HIV-infected patients compared with their HIV-negative controls. There now seems to be sufficient evidence to discount any ethical questions surrounding the use of kidneys for HIV-infected patients.

Medical Management

Dialysis Care

The National Kidney Foundation–Dialysis Outcome Quality Initiative (NKF-K/DOQI) recommendations should be followed for HIV-infected patients with ESRD. As noted previously, native arteriovenous fistulas are preferred in these patients in order to reduce the incidence of catheter and graft infections. The goals for Kt/V, renal osteodystrophy and anemia management, and vascular access monitoring should be followed as outlined in the NKF-K/DOQI recommendations.

Considerable confusion exists in the use of recombinant human erythropoietin (rHuEPO) in HIV-infected patients with chronic kidney disease. Based on limited data, HIV medical providers currently use rHuEPO in anemic HIV-infected patients without chronic kidney disease. In HIV-infected patients without renal disease and baseline endogenous serum erythropoietin level <500 mU/mL, a dose of 40,000 units subcutaneously per week is commonly used in these patients when Hg level is below 12 g/dL. However, HIV-infected patients with chronic kidney disease and anemia should be treated according to established clinical practice in patients with chronic kidney disease. HIV-infected patients with chronic kidney disease respond to rHuEPO in a similar manner to patients with chronic kidney disease without HIV infection. For example, one study compared the response to 100 units/kg given three times a week in a group of HIV-infected patients versus non–

Table 56–1

Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis

Nucleoside/Nucleotide Analogues

Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis			References
Abacavir	300 mg PO BID	Dose adjustment for renal insufficiency does not appear necessary			(1), Ziagen package insert 9/05
Didanosine (enteric-coated capsules)	250 mg to 400 mg PO QD, depending on wt	ClCr (mL/min)	Wt ≥60 kg	Wt <60 kg	(2, 3), Videx EC package insert 10/05
		≥60	400 mg QD	250 mg QD	
		30–59	200 mg QD	125 mg QD	
		10–29	125 mg QD	125 mg QD	
		<10	125 mg QD	125 mg QD	
		HD	125 mg QD	125 mg QD	
Emtricitabine	200 mg PO QD	ClCr (mL/min)			Emtriva package insert 9/05
		≥50	200 mg QD		
		30–49	200 mg Q 48 H		
		15–29	200 mg Q 72 H		
		<15	200 mg PO Q 96 H		
		HD	200 mg Q 96 H, give dose after dialysis		

Table 56–1

Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis —Cont'd

Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis			References
Lamivudine	150 mg PO BID or 300 mg PO QD	ClCr (mL/min)			(4–6), Epivir package insert 11/05
		≥50	150 mg BID or 300 mg QD		
		30–49	150 mg QD		
		15–29	150 mg first dose, then 100 mg QD		
		5–14	150 mg first dose, then 50 mg QD		
		<5	insufficient data, consider 150 mg first dose, then 25 mg QD		
Stavudine	20 mg to 40 mg PO BID, depending on wt	ClCr (mL/min)	Wt >=60 kg	Wt <60 kg	(7), Zerit package insert 9/05
		>50	40 mg BID	30 mg BID	
		26-50	20 mg BID	15 mg BID	
		10-25	20 mg QD	15 mg QD	
		HD	20 mg QD	15 mg QD	

Table Continued

Table 56–1

Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis —Cont'd

Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis		References
Tenofovir	300 mg PO QD	Experience in patients with ClCr <60 mL/min is limited. Preliminary data suggest:		(8), Viread package insert 3/06
		ClCr (mL/min)		
		>=50	300 mg QD	
		30-49	300 mg Q 48 H	
		10-29	300 mg twice weekly (ie, Q 3-4 days)	
		HD	300 mg QW	
Zidovudine	300 mg PO BID	ClCr (mL/min)		(9,10,11), Retrovir package insert 9/05
		<15	100 mg TID	
		HD	100 mg TID	

Table 56–1

Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis —Cont'd

Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis	References
Fixed-Dose Combinations			
Combivir (zidovudine/lamivudine)	1 tab PO BID	Substitute component drugs, dose adjusting each drug for ClCr	Combivir package insert 11/05
Epzicom or Kivexa (abacavir/lamivudine)	1 tab PO QD	Substitute component drugs, dose adjusting each drug for ClCr	Epzicom package insert 11/05
Trizivir (zidovudine/lamivudine/abacavir)	1 tab PO BID	Substitute component drugs, dose adjusting each drug for ClCr	Trizivir package insert 11/05
Truvada (emtricitabine/tenofovir)	1 tab PO QD	ClCr (mL/min) ≥50 1 tab QD 30–49 1 tab Q 48 H <30 Substitute component drugs, dose adjusting each drug for ClCr	Truvada package insert 11/05
Non-nucleoside Reverse Transcriptase Inhibitors			
Delavirdine	400 mg PO TID	Dose adjustment for renal insufficiency does not appear necessary	Rescriptor package insert 6/01
Efavirenz	600 mg PO QHS	Dose adjustment for renal insufficiency does not appear necessary	Sustiva package insert 4/05
Nevirapine	200 mg PO BID	Dose adjustment for renal insufficiency does not appear necessary	(12–14), Viramune package insert 11/05

Table Continued

Table 56–1

osing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis —Cont'd

Protease Inhibitors Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis	References
Amprenavir	As of June of 2005, no longer manufactured for adult dosing; consider fosamprenavir.	—	—
Atazanavir	400 mg PO QD, or 300 mg PO QD with ritonavir 100 mg PO QD	Dose adjustment for renal insufficiency does not appear necessary	Reyataz package insert 1/06
Darunavir	600 mg PO BID with ritonavir 100 mg PO BID	Dose adjustment for renal insufficiency does not appear necessary	Prezista package insert 7/06
Fosamprenavir	1400 mg PO QD, or 1400 mg PO QD with 200 mg ritonavir PO QD, or 700 mg PO BID with ritonavir 100 mg PO BID	Dose adjustment for renal insufficiency does not appear necessary	Lexiva package insert 11/05
Indinavir	800 mg PO Q 8 H	Dose adjustment for renal insufficiency does not appear necessary	(15–16), Crixivan package insert 10/05
Lopinavir/Ritonavir	400 mg/100 mg (2 tablets) PO BID	Dose adjustment for renal insufficiency does not appear necessary	(17), Kaletra package insert 10/05

Table 56–1

Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis —Cont'd

Drug	Standard Dosage	Dosing in Renal Insufficiency and Hemodialysis	References
Nelfinavir	1250 mg PO BID	Dose adjustment for renal insufficiency does not appear necessary	(14, 18, 19), Viracept package insert 9/04
Ritonavir	600 mg PO BID (as a single PI); 100 mg or 200 mg, QD or BID (in combination with other PIs)	Dose adjustment for renal insufficiency does not appear necessary	(12), Norvir package insert 1/05
Saquinavir (hard-gel capsules or tablets)	1000 mg PO BID with 100 mg ritonavir PO BID (should not be used as sole PI; must be boosted with ritonavir)	Dose adjustment for renal insufficiency does not appear necessary	(20), Invirase package insert 9/05; Norvir package insert 1/05
Tipranavir	500 mg PO BID with 200 mg ritonavir PO BID (should not be used as sole PI; must be boosted with ritonavir)	Dose adjustment for renal insufficiency does not appear necessary	Aptivus package insert 11/05
Fusion Inhibitors			
Enfuvirtide	90 mg SC BID	Dose adjustment for renal insufficiency does not appear necessary	Fuzeon package insert 4/05

Table Continued

Table 56–1

List of abbreviations:
BID = 2 times per day
ClCr = creatinine clearance
H = hour(s)
HD = hemodialysis
PI = protease inhibitor PO = orally
Q = every
QD = daily
QHS = at bedtime
QW = once weekly
SC = subcutaneous (injection)
TID = 3 times per day
Wt = body weight

Table adapted from HIV InSite, *http://hivinsite.ucsf.edu.*

1. Izzedine H, Launay-Vacher V, Aymard G, Legrand M, Deray G. Pharmacokinetics of abacavir in HIV-1-infected patients with impaired renal function. Nephron 2001;89:62–67.
2. Singlas E, Taburet AM, Borsa Lebas F, Parent de Curzon O, Sobel A, Chauveau P, et al. Didanosine pharmacokinetics in patients with normal and impaired renal function: Influence of hemodialysis. Antimicrob Agents Chemother 1992;36:1519–24.
3. Knupp CA, Hak LJ, Coakley DF, Falk RJ, Wagner BE, Raasch RH, et al. Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1996;60:535–42.
4. Bohjanen PR, Johnson MD, Szczech LA, Wray DW, Petros WP, Miller CR, et al. Steady-state pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with end-stage renal disease receiving chronic dialysis. Antimicrob Agents Chemother 2002;46:2387–92.
5. Izzedine H, Launay-Vacher V, Deray G. Dosage of lamivudine in a haemodialysis patient. Nephron 2000;86:553.

6. Johnson MA, Verpooten GA, Daniel MJ, Plumb R, Moss J, Van Caesbroeck D, et al. Single dose pharmacokinetics of lamivudine in subjects with impaired renal function and the effect of haemodialysis. Br J Clin Pharmacol 1998;46:21–27.
7. Grasela DM, Stoltz RR, Barry M, Bone M, Mangold B, O'Grady P, et al. Pharmacokinetics of single-dose oral stavudine in subjects with renal impairment and in subjects requiring hemodialysis. Antimicrob Agents Chemother 2000;44:2149–53.
8. Personal communication with J. Flaherty, 2002.
9. Kimmel PL, Lew SQ, Umana WO, Li PP, Gordon AM, Straw J. Pharmacokinetics of zidovudine in HIV-infected patients with end-stage renal disease. Blood Purif 1995;13:340–46.
10. Pachon J, Cisneros JM, Castillo JR, Garcia-Pesquera F, Canas E, Viciana P. Pharmacokinetics of zidovudine in end-stage renal disease: Influence of haemodialysis. Aids 1992;6:827–30.
11. Tartaglione TA, Holeman E, Opheim K, Smith T, Collier AC. Zidovudine disposition during hemodialysis in a patient with acquired immunodeficiency syndrome. J Acquir Immune Defic Syndr 1990;3:32–34.
12. Izzedine H, Launay-Vacher V, Deray G. Pharmacokinetics of ritonavir and nevirapine in peritoneal dialysis. Nephrol Dial Transplant 2001;16:643.
13. Izzedine H, Launay-Vacher V, Aymard G, Legrand M, Deray G. Pharmacokinetic of nevirapine in haemodialysis. Nephrol Dial Transplant 2001;16:192–93.
14. Taylor S, Little J, Halifax K, Drake S, Back D. Pharmacokinetics of nelfinavir and nevirapine in a patient with end-stage renal failure on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 2000; 45:716-7.
15. Guardiola JM, Mangues MA, Domingo P, Martinez E, Barrio JL. Indinavir pharmacokinetics in haemodialysis-dependent end-stage renal failure. Aids 1998; 12:1395.
16. Izzedine H, Aymard G, Hamani A, Launay-Vacher V, Deray G. Indinavir pharmacokinetics in haemodialysis. Nephrol Dial Transplant 2000; 15:1102-3.
17. Izzedine H, Launay-Vacher V, Legrand M, Lieberherr D, Caumes E, Deray G. ABT 378/r: a novel inhibitor of HIV-1 protease in haemodialysis. Aids 2001; 15:662-4.
18. Armbruster C, Vorbach H, El Menyawi I, Meisl FT, Neumann I. Pharmacokinetics of nelfinavir during haemodialysis in a patient with HIV infection. Aids 2000; 14:99-101.
19. Paci-Bonaventure S, Hafi A, Vincent I, Quertainmont Y, Goujard C, Charpentier B, Taburet AM. Lack of removal of nelfinavir during a haemodialysis session in an HIV-1 infected patient with hepatic and renal insufficiency. Nephrol Dial Transplant 2001; 16:642-3.
20. Izzedine H, Launay-Vacher V, Legrand M, Aymard G, Deray G. Pharmacokinetics of ritonavir and saquinavir in a haemodialysis patient. Nephron 2001; 87:186-7.
21. Ian R. McNicholl, PhamD, University of California San Francisco.

HIV-infected patients with and without diabetes. All three groups had similar responses to intravenous rHuEPO therapy as measured by rise in hematocrit.

Nutrition and Diet

Already a major problem in ESRD patients, malnutrition can be a life-threatening condition in HIV-infected ESRD patients—and hypoalbuminemia at the initiation of dialysis therapy is as strong a predictor of mortality as a low CD4 count. The prevalence and treatment of malnutrition or wasting among HIV-infected ESRD patients is not well understood. Successful initiation of antiretroviral therapy may increase weight and should be the first step in addressing malnutrition in these patients. Aggressive dietary interventions should also be initiated in any HIV-infected patient with ESRD and significant weight loss.

Other therapies that have been studied in HIV patients with wasting include exercise, caloric supplements, the administration of hormones, and the administration of hormone-like drugs. The hormonal agents are reserved for HIV patients with documented endocrine deficiencies. Most studies utilizing these agents have not included patients with chronic kidney disease and have only demonstrated short-term benefits. In addition, the risks of these agents are not well understood—especially in patients with HIV infection and chronic kidney disease.

Hepatitis C and Hepatitis B Co-infection

Co-infection with hepatitis C virus (HCV) is very common in HIV-infected ESRD patients. More than 50% of patients with HIVAN are intravenous drug users, and 40 to 90% of intravenous drug users are infected with HCV. Non-ESRD patients co-infected with HIV and HCV may progress more rapidly to end-stage liver disease than non HIV-infected patients. In non–HIV-infected patients, interferon and ribavirin are the standard treatments for selected patients.

Optimal therapy for HCV infection in the ESRD patient is not established, in part because ribavirin is not recommended in patients with renal failure. At a minimum, patients co-infected with HIV and HCV should be discouraged from alcohol use and should be vaccinated for hepatitis A virus. In the absence of ESRD, HIV-infected patients have an 88% antibody response rate to hepatitis A virus vaccine but only a 50% response to hepatitis B virus vaccine.

HIV Care

Recent improvements in the survival of HIV-infected patients are due not only to HAART but to improved prophylaxis and treatment of opportunistic infections. It is beyond the scope of this chapter to review current guidelines for prophylaxis and treatment of opportunistic infections. All HIV-infected ESRD patients with advanced HIV disease and low CD4+ cell counts should receive standard prophylaxis for *Pneumocystis carinii* pneumonia and *Mycobacterium avium*-complex infections.

The current recommendations for initiation of HAART are well outlined in the consensus statement by the U.S. panel of the International AIDS Society published in the *Journal of the American Medical Association*. In brief, treatment is guided by CD4+ cell count and viral load. Treatment is recommended in all symptomatic persons and in asymptomatic persons when the CD4+ cell count is less than 350/microL and before it declines to 200/microL. The virologic target for patients with treatment failure is a plasma HIV RNA level below 50 copies/mL. A non-nucleoside reverse transcriptase inhibitor or a protease inhibitor boosted with low-dose ritonavir each combined with 2 nucleoside (or nucleotide) reverse transcriptase inhibitors was recommended for initial treatment for adult HIV infection in the 2006 Recommendations of the International AIDS Society.

In addition, several of the antiretroviral medications are excreted primarily through the kidney and must be dose adjusted accordingly (Table 56.1). There are limited data on the pharmacokinetic properties of the non-nucleoside reverse transcriptase inhibitors and protease inhibitors in patients with renal function impairment. However, the pharmacokinetic profile of these drugs suggests a minimal effect on drug elimination. The nucleoside reverse transcriptase inhibitors require dose adjustments in patients with renal insufficiency (Table 56.1).

Recommended Reading

Brau N. Treatment of chronic hepatitis C in human immunodeficiency virus/hepatitis C virus-coinfected patients in the era of pegylated interferon and ribavirin. Semin Liver Dis 2005;25(1):33–51.

This article is a review of the special management issues in the HIV and HCV co-infected patient.

Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005;40(11):1559–85. E-pub 22 April 2005.

This article provides evidence- and opinion-based guidelines on management of CKD in the HIV-infected patient.

Hammer SM, Saag MS, Schechter M, Montaner JS, Schooley RT, Jacobsen DM, et al. for the International AIDS Society-USA panel. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA 2006;296(7):827–43.

This article is the most recent update of the recommendations for treatment of adult HIV infection by the International AIDS Society.

MMWR. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep 2001;50(RR-5):1–43.

This report represents the most recent Centers for Disease Control guidelines on management of HIV and other infectious issues in the dialysis unit.

Qiu J, Terasaki PI, Waki K, Cai J, Gjertson DW. HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients. Transplantation 2006;81(12):1658–61.

This original article represents one of many papers reporting the encouraging kidney transplantation results in HIV-infected ESRD patients.

Rodriquez RA, Mendelson M, O'Hare AM, Hsu L, Schoenfeld P. Determinants of survival among HIV-infected chronic dialysis patients. J Am Soc Nephrol 2003;14(5):1307–13.

This original article reviews the reports of improved survival and predictors of survival among HIV-infected ESRD patients.

CHAPTER 57

Anemia in Patients with End-Stage Renal Disease

Rebecca J. Schmidt, DO, and Anatole Besarab, MD

Anemia remains one of the most characteristic and visible manifestations of chronic kidney disease (CKD) since the association was recognized more than 150 years ago. As typified by the anemia of chronic disease, renal anemia is generally normocytic and normochromic with bone marrow of normal cellularity. For purposes of evaluation and treatment, the recommended threshold for diagnosing renal anemia is at hemoglobin (Hb) concentrations of less than 13.5 g/dL in men and less than 12.0 g/dL in women.

The anemia of renal failure begins early in the development of kidney disease and in some patients is clinically evident by stage 3 or an estimated glomerular filtration rate (GFR) of less than 60 mL/minute. With progressive destruction of kidney tissue, the degree of anemia increases—typically progressing in parallel with the deterioration of renal function. Renal anemia is most severe in anephric patients who prior to the introduction of therapeutic recombinant epoetin (rHuEPO) were almost invariably transfusion dependent. Although end-stage renal disease (ESRD) patients tolerate the associated anemia, many of the symptoms formerly attributed to uremia have been alleviated with correction of anemia. Approximately 30% of patients with anemia of CKD are treated prior to reaching ESRD, although nearly half are not optimally treated and start dialysis anemic.

Primary Causes

The anemia associated with ESRD is primarily a failure of kidney endocrine function, resulting in deficient levels of renal erythropoietin (EPO) production. Experimental and clinical observations of the effects of dialysis, bilateral nephrectomy, and therapy with rHuEPO have clarified many pathophysiologic mechanisms. In anemic but otherwise normal individuals, a negative biofeedback system induces renal EPO production as reflected by increased plasma EPO concentrations. The driving force for renal EPO production is intrarenal tissue hypoxia, which results from an imbalance between oxygen delivery and metabolic needs. In normal

individuals without kidney disease, as hematocrit (Hct) decreases from values greater than 40% to mildly anemic levels of 30 to 35% plasma EPO levels increase from average values of 10 to 12 to 100 mU/mL.

Normal renal capacity for augmenting EPO production is formidable. EPO concentrations may rise in excess of 1000 mU/mL when Hct levels fall below 20%. In early CKD, the kidney produces EPO in an expected fashion—and suppression of red blood cell synthesis by poorly defined toxins or from shortened red blood cell survival is the dominant mechanistic force behind the anemia at this early stage. As CKD advances, EPO production decreases and EPO levels become lower than those expected for the degree of anemia. True EPO deficiency exists as the biofeedback mechanism becomes progressively impaired.

As GFR approaches 20% of normal, the great majority of patients become anemic with Hct levels less than 30%. Average EPO levels of 20 to 25 mU/mL in anemic ESRD patients are above-abnormal values in nonuremic individuals but reach only 1/4 the level of EPO production expected for the degree of anemia. Thus, the overriding feature in the anemia of ESRD is inadequate production of EPO by the diseased kidneys in total—although production by individual functioning nephron units may in fact be normal. In general, there is a direct although imprecise relation between the degree of renal insufficiency and the degree of anemia.

Although the end-stage kidney continues to produce relatively low levels of EPO, it is incapable of augmenting EPO production adequately in response to an appropriate anemic hypoxic stimulus. Maintenance of "appropriate" plasma levels during severe anemia would require that the residual renal tissue have the capacity to increase EPO production by about 5- to 20-fold if metabolic clearance rate were independent of plasma concentration. Molecular biology techniques have shown that the normal kidney responds to hypoxia or anemia by recruitment of additional production sites isolated in the peritubular or vascular space.

In the diseased kidney, these sites have been destroyed or impaired—leading to changes in the hemoglobin-oxygen affinity of uremic erythrocytes (which is already decreased to a greater extent than that of erythrocytes from comparably anemic nonuremic individuals). In well-dialyzed patients, the intracellular concentration of 2,3-diphosphoglycerate (2,3-DPG) is appropriately increased in response to the level of anemia and the mild hyperphosphatemia—and the affinity of hemoglobin for oxygen is appropriately decreased. Systemic metabolic acidosis from renal failure (usually mild) further augments this decrease in oxygen

affinity by shifting the oxygen dissociation curve to the right (Bohr effect). Overall, however, the effect of decreased oxygen affinity on oxygen transport in hemodialysis patients is minimal, delivery of oxygen to peripheral tissues is slightly augmented, and the changes do not explain intra- or interdialytic symptoms.

Most renal diseases render the kidney incapable of augmenting EPO production chronically in response to an appropriate anemic hypoxic stimulus, the exception being autosomal dominant polycystic kidney disease (which is typically associated with higher EPO levels and mild to no anemia). In contrast, the absolute deficiency of endogenous EPO in anephric patients rendered them blood transfusion–dependent prior to the advent of rHuEPO therapy.

Secondary Causes

Although inadequate production of EPO is of paramount importance in the pathogenesis of anemia in ESRD, other factors contribute to cause the mild anemia that persists despite the use of rHuEPO. Chief among these are shortened erythrocyte survival, blood loss, iron and other nutritional deficiencies, and perhaps the effects of uremic inhibitors on the stimulatory action of EPO on the bone marrow. Secondary causes contribute to the severity of renal anemia and if left unattended will influence the outcome of rHuEPO treatment.

Erythrocyte survival is shortened in renal failure, decreasing from 100 to 140 days to 70 to 80 days. This decrease in red cell survival is likely due to both metabolic and mechanical factors triggering premature exit of erythrocytes from the circulation. Repeated vascular access punctures, residual blood left in dialyzers and bloodlines, occasional blood leaks, and blood retention in clotted dialyzers all contribute to ongoing blood loss—resulting in premature removal of circulating erythrocytes. Gross mechanical factors related to hemodialysis include malocclusion of the roller pump, shearing effects from negative pressures in needles, and sublethal thermal injury.

Modern conductivity sensors have virtually eliminated osmotic injury to the erythrocyte from hypotonic dialysate. Acute hemolysis is avoided by using a water supply devoid of chloramine, copper, zinc, nitrates, and reprocessed dialyzers that are free of residual formaldehyde. Older studies suggest a modest decrease in the red blood cell life span in uremic patients. More recent studies in well-dialyzed patients indicate that the red blood cell life span can approach normal if blood losses associated with hemodialysis are avoided. Metabolic effects of the uremic environment include

abnormal erythrocyte cation transport, which alters membrane deformability and thus shortens erythrocyte survival.

Premature removal of erythrocytes by the reticuloendothelial system may occur. Rarely, profound splenic sequestration requiring splenectomy occurs. Occult gastrointestinal blood losses due to platelet dysfunction commonly contribute to chronic blood loss in ESRD. The increasing use of aspirin and clopidogrel in elderly dialysis patients with coronary heart disease only adds to such occult blood loss.

Borderline or frank iron deficiency is the most common nutritional deficiency and is a major impediment to the cost-effective use of epoetin. Iron absorption is impaired by H2 blockers, H+ ion pump inhibitors, and phosphate binders. Three factors have been implicated in the pathogenesis of iron deficiency in renal failure patients: blood loss caused by retained erythrocytes in dialyzers and blood tubing and on dressings, and by frequent phlebotomies for diagnostic testing; the bleeding diathesis caused by uremia; and malabsorption of iron due to H2 blockers, H+ ion pump inhibitors, nonaluminum-based phosphate binders, and historically aluminum-containing phosphate binders.

Although iron turnover appears normal in severe renal impairment, iron utilization is regularly decreased—particularly in inflammatory renal disorders. In rare cases of nephrotic syndrome, urinary losses of transferrin can cause low iron-binding capacity—with impairment in the metabolic cycling of iron. Although iron absorption may be decreased in some patients, Eschbach et al. observed that (as expected) the percentage of iron absorbed from the gastrointestinal tract of uremic subjects varies inversely with iron stores.

Although they concluded that uremia per se does not interfere with the physiologic regulation of iron absorption, the amount of iron taken orally is often not sufficient to meet the needs of active erythropoiesis—particularly after rHuEPO administration. Parenteral iron may therefore be necessary. In addition, repetitive blood losses render the nontransfused patient on hemodialysis prone to iron deficiency. At a target hematocrit of 30 to 36%, such losses of red blood cells equate to an additional 6- to 7-mg iron loss per dialysis above normal obligatory daily iron losses of 1 to 2 mg per day. With the additional losses from periodic laboratory tests, the yearly iron losses can exceed normal total body stores of iron of approximately 1200 mg. Standard of care for most hemodialysis programs includes iron supplementation (averaging 2 g per year, usually parenterally) to prevent iron deficiency.

In patients with ferritin levels exceeding 200, a level common in ESRD (due to inflammation) and the minimum value recommended even in noninflamed patients, oral iron absorption virtually ceases. In many individuals, therefore, even large amounts of oral iron are not sufficient to meet the needs of active erythropoiesis—particularly after rHuEPO administration—prompting the growing use of parenteral iron, which has rapid efficacy in improving iron stores. Parenteral iron is used nearly universally as primary therapy in most dialysis units and is administered by nurse-driven maintenance iron protocols. The benefits of intravenously administered iron must be weighed against the small risk of allergic reactions, although since the virtual replacement of iron dextran with iron gluconate and iron sucrose these risks are diminished.

Additional contributing factors unique to anemia in ESRD include those related to nutrition, vitamin deficiencies, and the dialysis process. ESRD patients are prone to anorexia, intercurrent illnesses, and dietary restrictions. Dialysis can also produce dialysate nutrient losses. All patients should be observed for malnutrition and vitamin deficiency syndromes. Folate deficiency in dialysis patients is uncommon because routine use of supplements replaces dialysate losses. Most centers supplement their patients with 1 mg per day of folic acid. This is generally safe, as vitamin B12 deficiency is uncommon in dialysis patients.

More recently, higher doses of folate have been used to reduce homocysteine levels—although evidence of an associated clinical benefit has yet to be demonstrated. Because of the water solubility of thiamine, pyridoxine, and vitamin B12, deficiencies in one or more of these vitamins could theoretically develop from dialytic removal—although this is not commonly reported. Currently, only pyridoxine supplementation is recommended (5 mg per day for those with progressive renal failure and 10 mg per day for dialysis patients).

Clinical trials of rHuEPO were initiated in 1985, and replacement therapy with rHuEPO quickly became the most rational therapy for anemia of renal disease. Initial clinical trials convincingly demonstrated that the Hct could be increased by up to 10 points or more and maintained at a level greater than 30% in more than 90% of patients. Dialysis patients treated with rHuEPO three times weekly increased their Hct in a dose-dependent manner, although the need for thrice-weekly maintenance intravenous doses to maintain steady-state hematocrits greater than 31% varies significantly among study patients.

Tertiary Causes

Secondary hyperparathyroidism can lead to myelofibrosis in ESRD patients, and affected patients often require high doses of rHuEPO to achieve target hemoglobin levels. Correction of hyperparathyroidism by parathyroidectomy has been shown to reduce rHuEPO requirements needed to reach adequate hematopoietic response in some ESRD patients. The improvement of anemia demonstrated following parathyroidectomy is due to the resolution of marrow fibrosis rather than to the removal of erythropoietic inhibition.

The presence of excess aluminum in the blood may interfere with rHuEPO responsiveness. Iron utilization signals the intestinal mucosa to increase iron absorption, a process that may concurrently increase aluminum absorption. With the decline in use of aluminum binders in ESRD, this is rarely a problem. Several studies have shown that the response to rHuEPO is impaired not only in states of frank aluminum overload but at levels previously considered acceptable. Nonrenal nondialysis factors may be superimposed on the anemia of ESRD. These include malignancy (myeloma, metastatic cancer), hemolysis (systemic lupus erythematosus or sickle cell disease), drug-induced anemias, and drug-induced bleeding (nonsteroidal antiinflammatory drugs). Infection, inflammation, and hypothyroidism all suppress bone marrow erythropoiesis.

Decreased serum levocarnitine levels are associated with rHuEPO hyporesponsiveness, and replacement therapy has improved the response to rHuEPO therapy. Improved red blood cell survival and decreased Na/K-ATPase activity have been proposed as potential mechanisms, and many nephrologists employ intravenous supplemental levocarnitine for its potential rHuEPO-stimulating effect—although proof of efficacy is still weak. Bone marrow suppression by the uremic milieu may also be a contributing factor to the anemia of ESRD. Plasma from uremic individuals has been shown to inhibit heme synthesis and erythroid stem-cell proliferation in vitro.

Despite clinical experience showing that exogenous rHuEPO overcomes the effects of such putative inhibitors, studies on uremic inhibitors continue because control of such factors could reduce the amount of rHuEPO needed. Recent studies have focused on the effects of albumin-bound furancarboxylic acid, activated monocytes, and polymorphonuclear leukocyte products and cytokines on erythropoiesis. Quinolinic acid levels correlate positively with creatinine concentration and negatively with endogenous EPO levels in uremic rats. Urea-derived cyanate carbamylates endoge-

nous EPO and may decrease its biologic activity. Cobalt-stimulated erythropoiesis was suppressed dose dependently in chronic quinolinic acid-treated rats. Moreover, quinolinic acid had a dose-dependent inhibitory effect on hypoxia or caused a cobalt-induced EPO release and EPO gene expression—suggesting disruption of EPO gene activation by HIF-1.

T cells from uremic subjects may be unable to release general growth cytokines needed for optimal erythropoiesis. In addition, inflammation-associated cytokines inhibit erythropoiesis. CFU-colony formation is suppressed by soluble factors in uremic sera that lead to the production of interferon-γ and tumor necrosis factor-α. Interleukin-6 (a proinflammatory cytokine) is present at 8- to 10-fold higher levels in hemodialysis patients, is higher in patients treated with less-biocompatible membranes, and inhibits EPO-induced bone marrow proliferation. More intensive dialysis increases response to exogenous rHuEPO. Ifudu et al. found a direct relationship between Hct and urea reduction ratio (URR) after adjustment for other variables. Analysis of Medicare data also shows a direct relationship between higher URR and higher Hct at lower rHuEPO doses.

The role of high-flux membranes compared to low-flux membranes is unclear. Overall, the impact of such inhibitors on the genesis of anemia is probably minor because it can be corrected in most patients by good dialysis. Further, the effects of uremic inhibitors are easily overcome in most patients by rHuEPO. Abnormal regulation of proinflammatory cytokines in the absence of infection may also play a pathogenic role in renal anemia and EPO resistance. Although interleukin-1, tumor necrosis factor alpha, and interferon gamma have been implicated for their purported suppressor effects on erythropoiesis, interleukin-12 may actually enhance this process.

In hemodialysis patients, interleukin-6, tumor necrosis factor alpha, and interleukin-12 may correlate with rHuEPO dose requirements. The process of hemodialysis can also potentiate further changes in cytokine production, which may be operative in the hyporesponsiveness to EPO seen in some ESRD patients. Causal relationships between particular cytokines and the influence of both the uremic milieu and the hemodialysis membrane on derangements of hematopoiesis have not been specifically delineated.

Transfusions

Since the advent of rHuEPO, and more recently darpopoietin alfa, the need for blood transfusions in the ESRD population has

significantly declined with the use transfusions reserved for the symptomatic or potentially symptomatic patient. Patients with sickle cell disease or thalassemia who do not respond to "reasonable" doses of rHuEPO may require transfusions. Those with underlying ischemic heart disease, in whom it is unsafe to wait for sometimes weeks for the increase in Hct anticipated with rHuEPO, may also need transfusions. In situations of gastrointestinal bleeding, postoperative blood loss, or hemolysis, transfusions still remain the mainstay of therapy.

Younger patients can tolerate anemia until it can be corrected with rHuEPO, because of changes in cardiac output and release of oxygen to tissues (increased 2,3-diphosphoglycerate and the presence of mild anemia). Patients with severe anemia in the setting of coronary artery disease, peripheral vascular disease, chronic pulmonary disease, and symptoms of dyspnea, palpitations, or angina pectoris can be transfused until rHuEPO therapy has raised the hemoglobin to 11 to 12 gm/dL. In addition, patients with acute blood loss or hemolysis may require transfusions to rapidly restore (respectively) blood volume and correct anemia.

Blood transfusions still carry risks, albeit lower than in the past—including transmission of disease (hepatitis B and C, and HIV) and antibody sensitization. Both of these complicate future renal transplantation. Transfusions may also suppress endogenous erythropoiesis and lead to hemosiderosis. Given the infection risks of transfusion and the sensitization of potential transplant recipients, transfusions should be used prudently.

Androgens

Stimulation of renal and extrarenal EPO production can be achieved by the administration of androgens. Their hematopoietic effect is more pronounced in patients with some residual native renal function. The use of androgens is associated with side effects; notably, hirsutism, acne, and cholestasis. Prior to the development of rHuEPO, androgens were a mainstay in the treatment of renal anemia. However, issues of side effects, safety, and efficacy associated with the ability of rHuEPO to achieve target hemoglobin levels have promoted a waning interest in their use.

Response to rHuEPO can be augmented by anabolic androgens and is used by health care systems with limited resources. This therapy consists of blood transfusions with or without the administration of androgenic-anabolic steroids. Androgenic steroids

increase the Hct of uremic patients by increasing EPO production and to a lesser extent by stimulating committed bone marrow stem cells. Fluoxymesterone and oxymetholone are given by mouth in doses of 10 to 20 mg per day and 1 to 4 mg/kg body weight per day, respectively. Parenteral preparations (such as nandrolone decanoate, testosterone propionate, and enanthate) are presumed more effective. They are given in doses of 1 to 4 mg/kg body weight once a week.

Recent studies have explored the use of androgens along with rHuEPO. One study found synergy between rHuEPO and nandrolone decanoate, with few side effects. The other found no synergy and many side effects. A third study found that the use of androgens in men younger than 50 years was as effective as epoetin and less costly. In view of the known side effects of androgen therapy, particularly in women, we do not advocate its use alone or in combination with rHuEPO. Recent Kidney Disease Outcome Guidelines for anemia also reject the adjuvant use of anabolic steroids.

Recommended Reading

Erslev A, Besarab A. The rate and control of baseline red cell production in hematologically stable uremic patients. J Lab Clin Med 1995;126:283.

Erythrokinetic study of hematologically stable patients with dialysis-dependent ESRD.

Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: Results of a phase III multicenter clinical trial. Ann Intern Med 1989;111:992.

Controlled clinical multicenter trial evaluating the effect and safety of recombinant human erythropoietin in hemodialysis patients with uncomplicated renal anemia.

Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: Results of combined phase I & II clinical trials. N Engl J Med 1987;316:73.

Controlled clinical trial evaluating the efficacy of recombinant human erythropoietin in the correction of anemia in patients with ESRD.

Eschbach JW, Funk D, Adamson JW, et al. Erythropoiesis in patients with renal failure undergoing chronic dialysis. N Engl J Med 1967;276:653.

Review of the pathophysiology of erythropoiesis in dialysis-dependent patients with ESRD.

Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. N Engl J Med 1989;321:158.

Single-center study evaluating the effect of recombinant human erythropoietin on renal anemia and rate of renal deterioration.

Ifudu O, Feldman J, Friedman EA. The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. N Engl J Med 1996;334:420.

Prospective randomized study associating inadequate hemodialysis with suboptimal response to human recombinant erythropoietin.

Rao DS, Shih M-S, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. N Engl J Med 1993;328:171.
Cross-sectional single-center study evaluating the impact of secondary hyperparathyroidism and bone marrow fibrosis on erythropoietin dose requirement.
Spivak JL. The mechanism of action of erythropoietin. Int J Cell Cloning 1986;4:139.
Review of the mechanism of action of erythropoietin.
USRDS. *Annual Data Report of the United States Renal Data System.* 2006.
Annual report of the national data system, which collects, analyzes, and distributes information about ESRD in the United States.

CHAPTER 58

Use of Erythropoietic-Stimulating Agents in Hemodialysis Patients

Arthur Tsai, MD, and Jeffrey S. Berns, MD

Introduction

Erythropoietin is necessary for the survival, proliferation, and differentiation of bone marrow–derived erythroid cells that ultimately become mature circulating red blood cells. In the vast majority of patients on hemodialysis, erythropoietin synthesis is insufficient to stimulate adequate levels of erythrocyte production by the bone marrow, and anemia develops as a result. Although factors such as iron deficiency, inflammation, infection, and other co-morbid conditions contribute to the anemia seen almost universally in hemodialysis patients, a relative deficiency of erythropoietin is the most important factor in most patients. Anemia in hemodialysis patients is associated with increased risk of death from noncardiac and cardiac causes, increased frequency and duration of hospitalizations, cardiac dysfunction, reduced quality of life and functional status, and exercise intolerance.

Replacement therapy with recombinant human erythropoietin (rHuEPO, epoetin alfa), first reported in hemodialysis patients in 1987 (Figure 58.1) and approved by the U.S. Food and Drug Administration (FDA) in 1989, revolutionized the management of anemia in these patients—as well as other patients with chronic kidney disease (CKD) not on dialysis and those on peritoneal dialysis. Treatment with epoetin alfa raised hemoglobin and hematocrit levels, reduced transfusion requirements and symptoms related to anemia, and improved patients' quality of life and functional status. Subsequent studies have confirmed and extended these initial observations. Optimal utilization of epoetin and the newer erythropoietic-stimulating agent (ESA) darbepoetin alfa, as well as newer ESAs that may become available, requires understanding of the pharmacology of these biopharmaceuticals, their clinical effects and side effects, practical aspects of their use, an appreciation of related economic issues, and knowledge of clinical practice recommendations related to their use.

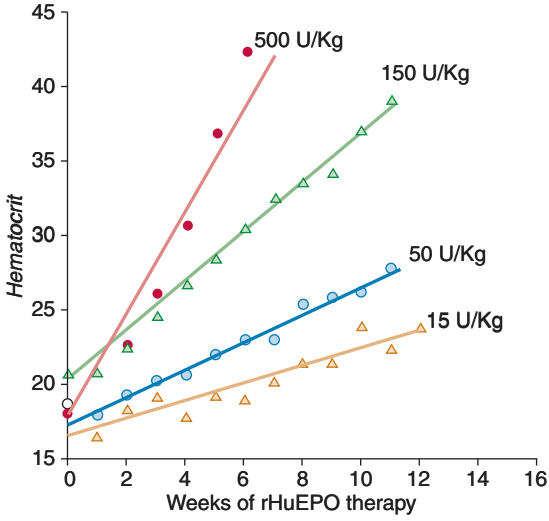


Figure 58–1

Mean weekly hematocrit levels among the four to five patients in each dosing group, showing response to varying doses of recombinant human erythropoietin. (*Used by permission of the* New England Journal of Medicine.)

Epoetin and Darbepoetin: Overview

There are two ESAs currently available in the United States: epoetin alfa and darbepoetin alfa. Epoetin alfa (Epogen, Amgen, Inc.) is licensed in the United States for use in dialysis patients; Procrit, Ortho-Biotech is licensed in the United States for other indications) is a 165-amino-acid glycoprotein with three N-linked and one O-linked carbohydrate chains produced using recombinant DNA technology. The amino acid structure is identical to the native human erythropoietin hormone. Two other epoetin types, epoetin beta and epoetin omega (which are commercially available outside the United States), contain the same amino acid sequence as epoetin alfa but differ in their glycosylation and sialic acid content. For epoetin alfa, the terminal half-life following intravenous (IV) administration is approximately 8 hours, and following subcutaneous administration is approximately 24 hours.

Darbepoetin alfa (Aranesp; Amgen, Inc.) was approved by the FDA in 2001 for the treatment of anemia in patients with CKD, including dialysis patients and those with anemia related to chemotherapy for certain malignancies. This newer ESA, also produced using recombinant DNA technology, differs in five amino acids compared to the native hormone and contains five N-linked carbohydrate chains rather than three (as are present in the epoetins). To stimulate erythropoiesis, the epoetins and darbepoetin alfa interact with the same receptor on erythroid progenitor cells as the native erythropoietin. As a result of its increased glycosylation, affinity of darbepoetin alfa for the erythropoietin receptor is diminished. However, due to an increase in serum half-life clinical efficacy is enhanced compared to epoetin alfa. IV darbepoetin alfa exhibits a two- to threefold longer pharmacologic half-life than IV epoetin alfa. This half-life is about 24 hours, which is similar to that of subcutaneously administered darbepoetin alfa.

Given the pharmacokinetic differences, subcutaneous administration of epoetin alfa is more effective than IV administration. As a result, most patients can be treated with a lower epoetin dose when it is given subcutaneously rather than intravenously—with an overall reduction in epoetin dose of about 25 to 30% while maintaining the same target hemoglobin level. The relatively short half-live of IV epoetin predicts the need to dose this medication more frequently than when it is administered subcutaneously—and to dose it more frequently than darbepoetin alfa. In practice, whether administered intravenously or subcutaneously, epoetin is typically administered three times weekly for hemodialysis patients, with IV injection much more common. Subcutaneous and IV darbepoetin alfa appear to be of similar efficacy when administered weekly or every other week. Comparisons of the efficacy of subcutaneous and IV darbepoetin alfa or other ESAs with more extended dosing intervals have not been published.

Dosing and Administration Guidelines

More than 95% of hemodialysis patients in the United States are treated with epoetin alfa. For reasons of convenience and patient preference, despite the reported superior efficacy of epoetin when administered by subcutaneous injection, most U.S. hemodialysis patients have been treated with IV injections at each dialysis treatment. Until recently, many hemodialysis patients outside the United States received subcutaneous epoetin therapy due to the greater efficacy and resulting potential for lower costs for any

specific achieved hemoglobin level. With the recent development of pure red cell aplasia linked to subcutaneous administration of a certain epoetin preparation (see material following), IV administration has become more generally widespread and is now specifically recommended for hemodialysis patients in the United States by the drug's package insert and by regulatory and health authorities in some other countries.

There is a very wide inter-individual variability in responsiveness to epoetin and darbepoetin, and also tremendous variation in mean epoetin doses around the world. For instance, in the United States the mean epoetin dose is between about 13,000 and 17,000 IU/week—whereas in Japan, Europe, and the United Kingdom mean dosage levels are typically about 5000 to 8000 IU/week. These dose differences are in part attributable to differences in achieved hemoglobin levels, but other factors may also be involved—such as more frequent use of subcutaneous administration and IV iron and differences in body mass and dialysis therapies.

Specific dosing practices and goals of therapy with epoetin alfa in hemodialysis patients have been influenced over the years by the package labeling, reimbursement policies, findings from clinical studies, and clinical practice guidelines—which have often been in discordance with FDA-approved labeling. There is no evidence to support any specific ESA dosing protocol over another, and each dialysis clinic or provider will generally have developed a protocol for use in their dialysis facility. The approved labeling in the United States recommends a starting dose of 50 to 100 IU/kg three times weekly for adults and 50 IU/kg three times weekly for pediatric patients on hemodialysis, with a target hemoglobin range of 10 to 12 g/dL.

Dose reductions of 25% are suggested as the hemoglobin level approaches 12 g/dL or the hemoglobin level increases by more than 1 g/dL in a 2-week period. Dose increases of 25% are suggested if the hemoglobin level does not increase by 2 g/dL after 8 weeks of therapy and is below the target hemoglobin range, with dose adjustment made no more frequently than once monthly. These starting doses and recommendations for subsequent dose adjustments are reasonable and consistent with clinical practice (see material following for additional discussion of target hemoglobin level recommendations for hemodialysis patients).

Darbepoetin alfa is also approved for treatment of anemia in hemodialysis patients but it has not yet been used extensively for this purpose in the United States and most other countries. The starting dose recommended in the U.S. package insert is

0.45 mcg/kg body weight as a weekly injection. As with epoetins, the IV route is recommended for hemodialysis patients. Subsequent dose adjustments to account for individual patient variability are necessary, and some hemodialysis patients have been treated with injections once every 2 to 4 weeks. In patients previously treated with epoetin alfa, dose conversions for darbepoetin alfa are recommended in the package insert (Table 58.1)—although other dosing strategies have been employed. In addition, as with epoetin therapy there is significant variability in responsiveness. Similar to the labeling recommendations for treatment with epoetin alfa, the FDA-approved labeling for darbepoetin alfa also indicates that the target hemoglobin level should not exceed 12 g/dL. Recommendations for darbepoetin alfa dose adjustments to achieve target hemoglobin levels are the same as those recommended for epoetin alfa–treated patients.

Prospective clinical trials in dialysis patients comparing once-weekly IV darbepoetin and 2- to 3-times-weekly IV epoetin alfa have found that they have similar clinical efficacy with regard to endpoints such as absolute level of hemoglobin increase, time to achieve a hemoglobin response, ability to maintain target hemoglobin, and reduction in transfusion requirement. In many of these trials, the initial darbepoetin dose was based on the total weekly epoetin dose—using a conversion scale of 200 (IU) epoetin to 1 mcg

Table 58–1

Dosing Conversion Between Epoetin and Darbepoetin for Patients Previously on Epoetin Alfa

Previous Weekly Epoetin Alfa Dose (IU/wk)	Predicted Weekly Darbepoetin Dose (mcg/wk)	
	Adult	***Pediatric***
<1500	6.25	See text
1500 to 2499	6.25	6.25
2500 to 4999	12.5	10
5000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥90,000	200	200

a) For pediatric patients receiving a weekly epoetin alfa dose of <1500 units/week, the available data are insufficient to determine a darbepoetin alfa dose.
From darbepoetin alfa package insert, Amgen, Inc.

of darbepoetin (based on calculated equivalent protein mass). For instance, in one such study the average weekly dose was 63 mcg for darbepoetin and 12,700 IU for epoetin alfa to maintain hemoglobin levels in the target range.

In another study, more than 95% of patients had hemoglobin levels successfully maintained at target levels with a median weekly dose of 0.41 mcg/kg of darbepoetin (25th through 75th percentiles at 0.26–0.65 mcg/kg). Once-monthly dosing of darbepoetin alfa has also been used successfully in a limited number of hemodialysis patients, with median doses of about 50 to 120 mcg per month maintaining hemoglobin levels of 10 g/dL or greater in more than 80% of patients in one study.

In the United States, the most influential clinical practice guidelines addressing the use of epoetin alfa in hemodialysis patients have been the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines. Published initially as the Dialysis Outcomes Quality Initiative (NKF-K/DOQI) in 1997 and revised as NKF-K/DOQI guidelines in 2001 to include patients not on dialysis, updated revisions to these guidelines were published in 2006 and 2007. Specific recommendations concerning anemia management in patients with CKD (including those on dialysis) are outlined in Table 58.2. These guidelines state that all patients with CKD, including those on hemodialysis, the selected hemoglobin target should generally be in range of 11.0 to 12.0 g/dL and should not be above 13.0 g/dL.

Although hemoglobin levels above this level have been associated with improvement in certain quality of life measures, exercise capacity, and cognitive function, other outcomes (such as reduction in development of left ventricular hypertrophy and hospitalization and mortality rates) have not been shown in prospective studies to be improved compared to when hemoglobin levels are above 11 g/dL but less than 13 g/dL. In fact, as discussed in material following, a randomized controlled trial in hemodialysis patients with prior cardiac disease who were targeted to achieve serum hemoglobin levels of 10 g/dL versus 14 g/dL using epoetin was terminated early when it was observed that the higher hemoglobin level group had a trend toward increased risk of death or first nonfatal MI (myocardial infarction) compared to the lower hemoglobin group.

These concerns were reinforced when a study in CKD patients not on dialysis was also terminated early because of a higher risk of experiencing the composite endpoints of mortality, stroke, MI, and hospitalization due to congestive heart failure in patients randomized to a target hemoglobin of 13.5 g/dL compared to

Table 58–2

NKF-K/DOQI Clinical Practice Guidelines and Recommendations for Treatment of Anemia in ESA-Treated Hemodialysis Patients

- Hemoglobin should be 11 g/dL or greater, with insufficient evidence to recommend routinely maintaining hemoglobin levels of 13 g/dL or greater.
- Hemoglobin levels should be monitored at least monthly.
- More frequent monitoring is appropriate for unstable and out-of-target hemoglobin levels, and in hemodialysis patients.
- More frequent monitoring is favored in hemodialysis patients.
- The initial ESA dose and subsequent ESA dose adjustments should be determined by the patient's hemoglobin level, the target hemoglobin level, and the rate of increase in hemoglobin level. ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of hemoglobin level is needed. Scheduled ESA doses that have been missed should be replaced at the earliest possible convenience.
- The goal of therapy should be to increase the hemoglobin level by about 1 to 2 g/dL per month.
- Adjustments in ESA dose should not generally be made more frequently than every 2 to 4 weeks.
- Hypertension, vascular access occlusion, inadequate dialysis, history of seizure, or compromised nutritional status are not contraindications to ESA therapy.
- Convenience favors intravenous ESA administration in hemodialysis patients.

Adapted from National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2007, in press.

patients assigned a target hemoglobin level of 11.3 g/dL. There has also been concern for other adverse effects associated with ESA-mediated increases in hemoglobin above 13 g/dL, including hypertension, stroke, and hemodialysis-access thrombosis.

Approaches to epoetin alfa dosing and target hemoglobin levels in the United States have also been significantly impacted by reimbursement policies of the Centers for Medicare and Medicaid Services (CMS; formerly known as the Health Care Financing Agency, HCFA), which governs payment for patients receiving Medicare benefits. CMS policies have changed over the years; most recently in 2006. The new policy requires that when the hematocrit level reaches 39.0% or the hemoglobin reaches 13 g/dL the ESA dose should have been reduced by 25% some time during the preceding month.

If the dose has been reduced by 25%, dialysis facilities are to report a specific code on the claim for payment—which will be paid based on the reported dose. Without this specific code, payments for claims in which hematocrit or hemoglobin levels are greater than 39% or 13 g/dL (respectively) are automatically reduced by 25%. In addition, if the dose of epoetin is greater than 500,000 IU/month or the dose of darbepoetin alfa is greater than 1500 mcg/month the claim is to be unpaid and returned as a "medically unbelievable error." The effect of this policy on ESA use and hemoglobin levels remains to be determined.

Adequate iron availability is necessary for maintaining an optimal response to ESA therapy (see section following on ESA hyporesponsiveness). Unfortunately, there is no single test that completely and accurately measures total body iron stores and the amount of iron readily available for erythropoiesis. The two most commonly used tests are the serum ferritin and the percent saturation of serum transferrin (TSAT). The most recent NKF-K/DOQI guidelines recommend that in order to support erythropoiesis in ESA-treated patients on hemodialysis supplemental IV iron should be used as necessary to maintain the serum ferritin level at 200 ng/mL or greater and the TSAT at 20% or greater. Oral iron is not well tolerated and is of limited efficacy in hemodialysis patients, and is not recommended.

Clinical Outcomes Associated with ESA Treatment in Hemodialysis Patients

The clinical benefit of ESA treatment and higher hemoglobin levels in hemodialysis patients has been repeatedly documented from both prospective clinical trials and retrospective analysis of large databases—largely from Medicare and HCFA, the United States Renal Data System (USRDS), large corporate dialysis chains, and the international Dialysis Outcomes and Practice Patterns Study (DOPPS). Clinical studies of ESA treatment, most using epoetin alfa, have shown that the vast majority of iron-replete hemodialysis patients (>90%) achieve target hemoglobin levels within 6 months after initiating ESA therapy. The time to achieve target hemoglobin and the percentage of patients achieving target hemoglobin levels appear to be similar for darbepoetin alfa and epoetin alfa.

Higher hemoglobin levels in ESA-treated hemodialysis patients correlate with improved quality of life measures (less fatigue, depression, cognitive deficits, and exercise intolerance), decreased mortality risk from cardiac and noncardiac causes, reduced fre-

quency and duration of hospitalizations, and decreased severity of cardiac dysfunction. Most recent studies have tended to support an increased morbidity and mortality risk with hemoglobin levels less than 11 g/dL. A benefit from raising the hemoglobin above 11 to 12 g/dL using ESA therapy has been less consistently seen, although some observational studies have reported lower risk of hospitalization and mortality with hemoglobin levels above 12 to 13 g/dL (equivalent to hematocrit levels of 36 to 39%) compared to lower levels.

There have been remarkably few large prospective studies in ESA-treated hemodialysis patients. Those that have been published generally support the goal of maintaining hemoglobin levels at approximately 11 to 12 g/dL. Only a single sufficiently large randomized controlled trial examined higher hemoglobin levels (14 g/dL compared to 10 g/dL) in ESA-treated hemodialysis patients. Patients assigned to the higher hemoglobin group had an increased rate of composite outcome of death or first nonfatal MI and the study was stopped early as a result.

There were no differences between groups for all-cause hospitalization or other endpoints, with the exception of a higher thrombosis rate for AV (arteriovenous) fistulas and grafts in the higher target group. In another study, however, there was increased risk of cerebrovascular events among incident ESA-treated hemodialysis patients randomly assigned to hemoglobin levels of 13.5 to 14.5 g/dL versus 9.5 to 11.5 g/dL. Other studies have not found an increase in mortality or significant morbidity at hemoglobin levels approaching normal levels in ESA-treated hemodialysis patients, but they have not been of sufficient size and duration to meaningfully assess this.

Several small prospective studies have shown improvement in some quality of life measures—such as physical symptoms, vitality, fatigue, exercise performance, and neurocognitive function—as hemoglobin levels are raised toward normal with ESA treatment in hemodialysis patients. Higher hemoglobin levels do reduce the need for blood transfusions—once the mainstay of anemia treatment in hemodialysis patients. Clinical studies, primarily retrospective in nature, have suggested an association between anemia and left ventricular hypertrophy (LVH) and dilatation. Prospective studies in hemodialysis patients have generally failed, however, to demonstrate that treatment of anemia with ESA therapy to a hemoglobin level above 10 or 11 g/dL results in regression of LVH or amelioration of LV dilatation.

The cost of achieving higher hemoglobin levels using ESA therapy in hemodialysis patients bears some consideration. Expen-

ditures for epoetin in U.S. hemodialysis patients are approximately $1.5 billion annually. One recent analysis concluded that the cost per quality-adjusted life year (QALY) for a hemoglobin target of 11.0 to 12.0 g/dL compared to 9.5 to 10.5 g/dL was approximately $55,000. The cost per QALY to maintain hemoglobin levels of 12.0 to 12.5 g/dL compared to 11.0 to 12.0 g/dL was in excess of $600,000, and the cost per QALY to maintain a hemoglobin level of 14 g/dL compared to 12.0 to 12.5 g/dL was more than $825,000.

Side Effects of ESA Therapy

Serious side effects directly related to use of epoetin and darbepoetin alfa are uncommon. These agents have similar side-effect profiles in hemodialysis patients. Use of these agents is contraindicated in patients with uncontrolled hypertension or with prior hypersensitivity to the drug (see discussion following on pure red cell aplasia) or to its carrier components (i.e., polysorbate and albumin). Clinical trials and extensive experience with these medications have shown that the most common minor adverse effects are pain at the site of subcutaneous injection and rarely mild flu-like symptoms. More significant adverse effects include vascular-access thrombosis, seizures, and hypertension. Vascular-access thrombosis rates appear to be greater in ESA-treated patients with higher hemoglobin levels and may be more of a problem for patients with synthetic arteriovenous grafts than with primary AV fistulas. Whether this increased vascular-access thrombosis rate is due to the higher hemoglobin level itself or to other factors, including the higher ESA doses needed to achieve these hemoglobin levels, is not known.

The appearance of hypertension or worsening of existing hypertension is seen in as many as 30% of hemodialysis patients treated with epoetins. The specific mechanism for this is not defined but is thought to include direct effect of the ESA on endothelial cells, alterations in vascular reactivity with increased vasoconstriction and impaired vasorelaxation due to improvement in the anemia and effects on factors such as nitrous oxide and endothelin, increased blood viscosity and plasma volume related to higher red cell mass, and increased cardiac output. Seizures related to ESA therapy are very rare in hemodialysis patients but may be due to severe hypertension and very high hemoglobin levels—predisposing to cerebrovascular sludging and impaired cerebral blood flow. Allergic reactions such as urticaria and skin

rash are uncommon and are rarely serious, but anaphylactic-like reactions have been described.

The epoetins and darbepoetin are rated pregnancy category C (no teratogenicity or fetotoxicity in animal studies), but have been associated with an increased risk of postimplantation fetal loss in animal fertility studies. ESA-related pure red cell aplasia (PRCA) is a rare but potentially life-threatening condition characterized by severe anemia associated with a very low reticulocyte count, the nearly complete absence of erythroid precursor cells in the bone marrow, and the development of neutralizing antierythropoietin IgG antibodies in the blood. These antibodies cross-react with the endogenous hormone as well as recombinant ESAs. PRCA has been reported predominantly in patients with kidney disease who were treated with one particular epoetin alfa product made outside the United States (Eprex; Ortho-Biotech, Inc.), but it has occurred much more rarely with other epoetin preparations as well as with darbepoetin alfa.

PRCA may develop at any time beyond the first 3 to 4 months after initiation of ESA therapy, even months to years later. Prior to 1998, PRCA was reported only very rarely in epoetin-treated patients. Beginning in 1998, there was a sudden increase in the number of reported cases of antibody-mediated PRCA attributable to ESA therapy. Most of these patients—primarily from Europe, the United Kingdom, and Canada—were treated with single-use syringes of Eprex by subcutaneous injection. This eventually prompted regulators to restrict or strongly recommend Eprex use by the IV route. Fortunately, with recommendations for changes in the storage and handling of Eprex and discontinuation of its subcutaneous injection the incidence of ESA-related PRCA has dramatically declined.

The timing of the rather sudden increase in ESA-related PRCA coincided with the use of a new formulation of epoetin alfa (Eprex), which contained polysorbate instead of human serum albumin as a stabilizing agent and was packaged in prefilled syringes with uncoated rubber stoppers from which organic compounds may have leached into the drug solution. The immunogenicity of the epoetin molecule may have been altered by these formulation and packaging changes. It has also been suggested that subcutaneous injection and perhaps incorrect storage and handling may have further potentiated this particular product's immunogenicity.

Any hemodialysis patient who previously had a stable and adequate response to ESA therapy and who suddenly develops severe anemia and loss of response to epoetin or darbepoetin in

the presence of normal platelet and white blood cell counts should be suspected of having PRCA, especially if the reticulocyte count is abnormally low (less than 10,000/μl) and the patient was receiving subcutaneous administration of the ESA. Once other potential causes of ESA hyporesponsiveness are excluded (see material following), the epoetin or darbepoetin alfa should be withheld and assays for binding/neutralizing antierythropoetin antibodies (available through the ESA manufacturer) should be performed. Switching to a different ESA or from subcutaneous to IV injection is not sufficient to eliminate the antibody-mediated risk. Immunosuppressive therapy with prednisone and cyclophosphamide or cyclosporine is generally recommended for patients with ESA-related PRCA because spontaneous remission is rare. Other therapies have been used, including IV immune globulin, plasmapheresis, and mycophenolate mofetil. Recovery after renal transplantation has also been described. Subsequent rechallenge with a different ESA once antibody levels have become undetectable has been reported without recurrence of PRCA, but this is not generally recommended.

ESA Hyporesponsiveness in Hemodialysis Patients

When the serum Hb does not increase as expected in response to ESA therapy perceived as being adequate in anemic hemodialysis patients, a correctable underlying disease or nutritional deficiency state that limits erythropoiesis should be suspected. (This topic is discussed in detail in the chapter on refractoriness to recombinant human erythropoietin treatment.) Such states include iron deficiency due to chronic blood loss, hemolysis, hemoglobinopathies, malignancy, infectious and inflammatory disorders, severe malnutrition, folic acid or vitamin B12 deficiency, severe hyperparathyroidism with marrow fibrosis, and infiltrative processes of the bone marrow such as leukemia and multiple myeloma.

Although there is no single generally accepted definition of ESA hyporesponsiveness, the recently published NKF-K/DOQI clinical practice recommendation suggests that evaluation for specific causes of hyporesponsiveness should be undertaken when the Hb level is considered inappropriately low for the ESA dose, when there is a significant increase in ESA dose needed to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose, and when there is a failure to maintain the Hb level greater than 11 g/dL despite an ESA dose equivalent to 500 IU/kg/week of epoetin. Among hemodialysis patients with

initial hemoglobin levels below 11 g/dL, approximately 90% will have achieved a hemoglobin level greater than 11 g/dL within 6 months. Furthermore, less than 1% of U.S. hemodialysis patients with hemoglobin levels below 11 g/dL who are treated with epoetin doses of more than 30,000 IU/week (i.e., greater than 500 IU/kg/week in a 60-kg patient) remain with hemoglobin levels below 11 g/dL after 6 months of therapy.

Iron deficiency is the primary cause for ESA hyporesponsiveness. Many hemodialysis patients are either iron deficient when ESA therapy is initiated or have inadequate iron stores to support the enhanced erythropoiesis that develops in response to ESA therapy. These patients quickly become iron deficient. Therefore, most ESA-treated hemodialysis patients require iron supplementation. The recent NKF-K/DOQI guidelines recommend iron treatment in hemodialysis patients to maintain TSAT greater than 20% and serum ferritin greater than 200 ng/mL. The preferred route of iron administration in hemodialysis patients is intravenously.

Pharmacologic agents other than iron have been reported in some small-scale studies to be effective for treating erythropoietin-resistant anemia. In the absence of documented folate or vitamin B12 deficiency, there is no role for routine supplementation of either of these compounds. Prior to the availability of ESAs, androgens were often administered by intramuscular injection to stimulate erythropoiesis. These agents are now not recommended because of their toxicity (including acne, virilization, liver disease, and injection site pain) and because of limited evidence that they enhance the response to ESA therapy.

L-carnitine is a carrier molecule involved in the transport of long-chain fatty acids into mitochondria, where they are oxidized to produce energy. It is also thought to be involved in the conversion of acyl coenzyme A, which may be toxic to cells, to the less toxic acyl carnitine. An L-carnitine deficiency state has been described in hemodialysis patients, and anemia in hemodialysis patients has been attributed to this deficiency—although the pathogenetic mechanisms remain speculative. IV and oral L-carnitine have been studied for possible enhancement of ESA responsiveness, largely in case reports and small uncontrolled studies. There are some reports and consensus conference statements supporting the use of IV L-carnitine in ESA-hyporesponsive hemodialysis patients. In the United States, Medicare coverage is available for selected patients who have been on dialysis for at least 3 months, have a plasma-free carnitine level less than 40 μmol/L, and have ESA-resistant anemia with a hematocrit less than 30% for which other causes have been investigated and treated. The NKF-K/DOQI anemia

work group concluded, however, that there was not enough evidence of efficacy to recommend the use of L-carnitine in the treatment of anemia in hemodialysis patients.

Vitamin C (ascorbate) may increase the release of iron from stores, improve iron utilization for red cell production, and modulate oxidative stress. Oral vitamin C can enhance absorption of iron from the gastrointestinal tract. There is no evidence that oral vitamin C is an effective adjuvant to ESA therapy. Studies of IV vitamin C have produced conflicting results. The NKF-K/DOQI anemia guidelines concluded that there was not enough evidence to recommend the use of IV vitamin C as an adjuvant to ESA therapy.

A more recent study, published at about the same time as the NKF-K/DOQI guidelines, included 42 hemodialysis patients who had been treated with IV iron and epoetin for at least 6 months at a dose of 450 U/kg/week or more and had an average 3-month hemoglobin level of 11 g/dL or less, a ferritin level of at least 500 ng/mL, and TSAT of at least 50%. Patients were randomly assigned to a group that received 300 mg of IV vitamin C with each dialysis session or to a control group that continued to receive standard care without vitamin C for 6 months. At 6 months, hemoglobin levels significantly increased in vitamin C–treated patients (from 9.3 to 10.5 g/dL) but not in the control group. The epoetin dose also declined only in the vitamin C–treated patients, as did CRP and ferritin levels.

It was concluded that in hemodialysis patients with refractory anemia and hyperferritinemia vitamin C improved responsiveness to epoetin, either by augmenting iron mobilization from its tissue stores or through antioxidant effects. Whether such treatment affects clinical outcomes such as quality of life, hospitalization rates, and mortality remains to be determined. Concern about toxicity of long-term use of high-dose IV vitamin C related to systemic secondary oxalosis and possible prooxidant effects of ascorbate itself or its related mobilization of iron is also an issue.

Other pharmacologic agents (including statins, pentoxifylline, and vitamin E) have not been studied sufficiently to recommend their use at this time. Modifications of the hemodialysis treatment to enhance ESA responsiveness have been studied, including increasing the dose of dialysis, changes in dialyzer membrane composition and/or permeability, use of ultrapure dialysate, hemodiafiltration, and use of daily and nocturnal dialysis rather than standard thrice-weekly hemodialysis. Data on all of these are inconclusive. The use of ultrapure dialysate and perhaps

nocturnal hemodialysis seem to hold the greatest promise but further studies are needed.

Summary

ESA treatment has revolutionized the treatment of anemia in hemodialysis patients, but at substantial economic costs. Based largely on experience with epoetin rather than with the more recently available darbepoetin alfa, currently available data and recent clinical practice recommendations support the use of ESA therapy in maintaining hemoglobin levels of at least 11 g/dL in hemodialysis patients. Adequate amounts of iron, usually administered intravenously, should be provided to support erythropoiesis and efficient ESA therapy.

Limited evidence of clinical benefit other than improvement in some quality of life measures from maintaining hemoglobin levels above 12 g/dL and concern about increased risk with these hemoglobin levels have led to the recent recommendation that hemoglobin levels of 11.0 to 12.0 S/dL should generally to the target of ESA treatment in hemodialysis patients. As results from new studies emerge, and as other ESAs become available, the goals of anemia therapy in hemodialysis patients will continue to be examined.

Recommended Reading

Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: Results of a combined phase I and II clinical trial. New Engl J Med 1987;316:73–78.

Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease: Results of a phase III multicenter trial. Ann Intern Med 1989;111:992–1000.

These two articles are the first reported results in dialysis patients of the use of recombinant human erythropoietin. The results are important in terms of how this transformed anemia management in patients on dialysis and subsequently with anemia due to other conditions.

Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson R, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. New Engl J Med 1998;339:584–90.

This article describes what remains as the largest clinical trial prospectively studying the clinical outcomes resulting from low versus normal hematocrit/hemoglobin levels in dialysis patients. There was a trend toward a higher combined mortality and first nonfatal myocardial infarction in the higher hematocrit group, leading to the early termination of the study.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47(3):S1–146.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for American Chronic Kidney Disease. 2007 Update on Hemoglobin Target. Am J Kidney Dis, 2007, in press.

These two articles are the most recent revisions to the NKF-K/DOQI clinical practice guidelines and recommendations for adults and children with anemia and CKD.

Collins AJ, Li S, St. Peter W, Ebben J, Roberts T, Ma JZ, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. J Am Soc Nephrol 2001;12:2465–73.

Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol 1999;10:610–19.

This article reviews two observational studies that examined the association between hematocrit and outcomes in hemodialysis patients using Medicare/HCFA databases that support the clinical practice of maintaining hemoglobin levels in the range of 11 to 12 g/dL.

Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002;346:469–75.

This is the original description of pure red cell aplasia due to antierythropoietin antibodies.

Strippoli GFM, Craig JC, Manno C, Schena FP. Hemoglobin targets for the anemia of chronic kidney disease: A meta-analysi of randomized controlled trials. J Am Soc Nephrol 2004;15:3154–65.

Volkova N, Arab L. Evidence-based systematic literature review of the literature of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis 2006;47:24–26.

This article reviews the available studies concerning the outcomes associated with hemoglobin levels in hemodialysis patients.

CHAPTER 59

Treatment of Anemia in Peritoneal Dialysis Patients

Curtis A. Johnson, PharmD; Maureen Wakeen, MSN, CNN; and Stephen W. Zimmerman, MD

Effective treatment of anemia in adult and pediatric peritoneal dialysis (PD) patients consists of an erythropoiesis-stimulating agent (ESA) usually in combination with iron supplementation. Epoetin alfa (epoetin) and darbepoetin alfa (darbepoetin) are the two ESAs presently available in the United States. Both products are effective in increasing hemoglobin values. However, anemia remains more prevalent in pediatric compared to adult PD patients. Data from the Centers for Medicare & Medicaid Services ESRD Clinical Performance Measures Project indicate that 88% of sampled adult PD patients and 94% of pediatric PD patients in the United States received an ESA during the period of October of 2004 to March of 2005. The prescribing pattern for ESAs in adult PD patients was 96% epoetin and 6% darbepoetin (groups not mutually exclusive). For pediatric patients, it was 92% epoetin and 11% darbepoetin (groups not mutually exclusive). Table 59.1 provides additional information on the use of epoetin in the United States from October of 2004 to March of 2005.

A randomized prospective double-blind placebo-controlled trial as well as more than 15 years of additional clinical experience have clearly demonstrated the efficacy of epoetin in PD patients. Experience with the use of darbepoetin in PD patients is less extensive, although the product appears to have similar efficacy and safety in PD patients. This chapter provides information regarding the use of epoetin and darbepoetin in PD patients and addresses unique aspects of iron therapy in this population. A more general discussion of iron administration, therapeutic monitoring, and reasons for hyporesponsiveness to ESA therapies are presented elsewhere and are not addressed here.

Goal of Therapy

According to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines, the recommended target hemoglobin value for all

Table 59–1

Adult/Pediatric PD/HD Patient Epoetin Use Patterns from December 2005 ESRD Clinical Performance Measures Project Annual Report

Patient Group	Route of administration (% Patients Prescribed Epoetin)[a]	Mean ± SD Weekly Dose (Units/kg)
Adult PD patients	• Subcutaneous: 98 • Intravenous: 7	• 154 ± 150 • 188 ± 173
Adult HD patients	• Subcutaneous: 5 • Intravenous: 96	• 215 ± 233 • 281 ± 281
Pediatric PD patients	• Subcutaneous: 97 • Intravenous: 6	• 228 ± 214 • 317 ± 218
Pediatric HD patients	• Subcutaneous: 10 • Intravenous: 91	• 275 ± 241 • 364 ± 358

a. Groups not mutually exclusive.

dialysis patients is 11.0 g/dL or greater. However, safety concerns from recent clinical trials have prompted many clinicians to generally use a target hemoglobin value of 11–12 g/dL, while avoiding hemoglobin values greater than 13.0 g/dL. An accompanying clinical practice recommendation further indicates that to achieve the target hemoglobin value in patients receiving PD a transferrin saturation >20% and a serum ferritin concentration >100 ng/mL should be maintained.

At present, there are no clinical practice guidelines for anemia management in pediatric PD patients. However, clinical practice recommendations for anemia management in children are now available. These recommendations for hemoglobin, transferrin saturation, and serum ferritin mimic those for adult patients receiving PD.

Hemoglobin values less than the NKF-K/DOQI-recommended target are associated with increased adjusted mortality hazard ratios and increased risk of adjusted first-hospitalization rate in adult PD patients.

Dosing and Route of Administration of Epoetin

Because patients receiving PD do not have ready venous access, the intravenous (IV) route of epoetin administration is impractical

and infrequently used. Due to its pharmacokinetic and pharmacodynamic profile, subcutaneous administration provides the easiest and most economical route for PD patients. Subcutaneous injection into the thigh area may provide the most favorable serum concentration profile, followed by the upper arm (mid-deltoid region) and the abdomen. Although pharmacokinetic and efficacy studies have demonstrated that intraperitoneal (IP) dosing is a viable alternative in PD patients, IP dosing is seldom prescribed. However, this route of administration remains a suitable option—especially for pediatric PD patients for whom subcutaneous (SC) dosing is distressing.

Epoetin dosing guidelines for PD patients are similar to those of HD patients. Generally, an SC starting dose of 30 to 50 U/kg twice weekly leads to adequate response. Dose adjustments may be made, usually once a month, by increasing or decreasing the dose of epoetin—or conversely by shortening or lengthening the dosing interval. The goal of therapy should be to achieve the target hemoglobin value over a minimum of 8 weeks. Many PD patients can be successfully treated with once-weekly epoetin dosing. A European study of 74 PD patients treated with SC epoetin beta demonstrated that dosing every 2 weeks was successful in maintaining target hemoglobin concentrations. All study participants received a stable once-weekly dose of epoetin beta before entry into the study treatment period.

Epoetin (Epogen, Procrit) is commercially available in the United States in two formulations. The first is a preservative-free preparation, which some patients describe as causing discomfort upon SC administration. The second is a preparation that contains the preservative benzyl alcohol. This preservative-containing product is less likely to cause discomfort upon injection. Patient discomfort can also be minimized by using small-gauge needles (e.g., 29-gauge) and a small injection volume, and by reducing the frequency of dose administration. Pain upon injection may be a particularly troublesome issue for children receiving PD.

Dosing and Route of Administration of Darbepoetin

The recommended starting dose of darbepoetin for adult patients not receiving any other ESA is 0.45 μg/kg body weight, given intravenously or subcutaneously once a week. The target hemoglobin is the same as for epoetin therapy. Dose adjustments should be made approximately once a month until a stable target hemoglobin concentration is achieved.

There are no head-to-head clinical trials comparing the efficacy and safety of darbepoetin and epoetin in PD patients. Nevertheless, clinical studies have confirmed that darbepoetin can be used successfully in adult and pediatric PD patients. Because darbepoetin has a longer plasma elimination half-life than epoetin, darbepoetin dosing intervals are usually more extended than those of epoetin.

Eleven PD patients were among 1502 dialysis patients switched from epoetin to darbepoetin for the purpose of evaluating the safety and efficacy of darbepoetin given at extended dose intervals. All patients receiving epoetin two or three times a week were switched to darbepoetin once a week. Patients receiving epoetin once a week were switched to darbepoetin every 2 weeks. The initial mean weekly darbepoetin dose was calculated from the baseline epoetin dose in a ratio of 200 IU epoetin to 1 μg darbepoetin and was adjusted according to hemoglobin response. The results of the study indicated that darbepoetin given once a week or once every other week was successful in maintaining target hemoglobin concentrations. The authors did not present a separate data analysis for PD patients.

The results of this study are similar to those of an evaluation of 17 adult PD patients receiving stable SC epoetin doses once, twice, or three times weekly who were then switched to every-other-week darbepoetin dosing. A 200-unit to 1-μg epoetin/darbepoetin conversion ratio was used. Subsequent doses were titrated for up to 24 weeks to maintain the target hemoglobin close to the baseline value and within a range of 10 to 13 g/dL. The authors concluded that every-other-week SC dosing of darbepoetin was successful at maintaining desired hemoglobin concentrations.

Limited clinical experience suggests that PD patients can be successfully treated with darbepoetin dosed once a month. Eleven stable PD patients treated with once-weekly epoetin doses were switched to the equivalent weekly SC darbepoetin dose once a month. The mean weekly epoetin dose (in units) was divided by 200 to determine the mean weekly darbepoetin dose (in μg), which was then multiplied by 4 to determine the monthly darbepoetin dose. During the 24-week study duration, hemoglobin and hematocrit values during darbepoetin treatment were similar to baseline values with epoetin therapy. This small study provides justification for considering monthly SC dosing of darbepoetin in adult PD patients. A monthly dosing schedule offers the opportunity for dose administration to occur as part of monthly clinic visits.

Nine pediatric PD patients were given darbepoetin alfa as part of an open-label uncontrolled study of 33 children with chronic kidney disease. The initial darbepoetin dose was 0.45 μg/kg/week

given subcutaneously and was adjusted according to hemoglobin response. Patients were observed for 28 weeks. The authors reported that at 12 and 28 weeks, respectively, 73% and 87% of patients were receiving darbepoetin less than once weekly. However, the results of PD patients were not identified separately. The average darbepoetin treatment dose was approximately 0.5 μg/kg/week.

Darbepoetin (Aranesp) is commercially available in the United States in single-dose vials and prefilled syringes. The solution is preservative free and does not contain benzyl alcohol. Darbepoetin may be administered subcutaneously and intravenously.

Other Dosing Considerations

Final SC dose requirements may be considerably less than those required for HD patients receiving epoetin intravenously, as is evident from Table 59.1. An analysis of Medicare claims data for patients starting dialysis from 1995 to 2000 indicated that steady-state monthly epoetin dose requirements for HD patients (primarily IV dosing) were double those of PD patients (primarily SC dosing). Other studies have noted that the average SC dose of epoetin is approximately 1/3 less than the average IV dose. This observation suggests that patients being converted from IV to SC dosing will likely require dose reduction to maintain stable hemoglobin values. In the case of darbepoetin, however, no dose adjustment is required when converting from IV to SC dosing. Patients switching from HD to PD are often candidates for converting from IV to SC ESA administration. Hemoglobin should be monitored closely during the transition from one route of administration to the other.

Conversion from one ESA to the other can be accomplished in various ways. One published approach uses a fixed ratio of 200 units epoetin to 1 μg darbepoetin. Another approach is to use a dose conversion table published in the prescribing information for the two products. This sliding scale approach to dose conversion uses a ratio that ranges from approximately 200 units epoetin to 1 μg darbepoetin up to >450 units epoetin to 1 μg darbepoetin. Some clinicians have created dose conversion protocols that are intermediate between these two approaches.

Adverse Effects of Epoetin and Darbepoetin

Hypertension, the most common adverse event associated with the use of epoetin and darbepoetin in patients with chronic kidney disease, occurs in approximately 1/4 of patients. This topic is discussed in greater detail in another chapter. Other less common

adverse events associated with the use of these products are described in the prescribing information provided by the manufacturer.

A relatively small number of patients who have received epoetin and darbepoetin have developed pure red cell aplasia (PRCA) due to the formation of antierythropoietin-neutralizing antibodies. PRCA leads to severe anemia with impaired reticulocyte formation. The development of PRCA has occurred predominantly in patients receiving epoetin or darbepoetin by the SC route, the route of administration most often prescribed for PD patients. PRCA should be considered part of the evaluation of sudden loss of response to these erythropoietic hormones.

Parenteral Iron Administration to PD Patients

Because PD patients do not have ready access for the administration of IV iron, oral iron supplements are commonly prescribed. For various reasons, however, many PD patients are unable to remain iron replete with oral iron therapy alone. A recent report indicated that among prevalent PD patients treated with epoetin in 2002 19.3% received IV iron. According to the 2005 ESRD Clinical Performance Measures Project, 56% of sampled adult PD patients and 84% of pediatric PD patients were prescribed oral or IV iron at least once during the 6-month study period. Overall, 25% of adult PD patients were prescribed IV iron. Further details about iron prescription are presented in Table 59.2.

Iron dextran (INFeD, Dexferrum), sodium ferric gluconate complex (Ferrlecit), and iron sucrose (Venofer) are the commercial parenteral iron products available in the United States. Each has

Table 59–2

Adult/Pediatric PD Patient Iron Use Patterns from December 2005 ESRD Clinical Performance Measures Project Annual Report

Group	Route of Administration (% Patients Prescribed Iron)[a]
Adult PD patients	• Oral: 63 • Intravenous: 44
Pediatric PD patients	• Oral: 95 • Intravenous: 13

a. Groups not mutually exclusive.

Table 59–3

IV Iron Dosing Protocols for Adult PD Patients[a]

	Iron Dextran	Sodium Ferric Gluconate Complex	Iron Sucrose
Test dose recommended?:	Yes	No	No
Dosing scheme:	25 mg diluted in 50 mL normal saline; infuse over 30 min. Follow with 475 mg diluted in 300 mL normal saline; infuse over 4–5 h 25 mg diluted in 50 mL normal saline; infuse over 30 min. Follow with 975 mg diluted in 500 mL 1/2 normal saline; infuse over 5 h.[b]	125 mg diluted in 100 mL normal saline; infuse over 60 min 250 mg diluted in 100 mL saline; infuse over 1 h.	500 mg diluted in 300 mL normal saline; infuse over 4–6 h 200 mg diluted in 150 mL normal saline; infuse over 1 h 50 mg undiluted over 5 min 200 mg undiluted over 2 min 1000 mg total cumulative dose. Give 2 infusions of 300 mg over 1.5 h 14 d apart followed by one 400 mg infusion over 2.5 h 14 d later. Dilute each dose in a max of 250 mL of normal saline.

a. These protocols do not necessarily conform to FDA-approved product labeling.
b. This dosing scheme may be associated with increased dose-related adverse events.

been used effectively and safely for intermittent dosing in PD patients. Numerous reports describe various methods of dosing these products safely with a minimum of patient inconvenience. Table 59.3 offers representative published dosing schemes for administering IV iron to PD patients.

There is very little published information regarding the administration of IV iron to pediatric PD patients. Oral iron is recommended whenever possible. IP iron dextran administration has been advocated in a few publications. However, due to scarcity of data on long-term safety and efficacy of IP iron in humans this route of administration cannot be recommended at this time. The development of erythropoietic hormones has improved anemia management for the majority of patients receiving PD. Newer ESAs and less frequent dosing schedules have made ESA administration more convenient.

Recommended Reading

Brunkhorst R, Bommer J, Braun J, et al. Darbepoetin alfa effectively maintains haemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. Nephrol Dial Transplant 2004;19:1224–30.

Review of a prospective study of hemodialysis and peritoneal dialysis patients converted from erythropoietin to darbepoetin. The study demonstrated stable hemogloblin values when extending the interval of dosing.

Centers for Medicare & Medicaid Services. 2005 Annual Report, End Stage Renal Disease Clinical Performance Measure Project. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of Clinical Standards & Quality, Baltimore, Maryland, December 2005.

This is the 2005 annual report of the ESRD Clinical Performance Measures Project that details the most current information available regarding anemia management in adult and pediatric PD patients.

Geary DF, Keating LE, Vigneux A, et al. Darbepoetin alfa (Aranesp) in children with chronic renal failure. Kidney Int 2005;68:1759–65.

This prospective study demonstrated safety and efficacy of darbepoetin in children with chronic kidney disease or ESRD. It also presented dosing guidelines for pediatric patients.

Mahajan S, Boulton H, Gokal R. A trial of subcutaneous administration of darbepoetin alfa once every other week for the treatment of anemia in peritoneal dialysis patients. J Nephrol 2004;17:687–92.

This prospective study in patients on peritoneal dialysis demonstrated stable hemoglobin values in patients converted from erythropoietin to darbepoetin every other week.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia of Chronic Kidney Disease. Am J Kidney Dis 2006;47(3):S1–145.

This is the 2006 anemia management update from the NKF-K/DOQI. This document contains clinical practice guidelines and recommendations for anemia management in patients with chronic kidney disease.

Nissenson AR, Korbet S, Burkart J, et al. Multicenter trial of erythropoietin in patients on peritoneal dialysis. J Am Soc Nephrol 1995;5:1517–29.

Review of a prospective randomized trial validating the safety and efficacy of epoetin in patients on peritoneal dialysis. Nearly 90% of patients receiving subcutaneous epoetin experienced amelioration of anemia by the twelfth week of the study.

Schröder CH for the European Pediatric Peritoneal Dialysis Working Group. The management of anemia in pediatric peritoneal dialysis patients: Guidelines by an ad hoc European committee. Pediatr Nephrol 2003;18:805–09.

This group established guidelines for the evaluation and treatment of anemia in children.

St. Peter WL, Obrador GT, Roberts TL, et al. Trends in intravenous iron use among dialysis patients in the United States (1994–2002). Am J Kidney Dis 2005;46:650–60.

This article reviews the use of IV iron in incident Medicare dialysis patients from 1994 to 2002. The authors found a shift in iron prescribing patterns from iron dextran to sodium ferric gluconate complex and iron sucrose.

Theodoridis M, Passadakis P, Kriki P, et al. Efficient monthly subcutaneous administration of darbepoetin in stable CAPD patients. Perit Dial Int 2005;25:564–69.

This prospective study in PD patients demonstrated stable hemoglobin values with monthly SC darbepoetin dosing.

Vanrenterghem Y, Bárány P, Mann JFE, et al. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. Kidney Int 2002;62:2167–75.

This prospective study compares the efficacy and safety of IV and subcutaneous darbepoetin and epoetin in hemodialysis and peritoneal dialysis patients. Darbepoetin was as effective, with a similar safety profile, as epoetin—but with a reduced dose frequency.

CHAPTER 60

Hypertension and Epoetin Use in Dialysis Patients

Nosratola D. Vaziri, MD, and Madeleine V. Pahl, MD

Cardiovascular complications remain the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Numerous metabolic and hemodynamic disorders contribute to the development of cardiovascular disease in this population. Two of the many culprits involved in the pathogenesis of cardiovascular complications in ESRD patients (namely, hypertension and anemia) are relevant to the present chapter. By raising the left ventricular (LV) afterload, chronic hypertension promotes LV hypertrophy (LVH)—and ultimately LV dilation and congestive heart failure. In addition, hypertension contributes to coronary arteriosclerosis and ischemic heart disease.

Likewise, by necessitating a high cardiac output and hence cardiac workload long-standing severe anemia promotes LVH, which is a major risk factor for cardiovascular complications. Hence, hypertension and anemia (the two most common features of ESRD) work in concert to impair cardiac function and structure—compounding the effects of numerous other risk factors (such as dyslipidemia, hypervolemia, oxidative stress, inflammation, hyperhomocystinemia, glucose intolerance, and vascular calcification) frequently present in this population.

More than 80% of ESRD patients have hypertension at the onset of maintenance dialysis therapy. Although hypervolemia is the dominant cause of hypertension in the majority of ESRD patients, increased vascular resistance is also involved in the genesis of hypertension in many cases. Despite the availability of highly effective antihypertensive agents, the use of ultrafiltration for fluid management, and relatively close medical supervision, hypertension is not adequately controlled in a large percentage of this high-risk population.

Recombinant human erythropoietin (r-HuEPO) administration is highly effective in ameliorating the anemia of renal disease. Correction of severe anemia mitigates the elevation of cardiac output and the resultant LVH in both predialysis and dialysis-dependent patients with renal disease. However, these effects are less pronounced in hemodialysis patients with high-capacity arte-

riovenous blood accesses than they are in peritoneal dialysis patients, in dialysis-independent patients, or in those with nonrenal anemia. The residual high-cardiac output occasioned by shunting of the blood through the low-resistance circuit (i.e, the blood access) is the reason for this phenomenon.

Although amelioration of anemia improves the associated high-cardiac output state and LV function/structure, it frequently raises arterial blood pressure—which if left untreated can augment the risk of cardiovascular complications. Fortunately, with rare exceptions r-HuEPO-induced hypertension can be readily corrected—thus minimizing the risk while retaining the benefits of r-HuEPO therapy. In addition, r-HuEPO therapy reduces hemodynamic instability during dialysis—which when present can limit fluid removal by ultrafiltration. Thus, r-HuEPO therapy can enhance the ability to remove excess fluid and achieve euvolemia.

Clinical Features

Initial multicenter clinical trials of r-HuEPO revealed a rise in mean arterial blood pressure exceeding 10 mmHg in approximately 70% of the treated patients within 2 weeks to 6 months after the onset of r-HuEPO therapy. The rise in arterial blood pressure was considered clinically significant in at least 40% of the treated patients. Thus, maintenance r-HuEPO therapy can cause de novo hypertension or exacerbation of preexisting hypertension in a substantial segment of the ESRD population. The observed rise in blood pressure is generally mild to moderate and readily controlled by intensification of fluid removal by ultrafiltration alone, or together with initiation or adjustment of antihypertensive medications.

Rarely, however, r-HuEPO therapy can cause severe hypertension—leading to encephalopathy and seizures requiring hospitalization and intensive antihypertensive therapy, along with a temporary cessation of r-HuEPO therapy. Several conditions have been considered associated with an increased risk for development of hypertension with r-HuEPO therapy, including severe pretreatment anemia, preexisting hypertension, high r-HuEPO dosages, use of intravenous as opposed to subcutaneous route of r-HuEPO administration, and possible angiotensinogen gene polymorphisms.

Mechanisms

Expansion of erythrocyte mass with r-HuEPO therapy theoretically can raise blood volume and thus blood pressure. However,

cardiac output tends to fall with amelioration of anemia that is accompanied by a high-output state. Moreover, by conferring greater cardiovascular stability r-HuEPO therapy facilitates fluid removal by dialysis. Consequently, the rise in blood pressure with r-HuEPO therapy is not related to volume expansion. Rather, it is due to increased systemic vascular resistance. The rise in systemic vascular resistance with r-HuEPO therapy was originally attributed to an increase in blood viscosity from subnormal to near normal levels due to r-HuEPO-mediated amelioration of anemia.

In addition, loss of hypoxia (anemia)–induced vasodilatation and enhanced diversion of endothelium-derived nitric oxide by hemoglobin were considered to cause vasoconstriction. However, in a series of clinical and laboratory experiments we found that contrary to the original view the rise in systemic vascular resistance and arterial blood pressure with r-HuEPO therapy is not due to the associated increase in hematocrit. In fact, r-HuEPO therapy raised blood pressure to the same extent in iron-deficient subjects with persistent anemia as in iron-sufficient subjects showing a robust increase in hematocrit.

The role of r-HuEPO therapy as opposed to anemia correction was further supported by the observation that gradual correction of anemia with multiple small red blood cell transfusions designed to simulate the effect of r-HuEPO therapy did not alter blood pressure. In this regard, lack of concordance between changes in blood pressure and hematocrit had been originally noted in some patients, but largely ignored. This was because the temporal association of increases in hematocrit and blood pressure seen in most cases was wrongly assumed to imply causality.

It is now clear that r-HuEPO therapy raises both resting and stimulated levels of cytoplasmic ionized calcium $[Ca^{++}]_i$, which is the ultimate determinant of vascular smooth muscle tone/reactivity and thereby systemic vascular resistance and blood pressure. This effect appears to be mediated by activation of r-HuEPO receptors, which are now known to be expressed in erythroid progenitor cells—as well as in a wide array of other cell types, including megacaryocytes, vascular smooth muscle cells, and endothelial cells. The r-HuEPO-induced rise in $[Ca^{++}]_i$, in turn, results in acquired resistance to the action of nitric oxide (otherwise known as endothelium-derived relaxing factor) that works by lowering $[Ca^{++}]_i$ through a cGMP-mediated process.

Moreover, r-HuEPO raises the level of naturally occurring nitric oxide synthase inhibitor asymmetrical dimethylarginine (ADMA) by inhibiting the activity of dimethylarginine dimethylaminohydrolase (which degrades ADMA). Consequently, r-HuEPO can

reduce production of nitric oxide by vascular endothelial cells. In addition, r-HuEPO therapy augments the tissue (not circulating) renin-angiotensin system, raises endothelin and vasoconstrictive prostaglandins, and lowers vasodilatory prostaglandins. These events work in concert to promote vasoconstriction and hypertension. Furthermore, r-HuEPO stimulates angiogenesis and vascular cell proliferation in vitro. Chronic r-HuEPO therapy, therefore, may directly and indirectly (by raising blood pressure) promote vascular remodeling—leading to a fixed rise in vascular resistance.

Management

The ideal management of hypertension in dialysis-dependent patients is one that provides optimal blood pressure control between dialysis treatments while avoiding significant hypotension during and after dialysis. Judicious use of a combination of volume control by ultrafiltration and antihypertensive medications is frequently effective in achieving this objective. However, in some instances it is exceedingly difficult to achieve optimal interdialytic blood pressure control without encountering intradialytic hypotension. Given the greater risk of sustained uncontrolled hypertension and the relatively low risk of mild transient hypotension, it is inappropriate to tolerate poorly controlled hypertension in order to minimize the latter condition.

Because r-HuEPO-induced hypertension is primarily due to vasoconstriction as opposed to hypervolemia, it is more responsive to appropriate antihypertensive medication and less responsive to ultrafiltration. In some cases, r-HuEPO therapy results in moderate to severe hypertension that may be relatively refractory to antihypertensive medications. A reduction in the dosage, or a temporary cessation of r-HuEPO therapy, may be considered in such instances. In addition, a change in the mode of r-HuEPO administration from an intravenous route to a subcutaneous route may prove beneficial.

Use of Ultrafiltration

Judicious use of ultrafiltration is necessary to correct hypervolemia in all dialysis-dependent patients. However, overreliance on fluid removal as the main strategy for treating hypertension frequently results in intradialytic and postdialytic hypotension, nausea and vomiting, muscle cramps, orthostatic symptoms, and postdialysis fatigue. Patients with left ventricular hypertrophy and diastolic dysfunction are particularly sensitive to fluid removal.

Several measures have been shown to limit the side effects of fluid removal.

These measures include the use of bicarbonate-based (as opposed to acetate-based) dialysates, infusion of hypertonic saline during dialysis, use of sodium modeling, refraining from eating during dialysis, lowering dialysate temperature, increasing the duration of dialysis, and limiting interdialytic fluid gain. As noted previously, chronic r-HuEPO therapy is primarily associated with a vasoconstriction-dependent hypertension. Therefore, use of excessive ultrafiltration and induction of hypovolemia is inappropriate for the treatment of r-HuEPO-induced hypertension and can cause undesirable symptoms. Use of antihypertensive medications is necessary in patients with persistent hypertension despite euvolemia.

Antihypertensive Drug Therapy

Several classes of antihypertensive medications have been successfully employed in the management of r-HuEPO-induced hypertension. Because chronic r-HuEPO therapy raises cytoplasmic Ca^{++} concentration (the final determinant of vascular tone), the use of long-acting L-type calcium channel blockers (which lower cytoplasmic Ca^{++}) is appropriate in the treatment of the associated hypertension. In fact, long-acting calcium channel blockers are widely used in this condition. We recently showed that dihydropyridine and benzodiazepine, but not phenylalkylamine, classes of L-type channel blockers increase nitric oxide production and nitric oxide synthase expression in cultured human endothelial cells.

We also demonstrated that r-HuEPO therapy causes nitric oxide resistance. Thus, administration of a long-acting dihydropyridine or a benzodiazepine calcium channel blocker is a logical approach in this case. In addition, angiotensin-converting enzyme (ACE) inhibitors and AT-1 receptor blockers that interrupt the renin-angiotensin system have been successfully used in this setting. As noted previously, r-HuEPO therapy enhances the tissue renin-angiotensin system—which may account for the efficacy of ACE inhibitors and AT-1 receptor blockers in the treatment of r-HuEPO-induced hypertension. Alternatively, drugs that target the adrenergic system (such as a_1 blockers, beta blockers, and centrally acting sympatholytic agents) can be used in situations in which increased adrenergic tone is suspected. Caution should be exercised, however, with the use of the sympatholytic agents because they tend to cause intradialytic and orthostatic hypotension.

Because r-HuEPO therapy raises endothelin production, ET-A receptor blockade theoretically may be effective in the treatment of r-HuEPO-induced hypertension. However, ET-A receptor blockers are not yet available for clinical use. In rare patients with refractory hypertension, we have successfully used the potent direct vasodilator minoxidil together with a selective beta blocker. Finally, neutral endopeptidase inhibitors (which simultaneously block generation of angiotensin II and inhibit inactivation of bradykinin and atrial natriuretic peptide) may be of value in the treatment of r-HuEPO-induced hypertension. However, data on the safety and efficacy of this class of antihypertensive agents in the treatment of r-HuEPO-associated hypertension are lacking and await future investigation.

In many cases, multiple antihypertensive drugs may be needed to accomplish satisfactory blood pressure control. Moreover, blood pressure may vary at different points during the intra- and inter-dialytic periods—requiring specific dosing regimens for a given patient. For example, the pre-dialysis dose of antihypertensives may have to be withheld in individuals prone to severe intradialytic hypotension. Similarly, the drug(s) may have to be withheld on dialysis days for those patients who exhibit low blood pressure after dialysis—whereas additional dosages may be required in patients with intradialytic hypertension. In a minority of dialysis-dependent patients, blood pressure rises during dialysis despite fluid removal by ultrafiltration.

Several mechanisms may be involved in the pathogenesis of this condition, which is commonly known as paradoxical hypertension. For example, removal by dialysis of dialyzable antihypertensive drugs (such as atenolol, nadolol, methyldopa, minoxidil, AT-1 receptor blockers, and ACE inhibitors) can potentially account for intradialytic hypertension. In this case, intradialytic dosing of the drug can help prevent or correct hypertensive episodes. However, in most instances paradoxical hypertension is due to intense activation of the sympathetic and/or renin-angiotensin systems in response to fluid removal. Sympatholytic drugs or ACE inhibitors are frequently effective in such circumstances. In addition, moderation in fluid removal and upward adjustment of the estimated dry weight is frequently helpful in mitigating paradoxical hypertension.

r-HuEPO therapy has been shown to reverse uremic platelet dysfunction by enhancing calcium signaling. Interestingly, several studies have demonstrated attenuation of r-HuEPO-induced hypertension by antiplatelet agents. The precise mechanisms(s) by which antiplatelet agents exert this effect is uncertain and requires further investigation.

Management of Accelerated Hypertension

On rare occasions, r-HuEPO therapy results in a hypertensive crisis—defined by severe elevation of blood pressure together with evidence of encephalopathy, retinopathy, and/or LV dysfunction (congestive heart failure, pulmonary edema, or angina). In such cases, intravenous administration of nitroprusside or nitroglycerin (when cardiac ischemia is present) under close cardiovascular monitoring is indicated. Asymptomatic patients may be treated in an ambulatory facility with oral agents such as calcium channel blockers, ACE inhibitors, and sympatholytic agents. However, patients should be monitored to ensure adequate blood pressure control and clinical stability before being released.

When gross hypervolemia is present, excess fluid should be acutely removed by dialysis as part of the treatment regimen. Caution should be exercised to avoid rapid lowering of blood pressure in patients with a history of cerebrovascular disease or in those patients with carotid bruits. In patients exhibiting r-HuEPO-induced hypertensive crisis, it may be necessary to discontinue r-HuEPO administration and to resume therapy cautiously at a reduced dosage after the crisis is fully averted.

Recommended Reading

Buckner FS, Eschbach JW, Haley NR, Davidson RC, Adamson JW. Hypertension following erythropoietin therapy in anemic hemodialysis patients. Am J Hypertens 1990;3:947–55.

This article analyzes changes in blood pressure during an initial multicenter clinical trial of r-HuEPO therapy.

Kusano E, Inoue M, Akai Y, Furuya H, Ando Y, Tabei K, et al. Effect of ticlopidine hydrochloride on erythropoietin-induced rise in blood pressure in patients on maintenance hemodyalisis. Nephron 2002;91(4):654–58.

Provides data suggesting that the antiplatelet agent ticlopidine may prevent r-HuEPO-induced hypertension, possibly through enhancement of nitric oxide production.

Rodrigue M, Moreau C, Lariviere R, Lebel M. Relationship between eicosanoids and endothelin-1 in the pathogenesis of erythropoietin-induced hypertension in uremic rats. J Cardiovas Pharmacol 2003;41(3):388–95.

The study provides evidence that vasoconstrictor autacoids such as thromboxane A2 and endothlin-1 are involved in the pathogenesis of r-HuEPO-induced hypertension.

Scalera F, Kielstein JT, Martens-Lobenhoffer J, Postel SC, Tager M, Bode-Boger SM. Erythropoietin increases asymmetric dimethylarginine in endothelial cells: Role of dimethylarginine dimethylaminohydrolase. J Am Soc Nephrol 2005;16(4):892–98.

This study provides additional insight into the mechanisms of r-HEPO-induced hypertension and implicates altered nitric oxide synthesis in this process.

Vaziri ND. Mechanism of erythropoietin-induced hypertension. Am J Kidney Dis 1999;33:821–28.

This article provides a comprehensive review of the mechanisms involved in the pathogenesis of r-HuEPO-induced hypertension.

Vaziri ND, Zhou XJ, Naqvi F, Ovesi F, Wang ZQ, Purdy RE. Role of nitric oxide resistance in erythropoietin-induced hypertension in rates with chronic renal failure. Am J Physiol 1966;271:E113–22.

This study provided convincing evidence for the role of r-HuEPO as opposed to anemia correction in the genesis of r-HuEPO-induced hypertension. The study further showed the rise in cytosolic Ca++ and the occurrence of nitric oxide resistance with chronic r-HuEPO therapy.

Zhou XJ, Vaziri ND. Defective calcium signaling in uremic platelets and its amelioration with long-term erythropoietin therapy. Nephrol Dial Transpl 2002;17:992–97

This study demonstrated the presence of impaired calcium signaling in uremia and its reversed by r-HEPO therapy. This observation may in part provide the basis for the reported benefit of the antiplatelet agent ticlopidin in amerliorating rHEP-induced hypertension.

CHAPTER 61

Epoetin and Iron Deficiency

Rajiv Agarwal, MD

Epidemiology of Iron Deficiency in Chronic Kidney Disease

In the adult U.S. population, 1.2 million women and 390,000 men have anemia attributable to chronic kidney disease (CKD). In a population-based survey of adults in the United States, CKD-attributable anemia occured early in the course of kidney disease. Significant reduction in Hgb was seen in men with a calculated creatinine clearance of <70 mL/minute and in women with a calculated creatinine clearance of <50 mL/minute. Although gender-based thresholds exist for the definition of anemia in the general population (<12 g/dL in women and <13.5 g/dL in men), in people with CKDa Hgb <12 g/dL is considered anemic. Thus, it is of little surprise that more women are anemic than men.

Interestingly, blacks are more often anemic compared to other ethnicities for unknown reasons. Approximately 40% of women and 20% men have transferrin saturation of <20% irrespective of calculated creatinine clearance. For stage 4 CKD, approximately 40 to 50% of people have serum ferritin concentration of <100 ng/mL. Because most patients with advanced CKD will need replacement EPO (Epoetin) to treat anemia, most patients will also need iron for effective erythropoiesis.

Pathophysiology

Unlike most ions and minerals, the concentrations of which are regulated by the kidneys, the regulation of iron content in the body occurs in the small intestine and there is no significant excretion of iron by the kidneys. Dietary absorption of iron is only 1 mg, but formation of red blood cells requires about 30 mg of iron daily—provided by the release of reticuloendothelial iron recovered from senescent red blood cells (RBCs).

A normal diet should contain 13 to 18 mg of iron per day, which normally consists of heme and nonheme iron. Iron absorption is maximal in the duodenum, less in the jejunum, and least in the ileum. Nonheme iron is absorbed mainly in the duodenum, where low pH favors solubility of iron. Iron is absorbed by the divalent

metal transporter (DMT1) expressed on the surface of enterocytes in the upper small intestine (Figure 61.1). DMT1 only transports ferrous iron, whereas dietary iron is largely ferric. A ferric reductase called duodenal cytochrome b (Dcytb) is therefore required. The expression of this enzyme is regulated by iron deficiency and follows the expected gradient from duodenum to ileum.

Heme iron can be directly absorbed via the heme-carrier protein 1 (HCP-1) via apical enterocytes of the duodenum. In addition, heme-efflux proteins are present in enterocytes and other cells to prevent toxicity due to heme overload. On the basolateral aspect of enterocytes, iron is released into the circulation via ferroportin

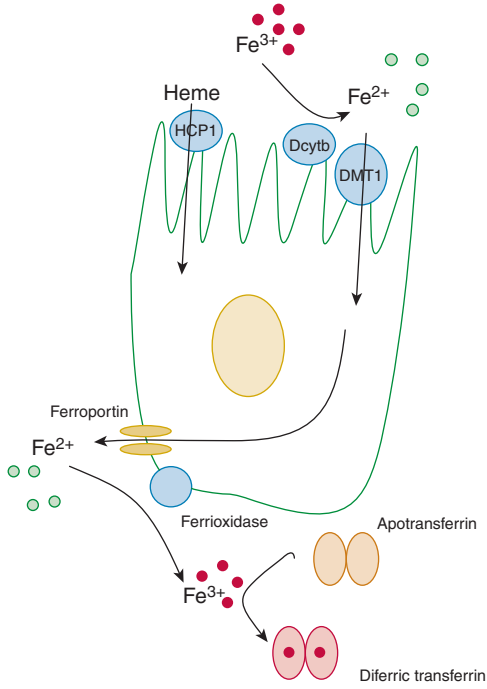


Figure 61–1

Iron is absorbed by the divalent metal transporter (DMT1) expressed on the surface of enterocytes in the upper small intestine.

(also known as IREG1 and MTP1) in combination with other proteins (a ferroxidase hephestin as well as ceruloplasmin, which convert ferrous iron to ferric ion)—where it is captured by the butterfly-shaped transferrin that can hold two atoms of iron-1 in each wing. The diferric transferrin molecule preferentially binds to transferrin receptors expressed on tissues that require iron for cellular function, including erythroblasts, and through clathrin-coated pits is internalized (Figure 61.2).

The resulting endosome is acidified to release iron in the cell, and transferrin devoid of iron (called apotransferrin) is recycled back to the circulation. However, depleted iron stores increase gut iron absorption (and vice versa). Whereas factors that regulate iron absorption are not entirely clear, hepcidin (a hepatic antimicrobial peptide) may be an important signal for gut iron absorption. In

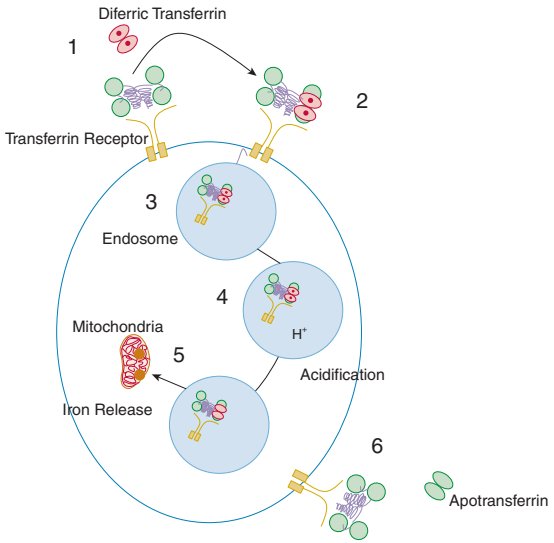


Figure 61–2

The diferric transferrin molecule preferentially binds to transferrin receptors expressed on tissues that require iron for cellular function, including erythroblasts, and through clathrin-coated pits is internalized.

inflammatory and iron overload states, when hepcidin is overproduced gut absorption of iron is suppressed. Furthermore, the release of iron from the reticuloendothelial system is also impaired when hepcidin concentrations are increased. These emerging data on the important role of hepcidin in iron biology shift the focus of regulation of iron absorption from the gut (and iron release from the reticuloendothelial system) to the liver. How hepcidin interacts with the enterocyte or with the reticuloendothelial system to regulate iron absorption is unknown.

Iron deficiency is commonly seen in patients with CKD due to mismatch between supply and demand for iron. Iron is lost from the body due to a bleeding diathesis (such as through platelet dysfunction or aspirin use), gastrointestinal erosions and arteriovenous malformations, and blood sampling. Dietary iron intake or absorption may be inadequate to keep up with ongoing iron losses, which in part may be due to the use of phosphate binders. Furthermore, an inflammatory state that often goes hand in hand with CKD may trigger hepcidin release, block gut iron absorption, and sequester iron in the reticuloendothelial system. In hemodialysis (HD) patients, dietary iron absorption far exceeds losses—and intravenous (IV) iron is almost always required. In fact, in the pre-EPO era ferrokinetic studies demonstrated that gut iron absorption was essentially arrested when serum ferritin concentration exceeded 50 to 75 ng/mL. Whereas the ferritin is not causal in arresting gut iron absorption, ferritin likely reflects iron sufficiency and arrests gut iron absorption.

Heme iron absorption may not be regulated in the same way as inorganic iron. For example, in iron-deficient rats nonheme iron absorption was increased several-fold. However, heme iron absorption was unaffected. Other studies in iron-deficient rats demonstrated a 3- to 10-fold increase in the absorption of heme iron compared to controls. Whereas data in animals is conflicting, in subjects with serum ferritin concentration of >400 ng/mL heme iron absorption was 10 times greater than that of iron salts alone. These data are important when making clinical decisions regarding choice of oral iron.

Diagnosis of Iron Deficiency in Chronic Kidney Disease Patients

Serum iron divided by transferrin iron-binding capacity is known as transferrin saturation. Together with serum ferritin concentration it is the most widely employed marker for evaluation of body iron stores and the ability to deliver iron to erythroblasts.

Transferrin saturation of <25% and/or serum ferritin concentration of <200 ng/mL signals the need for iron in a patient with CKD requiring EPO. However, states of inflammation may increase serum ferritin and reduce transferrin levels—thus confounding the relationship of iron sufficiency with these parameters. CKD and inflammation often coexist in the same patient. Therefore, it may be difficult to assess iron stores in these individuals.

The term *functional iron deficiency* refers to an empiric diagnosis in patients who have normal transferrin saturation and serum ferritin yet respond to parenteral iron with a rise in Hgb at a stable EPO level. Although response to intravenous iron is taken to justify a diagnosis of functional iron deficiency, this may not be so. This is because conditions that cause hyporesponsiveness to EPO (such as inflammation, hyperparathyroidism, and infection) may coincidentally resolve following administration of iron and an erroneous diagnosis of functional iron deficiency may be made.

Reticulocyte Hgb content (CHr) reflects the Hgb content in the youngest of the erythrocytes-reticulocytes. Low levels of CHr suggest iron-deficient erythropoiesis. Although target CHr is not entirely clear, a level of >29 pg according to some and >32 pg according to others is considered appropriate. A level of hypochromic red cells—not be confused with mean corpuscular hemoglobin concentration (MCHC)—>6% also suggests iron-deficient erythropoiesis.

None of the available markers of iron stores are sufficiently sensitive and specific to prove reliable in making a diagnosis of iron deficiency anemia. Emerging markers such as percentage of hypochromic red cells and percentage of reticulocyte Hgb index appear most promising in refining the diagnosis of iron deficiency in CKD patients.

Iron Use in Chronic Kidney Disease Patients Not on Hemodialysis

In one randomized controlled trial, 28% of patients with CKD not on hemodialysis had an improvement in Hgb of 1 g/dL or more over 8 weeks with oral iron use. IV iron raised Hgb in 44%. However, cost, need for IV access, and potential adverse effects of IV therapy are limiting factors. The mean increase in Hgb was 0.4 g/dL in the oral iron group and 0.7 g/dL in the IV iron group.

Three patients of 95 in the IV iron group (3.3%) and none of the 93 patients in the oral iron group were thought to have an adverse event related to the study drug. In fact, 2 of 30 patients who received high-dose iron (500 mg as an infusion) experienced

serious hypotension. In patients on peritoneal dialysis, IV iron was superior to no iron in increasing the peak Hgb response. Again, the differences were small. Based on the results of these randomized controlled trials, one approach to treating iron deficiency in patients not on hemodialysis is to use oral iron and switch to IV only if the expected Hgb response is suboptimal.

Iron Use in Hemodialysis Patients

Because heme iron absorption may occur independently of iron stores, it is possible that heme iron is superior in maintaining iron balance. In an open-label randomized controlled study of orally administered heme iron polypeptide versus IV iron in maintenance HD patients, the heme iron group maintained target Hgb without concomitant IV iron use. A significant reduction in serum ferritin was seen at months 4 through 6 in the heme iron group, whereas serum ferritin remained increased in the IV iron group. These data suggest a role for heme iron in HD patients on maintenance EPO therapy.

Randomized controlled trials have consistently demonstrated that IV iron is superior to oral nonheme iron in patients on HD treated with EPO. Most patients treated with EPO will require IV iron to treat anemia and increase responsiveness to EPO. Acute allergic and anaphylactic reactions were of major concern when dextran containing iron was used. This was particularly common with high-molecular-weight dextran containing iron and much rarer with non-dextran irons. Iron sucrose and iron gluconate are much safer compared to iron dextran in reducing anaphylactic reactions and deaths associated with such reactions. High doses of iron sucrose (>300 mg over 2 hours) or iron gluconate (>250 mg infused over 2 hours) should be avoided due to an unacceptably high rate of adverse events that include a constellation of symptoms that may include abdominal discomfort or pain, dysguesia, swelling of hands, and hypotension.

Independent Benefits of Iron Unrelated to Correction of Anemia

Several independent benefits of iron use traditionally thought to be due to repair of anemia are now believed to be due to correction of the underlying iron deficiency. Several enzymatic hemoproteins (such as catalase, peroxidase, cytochrome c, cytochrome p450, nitric oxide synthase, and NADPH oxidase) are ubiquitous and serve important functions. Thus, the benefits of iron repletion may extend

beyond repair of anemia. For example, IV iron use in CKD patients is associated with increased feeling of well-being beyond that produced by oral iron alone. In another double-blind placebo-controlled trial, high-dose iron dextran infusions in ESRD patients led to a significant but transient reduction in symptoms of restless leg syndrome. This may be due to a more complete correction of iron deficiency in tissue other than the red blood cells.

Potential Long-term Concerns of Harm with Intravenous Iron Use

Iron through what is known as the Haber-Weiss reaction generates the highly reactive hydroxyl ion responsible for creating oxidative stress. Although oxidative stress can be quenched by normal individuals, in those with CKD the mechanisms to combat oxidative stress are impaired. Thus, iron can be a particularly powerful pro-oxidant in these individuals. Oxidative stress can generate endothelial dysfunction, promote atherosclerosis, and accelerate the progression of CKD.

In addition, iron is a growth factor for bacteria. This includes even common bacteria such as *Staphylococcus epidermidis*. Iron is thought to limit absorption of zinc, the deficiency fo which can impair immune response to infection. Iron blocks the transcription of inducible nitric oxide synthase (iNOS), important in the killing of pathogens. Excess iron deposits in the liver are detrimental to response to interferon therapy in hepatitis C–infected patients and iron load may promote the progression of hepatitis C. The inflammatory response to bacterial infections and even nonbacterial infections is enhanced with IV iron, which at least in animals is associated with increased morbidity and mortality.

Direct evidence of harm exists in a randomized placebo-controlled trial of oral iron and folic acid with or without zinc in 24,076 preschool children in Zanzibar, a country with a high malaria transfer setting. Those treated with active drug were 12% more likely to die or need treatment in a hospital for an adverse event, and 11% more likely to be admitted to the hospital, than the placebo group. Infection or malaria-related causes were the most likely reasons for admission to the hospital. Notably, those who were iron deficient and anemic had half the event rate when treated with active drug compared to placebo. The evidence of harm was mainly seen in those children who were iron replete but received iron. These putative harmful effects of iron have not been carefully examined in well-designed long-term randomized controlled trials in patients with CKD, and therefore the concerns remain speculative.

Recommended Reading

Agarwal R, Warnock D. Issues related to iron replacement in chronic kidney disease. Semin Nephrol 2002;22(6):479–87.
Potential long-term deleterious consequences of iron in patients with CKD.
Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 2002;13(2):504–10.
Discusses the epidemiology of anemia and iron deficiency in people with CKD.
Miret S, Simpson RJ, McKie AT. Physiology and molecular biology of dietary iron absorption. Annu Rev Nutr 2003;23:283–301.
Excellent review that discusses iron absorption from the gut.
Nissenson AR, Berns JS, Sakiewicz P, Ghaddar S, Moore GM, Schleicher RB, et al. Clinical evaluation of heme iron polypeptide: Sustaining a response to rHuEPO in hemodialysis patients. Am J Kidney Dis 2003;42(2):325–30.
This is a randomized controlled trial demonstrating effectiveness of heme iron in sustaining erythropoiesis over 6 months in hemodialysis patients.
NKF-K/DOQI Guidelines: *http://www.Kidney.org/professionals/NKF-K/DOQI/guidelines_anemia/index.html. Accessed May 25, 2007.*
NKF-K/DOQI guidelines for management of anemia in CKD.

CHAPTER 62

Refractoriness to Recombinant Human Epoetin (rHuEPO) Treatment

John C. Stivelman, MD

Refractoriness to rHuEPO Treatment

Nearly two decades' availability of rHuEPO for treatment of the anemia of chronic renal failure has fundamentally changed the functional status and quality of life of patients receiving renal replacement therapy. Through its use, maintenance red cell transfusions as part of anemia treatment in end-stage renal disease (ESRD) have been eliminated outside the acute setting—and the risk of transfusion-borne infections has been markedly decreased. Exercise tolerance, sexual and cognitive function, and overall quality of life gain quantifiable improvement with successful therapy—which in the vast majority of patients is of strikingly low morbidity. To ensure continuous benefit of therapy, however, detection of early resistance to treatment both at its outset and throughout the patient's clinical course is required—so that its sources can be identified and reversed where possible.

Analysis of rHuEPO use since its release, accrued through data accumulated in several iterations of the NKF-K/DOQI (National Kidney Foundation–Dialysis Outcomes Quality Initiative) Anemia Guidelines, the regularized reports of Clinical Performance Measures by CMS/NIH (Centers for Medicare and Medicaid Services / National Institutes of Health), careful epidemiologic studies performed by the USRDS (United States Renal Data System) and individual investigators—and research from both large and small dialysis organizations. This has obligated reexamination of treatment resistance. This reevaluation has been important in view of our greater understanding of its differential diagnosis, and the recognition of its importance as a barometer of the patient's general health. Of significant note is that in the majority of patients receiving treatment reversible resistance to treatment with rHuEPO is a common rather than exceptional event.

Current definitions of rHuEPO treatment failure have complex antecedents. In initial trials, hormone efficacy was initially assessed

only in ESRD patients—without comparison to similarly treated normal controls. Thus, prior to the NKF-K/DOQI, assessing response to treatment was accomplished through comparisons of individual patient responses to those derived from phases I through III trials. In these early studies, increments in hematocrit during the induction phase of treatment ranged from 5 to 22% vol over a dose range of 15 to 500 u/kg three times a week and required 6 to 12 weeks of treatment (Figure 62.1).

The vast majority of patients in the phase III trial could be maintained at hematocrits of 35 ± 3% at doses between 25 and 150 u/kg three times per week, with a median dose of 75 u/kg three times per week (Figure 62.2). That distribution, however, reflects higher doses than those subsequently employed effectively in day-to-day practice, and the evidence-based range recommended by the 1997 NKF-K/DOQI Workgroup gleaned from data

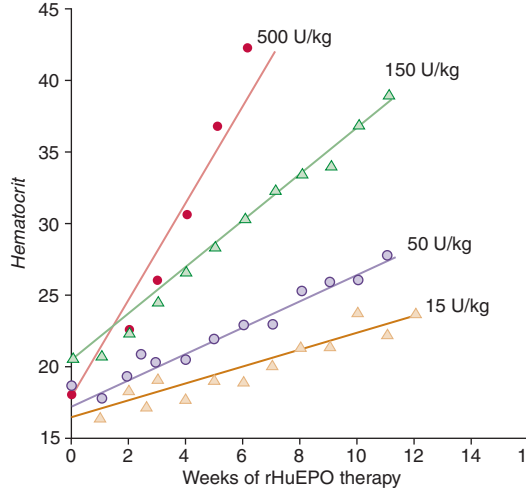


Figure 62–1

Ranges and rates of increase in hematocrit at various starting doses of rHuEPO. *(Reprinted with permission from Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. New Engl J Med 1987;316(2):73.)*

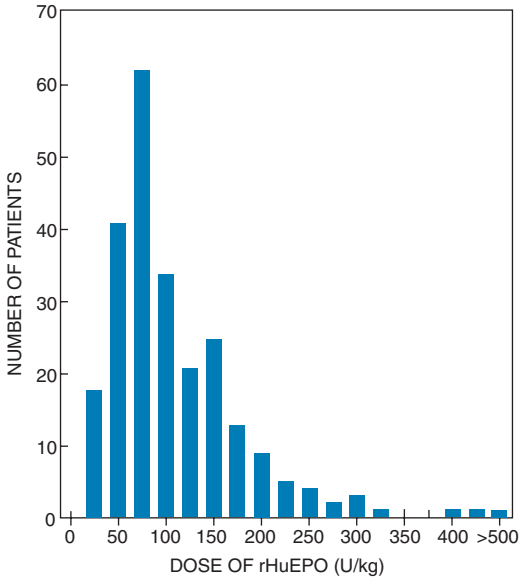


Figure 62–2

Distribution of maintenance doses of rHuEPO, administered IV three times weekly to maintain a hematocrit of 35 ± 3 vol % during the phase III trial. Therapeutic ranges drawn from evidence-based literature review in NKF-K/DOQI Anemia Workgroup reports recommended a lower range of initiating doses: 80 to 120 u/kg/week SC and 120 to 180 u/kg/week IV (or normalized to thrice-weekly administration for easier comparison to the figure, 27–40 u/kg thrice-weekly SC and 40–60 u/kg thrice weekly IV) to attain a target hematocrit of 33 to 36%. This may have reflected evolution of improved iron management. *(Reprinted with permission from Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Ann Int Med 1989;111:992.)*

published through 1995 was therefore somewhat lower: 80 to 120 u/kg/week administered subcutaneously (SC) (approximately equivalent to 27–40 u/kg three times per week) and 120 to 180 u/kg/week administered intravenously (IV) (approximately equivalent to 40–60 u/kg three times per week) for induction and maintenance of a hematocrit between 33 and 36% (Figure 62.2).

Such differences may have reflected increasing sophistication gained over subsequent years in the utilization of intravenous iron. Hormone resistance, however, came to be defined in the NKF-K/DOQI according to the higher dose range noted in the phase III trial; namely, as the inability to achieve target hematocrit given adequate iron stores at 450 u/kg/week IV (300 u/kg/week SC) within 4 to 6 weeks of treatment or failure to maintain target hematocrit at that dose.

These definitions have undergone significant transformation as a result of further experience with rHuEPO and a broader understanding of the interaction of rHuEPO treatment, repetitive iron therapy, the often disruptive effects of what many call "clinical history" on effective maintenance of hemoglobin, and new federal expectations for clinical performance outcomes (Figure 62.3). Recent examination of the distribution of rHuEPO doses in the

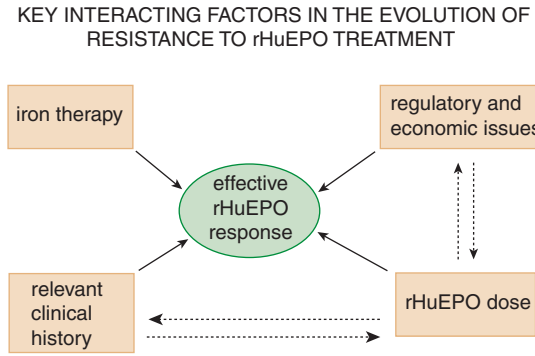


Figure 62–3

Effective treatment of the anemia of CKD/ESRD requires favorable interaction of clinically appropriate iron therapy, longitudinal attention to relevant clinical history and laboratory values, adequate hormone delivery to provide response, and a regulatory environment that permits appropriate delivery of these elements. Significant interference with any of these components or changes in their interactions may give rise to ineffective rHuEPO response. Of note are the potentially significant additional interactions (dashed arrows) between clinical history and rHuEPO dose, and that of regulatory and economic issues with provision of appropriate and adequate rHuEPO therapy.

United States reveals that when dose is normalized per administration the upper quintile of patients receiving erythropoietic stimulation consumes substantially more hormone administered compared to the lower four. Furthermore, a difference of almost 30-fold exists between the lowest and highest percentile doses calculated on the same basis. Nearly 1/5 of patients receive the equivalent of 30,000 units per week (normalized to 70 kg, almost 430 u/kg/wk), a significant variance from the clinical experience of the mid 1990s. Given this information at present, it would appear prudent to evaluate patients for resistance to therapy per the most recent NKF-K/DOQI if:

- Hemoglobin is inappropriately low for the magnitude of rHuEPO administered
- An increasing rHuEPO dose is needed to maintain stable hemoglobin
- A decrease in hemoglobin in at a constant dose of rHuEPO is noted
- A dose of greater than 500 u/kg/wk does not increase hemoglobin to above 11 g

Disorders Inducing Refractoriness to Treatment

Refractoriness to treatment should be approached in a physiologically rational fashion. A wide variety of clinical events and pathologic states engendering resistance may occur at any time during treatment. Those most commonly encountered during chronic treatment true and functional iron deficiency, and inflammatory blockade pose particular problems in the maintenance of stable hemoglobin which is detailed below (Table 62.1).

Iron and Other Cofactor Deficiencies

Clinical experience with use of rHuEPO has shown that most refractoriness to therapy has its origins in either iron deficiency (induced by effective rHuEPO treatment, iron deficiency, or undetected functional iron deficiency) or inflammatory reticuloendothelial blockade. As hemoglobin synthesis rises following marrow stimulation with rHuEPO (particularly when treatment is started), iron stores are consumed. With exhaustion of iron stores, loss of therapeutic response ensues—which can be overcome initially by increasing rHuEPO dose. This strategy ultimately fails, however, and response is lost with exhaustion of stores.

Table 62–1

Etiologies of rHuEPO Refractoriness

Occurring Any Time During rHuEPO Therapy	Occurring Commonly in the Setting of Successful Chronic rHuEPO Therapy
	• Iron deficiency • Inflammatory blockade inflammatory blockade • Aluminum intoxication hemoglobin "cycling" • Hyperparathyroidism • Hemoglobinopathy • Myelophthisic states • Hemolysis • ACEi treatment • Carnitine deficiency • Pure red-cell aplasia • Hemolysis • ACEi trcarnitine deficiency

The rapidity with which this occurs depends on adequacy pretreatment, as well as chronic maintenance. Iron stores sufficient to attain target hemoglobin are consequently very desirable prior to or early in the course of rHuEPO treatment. Although a simple relationship using hemoglobin, desired iron indices, and ferritin can predict whether adequate iron stores to achieve the desired hemoglobin concentration are present—Iron stores = [iron reserves – iron needs], where iron reserves [mg] = 400 × [log(ferritin)-log(30)] and Iron needs [mg] = $150 \times [Hb_{desired} - Hb_{start}]$—a negative value for iron stores indicates that iron deficiency will occur before target hemoglobin is reached. The general employment of protocol-based treatment has resulted in heavy reliance on serum iron, total iron binding capacity (TIBC), percent transferring saturation (TSAT), and serum ferritin concentration to provide this information instead. All of these methods, as detailed in the sections that follow, have major shortcomings.

Tools for Diagnosis

The most direct methods for assuring adequacy of iron stores (whether beginning rHuEPO treatment or maintaining stable hemoglobin levels) require measurement of serum iron, total iron binding capacity, transferrin saturation (TSAT, Fe/TIBC × 100), and

serum ferritin. Desirable adjuncts to these measurements should include either reticulocyte count or reticulocyte hemoglobin content (CHr). The reliability of transferrin saturation and ferritin in the diagnosis of iron deficiency has been subjected to heavy scrutiny, particularly in view of the stubborn and often subtle clinical reality of functional iron deficiency and the lack of optimal sensitivity and specificity of both tests. Reliance on serum ferritin values to assess iron stores—particularly without concomitant assessment of serial changes in transferrin saturation, rHuEPO dose, serial hemoglobin values, and retrospective evaluation of clinical history, may also provide a misleading assessment of iron stores because serum ferritin is an "acute-phase" protein. Thus, fever, underlying inflammation, and liver disease affect its synthesis regardless of total body iron stores. In addition, rapid response to rHuEPO may consume transferrin-bound iron (see material on functional iron deficiency follow-ing) before parenchymal stores and serum ferritin concentration decline, leading to an incorrect estimation of iron stores readily available for hemoglobin synthesis. Finally, serum ferritin may be elevated at baseline in dialysis patients compared to normal individuals, for reasons that are poorly understood.

In the absence of more reliable serologic markers at the present time, available evidence suggests a transferrin saturation of >20% and ferritin >200 ng/mL is necessary (peritoneal dialysis patients or pre-dialysis CKD patients require a ferritin concentration ferritin >100 ng/mL) to initiate and maintain successful response in hemodialysis patients. Patients with lower transferrin saturation and serum ferritin values have a degree of iron deficiency likely to impede effective therapy and require iron supplementation to ensure successful response, regardless of the relationship of these values to the time course of rHuEPO treatment. If iron deficiency is found on the initial evaluation prior to beginning treatment, its potential source needs identification and correction to ensure the adequacy of substrate. Finally, the sufficiency of cofactors essential for red cell synthesis (such as B_{12} and folate) should be ensured.

Differential Diagnosis

Iron deficiency as a source of evolving resistance to treatment must be excluded at the beginning or midcourse of treatment, and should be suspected either in the patient requiring progressively higher rHuEPO doses during treatment or in the patient whose hemoglobin and reticulocyte count fall despite stable rHuEPO therapy. Most often, exhaustion of iron available for erythropoiesis

simply reflects rHuEPO-stimulated incorporation into new erythrocytes. Although the periodic administration of intravenous iron for the majority of hemodialysis patients as recommended in NKF-K/DOQI has evolved as standard therapy specifically to obviate this problem, other causes of iron deficiency (including gastrointestinal and dialysis-related losses) still require exclusion.

Isolating the source of iron loss may be elusive, and obliges careful scrutiny of technical components of the dialysis procedure for additional treatment-related losses (frequency and volume of routine phlebotomy; reuse procedures, particularly average reuses per dialyzer and rapidity of fiber bundle volume loss; adequacy of intradialytic heparinization; clotting frequency of dialyzer and tubing; postdialysis bleeding from sites; and so on) as well as losses unrelated to it. The magnitude of the latter should be inferred from medical history, physical findings, stool guaiacs, review of individual patient recent medical events, and recent hospitalization and surgical history (Table 62.2).

Functional Iron Deficiency

Functional iron deficiency evolves most often in the setting of effective treatment with rHuEPO, in which transferrin-bound iron is incorporated into red cell precursors more rapidly than tissue stores are mobilized to replace it (in contrast to true iron deficiency, which is characterized by both depleted tissue and circulating protein-bound stores). In the setting of continuous stimulation of erythropoiesis by rHuEPO, the ability to deliver iron to synthetic sites falls, transferrin is desaturated, and responsiveness to treatment (which can initially be sustained by increasing rHuEPO dose) ultimately wanes.

Table 62–2

Potential Sources of Iron Loss

- Clotted dialyzers and tubing
- Poor reuse technique
- Slow clotting of access puncture sites postdialysis
- Occult GI blood loss
- Hospitalization, particularly with multiple caregivers/consultants
- Recent surgeries, particularly thrombectomies (especially if repetitive)
- Increased phlebotomy frequency at the dialysis unit

This clinical scenario (readily reversible by further iron administration) underscores the need for thoughtful joint surveillance of transferrin saturation, serum ferritin, and hemoglobin, and an appreciation of their dynamic relationship to one another over time (see material on solving iron issues following). Functional iron deficiency often evolves accompanied by seemingly "appropriate" serum ferritin values and may occur manifesting only modest depressions of transferrin saturation or even values within the normal range (Figure 62.4).

Treatment of Iron Deficiency

To avoid induction of iron deficiency, the NKF-K/DOQI Anemia Workgroup report has recommended weekly to biweekly follow-up of hemoglobin after initiation of rHuEPO or dose adjustment, with routine values obtained at biweekly or monthly intervals once stable hemoglobin is attained. Percent transferrin saturation and serum ferritin should be obtained at least quarterly, and although more frequent assessment is desirable present reimbursement structures in the United States do not readily support it. Most hemodialysis patients maintain adequate iron stores in the face of chronic rHuEPO therapy with weekly intravenous administration of 62.5 to 125 mg of sodium ferric gluconate or 50 to 100 mg of iron sucrose.

Patients who in the course of treatment see TSAT and ferritin falling below established thresholds (as noted previously), however, require iron repletion, usually with 1000 mg of intravenous iron administered in divided doses over each dialysis, in amounts dependent on which agent is used and with demonstration of adequate iron stores thereafter. Use of isolated or adjunctive oral iron therapy is rarely effective in hemodialysis patients in either increasing or sustaining hemoglobin production, produces undesirable side effects, and is inappropriate therapy.

Identifying Clinical Problems in Iron Consumption and Bioavailability

Treatment failure resulting from iron deficiency (whether true or functional) is often avoidable with close surveillance of hemoglobin, serum ferritin, and transferrin saturation over periods of months. The availability of up to 12 months of these data, arranged chronologically and amplified by the physician's thorough knowledge of the patient's recent clinical history, is indispensable in assessing whether a subtle change in one or more components

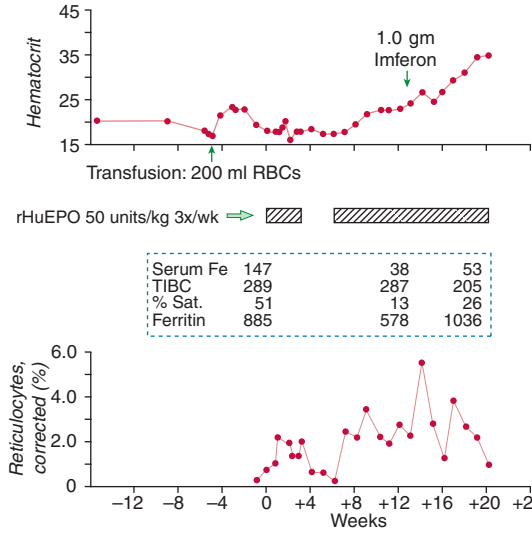


Figure 62–4

The top panel illustrates one patient's response to rHuEPO treatment. The bottom panel shows the course of his reticulocyte count in response to therapy. The values in the hatched box reflect the change in his iron indices occurring with treatment. The patient's hematocrit rises, despite a brief hiatus in therapy, but reaches a plateau between weeks 8 and 12. At that time, the patient's protein-bound iron stores are depleted, manifested by a fall in transferrin saturation, and his reticulocyte response reaches a plateau. The ferritin, although slightly decreased by week 12, remains robust. Following 1 g of further iron loading, transferrin saturation rises and response is restored, demonstrating the presence of functional iron deficiency. *(Reprinted with permission from Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. New Engl J Med 1987;316(2):73.)*

of the patient's iron profile is occurring and in assessing the mechanics of poor response to treatment.

Although joint examination of TSAT and ferritin over time may aid in defining the patient's progressive iron surfeit or deficiency, this analysis may gain depth in an understanding of both

iron consumption and bioavailability through scrutiny of TSAT and ferritin in relationship to each other, the rHuEPO dose, the ongoing iron dose, and the patient's hemoglobin. For example, TSAT and ferritin that decline in the same direction suggest that iron consumption is occurring. Similarly, TSAT and ferritin that fail to rise to some degree with iron repletion suggest ongoing iron losses or very rapid consumption is occuring. On the other hand, TSAT and ferritin which over time appear to diverge from each other in the setting of increasing rHuEPO dose, suggest the advent of an inflammatory insult, or an inflammatory insult exacerbated by either true or functional iron deficiency (the presence or absence of iron deficiency is more difficult to assess in such patients, who comprise a large fraction of a those seen today, and may require employment of adjunctive indices such as CHr or percent hypochromic erythrocytes). It is thus through the careful longitudinal analysis of routinely obtained data that the most fruitful assessment of treatment failure related to inflammation or iron deficiency ensues.

Underlying Inflammatory Disease

If substrate depletion is not detected in the patient with a poor or absent initial response or a tapering response, an inflammatory basis for treatment resistance should be sought and addressed. Inflammatory sources of rHuEPO resistance encompass infectious, neoplastic, and rheumatologic illnesses, as well as the postoperative state (the latter includes minor procedures such as revision or replacement of vascular or peritoneal access). Extended investigation is often required to uncover sources of poor rHuEPO response, which can include lesions as varied as occult infections in nonfunctional vascular accesses, stitch abscesses in anchored central lines, tunnel infections in cuffed catheters, periapical abscesses, paronychiae, urinary tract infections, diverticulitis, and occult carcinoma or lymphoma.

The pathophysiology of inflammatory "reticuloendothelial blockade" is multifaceted, and although previously ascribed to diminished red cell survival and blockade of iron transfer from reticuloendothelial system to red cell precursors recent investigations have suggested the active role of IL-1, IL-6, activated lymphocytes, TNF, and hepcidin in both antagonism of marrow response to native and exogenous erythropoietin and sequestration of iron from bioavailiability.

A rapidly expanding contemporary literature, however, has demonstrated increasingly that ESRD per se is a chronic inflam-

matory state—and by extension has intimated that poor response to rHuEPO in certain patients reflects the presence of a more global humoral disorder. Repetitive blood-membrane exposure, the catabolic effects of elevated parathyroid hormone activity, waxing and waning degrees of metabolic acidosis, and the indirect effect of both vascular insufficiency and progressive atherosclerosis all contribute to a chronic state of inflammation. The manifestations of this process (if severe) may include loss of visceral protein stores, hypoalbuminemia, anemia, and suboptimal rHuEPO response. In support of this observation, clear relationships have been shown between C-reactive protein levels and rHuEPO response, C-reactive protein levels and serum albumin concentration, as well as anemia and serum albumin concentration.

By virtue of the diverse insults responsible for this form of treatment resistance, the length of diminished response or unresponsiveness to treatment varies widely, particularly among patients who have had recent surgery, and treatment with even pharmacologic doses of rHuEPO to raise hemoglobin in the postoperative or other hospitalized setting (although rational therapy, as suggested by the most recent NKF-K/DOQI Guidelines) requires more study to show definitive benefit. Following identification and elimination of the inflammatory problem, effective rHuEPO treatment usually returns. Protracted lack of response should suggest incomplete resolution of the initial problem or a new superposed insult requiring new investigation.

Pervasiveness of Resistance to rHuEPO Treatment

Substantial literature over the last 5 years has shown resistance to therapy to be a common event interrupting effective treatment. Lacson et al. (Figure 62.5) have shown in the Fresenius Medical Care cohort of 70,000 patients that nearly 28% of patients with hemoglobin concentration >12 g/dL during the first quarter of the year finished the year at values <11 g/dL, *and* vice versa, demonstrating a high degree of intrapatient variability of both hemoglobin (and by this author's inference, likely rHuEPO requirements) during the course of the year. Eschbach et al. have shown similarly that the vast majority of patients seen at a large regional provider who manifested either poor response or rHuEPO doses in excess of 500 u/kg/week to maintain hemoglobin during an indexed year of observation in fact had reversible causes of resistance attributable to infectious processes, hospitalizations, or iron deficiency. In less than 10% of patients

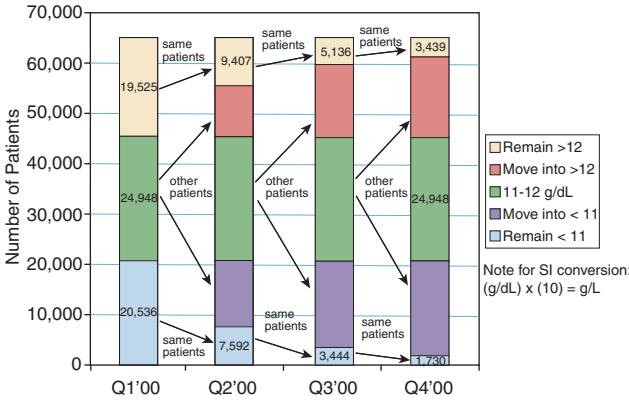


Figure 62–5

This diagram displays the movement of patients between categories of hemoglobin values (<11, 11–12; >12 g/dL) over the space of four quarters, as derived from the Fresenius Medical Care database covering nearly 70,000 patients. Striking movement is noted between hemoglobin categories, both upward and downward, from the first to the fourth quarter of the year. Of note, hemoglobin levels changed from less than 11 g/dL to greater than 12 g/dL (and vice versa) in more than 28% of patients. *(Reprinted with permission from Lacson E, Ofsthun N, Lazarus JM. Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis 2003;41:111–24.)*

was "resistance" intractable and not reversible with appropriate antibiotics, erythropoietic therapy, or addressing the underlying cause of illness. Thus, reversible resistance to therapy should be a potentially anticipated complication of most ESRD patients requiring hospitalization for a serious illness or surgical issue, or who develop a detectable deterioration in clinical status. It may in fact be worthwhile to consider resistance to rHuEPO in itself a useful initial manifestation of that change in status.

Other Disorders Inducing Initial Refractoriness to Treatment

The pathologic states detailed below all impair the erythropoietic effect of rHuEPO treatment, but in the aggregate account for this phenomenon far less commonly than does iron deficiency

or inflammatory reticuloendothelial blockade. Despite the experience of 18 years with this therapy, the relative contributions of each of these entities to the overall spectrum of poor response have not been reliably estimated.

Aluminum Intoxication

Aluminum intoxication may cause poor initial response by inducing modest resistance to rHuEPO that can usually be overcome by an increase in dose. However, this problem has dramatically diminished in frequency in recent years given federal expectations for uniform water quality, the near disappearance of routine use of aluminum-containing phosphate binders, and use of selective vitamin-D analogues with less phosphatemic effect. Past studies in both animals and humans demonstrated a correlation between the degree of aluminum loading (as defined by unstimulated aluminum level, DFO [deferoxamine] stimulation test, or bone biopsy) and either rHuEPO dose or treatment time required to reach target hemoglobin. The mechanisms most frequently cited to explain this phenomenon have included aluminum-mediated impairment of iron uptake from transferrin into red cell precursors and its inhibition of enzymatic iron incorporation into heme. In each instance, iron incorporation into heme declines, and anemia (occasionally microcytic) evolves despite normal transferrin saturation.

Aluminum-mediated rHuEPO refractoriness (now distinctly unusual) may be entertained in the nonresponding or poorly responding patient with sufficient iron stores and microcytic anemia (this useful finding is seen, at best, in 25% of affected patients), low turnover bone disease and refractory normochromic normocytic anemia, abnormal unstimulated plasma aluminum concentration and anemia, and chronic aluminum exposure with anemia that is otherwise unexplained. In such patients, methodical evaluation of anemia, exclusion of other reversible causes of initial treatment failure, and assessment of body aluminum burden with DFO challenge and/or bone biopsy may be considered. If clinical suspicion of aluminum-related rHuEPO resistance is high but evaluation inconclusive, empiric treatment may entail exclusion of exogenous aluminum, serial monitoring of blood aluminum levels as well as iron stores, and progressive increases in rHuEPO dose. Patients receiving DFO for any clinical indication require close follow-up of iron stores, as treatment will enhance dialytic removal of both cations and potentially induce iron deficiency. At present, the benefits of presumptive treatment with DFO without tissue documentation of aluminum excess must be weighed

heavily against the well-known risks of opportunistic infection and neurotoxicity potentially complicating its chronic administration. Treatment endpoints are imprecise, but might reasonably include improved response to rHuEPO persisting after discontinuation of DFO, diminishing rHuEPO requirements and stable hemoglobin with either DFO treatment or aluminum exclusion, or tissue verification of aluminum removal.

Secondary Hyperparathyroidism

Laboratory assessment of parathyroid gland activity is often first obtained during progressive CKD or early in ESRD. Poor response to rHuEPO in the presence of very elevated PTH (pacathyroid hormone) levels (>500–1000 pg/mL) should prompt suspicion that PTH is etiologic, the exclusion of more common causes of resistance discussed previously, and possibly radiographic confirmation of high bone turnover. A variety of pathophysiologic mechanisms have been postulated in the contribution of hyperparathyroidism to both anemia and rHuEPO resistance. In the pre-rHuEPO era, these centered on a direct toxic effect of PTH on red cell precursor proliferation in the marrow and antagonism of the effect of endogenous or exogenous erythropoietin. Studies in the 1990s, however, focused on the physical effects of high-turnover bone disease on the size of the erythron. In the rHuEPO-treated patient, a relationship was demonstrated between the degree of trabecular fibrosis and rHuEPO dose. Recent transnational comparisons have borne out this relationship between hemoglobin attainment and effective treatment of high-turnover bone disease. Very recently, a few interesting reports evaluating treatment of hyperparathyroidism with vitamin D have suggested it could have a role in enhancing erythrocyte maturation or in augmenting the erythropoietic effect of rHuEPO. In patients with very elevated PTH and alkaline phosphatase levels and in whom other etiologies for poor response have been excluded, effective treatment of secondary hyperparathyroidism and/or progressive increases in rHuEPO dose may improve response. For those patients who fit this clinical picture but continue to do poorly despite aggressive medical therapy, a bone biopsy may be required for further evaluation or another diagnosis sought.

Hematologic Disorders

In patients with hemoglobinopathies, immunologically mediated hemolytic processes and myelophthisic states, initial response to

rHuEPO treatment is often poor. In patients with sickle cell anemia, initial expectations that aggressive rHuEPO therapy would be beneficial in reducing transfusion requirements did not fully materialize. Alpha and beta thalassemia may also respond poorly, requiring very high doses. Resistance has been reported among dialysis patients with hemolytic anemia resulting from chloramine exposure, reuse-related formaldehyde exposure (anti-N_{form} hemolysis), and prosthetic cardiac valves. In patients with multiple myeloma, effective initial treatment may ensue with both moderate and high weekly doses. In all of these clinical settings, treatment of poor responders with pharmacologic doses of rHuEPO may be of some value, but expectations of a brisk response should be low.

Recent changes in payment regulations in the United States have placed a treatment ceiling of 500,000 units of rHuEPO per patient per month to quality for reimbursement—limiting utilization to approximately 35,000 units per dialysis and thus defining treatment futility, particularly in this subset of patients, in economic as well as physiologic terms.

Angiotensin-Converting Enzyme Inhibitors

A relationship between activation of the renin-angiotensin system and erythropoietin production has been recognized for many years but has not been well understood. Activation of the renin-angiotensin system as seen in renal artery stenosis is often accompanied by erythrocytosis, whereas polycythemia occurring post–renal transplant is often reversed by employment of angiotensin-converting enzyme inhibitors (ACEi). The physiologic basis for this relationship is unclear. In the rHuEPO era, the role of ACEi in this phenomenon has been inconsistently demonstrated. One interesting mechanism may entail ACEi-mediated increases in levels of N-acetyl-seryl-aspartyl-lysyl proline (an inhibitor of stem cell recruitment) or possibly interaction of ACEi with androgen elaboration. Many studies over the last several years reveal divided opinions on the clinical impact of ACEi therapy on rHuEPO response. This suggests a potentially modest effect of ACEi, which could be offset by increases in rHuEPO dose. Data on angiotensin II receptor blockers are insufficient as yet to draw similar conclusions.

Carnitine Deficiency

A role has been suggested for carnitine deficiency in impairing rHuEPO response in ESRD, possibly by altering erythrocyte mem-

brane stability or marrow sensitivity to rHuEPO. Studies addressing this question have required long study periods to demonstrate modest or equivocal results from which good evidence basis for treatment has been difficult to extract. Stringent criteria for Medicare reimbursement for carnitine treatment in the United States now require demonstration of subnormal plasma carnitine levels, the presence of intractable hypotension, or rHuEPO-resistant anemia with exclusion of all other reasonable etiologies for resistance—all factors that have limited its use in this country since 2002.

Adequacy of Dialysis

The effect of delivered dialysis dose on rHuEPO responsiveness remains unresolved. One report suggests a relationship between URR (urea reduction ratio) and hematocrit in a large geographic area, with higher hematocrits noted in patients with URR >70%. The same group has previously noted a relationship of modest increases in Kt/V and membrane change to improvement in rHuEPO response over a short interval. Investigators in Tassin, France—whose baseline dialysis prescription in past years has been more aggressive than that of the United States, demonstrated that a mean delivered Kt/V of 1.67 resulted in an average hematocrit of 28% unassisted by rHuEPO therapy. Understandably, such reports are suggestive but not directly comparable, and the impact of solute removal, delivered dose, and polymer choice on the efficiency of rHuEPO therapy still remains an issue. With the prospect of wider use of novel therapies (daily hemodialysis, slow nocturnal dialysis) capable of delivering substantially higher weekly dialysis doses resolution of this provocative issue may soon be realized.

The recent results of the NIH-sponsored HEMO Study, as well as the experience of rHuEPO treatment in the setting of quotidian dialysis therapies (whether nocturnal or daily), may by inference offer some insight into this issue. The HEMO Study has demonstrated that in the conventional paradigm of thrice-weekly in-center treatment, little improvement in survival can be obtained for the range of delivered dialysis dose conventionally provided in the United States. Assuming an important relationship exists between delivered dialysis dose and response to rHuEPO (whether involving removal of an inhibitory substance or improvement in red cell survival, although the latter would appear more probable), the therapeutic window in which this will be demonstrated—and to which some of the experience in rHuEPO with daily therapy

alludes—may be in delivery of Kt/V far higher than that seen among the best conventional thrice-weekly in-center therapies. Although tantalizing if inconsistent evidence exists to suggest this may be possible, far longer trials utilizing either nocturnal or daily therapies are required for proof.

Hemoglobin Cycling

An interesting and recently appreciated demonstration of relative resistance to rHuEPO therapy has been the phenomenon of hemoglobin cycling. This observation, which is at least in part an unanticipated and undesirable consequence of regulatory processes, describes the sinusoidal cycling of hemoglobin in response to variations in rHuEPO dose. Changes in rHuEPO dosing patterns in the United States have been closely linked to payment: for the last decade payers have utilized variants of a schema permitting reimbursement for hemoglobin values between 11 and 12 g without requiring further justification; whereas penalties, withholdings of reimbursement, or postpayment reviews have resulted from persistent upward deviation from this range. Careful management of rHuEPO dosing has resulted in attempting to remain within the upper limit of this range, with consequent oscillation in hemoglobin and failure to maintain steady-state levels. A similar problem occurs in patients who have been hospitalized. These patients may present with, or sustain, substantial inflammatory insults either just before or during the course of their hospitalization, resulting in impaired response to rHuEPO (a problem often compounded by either inadequate or ineffective rHuEPO replacement) or suboptimal iron therapy during the patient's hospital stay. The patient's rHuEPO dose at the time of discharge is then "reset" to address a diminution in hemoglobin sustained while hospitalized, resulting in "cycling." These two issues have contributed significantly to the "roller-coaster effect" of alterations in rHuEPO dosing in the maintenance of stable hemoglobin, and if not taken carefully into account may be confused for other processes contributing to treatment resistance.

Pure Red Cell Aplasia

Casadevall et al. reported 21 patients developing pure red cell aplasia in the setting of rHuEPO treatment between 1998 and 2001, traced to the presence of a neutralizing antibody that inhibited a red cell proliferation from normal marrow. Nearly all patients

developing this problem were treated with Eprex via subcutaneous injection, and in most cases responded to discontinuation of rHuEPO or to immunosuppressive treatment. Exhaustive evaluation by both manufacturers and investigators over the last several years has demonstrated that products leaching from the stoppers of the hormone vials were the agents generating the antibody response to rHuEPO administration. This issue has gradually resolved with substitution of a fluoro-resin coating for the stoppers.

Future Developments

The ability to obviate resistance to treatment in upcoming years may take several forms. First of relevance in the United States is the recent lifting of the payment limit for rHuEPO administration up to a range of 13 g hemoglobin. The net effect of this maneuver in the United States remains to be seen. The absorption of additional costs for this significant regulatory change will be ascertained in coming months. Second, a variety of erythropoietic-stimulating agents are now undergoing evaluation with mechanisms of action and half-lives different from epoetins currently available, which may, over the course of human trials, have different issues affecting their therapeutic ratio. The place of other nonbiologic tools in enhancing rHuEPO response, such as computerized modeling of dosage adjustment and employment of neural networks in assessing dosage modification remain to be seen.

Recommended Reading

Barany P, Divino Filho JC, Bergstrom J. High C-reactive protein is a strong predictor of resistance to erythropoietin in hemodialysis patients. Am J Kidney Dis 1997;29(4):565–68.

This report demonstrates the close linkage among inflammation, hypoalbuminemia, and rHuEPO resistance.

Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002;346:469–75.

An important exposition of the phenomenon of pure red-cell aplasia with rHuEPO treatment.

Eschbach JW, Varma A, Stivelman JC. Is it time for a paradigm shift? Is erythropoietin deficiency still the main cause of renal anaemia? Nephrol Dial Transplant 2002;17(suppl 5):2–7.

This article provides an accounting of causes of resistance to treatment over one year in a large regional dialysis provider, indicating that the vast majority of resistance is reversible.

Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 2005;68:1337–43.

This contribution provides a thoughtful and compelling exposition of the impact of intercurrent illness, hospitalization, and regulatory expectations on the stability of response to rHuEPO treatment.

Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK. The evaluation of iron status in hemodialysis patients. J Am Soc Nephrol 1996;7:2654–57.

This article is an important exposition of the value and reliability of TSAT and ferritin values in assessing the presence of true iron deficiency.

Kalantar-Zadeh K, Ikizler TA, Block G, et al. Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. Am J Kidney Dis 2003;42:864–81.

An overall review of the malnutrition-inflammation complex syndrome and its sequelae.

Lacson E, Ofsthun N, Lazarus JM. Effect of variability in anemia management on hemoglobin outcomes in ESRD. Am J Kidney Dis 2003;41:111–24.

This article outlines the high likelihood of major hemoglobin fluctuation in large populations occurring during the average patient-year interval, and the striking potential variability within a single patient's values.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47(suppl 3):S1–146.

This monograph offers the third series of evidence-based guidelines for treatment of the anemia of chronic renal failure, including appropriate hemoglobin goals, guidelines for rHuEPO and intravenous iron therapy, mechanisms for optimizing hemoglobin, and sources of resistance to therapy.

CHAPTER 63

Erythropoietin and Quality of Life in Chronic Kidney Disease

Steven D. Weisbord, MD, MSc, FASN,
and Paul L. Kimmel, MD, FACP, FASN

Introduction

Since its advent decades ago, chronic maintenance dialysis has been a life-sustaining therapy for patients with end-stage renal disease (ESRD). Most recipients of this treatment experience dramatic improvements in life expectancy yet suffer marked decrements in quality of life (QOL). The physical, psychological, social, and vocational effects of a thrice-weekly hemodialysis or daily peritoneal dialysis schedule have been shown to play important roles in mediating the impaired QOL in this patient population. Similarly, metabolic derangements that occur almost universally among dialysis patients influence the QOL of this patient group.

Principal among these is the anemia of renal failure, the pathogenesis of which is principally related to impaired erythropoietin production. Anemia has been linked to fatigue, which affects as many as 80% or more of dialysis-dependent patients—as well as to dyspnea, cold intolerance, impotence, and cognitive dysfunction. Nearly two decades ago, recombinant human erythropoietin was introduced as a novel therapy for the anemia of renal disease. Widespread use of this agent revolutionized the care of the dialysis population by facilitating the correction of anemia, patient morbidity due to iron overload and transfusion-related infections, and largely eliminating the need for routine blood transfusions.

Following the introduction of erythropoietin therapy, a plethora of research emerged revealing its beneficial effects on reducing patient morbidity. Many of these same studies also served to elucidate the important role this treatment plays in attenuating the decrements in QOL that plague those dependent on dialysis. Nonetheless, recent trials in patients with non-dialysis dependent chronic kidney disease have begun to transform our thinking about the balance between improved QOL and cardiovascular risk with the use of erythropoietin.

The Definition and Measurement of Quality of Life

One of the principal challenges to accurately and reliably assessing health-related QOL involves identifying the specific domains that contribute to the overall quality of a patient's life. Functional capacity, physical functioning, mental well-being, social adaptation, and symptom burden represent commonly cited facets of QOL—yet collectively these factors may not effectively encompass the paradigm of QOL as viewed from the perspective of the patient. Likewise, different instruments used to assess this construct may comprehensively describe particular aspects of QOL while failing to capture other important components.

Instruments used to assess QOL have historically been categorized as generic or disease specific, and the choice of instrument has important implications for the interpretation and generalizability of the findings. Early efforts to examine QOL in the dialysis population utilized general measures that transcended disease states and allowed comparisons across clinical conditions. Principal among these was the Medical Outcomes Study Short Form 36 (SF-36), which contains 36 items comprising 8 scales and 2 summary measures. Each scale is scored from 0 to 100, with higher scores indicating better QOL.

The Sickness Impact Profile (SIP) is another widely used generic instrument, containing 136 items that collectively describe an illness's impact on patient behavior. Other examples of non–disease-specific measures include the Nottingham Health Profile (NHP)—which measures the effect of physical, social, and emotional health problems on functioning—and the Karnofsky Scale, which consists of 11 categories that rank performance status from a score of 0 for death to 100 for normal functioning.

With the recognition that ESRD and chronic dialysis presented patients with a unique set of physical, psychological, social, and occupational challenges came the development of kidney disease–specific QOL questionnaires. Principal among these were the Kidney Disease Quality of Life instruments and the Kidney Disease Questionnaire. The Kidney Disease Quality of Life Long and Short forms contain the SF-36 as a core, around which multi-item scales are included to target specific issues pertinent to the patient with ESRD treated with hemodialysis. The Kidney Disease Questionnaire was designed for patients receiving hemodialysis and consists of 26 questions encompassing 5 dimensions of QOL.

These questionnaires, among others, have been validated in the ESRD population and have been instrumental in characterizing the impact of ESRD and renal replacement therapy on QOL. Many

of these same instruments have provided the means by which the impact of erythropoietin on dialysis-related burden of illness and the disease experience of patients dependent on chronic renal replacement therapy have been studied.

Overall Quality of Life and Erythropoietin

In 1985, Evans and colleagues published a seminal article describing the QOL of dialysis patients compared with that of ESRD patients who had received renal transplants. Based on scores from the Karnofsky Scale and the Index of Psychological Affect, Index of Overall Life Satisfaction, and Index of Well-Being, multiple facets of QOL were shown to be lower among those treated with dialysis than among transplant recipients. Soon thereafter, erythropoietin emerged as a new therapy for anemia and studies on its clinical impact began to appear. After early phase I and II studies on erythropoietin revealed favorable short-term effects, Evans et al. reported the results of a phase III study in 329 chronic hemodialysis patients receiving care in 9 different dialysis centers as they related to erythropoietin's effect on QOL.

Hematocrit values were obtained at baseline and at two follow-up intervals approximately 4 and 10 months following the initiation of erythropoietin therapy. Using the Karnofsky Scale, NHP, one subscale of the SIP, and a series of other indices, specific domains of QOL were compared between the baseline and the second follow-up periods. Functional capacity, energy level, eating and dietary behavior, and several individual symptoms improved at second follow-up—at which time anemia had been effectively treated with erythropoietin.

Likewise, subjective well-being, psychological effect, life satisfaction, sleep behavior, and level of happiness had improved with increased hematocrit level. At baseline, 36.2% of patients reported experiencing "good" or "excellent" health compared to 59.9% at the second follow-up point. Little change in employment status or patient-reported vocational capacity was observed. This study provided an early glimpse into the specific aspects of QOL that were likely related to anemia, and to components of the disease experience of dialysis patients that were likely to be ameliorated with erythropoietin treatment.

Building upon these findings, the National Cooperative Recombinant Human Erythropoietin study was implemented to confirm the early reports of short-term benefits with erythropoietin and to evaluate longer-term effects in a broadly representative sample of dialysis patients. Interim findings of more than 300 patients who

commenced erythropoietin therapy and completed 12 months of study participation were reported in 1993. As part of this study, QOL was assessed at baseline and at 3, 6, and 12 months after the initiation of the study using selected components of the SF-36 and the Karnofsky Scale. The nearly twofold reduction in the proportion of patients with hematocrit levels less than 30% at the time of the first interim follow-up was accompanied by a notable improvement in patient-reported vitality.

More modest benefits in physical functioning, mental health, and sexual satisfaction were found, whereas pain appeared to worsen at first follow-up. A comparison of study patients' QOL scores with those previously described in the general population and in healthy individuals revealed markedly lower QOL in study patients both at baseline and after the initiation of erythropoietin therapy. Although the QOL of dialysis patients with partial correction of anemia remained markedly impaired compared to the general population, this study provided further evidence that treatment of anemia with erythropoietin appeared to effect a notable improvement in several QOL domains.

A subsequent examination of the National Cooperative Recombinant Human Erythropoietin study findings further expanded our understanding of the relationship between erythropoietin and QOL. The effect of therapy with erythropoietin was assessed using six components of the SF-36 and additional items that aimed to capture health concepts pertinent to patients with chronic kidney disease. Baseline and follow-up QOL scores among 484 patients who had not been previously treated with erythropoietin (incident) and 520 patients who had previously been treated with erythropoietin (prevalent) were compared. In addition, the strength of association between hematocrit level and QOL was explored using regression analyses. Among incident erythropoietin users, four of six SF-36 scale scores improved from baseline to follow-up—during which time hematocrit levels increased from 25.5 to 29.9%.

Improvements in satisfaction with sexual activity, social life, interests/hobbies, and looking after the home were described, whereas indices of home life and vacation were similar at baseline and follow-up assessment. Prevalent erythropoietin users demonstrated no interval change in QOL parameters, but SF-36 scores in this cohort were comparable to follow-up scores among incident patients. Change in hematocrit level was found to be an important predictor of the measured improvements in general health, vitality, and social functioning. These results were bolstered by adjustments for multiple comparisons, and served to reinforce the belief

that erythropoietin therapy of anemia was associated with multidimensional QOL benefits.

It is also important to note the findings of the Canadian Erythropoietin Study, which randomized 118 patients to receive erythropoietin to achieve one of two target hemoglobin levels (9.5–11 g/dL or 11.5–13 g/dL) or to receive placebo. Several domains of QOL on the Kidney Disease Questionnaire and SIP were favorably affected by erythropoietin therapy. However, when patients were asked to judge the number of years of perfect health they would be willing to trade for their current health status using the Time Trade-off technique, no differences among the groups was found.

Quality of Life, Hemoglobin, and Erythropoietin in Peritoneal Dialysis Patients

Most studies to date have focused on the effect of erythropoietin on QOL among patients treated with hemodialysis. There are data supporting its efficacy in the peritoneal dialysis population. In an early study by Auer and colleagues, improvements in energy level, social life, relationships at home, and leisure pursuits as measured by the NHP accompanied an observed increase in hematocrit among a small cohort of continuous ambulatory peritoneal dialysis patients. Furthermore, approximately 10% of participants in the QOL analysis of the National Cooperative Recombinant Human Erythropoietin study were peritoneal dialysis patients.

Although the relatively small number of peritoneal dialysis in this study precluded meaningful subgroup analyses for this cohort, the overall results suggest that erythropoietin's effects extend to patients receiving this form of renal replacement therapy. These observations are supported by cross-sectional data from Merkus and colleagues, who demonstrated that lower hemoglobin was an important predictor of impaired QOL measured by the SF-36 among a group of 106 peritoneal dialysis (and 120 hemodialysis) patients who had recently initiated renal replacement therapy.

Target Hemoglobin Level

There has been and continues to be substantial debate on the precise hematocrit level that optimizes survival and reduces morbidity in patients with chronic kidney disease. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines on the treatment of anemia

recommended a target hemoglobin level of 11 to 12 g/dL in patients treated with dialysis. This recommendation, at least in part, reflected the findings of a prospective study of 1233 patients by Besarab et al. The study demonstrated that targeted correction of the hematocrit to 42% among chronic hemodialysis patients with congestive heart failure or ischemic heart disease was associated with a trend toward increased mortality and nonfatal myocardial infarctions compared with patients who had hematocrit maintained at a target of 30%. Interestingly, this study also demonstrated an improvement in the SF-36 physical function score among patients assigned to the higher hematocrit arm.

The Canadian Erythropoietin Study provided an early opportunity to examine the association between hematocrit level and QOL. Patients who were randomized to receive higher-dose erythropoietin reached a mean hemoglobin level of 11.7 gd/L yet demonstrated no significant differences in QOL or exercise capacity compared to patients who received lower-dose erythropoietin and reached a mean hemoglobin of 10.2 g/dL. Nonetheless, a series of more recent reports has suggested that correcting the hematocrit to higher levels with erythropoietin results in improvements in various QOL parameters.

The Spanish Cooperative Renal Patients Quality of Life Study Group undertook a prospective study to examine the effect of hematocrit normaliza-tion on functional status and QOL. The SIP and Karnofsky Scale were administered at baseline, at which time the mean hematocrit was found to be 30.9%, and at a 6-month follow-up point after mean hematocrit had increased to 38.4%. Of 115 patients who completed the study, improvements in physical, psychological, and global scores on the SIP as well as in functional capacity were documented at the time of follow-up assessment. No patient deaths occurred and adverse cardiovascular effects were minimal. However, it is important to note that patients with heart failure, ischemic heart disease, and/or severe comorbid illness burden were excluded from this study. Another similar trial randomized 253 Swedish dialysis patients to normal (13.5–16.0 gm/dL) or subnormal (9–12 gm/dL) hemoglobin levels and compared QOL scores—assessed with the Kidney Disease Questionnaire. Patients achieving normal hemoglobin levels manifested a reduction in physical symptoms, fatigue, frustration, and depression. Hemoglobin level correlated with scores on the Kidney Disease Questionnaire. Adverse events were comparable in the two groups, although the prevalence of preexisting heart disease in the study cohort was relatively low. The disparate results of the Canadian Erythropoietin Study

and these European studies may relate to the differences in the achieved hematocrit levels and sample sizes, or to other differences between the study populations. Nonetheless, these latter two studies suggest that near-normalization or normalization of hematocrit among certain dialysis patients translates into improved QOL. Lastly, in a recent study by Parfrey and colleagues, dialysis patients without symptomatic heart disease were randomized to receive erythropoietin to achieve hemoglobin levels of 9.5–11.5 g/dL or 13.5–14.5 g/dL. The only observed difference in QOL was an improvement in SF-36 Vatality scores among patients randomized to higher hemoglobin levels compared to patients with lower hemoglobin targets. Normalization of hemoglobin was not found to have beneficial effect on cardiac structure. Whether these potential QOL benefits offset the potential risks for adverse cardiovascular outcomes among the broader dialysis population including patients with heart disease remains an important unanswered question. Table 63.1 summarizes domains of QOL favorably affected by erythropoietin treatment of anemia in select studies of dialysis patients.

Erythropoietin in Patients with Early-stage Chronic Kidney Disease

Among patients who develop chronic kidney disease, anemia typically manifests as the glomerular filtration rate approaches 30 mL/minute/1.73 m^2, although a decline in hematocrit can occur well before renal dysfunction reaches this level. Some studies suggest that pre-dialysis patients experience improved QOL with correction of anemia. An early study by Kleinman and colleagues randomized 14 non dialysis-dependent patients with chronic kidney disease to receive erythropoietin or placebo. The increase in hematocrit level in the erythropoietin-treated patients was accompanied by an improvement in QOL. However, the findings were based on very small numbers of patients and QOL questions with unknown psychometric characteristics in the pre-dialysis population. Nonetheless, these early observations have been substantiated in more recent analyses.

Revicki and colleagues randomized 83 non dialysis-dependent patients with serum creatinine concentrations of 3.0 to 8.0 mg/dL to either receive erythropoietin targeting a hematocrit of 36% or to receive no erythropoietin treatment. QOL was assessed with individual scales of the SIP, SF-36, other Medical Outcome Study measures, and a Life Satisfaction Scale at baseline and after 16, 32, and 48 weeks of participation.

Table 63–1

Domains of Quality of Life Favorably Affected by Erythropoietin Among Cited Studies

Evans et al.[a]	Beusterien et al.	Laupacis et al.[b]	Furuland et al.	Moreno et al.
• Functional capacity	• Vitality	• Energy/strength	• Physical symptoms	• Physical well-being
• Energy level	• Physical functioning	• Physical symptoms	• Energy	• Psychosocial well-being
• Eating behavior	• Mental health		• Depression	• Functional status
• Sleep behavior	• Sexual satisfaction			
• Health satisfaction	• Social functioning			

a. Denotes 1990 study from the *Journal of the American Medical Association*.
b. Denotes the Canadian Erythropoietin Study Group.

Within and between groups comparisons were performed using intent-to-treat analyses. Of those patients treated with erythropoietin, 79% reached a hematocrit level of 36% (mean increase from baseline level of 4.7%)—whereas none of the untreated patients attained this level of hematocrit (mean decrease from baseline level of 1%). At various interval follow-up points, treated patients demonstrated improvements in energy, physical function, cognitive function, sexual function, role function, social activities, and home management. Change in hematocrit was found to be correlated with several of these domains and with improved sexual function. The absence of adjustment for multiple comparisons, relatively small sample size, and large proportion of patient dropouts were limitations in these analyses. Nevertheless, Revicki's findings were important in documenting the potentially beneficial impact of erythropoietin on pre-dialysis patient functioning and well-being. Despite these observations, there remain a considerable proportion of incident dialysis patients who initiate renal replace-ment therapy with hematocrit values below target levels. This may have implications for the morbidity and mortality of such patients and reinforces the importance of referral of those with early-stage chronic kidney disease to renal specialists.

Other Interventions to Improve Quality of Life

Reviewing the impact of other interventions on the QOL of dialysis patients provides perspective on the importance of erythropoietin. Remarkable technological advancements in the dialysis apparatus and in our understanding of the life-prolonging features of the dialysis process have been made over the past few decades. Use of larger and more biocompatible hemodialysis membranes has become commonplace, and substantial light has been shed on the association between dialysis dose and patient outcomes. Unfortunately, dialysis-related innovations and a broader understanding of the relationships among dialysis dose, membrane type, and health care outcomes have had relatively little impact on the goal of improving QOL.

As part of the recently completed HEMO Study, Unruh and colleagues described the impact of higher Kt/V and membrane flux on QOL in a large, diverse cohort of patients receiving thrice-weekly hemodialysis. Using the Kidney Disease Quality of Life Long Form and Index of Well Being, the investigators found that higher-dose hemodialysis favorably influenced only two health domains (physical health and bodily pain)—whereas higher-flux hemodialysis had no impact on any of the QOL parameters

examined. The clinical significance of the small changes in these QOL parameters remains unclear. These findings serve to underscore the magnitude of the impact erythropoietin has had on QOL.

With the recognition that fatigue and weakness are prevalent in the ESRD population, efforts have been put forth to assess the impact of exercise and rehabilitation programs on QOL. Early investigations revealed mixed results and were confounded by nonrandomized study designs and the use of co-interventions. Tawney and colleagues assessed the effect of a self-administered physical activity intervention on physical function in a randomized trial of 82 hemodialysis patients. After multiple adjustments, patients randomized to receive the rehabilitation program experienced better physical function as assessed by the Kidney Disease Quality of Life Short Form.

In 2002, DePaul reported the results of a trial that randomized 38 patients to an aerobic exercise and strength training intervention or a control low-intensity range-of-motion protocol. Early and sustained benefits in strength and exercise capacity among patients in the intervention group were not accompanied by improvements in QOL or patient-reported symptoms. Although the role of exercise and physical rehabilitation have not been conclusively delineated, any potential impact on QOL of these interventions is likely to be much less than that of erythropoietin.

Quotidian dialysis, which has gained increasing attention, has been shown in small studies and case series to have favorable effects on fluid management and hypertension, control of serum phosphate, and optimization of nutritional status. Whether these effects lead to meaningful improvements in QOL is a matter of ongoing investigation. As part of the London Daily/Nocturnal Hemodialysis Study, QOL assessments were performed using the SF-36, Global Health Utilities Index, and an ad hoc renal-disease questionnaire in 23 patients receiving short daily or long nocturnal hemodialysis and 22 conventionally treated patients.

The Time Trade-off scale was administered to gauge the patient-perceived burden of quotidian therapy. A reduction in several symptoms including cramping, headache, dizziness, dyspnea, fatigue, and cold intolerance, as well as in psychological stress was seen among those treated with quotidian dialysis. Findings on SF-36 scores were mixed, although results of the Time Trade-off suggested greater acceptance of quotidian dialysis than conventional thrice-weekly therapy.

These results are based on very small numbers of patients in nonrandomized studies, yet they suggest that quotidian dialysis may hold promise as a means of improving QOL. However, the data on the effect of this intervention on QOL are much less robust

than that of erythropoietin—and the widespread acceptability and superiority of this mode of dialysis remain largely unknown in the absence of well-designed randomized controlled trials. Table 63.2 summarizes the impact of various interventions on the QOL of dialysis patients.

Erythropoietin and Other Health-related Domains

Cognitive abnormalities are strongly associated with the uremic milieu, yet some patients continue to demonstrate impairments in cognitive capacity in the well-dialyzed state. A series of studies has shown that improvements in cognition are realized with increases of the hematocrit level to 32 to 36%, with additional benefits seen with normalization of the hematocrit. It has been hypothesized that anemia correction protects against hypoxia-induced damage of neuronal cells.

Data from several studies suggest that as many as 20% or more of dialysis patients suffer from depression. The etiologies of depressive affect this population are likely multifactorial. Unfortunately, data on the impact of anemia correction on depression are limited. Whether erythropoietin-mediated improvements in specific QOL parameters such as functional status, symptom burden, and social adaptation translate into meaningful reductions in depression remain largely unknown.

Table 63–2

Effects of Various Interventions on Quality of Life in Dialysis Patients

Intervention	Effect[a]
Erythropoietin therapy	+
Renal transplantation	+
Carnitine supplementation[b]	+
Exercise therapy	+/–
Quotidian dialysis[b]	+/–
Increased Kt/V[c]	+/–
Increased membrane flux[c]	–
Low dialysate calcium[b]	–

a. (+) Denotes favorable effect, (–) denotes lack of effect, (+/–) denotes indeterminate effect.
b. Based on limited data.
c. Based on findings from the HEMO Study.

Summary

Dialysis has been a life-extending therapy for patients with ESRD, but its benefits have been offset by poor patient adaptation, functionality, and well-being. Impaired QOL has been shown to be associated with mortality among dialysis patients, and interventional efforts to improve the QOL of this patient population have been protean. Other than renal transplantation, which mediates marked improvements in QOL, no intervention may be more effective than the use of recombinant erythropoietin to treat anemia.

Multiple facets of QOL (some intuitive, and some unpredicted) are favorably influenced by erythropoietin therapy. However, findings to date on erythropoietin's benefits should not negate the importance of continued investigation of this therapeutic agent. The relative paucity of data on erythropoietin's precise impact on QOL among peritoneal dialysis patients underscores the importance of further study of this patient group. Moreover, future studies to elucidate the precise hematocrit level that minimizes mortality and maximizes QOL are essential—as are efforts to increase the proportion of patients who initiate dialysis with hematocrit levels in the target range. Such efforts become increasingly important as the number of patients who require renal replacement therapy grows.

Recommended Reading

Ajuria JL, Kimmel PL, Siegel RS. Anemia in renal disease. In Weiss G, Gordeuk VR, C Hershko (ed.), *Anemia of Chronic Disease*. Boca Raton, FL: Taylor and Francis 2005:671–726.

Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 2002;162:1401–08.

Auer J, Simon G, Stevens J, Griffiths P, Howarth D, Anastassiades E, et al. Quality of life improvements in CAPD patients treated with subcutaneously administered erythropoietin for anemia. Perit Dial Int 1992;12:40–42.

Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584–90.

Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE Jr. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. J Am Soc Nephrol 1996;7:763–73.

Canadian Erythropoietin Study Group. Association between recombinant heman erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Br Med J 1990;300:573–78.

DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: A randomized controlled trial. Am J Kidney Dis 2002;40:1219–29.

Evans RW, Manninen DL, Garrison LP Jr., Hart LG, Blagg CR, Gutman RA, et al. The quality of life of patients with end-stage renal disease. N Engl J Med 1985;312:553–59.

Evans RW, Rader B, Manninen DL. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin: Cooperative Multicenter EPO Clinical Trial Group. JAMA 1990;263:825–30.

Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant. 2003;18:353–61.

Heidenheim AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. Am J Kidney Dis 2003;42(1):36–41.

Kimmel PL, Patel SS. Quality of life in patients with chronic kidney disease: Focus on end-stage renal disease treated with hemodialysis. Semin Nephrol 2006;26:68–79.

Kimmel PL, Peterson RA. Depression in end-stage renal disease patients treated with hemodialysis: Tools, correlates, outcomes, and needs. Semin Dial 2005;18:91–97.

Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH, Abels RI. The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: A double-blind, placebo-controlled trial. Am J Kidney Dis 1989(6):486–95.

Kurella M, Suri RS, Chertow GM. Frequent hemodialysis and psychosocial function. Semin Dial 2005;18:132–36.

Levin NW, Lazarus JM, Nissenson AR. National Cooperative rHu Erythropoietin Study in patients with chronic renal failure: An interim report. The National Cooperative rHu Erythropoietin Study Group. Am J Kidney Dis 1993;22(2/1):3–12.

Lew SQ, Piraino B. Quality of life and psychological issues in peritoneal dialysis patients. Semin Dial 2005;18:119–23.

Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. The Necosad Study Group. Am J Kidney Dis 1997;29:584–92.

Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients: Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. J Am Soc Nephrol 2000;11:335–42.

Nissenson AR, Nimer SD, Wolcott DL. Recombinant human erythropoietin and renal anemia: Molecular biology, clinical efficacy, and nervous system effects. Ann Intern Med 1991;114:402–16.

NKF. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000 American Journal of Kidney Diseases, 2001, Vol. 37, Issue 1.

Pereira AA, Weiner DE, Scott T, Sarnak MJ. Cognitive function in dialysis patients. Am J Kidney Dis 2005;45:448–62.

Revicki DA, Brown RE, Feeny DH, Henry D, Teehan BP, Rudnick MR, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis 1995;25:548–54.

Tawney KW, Tawney PJ, Hladik G, Hogan SL, Falk RJ, Weaver C, et al. The life readiness program: A physical rehabilitation program for patients on hemodialysis. Am J Kidney Dis 2000;36:581–91.

Unruh ML, Benz R, Greene T, Yan G, Beddhu S, DeVita M, et al. Effects of hemodialysis dose and membrane flux on health-related quality of life in the HEMO Study. Kidney Int 2004;66:355–66.

Unruh ML, Weisbord SD, Kimmel PL. Health-related quality of life in nephrology research and clinical practice. Semin Dial 2005;18:82–90.

CHAPTER 64

Target Hemoglobin

Mitchell H. Rosner, MD, and W. Kline Bolton, MD

Based on the current definitions of anemia in the general population [a hemoglobin (Hb) value of less than 13.0 g/dL in adult males and postmenopausal females and less than 12.0 g/dL for premenopausal women], nearly all patients with end-stage renal disease (ESRD) would be considered anemic. Data from the United States Renal Data Service (USRDS) indicate that nearly 3/4 of all patients starting dialysis have baseline hemoglobin values less than 11 g/dL (Figure 64.1).

Anemia is clearly associated with significant and debilitating symptoms of fatigue, depression, reduced exercise tolerance, dyspnea, muscle weakness, reduced sexual function, impaired cognitive function, and overall decreased quality of life. Furthermore, anemia has been associated with the development of left ventricular hypertrophy (LVH), left ventricular systolic dysfunction, increased risk for hospitalization, increased cardiovascular problems, depressed immune function, and generalized morbidity and mortality.

Although anemia in patients with ESRD may be secondary to gastrointestinal losses of blood, iron or vitamin deficiencies, or a generalized inflammatory state, the most important factor is deficiency of endogenous erythropoietin production. With the advent of recombinant human erythropoietin in 1989 (approved by the FDA in June of 1989), patients with ESRD had the ability to have anemia treated effectively without exposure to numerous blood transfusions with the attendant hope that many of their debilitating symptoms could be improved. Along with the availability of erythropoietin came the important question of what hemoglobin should be targeted as the goal of therapy.

Shortly after the introduction of erythropoietin, there was a consensus that partial correction of anemia with erythropoietin could significantly improve quality of life and mortality. Although a lower limit on Hb goals could be easily ascertained (at least greater than 10 g/dL), reaching consensus on an upper limit of Hb correction has proven more difficult. The answer to this key question has involved input from dialysis providers, prospective and retrospective clinical trials, international expert panels, and health care payers—eventually leading to regulatory and fiscal policies that

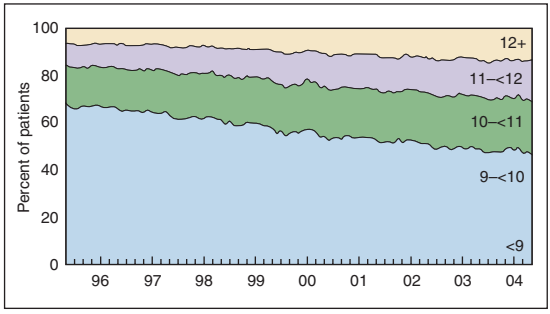


Figure 64–1

USRDS 2005 patient distribution by mean monthly hemoglobin (g/dL) at initiation of hemodialysis therapy.

govern the reimbursement for erythropoietin therapy and ultimately dictate practice patterns.

Target Hemoglobin and Mortality

Pathophysiologically, it is not difficult to rationalize that anemia could predispose patients to premature mortality. Foley and colleagues have investigated the effects of anemia on left ventricular (LV) function and structure in hemodialysis and peritoneal dialysis patients. Anemia led to LV dilation and hypertrophy—factors that have been associated with the risk of subsequent heart failure and sudden death. The relationship between achieved Hb using erythropoietin and mortality has been studied in both observational studies and randomized controlled trials.

Observational studies tend to be heterogeneous in terms of populations studied, length of follow-up, sets of covariates considered (for example, dose of dialysis, nutritional status, presence of diabetes, and history of cardiac disease), and whether Hb is considered a continuous or dichotomous variable. Furthermore, as is true with all observational studies a cause-and-effect relationship can never be firmly established.

Given these limitations, observational studies have generally concluded that mortality is increased when Hb levels are lower than the reference range studied (generally 10–11 g/dL or occasionally 11–12 g/dL) (Figure 64.2). However, the mortality risk associated with target Hb levels greater than the reference range tends to vary

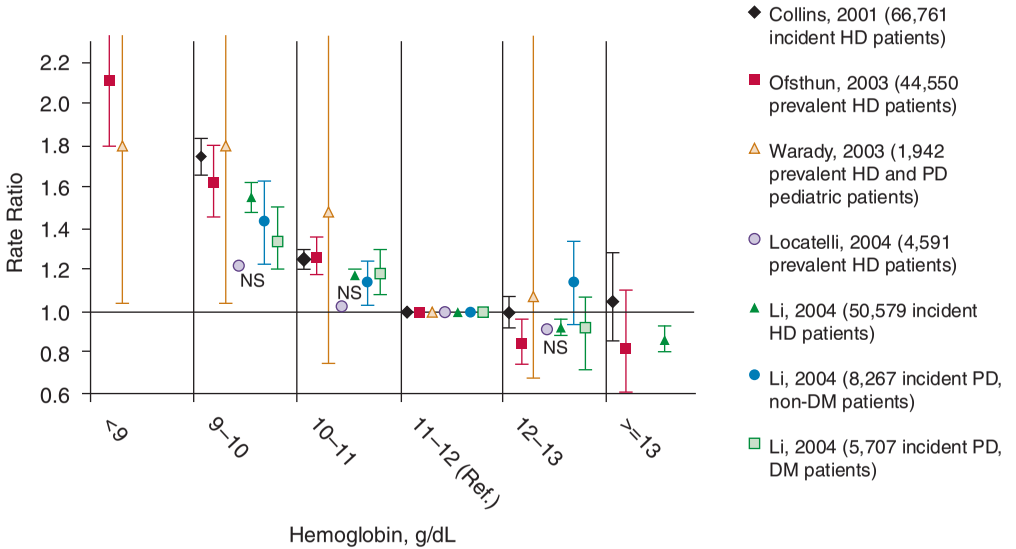


Figure 64–2

Relationship between Hb level and mortality: observational studies with reference group 11 to 12 g/dL. *(Reprinted from Volkova N, Arab L. Evidence-based systemic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis 2006;47:24–36, with permission from the National Kidney Foundation, Inc.)*

between studies. For example, a study by Li and Collins investigating 50,579 incident hemodialysis patients with a follow-up of 3 years for death demonstrated that the relative risk (RR) of all-cause mortality (using a reference Hb group of 11–12 g/dL) was 0.86 [95% confidence interval (CI) 0.80–0.93] for Hb values greater than 13 g/dL and 0.92 (95% CI 0.88–0.96) for Hb values 12 to 13 g/dL.

The same benefit of higher Hct values was also seen on risk of first hospitalization for cardiac disease and for cardiac causes of death. In a study of more than 44,000 hemodialysis patients, Ofsthun et al. also found that Hb levels of 12 to 13 g/dL were associated with a 16% lower mortality (RR of 0.84, $P = 0.007$) compared to the reference Hb level of 11 to 12 g/dL. Furthermore, there was a tendency toward decreased mortality as Hb values rose to above 13 g/dL (RR 0.82, $P > 0.05$).

Other studies have found no association with higher Hb values and decreased risk of death. A study by Collins et al. in more than 66,000 incident hemodialysis patients using a reference Hb level of 11 to 12 g/dL demonstrated an increased RR of death in patients with Hb levels of 10 to 11 g/dL [RR 1.25 (95% CI 1.20–1.30)] as well as Hb values less than 10 g/dL [RR 1.74 (95% CI 1.66–1.83)]. However, a benefit of Hb values above the reference range (either 12–13 g/dL or >13 g/dL) could not be found. Risk for hospitalization was 16 to 22% lower in those patients with Hb levels greater than 12 g/dL.

Other observational studies have also found no effect of higher Hb levels (generally greater than 12 g/dL) on lowering the risk of all-cause mortality (summarized in Figure 64.2). Once again, it is important to note that these observational studies assess anemia as a risk factor for morbidity and mortality but do not assess the efficacy of treatment of anemia with erythropoietin. Controlling for relative co-morbidities is of paramount importance in these studies, as a lower Hb may simply be a reflection of other adverse co-morbidities that are more important in determining the risk for mortality.

As recently reviewed by Volkova and Arab, five randomized controlled trials (RCTs) have been performed investigating the effects of erythropoietin therapy and target Hb on mortality. Two of these trials compare erythropoietin versus placebo, and three trials treated all patients with erythropoietin and randomly assigned patients to two goal Hb levels. These trials are summarized in Table 64.1 and Figure 64.3. In general (with the exception of the Besarab et al. study), these studies are small and not adequately powered to study mortality effects. Furthermore, follow-up tends to be less than 1 year. In the RCTs studying erythropoietin versus placebo, Hb levels greater than 11 g/dL were not achieved in

Table 64–1

Randomized Controlled Trials Investigating the Association Between Hemoglobin Levels and Mortality

Trial	Patient Population	Intervention Major Results
Bahlmann 1991	HD patients	Epo v. No Epo improved survival in group receiving epo (higher Hb group)
Klinkmann 1993	HD patients	Epo v. No Epo improved survival in group receiving epo (higher Hb group)
Besarab 1998	HD patients (with CV disease)	Hct 30 v. 42% higher RR for mortality in high Hct group
Foley 2000	HD patients (with LV hypertrophy)	Hb 9.5–10.5 v. tendency for decreased survival in 13–14 g/dL higher Hb group
Furuland 2003	HD, PD and pre-dialysis pts	Hb 9–12 v. 13.5–16 g/dL no significant difference between groups
Singh 2006	GFR 15-50 ml/min	Hg 13.5 associated with higher risk of CV events/mortality over Hg 11.5
Drueke 2006	GFR 15-35 ml/min	

Adapted from Volkova N, Arab L. Am J Kidney Dis 2006;47:24–36.

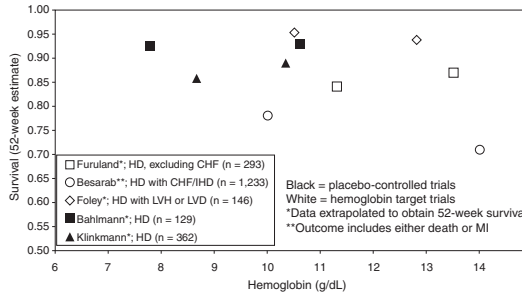


Figure 64–3

Clinical trials with a mortality endpoint: 52-week survival versus achieved Hb concentration. *(Reprinted from Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis 2006;47:24–36, with permission from the National Kidney Foundation, Inc.)*

the treatment arms—limiting their conclusions on the effects of higher Hb values.

The most important of these RCTs is the U.S. Normal Hematocrit Study, in which 1233 hemodialysis patients (mean age 65) with cardiac disease (congestive heart failure and/or ischemic heart disease) and a baseline Hb of 9 to 11 g/dL were randomized to receive erythropoietin to achieve either an Hb goal of 10+/–1 or 14+/–1 g/dL. The study was prematurely terminated by the data-monitoring committee secondary to a nonsignificant increased number of nonfatal myocardial infarctions and deaths in the higher (normal) Hb group (RR 1.3, 95% CI 0.9–1.9). However, it should be noted that patients in the higher Hb group had significantly improved quality of life and a reduced probability of requiring a blood transfusion compared with the lower Hb group.

Vascular access thrombosis was greater in the higher Hb group than in the lower Hb group (39% compared to 29%, P = 0.001). The higher Hb group required significantly higher doses of erythropoietin, as well as intravenous iron, which may confound the results. This trial suggested that patients with preexisting cardiac disease do not benefit from a higher Hb level and that this practice cannot be recommended.

The most recent RCT of Hb normalization was performed by Furuland et al. Patients were randomized to goal Hb levels of 9 to 12 g/dL versus 13.5 to 16 g/dL. Patients with significant heart disease were excluded from this study based on the findings of the U.S. Normal Hematocrit Study. The mortality rates were similar in the normal Hb and subnormal Hb groups (respectively, 13.4 versus 13.5%, P = 0.98). However, quality-of-life measures improved in the normal Hb group.

Supporting the conclusions of the RCTs is a large prospective observational study from the European Dialysis Outcomes and Practice Patterns Study (Euro-DOPPS), which could not demonstrate a significant mortality benefit among Hb values of 10 to 10.9 g/dL, 11 to 11.9 g/dL, and >12 g/dL. However, the RR of death in those patients with an Hb value less than 10 g/dL was 51% higher than those patients with an Hb value of 11 to 11.9 g/dL.

Interestingly, a recent RCT in the pre-dialysis chronic kidney disease (CKD) population also could not find a benefit from normalizing Hb in terms of mortality reduction. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, patients were randomized to an Hb of 11.3 or 13.5 g/dL. The study was terminated early given that the RR of death in the normal Hb was 1.337 (95% CI 1.025–1.743, P = 0.0312).

Target Hemoglobin and Other Outcome Measures

Several studies have assessed outcome measures other than mortality that are affected by targeting higher Hb levels. The majority of studies assessing quality of life have demonstrated that normalization of Hb is associated with improvement in scores on the Sickness Impact Profile and Karnovsky Scale. For example, the Spanish Cooperative Renal Patients Quality of Life Study Group demonstrated improved quality of life and functional status when the mean Hb was increased from 10.2 to 12.5 g/dL. Associated with this rise in Hb values in this study was a 58% reduction in the number of hospitalizations.

Studies have also demonstrated that increasing Hb levels leads to increased VO_2 (exercise capacity) and to an increase in the number of meters walked in 6 minutes. Cognitive function also improves as Hb values rise. In one study, a rise in Hb from 10.66 to 14.05 g/dL was associated with a significant decrease in EEG (electroencephalogram) slowing. Cognitive processing time was also significantly improved. Finally, normalizing the Hb concentration with erythropoietin is associated with improvement in immune function—especially delayed-type hypersensitivity. In one study, patients were randomized to an Hb of 10+/–1 or 14+/–1 g/dL. In the normal Hb group, there was significantly improved cutaneous reactivity, a decrease in anergy, and lower CD8 cell counts.

Finally, correction of anemia has significant effects on cardiac structure and function. In the Canadian Multicenter Study, the effect of a low Hb target (10 g/dL) and normalized (13.5 g/dL) Hb targets were assessed in patients with asymptomatic cardiomyopathy. In those patients with established LV dilation, no benefit of a higher Hb could be established. However, in patients with LV hypertrophy the authors demonstrated that for every 1 g/dL decrease in Hb level there was a corresponding increase in LV end diastolic volume of 8 mL/minute^2 ($P = 0.009$). This study suggests that early and aggressive treatment of anemia to a normalized Hb value can prevent deleterious LV dilation.

Summary of Effect of Target Hemoglobin on Outcome Variables

Given the limitations of the studies discussed, a Cochrane Review in 2003 concluded that an Hb level greater than 12 g/dL did not appear beneficial. They also cautioned that in those patients with cardiovascular disease higher Hb levels may be associated with greater mortality. However, given the beneficial effects of increased Hb levels on quality-of-life measures and cardiac structure (and

the fact that the largest negative effects in terms of mortality occur in patients with preexisting cardiac disease) it may be that select patients may benefit from a higher Hb. Further studies in this regard are needed.

Other considerations that must be factored into the analysis of the effect of increased target Hb levels include the potential effects of the requirement for increased doses of intravenous iron to achieve the higher Hb levels, the effects of higher Hb values on the risk for increased vascular access thrombosis, the effects of higher doses of erythropoietin on blood pressure, the effects of higher Hb values on dialysis adequacy as measured by Kt/V, and the economic costs of reaching and maintaining a higher Hb value (in the U.S. Normal Hematocrit Study, the mean erythropoietin dose was three-fold higher in the higher Hb group). All of these factors require more intensive study before a higher target Hb level can be recommended.

Clinical Practice Guidelines

Based on the data presented, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) in their year 2000 guidelines for the treatment of anemia of CKD recommend: "The target range for hemoglobin (hematocrit) should be 11 g/dL (33%) to Hb 12 g/dL (36%)." Similar recommendations are offered by the Canadian Society of Nephrology. The European Renal Association/European Dialysis and Transplantation Association recommended in 1999 that the Hb level should be maintained above 11 g/dL.

For patients with severe cardiovascular disease or diabetes, the upper limit of Hb was set at 12 g/dL. However, the guideline did not set an upper limit for Hb in other patients—stating "At the moment, no clear evidence exists either as to what the optimum Hb concentration above these levels may be, or as to whether there is a concentration above which costs and potential risks exceed benefits. Hence, no upper limit has been suggested, pending further data." However, based upon the recent CREATE and CHIOR results in patients with CKD (as well as results in other patient populations), the Food and Drug Administration (FDA) has placed an upper limit for target Hb at 12.0 g/dL. Recently, the agency issued a black boxed warning for ESAs in light of new data that suggested non-dialysis CKD patients who were taking Erythropoiesis Stimulating Agents (ESAs) at doses designated to raise Hb to above 13 g/dL had a higher risk of death, blood clots, strokes, and heart disease. Furthermore, the NKF-K/DOQI committee after reviewing the latest results from these controlled

trials about anemia management in chronic kidney disease was able to upgrade.

Fiscal Policy for Erythropoietin Reimbursement Based on Target Hemoglobin Levels

Given that current expenditures on erythropoietin for dialysis patients in the United States exceed $1.5 billon annually, it is not surprising that the Centers for Medicare and Medicaid Services (CMS) and their fiscal intermediaries are interested in closely monitoring the Hb levels achieved in ESRD patients and limiting expenditures based on caps on the maximum target Hb value allowed. Monitoring policies have periodically undergone revision, and the latest policy became effective 1 April 2006. This policy is based on the FDA labeling for erythropoietin that recommends a 25% reduction in the dose of erythropoietin as the Hct approaches 36%. In the current policy, Medicare contractors will not initiate monitoring until the Hct reaches 39.0%.

For any claims with Hct readings above the threshold of 39.0%, the erythropoietin dose is required to be reduced by 25% and documented by a report modifier code. For claims with Hct levels above 39.0% without the modifier code, Medicare contractors will reduce the dosage payable by 25% of that reported on the claim. Furthermore, Medicare contractors will not make payment for erythropoietin dosages in excess of 500,000 IUs per month or a dosage of darbopoieitin (Aranesp) greater than 1500 mcg per month. The CMS policy seeks to monitor incentives to keep hematocrit/hemoglobin levels in the target range while discouraging excessive dosing of EPO. Whether the policy will have its intended goal and what effect the policy will have on average Hb values in ESRD patients is subject to speculation at this time.

Conclusions

The availability of erythropoietin has revolutionized the care of ESRD and CKD patients. Clearly, targeting Hb values to a minimum value above 10 to 11 g/dL is associated with significant improvements in mortality, morbidity, and quality of life. However, it appears that full correction of Hb values to normal population levels (Hb >14 g/dL) is not clearly associated with additional benefit on mortality—and in some groups (those patients with preexisting cardiovascular disease) may have adverse consequences. Why this is the case is not clear. It may be that the process of reaching these higher Hb levels (with the use of high doses of erythropoietin and

intravenous iron) is in itself associated with poor outcomes rather than the effect of the Hb per se. Further studies directly comparing Hb levels of 11 to 12 g/dL with higher target values in RCTs are warranted to answer this important and lingering question.

Recommended Reading

Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effect of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. New Engl J Med 1998;339:584–90.

A prospective randomized controlled trial examining the effect of full correction of anemia in hemodialysis patients with cardiac disease (incremental positive effect of increasing hemoglobin but increased risk in process of achieving target hemoglobin in a high-risk population).

Foley RN, Parfrey PS, Morgan J, et al. for the Canadian Normalization of Haemoglobin Study Group. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 2000;58:1325–35.

Prospective trial of normal hemoglobin versus partial correction of anemia and its effect on cardiac structure in dialysis patients. Decreased risk of progressive LV dilatation.

Furuland H, Linde T, Ahlmen J, Christensson A, Stromborn U, Danielson BG. A randomized controlled trial of hemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant 2003;18:353–61.

The most recent RCT investigating normalization of Hb. Study demonstrated no mortality benefit in the higher Hb group.

Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. Kidney Int 2004;65:626–33.

A large retrospective analysis of the relationship between achieved Hb values and mortality, which demonstrated improved survival with higher Hb levels.

Moreno F, Sanz-Guajardo D, Lopez-Gomez J for the Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. J Am Soc Nephol 2000;11:335–42.

Prospective trial of near-normalization of hemoglobin in hemodialysis patients. Improved quality of life without major co-morbidities.

Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999;33:1122–30.

Prospective trial evaluating neurocognitive effects of normalizing hemoglobin. Incremental improvement in objective parameters with normalization versus anemic hemoglobin.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000. Am J Kidney Dis 2001;37(1):S182–238.

The current guidelines and the research evidence to support their use.

Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis 2006;47:24–36.

An excellent review of all observational and RCTs investigating the association between target Hb and mortality.

Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. J Am Soc Nephrol 1999;10:1309–16.

A 1-year study of hospitalizations in prevalent hemodialysis patients stratified by hematocrit level using the Medicare database. Decreased admissions, mortality, and length of stay with higher hematocrits.

CHAPTER 65

Hypertension in Chronic Dialysis Patients

Lionel U. Mailloux, MD, FACP, and Vito M. Campese, MD

Introduction

Hypertension is very common in the end-stage renal disease (ESRD) patient population. As both a cause of renal failure and a significant cardiac co-morbidity, hypertension presents a unique cardiovascular disease issue in the ESRD patient. It is important to realize there are no set guidelines for defining hypertension in this patient population. Nor are there target blood pressure (BP) levels to be considered as goals for control. It also is seen as a problem in numerous other countries, not just the United States. As a primary etiology, hypertension results in ESRD in more than 30% of patients requiring renal replacement therapies, a rate that has been increasing recently in the incident patients (Table 65.1 and Figure 65.1). In conjunction with other diseases, such as diabetes and chronic glomerulonephritis, uncontrolled hypertension hastens the progression to the end stage. As a co-morbidity, hypertension is increasing in prevalence—as are the other cardiac disorders associated with poorer dialysis outcomes (Figure 65.2).

Hypertension occurs in more than 80% of patients who have ESRD. Before the initiation of dialysis, the prevalence of hypertension averaged between 75 and 90%. The prevalence of hypertension in dialysis patients has been increasing, with 50 to 60% of hemodialysis patients and 40 to 90% of continuous ambulatory peritoneal dialysis (CAPD) patients now being hypertensive. Whatever the reason, BP is more poorly controlled in ESRD patients—now impacting directly on morbidity and mortality. Hypertension plays a major role in the unacceptably high cardiovascular morbidity and mortality rate of all renal failure patients (i.e., chronic renal insufficiency, ESRD, and transplant). In addition, more cardiovascular diseases are seen in more incident ESRD patients—with a steady increase in the last 10 years (Figure 65.2).

Cardiovascular diseases remain the leading cause of death in these patients despite all the advances in medical and technical

Table 65–1

Percent Distribution[a] of and Adjusted Rate/Million of Major ESRD Diagnoses in Incident Dialysis Patients for the Years 1996 Through 2004[b]

Year and *n*	Diabetes Mellitus	Hypertension	Chronic Glomerulonephritis	Cystic Diseases
1996/62,930	51.5%/128.1	31.9%/78.5	13.7%/33.4	2.9%/7.4
1998/70,760	52.6%/141.5	32.1%/85.7	12.3%/32.5	3.0%/8
2000/75,762	53.8%/148.7	32.3%/89	11.1%/30.3	2.8%/7.8
2002/80,833	53.5%/152.3	33.3%/94.3	10.5%/29.6	2.7%/7.7
2004/82,117	53.8%/148.8	33.6%/93.1	9.9%/27.6	2.7%/7.5

a. The *n* represents the four major renal diagnoses and percentages based on these entities.
b. USRDS 2006.

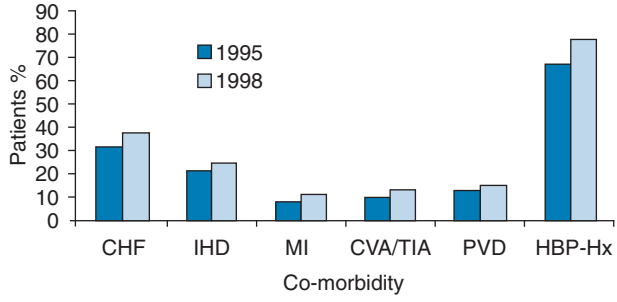


Figure 65–1

Changing distribution of the major ESRD diagnoses in the incident dialysis population (1988–2004).

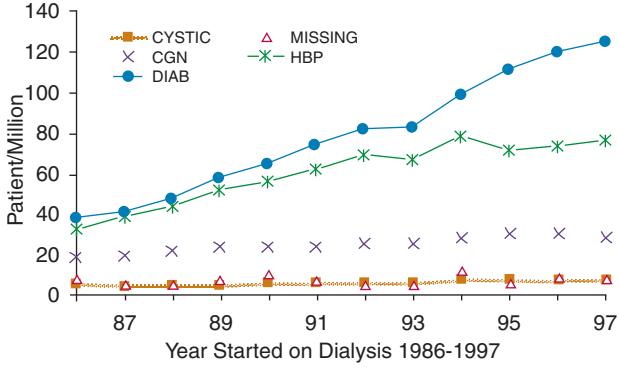


Figure 65–2

Changes in vascular co-morbidity: Incident ESRD patients 1996, 1999, and 2002.

therapies, but some of these "advances" might be directly related to the difficulty with the control of hypertension (e.g., ultrashort dialysis). This mortality rate is undoubtedly related to long-standing hypertension, presence of other cardiovascular disease risk factors, accelerated atherosclerosis, ventricular fibrosis,

ventricular hypertrophy, and a high level of continuous sympathetic activation. In dialysis patients, hypertension is an extremely important factor in the pathogenesis of severe cardiovascular disease. Both morbidity and mortality in these patients are determined primarily by cardiovascular complications. Both the European Dialysis and Transplantation Association registry and the U.S. Renal Data System agree with the high prevalence of cardiovascular-related deaths in dialysis patients.

Not only are cardiovascular complications the cause of death in more than half of patients with ESRD but hypertension itself is among the most important factors in determining the severity of cardiovascular disease. It has been noted that hypertension is the single best predictive factor for determining the rate of development of coronary artery disease in uremic patients, even more predictive than cigarette smoking or hypertriglyceridemia. Hypertension and other mediators damage the vascular endothelium, facilitating the flux of platelets and plasma lipoproteins into the vessel wall. In addition, it and uremic toxins cause left ventricular hypertrophy—especially in diabetics—and end-organ damage to the brain, retina, and kidneys.

Pathogenesis

The etiology of hypertension in ESRD is multifactorial, with extracellular fluid expansion, increased sympathetic nervous system activation, and nonsuppression of the renin-angiotensin-aldosterone axis being the major factors. A full list of the major

Table 65–2

Pathogenetic Mechanisms of Hypertension in ESRD Patients

- Expanded extracellular volume
- Increased sympathetic activity
- Renin angiotensin aldosterone stimulation
- Erythropoietin administration
- Endogenous digitalis-like factors
- Prostaglandins/bradykinins
- Altered function of endothelium-derived factors and nitric oxide (vasoconstrictors and vasodilators)
- Parathyroid hormone secretion
- Calcified arterial tree
- Worsening of preexisting essential hypertension
- Renal vascular disease

etiologic factors is found in Table 65.2. A brief description of the more relevant factors follows. Theoretically, identifying the specific factor could result in more selective therapeutic strategies, but most patients present with overlapping causes—making an evaluation time consuming, expensive, and in most cases superfluous.

In an estimated 60 to 80% of hypertensive patients with chronic renal failure, removal of excess fluid volume and achievement of dry weight by dialysis results in normalization of BP without the use of antihypertensive agents. Patients with ESRD manifest a rise in cardiac output that is proportional to the degree of anemia. In the normotensive patient with ESRD, the rise in cardiac output is compensated for by a decrease in peripheral vascular resistance—and thus the BP does not rise. In the hypertensive patient, however, this adaptation of peripheral vascular resistance does not occur.

Expanded Extracellular Fluid Volume

Although not universally accepted as the sole cause of hypertension, expanded extracellular fluid (ECF) volume expansion is the most constant finding in hypertensive ESRD patients. The volume expansion may be subtle and not lead to edema. This is supported by data from Tassin, with outstanding dialysis survivals when ECF volume is controlled by long dialysis. Long-term CAPD patients also become hypertensive as their peritoneal membrane loses ultrafiltrating capacity. Volume expansion leads to an elevation in BP via increased cardiac output in the presence of an inappropriately high peripheral vascular resistance, complicated by failure to fully suppress vasoconstrictor systems [e.g., renin-angiotensin-aldosterone system (RAS) and sympathetic nervous system (SNS)].

Activation of the Renin-Angiotensin-Aldosterone System

One of the more difficult areas to understand is the evidence that there is an inappropriately increased angiotensin II in relation to the expanded volume and increased exchangeable sodium. The RAS is not the only mediator of increased vascular constriction. Impaired autoregulation also plays an important role in the increased total peripheral resistance response to the increased cardiac output. Various factors may be responsible for the absence of autoregulatory adaptation. Several lines of evidence suggest

that the renin-angiotensin system may be primarily responsible for these hemodynamic abnormalities.

First, in hypertensive ESRD patients there is frequently an abnormal relationship between exchangeable sodium (and/or blood volume) and plasma renin activity or serum levels of angiotensin II. Studies show the presence of abnormally high levels of renin and angiotensin II in relation to exchangeable sodium in hypertensive patients. Even normal levels of these hormones are inappropriate in the face of sodium excess and increased blood volume commonly found in the ESRD patient. Second, bilateral nephrectomy results in normalization of BP in most of these patients, further suggesting a role for angiotensin II. Finally, drugs that suppress the activity of the renin-angiotensin system are frequently effective in the management of hypertension in these patients.

Sympathetic Nervous System Activation

The extent to which the uremic state leads to enhanced sympathetic tone is unclear, but based on peroneal nerve studies it clearly may contribute to the increased arterial pressure in uremic patients. Sympathetic nervous system (SNS) overactivity is a well-documented finding in ESRD—correlating well with the increase in both vascular resistance and systemic BP. The afferent signal arises from within the kidney (this heightened sympathetic activation is not seen in anephric patients). Most studies report elevated serum concentrations of epinephrine and norepinephrine in ESRD patients. It should be noted, however, that the interpretation of serum catecholamine levels is fraught with difficulty due to the fact that ESRD patients display derangements in both the metabolism of and response to these amines.

Altered Endothelial Function

Some investigators have observed elevated plasma levels of endothelin-1 in uremic subjects, with levels of other isoforms also being increased. However, only endothelin-1 has been linked to hypertension. However, these observations do not prove a cause-and-effect relationship. The endothelium produces vasodilators [e.g., prostacyclin and nitric oxide (NO) or endothelium-derived relaxing factor]. There is recent evidence that uremic plasma contains a higher than expected level of asymmetrical

dimethylarginine that inhibits NO synthesis, raising the possibility that NO deficiency plays a significant role in the development of hypertension.

Parathyroid Hormone Levels and Hypercalcemia

Correction of hyperparathyroidism by vitamin D administration or parathyroidectomy has been shown to lower BP. These findings are compatible with the hypothesis that an increase in intracellular calcium induced by parathyroid hormone excess causes vasoconstriction and hypertension. When hypercalcemia ensues in ESRD patients, it may either cause or aggravate existing hypertension—resulting primarily from a rise in total peripheral resistance. Among the more important causes of hypercalcemia in ESRD are the effects of exogenous vitamin D analogs, vitamin A toxicity, excess use of oral calcium supplementation, granulomatous diseases, and myeloma.

Erythropoietin Use

Recombinant human erythropoietin (rHuEPO) has been a major advance in the management of patients with chronic renal failure, as it improves anemia and leads to decreased hospitalizations and cardiac problems with a concurrent improvement in the quality of life. Included among its various side effects is the development or worsening of preexisting hypertension in approximately 30 to 40% of patients. This BP increase is mediated via increased total peripheral vascular resistance related to increased viscosity and decreased hypoxic vasodilatation. However, there are some current reports suggesting that this may not be the case and that BP does not increase. One should monitor hemoglobin levels carefully in the dialysis patient population because there are compelling data suggesting that chronic kidney disease patients with higher hemoglobins have increased mortality rates. However, the studies may not be truly applicable to the ESRD patient population.

Prostaglandins and Renomedullary Lipids

Prostaglandin and prostacyclin are intrarenal prostaglandins that influence renin secretion and renal adrenergic activity and that act as vasodilators. They may blunt vasoconstriction.

Management of Hypertension in Dialysis

Therapeutic Approaches

There are three major approaches to therapy of hypertension in this patient population: proper diet, sodium and fluid restriction, and dialysis control of fluid and volume status. Non-drug therapy should be considered strongly before the initiation of any antihypertensive agent because that may interfere with the efficacy of the dialysis treatment. Most patients are responders to this conservative approach and have controllable hypertension with dialysis. In the remaining patients, BP control can usually be achieved with the concomitant administration of antihypertensive agents. Only in a small number of patients are hypertension resistant to drug therapy, and it is in this group that the challenge of BP control becomes an issue. A variety of mechanisms may be at play in the nonresponder group (Table 65.3).

Diet

Although most ESRD patients are following some form of "renal" diet, many do not realize the importance of diet in their overall health. Because it has been shown to lower the BP significantly in essential hypertension, the DASH diet has gained considerable popularity in the treatment of hypertension. This diet has not been specifically tested in ESRD or chronic renal failure but does appear to be prudent enough that it should be safe for some of this patient population with residual renal function and decent urinary outputs. Because the diet strongly recommends legumes, fruits, and milk products, the DASH diet may not be appropriate for many dialysis patients—especially those who are significantly

Table 65–3

Causes of Resistant Hypertension in Dialysis Patients

- Patient noncompliance
- Inadequate antihypertensive regimen
- Inadequate dialysis
- Misdiagnosis requiring home monitoring or 24-hour ABPM
- Drug interactions (prescription and over-the-counter)
- Pseudoresistance
- Secondary hypertension (e.g., renal vascular disease, pheochromocytoma, hyperparathyroidism with hypercalcemia, and unrecognized pressor mechanisms)
- Alcohol or drug abuse

hyperkalemic and hyperphosphatemic. However, a competent dietitian should be able to balance out the various aspects of the diet in relationship to its fiber and mineral content and make it applicable for the dialysis patient (it might not be at all like the original diet). It certainly might be tolerated by patients doing daily nocturnal dialysis in whom potassium and phosphorus often are repleted by drugs.

Sodium Restriction

Decreasing dietary sodium intake is a reasonable approach to follow unless there is pre-dialysis hyponatremia. This latter group of patients would require both salt and water restriction. Many nephrologists still restrict fluids in the patient with normal serum sodium and excessive weight gain. The major problem in this group of patients is excessive sodium intake, driving a powerful thirst mechanism. Attempts should be made to restrict dietary sodium to 1 to 1.5 g/day. In intermittent hemodialysis (three treatments per week), fluid intake should be limited to that quantity equivalent to limit the weight gain to manageable levels for easy ultrafiltration the next dialysis (e.g., 1 kilo during the week and 1.5 to 2.0 kilos on the weekend).

Similarly, in peritoneal dialysis patients the fluid intake should match ultrafiltration capacity of the peritoneum—especially as residual renal function declines. With daily nocturnal hemodialysis, fluid intake is not a big problem. A strict fluid restriction should be reserved for hyponatremic patients. Another approach to this problem would be to use low sodium dialysate, but this was abandoned years ago because of severe muscle cramps—especially in the elderly with atherosclerotic peripheral vascular disease. Sodium modeling is an approach that may address this problem. It should also be noted that Charra and Ozkahya continue to restrict sodium in their patients with excellent outcomes. BP control rates are excellent in both groups, with very low mortality rates and reversal of left ventricular hypertrophy.

Dialysis Control of Fluid Volume

Sodium and fluid retention commonly occur in patients with impaired renal function, and these retentions are accentuated once dialysis is begun. This leads to expansion of extracellular volume and increased cardiac output. The control of fluid and volume status with the maintenance of dry weight is therefore of primary importance in the management of ESRD patients. Therefore, dry weight should be achieved and maintained by ultrafiltration with hemodialysis or peritoneal dialysis. When initiating dialysis,

achievement of dry weight should be accomplished gradually over 4 to 12 weeks. The negative fluid balance should not exceed 1 to 2 kg/week.

Overzealous ultrafiltration may result in hypotension and may affect residual renal function. In predisposed patients, cerebral or coronary ischemia may result. Furthermore, a paradoxical hypovolemic hypertension may occasionally develop—mediated by activation of the RAS in response to low circulating volume. Aggressive ultrafiltration is indicated only in patients with signs of left ventricular failure or other hypertensive emergencies, such as malignant hypertension, hypertensive encephalopathy, acute pulmonary edema, dissecting aneurysm of the aorta, and so on.

At the beginning of dialysis and until dry weight is achieved, antihypertensive therapy should not be instituted in patients who display only mild hypertension (diastolic BP 90 to 105 mmHg or a calculated mean ≥107). In fact, there is a lag phase between the achievement of dry weight and the development of anabolic metabolism and BP control.

In patients already taking antihypertensive agents, the close of these drugs should be tapered as BP decreases with ultrafiltration. Antihypertensive therapy should be immediately instituted in patients with severe (diastolic BP >115 mmHg) or accelerated hypertension. Patients with hypertension complicated by severe retinopathy, congestive heart failure, other preexisting condition, cerebrovascular accidents, or aortic aneurysm should also be treated without delay.

When dry weight is achieved, more than half of the patients become normotensive and maintain normal BP as long as the body weight remains close to dry weight. During the interdialytic period, BP rises in proportion to the amount of sodium and fluid retention. If the diastolic BP does not exceed 95 mmHg during the interdialytic period, antihypertensive therapy should be withheld. Administration of antihypertensive agents prior to dialysis may result in more frequent and severe hypotensive episodes during dialysis.

To limit the adverse effects of ultrafiltration, such as hypotension and muscle cramping, sequential ultrafiltration dialysis is recommended. The common practice of ultrashort aggressive dialysis or administration of antihypertensive agents immediately before dialysis limits the ability to remove fluid and achieve dry weight. Antihypertensive therapy further compromises effective dialysis and ultrafiltration. This leads to a vicious cycle of hypotension, fluid overload, and hypertension. A regimen of physical exercise for the ESRD patient has been demonstrated to provide an impres-

sive improvement in hypertension control. Reduction in alcohol intake and avoidance of drugs such as cocaine or amphetamines may also result in improved BP control in some ESRD patients.

Estimating Dry Weight

Estimating a patient's dry weight is probably the thorniest clinical problem facing clinical nephrologists. Examples of "accepted" clinical definitions of dry weight are "...not merely the absence of edema, but that body sodium content and volume of body water or critical component thereof below which further reduction results in hypotension" (G. Thomson) and "Dry weight is that body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis without antihypertensive medication" (B. Charra).

Many biomedical and laboratory tests have been devised to assess volume status of the ESRD patient: bioimpedance plethysmography, measurement of the inferior cava diameter, plasma atrial natriuretic peptide concentrations, arteriovenous pressure levels, and blood volume. No prospective study has been performed to compare any of these methods to clinical assessment, and most of these techniques are impractical and cumbersome. Therefore, the nephrologist is left to his or her experience and clinical acumen to determine the dry weight for each dialysis patient.

Antihypertensive Drugs

A list of classes of antihypertensive medications can be found in Table 65.4. When hypertension in the dialysis patient cannot

Table 65–4

Classes of Antihypertensive Drugs

- Diuretics
- Beta adrenergic blockers
- Alpha 1 adrenergic antagonists
- Alpha 1/beta antagonists
- Central alpha 2 agonists
- Adrenergic neuronal blockers (central and peripheral)
- Vasodilators
- Calcium channel antagonists
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor antagonists
- Vasopeptidase inhibitors

be controlled with ultrafiltration and aggressive dialysis alone, antihypertensive agents must be used. The pharmacologic treatment of dialysis-resistant hypertension, with the exception of diuretic use, does not differ significantly from the treatment of essential hypertension. Agents that block the secretion of renin or activation of the renin-angiotensin system appear to be particularly effective. There is data suggesting that ACE inhibitors may be of additional help in preserving renal function in the CAPD patient population. Agents that interfere with the activity of pressor substances, such as vasodilators and calcium channel blockers, are also useful in ESRD patients. It may be necessary to monitor home BP levels to accurately diagnose hypertension in these patients. Once the patient has stabilized into his/her dialysis pattern, it may be possible to decrease the anithypertensive dosage.

In patients with renal failure, the metabolism and disposition of antihypertensive agents are altered—resulting in accumulation of either the intact drug or its metabolites. Furthermore, the dialyzability of the various antihypertensive agents is essential information for the clinician. In general, water-soluble agents dialyze with ease—and thus converted enzyme inhibitors tend to be removed by dialysis (whereas calcium channel blockers are not). Postdialysis hypertension is also more likely to occur in patients treated with dialyzable agents, because the removal of the drug by dialysis may result in decreased blood levels of the agent and precipitate a rise in BP. Therefore, the antihypertensive prescription in patients with ESRD requires clear knowledge of how the impairment in renal function and the dialysis procedure itself affect the pharmacodynamic and pharmacokinetic properties of these agents (Table 65.5). For these reasons many nephrologists recommend ingestion of antihypertensives at night.

Therapy with antihypertensive drugs is primarily indicated in the minority of patients in whom hypertension persists despite seemingly adequate volume control. Elevated BPs can usually be controlled by most classes of antihypertensive agents. The selection of antihypertensive agents is frequently dictated by the presence of co-morbid conditions. There is no information available on whether BP control with antihypertensive drugs is as beneficial for long-term survival as adequate dialysis, although there is reason to believe that antihypertensive treatment alone may not be adequate to prevent cardiovascular sequelae.

In many ESRD patients, especially the elderly vasculopath, cardiovascular agents and antihypertensives are often prescribed for coexistent noncardiac and nonrenal diseases. This may make effective dialysis more difficult to deliver. The initiation of anti-

Table 65–5

Pharmacodynamics and Pharmacokinetics of the Various Antihypertensive Agents

	$T^{1}/_{2}$ (hours) Oral Bioavailability	Renal Excretion of Unchanged Protein Binding			Removal with Dialysis Dose				
				Unchanged		Change with		Active	
	(%)	(%)	Normal	(ESRD)	(% dose)	ESRD	Hemo	Peritoneal	Metabolites
Antiadrenergic Agents									
Clonidine	75	20–40	5–13	17–40	50	↓ (50–75%)	5%	?	No
Guanabenz	40	40	50–100	83–323	Small	↓ (Yes)	None	None	No
Guanethidine	5–60	0	48–72	Prolonged	30–50	↓ (Yes)	None	None	Slight
Guanfacine	100	65	15–20	Slightly increased	30–50	↓ (Yes, lowered dose)	None	None	No
Methyldopa	26–74	<20	1–2	1.7–3.6	50	12–24%	60%	30–40	Yes
Monoxidine	90	7–9	1.7–3.5	3.2–10.6	55–65	50%			
Rilmenidine	100	7–8	7–9	31–37	60–70	50%			
Alpha Adrenergic Blocking Agents									
Doxazocin	60–70	98–99	10–15	10–15	9	None	None	NA	Yes/None
Guanadrel	70–80	20	3–5	10–30	40–50	↓	?	NA	
Prazosin	48–68	97	2.5–4.0	2.5–4.0	<10		None	None	None
Terazocin	80–90	90–94	10–15	10–15	40	None	?	NA	None
Urapidil	70–75	79–82	2–5	5–8	10–15	None	None	None	Yes

Table Continued

Table 65–5

Pharmacodynamics and Pharmacokinetics of the Various Antihypertensive Agents—Cont'd

	$T^1/_2$ (hours)	Oral Bioavailability	Renal Excretion of Unchanged	Protein Binding		Removal with Dialysis		Dose Change with		Active	
		(%)	(%)	Normal	Unchanged (ESRD)	(% dose)		ESRD	Hemo	Peritoneal	Metabolites
Beta Adrenergic Blocking Agents											
Acebutolol	50	30	3.5	3.5	40			↓ 70%	50%	?	Yes
Atenolol	50	<5	6–9	<120	85–100			↓ 75%	53%	48%	No
Betaxolol	89 ± 5	50	14–22	28–44	15			50%	None	None	No
Bisoprolol	80–90	30	10–12	20–25	45–55			50%	None	None	No
Carteolol	80–85	20–30	5–7	30–40	55–65			25%	NA	NA	Yes
Carveditol	25	95	4–7	4–7	2			None	None	None	Yes
Cetamolol			6–8	10–12	30–40			33%	NA	NA	NA
Esmolol	—	55	7.2	7.1	2			None	None	None	Slight
Labetalol IV	NA	50	5.5	5.5	50–60			Smaller doses work	<1%	<1%	No
Labetalol PO	33	50	3–4	3–4	20–40			Slight ↓	<1%	<1%	No
La-propranolol	20	90	10	10	<1			Slight ↓	None	None	Yes
Metoprolol	40–50	12	3–4	3–4	13			None	High	?	Slight
Nadolol	30	30	14–24	45	70			50% ↓	High	?	Yes
Pindolol	90	57	2–3	2–3	40			Slight ↓	Probable	?	No
Propranolol	30	90	2–4	2–4	<1			Slight ↓	None	None	Yes
Timolol	75	10	4–6	4–6	20			Slight ↓	?	?	No

Table 65–5

Pharmacodynamics and Pharmacokinetics of the Various Antihypertensive Agents—Cont'd

$T^{1}/_{2}$ (hours) Oral Bioavailability	Renal Excretion of Unchanged Protein Binding			Removal with Dialysis					
				Unchanged		Dose Change with		Active	
	(%)	(%)	Normal	(ESRD)	(% dose)	ESRD	Hemo	Peritoneal	Metabolites
ACE Inhibitors									
Alacepril			4–6	15–20					
Benazepril	37	97	10–11	Prolonged	1	Yes ↓[b]	None		No
Captopril	75	30	2–3	20–30	30–40	Yes[b]	Yes	?	No
Cilazapril	77		2–3	4–6	65–85	25%	Yes		
Delapril	55		0.5		2	?			Yes
Enalapril	60	High	11	Prolonged	70	Yes[b]	35%	?	Yes
Fosinopril	36	95	12	Prolonged	Negligible	None	2	7	Yes
Lisinopril	25–30	3–10	12.7	54.3	29	↓ 75%	50%	?	Yes
Moexipril	13		2–9						
Pentopril	50		0.7–1.0	No change	20–25				
Pentoprilat			2–3	10–14	35–45	↓			
Perindopril	66				78	Yes			
Quinapril	60	97	2–3	Prolonged	5–6	NA	NA	NA	Yes
Ramipril	54–65	73	10.8	Prolonged	2	50%	Yes	?	Yes
Trandolapril	10	60	6	12	33	50%			Yes
Zofenopril	96	80–85	5–6	10	5	50%			

Table Continued

Table 65–5

Pharmacodynamics and Pharmacokinetics of the Various Antihypertensive Agents—Cont'd

	$T^1/_2$ (hours)	Oral Bioavailability	Renal Excretion of Unchanged	Protein Binding		Removal with Dialysis			
					Unchanged	Dose	Change with		Active
	(%)	(%)	Normal	(ESRD)	(% dose)	ESRD	Hemo	Peritoneal	Metabolites
Vasolidators									
Diazoxide	Low	85	20–36	Prolonged	50	None	Yes	Yes	?
Hydralazine	10–30	90	2–4	Prolonged	10	Yes, slight ↓	NA	None	No
Minoxidil	95	Minimal	2.8–4.2	4.2	10	None	Yes	Yes	No
Nitroprusside	0	?	3–4 min	Prolonged	High	None	Yes	Yes	No
Calcium Channel Blockers									
Amiodipine	60–70	97	30–50	10%	<1	None	NA	NA	?
Ditiazem	20	80	α: 20 h	Unchanged	35	None	?	?	No
(β: –4 H)									
Felodipine	15–20	97	10–20	<.5%	<.5%	None			
Isradipine	15–20	96	8–12	Unchanged	<5				
Nicardipine (dose dependent)	6–30	98–99	3–6	Unchanged	<5	Decreased			No
Nifedipine	65	90	α: 2.5–3.0 h	Unchanged	70–80	None	Low	Low	No

Table 65–5

Pharmacodynamics and Pharmacokinetics of the Various Antihypertensive Agents—Cont'd

$T^1/_2$ (hours) Oral Bioavailability	Renal Excretion of Unchanged	Protein Binding		Removal with Dialysis Dose		Change with		Active	
	(%)	(%)	Normal	Unchanged (ESRD)	(% dose)	ESRD	Hemo	Peritoneal	Metabolites
β: 5 h									
Nivadipine	15	85–90	10–13		<5				
Nimodipine	6–10	98	1–1.5		<1				No
Nisoldipine	8–10	98–99	1.0–1.5		<1	None			No
Nitrendipine	10–30	98	1.0–1.5		<1	None			No
Verapamil	10–32	90	α: 15–30 h	α: 4.5	3	None	?	?	Yes
β: 3–7 h*	**(β: 2.3 h)***								
Angiotensin II Inhibitor									
Losartan	33	99	2	4	4	None	None	None	Yes
Valsartan	10–35	95	6	?	13	?	None	None	No
Irbesartan	60–80	90	11–15	11–15	22	None	None	None	No
Eprosartan	13	98	4.5–9	1 by 60%	30	None	None	None	No
Candersartan	15	99	9	18 (?)	26	None	None	None	No
Temisartan	42–58	99.5	24	Unchanged	None	None	None	None	No

a. Initial fast $T^1/_2$; b = late slow $T^1/_2$.
b. Maximum dose is same. Start with lower dose (50% ↓); it usually works.
Adapted from Henrich WL. *Principles and Practice of Dialysis, Second Edition*. Baltimore: Williams & Wilkins 1999.

hypertensive agents should be a well thought out and clinically well-founded decision. Specific information about the pharmacology of these agents can be found in textbooks of pharmacology hypertension and/or dialysis. However, several points about the use of specific classes of antihypertensive drugs in dialysis patients deserve mention.

Angiotensin-Converting Enzyme Inhibitors

By inhibiting kininase II, ACE inhibitors reduce production of angiotensin II and may also decrease degradation of vasodilating bradykinins and prostaglandins. Peripheral vascular resistance is decreased without a change in cardiac output or heart rate. These agents are effective and well tolerated in patients with hypertension, cardiovascular disease, and heart failure due to systolic dysfunction. They have been shown to decrease mortality, both cardiac and all-cause, in the non-ESRD patient. Whether this is true in advanced renal failure remains to be determined.

ACE inhibitors are also effective in delaying the progression of renal disease in proteinuric renal insufficiency, whether caused by diabetes mellitus or chronic glomerulonephritis. They do, however, have two unique side effects in ESRD: they may aggravate anemia by reducing the action of erythropoietin (an effect that has been best described after transplantation) and they can trigger an anaphylactoid reaction in patients dialyzed with a PAN membrane dialyzer. They have been shown to cause the regression of left ventricular hypertrophy in combination with a good dialysis regimen.

These agents acutely diminish the circulating levels of angiotensin II and aldosterone, while increasing plasma renin activity. However, aldosterone and angiotensin II levels return toward normal with chronic use. Thus, to the extent that the maintenance of BP is dependent on the renin-angiotensin system, converting enzyme inhibitors (CEIs) reduce BP.

These agents decrease peripheral vascular resistance without an increase in heart rate or cardiac output. In addition, capillary wedge pressure does not change and the sympathetic nervous system is not stimulated. Cerebral blood flow is maintained even in the face of decreased systemic BP, apparently due to constriction of small resistance vessels following CEI-induced dilation of large resistance vessels.

These agents are particularly effective in patients with high renin hypertension and in those refractory or intolerant to standard antihypertensive regimens. In addition, they are quite effective in reversing left ventricular hypertrophy—which is

prominent in the ESRD population. These drugs improve insulin sensitivity, help reduce arteriolar hypertrophy, and can restore endothelial function in hypertensive individuals.

Therapeutic Classes

CEIs can be classified into three main chemical categories: sulfydryl, carboxyl, and phosphoryl containing. The sulfhydryl agents are pro-drugs converted in vivo to captopril. The carboxyl-containing CEIs (of which enalapril is an example) are also pro-drugs converted in vivo to the active metabolite. These are principally excreted by the kidney and may require dose adjustment in renal failure. Some of these agents are thought to have enhanced tissue ACE-inhibitor effects. Examples of this subgroup include benazepril, lisinopril, quinapril, ramipril, perindopril, and enalapril. The third subgroup is the phosphoryl-containing group (e.g., fosinopril). Because it is partially eliminated by the liver, the dose need not be adjusted in renal failure.

Side effects such as cough, skin rash, dysgeusia, and leukopenia are reported with most of these agents. Neutropenia and agranulocytosis have been reported, particularly in patients with autoimmune collagen vascular diseases. Another notable side effect is the worsening of anemia in dialysis and transplant patients treated with captopril and enalapril, correlating with levels of angiotensin II and a decrease in reticulocytes. The effect disappears after withdrawal of the agent and does not correlate well with circulating levels of erythropoietin.

Of particular interest is the appearance of reports describing an anaphylactic reaction in dialysis patients treated with CEIs. Specifically, this phenomenon has been observed in patients treated with CEIs while undergoing dialysis with a high-flux (AN69) capillary dialyzer. Symptoms range from mild edema of the mucosa of the eyes to nausea and vomiting, bronchospasm, hypotension, and angioedema.

Angiotensin II Receptor Antagonists

Currently, there are several antagonists available—with little data about long-term use in either chronic renal failure or dialysis patients. In a study of 89 patients, of whom 20 were hemodialysis patients, BP responded well and no significant biochemical alterations were noted—although some increase in potassium occurred in 25% of patients with moderate to severe renal dysfunction. Unlike ACE inhibitors, angiotensin II receptor antagonists are not associated with altered kinin metabolism and therefore are not expected to elicit chronic cough or anaphy-

lactoid reaction to PAN high-flux membranes. These agents are being used with increasing frequency in cardiac patients. They also possess antiproteinuric effects. In essential hypertension they reverse left ventricular hypertrophy, restore endothelical function, and improve arteriolar compliance.

Calcium Channel Antagonists

The calcium channel antagonists lower BP by inhibiting the influx of extracellular calcium across and into vascular smooth muscle and cardiac cells, thereby interfering with the normal excitation-contraction process. This promotes arteriolar dilatation, resulting in increased peripheral vascular resistance. The chemical structures of these agents are quite dissimilar. Nifedipine is a dihydropyridine derivative. Verapamil is structurally similar to papaverine, whereas diltiazem is related to the benzodiazepines. Several classifications for these drugs have been proposed, but the division into type I and type II agents is used most often. Type I refers to the dihydropyridines, such as nifedipine, felodipine, amlodipine, nitrendipine, nimodipine, isradipine, nisoldipine, nilvadipine, and some others still under investigation. Type 2 agents include verapamil, diltiazem, and tiapamil.

The dihydropyridines, type I agents, have a significant hepatic first-pass effect and their bioavailability is between 6 and 30%. Less than 1% of the dose is excreted in urine as unchanged drug with felodipine, nisoldipine, nitrendipine, and nimodipine. For the other dihydropyridines, 10% is excreted unchanged in the urine. These agents form many metabolites, although they are inactive. For these reasons, the pharmacokinetics of these agents does not differ in patients with renal failure—and therefore these drugs may be used in dialysis patients without any change in dose or frequency of administration. Furthermore, due to their poor water solubility, high protein binding, and large volume of distribution the dihydropyridines are not significantly cleared by hemodialysis—eliminating the need for a supplementary postdialysis dose.

Some calcium channel blockers provide the advantage of treating co-morbid conditions in addition to their primary use for BP control. Verapamil is well known for its use in supraventricular tachycardia. In the setting of cerebrovascular accident, nicardipine and nimodipine appear to have potent selective cerebral vasodilatory effects. Their administration may prevent mitochondrial overload from excess calcium entry into ischemic neurons during reperfusion. Verapamil has been used for prophylaxis of migraine headaches. Calcium channel blockers

as a class lower enhanced peripheral resistance, which may ameliorate the incidence of dialysis-related Raynaud's phenomenon.

The use of calcium channel blockers is of particular interest in regard to the accelerated degree of atherosclerosis associated with uremia. In long-term nonrenal patient studies, these agents have been shown to inhibit the progression of atherosclerosis by a variety of mechanisms. In addition, they exert no negative influence on lipid metabolism—as cholesterol and triglyceride levels are unaffected during therapy. There also appears to be a positive effect on carbohydrate metabolism, as some studies have shown increased glucose tolerance with these agents.

The side effects of these drugs include hypotension, headache, flushing, ankle edema, nausea, and constipation. Flushing is more common with the dihydropyridines, whereas verapamil is more likely to cause conduction disturbances, bradycardia, and constipation.

Calcium antagonists have also been shown to be effective in reducing left ventricular mass in non-ESRD patients. Therefore, they may be particularly useful in patients with left ventricular hypertrophy and diastolic dysfunction. These agents are both very effective and well tolerated in dialysis patients, even in those who are volume expanded. Calcium channel blockers do not require supplementary postdialysis dosing. Certain of these agents have a negative ionotropic and negative chronotropic effect on the myocardium.

Others may elicit reflex neuro-humoral stimulation. Newer agents, such as filodipine and amlodipine, are long acting and in low doses may not have these negative characteristics. The same precautions on the use of short-acting dihydropyridines in the general hypertensive population apply to the hypertensive ESRD population. The negative chronotropic and inotropic effects of diltiazem and verapamil should be kept in mind if the ESRD patient has any cardiac dysfunction or history of congestive failure. Some of the dihydropyridines are being used with increasing frequency in patients with diastolic dysfunctioin.

Beta Blockers

Beta blockers are particularly useful in hypertensive patients who have had a recent myocardial infarction. Potential side effects include central nervous system depression (an effect that may be more prominent with lipid-soluble drugs that cross the blood-brain barrier), bradycardia, altered lipid profiles, hyperkalemia, altered response to hypoglycemia, and bronchospasm. Sympathetic overactivity may be improved by beta blockers. These agents may

also aggravate claudication, impotence, and sleep disturbances. Atenolol and nadolol, with low lipid solubility, are renally excreted (requiring altered dosage schedules). This class of drugs should be used cautiously in patients also taking certain calcium channel blockers, because there may be additive negative chronotropic and inotropic actions.

An alpha beta blocker, labetolol, may be of particular benefit in patients with ESRD—having a lower incidence of bronchospasm and not affecting plasma lipid levels. No information about the use of carvedilol in the hypertensive ESRD is available, but this agent has been used successfully in the renal transplant population and is widely prescribed in patients with congestive heart failure. In the past, the beta blockers were used extensively in the management of hypertension in patients with chronic renal failure because of their well-established efficacy and safety. The mechanism of action of these agents is complex and not completely understood, but their antihypertensive effects are due at least in part to inhibition of renin release. Presently, most patients can be best controlled with converting enzyme inhibitors and angiotensin II blockers. Most beta blockers decrease cardiac output, but the antihypertensive activity does not correlate with this alteration. Peripheral resistance initially increases, but subsequently decreases without actually reaching pretreatment levels. On the other hand, some beta blockers with intrinsic sympathomimetic activity, such as pindolol and acebutolol, decrease peripheral vascular resistance with minimal effect on cardiac output.

A large number of beta-blocking agents with differing pharmacodynamic and pharmacokinetic properties are available (Table 65.2). The most important pharmacologic differences among these agents are lipid solubility, intrinsic sympathomimetic activity, and selectivity for beta adrenergic receptors (cardioselectivity).

The degree of lipid solubility affects both central nervous system penetration and extent of hepatic metabolism. High lipid solubility results in both more central nervous system side effects and more extensive hepatic metabolism. For example, propranolol, acebutolol, and metoprolol are well absorbed from the small intestine. However, because of extensive first-pass metabolism by the liver only 30 to 50% of these drugs reaches the systemic circulation. The concomitant use of drugs that affect hepatic blood flow may further reduce the bioavailability of these beta blockers. Conversely, atenolol, acebutolol, and nadolol (agents with low degrees of lipid solubility) are primarily renally excreted. Accumulation of beta blockers with low lipid solubility

may result in excessive bradycardia. Consequently, the dose of most liposoluble agents need not be adjusted in renal failure—whereas the dose of agents with low lipid solubility should be adjusted.

Cardioselectivity, the second important characteristic distinguishing these agents, is considered to have limited clinical relevance with respect to antihypertensive efficacy but is of considerable importance with respect to side effects. Cardioselective beta blockers are in fact less likely to cause bronchospasm, Raynaud's phenomenon, or disturbances of lipid and carbohydrate metabolism. The beta1-selective beta blockers include atenolol, metoprolol, and acebutolol.

The third characteristic is intrinsic sympathomimetic activity (ISA). Some agents have a dual action of blocking and directly stimulating beta adrenoreceptors. Hemodynamically, this results in not only decreased peripheral vascular resistance but less pronounced reductions in heart rate, cardiac output, and plasma renin secretion. Pindolol and (to a lesser degree) acebutolol have ISA.

Except for beta blockers that are renally excreted (i.e., not highly lipid soluble), most β-blockers do not require dose adjustment in dialysis patients. Atenolol and nadolol are removed in significant amounts by hemodialysis and should therefore be administered after the dialysis treatment. Hemodialysis also removes 50% of the metabolites of metoprolol from the bloodstream.

Simultaneous administration of beta blockers and calcium channel blockers must be avoided in patients with chronic renal failure in order to avoid an increase of the negative inotropic effect each of these agents exerts on the heart. Similarly, administration of cyclooxygenase inhibitors should be avoided because they may antagonize the antihypertensive effect of beta blockers. Hypotensive episodes during hemodialysis may occur more frequently with the use of beta blockers as a result of a blunting of reflex tachycardia.

Alpha and Beta Receptor Blockers

Some agents have combined alpha- and beta-blocking properties. The prototype of this group is labetalol hydrochloride. Acutely, labetalol lowers both cardiac output and peripheral vascular resistance. However, after chronic administration the decrease in BP is primarily due to decreased peripheral vascular resistance. Acutely, labetalol tends to decrease plasma renin activity. After chronic administration, however, plasma renin activity tends to

increase and aldosterone remains unchanged. The intravenous form of this agent is very useful in the treatment of hypertensive crisis, whereby 5 to 10 mg can be given every 15 to 30 minutes to bring about a smooth and safe reduction in dangerously elevated BP.

Central Sympathetic Agonists

The central sympathetic agonists, such as clonidine and methyldopa, are used less frequently because of their adverse effects involving the central nervous system. The antihypertensive action of a-methyldopa and clonidine is caused primarily by activation of alpha2-adrenergic receptors in the brain stem, although methyldopa gets transformed into a false neurotransmitter. These agents may also elicit dry mouth, which may aggravate excess fluid intake and orthostatic hypotension. Some physicians have found clonidine patches to be effective and well tolerated, but this is not a universal finding. Because 40 to 50% of the drug is excreted by the kidneys, the dosage should be reduced in ESRD patients.

Clonidine is only minimally removed by hemodialysis compared to methyldopa. Clonidine has been reported to be useful in the treatment of the restless leg syndrome of chronic dialysis. Hypertensive crisis may occur when the drug is discontinued abruptly. This rebound effect becomes more pronounced when the drug is given in doses exceeding 0.6 mg/day or when given in combination with alpha-adrenergic-blocking agents. Clonidine should be given at initial doses of 0.05 to 0.1 mg twice daily. The total daily dose should not exceed 0.3 mg twice daily. When given in conjunction with beta blockers, the maximum dose should not exceed 0.4 mg/day. Guanabenz and guanfacine are very similar to clonidine.

Alpha-Adrenergic-Blocking Agents

These agents are commonly used in patients who have concomitant prostatism. Orthostatic symptoms may occur, especially in older patients. They have a favorable metabolic side effect profile and may be synergistic with ACE inhibitors and other antihypertensive agents. Alpha blockers have a favorable effect on the lipid profile in that they decrease low-density-lipoprotein cholesterol and may increase the high-density-lipoprotein cholesterol. Prazosin is a quinazoline derivative with a dual mechanism of antihypertensive activity consisting of direct smooth muscle relaxant effects and peripheral alpha-adrenergic receptor inhibition.

This latter property does not significantly affect the presynaptic alpha2 receptors and therefore allows epinephrine and norepi-

nephrine to occupy the presynaptic inhibitory alpha2 receptors, thereby reducing further release of catecholamines from the sympathetic end terminals. This may partially explain why this vasodilator stimulates neither heart rate nor plasma renin release. It is metabolized primarily in the liver, and thus no dose adjustment is necessary in renal failure. The most troublesome side effect of prazosin is the "first-dose phenomenon," which consists of significant orthostatic hypotension occurring after administration of the first dose. This phenomenon is particularly common in patients receiving ultrafiltration with dialysis or on sodium restriction.

Other side effects include syncope, dizziness, diarrhea, and nausea in addition to postural hypotension that is independent of the first-dose effect. Terazosin and doxazosin are very similar, but with more gradual absorptions—resulting in higher blood levels 8, 12, and 16 hours after administration of an oral dose. Doxazosin is also a quinazoline derivative with a long half-life, making it suitable for once-a-day administration. The main route of elimination is the gut, and the drug is poorly dialyzed. These drugs are used more frequently in men with prostatic enlargement.

Sympathetic inhibitors reserpine and guanethidine are very infrequently prescribed. They have a very high side effect to efficacy ratio. Reserpine should be avoided in patients with chronic renal failure as well as in transplant recipients, due to the high incidence of depression, psychosis, Parkinson-like syndrome, impaired ejaculation, and reactivation or induction of peptic ulcer disease. Guanethidine also has virtually no role in the management of patients with renal failure because of a high incidence of severe side effects (e.g., orthostatic hypotension, impotence, diarrhea, bradycardia, and retardation). Guanadrel is an analogue of guanethidine (with a shorter half-life and shorter duration of action) and should also be avoided.

Vasodilators

Vasodilators exert their antihypertensive effect by a direct action on vascular smooth muscle cells. There are two oral vasodilators: hydralazine and minoxidil. The intravenous preparations (such as sodium nitroprusside, hydralazine, and diazoxide) are more suitable for the treatment of hypertensive emergencies, whereas the oral forms are more suitable for chronic therapy. Hydralazine-hydralazine is available in both oral and injectable forms. Hydralazine is predominantly an arteriolar vasodilator. The drug causes activation of the SNS and the RAS, which can result in

tachycardia, increased cardiac output, and sodium retention. Thus, it is of little therapeutic use when administered as monotherapy.

Conversely, it is quite effective when used in conjunction with a beta blocker or antiadrenergic agent. In addition, hydralazine is of particular use when given in combination with nitrates in patients with congestive heart failure. Hydralazine is metabolized primarily by the liver, but in dialysis patients dose adjustment is required. To prevent side effects, a daily dose of 200 mg should not be exceeded. The most frequent side effects are headache, tachycardia, nausea, vomiting, palpitations, dizziness, fatigue, angina pectoris, sleep disturbances, nasal congestion, and a lupus-like syndrome. Minoxidil-minoxidil is an orally administered vasodilator that is more potent than hydralazine. It dilates primarily arterioles and has little effect on capacitance vessels.

For patients with the most refractory forms of hypertension, it has been advocated as a valid alternative to bilateral nephrectomy. The drug is primarily metabolized by the liver, and dose adjustments are not required in patients with renal failure. The drug induces reflex stimulation of the SNS as well as the RAS, producing tachycardia, increased cardiac output, and marked sodium and water retention. This combination of effects may result in pericardial effusion, the exact incidence rate of which is unknown. Thus, minoxidil should be used in combination with a beta blocker or a converting enzyme inhibitor.

Patients receiving maintenance hemodialysis who are treated with minoxidil usually experience a greater increase in body weight during the interdialytic period, probably due to an increase in thirst and appetite for salt caused by reflex stimulation of the renin-angiotensin system. The most common adverse effects, aside from fluid and sodium retention, are tachycardia, angina pectoris, and ischemic electrocardiographic changes. Hypertrichosis is commonly seen, and this may limit use of the agents among females for cosmetic reasons.

Resistant and Accelerated Hypertension in Dialysis Patients

Dialysis-resistant hypertension is an uncommon occurrence in the face of a prudent diet, adequate dialysis with ultrafiltration, and appropriate antihypertensive drug combinations. Nonetheless, this entity does occur and can be difficult to manage. For dialysis patients in whom previously controlled hypertension has now become resistant or responds poorly to increased anti-

hypertensive doses, secondary forms of hypertension (renal artery stenosis or pheochromocytoma), drug-drug interactions, or embolic phenomena to the kidney may be considered.

Hypovolemic hypertension, wherein BP paradoxically rises with fluid removal, may be suggestive of stimulated SNS or renin-angiotensin system stimulation from renal artery stenosis. In addition, noncompliance may contribute to resistant hypertension. Patients may become noncompliant after experiencing side effects of rapid ultrafiltration, dietary indiscretions, or the inability to afford expensive medications. Lack of motivation, information, or communication may also contribute to noncompliance. The physician should always seek evidence of noncompliance, such as failure to keep appointments and renew prescriptions, missing dialysis, pill counts that are higher than expected, and failure to know the type and dose of medications prescribed.

If the patient is compliant, the possibility of drug interactions should be considered. Nonsteroidal anti-inflammatory agents and Cox-2 inhibitors may accentuate fluid retention (in patients with significant residual renal function), cause vasoconstriction, or interfere with the effectiveness of converting enzyme inhibitors. Use of contraceptive estrogens or sympathomimetic amines such as those in cold remedies, appetite suppressants, and nasal sprays may also contribute to resistant hypertension.

Alcohol abuse and the use of drugs such as cocaine and amphetamines can cause BP to be refractory. Reports in the literature describe resistant hypertension being caused by pheochromocytoma in dialysis patients. Thyroid disease should be considered as well, although results must be interpreted carefully. Pseudohypertension may be diagnosed when the radial and/or brachial pulse is still palpable when the cuff has been maximally inflated (Osler maneuver). It may be necessary to consider a full evaluation of the patient for a secondary cause if this situation exists. In addition, recent reports have readvocated the use of bilateral nephrectomy in these patients—the results of which are very encouraging.

Hypertensive emergencies are not usually dealt with in the dialysis units, but dialysis patients can certainly develop them leading to the need for hospitalization. Depending on the nature of the clinical problem, the patient may be treated with nitroprusside, diazoxide, labetalol, or fenoldopam. Each of these agents has side effects peculiar to its compound. A full discussion of this topic is beyond the scope of this chapter.

Summary

Uncontrolled hypertension is a serious problem in the chronic kidney disease patient. It is a major cause of progressive chronic renal failure and accelerates all other etiologies of ESRD. In that regard, it is a unique situation to which clinicians must pay far more attention than they have in view of the increasing cardiovascular co-morbidity and prevalence of uncontrolled hypertension. If the patient initiates dialysis with controlled BP levels, it is quite likely the drugs can be stopped. One wants to avoid hypotension, especially in the older ESRD patient population.

Salt restriction and adequate dialysis remain the major therapies for this. The initiation of drug therapy should be considered only when all other avenues have failed. If severe hypertension persists despite this, one might wish to consider either minoxidil or bilateral nephrectomy. Short dialysis time is one of the major reasons nephrologists are doing more poorly in the control of hypertension. There have been very encouraging results in patients on daily overnight dialysis and prolonged regular hemodialysis—with reversal of left ventricular hypertrophy, no need for antihypertensive drugs, and improved survivals.

Recommended Reading

Agarwal R, Brim NJ, Mahenthiran J, Andersen MJ, Saha C. Out-of-hemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. Hypertension 2006;47(1):62–68. E-pub 12 December 2005.

Suggests the need for 24-hour ambulatory BP monitoring and other sources of readings for BP monitoring in this patient population.

Amar J, Vernier I, Rossignol E, Bongard V, Arnaud C, Conte JJ, et al. Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. Kidney Int 2000;57(6):2485–91.

This article demonstrates the hypertensive pattern in ESRD patients.

Bianchi S, Bigazzi R, Campese VM. Altered circadian blood pressure profile and renal damage. Blood Press Monit 1997;2:339–45.

One of original articles demonstrating lack of diurnal pattern.

Bishu, K, Gricz, KM, Chewaka, S, Agarwal, R, et al. Appropriate ness of antihypertensive drug therapy in hemodialysis patients. Clin J Am Soc Nephrol 2006;1:820–25.

Good review of drug therapy for ESRD patients.

Campese VM. Neurogenic factors and hypertension in renal disease. Kidney Int 2000;57(75):S2–6.

Excellent description of altered sympathetic pathways as an etiology of the hypertension in ESRD patients.

Charra B, Calemard E, Ruffet M, Chazot C, Terrat J-C, Vanel T, et al. Survival as an index of adequacy of dialysis. Kidney Int 1992;41:1286–91.

This is the classic article demonstrating better survival rates in patients with good BP control (prospective and long-term). Their patient population does not mirror the current ESRD patients. This group has published more recent

articles showing their excellent results. They also use salt restriction as a very important modality.

Conlon PJ, Kovalik E, Schumm D, Minda S, Schwab SJ. Normalization of hematocrit in hemodialysis patients with cardiac disease does not increase blood pressure. Ren Fail 2000;22:435–44.

Of interest because all patients receive erythropoietin at their dialysis.

Fenton SS, Trpeski L. Australia and New Zealand Dialysis and Transplant Registry;

Herrera-Acosta J. Hypertension in chronic renal disease. Kidney Int 1982; 22:702–12.

An original review of historic note.

Innes A, Charra B, Burden RP, Morgan AG, Laurent G. The effect of long, slow haemodialysis on patient survival. Nephrol Dial Transplant 1999;14:919–22.

Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: An overview. J Am Soc Nephrol 1999;10:392–98.

Good review of the difficulties in determining estimated dry weight. This is still a problem in 2007.

NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations 2006: Updates to Hemodialysis Adequacy, Peritoneal Dialysis Adequacy, and Vascular Access. Am J Kidney Dis 2006;48(1):S1.

Fairly standard reference.

Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. for the National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to learn? Where do we go from here? Am J Kidney Dis 1998;32(3):5–200.

The task force recommendations were first published in this NKF publication. Very complete bibliographies in all areas of CVD risk factors as they apply to all patients with chronic kidney disease. This is an important permanent reference for anyone interested in chronic kidney disease and CVD.

McDonald SP for the European Renal Association–European Dialysis and Transplant Association Registry; Jager KJ, van Dijk PC for the Finnish Registry for Kidney Diseases; Finne P for the Swedish Registry for Active Treatment of Uremia; Schon S for the Norwegian Renal Registry; Leivestad T for the Danish National Registry on Regular Dialysis and Transplantation; Lokkegaard H for the Dutch-speaking Belgian Society of Nephrology; Billiouw JM for the Austrian Dialysis and Transplant Registry; Kramar R for the Basque Renal Patients' Registry; Magaz A for the Catalan Renal Registry; Vela E for the Valencian Renal Registry; Garcia-Blasco MJ for the Hellenic Renal Registry; Ioannidis GA for the Malaysian National Renal Registry; and Lim YN. The enigma of hypertensive ESRD: Observations on incidence and trends in 18 European, Canadian, and Asian-Pacific populations, 1998 to 2002. Am J Kidney Dis 2006;48(2):183–91.

Describes the proportion of ESRD patients with hypertensive nephropathy beginning dialysis in each of these registries. Interesting to note differences between various countries and the United States.

Mailloux LU. The overlooked role of salt restriction in dialysis patients. Semin Dial 2000;13:150–51.

Review of the role of salt restriction in the therapy of hypertension in ESRD patients.

Mailloux LU, Haley W, Heyka R, Kaplan A, Lauer A, Nally J, et al. for the joint Clinical Practice Committee of the RPA and American Society of Nephrology. Hypertension in the ESRD patient: A review of the pathophysiology, therapy, outcomes and future direction. American Journal of Kidney Diseases 1998;32:705–19.

This article has one of the most exhaustive bibliographies dealing with high BP in patients with ESRD. It was an attempt at developing a practice guideline.
Mazzuchi N, Carbonell E, Fernandez-Cean J. Importance of blood pressure control in hemodialysis patient survival. Kidney Int 2000;58:2147–54.
PDR. [title]. *Sixtieth Edition*. Montvale, NJ: Medical Economics Press 2006.
For drug info.
Pierratos A. Nocturnal home haemodialysis: An update on a 5-year experience. Nephrol Dial Transplant 1999;14:2835–40.
Demonstrates quite clearly the benefits of long, slow dialysis. BP control is achieved without medication.
Rahman M, Fu P, Sehgal AR, Smith MC. Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. Am J Kidney Dis 2000;35:257–65.
An attempt to describe the pathophysiology of hypertension in the current dialysis population.
Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10.
Evidence for low sodium intake. Salt restriction is not regularly prescribed to our patients and should not be overlooked.
Scribner BH. A personalized history of hemodialysis. Am J Kid Dis 1990; 16:511–19.
A wonderful commentary by the master himself. Describes the problems of dialysis and its related issues.
Scribner BH Can antihypertensive medications control BP in haemodialysis patients: Yes or no? Nephrol Dial Transplant 1999;15:2599–2601.
Philosophy about BP control. Unclear whether it applies to the current ESRD population.
Singh AJ, Szczech L, Tang L, Barnhart P, Sapp S, Wolfson M, et al. for the CHOIR Investigators. Correction of anemia with epoetin alpha in chronic kidney disease. N Engl J Med 2006;354:[pages].
Article describes the hazards of too great a correction of the anemia in chronic kidney disease patients, leading to increases in cardiovascular morbidity and mortality.
Stewart JH, McCredie MR, Williams SM. Canadian Organ Replacement Register;
Thomson GE, Waterhouse K, McDonald HP Jr., Friedman EA. Hemodialysis for chronic renal failure. Arch Int Med 1967;120:153–67.
First clinical attempt to define dry weight. Important paper because it developed the concept of fluid overload without edema.
United States Renal Data System. USRDS 1997, 1998, 1999, 2000 Annual Data Report. U.S. Department of Health and Human Services. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, August 1997 to 2006.
The standard reference for cardiovascular co-morbidities in the incident ESRD patient population. An extremely valuable resource describing diagnoses, therapies, outcomes, and so on.
Vertes V, Cangiano JL, Berman LB, Gould A. Hypertension in end-stage renal disease. N Engl J Med 1969;280:978–81.
An original investigation into the pathophysiology of hypertension in ESRD patients. A seminal article in the field.
Zazgornik J, Biesenbach G, Janko O, Gross C, Mair R, Brucke P, et al. Bilateral nephrectomy: The best, but often overlooked, treatment for refractory hypertension in hemodialysis patients. Am J Hypertens 1998;11:1364–70.
Describes a forgotten therapy.

CHAPTER 66

Management of Ischemic Heart Disease, Heart Failure, and Pericarditis in Hemodialysis Patients

Sean W. Murphy, MD, and Patrick S. Parfrey, MD

Introduction

Cardiovascular disease is exceedingly common in patients with end-stage kidney disease (ESKD). Cardiovascular events are the most frequent cause of death in dialysis patients, explaining 40 to 50% of the total mortality in this population. This high mortality rate applies to practically all groups of dialysis patients, regardless of primary renal disease, age, gender, race, or nationality. The rate of cardiovascular death in ESKD patients is substantially higher than that of the general population at all ages, but this is particularly the case in the younger subgroups. Heart disease is also a major contributor to the total morbidity of dialysis patients.

In this chapter we discuss the diagnosis and management the most common manifestations of cardiac disease in the context of the dialysis patient. Where possible we base our recommendations on evidence taken directly from the ESKD population. Unfortunately, cardiac disease in renal failure patients has been relatively understudied, and in some cases there is no trial data at all pertaining to this group. This may be part of the explanation as to why studies consistently show that dialysis patients with known cardiac disease are frequently not prescribed medications considered efficacious in the general population. Where specific evidence is not available, data from the general population must be the basis for treatment guidelines for dialysis patients.

Congestive Heart Failure

Disorders of left ventricular (LV) structure and function are highly prevalent in the dialysis population and begin long before dialysis therapy must be initiated. Approximately 80% of patients starting maintenance dialysis will exhibit left ventricular hypertrophy

(LVH) or systolic dysfunction, disorders predictive of congestive heart failure (CHF), ischemic heart disease (IHD), and death. Roughly 1/3 of these patients will have had a previous episode of CHF, a factor that doubles their risk of death independent of age, diabetes, and IHD. The risk of developing pulmonary edema requiring hospitalization or ultrafiltration after starting hemodialysis is about 10% per year. The etiology of myocardial dysfunction in renal failure is partly attributable to the high prevalence of traditional cardiac risk factors, but the metabolic and hemodynamic changes associated with kidney failure also contribute (Table 66.1).

CHF may result from systolic or diastolic dysfunction, the latter occurring because of concentric or eccentric LVH. In patients with diastolic dysfunction, CHF results from impaired ventricular relaxation. This leads to an exaggerated increase in LV end diastolic pressure for a given increase in end diastolic volume. As a result, a small excess of salt and water can rapidly lead to a large increase in LV end diastolic pressure—culminating in pulmonary edema. In dilated cardiomyopathy, cardiac output is maintained at the expense of an increase in both end diastolic fiber length and end diastolic volume. As ventricular volume increases, inadequate hypertrophy leads to an increase in wall stress and an increase in end diastolic pressure—also leading ultimately to pulmonary edema.

The clinical symptoms of CHF are easily recognized: dyspnea, jugular venous distension, bilateral lung crepitations, and the characteristic chest X-ray appearance. Although CHF is often attributed to "volume overload" in the dialysis patient, the

Table 66–1

Risk Factors for Cardiac Disease in Dialysis Patients

Traditional	Dialysis or Uremia Related
• Hypertension	• High lipoprotein (a)
• Dyslipidemia	• Hyperhomocysteinemia
• Diabetes	• Divalent ion abnormalities
• LV hypertrophy	• Chronic inflammatory response
• Smoking	• Hypoalbuminemia
• Sedentary lifestyle	• Fluid overload
• Anemia	
• A-V fistulae	
• Coagulation abnormalities	

appearance of such symptoms suggests an underlying cardiac abnormality. Echocardiography remains the method of choice for assessment of LV geometry and function. It should be noted, however, that the calculation of LV mass and volume are affected by volume status. The patient should ideally be within 1 kg of their "dry weight" at the time of the examination for most accurate results.

Management and Drug Therapy

For all patients with symptoms of CHF, potentially reversible precipitating and aggravating factors (i.e., ischemia, tachycardia, arrhythmias, or hypertension) should be sought and managed appropriately. Patients with severe dyspnea (i.e., acute pulmonary edema) will usually require hemofiltration for the treatment of their acute symptoms. An echocardiogram is often useful in planning ongoing management, as treatment differs for patients with systolic versus diastolic dysfunction (Figure 66.1). In addition, echocardiography will help diagnose valvular lesions that may be contributing to cardiac dysfunction.

A large number of studies have confirmed the utility of angiotensin-converting enzyme (ACE) inhibitors in nonrenal failure patients with CHF. ACE inhibitors have been found to consistently improve symptoms, reduce morbidity, and improve survival. No trials of ACE inhibition with clinical outcomes in the dialysis population have been published. Despite this, the overwhelming benefit seen in the general population makes it likely that ESKD patients will also benefit. Although there is a theoretical risk, in that these drugs may predispose dialysis patients to hyperkalemia, ACE inhibitors are generally considered safe as long as appropriate dose titration and monitoring are instituted. ACE inhibitor therapy is therefore recommended for dialysis patients with symptomatic CHF, post-MI (myocardial infarction) patients with an LV ejection fraction <40%, and asymptomatic patients with an LV ejection fraction <35%.

Current trial data suggests that angiotensin receptor blockers (AT_1 blockers) are also effective for the treatment of symptomatic CHF in the general population. Again, no comparable trials have been published regarding the dialysis population. However, AT_1 blockers are recommended as an alternative to ACE inhibitors for dialysis patients who do not tolerate them. The clinical benefit of combination ACE inhibitor and AT_1 blocker therapy is unclear. This has not been studied in the dialysis population, and for now such combination therapy should be employed with caution.

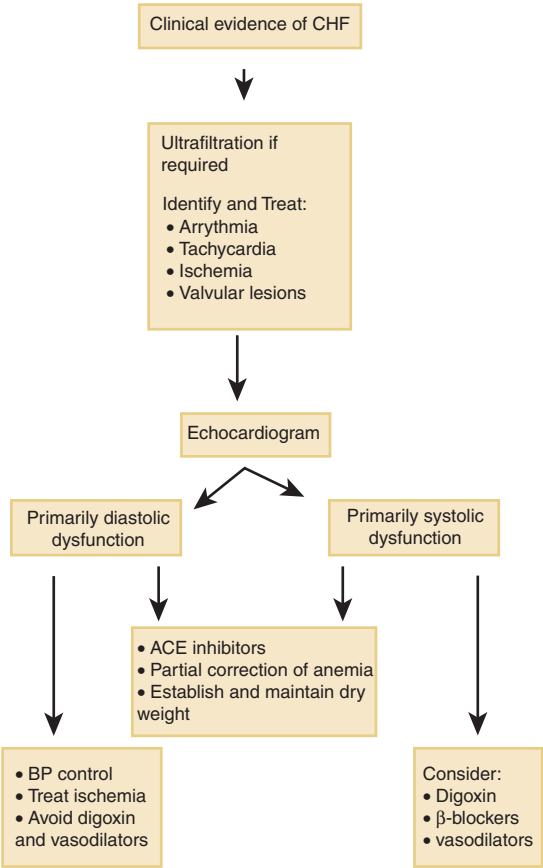


Figure 66–1

The investigation and management of heart failure in dialysis patients.

Diuretics remain an essential component of the symptomatic treatment of CHF in non dialysis-dependent patients but are less likely to be effective in patients on maintenance dialysis. Thiazide diuretics usually become ineffective with a GFR <30 mL/minute and are therefore not useful in patients with severe renal impair-

ment. Aldosterone antagonists, such as spironolactone, are similarly ineffective in patients with ESKD—and hyperkalemia can result when these drugs are combined with renin-angiotensin system blockade and beta-receptor antagonists. They should generally be avoided in dialysis patients.

Digoxin is useful in the treatment of patients with atrial fibrillation and CHF. Although digoxin does not improve survival, nonuremic patients with symptomatic LV systolic dysfunction have less morbidity and improved exercise tolerance when given digoxin in conjunction with standard therapy (i.e., diuretics and ACE inhibitors). Although trial data do not exist for the ESKD population, digoxin should be considered for dialysis patients with systolic dysfunction—given a reduction in dose appropriate to their level of renal impairment. Low dialysate potassium levels should be avoided for hemodialysis patients, as hypokalemia may predispose to arrhythmias in the presence of digoxin. Peritoneal dialysis patients will frequently require potassium supplementation to maintain normal levels. Digoxin should not be given to patients with primarily diastolic dysfunction, as the increased contractility could worsen diastolic impairment.

Beta-receptor antagonists are now widely used in the management of LV systolic dysfunction. Improvements in mortality and/or hospitalization have been shown in patients with mild to moderate symptomatic CHF treated with carvedilol, bisoprolol, or controlled-release metoprolol. Beta-receptor antagonists with intrinsic sympathomimetic activity appear to be detrimental and should not be used in patients with CHF. Current guidelines for the general population suggest the routine use of beta-receptor antagonists in clinically stable patients with an LV ejection fraction <40% and mild to moderate heart failure symptoms who are on standard therapy (i.e., diuretics, an ACE inhibitor, and digoxin). Such therapy should also be considered for asymptomatic patients with an LV ejection fraction <40%, but the evidence supporting its use in this setting is not as strong. Beta-receptor antagonists are not currently recommended for patients with severe symptomatic CHF.

In one of the few randomized trials performed in dialysis patients, Cice et al. have demonstrated that treatment of patients' dilated cardiomyopathy with carvedilol reduced mortality 2 years [51.7% in the carvedilol group compared to 73.2% in the placebo group ($p < 0.01$)]. Carvediol reduced cardiovascular deaths and hospital admissions. This, along with numerous observational data, supports the notion that beta-receptor antagonists may be safely used in the dialysis populations in the same manner

recommended for the general population. As in the nondialysis population, these agents should be started in low doses with careful clinical reevaluation during the titration phase.

The previous recommendations are primary for patients with systolic dysfunction. The treatment of diastolic dysfunction is less well defined. Attempts to eliminate the cause are generally the focus of therapy. This includes aggressive control of hypertension and IHD. Long-acting nitrates may be advantageous in some patients, and beta-receptor antagonists are useful for treating IHD and tachycardia. Digoxin and direct vasodilators (such as prazosin, hydralazine, or minoxidil) are generally contraindicated in this setting.

Ischemic Heart Disease

Among patients starting dialysis therapy, the prevalence of coronary artery disease approaches 40%. Approximately 22% have angina pectoris, whereas 18% will have had a prior MI. The annual incidence of angina or MI in patients on dialysis is approximately 10%. MI is the cause of death in approximately 14% of dialysis patients in the United States.

Symptomatic myocardial ischemia usually results from critical coronary atherosclerotic disease (CAD), but about 25% of patients will not have significant lesions on angiography. Small-vessel disease or a decrease in myocardial capillary density consequent to LVH or fibrosis may be responsible in the latter case. LVH itself predisposes to ischemia. The high prevalence of IHD in dialysis patients is at least partly due to the high prevalence of the traditional Framingham-type risk factors in this population. However, various factors unique to the uremic milieu may contribute (Table 66.1).

Diagnosis

Symptoms of myocardial ischemia in dialysis patients are generally similar to those in the nonuremic population, although silent ischemia may be more common due to the higher prevalence of diabetes. Dialysis patients with symptomatic IHD should be investigated in a manner similar to nonuremic patients, provided revascularization would be undertaken should critical CAD be identified. Because there is no evidence that revascularization of patients with silent ischemia will prolong their survival, routine screening for CAD in asymptomatic dialysis patients is not indicated. Patients being evaluated for renal transplantation are

an exception, and high-risk patients require screening for CAD even in the absence of symptoms. Figure 66.2 illustrates the suggested investigation of dialysis patients with potential CAD.

Biomarkers for Ischemic Heart Disease

Cardiac troponin T and troponin I (cTnT and cTnI) are currently the standard biomarkers of myocardial injury. The interpretation of these tests in patients with renal failure has been somewhat controversial. Studies using first-generation cTnT assays in dialysis patients without evidence of ischemia reported elevated levels in up to 71% of patients. cTnI, on the other hand, appears to be increased in approximately 7% of patients with renal failure. Although there is no difference between the diagnostic and prognostic accuracy of the two tests in the general population, the lower incidence of cTnI elevation in renal failure patients

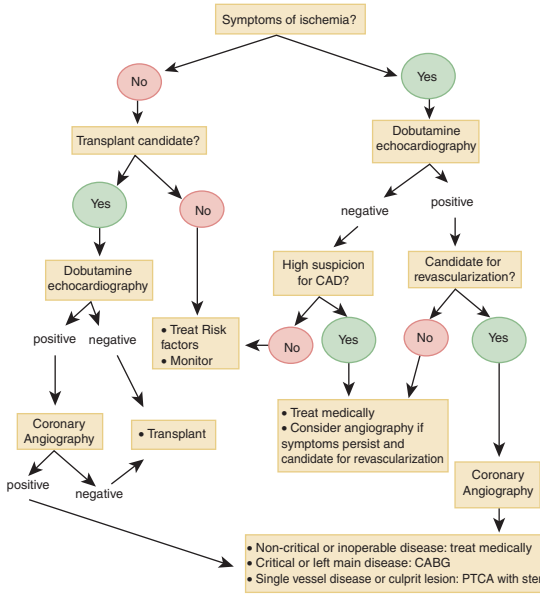


Figure 66–2

The investigation of ischemic heart disease in dialysis patients.

suggests that this is the preferred test in this clinical setting. For either marker, a normal level has useful negative predictive value. A sequential rise in either of the serum troponins is consistent with new myocardial damage regardless of symptoms.

Noninvasive Testing for Coronary Atherosclerotic Disease

Hemodialysis imposes a substantial load on the heart and may precipitate symptoms of IHD. It is therefore sometimes viewed as a type of stress test in itself. A variety of factors contribute to this phenomenon, including tachycardia, dialysis-related hypoxemia, and intradialytic hypotension. The emergence of symptoms of IHD on dialysis is an indication for further evaluation. In general, however, ECG changes associated with hemodialysis in otherwise asymptomatic patients do not correlate well with the presence of significant CAD.

Exercise electrocardiography has been the traditional method of noninvasive diagnosis of CAD. The sensitivity of this test is only 50 to 60% for single-vessel disease, but is greater than 85% for triple-vessel CAD in the general population. These figures are based on the assumption that the patient reaches an adequate exercise level (i.e., 85% of the age-adjusted predicted maximal heart rate). A large proportion of dialysis patients with ESKD are unable to achieve this target because of poor exercise tolerance or the use of cardiodepressant medications. Pharmacologic agents are therefore often used for noninvasive testing for CAD in these patients. The sensitivity of dipyridamole-thallium testing in ESRD patients ranges from 37 to 86%, with a specificity of approximately 75%. Dobutamine stress echocardiography may be the method of choice where it is available, as the reported sensitivity in patients with ESRD is relatively high (69–95%)—with a specificity of about 95%.

Coronary Angiography

Coronary angiography remains the "gold standard" for the diagnosis of CAD. The major side effects associated with this procedure in dialysis patients are the potential precipitation of pulmonary edema and the possible nephrotoxicity in those patients with some residual renal function. The risk of both of these complications is minimized with the use of nonionic contrast media. In general, however, coronary angiography should be limited to those patients who have persistent symptoms of myocardial ischemia despite

reasonable medical therapy and in whom revascularization would be considered reasonable. The latter decision is based largely on an assessment of operative risk and overall life expectancy.

Management

Drug Therapy

The treatment of both the acute coronary syndrome (ACS) and the nonacute presentations of CAD (stable angina and CHF) are generally the same as in the general population. Dialysis patients with stable angina who have not had an MI should be treated with antianginal agents for relief of symptoms. Some drugs, such as low-molecular-weight heparin, may require dosage adjustment. For patients who have had an MI, beta-receptor blockade is recommended indefinitely—as is an ACE inhibitor for patients with LV dysfunction.

There have been no studies of aspirin for the treatment of IHD in the dialysis population. Although the improvement in cardiac outcomes in nonuremic patients with IHD treated with aspirin is substantial, the risk of complications from aspirin is probably higher in dialysis patients. Consequently, the universal use of aspirin for the primary prevention of CAD in these patients is not recommended. However, the benefits likely outweigh the risks in dialysis patients with acute presentations of IHD or established IHD—and they should be treated with aspirin.

Risk Factor Modification

In all cases, patients who smoke should be encouraged to quit. Hypertension should be treated if present, but caution should be exercised such that drug interventions do not preclude adequate dialysis of the patient. The observational evidence linking dyslipidemia to CAD in dialysis patients is surprisingly weak. The results of the largest trial of lipid-lowering therapy with HMG-CoA reductase inhibitors were recently published. The 4D trial analyzed the efficacy of atorvastatin in 1200 hemodialysis patients with diabetes on hemodialysis.

The primary endpoint was a composite of death from cardiac causes, fatal stroke, nonfatal MI, or nonfatal stroke, whichever occurred first. Even though the impact on cholesterol reduction was similar to that observed in the general population, atorvastatin had no statistically significant effect on the composite endpoint (relative risk [RR], 0.92; 95% CI, 0.77–1.10; $p = 0.37$). This, along with the limited amount of other data available, casts doubt on the efficacy of these drugs for dialysis patients. Despite this,

the lack of evidence of harm and the clear benefit observed in the general population makes it reasonable to treat dialysis patients in a similar manner. The National Kidney Foundation's NKF-K/DOQI guidelines, published in 2003, recommend that LDL cholesterol levels ≥100 mg/dL (2.56 mmol/L) is the treatment threshold for dialysis patients and <100 mg/dL is the treatment target.

A cholesterol-lowering diet, weight loss, and exercise should be part of the treatment program—but most patients will require drug therapy. Despite the uncertain clinical benefit, HMG-CoA reductase inhibitors are safe and do lower lipid levels in dialysis patients. Appropriate screening for myositis is required. Fibrates are also effective, but dose reduction for renal failure is important. The combination of an HMG-CoA reductase inhibitor and a fibrate is associated with a high risk of muscle toxicity and should generally be avoided. There is no consensus on whether elevated triglycerides and low HDL cholesterol without elevated LDL cholesterol should be treated with drug therapy, but diet and exercise modification are recommended in most cases. A specific adjunct to therapy in patients with kidney disease is the treatment of proteinuria if it is present.

There is considerable experimental and clinical evidence that the disordered calcium metabolism and hyperparathyroidism associated with uremia contribute to LV dysfunction, atherosclerosis, myocardial ischemia, and vascular and cardiac calcification. Observational data indicates that hyperphosphatemia and raised calcium x phosphate product are independent predictors of mortality, especially death from coronary artery disease and sudden death. The appropriate use of vitamin D analogs and phosphate binders is recommended to achieve target levels for serum calcium and phosphate.

The recent availability of aluminum- and calcium-free phosphorus binders has significantly changed the management of dialysis patients. Polyallylamine hydrochloride (Renagel) is an effective, although costly, phosphorus binder that is not associated with hypercalcemia. Calcimimetic agents are now available and will likely further aid the treatment of hyperparathyroidism. As of this date, however, there is no direct trial evidence that the use of noncalcium phosphate binders or calcimimetics reduces clinical cardiac events or improves survival.

Revascularization

The indications for coronary revascularization in dialysis patients are generally the same as those in the nonuremic population (i.e.,

failure of medical therapy to control symptoms, left main CAD, or triple-vessel CAD) associated with ventricular dysfunction or easily inducible ischemia. However, the potential risks and benefits of these procedures in individuals on dialysis are quite different compared to other patients. The reported perioperative mortality of coronary artery bypass grafting (CABG) in dialysis patients is roughly three times the expected rate for non-ESRD patients, although other co-morbidity almost certainly contributes to this increased risk. The perioperative morbidity of CABG is also greater in dialysis patients than in matched controls. Two- to 5-year survival rates following CABG are comparable to those seen in the overall ESKD population, but are considerably lower than survival rates observed in nonuremic patients.

There have been no randomized trials of CABG versus medical management in uremic patients with symptomatic IHD. One small trial has shown a benefit of CABG compared with medical management in asymptomatic diabetic patients who were found to have CAD on screening coronary angiography prior to renal transplantation. It should be noted that medical therapy in this instance consisted only of a calcium-channel-blocking drug and aspirin. Irrespective of any survival benefit, CABG usually offers good relief from angina pain.

The role of percutaneous transluminal angioplasty (PTCA) in the treatment of dialysis patients with IHD has been controversial. Although the initial technical success rate in dialysis patients is high, PTCA seems to be associated with frequent recurrence of symptoms—usually resulting from re-stenosis. Studies combining PTCA with stenting of dilated vessels in uremic patients indicate a lower recurrence rate with this procedure.

There have been no head-to-head comparisons of dialysis patients treated with PTCA to medically managed patients to date. The majority of retrospective and uncontrolled studies of uremic patients treated with PTCA versus patients who had CABG have demonstrated no overall survival difference, but patients treated with PTCA have a significantly higher long-term risk of MI or recurrence of symptoms. CABG, therefore, appears to be the revascularization procedure of choice—although PTCA with stenting seems to be a reasonable alternative in select cases.

Dialysis-Related Interventions

Symptoms of established heart disease may be precipitated or aggravated by dialysis. For example, CHF may be exacerbated by a high-flow A-V fistula, and banding or revision of the fistula

may improve symptoms. CHF or CAD symptoms may be induced by anemia or increased LV end-diastolic pressure associated with extracellular volume overload. Ischemic symptoms may result from fluid shifts during hemodialysis or hypotension. The establishment and maintenance of an accurate dry weight is extremely important in the management of CHF, and some patients who tolerate intradialytic ECF (extracellular fluid) volume expansion poorly may require more frequent hemodialysis sessions. ESKD and dialysis also impose some long-term risk factors for cardiovascular disease on patients. Some of these are modifiable.

Anemia

Anemia has been associated with LV dilatation and LVH in patients with CKD and in patients on dialysis. Anemia is also a risk factor for the development of de novo cardiac failure and death in dialysis patients. In terms of anemia interventions, two questions have become prominent: does the correction of anemia reduce mortality, and what is the optimal hemoglobin target? A large American trial compared normalization of hemoglobin versus partial correction in patients on hemodialysis with preexisting IHD or CHF. It failed to demonstrate a survival benefit in the normalization group, and increased dialysis access losses were observed among these patients.

In a Canadian trial, patients on hemodialysis without symptomatic cardiac disease were allocated to normalization of hemoglobin with erythropoietin or to partial correction of anemia. Normalization of hemoglobin seemed to prevent progressive LV dilatation in those with normal cardiac volumes at baseline, but did not reverse it. These two studies suggest that full correction of anemia is not beneficial in patients with established cardiac disease but may prevent development of cardiomyopathy in those without it.

Whether hemoglobin normalization at an earlier stage of renal disease (e.g., in CKD) may be beneficial is still unclear. While awaiting such data, it is reasonable to follow the current NKF-K/DOQI guidelines for treatment of anemia for all patients—including those with cardiac disease. These guidelines recommend a target hematocrit of 33 to 36%, based on improvement in quality of life and exercise tolerance.

Hypertension

There is evidence that treatment of hypertension leads to regression of LVH in patients with renal disease. A number of classes of

antihypertensive agents lead to regression of LVH, although there is evidence that ACE inhibitors are more effective than other classes of drugs. For the general population, the Joint National Committee recommendations for hypertension treatment do not differ for patients with and without LVH. Symptomatic CHF is, however, considered a "compelling indication" for the use of ACE inhibitors (or AT_1 blockers in ACE-inhibitor-intolerant individuals). Other than this, it is reasonable to use the recommendations developed for target blood pressure and antihypertensive agents of choice in dialysis patients independent of their cardiac disease status.

Mode and Quantity of Dialysis

Although declining renal function has been associated with LV growth in patients with chronic renal failure, once patients reach ESKD the impact of quantity of dialysis on cardiac disease is not definitively known. The question as to whether dosing targets for dialysis higher than the current standard of a Kt/V ≥1.2 would result in improvements in cardiac outcomes has been addressed by the HEMO Study. A total of 1846 patients on thrice-weekly hemodialysis were randomized to either "standard" dose (target equilibrated Kt/V = 1.05) or "high" dose (target equilibrated Kt/V = 1.45). No difference in the primary outcome of all-cause mortality or any of the prespecified secondary outcomes was observed between the groups. Hence, there is no basis for recommending a change in Kt/V target.

Although some patients who are unable to tolerate the intradialytic volume expansion associated with intermittent hemodialysis may be more easily managed with peritoneal dialysis, there is no good evidence that either modality is associated with improved outcomes for patients with heart disease. Nocturnal hemodialysis has been associated with an improvement in many clinical parameters, including blood pressure and regression of LVH. Whether the observed cardiac benefits are due to amelioration of hypertension, improvement in anemia, or higher dialysis dose is not yet clear.

Uremic Pericarditis

Because of the earlier initiation of dialysis and higher delivered dialysis doses, clinically significant uremic pericarditis is now a relatively rare event. When it does occur, the symptoms may be sudden and have severe consequences if not recognized and

treated promptly. A high index of suspicion is therefore required. Between 50 and 70% of patients with uremic pericarditis will respond to intensified dialysis, suggesting that uremia itself is responsible in some cases. Cases that do not improve with dialysis may be due to other etiologies, such as viral pericarditis.

Diagnosis

The typical clinical presentation of pericarditis may include precordial pain, dyspnea, cough, or fever. The chest pain is not related to exertion, may be pleuritic in nature, and is often relieved by leaning forward. Most patients will have a pericardial friction rub. Those patients with a significant pericardial effusion may have jugular venous distention or a paradoxical pulse. Any of these symptoms in the presence of new-onset hypotension makes pericardial tamponade a likely diagnosis. Electrocardiograph findings (classically diffuse ST changes) are not sensitive or specific. Echocardiography should be performed in any patient suspected of having a pericardial effusion to estimate its size and guide further management.

Management

For the majority of patients who are hemodynamically stable and do not appear to have impending tamponade, intensification of dialysis and analgesia are usually all that is required. Nonsteroidal anti-inflammatory drugs, used cautiously, are useful for reducing pain but do not appear to hasten resolution of the pericarditis. Prednisone is not recommended and may actually increase morbidity. Heparin should be avoided during dialysis therapy if at all possible. Patients should be carefully monitored for clinical evidence of tamponade until all symptoms have resolved.

Hemodynamically unstable patients who have tamponade require immediate pericardiocentesis. Blind pericardiocentesis is associated with considerable risks and is therefore indicted only in the most urgent cases. Patients with a large pericardial effusion or those with unstable hemodynamics and/or echocardiographic evidence of cardiac-chamber compromise (even with a moderate pericardial effusion) should be referred for pericardiostomy, pericardial window, or pericardiectomy. The selection of the surgical procedure should be based on clinical and hemodynamic status, co-morbidities, and the experience of the surgeon. Pericardial window is often the procedure of choice.

Recommended Reading

Alpert MA, Ravenscraft MD. Pericardial involvement in end-stage renal disease. Am J Med Sci 2003;325(4):228–36.

A comprehensive discussion of the diagnosis and treatment of uremic pericarditis.

NKF-K/DOQI. NKF-K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45(4/3):S1–153.

Report of the NKF task force on cardiovascular disease, which makes comprehensive recommendations for the investigation and management of cardiac disease renal failure patients.

NKF-K/DOQI. NKF-K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003;41(4/3): I–IV, S1–91.

McCullough, PA. Evaluation and treatment of coronary artery disease in patients with end-stage renal disease. Kidney Int Suppl 2005;(95):S51–58.

A recent review of CAD management in uremic patients.

Parfrey PS. The clinical epidemiology of cardiovascular disease in chronic kidney disease. Semin Dial 2003;16(2):83–84.

A detailed review of various aspects of cardiac disease in dialysis patients.

CHAPTER 67

Management of Hyperlipidemia in Chronic Dialysis Patients

Ziad A. Massy, MD, PhD, and William F. Keane, MD

Hyperlipidemia (also referred to as dyslipidemia) is common in chronic hemodialysis (HD) and peritoneal dialysis (PD) patients. The most prevalent pattern is an increase in plasma triglyceride concentrations (linked to an accumulation of triglyceride-enriched apolipoprotein-B particles) and a decrease in plasma concentrations of high-density lipoprotein (HDL). In addition, PD patients usually have an increase in low-density lipoprotein (LDL) concentrations. Atherogenic changes in the composition of lipoproteins have also been documented in HD and PD patients.

Lipid abnormalities have been reported to correlate with cardiovascular disease (CVD) in a few observational studies in HD and PD patients. One recent intervention trial has failed to prove that antilipemic therapy is beneficial in type 2 diabetic patients on HD. However, other interventional trials are currently underway. Therefore, it is reasonable to await the results of these trials before concluding that the benefits of correcting lipid abnormalities in these patients are comparable to those found in the general population. This chapter examines existing data for treating lipid abnormalities in HD and PD patients.

Diet and Exercise

Management of lipid abnormalities by dietary carbohydrate and fat restriction alone is reported to be effective in dialysis patients. However, additional dietary restriction is difficult to achieve in the already fluid-protein-restricted patient, and the limited benefit of diet is counterbalanced by the risk of malnutrition in these patients. It may be possible in some HD and PD patients to achieve the lipid control with diet, but consultation with an experienced and motivated dietician is highly recommended.

A graded exercise program in order to achieve an ideal body weight can improve lipid abnormalities and other metabolic abnormalities in HD patients. Improved hemoglobin with erythropoietin therapy should assist in improving exercise tolerance, as well as in decreasing overall cardiovascular risk (e.g., left ventricular

hypertrophy). Interestingly, long-term erythropoietin treatment also positively affects lipid profiles. This effect may be blunted in some patients by increased food intake, and the cause of the observed improvement of lipid profile remains elusive. Thus, although control trials are needed to study the effects of exercise on dyslipidemia in HD and PD patients it seems reasonable (knowing the lack of adverse effects of exercise) to recommend when feasible that exercise be encouraged in such patients.

Lipid-Lowering Drugs

Several controlled and uncontrolled studies have examined the effects of different lipid-lowering drugs in HD and PD patients. Overall, these studies were of short duration, included few patients, were generally uncontrolled, and usually investigated one therapy. When we used meta-analysis to compare and contrast the relative efficacy of different lipid-lowering drugs in HD and PD patients, we found that only 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors and new fibric acid derivatives had a consistent and substantial effect on lipoprotein abnormalities.

The effects of other drugs (i.e., bile acid sequestrants, niacin, acipimox, pantetheine, probucol) were less consistent. New fibric acid derivatives, particularly gemfibrozil, were most effective in lowering triglyceride levels and raising HDL cholesterol levels in HD and PD patients—whereas HMG-CoA reductase inhibitors were most effective in lowering LDL cholesterol levels. However, newer HMG-CoA reductase inhibitors appear to have substantial triglyceride-lowering capabilities—as well as a positive effect on HDL levels. Of note, HMG-CoA reductase inhibitors can also be effective in reducing intermediate-density lipoprotein (an atherogenic lipoprotein class) in HD and PD patients.

Because the reduction in LDL that can be achieved with therapeutic lifestyle changes (i.e., diet and exercise) is generally modest, adequate doses of HMG-CoA reductase inhibitors should generally be added among pharmacologic agents in such patients to correct LDL levels. The efficacy and safety in controlling LDL level via long-term statin use with adequate dose has recently been tested by the Die Deutsche Diabetes Dialyse [4D] study, in which the authors compared atorvastatin at 20 mg/day with placebo on cardiovascular outcomes in 1255 type 2 diabetic patients on maintenance HD. Within a period of 4 weeks, atorvastatin lowered LDL cholesterol to 72 mg/dL (–41%). Triglycerides decreased (–20%), and HDL increased (4.5%). Over the 4-year study period, LDL-C stabilized at 70 mg/dL in the atorvastatin

group. The incidence of adverse events, including rhabdomyolysis, was comparable between groups and consistent with previous studies conducted in similar populations.

In this setting, the results of the 4D study comparing atorvastatin with placebo on cardiovascular outcomes came as a great and unsuspected surprise. An 8% relative risk reduction in the primary composite endpoint [cardiac death, nonfatal myocardial infarction (MI), and stroke] was observed in the atorvastatin group compared with placebo after a median follow-up of 4 years—which was not statistically significant. However, atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95% confidence interval, 0.68–0.99; $P = 0.03$, nominally significant) but not all cerebrovascular events combined (relative risk, 1.12; 95% confidence interval, 0.81–1.55; P = 0.49) or total mortality (relative risk, 0.93; 95% confidence interval, 0.79–1.08; $P = 0.33$).

Of note, there were more fatal strokes in the atorvastatin group compared with placebo (27 versus 13; relative risk 2.03; $P = 0.04$). Although these numbers are small, this higher risk could not be explained and could well be a chance finding. Nevertheless, it contributed to the numerically small but nonsignificant difference in risk reduction observed between atorvastatin and placebo for the primary endpoint.

Several possible explanations have been advanced to explain the negative results of the 4D trial, which include the presence of atypical CVD in dialysis patients (not only atherosclerotic disease), the fact that patients with diabetes mellitus are a special population (survivor effects), that LDL might not be the right target to correct in these patients (better focus being placed on non-HDL cholesterol), and/or the introduction of statin was too late in chronic kidney disease (CKD) progression (start treatment at an earlier stage of CKD). To answer to some of these questions, large trials are ongoing to generate randomized evidence (i.e., A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA] and the Study of Heart and Renal Protection [SHARP]).

Adjusted doses of new fibric acid analogues (particularly gemfibrozil) could be the first choice in dialysis patients with hypertriglyceridemia and high non-HDL cholesterol levels. Until the results of the ongoing trials become available, it is difficult to make evidence-based recommendations. Individual patient judgment should be used regarding use and class of lipid-lowering therapy in dialysis patients.

Other Lipid-Lowering Strategies

Fish oil may have beneficial effects on lipid metabolism in HD patients. However, the large dose that may be required and the somewhat unpalatable nature of fish oil remain important limitations to its widespread use at present. In one study, short-term treatment with adrenocorticotrophic hormone (ACTH) was effective in reducing the concentrations of LDL cholesterol—as well as those of lipoprotein(a)—in HD patients. Long-term controlled studies are needed to assess the efficacy and safety of this treatment.

Treatment with sevelamer hydrochloride (Renagel), which is a nonaluminum- and noncalcium-containing polymer, reduces serum phosphorus and LDL cholesterol in HD patients. These simultaneous effects make it an attractive drug for reducing the risk of CVD in HD patients. The recent demonstration of its preventative effects on advanced calcified deposits in arteries of dialysis patients makes this an intriguing agent for use in these patients.

L-carnitine is an essential cofactor for fatty acid transport into mitochondria for oxidation. Of all forms of renal replacement therapy, only HD is associated with free carnitine deficiency. The results of many trials of L-carnitine in dyslipidemic HD patients have been inconclusive. However, when the 25 published studies were pooled in a meta-analysis L-carnitine appeared to be effective in correcting lipid profiles in HD patients. Because L-carnitine has additional hematologic and muscular effects, it could be considered an adjunctive therapy to correct lipid abnormalities in these patients.

Systemic heparinization that is used routinely in HD could adversely affect plasma lipids through the depletion of lipoprotein lipase, leading to the accumulation of triglyceride-enriched apolipoprotein-B particles. Low-molecular-weight heparin preparations are expected to have a favorable effect on lipid metabolism, because only fractions of high molecular weight account for lipolytic effects. In some studies, using low-molecular-weight heparin in HD patients was associated with a reduction in both triglyceride and cholesterol levels. Moreover, when these studies were pooled in a meta-analysis only modest reduction in cholesterol was observed in HD patients treated by low-molecular-weight heparin. Reasons for these conflicting results include differences among preparations and modes of administration of low-molecular-weight heparin preparations.

To date, attempts to improve lipid profiles by altering dialysate composition in HD have been largely unsuccessful. Moreover,

studies examining the effects on serum lipids of different glucose-free dialysate fluids in PD patients are inconclusive. Modest reduction of triglycerides has been observed after the substitution of glucose by amino acid fluids in PD patients. The use of high-molecular-weight glucose polymer-based solution led to a nonsignificant 6 to 10% reduction in cholesterol and triglyceride levels over a 6-month period.

Uncontrolled and case-control studies have found that high-flux dialysis membranes favorably improve lipid profiles in HD patients. The mechanisms of such effects are not clear, but high-flux dialysis membranes could remove apolipoprotein CIII by adsorption and/or enhance advanced glycation end-product-peptide clearance. However, in a recent randomized controlled trial the use of a high-flux polysulphone membrane did not result in any favorable changes in lipid profiles when compared with low-flux polysulphone—suggesting that the benefits demonstrated in previous studies might be attributable to membrane biocompatibility and not to flux characteristics.

Summary

CVD is a major complication of dialysis. The lipid abnormalities in dialysis patients are complex and are frequently manifest by multiple disturbances in this metabolic pathway. In large population studies, many of these changes have been associated with increased cardiovascular risk. Treatment of LDL cholesterol abnormalities in the general population has been shown to reduce the morbidity and mortality of CVD in primary and secondary prevention trials. Moreover, a limited number of trials show that lowering plasma triglycerides and increasing HDL cholesterol reduces CVD in the general population. Because HD and PD patients frequently have a combination of high LDL or low HDL cholesterol levels (or both) and because these are often associated with high triglycerides (Table 67.1), one can assume that the risks associated with hyperlipidemia and the benefits of correcting lipoprotein abnormalities in dialysis patients are at least comparable to those found in the general population.

The results of the 4D study did not confirm this assumption and even indicated that the risk in type 2 diabetic patients on HD might originate from factors other than an atherogenic lipoprotein phenotype alone. Whether these results could be extended to nondiabetic dialysis patients is currently under evaluation. The lack of a pronounced effect in 4D study also suggests the necessity to start lipid-lowering treatment with a statin earlier in

Table 67–1

Lipid Abnormalities and Their Treatment in Dialysis Patients

LDL and Cholesterol	Triglycerides	HDL	Potential	Strategies
Hemodialysis	N	↑	¬	Diet and exercise
Sevelamer hydrochloride and high-flux and biocompatible hemodialysis membrane use				
Gemfibrozil or HMG-CoA reductase inhibitors				
Peritoneal dialysis	↑	↑↑	¬	Diet and exercise
Sevelamer hydrochloride and substitution of glucose in peritoneal dialysate				
HMG-CoA reductase inhibitors or new gemfibrozil				

Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein, HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A, N = normal.

stages of CKD in which co-morbid diseases and damage to the vasculature are less prominent.

Until the results of these ongoing randomized trials become available, we believe that a reasonable approach to patient management should follow the current recommendations of NKF-lipids-K/DOQI and European Best Practice guidelines. These include consideration for correcting lipid abnormalities in high-risk dialysis patients, particularly in those patients who have multiple risk factors for CVD and in those who have preexisting CVD. Treatment should be considered to reduce first LDL to <100 mg/dL and then to reduce non-HDL cholesterol to <130 mg/dL.

Promotion of exercise and maintaining patients at ideal weight will help to minimize hyperlipidemia. Treatment with sevelamer hydrochloride and high-flux and biocompatible HD membranes,

the substitution of glucose in peritoneal dialysate, and possibly L-carnitine supplementation could be additional strategies for correcting lipid abnormalities in dialysis patients. Appropriate doses of new fibric acid analogues (such as gemfibrozil) or HMG-CoA reductase inhibitors should be useful in HD and PD patients, depending on their lipid profile (Table 67.1).

Recommended Reading

Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). Kidney Int Suppl 2003;84:S207–10.

The largest ongoing randomized trial assessing the effects of simvastatin and ezetimibe on CVD in CKD patients stages 2 to 5.

Chertow GM, Burke SK, Dillon MA, Slatopolsky E. Long-term effects of sevelamer hydrochloride on the calcium x phosphate product and lipid profile of haemodialysis patients. Nephrol Dial Transplant 1999;14:2907–14.

First long-term study showing that sevelamer hydrochloride has simultaneous effects on lipids and serum phosphorus.

EBPG. European Best Practice Guidelines for Haemodialysis (Part1). Section VII: Vascular disease and risk factors. Nephrol Dial Transplant 2002;17(7):88–109.

European guideline on evaluation and treatment of high blood cholesterol in CKD patients.

Fellstrom B, Zannad F, Schmieder R, Holdaas H, Jardine A, Rose H, et al. for the AURORA Study Group. Effect of rosuvastatin on outcomes in chronic haemodialysis patients: Design and rationale of the AURORA study. Curr Control Trials Cardiovasc Med 2005;6(1):9.

Ongoing randomized trial assessing the effects of rosuvastatin on CVD in diabetic and nondiabetic patients on dialysis.

House AA, Wells GA, Donnelly JG, et al. Randomized trial of high-flux vs low-flux haemodialysis: Effects on homocysteine and lipids. Nephrol Dial Transplant 2000;15:1029–34.

First randomized controlled trial to compare high- and low-flux dialysis membranes on lipids.

NKF-K/DOQI. NKF-K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003;41(4/3): I–IV, S1–91.

National Kidney Foundation guideline on evaluation and treatment of high blood cholesterol in CKD patients.

Massy ZA, Ma JZ, Louis TA, Kasiske BL. Lipid-lowering therapy in patients with renal disease. Kidney Int 1995;48:188–98.

Large meta-analysis to compare the efficacy of lipid-lowering therapies in patients with renal disease.

Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. for the German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353(3):238–48.

First randomized trial assessing the effects of atorvastatin on CVD in diabetic patients on HD.

CHAPTER 68

Abnormalities of Thyroid Function in Chronic Dialysis Patients

Elaine M. Kaptein, MD, FACP, FRCP(C)

Hypothalamic, pituitary, or thyroid lesions (in addition to nonthyroidal illnesses and medications) may alter thyroid hormone metabolism in patients with end-stage renal disease (ESRD) (Table 68.1). Uremic sera may also alter serum thyroid hormone concentrations in vitro. Nonthyroidal changes in thyroid hormone metabolism do not induce clinical manifestations, are probably adaptive, and do not benefit from thyroid hormone therapy—which may be harmful. Concomitant hypothalamic, pituitary, or thyroid disease induces morbidity and requires specific therapy.

Thyroid Hormone Metabolism in Euthyroid Patients with ESRD

In the absence of hypothalamic, pituitary, or thyroid disease, ESRD patients frequently have reduced serum total T_4 (TT_4) and free T_4 estimate values—primarily due to impaired T_4 binding to thyroxine hormone-binding globulin (TBG)—whereas T_4 production rates in vivo are normal. Free T_4 estimates by most free T_4 assay methods other than direct ultrafiltration of undiluted sera may be misleadingly low in patients with nonthyroidal illnesses, including ESRD.

Even free T_4 levels by direct dialysis (radioimmunoassay of T_4 in dialysate in vitro) are reduced in 31% of euthyroid patients, presumably due to circulating dialyzable inhibitor(s) of T_4 binding to serum proteins. ESRD patients have elevated serum levels of 3-carboxy-4-methyl-5-propyl-2-furan propanoic acid (CMPF), indoxyl sulfate, and hippuric acid—as well as interleukin-1b and tumor necrosis factor-alpha, which are all potential inhibitors. When a serum inhibitor moves from serum into dialysate in vitro, serum T_4 binding increases—underestimating free T_4 concentrations. In contrast, reduced TT_4 and free T_4 values in hypothyroidism are secondary to decreased thyroid gland production of T_4 and result in a hypometabolic state that is reversed by L-T_4 therapy.

Table 68–1

Causes of Altered Thyroid Hormone Metabolism in Chronic Dialysis Patients

- Primary diseases of the hypothalamic-pituitary-thyroid axis
  - Hypothyroidism
    - Thyroid gland failure (>95%)
      - Permanent: autoimmune thyroiditis, radioiodine, surgical excision
      - Transient: iodine excess, thyroiditis
    - Pituitary gland failure
    - Hypothalamic lesions
  - Hyperthyroidism
    - Thyroid gland hyperfunction
      - Graves' disease
      - Multinodular toxic goiter
      - Toxic nodule
    - Tansient thyroiditis
    - Exogenous thyroid hormone administration
- Altered thyroid hormone metabolism due to nonthyroidal factors
  - End-stage renal failure
    - Secondary endocrine and metabolic derangements of ESRD
  - Malnutrition and catabolism
    - Concurrent systemic illnesses/inflammatory states
    - Dialysis therapy
  - Pharmacologic agents
    - Dilantin
    - Beta blockers (high doses)
    - Glucocorticoids
    - Iodinated contrast agents (ipodate and ioponate)
    - Iodine-containing solutions (povidone)
    - Amiodarone
    - Lithium

Euthyroid ESRD patients infrequently have elevated TT_4 or free T_4 estimate values. In nonrenal nonthyroidal disorders, euthyroid hyperthyroxinemia is primarily due to decreased T_4 clearance rates—whereas T_4 production rates are normal or reduced. In contrast, serum total and free T_4 values are increased in hyperthyroidism secondary to increased thyroidal T_4 production or release, or to excess thyroid hormone administration resulting in a hypermetabolic state.

In euthyroid patients with ESRD, serum TSH values were above the upper normal range of 5 mU/L in 10.5% of 287 patients, and above 10 mU/L in only 1%. All euthyroid patients with TSH

values between 10 and 20 mU/L had repeat TSH values below 10 mU/L, with normal TT_4 and/or free T4 index (FT4I) values. Euthyroid patients with nonrenal nonthyroidal illnesses may have transiently elevated TSH values above 20 mU/L during recovery from acute illnesses. These high TSH levels are associated with normal or rising TT_4 and free T4 estimate values, which return to normal with recovery from the nonthyroidal illness.

In contrast, sick patients with primary hypothyroidism have persistently elevated serum TSH values (typically above 20 mU/L in association with an exaggerated TSH response to TRH) and persistently reduced TT_4 and free T4 estimate values. Hypothalamic or pituitary hypothyroidism may result in near-normal TSH with reduced free T_4 concentrations—usually in association with deficiency of cortisol, LH, FSH, and/or growth hormone. Recent L-T_4 withdrawal or recent treatment of hyperthyroidism can also result in hypothyroidism with normal or reduced TSH concentrations due to persistent central TSH suppression.

Total T_3 levels were below 100 ng/dL in 76%, and free T_3 index values were under 100 in 66% of 287 euthyroid patients with ESRD. Free T3 values correlate inversely with IL-6, C-reactive protein, ICAM-1, and VCAM-1—indicating that the low T3 levels may be primarily related to inflammation in hemodialysis patients. Reduced T_3 levels may be due to decreased peripheral tissue conversion of T_4 to T_3, reduced T_3 binding to serum carrier proteins, and underestimation in vitro—whereas thyroid gland production of T_3 appears to be normal.

Although T_3 is the most metabolically active thyroid hormone, sick patients with low T_3 concentrations are clinically euthyroid. Decreased T_3 production and serum free T_3 levels may represent an adaptive phenomenon to minimize catabolism in these catabolic and frequently malnourished patients. Administration of exogenous T_3 to ESRD patients increases muscle breakdown. An elevated free T_3 estimate value is consistent with a diagnosis of hyperthyroidism, whereas a normal or reduced value does not exclude hyperthyroidism because extrathyroidal T_3 production may be reduced. Reverse T_3 concentrations are normal in patients with ESRD and their clinical significance is undefined.

Alterations in thyroid hormone metabolism in euthyroid ESRD patients may reflect severity of nonthyroidal illnesses induced by azotemia, concurrent nonthyroidal illnesses, catabolism, and/or malnutrition (Table 68.1). Total T_3 correlates with serum albumin and transferrin concentrations, serum albumin levels are significantly lower in dialysis patients with subnormal TT_4 levels, and serum albumin is a strong predictor of mortality in ESRD

patients—suggesting that serum albumin primarily reflects severity of nonthyroidal illnesses.

Goiter in Chronic Dialysis Patients

ESRD patients have an increased prevalence of goiter (up to 58%) compared to the general population. Goiters were present in 43% of 306 ESRD patients compared to 6.5% of hospitalized patients without renal disease of similar age, gender, and racial background. Goiter was more frequent in ESRD patients who had received hemodialysis therapy for more than 1 year (50%) than in those dialyzed for less than 1 year or not previously dialyzed (39%). The female-to-male ratio of patients with goiter was 1.4:1 in those with ESRD compared to 2.8:1 in the control group. Goiter frequency did not relate to age, race, presence of diabetes mellitus, elevated TSH or PTH levels, or increased antimicrosomal antibody titers.

Increased serum inorganic iodine levels in ESRD patients before and after chronic dialysis therapy may induce goiter because iodine excess blocks hormone synthesis and release in patients with preexisting thyroid gland abnormalities (such as autoimmune thyroiditis). In addition, thyroid gland size decreased with dietary iodine restriction in some hypothyroid Japanese patients with renal insufficiency. Geographic location may be a factor because goiters were most frequent in ESRD patients from Utah (58%), Illinois (37%), South Africa (32%), Israel (24%), Switzerland (20%), and Belgium (12%) and were not detected in those from Denmark, Vienna, London, or Alberta.

Thyroid gland enlargement is usually evident upon physical examination. Size and consistency of the gland (which may be soft or firm, diffuse or nodular) should be determined. Substernal goiters may be evident on chest X-ray as a superior mediastinal mass and/or tracheal deviation with or without evidence of compression. Once a goiter is detected, the presence of hypothyroidism or hyperthyroidism should be determined—as indicated in Figures 68.1 and 68.2. The presence of hypothyroidism or hyperthyroidism requires specific therapy (see material following). In euthyroid patients, therapy depends on the presence of a solitary or predominant nodule in the goiter, the presence or absence of local compressive symptoms, the growth history of the goiter, and the age, medical, nutritional, and cardiovascular status of the patient (Figure 68.3).

A solitary or predominant nodule requires exclusion of malignancy (Figure 68.4). If a benign euthyroid goiter is asso-

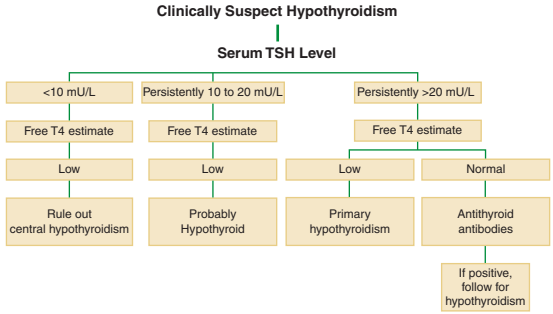


Figure 68–1

Algorithm for diagnosing hypothyroidism in chronic dialysis patients. Free T4 values measured by many methods may be misleadingly low due to concurrent nonthyroidal illnesses.

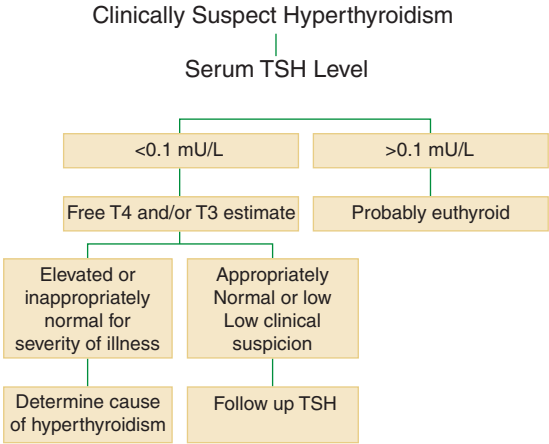
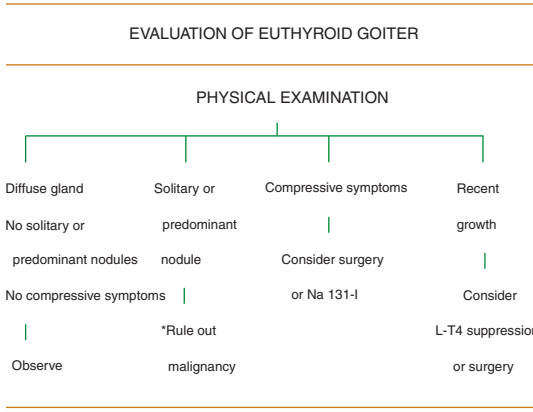


Figure 68–2

Algorithm for diagnosing hyperthyroidism in chronic dialysis patients. A second-generation assay has a 20% interassay coefficient of variation between a TSH level of 0.1 and 0.2 mU/L. A third-generation assay has a 20% interassay coefficient of variation between a TSH level of 0.01 and 0.02 mU/L.



*See Figure 68-4.

Figure 68–3

ciated with compressive symptoms, surgical excision or Na 131-I ablation should be considered. Na 131-I dosage should be reduced, depending on type, duration, and frequency of dialysis. Radioiodine therapy substantially reduces goiter size after one or more doses, but may induce transient hyperthyroidism—as well as permanent hypothyroidism in 25% of patients after 5 years and in 100% of patients after 8 years. Surgical excision should be performed for sudden goiter growth, bleeding leading to compression, a firm nodule, suspicious lymph nodes, vocal cord paralysis, or substantial tracheal obstruction.

Because established goiters frequently do not decrease in size following L-T_4 suppression therapy, a limited trial of L-T_4 suppression should only be considered with documented recent goiter growth if minimal or no adverse effects of L-T_4 therapy are anticipated. Risks of mild hyperthyroidism may be significant in patients with overt or subclinical ischemic cardiovascular disease, or in those who have a predisposition to catabolism and malnutrition. The majority of euthyroid patients with stable goiters only require clinical follow-up and measurement of serum TSH levels every 1 to 2 years.

If L-T_4 therapy is elected, the smallest dosage necessary to suppress TSH levels to below normal values should be employed

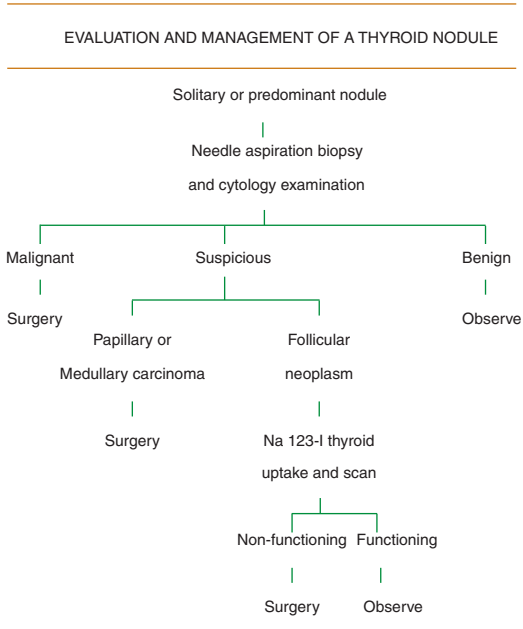


Figure 68–4

to minimize adverse effects. Overt hyperthyroidism may occur when usual dosages of L-T_4 are given to a patient with an autonomous thyroid gland, which continues to produce thyroid hormone. Thus, in older patients with known or potential ischemic heart disease an initial L-T_4 dosage of 0.025 mg/day should be given—with serum TSH values monitored in 6 to 8 weeks. If symptoms of thyroid hormone excess occur, therapy should be discontinued and the clinical significance of the goiter reevaluated. If the patient is asymptomatic and the TSH level remains within the normal range, the L-T_4 dosage may be cautiously increased every 6 to 8 weeks in increments of 0.025 mg/day until TSH is below the normal range. This therapy carries potentially significant risks of adverse cardiovascular effects in ESRD patients and is of limited proven efficacy.

Thyroid Nodules and Neoplasms

Thyroid nodules and carcinomas are approximately three times more common in ESRD patients than in the general population. A predominant or solitary thyroid nodule or mass requires exclusion of malignancy. The goal is to remove all malignant lesions while limiting surgery for benign disease. The most cost-effective and specific approach is to obtain a needle-aspiration biopsy of the nodule (Figure 68.4). Experienced personnel must perform the aspiration biopsy, and prepare and interpret the specimens. The procedure poses very little risk to the patient and is well tolerated.

If an adequate cytology specimen indicates a benign lesion, follow-up at regular intervals is required. Most benign nodules remain stable in size with long-term monitoring, and euthyroid patients do not benefit from L-T_4 suppression. Nodules that increase in size should have a repeat biopsy or be removed surgically. With follicular neoplasms, an adenoma cannot be distinguished from a carcinoma by cytopathology. If the nodule is functional on an Na 123-I scan, chances of malignancy are very small and the patient can be observed. On the other hand, risk of malignancy is significant for a hypofunctioning follicular neoplasm and excision is recommended. With suspicious lesions, surgical excision should be considered if surgical risk is acceptable.

If malignancy is diagnosed, near-total thyroidectomy is appropriate in patients with an acceptable surgical risk. These patients require lifelong L-T_4 suppression or replacement therapy, depending on the patient's cardiovascular status (see L-T4 therapy options under the section on hypothyroidism). Subsequent management may include Na 131-I ablation of the thyroid remnant and subsequent total-body scans in those with follicular malignancy who have a high risk for recurrent or metastatic disease. Serial serum thyroglobulin levels may be useful to evaluate the presence of metastatic lesions, and repeated Na 131-I therapy may be required to ablate functioning metastases. Those with medullary carcinoma should be followed with serum calcitonin levels and may require repeated surgical excision of metastases.

In patients with ESRD, dosages of Na 131-I must be reduced in proportion to iodine clearance by residual renal function plus dialysis to avoid excess radiation exposure to the bone marrow. During hemodialysis, Na 131-I clearance rates are five times higher than normal renal clearance rates. However, Na 131-I clearance by hemodialysis only occurs for 5 to 7% of the total week—with minimal Na 131-I clearance between treatments.

Timing of an Na 131-I dosage in relation to hemodialysis therapy is critical to determine the dosage adjustment necessary to minimize excessive bone marrow radiation dose in ESRD patients. An ESRD patient receiving hemodialysis on days 2, 3, and 4 after a radioiodine dosage should receive 21 to 28% of the dosage recommended for a similar patient with normal renal function.

If the hemodialysis is planned on days 2 and 4 after the radioiodine dosage, the dosage should only be 13 to 16% of that recommended for a similar patient with normal renal function. The radioiodine dosage should be administered immediately after a dialysis therapy. Dialysis with sorbent-based dialysis systems, which are still used in some instances, removes very little radioiodine—requiring further radioiodine dosage reduction to avoid bone marrow suppression. Contamination of equipment and exposure to personnel appear to be minimal when the usual precautions are taken.

In CAPD (continuous ambulatory peritoneal dialysis) patients receiving three to four dialysis exchanges per day, Na 131-I clearance is much slower than by hemodialysis (but is continuous). In our CAPD patients, Na 131-I clearance rates were 20% of normal renal function—requiring 80% reductions in Na 131-I ablative dosages to deliver comparable radiation doses to the red marrow. Thus, Na 131-I ablative doses in our CAPD patients with metastatic papillary thyroid carcinoma were 25 to 30 mCi rather than the prescribed dosage of 150 mCi given to patients with normal renal function—resulting in an appropriate radiation dose to the red marrow.

Preparation of thyroid cancer patients for Na 131-I ablation therapy requires a low-iodine diet and discontinuation of povodine-iodine containing antiseptics for 6 to 8 weeks or more if possible. Stimulation of Na 131-I uptake by residual thyroid tissue and/or functioning metastases can be achieved by induction of hypothyroidism following withdrawal of L-T_4 for 6 weeks, or by administration of intramuscular human recombinant TSH (Thyrogen). L-T4 withdrawal results in severe hypothyroidism and significant morbidity, which will not be encountered with Thyrogen administration. Na 131-I uptake by thyroid remnants and metastases is similar with both methods in patients with normal renal function.

Following remnant ablation, functioning follicular neoplastic tissue may be detected by measuring serum thyroglobulin levels and/or Na ^{131}I uptake following L-T4 withdrawal or recombinant

TSH administration. Na 131-I dosages greater than 2 mCi for total body scanning in patients with normal renal function result in marked reductions in uptake by the thyroid remnant and metastases of subsequent ablative dosages of Na 131-I ("stunning"). For remnant ablation, scanning provides minimal information and should not be done. For follow-up total-body scanning looking for functioning metastases, Na 131-I scanning dosages should be reduced to less than 2 mCi in ESRD patients to minimize stunning.

Hypothyroidism

Primary hypothyroidism occurs in up to 9.5% of patients with ESRD compared to 0.6 to 1.1% in the general population. Analysis of data from 14,623 patients studied in the Third National Health and Nutrition Examination Survey (NHANES III) indicated an increased prevalence of patients with serum TSH levels above 4.5 mU/L or patients receiving thyroid hormone with CKD stages 3 [relative risk (RR) 1.57], stage 4 (RR 1.81), and stage 5 (RR1.97). It should be noted that serum TSH levels may represent TSH that is immunoactive and not bioactive, and the criteria for diagnosing subclinical hypothyroidism in the general population may not apply to CKD patients.

In our study, 2.6% of 306 ESRD patients had overt primary hypothyroidism. All had TSH values persistently above 20 mU/L, as well as reduced serum TT_4 and free T4 index values. Of these patients, 88% were female, 75% were over the age of 50 years, 50% had elevated antimicrosomal antibody titers, 50% had goiter, and 50% had diabetes mellitus (Table 68.2). Hypothyroidism is nine times more common in females, occurs in 5 to 10% of people over 50 years of age, and induces hypercholesterolemia, hypertension, and cardiac dysfunction. Clinical manifestations of hypothyroidism are frequently mimicked or masked by concurrent ESRD, malnutrition, and other nonthyroidal disorders. Therefore, diagnosis requires a high index of suspicion in patients at risk for hypothyroidism. It also requires biochemical confirmation prior to L-T_4 therapy.

Multiple factors may induce hypothyroidism in ESRD patients (Table 68.2). The higher prevalence of hypothyroidism in ESRD may relate to reduced iodine excretion by residual renal function plus dialysis and to increased absorption of topical Povidone iodine. Serum iodine concentrations are four to nine times higher than normal in ESRD patients, which may impair thyroid

Table 68–2

Risk Factors for Hypothyroidism in Chronic Renal Failure

- Female gender
- Elderly
- Iodine administration
- Insulin-dependent diabetes mellitus
- Autoimmune thyroid disease
- Interferon therapy for hepatitis C

hormone synthesis and release. In hypothyroid Japanese patients with renal insufficiency, elevated serum iodine and TSH levels decreased with iodine restriction in 83% of patients—many of whom may have had an iodide organification defect. Insulin-dependent diabetic patients without ESRD have an increased frequency of elevated antimicrosomal antibody titers (17%), as well as hypothyroidism (3%), which may be a factor in some ESRD patients. Interferon therapy for hepatitis C induced thyroid gland dysfunction in 12% of patients, including thyroiditis with transient or permanent hypothyroidism. Thus, thyroid peroxidase antibodies and TSH levels should be monitored during and after interferon treatment.

Serum TSH may be the most effective screening test for hypothyroidism (Figure 68.1) because reduced TT_4 and FT_4I values were present in 24 and 13%, respectively, of euthyroid ESRD patients—whereas only 1% had TSH values above 10 μm/L, and all TSH values between 10 and 20 mU/L were transient. No ESRD patient with normal FT_4I values had overt hypothyroidism.

A serum TSH value below 10 mU/L with a low free T_4 value requires exclusion of hypothalamic or pituitary hypothyroidism, recent thyroid hormone withdrawal, or recently treated thyrotoxicosis. Patients with pituitary or hypothalamic hypothyroidism frequently have concurrent hypogonadism, evidenced by loss of axillary and pubic hair, early menopause in women, and hypoadrenalism. Adrenal insufficiency can result in profound volume-resistant hypotension upon stress (such as hemodialysis, infection, or surgery), can be confirmed with a reduced morning or stress-level serum cortisol concentrations, and requires glucocorticoid replacement therapy.

A serum TSH value between 10 and 20 mU/L with a reduced free T_4 estimate should be repeated. If the TSH is persistently elevated and the free T_4 low, primary hypothyroidism is likely and L-T4 treatment should be initiated. A serum TSH value above 20 mU/L with a reduced free T_4 is diagnostic of thyroid gland failure and warrants L-T_4 therapy. Because clinical symptoms and signs of hypothyroidism are indistinguishable from those of uremia and because the prevalence of hypothyroidism is increased, serum TSH values should be measured in high-risk ESRD patients.

Patients with established hypothyroidism should be started on a brand-name L-T_4 preparation. Brand-name preparations are *not* believed to be bioequivalent by endocrine and thyroid experts and should not be used interchangeably. If the patient must be changed from one brand-name preparation to another, serum TSH levels must be measured in 6 to 8 weeks and the L-T4 dosage adjusted accordingly. Generic L-T_4 and animal-derived products are inferior, and L-T_3 or combinations of L-T_4 and L-T_3 are nonphysiologic and are potentially hazardous—particularly in patients with cardiac disease. Initial L-T_4 dosage depends on the clinical status of the patient. Younger patients without cardiac disease may begin with a dosage of 0.075 to 0.100 mg per day.

A small initial dosage of 0.025 to 0.050 mg per day would be more prudent in elderly patients or in those with known or suspected cardiac disease or autonomous thyroid gland function. Because the half-life of T_4 is approximately 7 to 10 days, serum TSH levels should be evaluated and L-T_4 dosage adjusted only every 6 to 8 weeks. The daily L-T_4 dosage may be increased by 0.025 mg every 6 to 8 weeks (assuming cardiac symptoms do not occur) to return serum TSH levels to between 5 and 10 mU/L—values commonly observed in euthyroid ESRD patients. Free T4 values should not be normalized because they may be reduced due to nonthyroidal illnesses, including ESRD. During therapy with L-T_4, ESRD patients with primary thyroid gland failure have improvement or resolution of symptoms and signs of hypothyroidism that may have been mistakenly attributed to uremia.

Failure to respond to usual doses of L-T_4 (1.6 μg/kg body weight or 0.100 to 0.150 mg per day) may be secondary to multiple factors, as indicated in Table 68.3. Noncompliance is common. However, impaired small-bowel absorption due to disease states or binding by food or medications (or increased losses or degradation rates of T_4) may be responsible. L-T_4 should

Table 68–3

Reasons for Failure of L-T4 Therapy in Hypothyroid Patients[a]

- Noncompliance with the dosage regimen
- Interference with absorption
  - Mucosal diseases of the small bowel
  - Jejunoileal bypass and small-bowel resection
  - Diabetic diarrhea
  - Cirrhosis
- Pharmacologic agents
  - Sucralfate
  - Aluminum hydroxide
  - Calcium carbonate
  - Ferrous sulfate
  - Kayexalate
  - Cholestyramine
  - Colestipol
  - Lovastatin (possible)
  - Activated charcoal
  - Soya flour
  - Food
  - Raloxifene
  - Sevelamar (possible)
- Increased T4 losses
  - Peritoneal dialysis: 8 to 29 μg/d
  - Nephrotic syndrome: 13 to 69 μg/d
- Increased degradation rates of T4
  - Phenobarbital
  - Phenytoin
  - Sertraline/Zoloft (?)
  - Carbamazepine
  - Rifampin

a. L-T4 absorption is normally only 50 to 80%.

be taken at least 4 hours apart from medications that interfere with absorption.

Hyperthyroidism

Primary hyperthyroidism was present in 1.0% of our 306 ESRD patients compared to 0.3% in the general population, and only 14 cases have been reported. Eighty-six percent were female, and 50% were over 60 years old. Hyperthyroidism was due to

Graves' disease in 83% of patients. In addition, excess exogenous thyroid hormone therapy may induce hyperthyroidism. Clinical manifestations included palpitations in 78%; weight loss in 78%; atrial fibrillation or flutter in 44%; weakness, tremor, or irritability in 33%; and less frequently heat intolerance, confusion, nervousness, or hypotension during hemodialysis.

Presentations were atypical for hyperthyroidism in more than half of the patients. One elderly patient had recurrent paroxysmal atrial fibrillation, hypotension on hemodialysis, and sinus tachycardia—whereas another presented with cachexia and depression. A young woman had only weakness and severe weight loss. Only 75% had elevated TT_4 and free T4 estimate values, and all but one had normal or increased T3 levels. TSH levels were less than 0.1 mU/L in all reported cases for which TSH was measured. Thus, in ESRD patients hyperthyroidism may manifest as new signs and symptoms or exacerbate concurrent weight loss, atrial fibrillation, angina pectoris, or congestive heart failure. Interferon-alpha therapy for hepatitis C may induce hyperthyroidism due to thyroiditis or Graves' disease, and thus thyroid peroxidase antibodies and TSH levels should be monitored during and after therapy.

The most commonly used screening test for primary hyperthyroidism is a serum TSH concentration. Because hyperthyroid patients with severe nonthyroidal illnesses may have normal or even reduced free T_4 and T_3 values by all methods, these tests are less sensitive and specific than TSH. Serum TSH levels persistently <0.1 mU/L have not been reported in euthyroid patients with ESRD in the absence of concurrent or prior hyperthyroidism. As indicated in Figure 68.2, TSH values above 0.1 mU/L in a second-generation assay are probably euthyroid—whereas those with values below 0.1 mU/L may be hyperthyroid or euthyroid. In those patients with TSH values below 0.1 mU/L, a repeat TSH value should be measured in a third-generation assay that accurately measures values between 0.01 and 0.02 mU/L.

TSH values below 0.1 mU/L in association with an elevated free T_4 or free T_3 estimate indicate hyperthyroidism. If TSH levels are above 0.10 mU/L, primary hyperthyroidism is unlikely. Free T_4 levels by direct dialysis may be elevated in the absence of hyperthyroidism with nonthyroidal illnesses and in patients receiving heparin, which releases tissue-bound lipase that promotes lipolysis in vitro and inhibits T_4 binding to serum carrier proteins. Other binding inhibitors that may increase free T_4 levels include nonsteroidal anti-inflammatory drugs and anticonvulsants.

The most common causes of hyperthyroidism are exogenous thyroid hormone administration, Graves' disease, multinodular toxic goiter or toxic adenoma, transient thyroiditis, and iodide-induced thyrotoxicosis in patients with multinodular goiter. The etiology of hyperthyroidism is most readily established by performing an Na 123-I uptake and scan of the thyroid gland before initiating or after stopping antithyroid drug therapy. A high uptake with a diffuse pattern is consistent with Graves' disease, a high or normal uptake with a nodular pattern indicates multinodular toxic goiter, and normal or high uptake in a solitary nodule is consistent with toxic adenoma. A radioactive iodide uptake below 2% indicates thyroiditis, whereas an uptake below 10% may be associated with exogenous thyroid hormone administration or iodide excess.

Rapid relief of tachycardia, nervousness, and sweating can be achieved by using beta-blocking agents. Patients with painful or painless thyroiditis usually have mild and transient hyperthyroidism, which in many cases is followed by transient hypothyroidism. Thyroid ablation must be avoided, and antithyroid agents are ineffective. Those with painful thyroiditis may require analgesics, and if the condition is severe a short course of glucocorticoid therapy is indicated. Painless thyroiditis requires long-term follow-up for hypothyroidism.

Patients with excess thyroid gland production of thyroid hormones require specific therapy. Iodide uptake by the thyroid gland and further thyroid hormone synthesis can be blocked by the antithyroid agents propylthiouracil (PTU) and methimazole. PTU also blocks extrathyroidal production of T_3 from T_4 (the usual dose is 100 mg three to four times per day). Methimazole only reduces hormone synthesis by the thyroid gland (the dose is 10 mg twice per day). Because methimazole is not protein bound, it should be administered after hemodialysis.

Both PTU and methimazole can result in a skin rash, hepatic dysfunction, or (rarely) agranulocytosis. These agents usually render the patient with Graves' disease euthyroid in 4 to 6 weeks, whereas patients with multinodular toxic goiters may require a longer period to deplete the gland's hormone stores. Sodium iodide reduces T_4 and T_3 release from the thyroid, and can be used in unstable patients with severe thyrotoxicosis or cardiovascular manifestations. However, this must be administered after antithyroid drugs are initiated to prevent further iodide uptake by the thyroid.

After euthyroidism has been achieved with antithyroid drugs, thyroid ablation with radioactive iodine or surgery should be

considered in most chronic dialysis patients. Radioiodine therapy is appropriate in those with Graves' disease or multinodular goiter, and frequently results in permanent hypothyroidism. For toxic adenomas, surgical excision is curative. However, if surgery carries a significant risk Na 131-I ablation can be used. The appropriate Na 131-I dose depends on the thyroidal uptake of radioiodine, and on the type, duration, and frequency of dialysis therapy (as well as residual renal function). This has not been well defined.

Recommended Reading

DeGroot LJ, Hennemann G (eds.). The thyroid and its diseases. Endocrine Education, *www.Thyroidmanager.org*, 2006.

Continuously updated information regarding the diagnosis and management of common thyroid disorders provided by reliable experts.

d'Herbomez M, Forzy G, Gasser F, Massart C, Beaudonnet A, Sapin R. Clinical evaluation of nine free thyroxine assays: Persistent problems in particular populations. Clin Chem Lab Med 2003;41:942–47.

This article evaluates nine currently available free T4 assays in sera from 156 euthyroid controls, 27 untreated hyperthyroid patients, 34 untreated hypothyroid patients, and 22 patients with renal failure. Method-dependent biases were observed and confirmed with dilution experiments in sera from patients with renal failure. Thus, current FT4 assays that provide appropriate values in otherwise well patients with hypothyroidism or hyperthyroidism continue to have method-dependent artifacts in patients with renal failure.

Holst JP, Burman KD, Atkins F, Umans JG, Jonklaas J. Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. Thyroid 2005;15:1321–31.

A review of radioactive iodine treatment for hemodialyzed ESRD patients with thyroid cancer or hyperthyroidism. Their mathematical model suggests that the treatment dose of radioiodine for an ESRD patient with thyroid cancer on hemodialysis should be approximately 13 to 28% of a typical empiric dose of radioiodine for a patient with normal renal function.

Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocrine Reviews 1996;17:45–63.

A review of the literature. Patients with ESRD have multiple alterations of thyroid hormone metabolism due to nonthyroidal factors that alter serum thyroid hormone levels. They have an increased frequency of goiter and hypothyroidism, which may relate to impaired iodine excretion. In addition, an increased prevalence of papillary carcinoma has been reported—which if treated with radioiodine requires a reduced dosage (depending on type, frequency, and duration of dialysis).

Kaptein EM, Levenson H, Siegel ME, Gadallah M, Akmal M. Radioiodine dosimetry in patients with end-stage renal disease receiving continuous ambulatory peritoneal dialysis therapy. Journal of Clinical Endocrinology & Metabolism 2000;85:3058–64.

In ESRD patients receiving CAPD therapy, the radioiodine dosage for thyroid remnant ablation after thyroidectomy for papillary carcinoma was reduced from 150 to below 30 mCi, resulting in "normal" radiation doses to the red marrow. Pretreatment scanning doses with Na 131-I may markedly impair uptake of therapeutic doses of Na 131-I by thyroid remnants and metastases.

Kaptein EM, Wilcox RB, Nelson JC. Assessing thyroid hormone status in a patient with thyroid disease and renal failure: From theory to practice. Thyroid 2004;14:397–400.

Reduced serum free T4 levels determined by direct equilibrium dialysis in an ESRD patient treated with antithyroid medications for hyperthyroidism could be due to either a weakly bound dialyzable inhibitor in uremic serum interfering with the serum free T4 assay or to hypothyroidism due to persistent TSH suppression by prior hyperthyroidism. Paired serial dilutions of the patient's serum using an ultrafiltrate of the patient's serum (which would contain an unbound inhibitor as well as free T4 or an inert diluent) indicated appropriately low free T4 levels (due to hypothyroidism) rather than spuriously low free T4 measurements (secondary to an interfering inhibitor) in the patient studied. Thus, this patient was hypothyroid because of antithyroid drug ingestion, and TSH levels were suppressed due to prolonged central TSH suppression from preexisting hyperthyroidism. When methimazole was discontinued, serum total T4 and TSH values returned to normal.

Kaptein EM. The thyroid in nonthyroidal illness. In G Henneman, TJ Visser (eds.), *wwwhotthyroidologycom*. European Thyroid Association 2005.

This is a review of current data. Evidence does not support overt T4 or T3 deficiency in patients with nonthyroidal illnesses. Physiologic replacement doses of L-T4 or L-T3 in the absence of hypothyroidism do not improve outcome and may have detrimental effects in patients with nonthyroidal illnesses. Thyroid hormone replacement therapy in sick patients should be restricted to treating hypothyroidism due to documented hypothalamic, pituitary, or thyroid disease. The clinical focus should be to differentiate changes in serum thyroid hormone levels due to nonthyroidal illnesses from those due to concurrent hypothyroidism or hyperthyroidism, and on appropriately treating patients with concurrent hypothyroidism or hyperthyroidism.

Klein I, Danzi S. Evaluation of the therapeutic efficacy of different levothyroxine preparations in the treatment of human thyroid disease. Thyroid 2003; 13:1127–32.

Levothyroxine is a narrow therapeutic index drug requiring precise titration to achieve normal serum TSH levels and clinical euthyroidism. The FDA has approved seven levothyroxine formulations, although only four are available for patient use. Although levothyroxine preparations comply with FDA standards for bioavailability, their dissolution and absorption properties vary. Thus, these preparations are not interchangeable. If levothyroxine products are used interchangably, under-replacement or over-replacement can occur—resulting in significant clinical consequences.

Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047–52.

Data from the Third National Health and Nutrition Examination Survey were analyzed to assess the frequency of "hypothyroidism" at different levels of GFR (MDRD equation). Hypothyroidism was defined as a TSH >4.5 mIU/L and total T4 <4.5 μg/dL or treatment with thyroid hormone—with subclinical hypothyroidism defined as TSH >4.5 mIU/L and total T4 >4.5 ug/dL (questionable definitions in CKD patients). For 14,623 adults, "hypothyroidism" was more frequent with lower levels of GFR [mL/minute/1.73 m^2]—occurring in 5 to 11% of subjects with GFR >60, 20% with GFR 45 to 59, 23% with GFR 30 to 44, and 23% with GFR <30. Fifty-six percent of "hypothyroid" cases only had serum TSH levels above 4.5% (which is common in euthyroid ESRD patients and usually not indicative of hypothyroidism). Compared with GFR above 90 mL/minute/1.73 m^2, reduced GFR was associated with an increased risk

of "hypothyroidism" with adjusted odds ratio of 1.57 for GFR 45 to 59, 1.81 for GFR 30 to 44, and 1.97 for GFR <30 mL/minute/1.73 m². The clinical significance of these findings was not determined.

Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F. Low triiodothyronine: A new facet of inflammation in end-stage renal disease. J Am Soc Nephrol 2005;16:2789–95.

Free T3 levels correlated inversely with IL-6, C-reactive protein, ICAM-1, and VCAM-1 levels in 200 hemodialysis patients. Free T3 levels were significantly lower during intercurrent inflammatory/infectious processes than after resolution, suggesting a causal relationship.

CHAPTER 69

Metabolic Abnormalities: Evaluation of Sexual Dysfunction

Biff F. Palmer, MD

Introduction

Sexual dysfunction is a common finding in both men and women with chronic kidney failure. Common disturbances include erectile dysfunction in men, menstrual abnormalities in women, and decreased libido and fertility in both sexes. These abnormalities are primarily organic in nature and are related to uremia and the other co-morbid conditions that frequently occur in the chronic kidney failure patient. Fatigue and psychosocial factors related to the presence of a chronic disease are also contributory factors.

Sexual Dysfunction in Uremic Men

Erectile dysfunction is one of the most common manifestations of sexual dysfunction in men with chronic kidney disease. The prevalence of this disorder has been reported to be as high as 70 to 80% and is similar between patients on hemodialysis and peritoneal dialysis. In addition to abnormalities in blood flow and neural input to the penis, abnormalities in the pituitary-gonadal axis play a prominent role in the genesis of this disorder.

Chronic kidney disease is associated with impaired spermatogenesis and testicular damage, often leading to infertility. Semen analysis typically shows a decreased volume of ejaculate, either low or complete azoospermia, and a low percentage of motility. Histologic findings include damage to the seminiferous tubules and interstitial fibrosis and calcifications in the epididymis and corpora cavernosa. The factors responsible for testicular damage in uremia are not well understood, but chronic exposure to phthalates in dialysis tubing may play a role.

The endocrine function of the testes is also abnormal in chronic kidney disease (Table 69.1). Total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone–binding globulin are normal. Low testosterone

Table 69–1

Factors Involved in the Pathogenesis of Impotence in Uremic Men

I	• Vascular system
	A – Occlusive arterial disease
	B – Veno-occlusive disease and venous leakage
II	• Neurologic system
	A – Impaired autonomic function due to uremia and co-morbid conditions
III	• Endocrine system
	A – Gonadal function
	1. – Decreased production of testosterone
	B – Hypothalamic-pituitary function
	1. – Blunted increase in serum LH levels
	2. – Decreased amplitude of LH secretory burst
	3. – Variable increase in serum FSH levels
	4. – Increased prolactin levels
IV	• Psychologic system
V	• Zinc deficiency
VI	• Medications
VII	• Anemia
VIII	• Secondary hyperparathyroidism

levels lead to increased plasma concentration of the pituitary gonadotropin luteinizing hormone (LH) because testosterone normally inhibits LH release through a negative feedback loop. Follicle-stimulating hormone (FSH) secretion is also increased in men with chronic kidney disease, although to a more variable degree such that the LH/FSH ratio is typically increased. FSH release by the pituitary normally responds to feedback inhibition by a peptide product of the Sertoli cells called inhibin. The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to seminiferous tubules and presumably the lowest levels of inhibin. It has been suggested that increased FSH levels may portend a poor prognosis for recovery of spermatogenic function following kidney transplantation. Elevated plasma prolactin levels are commonly found in dialyzed men due primarily to increased production. Both increased parathyroid hormone and zinc deficiency have been implicated as playing a contributory role in the increased levels.

Gynecomastia occurs in approximately 30% of men on maintenance hemodialysis. This problem most often develops during the initial months of dialysis and then tends to regress as dialysis

continues. The pathogenesis of gynecomastia in this setting is unclear. Although elevated prolactin levels and an increased estrogen-to-androgen ratio seem attractive possibilities, most data fail to support a primary role for abnormal hormonal function. Alternatively, a mechanism similar to that responsible for gynecomastia following refeeding of malnourished patients may be involved.

Evaluation of Sexual Dysfunction in the Uremic Man

In evaluating and ultimately treating the impotent kidney failure patient, one must not only consider disturbances in the hypothalamic-pituitary-gonadal axis (discussed previously) but abnormalities in the sympathetic nervous system and derangements in the arterial supply or venous drainage of the penis. In addition, the psychological effects of a chronic illness and lifestyle limitations may negatively impact on sexual function.

A thorough history and physical can provide useful information during the initial evaluation of a patient with impotence. A history of normal erectile function prior to the development of kidney failure is suggestive of a secondary cause of impotence. Symptoms or physical findings of a neuropathy (as in a patient with a neurogenic bladder) would be particularly suggestive of a neurologic etiology. Similarly, symptoms or signs of peripheral vascular disease may be a clue to the presence of vascular obstruction to penile blood flow. One should look for the presence of secondary sexual characteristics, such as facial, axillary, and pubic hair. The lack of these findings and the presence of small soft testicles suggest primary or secondary hypogonadism as the cause of the impotence. Neurogenic and vascular causes are more likely to be associated with normal sized testicles. Even when the history and physical examination point to a specific abnormality, one must also consider that an individual patient may have more than one factor responsible for the erectile dysfunction and other causes may need to be ultimately evaluated.

A review of the patient's medications may reveal a drug that could be potentially playing a role in impairing sexual function. Antihypertensive medications are common offenders, with centrally acting agents and beta blockers being the most commonly implicated agents in causing impotence. The angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with a lower incidence of impotence and represent a useful alternative in kidney failure patients with hypertension. Other

drugs commonly implicated include cimetidine, phenothiazines, tricyclic antidepressants, and metoclopramide.

If the history and physical examination reveal no obvious cause, a psychological cause of erectile dysfunction may need to be considered. Testing for the presence of nocturnal penile tumescence (NPT) has been utilized in some centers as a means of discriminating between a psychological and organic cause of impotence. The basis for this test is that during the rapid eye movement stage of sleep males normally have an erection. The assumption is that a man with a psychological cause of impotence would still experience erections while asleep, whereas the absence of an adequate erection would make an organic cause more likely. If a patient is found to have nocturnal erections, psychological testing and evaluation is indicated. It should be noted that NPT testing is not infallible and that if a patient has a normal test and no psychological cause is found evaluation for an organic cause should still be pursued.

There are tests that may aid in the discrimination between a neurogenic and vascular cause of impotence. Tests utilized to exclude a vascular etiology of impotence include Doppler studies to measure penile blood flow, measurement of penile blood pressure, and penile pulse palpation. Neurogenic impotence is suggested by detecting a prolonged latency time of the bulbocavernous reflex or confirming the presence of a neurogenic bladder. With the availability of sildenafil (see material following) to use as a therapeutic trial, such tests are generally reserved for nonresponders who may eventually be considered for surgical placement of a penile prosthesis.

As discussed previously, hormonal abnormalities are frequently detected in chronic kidney failure patients. Endocrine tests that are useful in the evaluation of an organic cause of impotence include measurement of serum LH, FSH, testosterone, and prolactin levels. It should be noted that only a small percentage of uremic patients will have prolactin levels greater than 100 ng/mL. Imaging studies of the hypothalamic-pituitary region should be performed in patients with levels of greater magnitude to exclude the presence of a microadenoma or macroadenoma.

Treatment of Sexual Dysfunction in the Uremic Man

The treatment of sexual dysfunction in the uremic man is initially of a general nature (Figure 69.1). One needs to ensure optimal delivery of dialysis and adequate nutritional intake. Administration

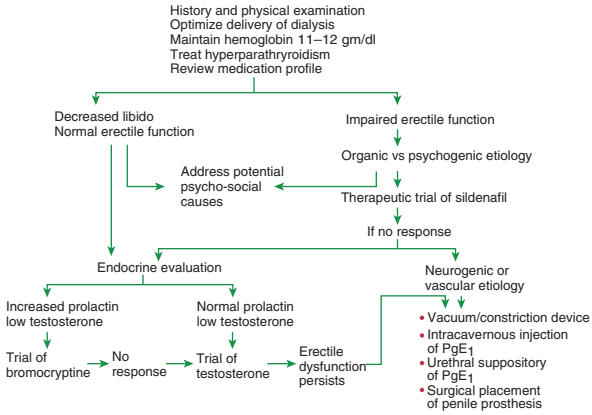


Figure 69–1

Approach to sexual dysfunction in uremic men.

of recombinant human erythropoietin has been shown to enhance sexual function—likely through the associated improvement in well-being that comes with the correction of anemia, although improvement in the pituitary gonadal feedback mechanism has also been reported. Controlling the degree of secondary hyperparathyroidism with 1,25 $(OH)_2$ vitamin D may be of benefit in lowering prolactin levels and improving sexual function in some patients.

One area that deserves further investigation is the impact of slow nocturnal hemodialysis on sexual function. In a pilot study of five patients undergoing dialysis 6 nights per week for 8 hours each night, serum testosterone levels increased in three patients over an 8-week period. Levels of LH and FSH remained unchanged. In a separate study, the percentage of patients who felt that sexual function was a problem declined from 80 to 29% after 3 months of nightly nocturnal hemodialysis.

Patients with normal NPT testing should be evaluated to determine if there is a psychological component to the impotence. If a problem is found, a trial of psychotherapy is warranted. The effectiveness of antidepressant medications and/or psychiatric counseling in chronic kidney failure patients with sexual dysfunction has not been well studied. Use of antidepressant medications can be problematic because many of these agents can cause sexual dysfunction.

It has become common clinical practice to first administer sildenafil to patients who complain of erectile dysfunction and reserve further workup for only those patients who fail to achieve a therapeutic response. A limited number of studies have now been published specifically examining the effectiveness of sildinafil in uremic men with chronic kidney failure. Each of these studies used the International Index of Erectile Function (IIEF) questionnaire as a means of gauging the effectiveness of therapy. The response rate ranged from 60 to 80%. Sildenafil was found to have similar efficacy in patients treated with either hemodialysis or peritoneal dialysis. It should be emphasized that sildenafil is contraindicated in patients currently taking organic nitrates. Caution should also be exercised when prescribing this agent to patients with known coronary artery disease. To limit the possibility of hypotension among dialysis patients, some clinicians recommend the use of sildenafil on nondialysis days.

In patients with low circulating levels of testosterone, correcting the deficit generally results in clinical improvement in other forms of gonadal failure. By contrast, administration of testosterone to uremic men usually fails to restore libido or potency—despite increased testosterone levels and reduced release of LH and FSH. In a hypogonadal patient whose primary complaint is decreased libido, a trial of testosterone may be warranted.

Patients found to have increased circulating levels of prolactin may benefit from a trial of bromocryptine. This agent is a dopaminergic agonist that has shown some efficacy in improving sexual function, presumably by reducing elevated prolactin levels. However, its usefulness has been limited by a relatively high frequency of side effects. Other dopaminergic agonists, such as parlodel and lisuride, seem to be better tolerated but have only been used in small short-term studies.

Zinc deficiency has also been suggested as a cause of gonadal failure. Uremic patients are often deficient in zinc—probably due to reduced dietary intake, zinc malabsorption, and/or possible leaching of zinc by dialysis equipment. In a controlled trial, supplemental zinc resulted in significant increases in the plasma testosterone concentration and sperm counts—as well as significant declines in LH and FSH levels—compared to a control group. Potency, libido, and frequency of intercourse also improved in those patients given zinc. It is possible that normalization of total body zinc may also be effective in correcting uremic hyperprolactinemia. Thus, the aggregate data suggest that the administration of zinc in a zinc-deficient man is a reasonable therapeutic option.

There are additional options for those patients with a neurogenic or vascular cause of impotence who have failed medical therapy involving a trial of sildenafil. One such therapy is a vacuum tumescence device. In a review of the experience of one kidney impotence clinic, vacuum tumescence devices were utilized in 26 impotent patients—all of whom had a normal pituitary-gonadal axis or hypogonadism corrected with testosterone replacement. The device completely corrected penile dysfunction in 19 individuals (73%).

Intraurethral administration of alprostadil (synthetic prostaglandin E_1) provides the delivery of prostaglandin to the corpus cavernosum, resulting in an erection sufficient for intercourse. The drug is supplied in an applicator that is inserted in the urethra. Alprostadil can also be injected into the penis shaft, resulting in vasodilation and inhibition of platelet aggregation. The major side effects of intrapenile alprostadil therapy are penile pain, priapism, and bleeding. Given the presence of platelet dysfunction with uremia, intracavernosal injections should be used with caution in patients with end-stage renal disease. Surgical placement of a penile prosthesis is typically considered in patients who fail the less invasive first-line treatments.

Sexual Dysfunction in Uremic Women

Disturbances in menstruation and fertility are commonly encountered in women with chronic kidney disease, usually leading to amenorrhea by the time the patient reaches end-stage renal disease. The menstrual cycle typically remains irregular, with scanty flow after the initiation of maintenance dialysis—although normal menses is restored in some women. In others, hypermenorrhagia develops—potentially leading to significant blood loss and increased transfusion requirements. Women on chronic dialysis also tend to complain of decreased libido and reduced ability to reach orgasm.

Indirect determination of ovulation suggests that anovulatory cycles are the rule in uremic women. For example, endometrial biopsies show an absence of progestational effects and a failure to increase basal body temperature at the time ovulation would be expected. In addition, the preovulatory peak in LH and estradiol concentrations is frequently absent. The failure of LH to rise reflects in part a disturbance in the positive estradiol feedback pathway because the administration of exogenous estrogen to mimic the preovulatory surge in estradiol fails to stimulate LH

release. Pregnancy can rarely occur in advanced kidney failure, but some degree of residual kidney function is usually present. As in men with chronic kidney disease, circulating levels of prolactin are increased. The secretion appears autonomous, and is resistant to maneuvers designed to stimulate or inhibit its release.

Postmenopausal uremic women have gonadotropin levels as high as those seen in nonuremic women of similar age. The age at which menopause begins in chronic kidney failure tends to be decreased compared to normal women.

Treatment of Sexual Dysfunction in Uremic Women

The high frequency of anovulation leads sequentially to lack of formation of the corpus luteum and failure of progesterone secretion. Because progesterone is responsible for transforming the endometrium into the luteal phase, lack of progesterone is associated with amenorrhea. For patients who desire to resume menses, administration of a progestational agent during the final days of the monthly cycle will usually be successful.

On the other hand, ongoing menses can contribute significantly to the anemia of chronic kidney disease—particularly in those patients with hypermenorrhagia. In this setting, administration of a progestational agent during the entire monthly cycle will terminate menstrual flow. Rarely, a patient may require hysterectomy for refractory uterine bleeding.

It is not known whether the usual absence of menses in women with chronic kidney failure predisposes to the development of endometrial hyperplasia and possible carcinoma. Because these patients are often anovulatory, there is no disruption of the proliferative effect of estrogen by the release of progesterone. It is therefore recommended that women with chronic kidney failure be monitored closely by a gynecologist. It may be desirable in at least some cases to administer a progestational agent several times per year to interrupt the proliferation induced by unopposed estrogen release (Figure 69.2).

Although pregnancy can rarely occur in women on chronic dialysis, restoration of fertility as a therapeutic goal should be discouraged. In comparison, the abnormalities in ovulation can usually be reversed and successful pregnancy achieved in women with a well-functioning kidney transplant. Uremic women who are menstruating normally should be encouraged to use birth control.

Studies addressing the therapy of decreased libido and sexual function in uremic women are lacking. Amenorrheic hemodialysis

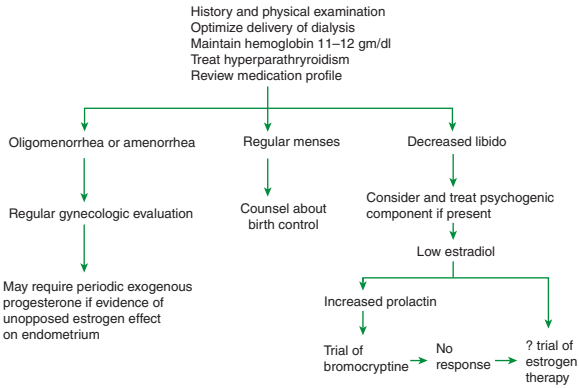


Figure 69–2

Approach to sexual dysfunction in uremic women.

patients may have low estradiol levels that can secondarily lead to vaginal atrophy and dryness and result in discomfort during intercourse. Such patients may benefit from local estrogen therapy or vaginal lubricants. Low-dose testosterone may be effective in increasing sexual desire but is rarely used secondary to potential toxicity. Use of a transdermal testosterone patch was recently shown effective in improving libido in nonuremic surgically menopausal women. However, this therapy is not yet approved. Bromocryptine therapy in hyperprolactinemic patients may help in restoring sexual function but has not been well studied. Estrogen supplementation may improve sexual function in those patients with low circulating estradiol levels. Successful transplantation is clearly the most effective means of restoring normal sexual desire in women with chronic kidney failure.

Recommended Reading

Rosas SE, Joffe M, Franklin E, Strom BL, Kotzker W, Brensinger C, et al. Prevalence and determinants of erectile dysfunction in hemodialysis patients. Kidney Int 2001;59:2259–66.

A study documenting the high prevalence of erectile dysfunction in hemodialysis patients using the self-administered International Index of Erectile Function-5 survey.

Bellinghieri G, Santoro G, Santoro D, Lo Forti B, Savica V, Favazzi P, et al. Ultrastructural changes of corpora cavernosa in men with erectile dysfunction and chronic renal failure. Semin Nephrol 2004;24:488–91.

A study describing the morphologic changes present in the penis of uremic men with erectile dysfunction.

Hauser R, Williams P, Altshul L, Calafat A. Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. Environ Health Perspect 2005;113:425–30.

A study providing support that exposure to phthalates in tubing may play a contributory role to the histologic changes that occur in the penis of uremic men with sexual dysfunction.

McPhatter LL, Lockridge RS Jr., Albert J, Anderson H, Craft V, Jennings FM, et al. Nightly home hemodialysis: Improvement in nutrition and quality of life. Adv Ren Replace Ther 1999;6:358–65.

A study describing a beneficial effect of more frequent dialysis on sexual dysfunction.

Palmer BF. Sexual dysfunction in men and women with chronic kidney disease and end-stage renal disease. Adv Renal Replacement Therapy 2003;10:48–60.

A comprehensive review of sexual dysfunction and its treatment in men and women with chronic kidney disease.

Lawrence IG, Price DE, Howlett TA, Harris KPG, Feehally J, Walls J. Correcting impotence in the male dialysis patient: Experience with testosterone replacement and vacuum tumescence therapy. Am J Kidney Dis 1998; 31:313–19.

A study of the effectiveness of testosterone replacement and vacuum tumescence therapy in men with erectile dysfunction followed in a dedicated renal impotence clinic.

Peng Y, Chiang C, Kao T, Hung K, Lu C, Chiang S, et al. Sexual dysfunction in female hemodialysis patients: A multicenter study. Kidney Intl 2005;68:760–65.

A study documenting the frequency of sexual dysfunction in women receiving hemodialysis.

Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab 2005;90:5226–33.

A study of the efficacy and safety of transdermal testosterone in treating hypoactive sexual desire disorder in surgically menopausal women without chronic kidney disease.

CHAPTER 70

Management of Uremic Peripheral Neuropathy

Morrell Michael Avram, MD, and Neal Mittman, MD

Introduction

Uremic polyneuropathy is one of the most common complications of chronic renal failure. Neuropathy is caused by uremic toxins and its severity is correlated with the extent of renal insufficiency. Polyneuropathy usually develops in advanced renal failure patients and its occurrence is an indication to start renal replacement therapy. Approximately 70% of all patients beginning maintenance dialysis therapy have uremic polyneuropathy. In a majority of these patients, uremic neuropathy is often subclinical and detectable only by electrophysiologic testing. Uremic neuropathy may occur at any age. It occurs more commonly in men than in women. The role of race in uremic polyneuropathy has not been studied.

Clinical Manifestations and Course

A broad spectrum of peripheral nerve disorders may be associated with chronic renal failure. Polyneuropathy is accompanied by segmental demyelination, axonal degeneration, and segmental remyelination. Coexistence of muscle weakness and atrophy, areflexia, sensory loss, and graded distribution of neurologic deficit in a patient with renal disease suggests the presence of uremic polyneuropathy. During long-term hemodialysis (HD), the symptoms of polyneuropathy stabilize—but they improve only in relatively few patients. Complete recovery, occurring over a period of 6 to 12 months, usually follows successful renal transplantation.

The polyneuropathy due to uremic toxins is a distal symmetric motor and sensory polyneuropathy affecting lower extremities more than upper extremities. Like other types of neuropathies, injury is directly related to axon length. Thus, longest axons are affected first. Sensory symptoms such as paresthesia, pain, and burning sensations usually precede motor symptoms. Paresthesia is the most common and usually the earliest symptom. Uremic polyneuropathy usually evolves slowly over many months, but a subacute or even fulminant progression can be seen.

Sensory Syndromes

Uremic polyneuropathy may be associated with one of the several sensory dysfunction syndromes. The secondary restless leg syndrome (RLS) occurs in 6.6 to 62% of long-term dialysis patients. Patients with RLS experience an extremely uncomfortable sensation characterized by a creeping, crawling, pruritic sensation deep within the legs. The patients experience an irresistible urge to move the legs. The syndromes worsen during inactivity and at night. Association of RLS with lower quality of life and increased risk of death has been reported. In burning foot syndrome, patients experience severe pain and burning sensation in the distal lower extremities.

This syndrome usually occurs in the early days of dialysis, possibly from the thiamine deficiency. Because thiamine is water soluble and is well dialyzed, patients develop thiamine deficiency. Routine administration of thiamine and other water-soluble vitamins eliminates this syndrome. Another sensory manifestation of uremic neuropathy is paradoxical heat sensation. This is sensory abnormality in the perception of heat in response to low-temperature stimuli. Paradoxical heat sensation has been reported to be common, and is often an early expression of the sensory neuropathy in uremia.

Carpal tunnel syndrome (CTS) is a painful progressive condition caused by compression of the median nerve in the wrist. CTS is one of the major problems of long-term HD. HD patients are at considerable risk of developing CTS in the wrist with an arteriovenous fistula. CTS is a clinical manifestation of dialysis-related amyloidosis (infiltration of amyloid deposits consisting of beta2-microglobulin). The most common symptoms of CTS are burning, pain, tingling, numbness, weakness, or pain of the fingers (or less commonly of the palm). Symptoms most often occur in the parts of the hand supplied by the median nerve.

Motor Symptoms

Motor involvement usually occurs as a late manifestation of uremic polyneuropathy and reflects a more advanced disease. Motor dysfunction can lead to muscle atrophy and myoclonus, and subsequent paralysis. Severe, rapidly progressive, and predominantly motor polyneuropathy has been reported in renal failure patients. This partly reversible disorder has been observed in association with critical illness, multisystem organ failure, sepsis, and so on.

Diagnosis

Electrophysiologic study is the most sensitive test for the diagnosis of neuropathy in patients with uremia. Nerve conduction velocities are reduced, even without any signs and symptoms of neuropathy. Only 50% of patients with electrophysiologic signs of impaired nerve conduction are symptomatic. Most commonly, motor function is assessed by measuring motor nerve conduction velocity (MNCV) in the peroneal nerve. However, MNCV is a relatively late sign of nerve dysfunction. Sensory nerve conduction velocity of the sural nerve is even more sensitive in detecting early nerve dysfunction, but is not widely used.

Recently, other neurophysiologic parameters (such as neurospecific current perception threshold, vibration perception threshold, and thermal discrimination threshold) have been studied in the diagnosis of uremic polyneuropathy. These studies are simple, rapid, and less noxious. However, these parameters are less sensitive in detecting an abnormality in uremic neuropathy than in a nerve conduction study. The most sensitive parameters in the diagnosis of uremic neuropathy were F-wave parameters from lower limbs, vibration detection threshold from the feet, and the sural nerve sensory action potential amplitude.

Management

Dialysis Therapy

Dialysis therapy [HD or peritoneal dialysis (PD)] stabilizes and stops the further progression of uremic polyneuropathy and slowly improves the symptoms in these patients. However, complete recovery is rare. The extent of recovery is inversely related to the degree of severity of the disease at the initiation of dialysis therapy. Severity of neuropathy at the onset of dialysis therapy is an important prognostic factor in dialysis patients. We have previously reported that severe sensory neuropathy independently predicts 5-year mortality in HD patients.

Since the accumulation of middle molecular weight substances, neurotoxins have been associated with uremic neuropathy, it has been suggested that underdialysis may be factor in progression of uremic neuropathy. Few studies have been reported in the literature concerning the relationship between uremic neuropathy and dialysis dose. HD patients with lower Kt/V had greater reduction in MNCV compared to those with higher Kt/V. In contrast, other studies failed to show any role of dialysis dose in the development and progression of uremic neuropathy.

In the past, PD was associated with a lower incidence of uremic neuropathy than HD. No significant differences have been demonstrated in the effects of PD and current high-flux membrane HD. Peripheral neuropathy may deteriorate during both HD and PD, but in significantly different ways—indicating that several pathogenetic mechanisms are probably involved in uremic neuropathy. Signs of uremic neuropathy have been reported to be similar in both HD and CAPD patients.

The recovery from autonomic neuropathy after bicarbonate HD has been reported. Effectiveness of different dialyzer membranes for the treatment of uremic polyneuropathy have been investigated. HD using polyacrylonitrile membranes (AN69) highly permeable to the middle molecular weight molecules (MMMs) increased the clearance of these molecules and significantly improved the neuropathy in patients with high levels of MMM. HD with a noncellulosic polyacrylonitrile (AN69) membrane acutely improved sensory conduction velocities (SCV) and motor conduction velocities (MCV), whereas this effect was not seen with a cellulose acetate membrane. It has been reported that the polyacrylonitrile membrane was more effective than the Cuprophan membranes at the clinical and at the neurophysiologic levels.

Renal Transplantation

The only potential cure for uremic neuropathy is renal transplantation. Renal transplantation, particularly at the early stage of uremic neuropathy, has achieved a favorable outcome in the treatment of uremic neuropathy. Patients with a short history of severe progressive uremic polyneuropathy have been reported to recover completely after renal transplantation. The remission after transplantation has two phases: an early rapid phase and a late slow phase in moderate to severe nephropathy. It is doubtful if standard dialysis techniques may effectively treat once autonomic lesions have developed.

Renal transplantation is much more efficient. Autonomic dysfunction in HD patients is reversible, and renal transplantation reverses the sympathetic and parasympathetic autonomic dysfunction simultaneously and at a relatively early stage. Renal transplantation provides the improvement of uremic cardiac sympathetic neuropathy assessed by (123)I-MIBG imaging, which may be a more sensitive (or at least an earlier marker) than heart rate variability. However, it should be noted that renal transplantation itself and the use of immunosuppressive drugs could cause neurologic complications.

Vitamin Supplementation

Vitamin deficiency (a common complication in dialysis patients) is caused by losses during dialysis, dietary restrictions, catabolic illness, and other factors. In patients with polyneuropathy, high doses of intravenous thiamine pyrophosphate can be helpful in this respect. Intravenous treatment with methylcobalamin, a vitamin B12 analogue, is a safe and a potentially beneficial therapy for neuropathy in chronic HD patients. It has been reported that methylcobalamin can be used in the treatment of autonomic and peripheral neuropathy in both diabetic and nondiabetic HD patients.

Biotin, a water-soluble low-molecular-weight B-complex vitamin, is a coenzyme loosely bound to the serum proteins. Biotin would likely to be lost during dialysis, resulting in biotin deficiency. Significant improvement has been reported with respect to disorientation, speech disorders, memory failure, myoclonic jerks, flapping tremor, restless leg, paresthesia, and difficulties in walking within 3 months of treatment with 10 mg biotin 3 times a day in nine HD patients. Biotin in vitro counteracts the inhibitory effect of uremic toxin on microtubule formation. Despite different opinions regarding the deficiency of these water-soluble vitamins, the supplementation of these vitamins is practiced in most dialysis centers.

Erythropoietin Therapy

In predialysis uremic patients, especially in nondiabetics, subcutaneous erythropoietin (EPO) therapy improved motor polyneuropathy. The improvement in MNCV may reflect remyelination. Improvement in MNCV was not significantly correlated to the increase in hemoglobin. This nonhematopoietic effect of EPO may be related to some direct action through EPO receptors on peripheral neuronal cells.

Treatment of Hyperparathyroidism

According to Avram et al. and other groups, in dialysis patients parathyroid hormone acts as a uremic toxin—especially affecting the integrity of central and peripheral nervous system. A possible pathogenetic link has been suggested between autonomic neuropathy and secondary hyperparathyroidism in uremic patients. The new calcimimetic agent cinacalcet hydrochloride lowers parathyroid hormone levels and improves calcium phosphorus homeostatis in dialysis patients. Lowering of PTH may be a potential target for the treatment of uremic neuropathy. So far

there are no reports in the literature indicating that lowering PTH improves uremic neuropathy.

Treatment of Restless Leg Syndrome

After the diagnosis of RLS, one of the most important strategies is to decrease exposure to potential exacerbating agents—such as tricyclic antidepressants, dopamine antagonists, lithium, and selective serotonin uptake inhibitors (SSRI). Paradoxically, it has been reported from a retrospective study that some patients experience improvement with the treatment of SSRI. As RLS is linked to iron deficiency, infusion of high-dose iron dextran (1000 mg) was associated with a significant reduction in symptoms (with continued benefits of up to 4 weeks).

In dialysis patients, optimum levels of hemoglobin and iron should be maintained with erythropoietin and iron. Dopaminergic agents such as levodapa and dopamine agonists (Pergolide) should be considered first-line options in the treatment of uremic RLS. Several other drugs—such as opoids, gabapentin, an alpha-adrenergic blocker (clonidine), and benzodiazepines—have been shown to be beneficial in the treatment of uremic RLS. Renal transplantation is the best treatment in curing uremic RLS symptoms.

Treatment of Carpal Tunnel Syndrome

Early diagnosis of CTS is essential because if left untreated nerve damage can progress, leading to weakness and ultimately loss of function of thumb and adjacent fingers. Echocardiographic evaluation of wrist thickness has been reported to be useful in assessing the progression of CTS. Although splints and injections may help temporarily, the definitive treatment for CTS is surgical decompression to free the median nerve from the constricting fibrous sheath. Nonsteroidal anti-inflammatory drugs and steroids may be used for acute pain relief.

Symptomatic Treatment

Paresthesia and painful neuropathy can be treated with anticonvulsants or tricyclic antidepressants. Dosing should be adjusted to the renal function or timing of dialysis. Tricyclic antidepressants [amitriptyline (Elavil), nortriptyline (Pamelor, Aventyl HCl)] have demonstrated effectiveness in the treatment of chronic neuropathic pain. The anticonvulsant gabapentin (Neurontin) has been proved to be effective in neuropathic pain, and carbamazepine has been

effective in the treatment of painful diabetic neuropathy and more useful in trigeminal neuralgia. Local anesthetics such as lidocaine can also be used for pain relief. Lidocaine stabilizes neuronal membrane, possibly by inhibiting ionic fluxes required for initiation and conduction of impulses.

Recommended Reading

Avram MM, Feinfeld DA, Huatuco AH. Search for the uremic toxin: Decreased motor-nerve conduction velocity and elevated parathyroid hormone in uremia. N Engl J Med 1978;298:1000–03.

This article investigates whether secondary hyperparathyroidism in uremia has a role in uremic peripheral neuropathy. The results of this study suggest a relationship between high parathormone levels and uremic neuropathy and implicate parathyroid hormone as a uremic toxin.

Telli M, Bidwell J, Kinninmonth A, Zoccali C. Prevalence and treatment of carpal tunnel syndrome in renal haemodialysis. Chir Organi Mov 2005;90:287–96.

This article investigates the prevalence and etiology of CTS and the effect of open carpal tunnel decompression (CTD) in 91 HD patients. The patients were assessed only by clinical means. CTS is a frequent and serious disease affecting renal dialysis patients, but its etiology remains uncertain. Nevertheless, CTD is an effective and lasting treatment for this condition.

Ropper AH. Accelerated neuropathy of renal failure. Arch Neurol 1993;50:536–39.

This article describes a syndrome of rapidly evolving polyneuropathy in four peritoneal dialysis patients with severe renal failure. The patients had an acute or subacute syndrome characterized by generalized limb weakness, severe imbalance, diminished reflexes, and numbness. The authors conclude that this partly reversible acute uremic neuropathy, which is probably caused by the metabolic disturbances of end-stage renal failure, simulates Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy and may be complicated by diabetic neuropathy.

Mittman N, Avram MM, Blanco M, Sreedhara R. Severe sensory neuropathy and urea reduction ratio (URR) independently predict mortality in non-diabetic hemodialysis patients. J Am Soc Nephrol 1996;7:1458.

This work was presented at the Twenty-ninth Annual Meeting of the American Society of Nephrology. Nerve function was measured in 117 nondiabetic HD patients by current perception threshold. The patients were followed to 5 years. Survival was analyzed by Cox's proportional hazards analysis. The presence of severe sensory neuropathy was associated with a twofold mortality risk in HD patients.

Robles NR, Cancho B, Pizarro J, Solis M, Alvarez MC, Sanchez CE. Acute effect of hemodialysis with polyacrylonitrile membrane on nerve conduction velocities. Ren Fail 2001;23:251–57.

In this study, the authors have evaluated the acute effect of HD on nerve conduction velocities in eight patients. Nerve conduction velocities were compared before and after HD with either polyacrylonitirile (AN69) or cellulose acetate (CA) membrane. After HD with AN69, MNCV and sensory nerve conduction velocities (SCV) were increased. After hemodialysis with CA, MNCV and SCV did not change. Hemodialysis with AN69 acutely improved SCV and MNCV.

Kurata C, Uehara A, Ishikawa A. Improvement of cardiac sympathetic innervation by renal transplantation. J Nucl Med 2004;45:1114–20.

In this article the authors have investigated whether renal transplantation can improve cardiac sympathetic innervation in dialysis patients. The authors analyzed time- and frequency-domain measures of 24-hour heart rate variability (HRV) and cardiac (123)I-MIBG scintigraphy before (and 1–3 months after) renal transplantation in 13 dialysis patients and in 10 control subjects. Renal transplantation improved uremic cardiac sympathetic neuropathy as assessed by (123)I-MIBG imaging, which may be more sensitive (or at least an earlier marker) than HRV.

Kuwabara S, Nakazawa R, Azuma N, Suzuki M, Miyajima K, Fukutake T, et al. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. Intern Med 1999;38:472–75.

This article reports the effects of the intravenous administration of methylcobalamin, an analogue of vitamin B12, for uremic or uremic-diabetic polyneuropathy in HD patients. Patients received 500-microgram methylcobalamin injections three times a week for 6 months. There were no side effects. In HD patients, intravenous methylcobalamin treatment is a safe and potentially beneficial therapy for neuropathy.

Hassan K, Simri W, Rubenchick I, Manelis J, Gross B, Shasha SM, et al. Effect of erythropoietin therapy on polyneuropathy in predialytic patients. J Nephrol 2003;16:121–25.

This article reports the effect of 5-month subcutaneous EPO therapy on polyneuropathy in 22 pre-dialytic patients with neuropathy detected by NCS. Subcutaneous EPO therapy improved motor polyneuropathy in uremic patients. The improvement was better in nondiabetic patients than in diabetic patients.

Block GA, Martin KJ, de Francisco ALM, Turner SA, Avram MM, Suranyi MG, et al. Cinacle for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350:1516–25.

This article reports the results of two identical randomized double-blind placebo-controlled trials evaluating the safety and effectiveness of the calcimimetic agent cinacalcet hydrochloride. Cinacalcet lowered parathyroid hormone levels and improved calcium-phosphorus homeostasis in patients receiving HD who had uncontrolled secondary hyperparathyroidism.

Trenkwalder C, Paulus W, Walters AS. The restless leg syndrome. Lancet Neurol 2005;4:465–75.

This article reviews the epidemiology, clinical findings, pathophysiology, and treatment of RLS.

CHAPTER 71

Electroencephalography in the Evaluation of Neurologic Function

Warren S. Brown, PhD

Chronic renal failure affects central nervous system (CNS) function, resulting in the appearance of the neurobehavioral syndrome of uremia. Predominant in this syndrome are diminished concentration, slowed and inefficient cognitive functioning, restlessness, and lowered arousal level or drowsiness. The more mild the renal disorder, the more likely it is that the effects will be manifest in higher cognitive processes, and the less likely they will appear in measures of general arousal level or sensory transmission.

Because the symptoms of the neurobehavioral syndrome are responsive to dialysis treatment or renal transplantation, sensitive ongoing monitoring of neurobehavioral status (particularly of the integrity of higher cognitive functions) is important for successful management of renal disorders. This chapter reviews electroencephalographic (EEG) measures of CNS status in renal disease, and describes the particular value of cognitive event–related EEG potentials in the monitoring of renal failure patients.

Electroencephalographic and Evoked Potentials in Chronic Renal Failure

Electrophysiologic techniques have been used successfully in monitoring the status of patients with renal disease. A number of studies have demonstrated the clinical utility of noninvasive, repeatable, and quantifiable EEG measures for the early detection of the need for dialysis, optimization of the dialysis regime for individual patients, and the discovery of preclinical stages of dementia. Quantifiable EEG measures of clinical state fall into three classes: frequency analysis of the ongoing EEG, sensory-evoked potentials (SEPs), and cognitive event–related potentials (ERPs).

Electroencephalographic Frequency Analysis

The most prominent effects of uremia on the EEG are slowing of the alpha rhythm in early stages of renal disorder, with a more dramatic downward shift in the dominant frequency from alpha (8–12 Hz) toward theta (4–7 Hz) as renal failure progresses. This is best seen as changes in the distribution of power in the computerized EEG frequency spectrum. The change in dominant frequency has been successfully quantified by Teschan using a ratio of power in the 3- to 7-Hz spectral band to the power from 3 to 13 Hz.

Some studies have shown that as blood urea nitrogen (BUN) and creatinine increase, predominant frequency shifts progressively downward. EEG frequency patterns tend toward normal after the first few dialysis treatments, and may completely normalize after successful renal transplantation. Thus, EEG frequency analysis can be a sensitive measure of the adequacy of dialysis and can be useful in deciding when dialysis should be initiated. However, the ongoing EEG (although sensitive to the uremic state) does not directly reflect higher cognitive processes. Rather, it reflects the more general arousal or attentional state of the individual. Thus, it is not likely to prove as sensitive to early and very mild renal dysfunction—or to subtle differences in forms of dialysis treatment as reflected in the efficiency of higher cognitive processing.

Sensory-Evoked Potentials

SEPs (such as the auditory brain stem–evoked response, the checker-reversal visual evoked potential, or somatosensory evoked potentials) involve a series of positive and negative waves that reflect peripheral and central conduction time of information in sensory pathways and receiving cortex. Chronic renal failure typically results in increased component latencies, suggesting increased sensory conduction time. For example, the latency of the major positive wave of the visual evoked potential (usually peaking at about 100 milliseconds) is often found to be greater than 120 milliseconds (i.e., more than 2 standard deviations longer than normal). The auditory brain stem–evoked potential typically shows increased brain stem conduction times, with longer wave I to wave III and wave III to wave V intervals. Studies have not consistently found correlations between SEP component latencies and BUN or creatinine. Similarly, reduced peripheral conduction velocities of somatosensory-evoked potentials have been shown in chronic renal failure.

With dialysis, EP latencies tend to normalize—but still remain somewhat prolonged. In contrast to the EEG frequency spectrum,

SEPs remain relatively stable across changes in general arousal associated with fluctuating renal status. That is, changes in SEPs occur over a longer period of time (days to weeks) than those occurring in the EEG frequency spectrum. Thus, sensory EPs provide information about the longer-term impact of uremia on the integrity of sensory pathways and cortical receiving areas. As was true of the EEG frequency spectrum, SEPs do not provide information regarding the ability of individuals to process the more complex aspects of the information provided by sensory input.

Cognitive Event–Related Potentials

Detection of subtle organically based changes in mental status in renal failure and dialysis treatment is not unlike the problem of the detection of changes in mental status in very early Alzheimer's disease. In the early stages of Alzheimer's disease, it is often difficult to distinguish organic brain pathology from the forgetfulness and trouble with complex operations associated with depression and anxiety (i.e., pseudodementia). However, in the case of Alzheimer's disease cognitive ERPs have proven an important tool for detecting changes in neural function associated with disease processes.

Cognitive ERPs reflect internal mental events involving such processes as stimulus recognition, evaluation, and decision making, rather than purely sensory aspects of cortical responses. The simplest and most typical paradigm for eliciting and recording ERPs is mental counting of target stimuli that occur randomly within a train of repeated nontargets. This procedure results in the occurrence of a P300 component (so labeled because it is a positive wave occurring approximately 300 milliseconds poststimulus). The P300 appears in response to targets, but is absent in response to nontargets. More complex versions of the target detection paradigm can also elicit P300s, such as the detection of a particular target digit or successive occurrences of the same digit in a random train of successively presented digits (often called the continuous performance task).

The amplitude of the P300 is related to the allocation of processing resources to the task. Thus, P300 is considerably diminished in amplitude if the subject has difficulty attending or if stimuli are ignored rather than counted. P300 latency (the time interval between the onset of a target stimulus and the peak of the wave) increases as the difficulty of target detection and discrimination increases. Thus, P300 latency is considered a measure of cognitive processing time.

P300 latency has been shown to be sensitive to changes in mental status in a number of disorders that affect the nervous system (e.g., Alzheimer's and multiple infarct dementia, mental retardation, Parkinson's disease, and reversible and nonreversible CNS toxic states). Whereas the latency of the P300 increases very gradually with normal aging (about 1 millisecond per year), P300 latency increases rather dramatically in dementing illnesses. A comparison of the ERP of a normal adult and that seen in an individual with early mild Alzheimer's disease can be seen in Figure 71.1. As indicated by the dashed vertical lines in the figure, P300 latency is prolonged in the individual with Alzheimer's disease (392 milliseconds versus 315 in the normal individual).

A consistent finding across a number of laboratories has been that even rather mildly demented Alzheimer's disease patients show significantly increased latency of the P300 peak. P300 in these individuals is correlated with neuropsychological measures of higher cognitive ability, particularly with performance on complex tasks that place a premium on the speed of mental operations. We have found P300 latency to discriminate between early mild Alzheimer's patients nearly as accurately as measures of glucose utilization from positron emission tomography. P300 latency was found to be strongly correlated with the metabolic rates in the parietal and frontal cortex. Finally, the P300 latencies of Alzheimer's patients become progressively longer as the severity of the disease increases over time.

Cognitive Event–Related Potentials and Renal Disease

Prolonged P300 latency is associated with diminished mental status in chronic renal failure. Although dialysis seems to normalize P300 latencies, most studies have shown that dialysis patients continue to have somewhat prolonged latencies. In one of our studies, 58% of patients on dialysis still had significantly prolonged P300 latencies. P300 latency was also found to differentiate CAPD (continuous ambulatory peritoneal dialysis) patients and hemodialysis patients from normal individuals to a greater extent than either auditory brain stem–evoked responses or visual evoked potentials. Thus, in these treated chronic renal failure patients residual abnormalities were apparent in the P300 that did not appear in SEPs. In addition, CAPD patients had more normal P300 latencies than hemodialysis patients when stimulus discriminations were simple (tones) but equally prolonged latencies for P300s elicited by more complex cognitive discriminations (numbers).

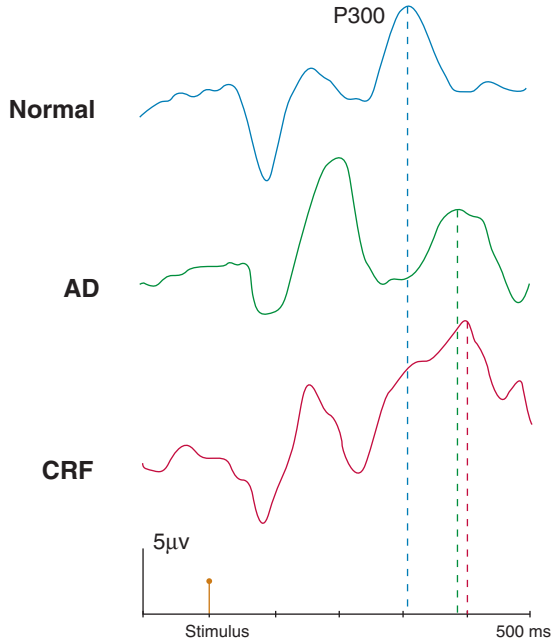


Figure 71–1

Examples of ERPs from a normal adult (Normal), an individual with early mild Alzheimer's disease (AD), and an individual with cognitive decline associated with chronic renal failure (CRF). The latency of the P300 wave is indicated by the dashed line intersecting the time scale at the bottom of the graph. Note the increased latency for the Alzheimer's disease and chronic renal failure individuals.

Procedures for P300 elicitation and recording have now been standardized and there is a sufficient database for routine clinical application of cognitive ERPs to chronic renal failure and dialysis patients. Although many of the critical studies of ERPs in renal disease have yet to be done, it is likely that cognitive ERPs will provide important, early, preclinical evidence of the onset of CNS dysfunction and the uremic neurobehavioral syndrome.

A particular value of electrophysiologic methods in the clinical assessment of chronic renal failure and dialysis treatment is that valid measurements can be made on a repeated basis in order to trace changes in cognitive status over time and per treatment manipulations. That is, there are no retest or practice effects in these electrophysiologic responses–as is often the case with many behavioral neuropsychological assessment instruments. Valid repeated measures of CNS function are particularly important for treatment outcome monitoring and for research.

In relationship to chronic renal failure, as well as other CNS disorders, it is important to note that affective states do not affect P300 latency measures. Depression, a common occurrence in hemodialysis patients, often has adverse affects on neuropsychological test performance. However, it does not result in prolonged P300 latencies. In a recent study of the effects of recombinant human erythropoietin (EPO) in dialysis patients, we found significant changes in mood and energy such that individuals generally felt much less depressed and fatigued with EPO. Also improved was performance on many standard neuropsychological test instruments.

Although P300 amplitude increased with EPO (likely due to improved attention), P300 latency did not change. We concluded that depression and fatigue had affected neuropsychological test performance, resulting in an exaggerated picture of cognitive dysfunction–whereas P300 latency (although somewhat prolonged) was unaffected by the EPO-related changes in mood and energy. Thus, P300 latency reflected CNS functional integrity in the pre-EPO state in a way not biased by depression and fatigue. Given the cognitive nature of the uremic neurobehavioral syndrome and the literature demonstrating that small differences in neurocognitive status are detectable using cognitive ERPs, it appears that ERPs will come to play an increasingly important role in the battery of clinical tests of the state of CNS function in patients with renal disease.

Recommended Reading

Evers S, Tepel M, Obladen M, et al. Influence of end-stage renal failure and hemodialysis on event-related potentials. J Clin Neurophys 1998;15:58–63.

Demonstrates prolonged P300 latency in uremia and reduced latency after hemodialysis treatment, and correlations with blood urea nitrogen, creatinine, and uric acid.

Kramer L, Madl C, Stockenhuber F, et al. Beneficial effect of renal transplantation on cognitive brain function. Kidney Int 1996;49:833–38..

Demonstrates decreased P300 latency and increased amplitude after renal transplantation associated with improved performance on neurocognitive test performance.

Lewis EG, O'Neil WM, Dustman RE, et al. Temporal effects of hemodialysis of measures of neural efficiency. Kidney Int 1980;17:357–63.
An example of use of visual and somatosensory-evoked potentials in assessing renal disease and dialysis effects.
Marsh JT, Brown WS, Wolcott D, et al. Electrophysiological indices of CNS function in hemodialysis and CAPD. Kidney Int 1986;30:957–63.
An example of the use of cognitive ERP latency in distinguishing normal and hemodialysis patients, and in comparing therapies.
Teschan PE. Electroencephalographic and other neurophysiological abnormalities in uremia. Kidney Int Suppl 1975;2:210–16.
A review of studies of EEG and sensory-evoked potential changes in uremia and hemodialysis.
Tilki HE, Akpolat T, Tunali G, Kara A, Onar MK. Effects of haemodialysis and continuous ambulatory peritoneal dialysis on P300 cognitive potentials in uraemic patients. Upsala J Med Sci 2004;109:43–48.
P300 latency was compared for hemodialysis and continuous ambulatory peritoneal dialysis. CAPD resulted in shorter P300 latencies. Both P300 amplitude and latency were correlated with mental status.

CHAPTER 72

Impact of Anemia and Its Correction on Brain Function

Allen R. Nissenson, MD

Abnormalities of brain function, which usually initially manifest as an inability to concentrate or to sustain attention to tasks, are some of the earliest manifestations of progressive renal failure. If appropriate renal replacement therapy is not initiated, these abnormalities may become more severe—progressing to memory loss and to myoclonic movements, and even to seizures and coma. For many years, it was believed that brain dysfunction in patients with renal failure was caused by the uremia itself—which was the result of the effects of retained uremic toxins on the brain. The improvement in the most severe symptoms when adequate dialysis (or kidney transplantation) was provided further reinforced this impression.

Recently, it became clear that even well-dialyzed patients have significant abnormalities of brain function—although these may be apparent only on careful questioning and appropriate testing. Many of these abnormalities have now been shown to relate to the severe anemia present in nearly all end-stage renal disease (ESRD) patients, and have been shown to be reversible if the anemia is improved or corrected with recombinant human erythropoietin (r-HuEPO). This chapter describes the tools used to assess central nervous system function in dialysis patients and discusses the impact of anemia treatment on this critical organ system.

Assessment of Brain Electrophysiology and Cognitive Function

The electroencephalogram (EEG) has been used extensively to assess brain function in ESRD patients. In the presence of uremia, there is a downward shift in the dominant frequency from alpha to theta waves. The ratio of power distribution in these two frequency speeds can be calculated, and has been shown to increase as the wave frequency decreases. In addition, some patients with ESRD demonstrate paroxysmal bursts of slow waves on the EEG–although this can also be seen in other forms of metabolic encephalopathy. Although there are a few studies that show an

inverse correlation of the standard EEG (with the power analysis described) with the BUN (blood urea nitrogen) or creatinine level, other studies have not confirmed this finding. There is agreement, however, that adequate dialysis therapy improves the power ratio, suggesting a role of uremia in the electrical abnormalities seen.

Even with adequate dialysis, however, significant abnormalities in the power ratio remain. It should be noted that such studies tend to worsen during the course of an individual dialysis treatment, probably as a result of cerebral edema—which accompanies the removal of small solutes. It is best to do such studies 24 hours following the last dialysis treatment to minimize the impact of such artifacts. Recent improvements in methods, such as the computerized spectral (frequency) analysis, may reveal more subtle differences in frequency content over time. However, they have yet to be fully validated in ESRD patients.

A more sensitive approach to brain electrophysiology in ESRD patients is the use of sensory-evoked potentials (EPs). This technique requires repeated delivery of a stimulus and signal-averaging techniques to assess brain function. EPs are elicited using visual, auditory, or somatosensory stimulation. In each case, signal averaging reveals a series of positive and negative waves of cortical origin with latencies between the stimulus and wave appearance of 50 to 150 milliseconds. In contrast to the EEG, EPs remain relatively stable across changes in general arousal and are thus less susceptible to artifacts. EPs provide information about the long-term impact of uremia on the nervous system, particularly about the integrity of sensory pathways and cortical receiving areas.

The presence of ESRD results in an increase in latencies of waves, although the correlation with the level of BUN or creatinine is poor. Dialysis leads to a decrease (improvement) in latencies, but they do not normalize. As with the EEG, changes in the latency of EP components is not specific to renal disease but is seen in other forms of metabolic encephalopathy. The current most frequently used form for visual EPs is the checkerboard pattern reversal. Pattern reversals have the advantage of a very small range of latency variation of the major positive component at 100 milliseconds in normal subjects. Small-check patterns have proved to be most sensitive in assessing dialysis effects.

The most sensitive approach to brain electrophysiology currently used is the cognitive event-related potential (ERP). These potentials appear only when a subject is engaged in some higher-level mental processing in relation to the stimulus. The most typical paradigm for recording ERPs is a mental counting of target stimuli occurring randomly within a train of repeated nontarget stimuli. This

procedure results in a P300 component (so labeled because it is a positive wave occurring approximately 300 milliseconds post-stimulus) in response to targets, which is absent in response to nontargets. P300 latency is sensitive to changes in mental status in a number of disorders that affect the nervous system, including uremia.

P300 latency changes, therefore, are a sensitive index of diminished cognitive function—particularly of slowed cognitive processing time. P300 latency is prolonged in ESRD patients, and improves somewhat with adequate dialysis. Dialysis modality may impact the P300 latency as well. Continuous ambulatory peritoneal dialysis (CAPD) patients have more normal P300 latencies than do hemodialysis patients when stimulus discriminations are simple, but the two have equally prolonged latencies to more complex cognitive discriminations.

Because of the high frequency of affective disorders in ESRD patients, it is important to note that P300 latency is specific to cognitive status and is not affected by mood. Depression, a common occurrence in ESRD patients, does not affect P300 latency. In recent years, the utility of the P300 component in assessing neurocognitive status has gained sufficient acceptance so that many of the prepackaged computerized EEG/EP systems now include routines for eliciting and recording the P300.

Finally, neuropsychologic testing has been applied in ESRD patients to more precisely assess cognitive function in these individuals. There are a number of domains of cognitive function that have been studied in ESRD patients, and many different cognitive function tests have been described for this purpose. The areas of cognitive function most commonly impaired in ESRD patients (performance on speeded perceptual-motor tasks that require flexibility of thinking, ability to shift sets, or mental manipulations; tests of learning and memory) have also proven to be sensitive to change in clinical research populations.

Some of the commonly used tests include number cancellation (assesses cognitive accuracy and speed); trailmaking, forms A and B (assesses attention, concentration, visual scanning, psychomotor speed, and the ability to sequence and shift cognitive sets); symbol digit modalities (assesses immediate visual memory, learning, hand-eye coordination, reading-writing ability); Rey auditory verbal learning test (assesses the ability to learn common words, immediate memory, and retrieval from long-term storage); and controlled oral word association test (assesses verbal fluency and retrieval from semantic memory). These tests should be performed by, or under the direction of, a neuropsychologist.

Brain Electrophysiology and Anemia

Many of the tools described have been used in research studies to better understand the impact of anemia and its correction on brain electrophysiology. Partial correction of anemia (up to a hematocrit of 36%) has been shown to normalize the overall power spectrum of the EEG and to move its distribution closer to that found in healthy controls. With normalization of the hematocrit there is further improvement in the power spectrum distribution.

When EPs are used to assess brain electrophysiology, there is a significant improvement in the latency and amplitude of the wave forms when the anemia is partially corrected—suggesting improved speed and efficiency of brain function. Finally, using the more sensitive ERPs the latency and amplitude of the P300 improve with partial anemia correction—and to an even greater extent with normalization of hematocrit. The bulk of evidence suggests that there is substantial impairment of brain function at a hematocrit below 30%, and that this improves significantly when the hematocrit rises to even 31 to 32%.

There is additional evidence that further increases in hematocrit to 36% and to normal incrementally improve brain electrophysiology and cognitive function. The latter findings support the data of several investigators who showed significant quality-of-life and functional improvements in dialysis patients whose hematocrit was normalized. The explanation for the improved brain function with normalization of hematocrit is likely an improvement in brain metabolism. Studies utilizing positron emission tomography show that full correction of anemia in ESRD patients returns cerebral blood flow to normal and leads to enhanced cerebral oxygen extraction—changes that would provide maximal oxygen to functioning brain tissue. The optimal hematocrit for maximum brain oxygen delivery seems to be 36 to 45%.

Neuroprotective Role of Erythropoietin

It has recently been found that receptors for erythropoietin (EPO) are located on many cells in addition to hematopoietic stem cells in the bone marrow. Of note is the fact that EPO can be produced locally in the brain, and EPO receptors (present in brain) are upregulated by hypoxemia. Pretreatment of animals with EPO prior to ischemic brain insult mitigates the extent of damage. The neuroprotective effects of EPO, independent of the level of hemoglobin, may be important in the improved brain function seen in EPO-treated CKD and dialysis patients—although this hypothesis has yet to be tested scientifically.

Summary

Uremic encephalopathy is caused in part by anemia. The manifestations of this brain dysfunction can be largely reversed by partial correction of anemia. Normalization of hematocrit leads to further improvements in brain electrophysiology and cognitive function. By using sophisticated tools for measuring brain function and metabolism, additional information should soon be available to guide clinicians to the appropriate target hematocrit to maximize brain function in individual ESRD patients.

Recommended Reading

Hasselblatt M, Ehrenreich H, Siren A. The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. J Neurosurg Anesthesiol 2006;18:132–38.

An excellent review of current knowledge regarding the impact of EPO on a variety of neurologic conditions.

Hirakata H, Kanai H, Fukuda K, et al. Optimal hematocrit for the maximum oxygen delivery to the brain with recombinant human erythropoietin in hemodialysis patients. Clin Nephrol 2000;53:354–61.

This study provides data on the relationship between hematocrit and brain oxygen delivery.

Metry G, Wilstrom B, Valind S, et al. Effect of normalization of hematocrit on brain circulation and metabolism in hemodialysis patients. J Am Soc Nephrol 1999;10:854–63.

A seminal study utilizing PET scanning to analyze brain metabolism after normalization of hematocrit.

Nissenson AR, Marsh JT, Brown WS, Wolcott DL. Central nervous system function in dialysis patients: A practical approach. Semin Dial 1991;4:115–23.

An excellent overview of the available tests of brain and cognitive function used in dialysis patients.

Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999;33:1122–30.

This study provides evidence that a normal hematocrit improves brain function to a greater extent than do lower hematocrit levels.

CHAPTER 73

Differential Diagnosis of Renal Osteodystrophy

Pouneh Nouri, MD; Bijan Nikakhtar; and Francisco Llach, MD

Most patients who develop end-stage renal disease (ESRD) do not have symptoms of bone disease when they start maintenance dialysis. Laboratory evidence of asymptomatic bone disease, though, is common in this group. If hyperphosphatemia and hypocalcemia remain uncontrolled—and if bone disease is not adequately treated—bone pain, fractures, and other consequences of severe renal osteodystrophy frequently develop during a patient's years on dialysis. A minority of patients may develop symptomatic bone disease before they require dialysis. These patients usually have slowly progressive renal disease and a prolonged course of chronic renal failure.

Aside from renal osteodystrophy, bone pain may be a consequence of amyloidosis due to beta-2-microglobulin in patients on long-standing dialysis. This is discussed in another chapter. Renal transplant patients may develop avascular necrosis and severe osteopenia related to steroid use.

Pathogenesis

Renal osteodystrophy can be divided into two subgroups based on histologic findings. High-turnover bone disease is associated with secondary hyperparathyroidism (HPT) and has the histologic picture of osteitis fibrosa cystica. Symptomatic bone disease is frequently seen in advanced cases of HPT. The low-turnover bone disease category includes adynamic bone disease (ABD) and aluminum-related osteomalacia (ARO). The latter is frequently symptomatic; the former is usually not. Mixed lesions share histologic characteristics of both the high-turnover and low-turnover states. Aluminum-related osteomalacia was a major problem 15 years ago, when high doses of aluminum-containing antacids were routinely prescribed for most dialysis patients. Since this practice has stopped, aluminum-related bone disease is now relatively uncommon.

High-Turnover Bone Disease

The main type of bone disease in dialysis patients is osteitis fibrosa, which is a reflection of secondary HPT. An increase in parathyroid hormone (PTH) levels is already present after renal function is reduced to 30 to 40% of normal. There are many factors involved in the generation of HPT, but the main factor may be a decrease in calcitriol production by the diseased kidney. Calcitriol is a naturally occurring potent hormone essential for calcium metabolism, bone function, and modulation of PTH secretion. Calcitriol and its analogues are inhibitors of PTH production. Because patients with renal failure have low to undetectable levels of calcitriol, the majority of patients need hormonal replacement. The administration of calcitriol (1,25-dihydroxy-Vitamin D_3) decreases the synthesis and secretion of PTH directly by inhibition of its synthesis at the pre-promessenger RNA level and indirectly by increasing calcium concentration and increasing the sensitivity of PTH suppression to calcium.

Hypocalcemia and hyperphosphatemia also play important roles in worsening HPT. Animal and human studies have shown that hyperphosphatemia has a direct effect on increasing PTH secretion and parathyroid cell proliferation, and that control of serum phosphorus reverses this. The role of hyperphosphatemia is evident in advanced renal failure. It is a late manifestation of renal failure and is typically present only after the glomerular filtration rate decreases below 25 mL/minute. Other factors that contribute to HPT are listed in Table 73.1.

Low-Turnover Bone Disease

ABD and ARO are low-turnover bone diseases. ABD occurs most commonly in particular subsets of patients: diabetics, the elderly,

Table 73–1

Factors That Contribute to the Development of Secondary Hyperparathyroidism

- Altered vitamin D metabolism and resistance to calcitriol
- Hypocalcemia
- Phosphorus retention
- Increased skeletal resistance to PTH
- Autonomous parathyroid cell proliferation
- Altered degradation of PTH
- Abnormal regulation of PTH release
- Abnormal calcium sensor receptor

patients on maintenance peritoneal dialysis, and patients with greater exposure to aluminum. The pathogenesis of ABD is obscure. Diabetic patients tend to have lower PTH concentrations and lower bone formation rates compared to nondiabetic patients on dialysis. Diabetic patients also tend to have parathyroid gland hyporesponsiveness to acute hypocalcemic challenges. In many patients, iatrogenic factors may contribute to a decrease in osteoblastic and osteoclastic activity—as well as to the low bone-formation rates seen in ABD. This may occur through excessive PTH suppression with inappropriately large doses of calcitriol and calcium-containing phosphate binders.

There is convincing data that aluminum toxicity is associated with osteomalacia, as well as with encephalopathy, hypochromic microcytic anemia, and occasionally hypercalcemia. Historically, toxic-aluminum exposure occurred by two routes: parenterally across the dialysis membrane if toxic aluminum levels were present in the dialysate water and orally by the ingestion of large doses of aluminum-based phosphate binders. The risk of osteomalacia has decreased dramatically in recent years, with the avoidance of aluminum-containing phosphate binders and the widespread practice of safe dialysate-water-treatment programs that ensure low levels of dialysate aluminum.

In ARO, aluminum deposits are noted along the mineralization front—which is the border between osteoid and mineralized bone. Several animal experiments suggest that parenteral aluminum loading impairs bone formation and induces osteomalacia. The mechanisms by which aluminum specifically produces its effects on bone are not clearly understood. Aluminum also accumulates preferentially in the parathyroid glands, and appears to inhibit PTH secretion directly. This inhibition of PTH release may slow bone turnover and render the bone more susceptible to osteomalacia.

Diagnosis

In most cases, the correct diagnosis can be made by evaluating the patient's symptoms, signs, and biochemical parameters. Occasionally, a bone biopsy may be needed to make a precise diagnosis.

Symptoms and Signs

Symptoms of bone disease usually appear late in the course of osteodystrophy, and they are seen typically in only the severe cases. Osteitis fibrosa due to secondary HPTH is characterized by bone tenderness, fractures, proximal muscle weakness, and arthritis and

periarthritis. The bone pain is often vague and deep seated, and may be diffuse or localized to the back, hips, knees, or legs. Lower back pain may be a symptom of a spontaneously collapsed lumbar vertebra, and sharp chest pain may be due to a rib fracture. In addition, periarticular calcification may lead to an acute inflammatory joint syndrome.

The proximal muscle weakness may progress to become a serious and debilitating problem. It may be caused by HPT, but other correctable causes should be sought—such as hypophosphatemia, vitamin D deficiency, and aluminum toxicity. Muscle weakness and bone pain may respond dramatically to several interventions: calcitriol therapy, sometimes even before PTH levels decrease; parathyroidectomy if severe HPT is present; and aluminum removal in the presence of aluminum toxicity. Spontaneous tendon ruptures may also be associated with severe secondary HPT. The quadriceps or triceps tendons or the extensor tendons of the fingers are the most common sites of rupture. Pruritus and corneal and conjunctival calcifications may also be related to HPT.

Aluminum bone disease is more symptomatic and crippling than secondary HPT. Thus, bone pain is more severe and fractures are more frequent. Furthermore, symptoms reflecting aluminum toxicity in other organs are present. These include encephalopathy, congestive heart failure, and anemia. There are no particular signs or symptoms related to adynamic bone disease.

Biochemical Findings

Serum calcium is usually normal or low in osteitis fibrosa. As HPT becomes severe, there is a gradual increase in serum calcium to even frank hypercalcemia. Serum phosphorus is usually mildly elevated, reflecting the patient's compliance with dietary restrictions. However, as HPT worsens bone resorption increases. This leads to release of phosphorus from bone and results in more severe hyperphosphatemia. The serum levels of alkaline phosphatase are usually elevated, reflecting increased osteoblastic function. Except in severe cases, however, serum alkaline phosphatase is not a reliable marker of the severity of HPT.

Intact PTH levels are invaluable in evaluating the response of HPT to calcitriol therapy. Patients with HPT usually have PTH levels from 300 to greater than 2000 pg/mL. In severe cases, the PTH level is usually above 600 pg/mL. Normal levels are 20 to 60 pg/mL.

Intact PTH levels correlate linearly with bone formation, osteoid volume, and marrow fibrosis. Bone histomorphometric studies have shown that PTH levels must be increased three to five times above normal nonuremic values (to about 200 pg/mL) in order to maintain normal degrees of bone turnover in uremic patients. Several factors may be important in causing this increased skeletal resistance to PTH noted in uremia. Recently, a novel mechanism for this resistance was described. The commonly used commercially available intact PTH immunoradiometric assay (IRMA; Nichols Laboratories, San Juan Capistrano, CA) measures both the biologically active 1-84 PTH molecule and the large inactive PTH fragments (likely the 7-84 fragment). The inclusion of PTH fragments is responsible for the fraction of serum PTH not suppressible by vitamin D. These inactive fragments accumulate in renal failure, and their levels are greater in uremia compared to those of normal controls.

Specifically, in uremic patients the inactive fragments may account for 35 to 50% of the intact PTH IRMA values measured by the commercially available methods—whereas they constitute only 10 to 20% in healthy individuals. Furthermore, these "inactive" fragments are competitive inhibitors of PTH actions. For instance, PTH (7-84) antagonizes the hypercalcemic effect of PTH (1-84) and inhibits its action on bone turnover. It has been suggested that this resistance to PTH caused by fragments in selected hormone target tissues such as distal nephrons occurs by internalizing and downregulating the PTH-1 receptor without accompanying activation of the receptor. Thus, the increased fragments of PTH and their possibly antagonistic effects are probably important factors for the elevated PTH levels needed for healthy bone in uremia.

To overcome the problem of measuring the inactive fragments as well as the active PTH level by intact PTH IRMA assay, a new generation of IRMA was developed to detect the entire PTH but not its amino-truncated fragments. This new-generation assay was manufactured by Nichols Laboratories under the name of "bio-intact PTH" assay, and by Scantibodies Laboratory under the name of Cyclase Activating PTH (CAP) or "bioactive PTH" assay. The latter is highly specific for the bioactive 1-84 molecule, and may be the only available assay that is accurate. Increasing variations among the assays emphasizes the fact that the interpretation of measurements must take into consideration the specific assay. In adynamic bone disease, PTH levels are inappropriately low. Serum calcium may be normal or increased.

Radiologic Findings

Radiologic images of the bone are usually normal in mild and moderate renal osteodystrophy, and are only abnormal in severe cases. Radiographs are therefore not reliable for the early detection of renal bone disease. In secondary HPT, the earliest findings are observed in the phalangeal bones. X-ray images of the hand may show increased subperiosteal resorption, which are observed best in the radial side of the middle phalanges; in particular, on the second and third fingers (Figure 73.1). The tufts of the distal phalanges may show erosions, which in severe cases may lead to blunting of the fingertips.

Co-striations resulting from enlarged haversian channels are also common in severe HPT. Radiographs of the skull can reflect increased bone resorption, with the finding of a diffuse mottled or granular appearance (the "salt-and-pepper" appearance). Finally, osteosclerosis (a form of increased density of bone) may occur because of increased thickness and number of trabeculae in spongy bone. The vertebral body, pelvis, ribs, skull, and long bones are most commonly involved. This may produce the classic "rugger jersey" appearance of the spinal vertebrae (i.e., alternating bands of dense and radiolucent zones).

Aluminum-induced osteomalacia rarely produces noticeable radiographic features in dialysis patients. The more specific findings are Looser zones or pseudofractures. These are wide, straight, radiolucent bands that are perpendicular to the long axis of the bone and abut the bone cortex. They occur in areas of bones that are subject to mechanical stress (pelvis, scapula, long bones, and clavicle).

Bone Biopsy

Bone biopsy may be indicated for the precise diagnosis of the type of bone disease in dialysis patients. For routine management of most cases of osteodystrophy, it is not necessary. Its indications are listed in Table 73.2.

Bone Histomorphologic Evaluation

Light microscopy is used to examine trabecular bone and marrow for histology, rate of bone formation, and amount of surface aluminum staining. The histologic examination assesses morphologic parameters, including the number of osteoclasts and resorption surface, the extent of endosteal fibrosis, the number and size of osteoblasts, and the amount and thickness of nonmineralized matrix (osteoid) that covers the trabecular surface. Bone formation

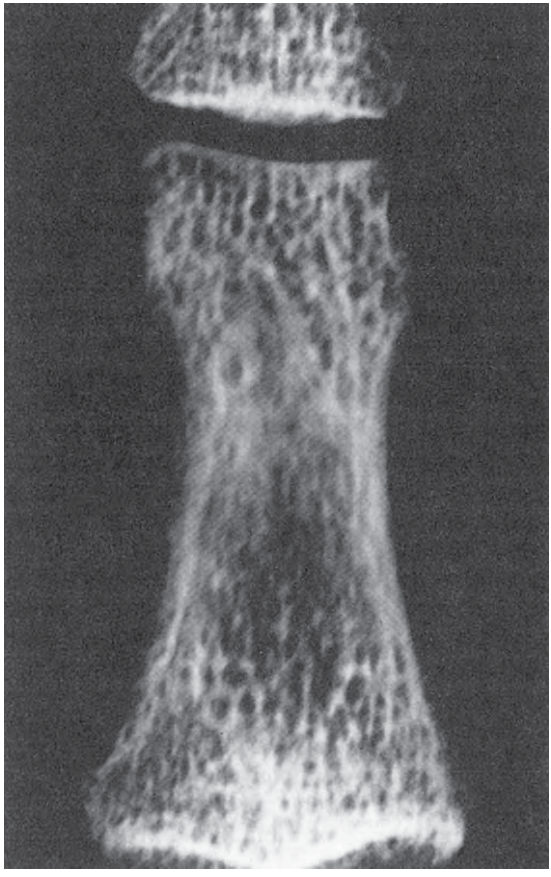


Figure 73–1

Irregularities on the radial side of the phalangeal bone, indicating significant increased bone resorption in a patient with hyperparathyroidism.

rate is a dynamic parameter that is evaluated after tetracycline labeling. Tetracycline is administered orally on two occasions, 12 days apart, and is deposited along the mineralization front. Tetracycline fluoresces, and thus examination of the biopsy under

Table 73–2

Indications for Bone Biopsy in Dialysis Patients

- Evaluation of severity of aluminum burden
- Evaluation of hypercalcemia and hyperphosphatemia before performing parathyroidectomy
- Evaluation of possible coexistence of hyperparathyroidism and aluminum toxicity

fluorescent microscopy enables the visualization of the deposited tetracycline along the mineralization front. Two fluorescent lines, images of the mineralization fronts 12 days apart, are observed. Thus, the distance between these two lines represents the rate of bone formation.

On the basis of these histologic findings in biopsy specimens, bone lesions can be categorized as follows. In osteitis fibrosa, there is an increase in both bone formation and resorption. As a result, the number of osteoblasts and osteoclasts is increased. In addition, endosteal fibrosis is increased. Unmineralized bone is formed at a rate higher than the mineralization rate, resulting in an increase in osteoid. The bone formation rate (tetracycline labeling) is increased, and the degree of aluminum staining is negative or very mild (less than 30% of trabecular surface).

Bone histology in aluminum bone disease is usually normal, but in severe cases osteomalacia is present with the finding of increased osteoid and a lack of cellular activity. Thus, few osteoblasts and osteoclasts are present. In addition, endosteal fibrosis is absent. The bone formation rate is reduced and aluminum deposits cover more than 30% of the trabecular surface. In many biopsies, a mixed lesion is observed with features of both osteitis fibrosa and osteomalacia. Aplastic or adynamic bone disease is characterized by low bone volume, decreased cellular activity, and absence of endosteal fibrosis. Unlike aluminum-induced osteomalacia, increased osteoid content is not present in this condition.

Prevention and Management

The general objectives of management of bone disease in dialysis patients are to control secondary HPT; to produce normal mineralization; to maintain serum concentrations of calcium, magnesium, and phosphorus near normal; to prevent extraosseous calcification;

and to avoid aluminum toxicity. These issues are discussed in the sections that follow.

Control of Hyperphosphatemia

Hyperphosphatemia (see the chapter on phosphorus binders) is a silent killer in the dialysis population, and control of hyperphosphatemia is critical. A national study of two large random samples of patients on hemodialysis showed that patients with elevated phosphorus or an elevated calcium-phosphorus product ($Ca \times PO_4$ product) had excessive mortality. Specifically, patients with serum phosphorus greater than 6.5 mg/dL had a 27% increase in mortality compared to patients with values of 2.6 to 6.4 mg/dL after adjustment for co-morbid conditions. A disturbing fact is that 39% of the patients were in this category. These findings were similar to another large study nearly a decade earlier. The cause of the increased mortality is uncertain, but it may be due to increased coronary, myocardial, and arterial calcifications and to cardiac conditions leading to death (see the section "Metastatic Calcification" following).

Factors that contribute to hyperphosphatemia in dialysis patients are noted in Table 73.3. In advanced uremia, dietary phosphorus intake in excess of 1.0 to 1.2 g/day may lead to hyperphosphatemia. With poor compliance with phosphorus-restricted diets, hyperphosphatemia will persist and will be resistant to phosphate binder therapy. If intake can be reduced to 800 to 1000 mg/day by modest dietary phosphorus restriction, serum phosphorus can be controlled with phosphate binders. The reduction of serum phosphorus toward normal is often associated with a small increase in serum calcium, a fall in serum PTH, and a reduced incidence of overt secondary HPT.

The aim of therapy with phosphate-binding agents is to reduce serum phosphorus to normal or near-normal levels; that is, between

Table 73–3

Factors Affecting Serum Phosphorus Levels

- Dietary phosphate intake
- Use of phosphate binders
- Frequency, duration, and efficiency of dialysis
- Administration of vitamin D analogues, particularly oral calcitriol
- Increased bone resorption in hyperparathyroidism

4.0 and 5.5 mg/dL. Dietary phosphorus intake should be restricted to 800 to 1000 mg/day, and phosphate binders should be taken with each meal and with large snacks. Serum calcium and phosphorus levels should be monitored at least monthly to permit appropriate dosage adjustment of phosphate-binding compounds. The available binders include sevelamer hydro-chloride (Renagel), calcium acetate (PhosLo), calcium carbonate, lanthanum carbonate (Fosrenol), magnesium carbonate, and aluminum-based binders. The aluminum-containing binders should be avoided because of the risk of aluminum-related bone disease and encephalopathy.

Sevelamer hydrochloride (Renagel) is a calcium- and aluminum-free polymer (cross-linked poly-allyl-amine hydrochloride), which is an effective phosphate binder. It also binds bile acids, which results in increased fecal bile acid excretion and a significant lowering of low-density (LDL) cholesterol. Because it is calcium free, the incidence of hypercalcemia is much lower than that seen with the calcium-based binders. The usual dose of sevelamer is 2 to 8 g/day, given in divided doses with meals and large snacks. The new 800-mg capsule makes compliance with these doses easier. A single supplemental oral calcium dose may be needed in some patients if hypocalcemia persists after hyperphosphatemia is controlled.

Recently, an increased incidence of coronary artery calcifications was described in patients undergoing dialysis. Patients with calcifications usually have higher serum phosphorus concentrations and a higher serum $Ca \times PO_4$ product, and their ingestion of calcium-containing phosphate binders is usually greater than that of patients without calcifications. This raises the concern that the ingestion of large amounts of calcium-containing binders and persistent poor control of hyperphosphatemia may have the adverse effect of contributing to coronary artery disease, a major cause of death in patients with ESRD. Sevelamer, being calcium free, may be beneficial in this regard. However, the effect of sevelamer on coronary artery calcification is not yet known.

Calcium acetate and calcium carbonate have been the mainstays of phosphate-binding therapy for the past decade. A major problem with these binders is the high incidence of hypercalcemia, particularly when calcitriol or another nonselective vitamin D analog is concomitantly administered to control HPT. Of the two, calcium acetate is the more effective binder. Approximately half the amount of calcium acetate is needed to bind similar amounts of phosphorus. Therefore, only half as much elemental calcium is ingested when calcium acetate is prescribed compared to calcium carbonate. As an alternative, the combination of magnesium

carbonate and calcium acetate (e.g., calcium acetate given with two meals and magnesium carbonate with one meal) can be used as phosphate binders. With this approach, serum phosphorus can be controlled and less calcium is ingested. Hypermagnesemia may develop, but it usually is not a clinical problem.

Lanthanum carbonate (Fosrenol) is a new noncalcium- and nonaluminium-based chewable phosphate binder for dialysis patients. Studies have shown that its tolerability and effectiveness in PTH suppression and in lowering the Ca × P product are at least comparable to standard therapy with calcium-based binders for up to 3 years of follow-up. Although lanthanum is a trace metal cation, its effects are not comparable to those of aluminum. Indeed, in clinical studies no toxic effect of it has been reported in up to 4 years of follow-up.

The bioavailability of lanthanum is extremely low, and the liver is the main route of its excretion. It can thus be localized in the lysosomes of hepatocytes. Unlike aluminum, lanthanum could not be detected in brain tissue. Treatment with Fosrenol was shown to be associated with normalization of bone histomorphometric parameters and a slower evolution toward low-turnover bone disease. Thus, it appears that lanthanum carbonate is a welcome phosphate binder for our ESRD patients because it is effective and safe. Despite prevention of hyperphosphatemia, secondary HPT persists or progresses in the majority of dialysis patients.

Calcium Concentration in Dialysate

The dialysate calcium concentration should be viewed as part of the integrated therapeutic regimen to control renal osteodystrophy and maintain normal mineral metabolism. The goals of this integrated approach are to keep the patient in a mild positive calcium balance, to maintain normal serum calcium levels, to control PTH levels to two to three times above normal values, and to avoid soft-tissue calcifications. Current clinical evidence suggests that a dialysate calcium concentration of 2.5 mEq/L is best for achieving these goals. Concomitant treatment with vitamin D and calcium-based phosphate binders contributes to a positive calcium balance. Dialysate calcium concentrations above this level may be harmful to patients.

Hemodialysis using a dialysate calcium of 3.5 mEq/L results in a significant load of calcium, which together with hyperphosphatemia may lead to extraskeletal calcification. Figure 73.2 shows the serum calcium levels during and after dialysis when a high-calcium (3.5 mEq/L) dialysate is used. As noted in Figure 73.2,

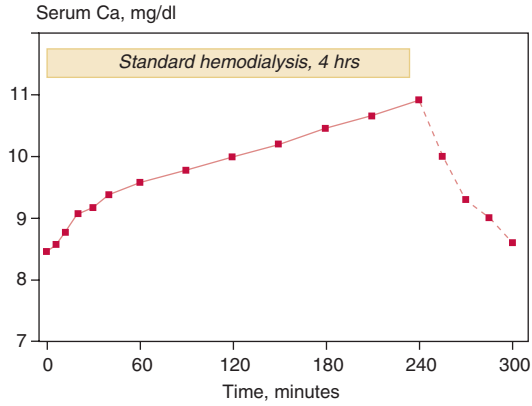


Figure 73–2

Serum calcium during and after dialysis with a high dialysate-calcium bath. Note the gradual rise in serum calcium during dialysis to mild hypercalcemia at the end of dialysis. Then, by 60 minutes postdialysis serum calcium drops precipitously to pre-dialysis levels.

the pre-dialysis borderline low serum calcium gradually rises during the 4-hour treatment and reaches mild hypercalcemia (11.0 mg/dL) at the end of dialysis. Then, 60 minutes postdialysis the serum calcium drops abruptly to 8.5 mg/dL—a value similar to that associated with pre-dialysis calcium. What is the fate of this calcium load? Some of it may be deposited in bone, but more likely it is deposited in soft tissues. Thus, the risks of soft-tissue calcifications seem to outweigh any potential benefit from transient hypercalcemia when high-calcium dialysates are used. Routine dialysis with high-calcium dialysates (3.5 mEq/L) should not be performed.

Dialysis with low dialysate-calcium concentrations may be beneficial in patients with evidence of severe soft-tissue calcifications (Figure 73.3). Massive periarticular calcifications have resolved with daily dialysis with low dialysate calcium concentrations of 1.0 to 1.5 mEq/L. Skin lesions from calciphylaxis may also improve with low-calcium dialysis (see the section "Metastatic Calcifications" following).

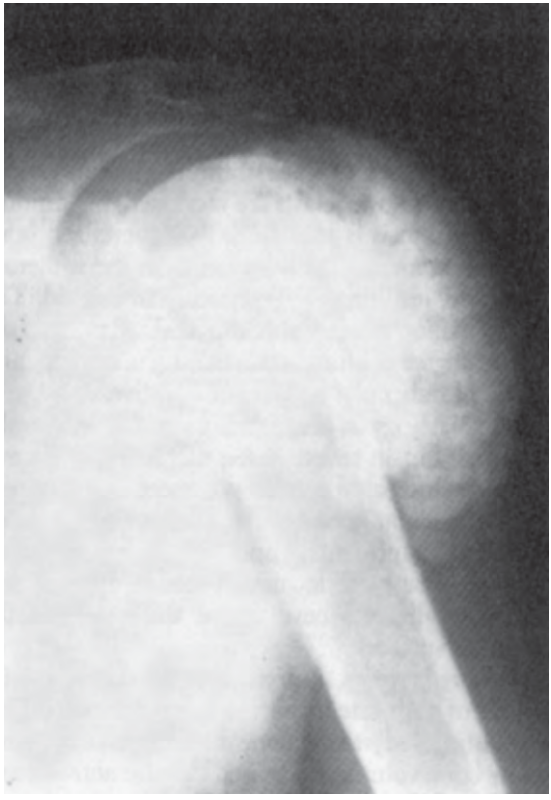


Figure 73–3

Right shoulder radiograph of a dialysis patient showing large periarticular calcifications.

Control of Hyperparathyroidism

It is not uncommon for overt HPT to persist and to worsen despite control of hyperphosphatemia by dietary phosphate restriction and phosphate-binder therapy. In the past, hypercalcemia was the only way of inhibiting PTH secretion. Then, in vitro and in vivo studies demonstrated that PTH secretion was directly inhibited by

calcitriol. Furthermore, patients with moderate renal failure were noted to have low levels of calcitriol that led to HPT. Thus, a deficit of calcitriol may be the most important factor in the pathogenesis of HPT and osteitis fibrosa.

It follows that most patients on dialysis should be treated with calcitriol at the start of dialytic therapy. The main criterion for treatment is the presence of an elevated PTH level (>200–250 pg/mL), as determined using IRMA. In addition, it is also important to consider keeping hemodialysis patients with normal PTH on low doses of vitamin D for the maintenance of normal bone formation. The suggested direct beneficial effects of vitamin D receptor (VDR) activation by vitamin D therapy in patients with chronic kidney disease include:

- Prevention of parathyroid gland hyperplasia
- Suppression of PTH synthesis
- Stimulation of calcium-sensing receptors (CaSRs) in parathyroid cells
- Maintenance of normal bone formation
- Decrease in renin and angiotensin II levels
- Reduction of proteinuria
- Improvement in immune function
- Enhancement of muscle mass/strength
- Decrease in mortality

Vitamin D Therapy

Most patients with chronic kidney disease have a low serum level of 1,25 $(OH)_2D_3$. The major contributor to this low level is reduction in kidney-specific 1-a-hydroxylase activity. The other etiologies are summarized in Table 73.4. Originally, various metabolites of vitamin D (cholecalciferol; see chapter on vitamin D sterols) were used in the treatment of dialysis patients. Table 73.5 lists the available vitamin D compounds for treatment in chronic kidney disease. Calcitriol, a naturally occurring hormone, emerged two decades ago as the therapy of choice. Abundant evidence showed that oral calcitriol (0.5–1 μg/day), if administered early, effectively controlled HPT.

Later, bolus intravenous injections of calcitriol became clinically available and constituted the main alternative for most patients when in vitro studies showed that PTH inhibition by calcitriol was dose dependent. Because serum calcitriol levels from IV calcitriol are substantially higher than those achieved with oral therapy, PTH suppression was noted to be greater with IV therapy. Even severe cases of HPT with PTH levels above

Table 73–4

Causes of Low Serum 1,25(OH)2D3 in Chronic Kidney Disease

- Reduced renal mass decreases 1α-hydroxylase activity
- Functional suppression of the 1α-hydroxylase by:
  - Hyperphosphatemia
  - Hyperuricemia
  - Metabolic acidosis
  - Other uremic toxins (xanthine, hypoxanthine)
- Low 25(OH) D_3 levels from:
  - Nutritional vitamin D deficiency (poor sunlight exposure, inadequate intake, age, dark skin)
  - Renal losses of 25(OH) D_3 due to proteinuria
  - Uremia-induced decreased skin photoconversion of 7-dehydrocholesterol
  - Low renal magalin levels from renal disease

Seminars in Dialysis 2005;18(4).

Table 73–5

Available vitamin D Compounds for Treatment in Chronic Kidney Disease

- Active (high affinity binding to vitamin D receptor)
- 1,25$(OH)_2D_3$ (calcitriol)
- 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol)
- Inactive (lack of high affinity binding to the vitamin D receptor)
- Vitamin D_2 (ergocalciferol): requires activation by liver and kidney
- Vitamin D_3 (cholecalciferol): requires activation by liver and kidney
- 25$(OH)D_3$ (calcifidol): requires activation by kidney
- 1a-$(OH)D_2$ (doxercalciferol): requires activation by liver
- 1a-$(OH)D_3$ (alphacalcidol): requires activation by liver

Seminars in Dialysis 2005;18(4).

2000 pg/mL can be effectively controlled after weeks to months of intravenous calcitriol therapy.

The starting IV dose of calcitriol should vary with the severity of HPT. Initial dosing guidelines, which are dependent on PTH levels, are outlined in Table 73.6. If the initial response is good and PTH levels decrease by 30 to 50% after 2 to 4 months of calcitriol therapy, the IV dose should be decreased by about 40

Table 73–6

Recommended Starting Doses of IV Calcitriol and Paricalcitol for the Treatment of Hyperparathyroidism Based on Serum PTH Levels[a]

Serum PTH (pg/ml)	Calcitriol (µg)	Paricalcitol (µg)
200–600	0.5–2	2–6
600–1200	2–4	6–12
1200–1800	4	12
>1800	4–6	12–18

a. PTH levels, calcium, and phosphorus levels must be monitored, and doses must be adjusted accordingly. See text for details.

to 50%. Further reductions should be done gradually, and even after a year of therapy the majority of patients need low maintenance doses. Another modality of calcitriol therapy is oral "pulse therapy." This consists of larger oral doses of calcitriol (2–6 µg) given two or three times a week. These higher oral doses achieve high blood levels of calcitriol, which theoretically result in greater suppression of PTH. Both oral and IV calcitriol induce a dramatic clinical improvement, an increase in serum calcium, and a progressive decrease in the serum level of alkaline phosphatase.

Alfacalcidol, 1a(OH)D3 is also effective in the prophylaxis and control of severe HPT. This synthetic form of calcitriol must be converted in the liver to calcitriol before it can exert its biologic activity. Both long- and short-term clinical trials prove its effectiveness. Hypercalcemia and hyperphosphatemia are common complications of vitamin D compounds. Not uncommonly, these complications limit or require the discontinuation of therapy. Some patients may become resistant to vitamin D, with the development of severe parathyroid hyperplasia. These problems led to a search for better vitamin D sterols that effectively inhibit PTH but have no or minimal calcemic or hyperphosphatemic actions.

Two vitamin D analogues with these properties were developed and are currently in clinical use: paricalcitol (19-nor-1a,25-dihydroxy-vitamin D_2, Zemplar), and doxercalciferol (1a-hydroxyvitamin D_2, Hectorol). Because the high incidence of hypercalcemia and hyperphosphatemia as well as a high Ca × P product have been associated with increased soft-tissue as well as coronary artery calcifications, new and more selective vitamin D analogues have been developed. Paricalcitol (a vitamin D

analogue) has such particular properties it is superior to calcitriol. Like calcitriol, paricalcitol effectively inhibits the parathyroid gland—but the development of hypercalcemia and hyperphosphatemia are less with paricalcitol.

Animal studies show that gut absorption of calcium and phosphorus and bone mobilization of these ions is 10 times less with paricalcitol than with calcitriol. A double-blind multicenter randomized controlled trial comparing the safety and effectiveness of IV paricalcitol and calcitriol in suppressing PTH concentration in hemodialysis patients has shown that paricalcitol dosed at a 4:1 ratio to calcitriol resulted in a more rapid decrease in PTH concentration. In addition, the incidence of hypercalcemia and/or calcium X phosphorus product of more than 75 in consecutive lab draws was shown to be significantly lower in a paricalcitol group.

The starting doses of paricalcitol are outlined in Table 73.6. For dosing purposes, comparable doses of paricalcitol to calcitriol are a ratio of 4:1. The use of paricalcitol is not a safeguard against hypercalcemia or hyperphosphatemia, and there are a small number of patients who do not respond to it with control of HPT. However, paricalcitol provides a much greater therapeutic window because of its lower inducement of hypercalcemia and hyperphosphatemia. There is evidence that suggests that initiating treatment with paricalcitol in hemodialysis patients results in fewer all-cause hospitalizations and improved hospitalization outcomes compared to calcitriol-treated patients. Thus, injectable paricalcitol should be the vitamin D therapy of choice to maximize PTH control and improve patient survival. Furthermore, two large independent cohort studies in chronic hemodialysis patients in the United States showed that patients treated with activated injectable paricalcitol had a significant survival advantage over a group of hemodialysis patients who did not receive it.

Currently, oral preparation of paricalcitol (Zemplar) is also available. It has been shown in three randomized placebo-controlled trials of either thrice-weekly or once-daily dosing regimen for 24 weeks that the Zemplar capsule was well tolerated and effectively decreased intact PTH levels, with minimal or no impact on calcium levels, phosphorus balance, and kidney function in patients with stages 3 and 4 chronic kidney disease.

Doxercalciferol (Hectorol) is another agent with proven efficacy in moderate and severe HPT. Double-blind preliminary studies show that the incidence of hypercalcemia is similar to calcitriol, and serum phosphorus levels increased in those patients treated with Hectorol compared to placebo-treated patients. There are oral and IV preparations of doxercalciferol.

Recognition of the complications of treatment with nonselective vitamin D compounds on calcium and phosphorus metabolism has led to the development of a new agent for treatment of secondary hyperparathyroidism in dialysis patients. Cinacalcet HCl is a calcimimetic agent that is agonistic of the calcium-sensing receptors (CaSRs) present on the surface of the parathyroid cells. Cinacalcet regulates PTH secretion by amplifying the CaSRs' sensitivity to extracellular calcium concentration and thus reducing PTH concentration. It also leads to a desirable and concomitant decrease of serum calcium and phosphorus. There is compelling evidence of long-term efficacy and safety of cinacalcet for the control of secondary hyperparathyroidism in dialysis patients. Thus, this agent is becoming standard therapy in ESRD patients with SHPT.

Parathyroidectomy

Parathyroidectomy (see corresponding chapter in this section) may be needed in severe and advanced cases of secondary HPT. However, it should be stressed that whenever nonemergent surgery is being considered a 2-month trial of high-dose IV paricalcitol or calcitriol should be attempted—because HPT may be controlled in some patients by this approach. Preliminary data suggest that the incidence of parathyroidectomy in patients with chronic kidney disease may be decreasing in the United States. This may be independent of changes in patients' characteristics. The effectiveness of medical therapy with new vitamin D analogues such as paricalcitol and the widespread use of cinacalcet may be the cause.

The indications for parathyroidectomy are listed in Table 73.7. Obviously, failure of all medical maneuvers to control HPT is usually the main indication. It is of utmost importance to establish the presence of high levels of intact PTH. Before surgery is planned, aluminum toxicity should be ruled out because parathyroidectomy results in a dramatic worsening of preexisting aluminum bone disease. If the patient has no history of exposure to aluminum and the plasma aluminum is less than 10 μg/L, aluminum toxicity is not a clinical concern. However, if there is a history of exposure to aluminum and if the plasma aluminum level is higher (especially if it is above 50 μg/L) aluminum bone disease is a strong possibility. In this case, a bone biopsy to evaluate for aluminum bone disease is mandatory prior to surgery. If aluminum bone disease is present, the patient should be treated with deferoxamine and should not undergo the parathyroidectomy.

Table 73–7

Indications for Parathyroidectomy

- Severe progressive overt osteitis fibrosa despite adequate medical management
- Persistent hypercalcemia associated with other mental symptoms or severe hypertension
- Severe hyperphosphatemia together with histologic and radiologic evidence of hyperparathyroidism
- Severe intractable pruritus associated with significant hyperparathyroidism
- Persistent severe soft-tissue calcification associated with hyperphosphatemia and evidence of hyperparathyroidism
- Idiopathic disseminated skin necrosis (calciphylaxis)
- Vertebral osteopenia

Surgical management of these patients requires an experienced surgeon, this being the single most important factor in patient outcome. The widely accepted procedures are subtotal parathyroidectomy, total parathyroidectomy, and total parathyroidectomy with autotransplantation of parathyroid tissue in the forearm. Recent reviews have shown similar outcomes with these procedures. Regardless of the type of surgery, the primary problem after parathyroidectomy is the recurrence of HPT—seen in about 10% of cases. In addition, in cases of autotransplantation malignancy-like changes in the transplanted tissue have been reported. Finally, a recent review of parathyroid autografts noted the occurrence of nodular hyperplasia and adenoma-like structures in the autograft tissue.

The postoperative course of parathyroidectomy is characterized by severe hypocalcemia and hypophosphatemia (the "hungry bone syndrome"). The severity of the hypocalcemia is directly related to the degree of HPT before surgery. If hypocalcemia does not occur, or if it is only mild, appropriate resection of the hyperplastic tissue may not have been performed and reexploration of the neck may be indicated. The hypocalcemia usually requires calcium replacement intravenously in large doses (400–800 mg/day). In addition, calcitriol is usually necessary (2–4 μg/day).

Metastatic Calcification

Metastatic calcifications (deposits of calcium in extraskeletal tissue) are particularly common in patients with ESRD, and their adverse

clinical effects have been until now generally underappreciated. Calcium deposits of the skin, cornea, and conjunctiva (and in the soft tissues and surrounding joints) can be easily identified. Visceral calcifications (in particular, cardiac calcifications) are more insidious, and their clinical implications are very serious. Calcifications of cardiac tissue have been reported in nearly 60% of dialysis patients at autopsy. These are found and are probably of greatest significance in the coronary arteries.

Coronary artery calcifications are much more common and more severe in patients on hemodialysis than in patients without renal failure. Noninvasive studies that use electron-beam computed tomography (EBCT) to detect coronary artery calcifications have illuminated this issue recently. EBCT is a fast technique with a high spatial and temporal resolution. In EBCT, the imaging is triggered by the patient's EKG rhythm—which makes it a tool well suited to cardiac imaging. Up to three images can be taken during diastole, and early coronary calcification is detected in high-resolution images. Calcification of atherosclerotic plaques is found in the advanced stages of plaque transformation.

The extent of calcification noted by this technique correlates well with the severity of atherosclerotic lesions detected by coronary angiography. Coronary artery calcifications detected by EBCT were found in the majority of patients on dialysis. Soft-tissue calcifications may be contributing to conduction abnormalities and arrhythmias, left ventricular dysfunction, aortic and mitral stenosis, ischemia, congestive heart failure, and death. Most studies have found correlations of calcifications with uncontrolled hyperphosphatemia, and an increased $Ca \times PO_4$ product. As mentioned previously, patients with larger intakes of oral calcium had a greater incidence of coronary artery calcifications.

These data suggest that long-term imbalances in calcium and phosphorus are factors in the development of cardiac calcifications. They also raise the concern that long-term treatment with high doses of calcium-based phosphate binders along with vitamin D therapy may contribute to these calcifications. Vigilant monitoring of serum calcium, phosphorus, and calcium-phosphorus product may reduce the incidence of cardiac calcification and its related morbidity and mortality.

Another serious problem of soft-tissue calcification is calcific uremic arteriolopathy (CUA), which is also known as calciphylaxis. These are necrotic skin lesions that usually present as painful violaceous mottling similar to livedo reticularis—or as painful nodules or panniculitis. The lesions may be in the distal extremities—involving the toes, fingers, or ankles ("acral" CUA)—or

they may be proximal, localized to the thighs or the buttocks ("proximal" CUA). Occasionally, they are bilateral and symmetric. As the lesions progress, they may become hemorrhagic—and deep ulcers may develop. Dry gangrenous digits can occur. Secondary infections and sepsis are common. The prognosis of patients with CUA is poor, especially proximal CUA, and many die from sepsis or ischemic events.

Recently, an increased occurrence of proximal CUA lesions has been described in morbidly obese dialysis patients (in particular, in white women). In one series, 57% of the patients with CUA were obese—with a body mass index (BMI) greater than 35 kg/m^2—whereas only 5% of the patients on hemodialysis were in this BMI category. We have noted similar findings: 15 of 18 patients with CUA were morbidly obese, most were women, and the lesions were predominantly proximal. Hypoalbuminemia and insulin-requiring diabetes may be additional risk factors.

Skin biopsies of these lesions show extensive calcium deposits within the arteriolar walls, endovascular fibrosis, and fat necrosis. Panniculitis is the most common lesion. The pathogenesis of CUA is unclear, but in the first descriptions it was linked to hypercalcemia, hyperphosphatemia, and HPT in the setting of uremia. The majority of the earlier cases described an uremic milieu together with a high $Ca \times PO_4$ product greater than 70 mg/dL. A link between CUA and HPT was supported by the early observations that parathyroidectomy dramatically improved the syndrome. Later, when PTH levels could be measured, severe HPT was present in many cases. The majority of these early descriptions were acral (distal) lesions.

Recent studies describe a somewhat different clinical picture. As mentioned, more patients are obese and have proximal (not acral) CUA—and the prognosis appears to be worse than for patients with typical acral lesions. In these patients, PTH levels are near-normal or only moderately elevated, and $Ca\ PO_4$ products are increased (>60 mg/dL). In patients without overt HPT, parathyroidectomy is of no benefit. However, improvements in such patients have been noted with frequent dialysis using a low-calcium dialysate.

Calciphylaxis appears to be an evolving entity. The combination of calcitriol together with a high intake of calcium mainly from calcium-containing phosphate binders and possibly from inappropriately high dialysate-calcium concentrations are most likely contributing to the high calcium content of the skin found in CUA. In patients considered at increased risk for CUA (patients with obesity, or with HPT and increased calcium × phosphorus products),

the use of calcium-containing phosphate binders should be avoided. In patients with CUA, the following therapy is recommended.

1. Stop oral calcium, use non calcium-containing binders, and try to control serum phosphorus to less than 6.0 mg/dL.
2. If the patient has laboratory evidence of overt HPT (intact PTH above 600 pg/mL), parathyroidectomy should be performed on an emergent basis.
3. If laboratory evidence of significant HPT is not present, daily (5 or 6 days a week) dialysis with a low calcium dialysate may be beneficial.
4. Debridement, local wound care, and antibiotic treatment are necessary.

Recommended Reading

Andress DL. Vitamin D treatment in chronic kidney disease. Semin Dial 2005;18:315–21.

Bushinsky DA (ed). *Differential Diagnosis of Renal Osteodystrophy*. Philadelphia: Lippincott-Raven, 1998.

Comprehensive coverage of the pathogenesis of renal osteodystrophy and its clinical aspects.

Coyne D, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. Am J Kidney Dis 2006;47:263–76.

Dobrez DG, et al. Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings. Nephrol Dial Transplant 2004;19:1174–81.

Friedman PA. PTH revisited. Kidney Int 2004;91:S13–19.

Gokal R, Hutchison A, Ritz E, Slatopolsky E (eds). Renal bone disease. Kidney International 1999;73.

This supplement highlights the findings of the current research in this field.

Llach F, Jordi B. Renal osteodystrophies. In Brenner BM, Rector FC (eds), *The Kidney*. Philadelphia: Saunders WB 2000;2103.

An encyclopedic approach to renal bone disease: causes, pathogenesis, clinical status, and therapy.

Moe SM, et al. Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 2005;20:2186–93.

Persy VP, et al. Lanthanum: A safe phosphate binder. Semin Dial 2006;19(3):195–99.

Ritz E. The clinical management of hyperphosphatemia. J Nephrol 2005;18:221–28.

Sprague SM, et al. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int 2003;63:1483–90.

Teng M, et al. Activated injectable vitamin D and hemodialysis survival: A historical cohort study. J Am Soc Nephrol 2005;16:1115–25.

Yudd M, Llach F. Renal osteodystrophy. In Owen WF, Pereira BJP, Sayegh MH (eds), *Dialysis and Transplantation: A Companion to Brenner and Rector's* The Kidney. Philadelphia: Saunders WB, 2000:253.

This chapter focuses on the clinical manifestations and treatment of renal osteodystrophy.

CHAPTER 74

Phosphate Binders

Laura Kooienga, MD; Antonio Bellasi, MD;
and Geoffrey A. Block, MD

Introduction

Hyperphosphatemia is associated with increased all-cause mortality, cardiovascular mortality, vascular calcification, and valvular calcification. Accordingly, the recommendations of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease (CKD) emphasize a strict control of serum phosphorus.

Recommendations include a target serum phosphorus less than 4.6 mg/dL in CKD stage 3 and 4 and between 3.5 and 5.5 mg/dL for those with CKD stage 5. Achieving these target levels (particularly in CKD stage 5) is challenging, is frequently unsuccessful, and typically requires a combination of dietary phosphorus restriction—removing phosphorus with thrice-weekly dialysis or daily peritoneal dialysis and reducing intestinal absorption with the use of phosphorus binders.

Phosphorus Overview and Balance

Phosphorus is the second most abundant element after calcium in the human body. Approximately 85% of phosphorus is located in bones and teeth, 14% is intracellular, and only 1% is extracellular. In normal adults, the fasting plasma phosphorus concentration ranges from 2.5 to 4.5 mg/dL (0.80–1.45 mmol/L). Under normal states, this represents the net balance of daily dietary intake, intestinal absorption, and urinary phosphate excretion. The average dietary intake of phosphorus ranges from 1000 to 1800 mg (18–36 mmol) per day. Important factors to consider in estimating patients' phosphorus intake include protein intake, phosphorus content of food, and phosphorus bioavailability.

Given that a highly significant correlation exists between dietary phosphorus intake and protein intake (Figure 74.1), foods high in phosphorus are typically those also high in protein (such as dairy products, meats, fish, and grain products). Bioavailability of phosphorus is greatly enhanced in processed foods, which

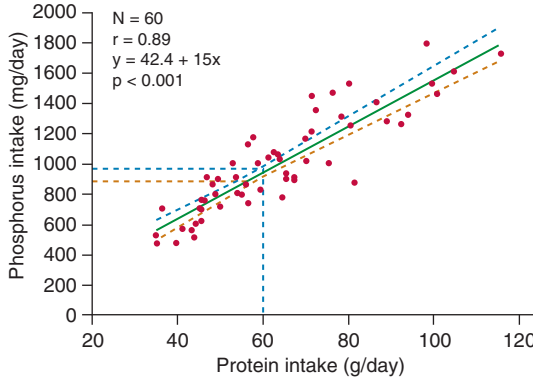


Figure 74–1

Relationship between dietary protein intake and phosphorus intake. *(Reprinted with permission from Rufino M, de Bonis E, Martin M, et al. Is it possible to control hyperphosphatemia with diet, without inducing protein malnutrition? Nephrol Dial Transplant 1998;13: 65–67.)*

contain added inorganic salts of phosphorus (polyphosphates and pyrophosphates). In contrast, plant sources contain phosphorus in the form of phytate—which requires the enzyme phytase, not present in humans, for absorption.

Intestinal absorption of phosphate occurs via a sodium-dependent phosphate co-transporter (NaPi-2b) and via a sodium-independent mechanism that occurs as a linear nonsaturable function of oral intake. Absorption of phosphorus is normally about 60% of that ingested. However, in the presence of active vitamin D absorption can be as high as 80% of that ingested or as low as 40% in the presence of phosphorus binders. Renal handling of phosphate occurs primarily by the type II-a sodium phosphate co-transporter (NaPi-2a) located in the luminal membrane of the proximal tubule.

The daily filtered load of phosphorus is approximately 4 to 8 g, and under normal conditions only 5 to 20% of the filtered phosphate is excreted. Dietary phosphorus intake, parathyroid hormone (PTH), $1\alpha,25(OH)_2D_3$, and more newly identified "phosphatonins" [such as fibroblast growth factor-23 (FGF-23), secreted frizzled related protein-4 (sFRP-4), fibroblast growth factor 7 (FGF-7), and matrix extracellular phosphoglycoprotein

(MEPE)] are key regulators of phosphorus reabsorption in the renal proximal tubule.

Hyperphosphatemia most commonly results from decreased urinary excretion as occurs in patients with both acute and chronic renal failure. Restriction of dietary phosphate alone is typically unsuccessful in normalizing phosphorus levels and often conflicts with the need to maintain adequate protein intake of 1.0 to 1.2 g/kg/day. In CKD, hyperphosphatemia is one of the factors responsible for the development of secondary hyperparathyroidism and mineral and bone disease (CKD-MBD). As glomerular filtration rate (GFR) declines, a compensatory elevated PTH level decreases proximal phosphate reabsorption—and hence maintains serum phosphorus within the normal range. However, as GFR further declines to about 20 to 25 mL/minute phosphate reabsorption is maximally suppressed and decreased phosphate reabsorption is no longer sufficient to balance that of intake. Thus, hyperphosphatemia ensues.

Phosphorus Binder Therapy

Phosphorus binders are frequently necessary to help lower serum phosphorus in patients with CKD. Binder selection is typically based on a variety of factors, including stage of CKD, co-morbid conditions, physician and patient preference, cost, binder tolerability, and compliance. A variety of agents have been used to create poorly soluble phosphorus complexes in the intestinal lumen. In doing so, they limit phosphorus absorption. Phosphorus binding of such agents is a function of dissolution of salt and pH.

Agents include aluminum salts, calcium salts, magnesium salts, lanthanum salts, and more recently non-aluminum/non-calcium agents. Unfortunately, essentially all of these agents are associated with significant side effects and/or limitations—contributing to the complexity and difficulty of managing hyperphosphatemia in patients with CKD.

Heavy Metal Compounds

Aluminum salts are highly effective phosphate binders, independent of pH. Unfortunately, they have systemic absorption and may result in dementia, encephalopathy, microcytic anemia, and osteomalacia. Although aluminum salts were standard therapy prior to 1985, they are currently of limited clinical utility and are typically used only as short-term therapy when other

means of controlling phosphorus have failed. Although some clinicians continue to use aluminum salts with regularity, it is generally well accepted that aluminum salts should be avoided in dialysis patients.

Like aluminum, lanthanum carbonate (LC) is another heavy metal that has recently received regulatory approval in Europe and the United States as a phosphate binder in dialysis patients. It is a rare earth element, effective in binding phosphate (doing so optimally at a pH of 3 to 5, but having binding activity at a pH of 1 to 7). In healthy individuals, it is normally detected only in trace amounts in the serum (with negligible intestinal absorption) and hence should have minimal potential for accumulation. Treatment with LC at doses of 500 to 3000 mg/day significantly reduces serum phosphate levels in a dose-related fashion (peak after 3 weeks of treatment), with a significantly lower incidence of hypercalcemia and calcium × phosphorus product compared to calcium-based binders.

LC generally has an adverse-event profile similar to placebo, although gastrointestinal complaints (nausea, vomiting, and diarrhea) are reported with increased frequency. Despite the reported very low systemic absorption of LC, recent reports describe an enhanced systemic absorption in uremic animals (5- to 10-fold increase compared to nonuremic animals). Furthermore, serum levels of lanthanum do not reflect tissue accumulation of LC and there is concern regarding progressive liver accumulation. Short-term effects of LC on bone histomorphometry have not shown evidence of adynamic bone disease. However, given LC similarity to aluminum its long-term effects on bone histology remain uncertain.

Overall, LC is a highly effective non-calcium/non-aluminum phosphate binder with a reasonable short-term safety profile. New formulations of LC (1000-mg tablet) have been developed that may help decrease pill burden and result in increased compliance and improved phosphate control. However, ongoing studies are needed to verify its long-term safety and role (if any) in attenuating vascular calcification.

Calcium-Based Compounds

After the discovery of the detrimental effects of aluminum-based binders, calcium-based binders became the most commonly prescribed phosphate binders. Calcium carbonate and calcium acetate are widely available and relatively inexpensive, but have a lower affinity for phosphorus compared to aluminum compounds.

Calcium salts require an acidic environment for dissolution, binding phosphorus optimally at a pH of greater than 5. Hence, they often require larger doses (as high as 20 g/day) involving an increased number of pills in order to achieve a satisfactory control of phosphate. In addition, they provide a substantial calcium load and increase the risk of hypercalcemia—especially in the setting of concomitant active vitamin D administration. More recently they have been implicated in the molecular mechanism underlying vascular calcification (VC), with potential synergy with phosphate in promoting calcification through enhanced expression of the sodium and phosphate co-transporter Pit-1 on the surface of vascular smooth muscle cells.

Unfortunately, serum calcium levels poorly predict the risk of VC because they do not correlate well with overall calcium load and may not reflect transient episodes of hypercalcemia. Several investigators have reported an association between increasing prescribed doses of calcium salts and VC progression. NKF-K/DOQI guidelines currently recommend not exceeding 1500 mg of elemental calcium intake per day from phosphorus binders. However, progression of calcification can also be seen in patients treated with calcium-based binders in the absence of a high calcium load. This was demonstrated in the Treat to Goal Study, in which progression of coronary artery and aortic calcification occurred in subjects treated with calcium acetate and carbonate with average elemental doses of calcium of about 1.2 g/day and 1.5 g/day (Figure 74.2).

Despite the low cost and widespread availability of calcium-containing binders, they have not significantly improved phosphorus control in patients receiving dialysis over the last two decades. In addition, they increase calcium burden, increase the risk of hypercalcemia, increase the progression of VC, and are likely ultimately to be associated with increased mortality. It is for these reasons they should be considered second-line therapy for the control of serum phosphorus.

Nonabsorbable Polymers

Sevelamer hydrochloride was the first non-aluminum/non-calcium–based phosphate binder developed for the management of hyperphosphatemia in ESRD. This synthetic ion-exchange polymer is as effective as calcium-containing binders in controlling phosphorus (Figure 74.3) and is generally well tolerated—with an adverse event profile similar to placebo. Its major drawbacks are the large pill burden, gastrointestinal side effects,

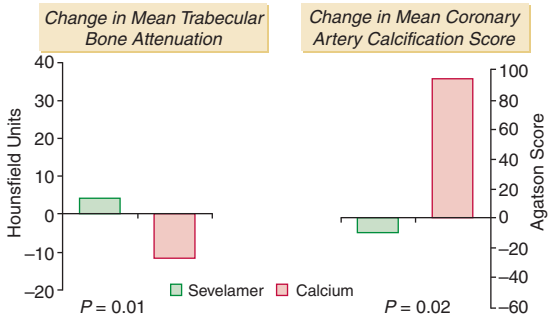


Figure 74–2

Change in mean trabecular bone attenuation and mean coronary artery calcification score based on treatment with sevelamer or calcium binder. *(Reprinted with permission from Raggi P, James G, Burke SK, et al. Decrease in thoracic vertebral bone attenuation with calcium-based phosphate binders in hemodialysis. J Bone Miner Res 2005;20:764–72.)*

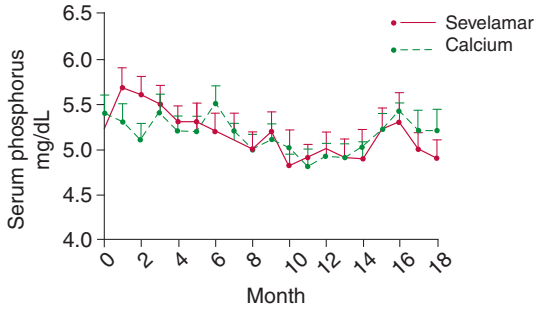


Figure 74–3

Average phosphorus control by month for treatment groups with Sevelamar and calcium binders. *(Reprinted with permission from Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815–24.)*

and high cost. However, when compared to other phosphorus binders sevelamer offers several advantages—including fewer hypercalcemic episodes, avoidance of a calcium load, an ability to lower total cholesterol and low-density lipoprotein (LDL) cholesterol, an anti-inflammatory effect, the ability to reduce uric acid levels, and a favorable effect on bone mineral attenuation (Figure 74.2).

Furthermore, in two recent randomized clinical trials including incident and prevalent HD patients receiving treatment for 12 to 18 months with sevelamer or calcium-based binders a significant reduction in the progression of coronary artery calcification was observed in the sevelamer-treated patients. Overall, the available data suggests that the clinical advantages of sevelamer support its use as a first-line phosphate binder in patients with CKD stage 5. It remains to be seen whether alternative (non–calcium-containing) phosphate binders have similar aggregate benefits.

Magnesium-Based Binders

Magnesium compounds such as magnesium hydroxide, magnesium carbonate, fixed-dose combinations of magnesium carbonate and calcium carbonate—as well as magnesium-containing mixed metal hydroxyl-carbonate compounds (see material following)—have been studied as phosphorus binders. Some authors have speculated that magnesium has a poorer gastrointestinal absorption relative to calcium and that hence more elemental magnesium relative to elemental calcium is available to bind phosphorus. However, in clinical studies magnesium hydroxide has been found to be a less potent binder of phosphorus than most calcium salts—with significant systemic absorption resulting in mild to moderate hypermagnesemia, diarrhea, and a tendency toward hyperkalemia.

Given the risk of hypermagnesemia, the use of magnesium-containing binders is currently restricted to CKD patients on dialysis. In this population, the use of magnesium-free dialysate to help avoid hypermagnesemia is poorly tolerated. However, standard magnesium (0.9 mg/dL) or low-magnesium dialysate concentrations (0.6 mg/dL) have been used successfully and are tolerated well. A recent small study found that a combination of magnesium carbonate and calcium carbonate can achieve equivalent phosphorus control with less elemental calcium absorption and lower pill burden per meal compared to calcium acetate alone.

Current formulations of magnesium salts such as magnesium carbonate and fixed-dose combinations are generally well tolerated, and the resulting hypermagnesemia can be controlled with standard or low-magnesium dialysate. They offer an alternative to calcium-based binders and a means of decreasing the dose of calcium binders. In addition, they have the potential benefit of inhibiting vascular calcification. Meema et al. found that elevated serum magnesium concentrations were associated with a reduced incidence of arterial and mitral valve calcifications. More research is needed to further define the potential risks and benefits of magnesium binders in determining their role in the CKD population.

Future Binders

Several new compounds are being investigated as future phosphate binders. These include ferric compounds (which consist of simple iron salts such as ferric citrate, ferric chloride, ferric ammonium citrate, and ferrihydrite) and complex compounds—such as cross-linked iron dextran [iron (III) oxide-hydroxide-modified dextran], stabilized polynuclear iron hydroxide, and cross-linked iron (III) chitosan. These compounds have consistently demonstrated the ability to bind phosphorus and reduce intestinal absorption, appear to be well tolerated, and have only a small amount of systemic absorption—which could be of benefit in a patient population prone to functional iron deficiency. Furthermore, compounds such as iron (III) chitosan may have an additional effect of lowering serum cholesterol.

Another newer class of binders known as mixed metal hydroxyl-carbonate compounds (MMH) consists of synthesized compounds that incorporate iron with either calcium or magnesium to bind phosphorus through a physicochemical reaction. An in vitro study found that iron- and magnesium-containing compounds had higher phosphorus binding capacity than iron- and calcium-containing compounds, which in turn had a higher phosphorus binding capacity than either magnesium hydroxide or calcium carbonate. Furthermore, they demonstrated that in rats there was little absorption of iron or magnesium from these compounds and hence no changes in iron studies or hypermagnesemia. Based on these studies, ferric compounds and MMH appear promising—with several potential advantages over conventional binders. These are undergoing further investigation.

Other agents potentially advantageous in managing phosphorus are nicotinamide, extended-release nicotinic acid, and MCI-196

(colestilan). Nicotinamide is a nicotinic acid derivative that in a rat model has been found to inhibit sodium-dependent phosphorus co-transport via the NaPi-2b transporter located in the intestinal brush border membrane. Correspondingly, extended-release nicotinic acid in a short-term clinical trial of 34 hemodialysis patients was found to significantly lower serum phosphorus and Ca × P product. Similar to sevelamer, MCI-196 (colestilan) is a nonabsorbed anion-exchange resin that decreases cholesterol levels by bile acid adsorption through the gastrointestinal tract.

MCI-196 has been found to decrease urinary phosphorus excretion rates and increase fecal phosphorus excretion in healthy volunteers. In a double-blind randomized placebo-controlled short-term trial in Japan, MCI-196 was found to significantly reduce serum phosphorus, Ca × P product, intact PTH, and LDL cholesterol compared with placebo—whereas serum calcium was unchanged. Both nicotinamide/nicotinic acid and MCI-196 warrant additional longer-term trials to investigate their safety and efficacy as adequate phosphate binders for dialysis patients.

Dialytic Control of Hyperphosphatemia

Even with optimal dietary phosphorus compliance, and use of phosphorus binders in conjunction with conventional hemodialysis (CHD), neutral phosphorus balance is difficult to obtain. Aside from dialysis duration and frequency, the major determinants of dialytic phosphate removal are dialyzer surface area and pre-dialysis serum phosphate level. This is in part due to the complex elimination kinetics of phosphorus. Within the first 60 to 90 minutes of initiation of hemodialysis there is a rapid reduction in serum phosphorus level, followed by a decreased phosphorus gradient between the plasma and dialysate—with resulting less-efficient transfer. Throughout the duration of the treatment, the rate-limiting step in phosphorus removal is the relatively slow movement of phosphorus from intracellular pools to the extracellular pool.

A large rebound of phosphorus occurs after the termination of dialysis, reaching about 80% of pre-dialysis serum phosphorus values. Phosphorus removal with a standard 4-hour hemodialysis treatment ranges between 600 and 1200 mg (1800–3600 mg/week), and with continuous ambulatory peritoneal dialysis averages 300 to 360 mg/day (2100–2520 mg/week). This amount is not substantially different as used by different dialyzers or types of renal replacement therapy or with buffer used in dialysate. Two alternatives to CHD are short daily hemodialysis

(defined as 3-hour sessions six times per week) and nocturnal hemodialysis, which is typically performed six nights per week for 8 to 10 hours while patients are sleeping. Both alternatives to CHD enhance phosphorus removal, and in some patients allow for an increased dietary phosphorus intake with a decreased requirement for phosphate binders (if required at all).

Calcimimetics as Phosphate-Modifying Agents

Cinacalcet is a type II calcimimetic agent that binds the transmembrane region of the calcium-sensing receptor, resulting in allosteric modulation. The change in receptor configuration makes it more sensitive to serum calcium and results in a reduction of serum PTH at lower levels of serum calcium. Although cinacalcet is not primarily used to lower serum phosphorus, clinical trials incorporating cinacalcet for the treatment of secondary hyperparathyroidism have consistently shown an improvement in both phosphorus and calcium × phosphorus product. Lowering of serum phosphorus by approximately 10% is seen quite rapidly after the introduction of cinacalcet and is evident even in patients with only mildly elevated PTH levels (300–500 pg/mL).

This clinically meaningful reduction in serum phosphorus occurs against a backdrop of no change in dietary habits, no change in phosphate binder therapy, and no change in dialysis frequency or intensity. Thus, this effect presumably represents the contribution of PTH-mediated release of phosphorus from bone. Although classically attributed to severe tertiary hyperparathyroidism and/or use of active vitamin D, phosphorus (and calcium) efflux from bone is undoubtedly contributing to the difficulties in adequately controlling serum phosphorus. Hence, the incorporation of cinacalcet into the treatment plan for secondary hyperparathyroidism could result in even further improvements in phosphorus control.

Summary

Given the emerging body of evidence associating hyperphosphatemia in CKD patients with increased all-cause and CV mortality, it seems reasonable to assume that the most favorable outcomes will be in the setting of normalized (3.0–4.5 mg/dL) phosphorus levels. Undoubtedly, phosphorus binders play a critical role in achieving this goal and often require intensive and meal-specific titrations.

It is important to avoid calcium binders in those with vascular calcification and to prevent transient episodes of hypercalcemia in all patients. Overall, the short-term toxicities of our treatments must not outweigh the long-term benefits of lowering phosphorus. Hopefully, with improvements in both dialysis methods and with the advent of better agents to lower phosphorus improvements can be made to the presently disheartening mortality rate of patients with ESRD.

Recommended Reading

Albaaj F, Hutchison AJ. Lanthanum carbonate (Fosrenol (R)): a novel agent for the treatment of hyperphosphataemia in renal failure and dialysis patients. Int J of Clinical Practice 2005;59:1091–1096.

This article provides a thorough review of lanthanum carbonate. It details its metabolism, effect on serum phosphorus level, calcium phosphate product, PTH, and bone as well as its safety and tolerability.

Ayus JC, Achinger SG, Mizani MR, et al. Phosphorus balance and mineral metabolism with 3 h daily hemodialysis. Kidney Int 2007;71:336–342.

An excellent prospective, non-randomized, controlled study which examined weekly dialytic phosphorus removal, phosphorus binder requirement, and achievement of mineral metabolism goals in subjects on daily hemodialysis compared to those on conventional hemodialysis.

Block GA, Spiegel DM, Ehrlich J et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815–1824.

An open label study of 129 patients new to hemodialysis randomized to treatment with a calcium containing phosphate binder or sevelamer over an 18 month observation period. Despite similar control of serum phosphorus those patients receiving a calcium containing binder with at least mild coronary artery calcification had a significantly greater and more rapid progression of their calcification when compared to the sevelamer treated patients. Those patients without coronary calcification at the time of initiated hemodialysis showed little development of calcification despite binder treatment.

Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002;62:245–252.

This is a well designed multi-center randomized controlled trial of 200 hemodialysis patients comparing sevelamer and calcium-based phosphate binders. Although the control of serum phosphorus was equivalent in both arms, those subjects which received calcium containing binders were found to have more episodes of hypercalcemia and had significant progression of coronary artery and aortic calcification as compared to those treated with sevelamer.

Cupisti A, Morelli E, D'Alessandro C et al. Phosphate control in chronic uremia: don't forget diet. J Nephrol 2003;16:29–33.

An excellent review article on the dietary management of phosphorus as part of an integrated approach to managing hyperphosphatemia in dialysis patients. This article details basic concepts of the phosphate content of common foods to help minimize phosphorus intake while maintaining adequate protein intake in dialysis patients prone to both hyperphosphatemia and protein malnutrition.

Li X, Yang H-Y, Giachelli C. Role of sodium-dependant phosphate cotransporter pit -1 in vascular smooth muscle cell calcification. Circ Res 2006;98:905–912.

A fascinating study confirming the complex and highly regulated cellular mechanisms of vascular calcification. It illustrates the critical role of phosphate uptake via the sodium-dependent phosphate cotransporter, Pit-1, in calcification of immortalized human smooth muscle cells.

Moe SM, Chertow GM, Coburn JW et al. Achieving NKF-K/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCI. Kidney Int 2005;67:760–771.

A secondary analysis of data combined from three similarly designed placebo-controlled, double-blind studies involving a total of 1136 subjects on chronic hemodialysis. This study demonstrated that in subjects on dialysis with secondary hyperparathyroidism cinacalcet effectively lowers iPTH, calcium, phosphorus, calcium phosphate product and hence increases the proportion of patients achieving NKF-K/DOQI targets.

Sherman, RA. Dietary phosphate restriction and protein intake in dialysis patients: A misdirected focus. Semin Dial 2007;20:16–18.

A brief article emphasizing the importance of phosphate-containing food additives as a potential therapeutic target in the control of hyperphosphatemia in dialysis patients.

CHAPTER 75

Use of Vitamin D Sterols in Patients with ESRD

Kevin J. Martin, MD, and Esther A. Gonzalez, MD

Chronic kidney disease is commonly complicated by disturbances in mineral metabolism that begin early in the course of chronic kidney diseases and progress as kidney function is reduced. A major part of these disturbances in mineral metabolism is the development of secondary hyperparathyroidism. Detailed investigations over the last three decades have uncovered the major pathogenetic factors involved in the generation and maintenance of secondary hyperparathyroidism. These include the retention of phosphorus as a consequence of decreased glomerular filtration rate and the impaired ability of the diseased kidney to produce the active vitamin D sterol calcitriol.

Both of these factors may act directly and/or as a result of their effects on the levels of serum calcium to contribute to the generation and maintenance of hyperparathyroidism and to facilitate parathyroid growth. The consequences of hyperparathyroidism are important with regard to both skeletal and extraskeletal effects, and accordingly this abnormality needs to be controlled in patients with decreased kidney function. As a result of a series of careful investigations that have uncovered the pathogenetic factors, therapies have been designed to target these abnormalities in order to control hyperparathyroidism. In general, these measures involve a multifaceted approach; namely, to provide calcium supplementation, to prescribe phosphate binders to control hyperphosphatemia, to administer vitamin D sterols, and to use calcimimetic agents. These strategies are often used in combination to achieve the control of hyperparathyroidism.

Because decreases in calcitriol production play a major role in initiating and maintaining secondary hyperparathyroidism, it is rational to include the use of vitamin D sterols as part of its treatment. In addition, because it has been established that vitamin D deficiency occurs commonly in chronic kidney disease it is desirable to correct this deficiency early in the course of kidney disease if possible. However, many patients are first seen when kidney disease is advanced, and supplementation with vitamin D (which can achieve normalization of 25-hydroxyvitamin D

levels) cannot overcome reduced ability of the remnant kidney to produce the active sterol calcitriol. Accordingly, in advanced kidney disease the use of these active sterols has major therapeutic benefits.

The Use of Calcitriol

Calcitriol, or 1,25-dihydroxyvitamin D_3, is the most active metabolite of vitamin D and has been shown to have many direct effects on parathyroid function—including suppression of PTH gene transcription, regulation of the parathyroid vitamin D receptor, increased expression of the calcium-sensing receptor, regulation of parathyroid cell growth, and possibly alteration of the set-point for calcium-regulated PTH secretion. These direct effects of calcitriol on the parathyroid emphasize the sound rationale for the inclusion of calcitriol in a treatment regimen. Calcitriol, however, has a major effect in increasing the absorption of calcium in the intestine—which may contribute to hypercalcemia.

It has also been demonstrated that calcitriol increases phosphorus absorption in the intestine, and this action can aggravate hyperphosphatemia—which is undesirable, both from the point of view of stimulating secondary hyperparathyroidism and from facilitating extraskeletal calcifications. Accordingly, when calcitriol is used it is important that the dosage be regulated to avoid such toxicities. Larger doses, however, are often utilized to control established hyperparathyroidism—and in these circumstances the therapeutic window between efficacy for the suppression of hyperparathyroidism and toxicity manifested by hypercalcemia and/or hyperphosphatemia is rather narrow. Accordingly, efforts were undertaken to try to minimize the toxicity of calcitriol while maintaining the beneficial effects on parathyroid function.

An early attempt to minimize calcitriol toxicity was to administer the sterol intravenously and intermittently with the goal of achieving suppression of parathyroid function and minimizing the toxicity. Some support for this idea was obtained in experimental animals, and it has achieved some support in clinical investigations in patients—which have shown that intravenous administration is somewhat more effective than oral administration and may have somewhat lesser toxicity. The therapeutic window still remains narrow, and further investigations sought to decrease the toxicities and widen the therapeutic window by structural alterations of the vitamin D sterol. These vitamin D sterols are listed in Table 75.1.

Table 75–1

Therapeutic Active Vitamin D Sterols

• 1,25-dihydroxyvitamin D_3	Calcitriol
Vitamin D Prohormones	
• 1-α-hydroxyvitamin D_3	Alfacalcidol
• 1-α-hydroxyvitamin D_2	Doxercalciferol
Vitamin D Analogs	
• 22-oxa-1,25-dihydroxyvitamin D_3	Maxacalcitol
• 26,27-hexafluoro-1,25-dihydroxyvitamin D_3	Falecalcitriol
• 19-nor-1,25-dihydroxyvitamin D_3	Paricalcitol

Vitamin D Prohormones: Alfacalcidol and Doxercalciferol

The vitamin D prohormone 1-α-hydroxyvitamin D_3 (alfacalcidol) is widely used throughout the world for the control of hyperparathyroidism and is most commonly administered orally, although intravenous preparations are also available. This vitamin D sterol becomes 25-hydroxylated by the hepatic 25-hydroxylase, and results therefore in the production of 1,25-dihydroxyvitamin D_3 (calcitriol). The use of this vitamin D prohormone appears to be equivalent to the use of calcitriol and is equally effective. However, it does not demonstrate any effect in decreasing potential toxicity.

More recently, 1-α-hydroxyvitamin D_2 (doxercalciferol) has been introduced. This vitamin D sterol, based on the vitamin D_2 structure, also becomes hydroxylated in the 25 position by the hepatic 25-hydroxylase and results in the production of 1,25-dihydroxyvitamin D_2. The sterols alfacalcidol and doxercalciferol have been investigated in detail in experimental animals, in which they were shown to be equivalent in ability to increase calcium and phosphorus absorption from the intestine and to raise serum calcium. However, an important observation was made that when administered at high dosage the sterol based on the vitamin D_2 structure appeared to have lesser toxicity.

This is now thought to be the result of alternative degradative pathways for sterols with the vitamin D_2 structure. Accordingly, it appeared that there may be potential benefit from the use of vitamin D_2–based sterols because of the lesser toxicity seen at high doses. In experimental animals in the therapeutic range,

there appears to be little difference between the vitamin D_2– and vitamin D_3–based sterols in terms of their ability to increase serum calcium or phosphate and decrease PTH. In clinical studies, intravenous 1-α-hydroxyvitamin D_2 has been shown to be effective in suppression of PTH—although it should be noted that there was significant calcemic and phosphatemic effect of this sterol in clinical trials. In these clinical trials, it was also noted that the intravenous administration appeared to be somewhat less toxic than oral administration.

Vitamin D Analogues

In an effort to maintain the efficacy of vitamin D sterols on the parathyroid and to find ways to minimize the toxicities of such therapies, structural alterations of vitamin D were undertaken to develop compounds that might have lesser toxicities and retain the efficacy on suppression of PTH. Thus, the goal was to try to find vitamin D analogues that might be relatively selective for the parathyroid effects. Currently, experimental and clinical evidence has been obtained for three such vitamin D analogues, which are in use for the treatment of secondary hyperparathyroidism. Others remain under development.

The vitamin D analogues in clinical use are 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol), 22-oxacalcitriol, and falecalcitriol. 22-oxacalcitriol (maxacalcitol) has an oxygen inserted at position 22 that results in decreased affinity for the vitamin D receptor, as well as for the vitamin D binding protein. This results in very rapid clearance from the circulation and may account for the lesser calcemic and phosphatemic effects. This analogue is in clinical use in Asia, but significant hypercalcemic effects are still seen. Falecalcitriol has fluoride substituted at carbons 26 and 27, which results in a very prolonged biological action. However, in clinical studies falecalcitriol has been shown to effectively suppress PTH.

19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol) lacks the exocyclic carbon of position 19, and has been studied extensively in experimental animals. It has been shown to suppress PTH in vivo and in vitro, with a potency close to that of calcitriol. In experimental animals, this vitamin D analogue was effective in suppressing PTH with less hypercalcemia and hyperphosphatemia than calcitriol. In the experimental setting, paricalcitol was found to be approximately 10 times less active than calcitriol in mobilizing calcium or phosphate from bone—and was much less effective in increasing calcium absorption from the intestine.

Interestingly, paricalcitol administration did not result in the upregulation of the vitamin D receptor in the intestine of experimental animals, in marked contrast to the effects seen with calcitriol—possibly accounting for the lesser toxicity of the analogue. Because of the results of these experimental studies, extensive clinical trials were conducted in patients on hemodialysis. In these trials, paricalcitol administered intravenously was found to markedly reduce PTH levels with minimal changes in calcium and phosphorus. Hypercalcemia was still seen, however, in some patients—but it appeared to occur only when PTH was suppressed to levels regarded as excessively low and may have been associated with low bone turnover, which can predispose to hypercalcemia.

Clinical studies have also been conducted to try to validate whether the relative selectivity of paricalcitol could be demonstrated in patients, as it was in experimental animals. In clinical studies, paricalcitol suppressed PTH quite effectively and was similar in efficacy to calcitriol. However, additional studies have shown that paricalcitol appears to be less effective than calcitriol in producing hypercalcemia—results that are similar to those seen in experimental animals. In clinical trials, studies by Sprague and others also demonstrated a lesser phosphatemic ability of paricalcitol—suggesting that the relative selectivity of this analogue is also demonstrable in patients.

Recent studies have also suggested that mortality in patients receiving the vitamin D analogue paricalcitol may be decreased compared to patients treated with calcitriol. The mechanism for this effect is not clear at the present time. Further studies are required to analyze the potential mechanisms involved. Further studies also need to examine whether the mechanism is due to the lesser calcemic or phosphatemic effects or whether improved patient outcomes are potentially due to the other effects of vitamin D sterols on systems unrelated to mineral metabolism, for which there is mounting evidence.

Recommended Reading

Dusso AS, Brown AJ, et al. Vitamin D. Am J Physiol Renal Physiol 2005;289(1): F8–28.

An excellent review of the metabolism of vitamin D and the systemic and paracrine actions of vitamin D, which details not only the classical effects of vitamin but describes the many nonclassical actions of the vitamin D system.

Martin KJ, González EA, et al. 19-Nor-1-a-25-Dihydroxyvitamin D2 (paricalcitol) safely and effectively reduces the levels of intact PTH in patients on hemodialysis. Journal of the American Society of Nephrology 1998;9(2):1427–32.

Review of a clinical trial of paricalcitol that demonstrates the effective suppression of PTH values with minimal changes in serum calcium or phosphorus.

Maung HM, Elangovan L, et al. Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison. Am J Kidney Dis 2001;37(3):532–43.

Review of clinical trials of both oral and intravenous doxercalciferol for the treatment of secondary hyperparathyroidism, showing that both routes of administration are effective (with the intravenous form being associated with less hypercalcemia than oral administration).

Sprague SM, Llach F, et al. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int 2003;63(4):1483–90.

A comparison of paricalcitriol and calcitriol showing the decreased toxicity of the vitamin D analogue.

Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003;349:446–56.

An intriguing observation showing that there appears to be a decrease in mortality in patients on hemodialysis who receive paricalcitol compared to those who receive calcitriol. This suggests a clinical benefit of the vitamin D analogue.

CHAPTER 76

Aluminum-Related Bone Disease in Dialysis Patients

William G. Goodman, MD

In the 1970s and early 1980s, aluminum toxicity was a common cause of metabolic bone disease among patients undergoing dialysis regularly. During this interval, aluminum toxicity played a pathogenic role in 20 to 40% of cases of renal osteodystrophy—resulting predominantly in the skeletal lesions of osteomalacia and adynamic bone. Because excretion in the urine is the primary route by which aluminum is eliminated from the body, patients with chronic kidney disease (CKD) stage 5 who have little or no residual renal function are at risk of developing aluminum retention and aluminum toxicity by two primary mechanisms.

Among those treated with hemodialysis, the use of inadequately purified water to prepare hemodialysis solutions can lead to intense parenteral aluminum exposure over several months or a few years. This epidemic form of aluminum exposure can also cause a distinct type of encephalopathy known as dialysis encephalopathy (or dialysis dementia). In contrast, aluminum loading may occur more gradually over many years in dialysis patients who ingest large amounts of aluminum-containing phosphate-binding medications to manage phosphorus retention and control hyperphosphatemia. Encephalopathy is uncommon in such patients, whereas aluminum-related bone disease (either alone or together with anemia) is the predominant finding clinically.

After the two major causes of aluminum loading were identified, the clinical management of patients with end-stage renal disease was modified in several important ways. First, water purification by reverse osmosis made it possible to produce dialysate with sufficiently low concentrations of aluminum to avoid parenteral aluminum loading during hemodialysis. The routine surveillance of aluminum levels in dialysate and in water processed by reverse osmosis (together with periodic serum aluminum determinations in patients undergoing hemodialysis regularly) provides ongoing assurance that water purification methods remain adequate.

Second, the use of calcium-containing compounds such as calcium carbonate and calcium acetate (rather than aluminum-

containing compounds) to manage phosphate retention among patients with CKD circumvents the potential for ongoing aluminum loading via the gastrointestinal route. These interventions have markedly reduced the prevalence of aluminum-related bone disease in the general dialysis population, and the disorder is now uncommon in economically developed countries in which adequate but costly water purification methods are used widely. The potential for aluminum loading and bone aluminum toxicity remains, however, in economically less-well-developed countries—where health care resources may be inadequate to implement effective and reliable methods of water purification for hemodialysis.

Despite these developments, aluminum-related bone disease remains an important consideration in the differential diagnosis of renal osteodystrophy—particularly among patients who have undergone dialysis for many years, in those with substantial previous exposure to aluminum-containing medications, and in patients who continue to ingest aluminum-containing compounds. Aluminum hydroxide is still used as a phosphate-binding agent in some patients with CKD. It is a potent phosphate-binding agent, and concerns have grown about the role of calcium-containing compounds as contributors to the development of soft-tissue and vascular calcification among patients undergoing long-term dialysis. The discussion that follows summarizes the clinical, biochemical, and histologic features of aluminum-related bone disease—and provides recommendations about prevention, diagnosis, and treatment.

Histology of Aluminum-Related Bone Disease

Osteomalacia and the adynamic lesion of renal osteodystrophy are the two most common histopathologic manifestations of aluminum-related bone disease. Indeed, adynamic renal osteodystrophy was described originally in association with bone aluminum toxicity. However, other causes now account for most cases of adynamic bone among patients with CKD. These include hypoparathyroidism, diabetes mellitus, age-related or postmenopausal osteoporosis, treatment with corticosteroids, malnutrition, immobilization, the use of large oral doses of calcium to manage phosphate retention, and the treatment of secondary hyperparathyroidism with large intermittent doses of calcitriol.

The histologic features of adynamic renal osteodystrophy include normal or reduced amounts of osteoid, which is unmineralized bone collagen. Osteoid seams are often thinner than normal, and the extent of trabecular bone surface covered with osteoid is diminished. These features differ strikingly from those of classical osteomalacia, in which osteoid seams are thickened and osteoid-covered bone surfaces are abundant. The number of osteoblasts and the number of osteoclasts are reduced in the adynamic lesion—changes that reflect overall reductions in bone formation and bone resorption. Bone formation is either subnormal or cannot be measured when assessed using the technique of double-tetracycline labeling because bone collagen synthesis by osteoblasts and mineralization are markedly diminished. Histologic evidence of hyperparathyroidism is absent. There is thus no peritrabecular or marrow fibrosis.

When adynamic renal osteodystrophy is due to bone aluminum toxicity, deposits of aluminum can be identified along trabecular bone surfaces using specific histochemical staining methods. Typically, more than 20 to 30% of the total trabecular surface stains positive for aluminum. Bone aluminum levels, as measured by flameless atomic absorption spectrometry, are also elevated. Values are higher in tissues obtained from patients with adynamic bone than in samples from patients with other types of renal bone disease, such as secondary hyperparathyroidism. Bone aluminum levels tend to be lower, however, in the adynamic form of aluminum-related bone disease than in aluminum-related osteomalacia. Such findings suggest that the adynamic lesion precedes the development of overt osteomalacia as bone aluminum accumulation progresses over time.

The skeletal lesion of osteomalacia is characterized by the presence of excess amounts of unmineralized osteoid due to a defect in skeletal mineralization. Osteoid seams are wide, and most have a lamellar or multilaminated appearance. The fraction of the trabecular bone surface covered with osteoid is also greater than normal. The number of osteoblasts is typically reduced, and most have a flattened cellular profile characteristic of inactive (resting) osteoblasts. Bone collagen synthesis and mineralization are both diminished, but mineralization is affected disproportionately. This disparity accounts for the accumulation of unmineralized osteoid and for the increase in osteoid seam thickness. Bone formation often cannot be measured because the uptake of tetracycline into bone is reduced markedly—an abnormality due not only to reductions in the number of

sites of new bone formation but also to a defect in the mineralization of bone matrix.

Patients with aluminum-related osteomalacia have very high bone aluminum levels when measured by biochemical methods. Deposits of aluminum can be demonstrated by histochemical staining methods in the calcification front immediately adjacent to osteoid seams, and within cement lines deeper within trabecular bone. The histologic severity of osteomalacia generally corresponds to the extent of trabecular bone surface that stains positive for aluminum.

As noted previously for adynamic renal osteodystrophy, bone aluminum toxicity is currently an uncommon cause of osteomalacia among patients with CKD stage 5 who are treated with dialysis. Other causes (such as persistent hypocalcemia, persistent hypophosphatemia, and/or nutritional vitamin D deficiency) account for the development of osteomalacia in patients who exhibit no biochemical or histochemical evidence of bone aluminum deposition.

The mixed lesion of renal osteodystrophy is a distinct subtype of renal bone disease with histologic features of both osteomalacia and hyperparathyroidism. The latter component is due to persistently high plasma parathyroid hormone (PTH) levels as a result of secondary hyperparathyroidism, whereas the osteomalacic component can be due to bone aluminum accumulation. The mixed lesion of renal osteodystrophy can thus represent a transitional skeletal lesion in patients who have a history of secondary hyperparathyroidism but who are accumulating aluminum in bone and developing aluminum-related bone disease. Conversely, mixed renal osteodystrophy is seen in some patients who develop secondary hyperparathyroidism after aluminum-related bone disease has been treated effectively.

Among patients with established aluminum-related bone disease, deposits of aluminum can be demonstrated by histochemical staining methods along 25 to 30% or more of trabecular bone surfaces. The extent of bone aluminum deposition is often considerably greater. Lesser amounts of surface-stainable aluminum indicate that substantial aluminum deposition has occurred, but most patients with values less than 20% do not have histopathologic evidence of bone aluminum toxicity as judged by disturbances in either bone formation or mineralization. Such patients are at risk of developing aluminum-related bone disease if aluminum loading continues, but other causes of osteomalacia and adynamic renal osteodystrophy are more likely when there is

little or no histochemical evidence of bone aluminum deposition on bone biopsy.

Aluminum Toxicity in ESRD Patients

Two distinct types of bone aluminum toxicity are seen clinically among patients undergoing maintenance dialysis. The epidemic type of aluminum-related bone disease results from exposures to large amounts of aluminum over relatively short periods. It occurs most often in patients treated with hemodialysis when inadequately purified water is used to generate dialysis solutions. Aluminum is found commonly in municipal water supplies, and reverse osmosis is the only highly effective method of removing it from water used to prepare dialysate. If aluminum is present in hemodialysis solutions, it is transferred readily across dialysis membranes into plasma during each treatment—where it is bound to plasma proteins and subsequently deposited in tissues such as bone and liver.

The syndrome of dialysis encephalopathy (dialysis dementia) is not uncommon with epidemic parenteral aluminum exposures. Acute or subacute aluminum intoxication can occur, however, if intestinal aluminum absorption is facilitated by the adminisration of citrate together with large doses of aluminum-containing medications. Citrate markedly increases the solubility of aluminum in aqueous solutions, and promotes aluminum transport across the intestinal epithelium. Bone disease can be a prominent finding in patients with the epidemic form of aluminum toxicity, but its presence may be overlooked because progressive dementia, seizures, myoclonus, and severe dysarthria dominate the clinical picture in cases of dialysis encephalopathy.

The endemic form of aluminum-related bone disease arises due to the gradual and progressive accumulation of aluminum in bone over extended periods. The disorder is a consequence of the long-term use of aluminum-containing phosphate-binding agents, which account for most cases of aluminum-related bone disease in developed countries.

Musculoskeletal manifestations predominate in the endemic form of aluminum toxicity, and dialysis encephalopathy is uncommon. In some patients, the clinical signs and symptoms of bone disease are unremarkable despite extensive bone aluminum deposition. As a result, aluminum-related bone disease must be considered in the differential diagnosis of renal bone disease among patients with few overt clinical manifestations. The

endemic form of bone aluminum toxicity is more common among patients with diabetes, in those who have undergone parathyroidectomy previously, among patients who have had a renal transplant with subsequent graft failure, and in those who have undergone bilateral nephrectomy.

Clinical Features

Bone pain is a prominent feature of aluminum-related bone disease, and muscle pain and weakness are common. These manifestations are often progressive. Patients may be unable to ambulate and may become confined to a bed or wheelchair. Muscle pain and weakness also occur in cases of advanced secondary hyperparathyroidism, but severe involvement is more typical of aluminum-related bone disease. In persons affected less severely, the presence of muscle aches, joint stiffness, and bone pain does not serve to distinguish between aluminum-related bone disease and secondary hyperparathyroidism.

Pathologic fractures can occur either spontaneously or after minor trauma in patients with aluminum-related bone disease. Fractures affect the axial skeleton, predominantly involving the ribs, vertebrae, pelvis, and hips. Healing is often delayed, and skeletal radiographs may show a poorly mineralized bone callus at sites of previous fracture.

Biochemical Features

Hypercalcemia is a common biochemical finding among patients with aluminum-related bone disease. It can occur in both osteomalacia and adynamic bone. Hypercalcemia may develop spontaneously, when patients are immobilized in bed during hospitalization, or after the administration of small oral doses of calcitriol or calcium-containing medications. Serum calcium levels become elevated in patients with aluminum-related bone disease because the uptake of calcium from plasma into bone is impaired. The same mechanism accounts for episodes of hypercalcemia among patients with adynamic renal osteodystrophy without bone aluminum accumulation.

Other causes of hypercalcemia that are not due to bone aluminum toxicity among patients undergoing dialysis include advanced secondary hyperparathyroidism, granulomatous diseases such as sarcoidosis or tuberculosis that result in extrarenal calcitriol production, treatment with calcitriol or other vitamin D sterols, and the ingestion of large amounts of calcium-containing

compounds. Indeed, hypercalcemia develops in as many as half of those who use large oral doses of calcium as a phosphate-binding agent.

Serum alkaline phosphatase levels are a reasonable index of the severity of secondary hyperparathyroidism among patients with CKD stage 5, but such measurements are of limited value in distinguishing between hyperparathyroidism and aluminum-related bone disease. Values are increased only minimally or remain normal in the epidemic form of aluminum-related bone disease. However, serum alkaline phosphates levels may be substantially elevated in the endemic form. Nevertheless, increases in serum alkaline phosphatase levels often occur during the successful treatment of aluminum-related bone disease—a finding that may reflect improvements in osteoblastic activity and skeletal remodeling. Measurements of bone-specific alkaline phosphatase rather than serum total alkaline phosphatase may be more useful in distinguishing between the high-turnover skeletal lesions of secondary hyperparathyroidism and the low-turnover lesions due to bone aluminum toxicity.

The utility of serum PTH measurements among patients with renal osteodystrophy depends largely on the type of assay used. Several assays for PTH are available commercially, but the relationship between bone histology and plasma PTH levels has been documented in only a few of them. Assessments must be made with an understanding of the relationship between plasma PTH levels (as determined by any particular assay) and the histologic features in bone.

Plasma PTH levels are often elevated only minimally among patients with aluminum-related bone disease, and values may fall within the normal reference range. Such findings differ strikingly from the marked elevations that characterize patients with overt secondary hyperparathyroidism. This biochemical feature may help to distinguish between the low-turnover skeletal lesions associated with bone aluminum toxicity and the high-turnover lesions of secondary hyperparathyroidism. In this regard, the double antibody immunoradiometric assays for PTH currently used by most clinical laboratories are far superior to older mid-region or carboxyterminal radioimmunoassays.

Although plasma PTH levels are generally lower among patients with aluminum-related bone disease than in those with other histologic subtypes of renal osteodystrophy, values remain elevated in some patients. A high serum PTH level thus does not exclude the diagnosis of aluminum-related bone disease. Moreover, adynamic renal osteodystrophy can develop in patients undergoing

dialysis regularly without evidence of bone aluminum deposition. Such individuals have normal or reduced plasma PTH levels, with values similar to those seen in cases of aluminum-related bone disease. A normal or low plasma PTH level cannot be taken as evidence of aluminum-related bone disease without evidence of bone aluminum deposition as confirmed by bone biopsy.

Plasma aluminum levels are often elevated modestly in patients with CKD and in those treated with maintenance dialysis. Values are usually below 15 μg/L, but levels of 20 to 40 μg/L are not uncommon. In patients treated in dialysis centers with adequate water purification, plasma aluminum levels are affected predominantly by the amounts of aluminum ingested during the several weeks or months immediately before blood samples are obtained. Aluminum 1evels in plasma do not reflect tissue stores, and measurements are of limited value in the diagnosis of aluminum-related bone disease. Results that consistently exceed 50 μg/L are a cause for concern, however, and they suggest some degree of aluminum loading in the recent past.

The deferoxamine (DFO) infusion test has been used by some investigators as a noninvasive tool for the diagnosis of aluminum-related bone disease. In asymptomatic patients, the magnitude of the increase in plasma aluminum after an intravenous infusion of DFO was not specific for patients with the disorder. Plasma aluminum levels also rose in patients with secondary hyperparathyroidism who had previously been taking aluminum-containing medications and who had little or no evidence of bone aluminum deposition. In contrast, a low plasma PTH level together with an increment in plasma aluminum exceeding 300 μg/L was useful in identifying patients with symptomatic aluminum-related bone disease.

Radiographic Features

The radiographic features of aluminum-related bone disease are much less striking than those of secondary hyperparathyroidism, and skeletal radiographs are often of little value in differential diagnosis. Pseudofractures are seen in some patients with aluminum-related osteomalacia. Subperiosteal erosions are a characteristic feature of osteitis fibrosa, but they may also be seen in patients with aluminum-related osteomalacia. The finding probably indicates that defective skeletal mineralization due to bone aluminum toxicity has precluded the resolution of pre-existing radiographic changes of secondary hyperparathyroidism. Fractures of the ribs and hips and compression frac-

tures of the vertebral bodies are more common among patients with aluminum-related osteomalacia than in patients with hyperparathyroidism.

Bone scans may reveal pseudofractures or extraskeletal calcifications, and localized increases in radioisotope uptake can occur in areas of fracture healing. Patients with secondary hyperparathyroidism typically have marked and symmetric increases in radioisotope activity throughout the skeleton. In contrast, the uptake of radioisotope into bone is often diminished in patients with aluminum-related bone disease. Despite these general trends, the findings on bone scan often do not correspond to bone histology among patients with CKD. Bone scintigraphy is thus of limited diagnostic value in renal osteodystrophy.

Diagnosis

Bone biopsy remains the definitive method of establishing a diagnosis of aluminum-related bone disease. Biopsy specimens should be obtained after double-tetracycline labeling to permit an assessment of bone cell activity, to evaluate the dynamics of skeletal mineralization, and to obtain direct measurements of the rate of bone formation. Histopathologic evidence of bone aluminum toxicity should be present. Such evidence includes reductions in the numbers of osteoblasts and osteoclasts, diminished rates of bone formation, and evidence of impaired mineralization. There must also be evidence of substantial aluminum deposition in bone, as judged by histochemical staining methods. Deposits of aluminum along 25 to 30% or more of trabecular bone surfaces are typical in aluminum-related bone disease.

Prevention and Treatment

The administration of aluminum-containing medications, specifically aluminum-based phosphate-binding agents, to patients undergoing regular dialysis should generally be avoided—particularly among children. If used as alternatives to calcium-containing compounds, these agents should be given for several weeks only (or for a few months at most). The concurrent administration of citrate-containing compounds must be avoided in anyone ingesting aluminum.

Calcium carbonate and calcium acetate are used extensively as aluminum-free phosphate-binding agents among patients with CKD. Both compounds are reasonably effective for this purpose,

but episodes of hypercalcemia are not uncommon. Moreover, the use of large oral doses of calcium has been implicated as a cause of vascular and soft-tissue calcification among patients undergoing dialysis regularly. For these reasons, current guidelines recommend that the daily intake of calcium be limited to 2000 mg (including dietary and medicinal sources) among patients undergoing dialysis.

Fortunately, aluminum-free phosphate-binding compounds such as sevelamer and lanthanum carbonate are available for use clinically. Other aluminum-free/calcium-free compounds are also being developed. It is thus no longer necessary to employ aluminum-containing phosphate-binding agents to manage phosphorus retention among patients with CKD.

The adequacy of water purification procedures in dialysis facilities must be documented by routine surveillance procedures, which include regular measurements of the aluminum concentration in dialysate and in water that has been purified during the preparation of dialysate solutions. Values should be less than 10 μg/L. Serum aluminum levels should also be measured periodically to detect inadvertent aluminum exposures from ingested sources. This is most often due to the use of aluminum-containing medications. When a number of patients in a single dialysis facility are found to have elevated plasma aluminum levels, technical errors in water purification are usually responsible.

When the diagnosis of aluminum-related bone disease has been established, any further use of aluminum-containing medications must be avoided. Similar measures should be taken in patients with bone biopsy evidence of tissue aluminum deposition, even in the absence of overt histopathologic changes of aluminum-related bone disease. Such patients should be asked about potential sources of citrate ingestion, which can markedly enhance aluminum absorption from the gastrointestinal tract.

Aluminum is extensively bound to plasma and tissue proteins. Only 10 to 15% of aluminum in plasma is available for ultrafiltration and removal by dialysis. As such, net aluminum removal during conventional hemodialysis is quite limited. DFO can mobilize aluminum from tissues, and its use increases the amount aluminum removed with each hemodialysis procedure. In the past, DFO was used commonly to treat aluminum intoxication and aluminum-related bone disease. More conservative measures should be employed, however, in all but the most severely affected patients because of certain untoward effects associated with DFO therapy (see material following).

When aluminum-containing medications are withdrawn, the amount of aluminum that can be detected in bone by histochemical staining methods decreases over 6 to 12 months. Such changes are associated with histologic improvement and with increases in the rate of bone formation. Treatment with DFO is thus not required in most patients with aluminum-related bone disease when the clinical manifestations are not severe and when additional aluminum exposure can be avoided.

In severely affected individuals, treatment with DFO for 4 to 12 months can substantially reduce the amount of aluminum in bone as measured by histochemical methods. Clinical, biochemical, and histologic improvements also occur. It remains uncertain, however, whether aluminum-related bone disease improves more rapidly in patients given DFO than in those who are managed conservatively by eliminating all potential sources of aluminum loading.

Several reports indicate that infections with *Yersinia* species occur more commonly among dialysis patients with aluminum-related bone disease who are treated with DFO. Fatal *Rhizopus* infections involving the central nervous system can develop. The overall risk of these serious complications is not well documented, but the decision to use DFO in this therapeutic context must be made carefully. Treatment with DFO should be limited to patients with life-threatening manifestations of dialysis encephalopathy, with severe manifestations of aluminum-related bone disease, or with aluminum-related bone disease that has not responded previously to conservative measures.

Bone biopsy should be repeated after 6 to 9 months of treatment to determine the interval change in bone aluminum deposition and to document the histologic response to treatment. Double-tetracycline labeling should be done to assess changes in osteoblastic activity and in bone formation. If the amount of aluminum detectable by histochemical staining has decreased substantially and if the histologic features of bone aluminum toxicity have diminished, DFO should be discontinued. Any further use of aluminum-containing medications should be avoided.

Recommended Reading

Andress DL, Nebeker HG, Ott SM, et al. Bone histologic response to deferoxamine in aluminum-related bone disease. Kidney Int 1987;31:1344–50.
A detailed description of the skeletal response to treatment with deferoxamine in dialysis patients with aluminum-related bone disease.
Coburn JW, Norris KC, Nebeker HG. Osteomalacia and bone disease arising from aluminum. Semin Nephrol 1986;6:68–89.

A thorough discussion of aluminum metabolism among patients with CKD and an overview of the role of aluminum in the pathogenesis of renal bone disease.

Goodman WG, Leite Duarte ME. Aluminum: Effects on bone and role in the pathogenesis of renal osteodystrophy. Miner Electrolyte Metab 1991;17:221–32.

A detailed discussion of the mechanisms by which aluminum alters bone metabolism.

CHAPTER 77

Management of Aluminum Toxicity

Antonios H. Tzamaloukas, MD, and Dominic S.C. Raj, MD

Patients on chronic dialysis (hemodialysis or peritoneal dialysis), and to a lesser extent those with impaired renal function but not yet on dialysis, are at risk of aluminum accumulation because of increased body load through gastrointestinal intake and of high aluminum concentration in the dialysate and decreased renal excretion. Compounding these factors, the capacity of regular hemodialysis to remove aluminum is greatly limited by the binding of this metal to serum transferrin. Aluminum accumulation is the cause of clinical manifestations, including a characteristic form of metabolic osteodystrophy, encephalopathy, and anemia. This chapter reviews the clinical and pathologic features of aluminum toxicity and discusses its treatment and prevention.

Clinical and Pathologic Features of Aluminum Osteodystrophy

The cardinal clinical features of aluminum osteodystrophy include severe and progressive bone pain (particularly in the axial skeleton), proximal muscle weakness, and pathologic fractures (primarily in the hips, ribs, pelvis, and vertebrae). Multiple fractures may lead to bone deformities and severe infirmity. In comparison to patients with osteitis fibrosa cystica, those with aluminum osteodystrophy tend to have higher serum calcium (with a tendency to develop hypercalcemia) and lower serum parathyroid hormone and alkaline phosphatase levels—whereas serum phosphorus concentration does not differ between the two groups. Extraosseous calcifications, including arterial wall deposits and tumoral calcifications, have been described in both groups.

Histologically, aluminum osteodystrophy is manifested by high aluminum content in bone—measured by histochemistry (auryl-tricarboxylic acid), atomic absorption spectroscopy, neutron activation analysis, or electron probe—and by two characteristic lesions. These two lesions are low rate of osteoid synthesis

and a defect of mineral deposition at the ossification front, the degree of which seems to exceed the degree of the defect in osteoid synthesis—resulting in a histology picture resembling that of osteomalacia. Double-tetracycline labeling brings into focus the very low rate of osteoid synthesis. The severity of the osteodystrophy parallels the aluminum burden of the bone. The histologic lesions of aluminum osteodystrophy are similar to the lesions of adynamic or aplastic bone disease, with the difference that aluminum bone deposits are light or absent in pure aplastic bone disease.

Manifestations of Aluminum Encephalopathy and Anemia

Aluminum toxicity was implicated in the majority of the cases of "dialysis dementia," a frequently fatal condition characterized by dyspraxia, progressive dementia, facial grimacing, myoclonus, asterixis, and convulsions. These symptoms in early cases tended to occur only during the later stages of hemodialysis session, but subsequently became permanent. The distinctive electroencephalogram showed diffuse multifocal slow waves (theta waves) interrupted by synchronous high-voltage complexes of slow, sharp, triphasic and spike waves.

The anemia of aluminum toxicity is not severe and has the hypochromic and microcystic morphologic features of iron deficiency. The pathogenesis of the anemia seems to involve impaired transfer of iron from transferrin into the bone marrow precursors of erythrocytes and inhibition of incorporation of iron into heme. Higher-than-usual doses of erythropoietin are required to overcome the anemia of aluminum intoxication.

Diagnosis and Treatment of Aluminum Toxicity

Although the definitive diagnosis of aluminum osteodystrophy requires a bone biopsy with double-tetracycline labeling and staining for aluminum, serum aluminum levels (measured preferentially by atomic absorption spectrometry) are the practical means of making this diagnosis. This approach to the determination of whole-body aluminum burden is complicated by the fact that the distribution of aluminum in plasma and the organs (principal among which are the bones, brain, liver, and heart) varies. Very high serum aluminum levels may result from a recent exposure and may not reflect total body burden. It is best,

therefore, that serum aluminum levels be measured some time (at least 2 months) after removal of all exposure to aluminum.

Normal levels of serum aluminum are <10 μg/L, whereas levels >100 μg/L in the absence of recent exposure are seen in patients with aluminum osteodystrophy or encephalopathy. Some patients with severe hyperparathyroidism may have serum aluminum levels >100 μg/L without a large load of aluminum in the bones. However, these patients may be at risk of developing aluminum osteodystrophy after parathyroidectomy.

The diagnosis of aluminum toxicity is more difficult in patients with serum aluminum levels below 100 μg/L. In such patients, the increment in serum aluminum after a dose of 1 g of deferoxamine (DFO) intravenously may be of help. The highest sensitivity of the DFO test in detecting large aluminum body burdens was reported in patients with relatively low serum PTH (parathyroid hormone) levels and baseline serum aluminum between 40 and 100 μg/L who had a rise in serum aluminum >150 μg/L after DFO infusion. Bone biopsy with aluminum staining, which is the only way to make the definitive diagnosis of aluminum osteodystrophy, is practically restricted to cases with diagnostic uncertainties.

The treatment of aluminum toxicity consists of removal of the sources of aluminum loading (see material on prevention of aluminum toxicity following) and repeated intravenous infusions of DFO. Removal of all sources of aluminum in the diet and the dialysate is the cornerstone of the prevention and management of aluminum toxicity. DFO chelates aluminum and leads to removal of aluminum from the tissues. The aluminum-DFO complex, which has a molecular weight of approximately 600 daltons, is removed by dialysis. Infusion of DFO seems to displace aluminum from the tissues rather than from the aluminum-transferrin serum complex. Therefore, serum aluminum levels in patients with aluminum toxicity increase after DFO infusion and return to pre-DFO levels only after several hemodialysis sessions.

For this reason, infusions of DFO should be performed no more frequently than once weekly—and should be accompanied by regular monitoring of serum aluminum levels. The capacity of continuous ambulatory peritoneal dialysis to remove aluminum is greater than that of the older, cellulose-based hemodialysis membranes. Newer, high-flux hemodialysis membranes exhibit substantially higher clearance rates for the aluminum-DFO complex than the older membranes.

Concomitantly with the rise in serum aluminum levels after DFO infusion, several patients were reported to have developed progressive neurologic symptoms—including seizures, coma,

and death. Therefore, patients with highly elevated baseline serum aluminum levels (>200 μg/L) should be first subjected to complete withdrawal of aluminum for several weeks and should be started at much lower DFO doses (0.25–0.5 g per infusion). In addition, the infusion of DFO—at least when the baseline serum aluminum levels are very high—should occur shortly (hours) before a hemodialysis session rather than at the end of the previous dialysis session.

DFO treatment has potentially severe side effects, in addition to the risk of acute neurotoxicity. Severe hypotension was reported in a number of patients. Slowing of the rate of the infusion, in some instances over the entire duration of a hemodialysis session, improves this complication. Cataracts, retinal abnormalities, and acute auditory neurotoxicity have been reported in a small number of patients. Another small number of patients developed hypersensitivity reactions to DFO. Desensitization should be considered in sensitized patients with severe symptomatic aluminum toxicity. Iron deficiency may also develop during prolonged DFO treatment, leading to temporary discontinuation of the DFO infusions and intravenous iron therapy.

DFO therapy may cause severe infections. DFO administration leads to formation of feroxamine, a chelate of iron. Feroxamine is normally eliminated by the kidneys, and its half-life is greatly prolonged in patients with renal failure. Certain microorganisms, particularly *Rhizopus* species, have receptors for feroxamine—which is used by these organisms as a siderophore to promote their growth and pathogenicity. Life-threatening infections due to *Rhizopus* (mucormycosis), *Yersinia*, and *Salmonella* developed in dialysis patients treated with DFO. Dialysis patients with mucormycosis, either disseminated or of the rhinocerebral variety, follow a rapidly worsening course despite amphotericin—with a case fatality rate of approximately 90%. Many cases were diagnosed only at autopsy. In most instances, patients developing mucormycosis had been treated with DFO for several months. However, there were case reports of mucormycosis developing in dialysis patients with much shorter exposures.

Because of its risks, DFO therapy should in general be limited to patients with symptomatic neuropathy or symptomatic aluminum osteodystrophy. DFO may also be considered for patients with a positive DFO loading test. However, in this second category of patients elimination of the sources of aluminum and monitoring of the clinical manifestations and of serum aluminum levels may be the more prudent approach.

Awareness of aluminum toxicities and of the potential sources of aluminum has led to virtual elimination of the need for DFO treatment in many dialysis units.

Prevention of Aluminum Toxicity

Prevention of aluminum toxicity can be effectively accomplished today. The sources of aluminum burden are either the tap water used for hemodialysis baths or absorption of aluminum from the gastrointestinal tract. Tap water contains high concentrations of aluminum in certain areas [for example, in places where alum is added to surface reservoirs to remove particulate matter or where acid rain (which increases the solubility of several aluminum salts) causes higher aluminum concentrations in surface water]. Epidemics of encephalopathy and pathologic fractures in clusters were described in patients dialyzed in areas with high concentrations of aluminum in tap water.

The American Association for the Advancement of Medical Instrumentation mandates periodic measurement of aluminum concentration in the dialysate and recommends that this concentration be kept at levels below 5 μg/L. "Ultrapure" dialysate with even lower aluminum concentrations is advocated by several nephrologists and may be of particular benefit for patients on quotidian hemodialysis who are exposed to the dialysate more frequently than patients on the traditional thrice-weekly schedule.

Purification of tap water used to construct the dialysate is necessary to maintain the recommended low dialysate aluminum levels. The most effective method of removing aluminum from tap water is reverse osmosis. In situations in which the aluminum concentration in tap water exceeds 100 μg/L, tap water should be passed through a deionizer before being processed by the reverse osmosis machine. Monitoring for aluminum loading involves periodic measurement of aluminum concentration in the dialysate, as noted, but also in the serum of the patients on chronic dialysis. Checking of purification systems and frequent measurement of tap water and dialysate aluminum concentration should be performed in dialysis units in which serum aluminum levels increase in all or a large majority of patients. If only a few patients in a dialysis unit have rises in their serum aluminum, increased intake and/or absorption of aluminum from the gastrointestinal tract should be suspected.

A main gastrointestinal source of aluminum has been the aluminum gels that constituted the primary oral phosphate binders

for decades. Chronic ingestion of these gels in large quantities led to considerable absorption of aluminum and clinical manifestations of aluminum toxicity, usually in the form of osteodystrophy with multiple pathologic fractures. In addition to gels used as phosphate binders, Sucralfate has a high aluminum content.

Citrate ingestion, as citric acid or citrate salts, markedly (more than 10-fold) augments the absorption of aluminum. Citrate ingestion can result from a prescription medication (e.g., Shohl's solution or Bicitra for the treatment of metabolic acidosis; calcium citrate as a phosphate binder), an over-the-counter medication (e.g., Alka Seltzer), or excessive intake of citrus fruit or juices (e.g., orange juice). Uremia also appears to increase the absorption of the ingested aluminum, through the effects of elevated PTH (which, however, seems to have a protective effect on the bones), administration of calcitriol, or other mechanisms. In addition to parathyroidectomy, iron deficiency, prolonged glucocorticoid ingestion, diabetes mellitus, and bilateral nephrectomy seem to increase the risk of aluminum osteodystrophy. Aluminum toxicities in patients without renal failure can result from intravenous infusions (for example, from infusion of oral solutions of methadone) or from inhalation of toxic fumes.

Currently, there is no place for chronic administration of aluminum-based antacids as phosphate binders to patients with chronic renal failure. Brief (2 weeks or shorter) courses of aluminum gels may be justified for starting the treatment of severe hyperphosphatemia. Prevention of hyperphosphatemia is currently based on the use of calcium salts and sevelamer. Lanthanum carbonate, which was recently introduced, has expanded the number of available oral phosphate binders. With the purification of the dialysate, the avoidance of ingestion of large aluminum loads, and the monitoring of aluminum levels in dialysate and serum, aluminum osteodystrophy is expected to acquire only historical significance in the near future.

Recommended Reading

Ackrill P, Ralston AJ, Hodge K. Successful removal of aluminum from patients with dialysis encephalopathy (letter). Lancet 1980;2:692–93.
Clinical improvement with the use of DFO.

Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome: Possible aluminum intoxication. N Engl J Med 1976;294:184–88.
Clinical description of "dialysis encephalopathy" and linkage with aluminum burden.

Andress DL, Ott SM, Maloney NA, Sherrard DJ. Effect of chronic parathyroidectomy on bone aluminum accumulation in chronic renal failure. N Engl J Med 1985;312:468–73.
Evidence that parathyroidectomy may lead to aluminum osteodysrophy in patients with high serum aluminum levels.
Boelaert JR, Fenves AZ, Coburn JW. Deferoxamine therapy and mucormycosis in dialysis patients: Report of an international registry. Am J Kidney Dis 1991;16:660–67.
The major risk of DFO therapy in dialysis patients.
Coburn JW, Mischel MG, Goodman WG, Salusky IB. Calcium citrate markedly enhances aluminum absorption from aluminum hydroxide. Am J Kidney Dis 1991;17:708–11.
Remarkable augmentation of aluminum absorption by citrate salts.
Hodsman AB, Sherrard DJ, Alfrey AC, et al. Bone aluminum and histomorphometric features of renal osteodystrophy. J Clin Endocrinol Metab 1982;54:539–46.
Pathologic description of aluminum osteodystrophy.
Ittel TH, Buddington B, Miller NL, Alfrey AC. Enhanced gastrointestinal absorption of aluminum in uremic rats. Kidney Int 1987;32:821–26.
Evidence that uremia leads to increased absorption of aluminum from the GI tract.
Kaenny WD, Hegg AP, Alfrey AC. Gastrointestinal absorption of aluminum from aluminum containing antacids. N Engl J Med 1977;296:1389–90.
Inference of absorption of aluminum ingested from findings of aluminum burdens in renal failure patients, not on dialysis, after chronic ingestion of aluminum.
Pei Y, Hercz G, Greenwood C, et al. Non-invasive prediction of aluminum bone disease in hemo- and peritoneal dialysis patients. Kidney Int 1992;41:1374–82.
Application of the deferoxamine infusion test.
Rosenlof K, Fyrquist T, Tenhunen R. Erythropoietin, aluminum and anaemia in patients on hemodialysis. Lancet 1990;335:247–49.
Evidence suggesting that aluminum intoxication interferes with heme synthesis.
Ward MK, Feest TG, Ellis HA. Osteomalacic dialysis osteodystrophy: Evidence for waterborne etiological agent, probably aluminum. Lancet 1978;1:841–45.
Linkage of symptomatic osteodystrophy to aluminum burden from the dialysate in hemodialysis patients.

CHAPTER 78

Parathyroidectomy

Phuong-Chi T. Pham, MD, and Phuong-Thu T. Pham, MD

Many cases of secondary hyperparathyroidism had been previously considered refractory until the advent of non-calcium/non-aluminum–based phosphate binders and calcimimetics. Available data suggest that the addition of calcimimetics to traditional medical therapy confers better normalization of biochemical parameters associated with secondary hyperparathyroidism as well as a significant reduction in the relative risk of parathyroidectomy [relative risk (RR) 0.07, with 95% confidence interval (CI), 0.01–0.055]. If this estimate proves accurate, a phenomenal fall in the need for parathyroidectomy secondary to renal failure will be observed over the next decade. Currently, however, existing cases of advanced hyperparathyroidism may not benefit from newer agents and may still require invasive therapies.

Invasive parathyroid intervention involves either direct parathyroid injection therapy or parathyroidectomy. As an adjunct to medical therapies and avoidance of surgery, a "pharmacologic parathyroidectomy" technique involving selective medical destruction of large resistant parathyroid glands and nodular hyperplastic tissues has been developed. In this technique, percutaneous ethanol is selectively injected into all large glands. This is combined with calcitriol pulse therapy. Doppler ultrasonography is subsequently used to monitor the loss of blood supply to the gland, an indication of successful destruction of the hyperplastic gland.

Although effective, the procedure is associated with an increased risk of transient recurrent laryngeal nerve palsies. Subsequent trials involving the substitution of ethanol for calcitriol proved similarly successful while avoiding the previously cited complication. The success of this technique has been attributed to the ability of the high local concentration of calcitriol to induce apoptosis of the hyperplastic parathyroid cells while sensitizing the remaining cells to calcitriol and calcium *via* upregulation of their respective receptors.

Direct parathyroid injection therapy, however, is not without limitations. The effectiveness of the procedure is limited to smaller parathyroid glands with two or fewer nodular lesions, target lesions that are accessible by ultrasonographic guidance,

and cases with no ectopic glands. Recurrent disease among non-transplant patients is another concern because the remnant parathyroid tissues are continuously exposed to the uremic milieu, the source for parathyroid hyperplasia. In addition, the procedure requires accurate technical expertise and may not be universally available. Finally, independent investigators have reported failure of the procedure to control secondary hyperparathyroidism in cases with advanced disease, parathyroid gland size >500 mg, and higher levels of PTH (parathyroid hormone). Nevertheless, parathyroid injection therapy remains a viable option for medically resistant nonsurgical candidates.

Indications for Parathyroidectomy

In regard to this section, see Table 78.1. In general, medically resistant hyperparathyroidism correlates with diffuse hyperplasia or hyperplastic nodular formation, or both. As secondary hyperparathyroidism progresses, the gland evolves from a diffuse polyclonal hyperplastic pattern into monoclonal hyperplasic nodules. Cells in the latter have diminished expression of both vitamin D- and calcium-sensing receptors, and hence a poor response to all agents whose therapeutic mechanisms require their presence.

For patients with medically resistant hyperparathyroidism who may not undergo direct parathyroid injection therapy, parathyroidectomy may be necessary. In 1982, the European Dialysis and Transplantation Association reported a parathyroidectomy incidence of approximately 5 per 1000 patient-years during the first 2 to 3 years of dialysis but greater than 40 per 1000 patient-years after 10 or more years. An analysis of the same issue based on the Lombardy Registry of Dialysis and Transplantation in Italy (involving patients on renal replacement therapy between 1983 and 1996) revealed an incidence of 3.3 per 1000 patient-years during the first 5 years, which increased to 30 per 1000 patient-years after 10 or more years of dialysis.

Based on the Kidney Dialysis Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines, parathyroidectomy is recommended for patients with severe hyperparathyroidism with persistently elevated levels of intact PTH >800 pg/mL in association with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. Clinical manifestations suggestive of resistance to medical therapies are summarized in Table 78.1. In the case of elevated PTH levels without radiologic evidence of high turnover bone disease, adynamic or aluminum bone disease must be ruled out because parathyroidectomy may worsen the

Table 78–1

Indications for Parathyroidectomy[a]

Nonrenal Transplant Patients
- Elevated intact PTH levels >800 pg/mL associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy (NKF-K/DOQI)[b]
- Clinical signs and symptoms associated with refractory hyperparathyroidism:
  - Hypercalcemia
  - Uncontrollable hyperphosphatemia
  - Evidence of osteitis fibrosa by bone biopsy, classic radiologic findings, or bone metabolic markers
  - Enlarged ± nodular parathyroid glands (>500 mg)
  - Calciphylaxis
  - Intractable pruritis
  - Progressive calcification of blood vessels
  - Severe skeletal deformity
  - Severe bone pain
  - Anemia resistance to erythropoietin
  - Peripheral neuropathy

Renal Transplant Recipients
- Severe and persistent hypercalcemia ≥11.5 mg/dL for ≥6-12 months
- Symptomatic/progressive hypercalcemia:
  - Nephrolithiasis
  - Persistent osteitis fibrosa
  - Progressive vascular calcification
  - Calciphylaxis
  - Calcium-related renal graft function deterioration

a. Indications for parathyroidectomy are opinion based.
b. NKF-K/DOQI (Kidney Disease Outcome Quality Initiative).

underlying bone disease. Once there is evidence of resistant hyperparathyroidism, the decision for parathyroidectomy must be promptly made to avoid progressive complications.

With a successful renal transplantation, approximately 50% of hyperparathyroidism cases will resolve by 3 to 6 months (and most by 1 year). Persistent hyperparathyroidism requiring parathyroidectomy, however, occurs at a typical prevalence of 5% (but may vary from 1 to 20% among different transplant centers). Persistent hyperparathyroidism following renal transplantation generally reflects a poor functioning graft or tertiary hyperparathyroidism in a normal functioning graft.

Indications for parathyroidectomy following renal transplantation include severe persistent hypercalcemia >11.5 mg/dL persisting for more than 6 to 12 months, symptomatic hypercalcemia, nephrolithiasis, persistent metabolic bone disease, vascular calcification/calciphylaxis, and calcium-related renal allograft deterioration (Table 78.1). Because spontaneous resolution of hyperparathyroidism may not occur rapidly, it may be advisable in some cases to delay any plan for parathyroidectomy to a year post-transplant.

Preoperative Considerations

Preoperatively, decisions must be made with regard to the method and utility of radiologic localization of the parathyroid glands, type of parathyroidectomy to be performed, and routine medical management. These issues are discussed in the sections that follow.

Preoperative Localization of Parathyroid Glands

Most experts agree that localization of abnormal parathyroid glands prior to the first parathyroidectomy is generally not indicated. Although experienced surgeons are able to localize the involved parathyroid glands intraoperatively in more than 90 to 95% of cases, good radionuclide localization techniques have a similar or slightly better sensitivity for detecting solitary adenomas (significantly less for multigland hyperplasia). Preoperative localization studies may even be discouraged for fear of overreliance on study findings and resultant negligence in searching for ectopic glands.

For repeat parathyroidectomy due to persistent or recurrent disease or altered neck anatomy secondary to previous neck surgeries, preoperative localization is recommended. Functional imaging studies of parathyroid tissues with ^{99m}Technetium (Tc)–labeled sestamibi with subtraction or washout imaging to delineate parathyroid from thyroid glands are generally the study of choice. High-resolution ultrasound may be combined to confirm equivocal scans. High-resolution computed tomography and magnetic resonance imaging have been disappointing and are generally not recommended.

The combined use of single-proton-emission computed tomography with functional sestamibi imaging may be considered in cases with etopic sites. Invasive procedures such as venous

sampling of PTH or needle aspiration are associated with higher morbidity and cost and are thus rarely used except in difficult reoperative cases in which imaging techniques have failed to localize abnormal tissues.

Types of Parathyroidectomy

Three types of parathyroidectomy—including subtotal parathyroidectomy, total parathyroidectomy with autotransplantation (typically into the forearm), and total parathyroidectomy without autotransplantation—have been reported to result in varying rates of success in the treatment of hyperparathyroidism secondary to renal failure. The type of parathyroidectomy to be performed can be determined by the typical outcome of the specific procedure and the patient's expected clinical course. In general, subtotal parathyroidectomy is the preferred procedure if a patient has a higher chance to develop hypoparathyroidism than recurrent hyperparathyroidism post-parathyroidectomy—whereas total parathyroidectomy with or without autotransplantation is the procedure of choice when the patient is expected to have a high risk of recurrent hyperparathyroidism.

In younger potential renal transplant recipients, a subtotal parathyroidectomy with a generous remnant gland may be preferred because hypoparathyroidism may develop following a successful renal transplant. For older nonrenal transplant candidates with permanent exposure to uremia and a history of exposure to aluminum, total parathyroidectomy with autotransplantation may be preferred to avoid the potential postsurgical complication of hypoparathyroidism and resultant worsening of aluminum bone disease. When hyperparathyroidism recurs with autotransplantation, resection of the autograft in the arm is more easily performed than reexploration for the remnant parathyroid gland within the altered neck anatomy. Despite this surgical advantage, uncontrolled local tissue and vascular invasion (as well as transformation into malignant tissue) has been reported with autotransplantation.

Delayed autotransplantation of cryopreserved parathyroid tissues *versus* immediate autotransplantation with fresh tissues may be an alternative option. Delayed autotransplantation may be advantageous because it allows for *in vitro* testing of the parathyroid tissues' potential for autonomous growth and may avert the reintroduction of irrepressible hyperplastic tissues. In addition, the delay may allow for abortion of the procedure in

patients who develop recurrent hyperparathryoidism at subsequent follow-up.

For permanent dialysis-dependent nonrenal transplant candidates with no history of aluminum exposure, a total parathyroidectomy without autotransplantation may be preferred because the risk of permanent hypoparathyroidism and subsequent aluminum bone disease in the persistently uremic state is relatively low. Several authors have shown that long-term hypoparathyroidism was relatively uncommon and that clinically significant adynamic bone disease was exceptionally rare. The absence of hypoparathyroidism was attributed to the eventual proliferation of unrecognized small embryonic residual parathyroid tissue.

Preoperative Medical Management

In preparation for parathyroidectomy, both hematologic and electrolyte abnormalities should be maximally corrected. In addition, basal levels of calcium, magnesium, phosphate, and intact PTH are obtained. Dialysis-dependent patients should receive dialysis the morning of surgery to optimize platelet function. Patients with severe anemia should receive blood transfusions to further minimize uremic bleeding diathesis.

Preoperative vitamin D sterols and calcium supplements have also been advocated to minimize the risk of postoperative hypocalcemia and hypophosphatemia. Reduction or discontinuation of phosphate binders may also be considered to avoid postoperative hypophosphatemia. In addition, preoperative direct or indirect laryngoscopy is recommended to assess vocal cord function in all patients who have had recent alteration in voice quality or previous thyroid or parathyroid operations.

Operative Procedure

A successful parathyroidectomy mandates a meticulous methodical approach and a comprehensive understanding of the embryologic development of the parathyroids as well as their common locations in adulthood. The variability in location of the parathyroid glands is summarized in Table 78.2.

During the operation, the patient is positioned with the neck extended to bring the thyroid and parathyroid glands anterosuperiorly to facilitate the exploration. The deeper structures within the neck are reached from the midline following lifting of the subplatysmal flaps and strap muscles off the thyroid

Table 78–2

Common Locations of Parathyroid Glands

	Location	Percentage
Superior glands	Cricothyroidal or juxtathyroidal (within 1 cm superior to the intersection of the RLN and the ITA)	75–80
	Upper pole of thyroid gland	20
	Intrathyroid	2–5
	Retroesophageal or retropharyngeal	1
Inferior glands	Tissue immediately adjacent to thyroid lower pole	40–60
	Tongue of thymic tissue (between the inferior border of the thyroid gland and clavicle)	40
	Intrathyroid	2–5
	Ectopic (migrational path from base of tongue to lower neck)	2
	Anterior mediastinum	1

Abbreviations: RLN = recurrent laryngeal nerve, ITA = inferior thyroid artery.

gland. The thyroid lobe is subsequently retracted out of the neck to expose the space between the thyroid gland and the carotid artery, trachea, and esophagus. Both laryngeal nerves are promptly identified prior to the search for any parathyroid gland. A systematic approach is used to identify the superior glands, followed by the inferior glands. Visualization of all parathyroid glands, including supernumerary glands, is crucial.

Excision of the fat tissue surrounding the parathyroid glands, bilateral removal of the thymic tongue, and exploration of the carotid sheaths bilaterally are required to uncover supernumerary glands. In total parathyroidectomy with autotransplantation, tissue suitable for grafting is selected following histologic examination of each gland on frozen section. The chosen tissue typically comes from the smallest gland without macroscopically visible nodules. The glandular tissue (50–90 mg) is sliced into approximately 30 $1 \times 1 \times 3$-mm pieces to be used for immediate autotransplantation into 20 to 30 pockets in the brachioradial muscle or cryopreserved for delayed autotransplantation. In

subtotal parathyroidectomy, the smallest and non-nodular gland is selected for partial resection and its viability is verified prior to resection of the remaining glands.

Intraoperatively, there are two valuable tools that may be used to optimize surgical outcomes. The most beneficial technical advance has been attributed to the development of a rapid intraoperative PTH assay. The short half-life of PTH (2–2.5 minutes) and the rapid turnaround time for PTH detection (as fast as 12 minutes) allow surgeons to intraoperatively assess the adequacy of parathyroid tissue resection and the need to search for ectopic glands. Likewise, the rapid PTH assay can prevent excessive glandular tissue removal and postoperative hypocalcemia. Intraoperative PTH measurements, however, may not be universally available.

Another technique surgeons may use intraoperatively to detect hyperfunctioning glands is nuclear mapping with ^{99m}Tc-sestamibi. In this technique, ^{99m}Tc-sestamibi is administered intravenously 2 to 6 hours before surgery. The characteristic differential and late retention of the isotope within the parathyroid tissue may be used to localize affected glands intraoperatively with a handheld gamma detector. It must be noted, however, that the sensitivity of gamma-probe localization has better sensitivity in detecting adenomas than hyperplastic glands. The best use of nuclear mapping involves cases in which significant scarring has occurred from previous neck surgeries or when ectopic glands are present.

Postoperative Management

In the postoperative period, close monitoring of different electrolytes is required because significant changes may occur (Table 78.3). Hypocalcemia, specifically, occurs in almost all cases. Serum calcium level may fall by as much as 60% of the preoperative level. The hypocalcemic nadir typically occurs during the first 2 to 4 postoperative days. Restoration to normal calcium level may occur within 2 weeks, but hypocalcemia may remain severe for several months in a subset of patients.

In patients undergoing autotransplantation, hypocalcemia may persist until the implanted tissue is able to provide adequate function in 2 to 3 weeks (sometimes up to a year) following surgery. Hypocalcemia-associated tetany and seizures have been observed to occur more frequently during or closely following dialysis unrelated to the lowest calcium level. We speculate that the degree of blood alkalanization with dialysis and resultant

Table 78–3

Electrolyte and Metabolic Abnormalities Following Parathyroidectomy

	Abnormality	Onset/Duration	Etiology	Management
Calcium	Hypocalcemia	first 2–4 d; usually normalizes within 2–3 weeks	"hungry bone syndrome"	calcium, calcitriol supplements
		may recover within 2–3 weeks	failure of autograft function	calcium, calcitriol supplements consider implantation of cryopreserved parathyroid tissue
		may be permanent		
		usually recovers with persistent uremic state (i.e., no renal transplant)	inadequate remnant gland	calcium/calcitriol supplements consider implantation of cryopreserved parathyroid tissue
	Hypercalcemia	days to weeks following surgery	excessive calcium/ calcitriol supplement	decrease calcium/ calcitriol use
		persistent hypercalcemia	missed ectopic gland inadequate gland removal	radiological ± invasive localization

Table 78–3

Electrolyte and Metabolic Abnormalities Following Parathyroidectomy—Cont'd

	Abnormality	Onset/Duration	Etiology	Management
Phosphorus	Hypophosphatemia[a]	first 2–4 d to one year	"hungry bone syndrome"	phosphorus supplement, encourage high intake of dairy products
Magnesium	Hypomagnesemia[a]	first 2–4 d to one year?	"hungry bone syndrome"	magnesium supplement
Potassium	Hyperkalemia	within first 10–12 h	Vitamin D deficiency and/or hypocalcemia associated reduction in insulin secretion	glucose and insulin; dialysis
Alkaline phosphatase		increases over 4 d postoperatively peaks at 7–14 d decreases by third week normalizes by 6 months	"hungry bone syndrome"	rule out liver abnormality

a. Uncommon among patients with poor renal function.

fall in ionized calcium may be contributory. Rapid correction of metabolic acidosis with dialysis is therefore not advisable.

The abrupt fall in calcium level following parathyroidectomy in patients with high bone turnover has been attributed to the marked reduction in osteoclastic activity in association with the fall in PTH and the unopposed osteoblastic activity, a phenomenon known as "hungry bone syndrome." The degree of hypocalcemia has been shown to correlate with the preoperative severity of the bone disease, serum alkaline phosphatase levels, and patient age. Early postoperative calcium levels may be used to predict hypocalcemia. An initial upsloping postoperative calcium curve based on two calcium measurements within the first 24 hours has been shown to be strongly predictive of a stable postoperative calcium level, whereas a steeply downsloping initial calcium curve may predict eventual hypocalcemia. Greater PTH levels correlate well with bone histology and osteoblastic activity and may be used as a surrogate predictor of post-parathyroidectomy hypocalcemia.

Strategies to treat post-parathyroidectomy hypocalcemia include the preoperative initiation of calcitriol, close postoperative calcium level monitoring, and aggressive postoperative calcium and calcitriol supplementation. Calcitriol may be initiated 2 days prior to surgery at 2 to 4 μg/day. As soon as the patient can tolerate oral intake, elemental calcium at 1 to 2 g orally three times a day may be given. At 4 hours post-parathyroidectomy, a serum calcium level must be obtained. A fall in serum calcium of greater than 10% is indicative of the need for intravenous calcium supplementation (100 mL of 10% calcium gluconate mixed in 150 mL 5% dextrose mixture to run at 20–30 mL/hour or approximately 90 mg of elemental calcium/hour). Otherwise, continuation of oral calcium supplementation may suffice.

Monitoring of calcium levels should be continued every 6 hours for the next 2 to 3 days and tapered off in frequency when calcium levels stabilize. In emergent cases of symptomatic hypocalcemia, 20 to 30 mL of the previously cited solution may be infused over 10 to 15 minutes—followed by a continuous infusion at 20 to 30 mL per hour as deemed necessary by subsequent calcium levels and symptoms. Postoperative continuation of vitamin D is recommended to minimize the mean postoperative reduction in serum calcium as well as the amount of calcium required for supplementation. Both vitamin D and calcium doses should be adjusted to maintain normal calcium levels.

New-onset hypercalcemia following parathyroidectomy is unusual but may occur as a result of excessive calcium and

calcitriol supplements. Alternatively, postoperative persistence of hypercalcemia may signify inadequate parathyroid gland removal, missed ectopic glands, or a misdiagnosed cause of hypercalcemia. Radiologic localization of the parathyroid glands is required in persistent hypercalcemic cases for surgical reexploration.

Post-parathyroidectomy hypophosphatemia is uncommon among patients with renal failure. Nonetheless, hypophosphatemia may occur due to reduced phosphate mobilization from bone and enhanced uptake for bone formation. Patients with significant existing periarticular calcium phosphate deposits may actually benefit from a higher degree of phosphorus mobilization and amelioration of hypophosphatemia. Supplementation with both oral and intravenous phosphate salts may be used with close monitoring. If there is concurrent hypocalcemia, phosphate supplementation must be given between meals to avoid binding with calcium in the gastrointestinal tract and resultant reduction in calcium absorption. As with hypophosphatemia, post-parathyroidectomy hypomagnesemia is uncommon among renal patients but may occur in association with hungry bone syndrome. Correction of hypomagnesemia to normal range is warranted to avoid other metabolic complications, including poor response to calcium supplementation among those with hypocalcemia.

Hyperkalemia may occur not infrequently following parathyroidectomy. A serum potassium level increase from a mean of 4.4 mEq/L preoperatively to 6.2 mEq/L has been observed within the first 10 to 12 hours following parathyroidectomy. The onset and degree of hyperkalemia seem to correlate with the time and degree of hypocalcemia, respectively. Although the responsible mechanisms for post-parathyroidectomy hyperkalemia have not been elucidated, we propose that vitamin D deficiency and hypocalcemia may induce insulin deficiency and resultant reduction in intracellular potassium shift. In mice lacking a functional vitamin D receptor, the expression of insulin mRNA has been shown to be suppressed. In addition, hypocalcemia *per se* may reduce insulin secretion. In patients with moderate or severe hyperkalemia, a trial of intravenous glucose and insulin may be administered. A low-level 5% dextrose infusion has not proved adequate in preventing postparathyroidectomy hyperkalemia. Life-threatening hyperkalemia may require hemodialysis.

Postoperative elevation of plasma-bone-specific alkaline phosphatase has also been described. A significant increase may be observed 4 days following parathyroidectomy, with a peak value at 7 to 14 days. A decrease in the alkaline phosphatase level is expected to occur by the third postoperative week,

with normalization by the sixth postoperative month. The postoperative change in plasma alkaline phosphatase level has been attributed to enhanced osteoblastic activity. Suggested perioperative management guidelines for parathyroidectomy are summarized in Table 78.4.

Other Post-parathyroidectomy Complications

In addition to the electrolyte and metabolic disturbances observed following parathyroidectomy, other complications may occur.

Table 78–4

Suggested Perioperative Management for Parathyroidectomy

Preoperative Period
- Routine preoperative evaluation
- Normalization of electrolytes as much as possible
- Transfusion with packed red blood cells to maintain hemoglobin above 8.5 gm/dL
- Start vitamin D supplement (i.e., calcitriol 2–4 μg/d × 2 d prior to surgery)
- Reduction or discontinuation of phosphate binders
- Dialysis morning of surgery if dialysis dependent
- Imaging of parathyroid glands for reexploration parathyroid surgery or altered neck anatomy

Postoperative Period
- Calcium supplement 1–2 g po tid as soon as oral intake is possible
- Intravenous calcium supplement (1–2 mg elemental calcium/kg body weight/hour)[a] if poor oral intake or significant hypocalcemia (ionized calcium <3.6 mg/dL or corrected total calcium <7.2 mg/dL)
- Continue with vitamin D supplement (i.e., calcitriol 2 μg/d)
- Electrolyte monitoring:[b]
  - Serum ionized calcium levels at 4–6 h postoperative, then q 6 h × 2–3 d; then q 12–24 h until stable
  - Serum potassium at 4 h postoperatively, then q 6 h × 2 or until stable
  - Serum phosphate, magnesium at 4 h postoperative; unless significantly abnormal, recheck levels the following morning
  - Intact PTH level and alkaline phosphatase the following morning; repeat and follow up as clinically indicated

a. See text for calcium solution mixture and rates of infusion.
b. Levels of different electrolytes may need to be checked more frequently if they are severely abnormal

Direct surgical complications include pain, poor wound healing, formation of a hematoma or seroma, and damage to the recurrent laryngeal nerve with vocal cord paralysis. As previously discussed, both hypo- and hyperparathyroidism may result. Hypoparathyroidism may result from inadequate remnant parathyroid mass or poor function of the remnant tissue due to infarction. In the setting of hypoparathyroidism, existing undiagnosed aluminum-related osteomalacia may worsen. Persistent hyperparathyroidism may occur secondarily to missed accessory glands or incomplete parathyroidectomy and may require reexploration.

Proliferation of the remnant tissue may contribute to recurrent hyperparathyroidism, particularly among patients with continuing exposure to the uremic milieu. Finally, in some patients with pre–end-stage renal disease, significant postoperative deterioration in renal function has been reported. Earlier case reports suggested that aggressive calcium and vitamin D supplementation may have been contributory, presumably due to significant renal cortical calcification. More recently, it has been suggested that PTH *per se* has vasodilatory effects on afferent arterioles and vasoconstrictive effects on efferent arterioles. The acute fall in PTH levels following parathyroidectomy causes a reversal in renal hemodynamics, and hence a fall in glomerular filtration pressure—an effect that may adversely affect patients with marginal renal function.

Recommended Reading

Canaff L, Hendy GN. Human calcium-sensing receptor gene: Vitamin D response elements in promoters P1 and P2 confer transcriptional responsiveness to 1,25-dihydroxyvitamin D. J Biol Chem 2002;277(33):30337–50.

This study showed that intraperitoneal injection of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) in rats significantly increased parathyroid, thyroid, and kidney CaSR (calcium sensing receptor) mRNA levels and similarly that treatment of human thyroid C-cell (TT) and kidney proximal tubule cell (HKC) with 1,25(OH)2D3 significantly increased CASR gene transcription.

Cozzolino M, Gallieni M, Corsi C, Bastagli A, Brancaccio D. Management of calcium refilling post-parathyroidectomy in end stage renal disease. J Nephrol 2005;17:3–8.

This article is a review involving the management of post-parathyroidectomy electrolyte disturbances.

Cunningham J, Danese M, Olson K, et al. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney Int 2005;68:1793–1800.

This study compared the relative risks of parathyroidectomy, fracture, and cardiovascular hospitalizations among 1184 patients with uncontrolled secondary hyperparathyroidism who were randomized to receive cinacalcet or placebo in addition to their standard therapies.

Denda M, Finch J, Brown AJ, Nishii Y, Kubodera N, Slatopolsky E. 1,25-Dihydroxyvitamin D_3 and 22-oxacalcitriol prevent the decrease in vitamin D receptor content in the parathyroid glands of uremic rats. Kidney Int 1996;50(1):34–39.

This study examined the regulation of VDR by 1,25-dihydroxyvitamin D3 (1,25-D3) and 22-oxacalcitriol (OCT) in parathyroid glands of uremic rats.

Fukagawa M, Kitaoka M, Tominaga Y, et al. Japanese Society for Parathyroid Intervention: Guidelines for percutaneous ethanol injection therapy of the parathyroid glands in chronic dialysis patients. Nephrol Dial Transplant 2003;18(3):iii31–3.

This article reviews the guidelines for percutaneous ethanol injection therapy of the parathyroid glands in chronic dialysis patients proposed by the Japanese Society for Parathyroid Intervention, including indications, techniques, and post-PEIT (percutaneous ethanol injection therapy) management.

Fukuda N, Tanaka H, Tominaga Y, et al. Decreased 1,25-dihydroxyvitamin D_3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremia patients. J Clin Invest 1993;92:1436–43.

In this study, the authors investigated the VDR (vitamin D receptor) distribution in surgically excised parathyroids obtained from chronic dialysis patients by immunohistochemistry.

Gogusev J, Duchambon P, Hory B, et al. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. Kidney Int 1997;51(1):328–36.

In this study, the authors compared the expression of the calcium-sensing receptor (CaSR) at the gene message and the protein level in parathyroid tissue obtained from patients with primary nonuremic and secondary uremic hyperparathyroidism with that in normal parathyroid tissue, using in situ hybridization and immunohistochemistry techniques.

Kettle AG, O'Doherty MJ. Parathyroid imaging: How good is it and how should it be done? Semin Nucl Med 2006;36:206–11.

This is a review of parathyroid imaging techniques.

Krempl GA, Medina JE, Bouknight AL. Surgical management of the parathyroids. Otolaryngol Clin N Am 2003;36:217–28.

This is a review involving a discussion on preoperative localizing techniques, the surgical management of hyperparathyroidism, and the utility of intraoperative PTH assay.

Tominaga Y, Kohara S, Namii Y, et al. Clonal analysis of nodular parathyroid hyperplasia in renal hyperparathyroidism. World J Surg 1996;20(7):744–50.

In this study, the clonality of parathyroid tissue in nodular and diffuse hyperplasia in renal hyperparathyroidism was analyzed.

CHAPTER 79

Dialysis Amyloidosis

Sergio R. Acchiardo, MD

Amyloidosis is a serious debilitating complication affecting patients with end-stage renal disease. Rarely, it is the cause of death. The principal constituent of amyloid deposits isolated from patients with bone or joint disease is β_2-microglobulin (β_2M) fibrils. There is a close relationship between duration of dialysis and incidence of amyloid, but this relationship is not absolute because the disease has been diagnosed in patients prior to the initiation of dialysis therapy. β_2M serum levels in dialysis patients are 15 to 30 times greater than normal. Even though this accumulation is important, the pathophysiology of the disease remains unclear. A prospective postmortem study showed that β_2M amyloid deposits are detectable in large joints much earlier than they are clinically apparent. Tissue deposition of amyloid occurs much earlier than clinical or radiologic manifestations. Twenty-one percent of patients had deposits within the first 2 years of hemodialysis, and more than 90% of patients had deposits after 7 years of hemodialysis.[1]

The incidence of amyloid in continuous ambulatory peritoneal dialysis (CAPD) patients is more difficult to evaluate because there are fewer patients dialyzed for a prolonged period of time. CAPD was reported to result in lower β_2M serum levels than did cuprophane hemodialysis. Two explanations are possible: the better preserved residual glomerular filtration rate in CAPD patients and better removal of β_2M across the peritoneal membrane.[2] Reports from two retrospective studies did not find any significant difference in the prevalence of carpal tunnel syndrome in patients dialyzed with CAPD compared to patients in hemodialysis with cuprophane membranes.

Clinical Manifestations

The most prominent and usually first clinical manifestation of dialysis-related amyloidosis (DRA) is carpal tunnel syndrome. There is a direct relationship between the incidence of carpal tunnel syndrome and time on dialysis. After 5 years of dialysis, 20 to 25% of patients develop carpal tunnel syndrome. After 10 years, the incidence is about 80%.

Carpal tunnel syndrome is usually bilateral and progressive, requiring surgery for relief of symptoms. The patient complains of numbness, hypoesthesia, paresthesias, and amyotrophy. Pain in the fingers usually worsens at night and during dialysis. Upon physical examination, muscle atrophy is evident. The incidence of carpal tunnel syndrome is higher in hemodialysis than in CAPD patients. Age may be a risk factor in this disorder, and in the evolution of these lesions. In 50% of patients affected by carpal tunnel syndrome, amyloid is found in the transverse carpal ligament.

Other clinical manifestations of DRA frequently present are spondyloarthropathies, hemarthrosis, and joint pain and immobility. The patients complain of shoulder pain, joint stiffness, soft-tissue swelling, and effusion. Aspiration of the joint reveals clear fluid containing aminofibrils. Pathologic fractures are seen primarily in patients with hip involvement. DRA can become systemic late in the course, with amyloid deposition principally in the gastrointestinal tract and heart.

Diagnosis

Screening for the disease is not practical and is not recommended. Patient evaluation should be performed based on clinical manifestations and on radiologic findings, with eventual histologic confirmation. The most prominent manifestation is carpal tunnel syndrome. The "gold standard" for diagnosis is a biopsy demonstrating positive Congo red staining and immunohistochemistry for the presence of β_2M. Other diagnostic techniques that have been used include scintigraphy, ultrasound, and magnetic resonance imaging.[3] The investigators reported that these techniques were useful, but joint biopsy was not utilized to confirm the diagnoses in most of these patients. The specificity and sensitivity of the radiologic techniques have not been determined. Characteristic radiologic changes have been described, including periarticular cystic bone lesions—which grow in number and size with the continuation of dialysis therapy.

The presence of amyloid can also be found in subcutaneous fat pad aspiration (positive in 36%) and in rectal submucosal biopsy. Skin biopsy is usually negative. The serum β_2M level is significantly elevated in dialysis patients. Although there are marked differences from patient to patient, the levels are relatively constant in the same patient over time once residual renal function is lost. Furthermore, no difference has been found

in β_2M level in those patients with and without DRA. Several studies have shown no correlation between β_2M levels and age, sex, or time on dialysis.

The radiologic findings in DRA are characteristic, especially in the late stages of the disease, and represent intra-articular and intraosseous deposits of amyloid. The presence of subchondral bone cysts and bone erosions is usually associated with soft-tissue swelling and displacement of periarticular fat pads. In general, tissue swelling precedes bony lesions—and ultrasonography is useful in detecting tendon thickness. Some of the bony defects, especially in the femoral head, may be associated with pathologic fractures. Radiologic lesions are usually present before the onset of pain. Because the radiologic findings are characteristic but not pathonogmonic of DRA, histologic confirmation is necessary.

Osteoarticular disorders in patients with DRA are different from those of secondary hyperparathyroidism. The former involves large joints and is characterized by the presence of juxta-articular cysts, development of erosive arthritis, and lack of correlation with subperiosteal reabsorption. DRA is a systemic disease. The deposition of amyloid has also been documented in extra-articular tissues, especially in the gastrointestinal tract and heart. The involvement of the gastrointestinal tract presents with acute abdomen, diarrhea, nausea and vomiting, and severe hemorrhage. Infrequently, macroglossia has been present.

Sonography has been useful in detecting the thickened synovial sheath often present in the afflicted shoulder. Magnetic resonance imaging may also be useful in detecting thickened joint structures and joint effusions. In a pilot study, Tc aprotinin seems to be a promising tracer for detecting DRA. In addition, recent reports suggest that using diagnostic radionuclear tracing and imaging of β_2M deposits by injections of either 123I-labeled serum amyloid P component or 131I-labeled β_2M may be helpful.

There is a direct relationship between deposition of β_2M in the skin and time on dialysis. Skin biopsies revealed that the content of β_2M increases rapidly during the first 5 years of dialysis and thereafter increases only minimally. Conceivably, osteoarticular β_2M deposition may accelerate once the skin binding site becomes saturated. Systemic tissue involvement has been described in some patients who have accumulation of β_2M in the blood, tissues, and synovial fluid—as well as formation of amyloid deposits in the heart, kidney, and prostate. Involvement of the adrenal gland has also been reported.

Pathogenesis

β_2M is an 11,800-dalton globular protein. The β_2M concentration in patients with normal renal function ranges from 1 to 3 mg/L. When hemodialysis is first initiated, patients have lower levels of β_2M in their serum because of residual renal function. However, once renal function disappears there is no further rise in β_2M levels—presumably due to increased deposition in tissues or decreased production. Dialysis patients have a markedly elevated serum concentration of β_2M. The retention of β_2M in patients on dialysis is *sine qua non* for the development of β_2M amyloidosis. The mean daily synthesis rate of β_2M is 3 mg/kg, which is slightly higher than in normal controls. The mean weekly rate is approximately 1500 mg. High-flux hemodialysis removes 400 to 600 mg/week, and the removal by CAPD is lower (only 300 mg/week). Despite this, as mentioned previously, serum levels of β_2M may be lower in CAPD patients compared to hemodialysis patients.

An important role of the dialysis membrane in the pathogenesis of DRA has been suggested. Patients dialyzed with cuprophane membranes have higher β_2M levels than patients dialyzed with more porous synthetic membranes. Studies performed in vitro and in vivo have shown increased synthesis of β_2M mediated by cytokines. This effect has been attributed to interleukin-2, tumor necrosis factor, and interferon alpha and gamma. It is possible that hemodialysis itself contributes to the increased synthesis of β_2M, adding to the retention of the amyloid precursor protein. However, in vivo evidence for this increased synthesis induced by hemodialysis is not available. Evidence supports the concept that changes in the concentration of β_2M during intradialytic periods are due to concomitant changes in extracellular fluid volume.

Patients over the age of 40 at the initiation of dialysis have a higher risk of developing DRA than do younger patients. In patients on hemodialysis for more than 6 years, derivatives of advanced glycation end products (AGEs) have been found in the intervertebral disc amyloid tissue by immunohistologic techniques.[4] They were also present in amyloidosis-related bone cysts when bone reabsorption by osteoclasts was observed. These findings support the hypothesis that amyloid fibrils are modified by AGEs in long-term hemodialysis patients.

Treatment

The progressive accumulation of β_2M in patients on long-term dialysis poses an interesting clinical question regarding adequacy of dialysis. We should consider the clearance of low-molecular-

weight substances (as a surrogate, we use urea) as well as medium-molecular-weight substances such as β_2M (11,800 daltons). In regard to adequacy, β_2M has been proposed as a surrogate for middle molecules. This is particularly apt because pathologic changes associated with the deposition of β_2M are clearly established in long-term dialysis patients. A recent study showed that the mean predialysis serum β_2M level over time was predictive of all-cause mortality, independent of the chronicity of dialysis and residual kidney function.[5]

We do not have an adequate treatment for DRA. Unquestionably, we need to prevent the accumulation of β_2M. However, the clearance of β_2M with low-flux membranes is nil.[6] High-flux synthetic ("biocompatible") membranes remove more β_2M (their β_2M clearance is 19 mL/minute) and slow the burden, but the weekly synthesis of β_2M is higher than this removal (1500 mg versus 400-600 mg, respectively). Biocompatible compare with non biocompatible membranes also decrease the production of cytokines and complement stimulation. The dialysate should be sterile and pyrogen free to further decrease cytokine-stimulated β_2M production. A study evaluating the prevalence of DRA, as judged by clinical and radiologic signs, showed the condition to have decreased dramatically between 1988 and 1996. Compared to 1988, in 1996 a greater number of patients were dialyzed with a more biocompatible membrane, more patients were using reverse osmosis to treat the dialysate water, and a larger number were using bicarbonate in the dialysate as a buffer.[7] More studies are necessary to evaluate these findings.

Other therapeutic approaches are the use of hemofiltration or adsorbent columns. Both techniques decrease β_2M levels, but their use has been limited by their cost. Hemodiafiltration achieves dialyzer clearances of β_2M that are approximately twice those obtained with high-flux dialysis. However, due to disequilibrium at the end of dialysis hemodiafiltration creates an important rebound. This rebound is due to a significant mass transfer resistance between the vascular and extravascular compartment.[8] This results in β_2M levels that are only slightly less compared to those obtained with high-flux dialysis. Therefore, to improve clearance of β_2M we need to increase the frequency of the treatments or their duration. New possibilities are short daily hemodialysis (1 to 4 hours, six times per week) and nocturnal hemodialysis, usually performed for 8 hours six times a week at low blood and dialysate flow rates (which demonstrate a significantly higher clearance of β_2M and considerably reduced β_2M levels[9]). Both techniques offer the promise of improved

clinical outcomes and quality of life. Unfortunately, we do not have long-term controlled studies evaluating these techniques.

Another attractive possibility for removing β_2M is renal transplantation. An early kidney transplant will prevent the accumulation of β_2M. However, it seems unlikely that kidney transplantation will be indicated only for this purpose. The patient should be transplanted before the manifestations of DRA appear. Following kidney transplantation, osteoarticular pain is almost completely suppressed. In part, this may be due to the anti-inflammatory effects of steroids. The radiologic signs of DRA are arrested in long-term transplant patients. Deposits of amyloid after 5 years of transplantation have been shown to be reduced, but bone cysts remained unchanged.[10] Successful kidney transplantation leads to rapid excretion of large amounts of β_2M, especially during the first day after transplantation—paralleling the fall of serum creatinine. β_2M levels are reduced to normal.

A practical approach to the problem of DRA has been suggested: patients older than 50 years of age should be dialyzed with highly compatible membranes, such as polysulfide or polyamid. The same is true for younger patients who have little chance of receiving a kidney transplant. Those patients with clinical manifestations of β_2M should be given a high priority for transplantation. Switching patients from hemodialysis to peritoneal dialysis does not seem to be an effective method of preventing DRA or delaying its onset.

The painful articular disease associate with β_2M amyloid can be debilitating. Treatment with nonsteroidal anti-inflammatory agents, systemic corticosteroids, deep therapeutic ultrasound, and physical therapy may be beneficial in selected patients. Early surgical correction of carpal tunnel syndrome is indicated.

References

1. Koch KM. Dialysis-related amyloidosis. Kidney Int 1992;41:1416–29.
   Excellent review of dialysis-related amyloidosis, with a case presentation and forum discussion.
2. Acchiardo S, Kraus A, Jennings BR. Beta-2 microglobulin levels in patients with renal insufficiency. Am J Kidney Dis 1989;13:70–74.
   These researchers measured β_2M levels in patients with chronic renal failure, hemodialysis and peritoneal dialysis patients, and in kidney transplant patients. They also evaluated removal of β_2M during dialysis with different membranes, and in post-transplant patients with good renal function.
3. NKF-K/DOQI. NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003;42(3):S102–08.
   Guidelines based on the best information available at the time of publication. They are designed to provide information and assist in decision making.
4. Miyata T, Iida Y, Notoya K, et al. Beta-2 microglobulin modified with advanced glycation end products enhances osteoclasts-induced bone

resorption: Role in the pathogenisis of dialysis-related amyloidosis. Nephrol-Dial Tranplant 1996;11:A240.
The presence of glycosylated β_2M in amyloid deposits may enhance the development of bone lesions through activation of cytokines and chemoattracting monocytes. Role of AGEs in the pathogenesis of amyloidosis.

5. Cheung A, Rocco M, Guofen Y, Leypoldt J, Levin, N, Green T, et al. Serum β-2 microglobulin levels predict mortality in dialysis patients: Results of the Hemo Study. J Am Soc Nephrol 2006;17:546–55.
Study analyzed the determinants of serum β_2M levels and the association of serum β_2M levels or dialyzer β_2M clearance with mortality. This association is supportive of the potential value of β_2M as a marker to guide chronic hemodialysis therapy.
6. Odell R, Slowiaczek P, Moran J, Schindhelm K. Beta-2 microglobulin kinetics in end-stage renal failure. Int Soc Nephrol 1991;39:909–19.
7. Schwalbe S, Holzhauer M, Schaeffer J, et al. Beta-2 microglobulin associated amyloidosis: A vanishing complication of long-term hemodialysis? Kidney Int 1997;52:1077–83.
Study performed at two points in time concluded that β_2M-associated amyloidosis has decreased in prevalence and severity. The study also evaluated the potential factors involved.
8. Ward RA, Greene T, Hartmann B, Samtleben W. Resistance to intercompartmental mass transfer limits Beta 2 microglobulin removal by post-dilution hemodiafiltration. Kid Int 2006;69:1431–37.
Study evaluated the disequilibrium that develops between body compartments for β_2M when dialytic removal exceeds the rate of transfer of solute from the extravascular compartment into the plasma. They also suggest strategies to further reduce plasma β_2M concentrations.
9. Raj DS, Ouwendyk M, Francoeur R, Pierratos A. Beta-2 microglobulin kinetics in nocturnal haemodialysis. Nephrol Dial Transplant 2000;15:58.
In this study, nocturnal hemodialysis was associated with a four times higher β_2M removal and a greater reduction in plasma β_2M concentration compared with conventional hemodialysis.
10. Jadoul M, Malghem J, Pirson Y, et al. Effect of renal transplantation on the radiological signs of dialysis amyloid osteoarthropathy. Clin Nephrol 1989;32:194.
This study demonstrated that bone cysts resolved slowly after successful renal transplantation, even with normal plasma β_2M concentration.

CHAPTER 80

Acquired Cystic Kidney Disease

Margaret MacDougall, MD, PhD

Cystic disease occurs in several forms and is seen in patients with renal insufficiency with etiologies unrelated to cyst formation. Now called *acquired cystic kidney disease* (ACKD) or *acquired renal cystic disease* (ARCD), these kidneys usually show multiple, bilateral, small cysts. However, these kidneys may also be associated with marked renal enlargement and other complications, including malignant tumor formation.

Pathophysiology

The specific etiology and pathophysiology of acquired cysts are not clear. Cysts have been reported in pre-dialysis patients with long-standing azotemia (serum creatinine >2.5 mg/dL) and in patients on all types of renal replacement therapy. Azotemia appears to be the only consistent factor for the development of ACKD, and cystic kidney transformation is prolonged and accelerated by dialysis. The incidence of acquired cysts in pre-dialysis patients has been noted to be <10%. In surveying large dialysis populations, the incidence increases to 40 to 50% overall—and to nearly 80% in patients dialyzed more than 3 years.

These cysts are formed from tubules, are lined with hyperplastic epithelium, and may contain papillomas—all suggestive of increased tubular cell growth. Cysts tend to be larger and more numerous, and to exhibit increased growth, in males compared to females. Initiating factors for the development of cysts are not known, but numerous etiologic factors have been proposed—including ischemia, intratubular obstruction from casts or calcium oxylate crystals, and interstitial fibrosis leading to extratubular constriction and obstruction. In addition, the abnormal accumulation of chemical substances due to decreased renal function has been postulated as causal.

Recent evidence has indicated increased levels of inflammatory cytokines, including interkeukin IL-1β, IL-6, and tumor necrosis factor-α, as well as IL-8 and c-*jun*. The proto-oncogene c-*jun* has been noted to be increased in early cyst formation associated

with hyperplastic epithelium. The presence of toxic substances from dialysis tubing or membranes has not been recognized as a significant etiologic factor because ACKD is seen in patients who have never been dialyzed. Although c-*jun* activation was not noted uniformly in cystic kidneys with renal cell carcinoma, other specific growth factors remain to be identified. It is also known that cyst growth is increased by substances that stimulate cyclic adenosine monophosphate (cAMP) and that high levels of cAMP are found in dialysis patients, possibly as a response to parathyroid hormone (PTH). Other potential "renotropic factors" remain to be identified.

Clinical Complications

ACKD would present few problems if it were not for its numerous associated complications. Although many patients may have acquired cystic disease for many years without problems, some patients may develop potentially lethal complications. Hemorrhage with hematuria is the most frequent complication, with perirenal or retroperitoneal hematomas also reported. Infection, renal rupture, and the development of multiple tumors (both with the cysts and elsewhere in the affected kidneys) have been reported.

The tumors are of particular interest. In the earliest reports, 36% of patients with cysts were found to have tumors. Many tumors were small and were renal adenomas histopathologically. Some tumors were renal adenocarcinomas. Many of the tumors were multifocal and bilateral. There are now numerous reported cases of these tumors in conjunction with acquired cystic disease. Some of these tumors actually occurred in the native kidneys of patients after they received a renal transplant. Approximately 20% of the reported patients developed metastatic disease, and some patients died from complications. Tumors have even occurred in pediatric patients who have been on dialysis for a prolonged period. Thus, these tumors are not merely pathologic curiosities and are not related to age of the patient but only the length of time of azotemia.

Although the numbers are small, the incidence of adenocarcinoma in this population is significantly greater than in the population with normal renal function. A previous report of a calculated incidence of ACKD was 0.27% per year, about 50 times greater than that given for normal population (0.005% per year). Other investigators have calculated an incidence of 134 times that of the general population. Therefore, it becomes important to identify and follow those patients at risk of ACKD and the potential complications.

Diagnosis and Screening

Two techniques have been used historically for the noninvasive detection of renal cysts. Ultrasonography is easy to perform and requires only moderately expensive equipment. However, chronically diseased kidneys are often shrunken and scarred and exhibit marked increased echogenecity—making cysts difficult to detect with ultrasonography. In addition, the resolution of the system may preclude the detection of small cyst and tumors (<0.5 cm diameter) often seen during the early stages of ACKD. Thus, ultrasonography is probably not the best screening technique for ACKD—although predialysis patients with less scarring of the kidneys may be considered for this technique.

Computer tomography (CT) is an alternative that although more expensive and difficult to perform affords higher resolution, enabling detection of small cysts and tumors in shrunken kidneys. The intravenous (IV) administration of contrast material may further enhance tumor detection (Figure 80.1). Helical CT with early enhancement rather than delayed enhancement may be superior in the detection of early tumors in ACKD. Magnetic resonance imaging (MRI) of the kidneys for further evaluation of complicated cystic lesions may prove more beneficial than CT alone.

Owing to the limits of ultrasonography for detection of cysts and tumors in chronically diseased kidneys, the author recommends the inclusion of CT in the initial evaluation of these patients. If the kidneys are found to be enlarged or have cysts >1 cm in diameter, ultrasonography could be used in follow-up. However, the detection of additional newly forming small tumors could still be missed with this approach, therefore a CT scan is preferred for extended follow-up.

Screening for ACKD is not considered economically advantageous, although patients are screened yearly in Japan. Specific screening should concentrate on those patients most at risk for this disease. In addition, screening should probably be limited to patients with a long expected life span; that is, the youngest and healthiest patients. Several factors should be considered when a patient is evaluated for screening. These factors include the duration of azotemia (serum creatinine >2.5 mg/dL for more than 5 years) and the length of time on dialysis. Patients on hemodialysis for more than 3 years should be considered for screening. Patients requesting transplantation should also be considered for screening.

The onset of symptoms such as hematuria or flank pain in a dialysis or chronically azotemic patient should lead to a prompt

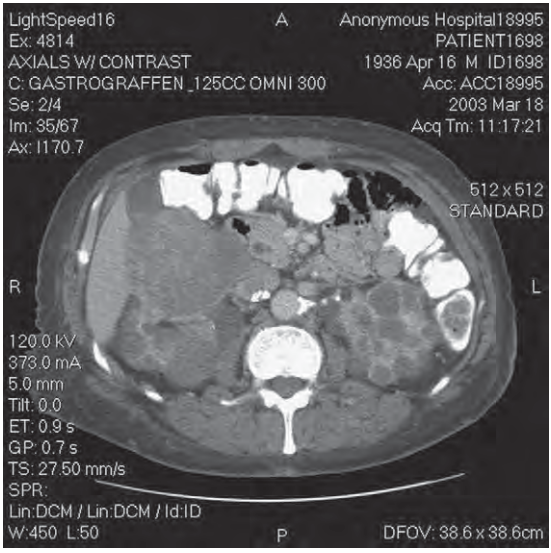


Figure 80–1

Large acquired cystic kidneys with a large tumor in the right kidney. This tumor was found due to gross hematuria and was noted to be metastatic.

investigation for ACKD. Other unexplained symptoms may be associated with acquired cysts. Unexplained anemia or polycythemia should also be investigated, as both increased and decreased hemoglobin have been reported with this disease. Particular attention should be paid to male patients in whom this disease progresses more rapidly. Males with acquired cysts may need evaluation more frequently, whereas females may be evaluated less often. The overall kidney size should be noted, as well as the presence or absence of mass lesions. The presence of any mass lesion or enlarged kidneys needs to be followed more often, such as every 3 to 4 months. Any mass lesion that increases in size within a 6-month period should be considered suspicious and should be removed.

Special consideration should be given to patients awaiting renal transplantation. All such patients should be screened for ACKD and tumors, regardless of the duration of azotemia or

dialysis. This screening will identify those patients with tumors before instituting active immunosuppression therapy.

Clinical Course

The growth of these acquired cysts rarely causes problems. However, tumor development in cystic kidneys needs to be followed closely. The differentiation between adenomas and adenocarcinomas is based on several factors, including size, local invasion, and microscopic evidence of anaplasia. Criteria for the diagnosis of a carcinoma (exclusive of metastasis) include a diameter >3 cm, a thick or irregular wall, and nonhomogeneity of the tumor. The size of the tumor is usually taken as the most consistent feature relating to the malignant potential of the mass. Any tumor >3 cm in diameter is usually considered an adenocarcinoma. However, the size of the end-stage kidneys is also important in determining the type of tumor present.

An evaluation of the occurrence of tumors in acquired cystic kidneys in relation to kidney weight found that kidneys that were smaller than normal kidneys had a low incidence of carcinoma (11.4%), whereas kidneys enlarged beyond normal had a 55.6% incidence of carcinoma. The incidence of adenomas was similar in both groups (26.6% in small kidneys and 22.9% in large kidneys). All kidneys with acquired cystic disease weighing >350 g (the weight of a normal nonazotemic kidney) contained carcinoma. The majority of adenocarcinomas occurred in males after prolonged dialysis therapy, and many were associated with cystic kidneys larger than normal. In two cases, no mass lesion was noted. However, adenocarcinoma was present throughout the entire enlarged kidney.

Although renal adenocarcinomas in the general population have been characterized as relatively slow-growing tumors with local spread occurring before distant metastases, the average growth of this cancer in the dialysis patient is not known but may be extremely rapid. In one patient, the tumor grew to four times its original size over a 2-month period. In another report, the patient died of complications of metastatic disease within 4 months of nephrectomy despite no documented metastases at the time of surgery. Thus, the presence of any solid renal mass requires prompt evaluation.

Treatment

Although many patients with chronic renal failure develop ACKD, only a small proportion of these patients appear to develop

complications. Hemorrhage into cysts or the collecting system is the most common complication. Usually, this bleeding requires only replacement of blood and control of pain. If the bleeding persists or becomes severe, wire-loop embolization of the affected kidney may stop the bleeding without the need for nephrectomy. Surgery may be indicated if bleeding cannot be controlled. A similar conservative approach is used for the treatment of retroperitoneal hematomas, although nephrectomy may be needed for uncontrollable hemorrhage or intractable pain.

Treatment of renal tumors in acquired cystic disease is not clearly defined. Several aspects of these tumors need to be considered, including their pattern of growth and malignant potential. The growth of these tumors appears to be variable. Some patients exhibit rapid tumor growth with systemic symptoms, whereas in other patients the carcinomas may be silent and found incidentally at autopsy or nephrectomy. The malignant potential of these tumors is also not understood. It is disturbing to note that several of the adenocarcinomas reported in the literature were considerably smaller than 3 cm in diameter. However, none of these small carcinomas was metastatic—suggesting that the malignant potential of these tumors is low when the size is small.

In my opinion, patients with tumors <3 cm in diameter should be followed with serial CT studies every 3 to 4 months so that growth of the mass can be tracked. CT scans may be repeated yearly if the tumor size remains stable. A tumor size >3 cm in diameter is an indication for nephrectomy. Nephrectomy should also be considered in all patients with acquired cystic kidneys larger than normal size or if the kidneys are increasing in size, even if no mass lesion if found.

The potential for malignant transformation in these enlarged cystic kidneys cannot be ignored. Nephrectomy should also be performed in all patients with tumors of any size or with enlarged kidneys who are candidates for renal transplantation. In addition, nephrectomy should be considered in patients with renal tumors of any size and symptoms suggestive of renal carcinoma—such as liver function abnormalities or persistent fever that cannot be otherwise explained. Although these guidelines for nephrectomy are not made lightly, the availability of erythropoietin now permits the removal of renal tissue without losing the residual hematopoietic effects. The availability of laparascopic nephrectomy has decreased the morbidity associated with a nephrectomy and would be the method of choice for surgical removal.

Recommended Reading

Ishikawa I, Sito Y, Onouchi Z, et al. Development of acquired cystic disease and adenocarcinoma of the kidney in glomerulonephritic chronic hemodialysis patients. Clin Nephrol 1980;14:1–6.

Initial description of the problem.

MacDougall ML. Acquired cystic kidney disease. In Jacobson HR, Striker GE, Klahr S (eds.), *The Principles and Practice of Nephrology*. Philadelphia: Decker BC 1990:376–78.

Good review with emphasis on clinical features and treatments.

MacDougall, ML, Welling LW, Wiegmann TB. Prediction of carcinoma in acquired cystic disease as a function of weight. J Am Soc Nephrol 1990; 1:828–31.

Predictive factors other than length of time on dialysis.

Oya M, Mikami, S, Ryuichi M, et al. C-jun activation in acquired cystic kidney disease and renal cell carcinoma. J Urology 2005;174:726–30.

Increased proto-oncogene activation in early tumors associated with acquired cystic kidney disease.

Park JH, Kim YO, Park JH, et al. Comparison of acquired cystic kidney disease between hemodialysis and continuous ambulatory peritoneal dialysis. Korean J Intern Med 2000;15:1–5.

Similar incidences for ACKD in patients on both modes of renal replacement therapy.

Sule N, Yakupoglu U, Shen S, et al. Calcium oxalate deposition in renal cell carcinoma associated with acquired cystic kidney disease: A comprehensive study. Am J Surg Pathol 2005;29:443–51.

An association of calcium oxalate crystal deposition in renal cell carcinomas in acquired cystic kidney disease.

Takebayahsi S, Hidai H. Chiba T, et al. Using helical CT to evaluate renal cell carcinoma in patients undergoing hemodialysis: Value of early enhanced images. Am J Radiol 1999;172:429–33.

Good evaluation of new techniques for adequate enhancement.

CHAPTER 81

End-Stage Renal Failure in the Diabetic Patient

Jeffrey Giullian, MD, and Anthony Langone, MD

Background and Epidemiology

Diabetes mellitus (DM) is the leading cause of end-stage renal disease (ESRD) in the United States and several other countries worldwide. Of the 99,034 new patients with ESRD in the United States in 2003, diabetes accounted for more than 43,000 of these cases—or approximately 44%. This escalation in diabetes-induced ESRD, up from 37% of incident cases in the early 1990s, has resulted from both the rising rate of obesity in the general population and improved survival of diabetics.

Dialysis-dependent diabetic patients utilize a disproportionate amount of Medicare resources. Of the 16.6 billion dollars spent on ESRD in 2003, diabetics accounted for 7.4 billion. The average cost of hemodialysis for diabetic patients exceeds $69,000 annually, nearly $5,000 more than for nondiabetics. This increased cost is largely due to an increased number and length of hospitalizations. Although peritoneal dialysis (PD) costs are not quite as high (at $54,000 per year), PD in diabetics is still performed at an increased cost versus nondiabetics.

Not all patients with diabetes develop diabetic nephropathy, and fewer still progress to ESRD. In the past, type 1 diabetics had a greater risk of developing nephropathy and eventual uremia compared with type 2 diabetics. This gap has narrowed in recent years, partially due to improved cardiovascular survival among the latter group. Of those diabetic patients that do progress, it remains unclear exactly which metabolic, genetic, and environmental factors predispose to renal disease. Genetic research in the realm of the human leukocyte antigen (HLA) points to an increased risk of developing both micro- and macroalbuminuria in patients with the HLA-A2 subclass. Studies also implicate short stature and low birth weight along with ethnicity as significant factors for progression. In addition, documented family clustering of nephropathy strengthens the hypothesis that genetics are partially to blame.

In population studies, certain genetic polymorphisms in the renin-angiotensin-aldosterone system (RAAS) coincide with increased risk for kidney disease. Likewise, a deletion polymorphism in the gene coding for the angiotensin-I-converting enzyme acts as a risk factor for vascular disease in diabetic patients. However, no substantial evidence has definitively linked one of these gene mutations to the development of diabetic nephropathy.

Many of the known RAAS polymorphisms occur more frequently in ethnic minorities (such as African Americans) than in Caucasians. This hypothesis helps explain the increased risk of developing renal disease among certain ethnic groups. Hispanics, African Americans, and Native Americans have a significantly greater chance of developing diabetic nephropathy compared to their Caucasian counterparts due in part to overall higher rates of diabetes. At the extreme, almost 75% of all Native Americans with ESRD have diabetes as the primary etiology.

The Pima Indians of Arizona tend to develop ESRD at a younger age and at an accelerated rate compared with other populations. Rapid progression of nephropathy occurs in spite of generally lower overall blood pressure and lipid levels. The hypothesis of oligoglomerulomegaly, which ultimately leads to higher incremental loss of single-nephron glomerular filtration rate (GFR), may explain this paradox.

Overall, diabetic patients tend to start dialysis at a higher GFR (lower creatinine) than other populations. According to the most recent U.S. Renal Data System (USRDS) database, in 2003 the average GFR (by MDRD (modification of diet in renal disease) formula) for incident diabetic ESRD patients was 10.4mL/minute compared to only 9.4mL/minute in nondiabetics. Many diabetic patients develop uremic symptoms earlier than nondiabetics, although symptoms of nonrenal diabetic complications (such as gastroparesis) may mimic symptoms of uremia. In the United States, Medicare will reimburse for dialysis when the estimated GFR falls below 15mL/minute in diabetics versus 10 mL/minute in the nondiabetic population. Like the general ESRD population, the majority of diabetics choose hemodialysis as their initial form of renal replacement therapy (RRT). In 2003, almost 42,000 incident ESRD diabetic patients started hemodialysis, compared to only 2900 diabetics who started PD and 367 who received preemptive renal transplantation.

Annual mortality among diabetics with ESRD tends to be higher than the overall death rate for other dialysis patients. Patients with ESRD and type 2 diabetes mellitus have an annual mortality rate greater than 25%, compared to 18% in nondiabetic dialysis patients.

Prevention

Overt diabetic nephropathy with macroalbuminuria (>300 mg albumin daily) often occurs within 5 to 10 years of the onset of microalbuminuria (defined as 30–300 mg albumin daily). During the initial phase of this nephropathy, GFR actually increases—due in part to glomerular hypertrophy and hyperfiltration. However, a precipitous decline in renal function often follows this initial honeymoon phase. On average, GFR drops 5 to 15 mL/minute each year after the onset of macroalbuminuria without treatment. The decline in GFR drops to less than 4mL/minute when properly treated with ACE inhibitors or angiotensin receptor blockers (ARBs).

In addition to the direct renal implications of micro- and macroalbuminuria, these patients have increased risk for cardiovascular disease and death. Type 2 diabetics with microalbuminuria have twice the 10-year mortality from cardiovascular causes as their normoalbuminuric diabetic counterparts. The increasing prevalence of type 2 DM and the prediction that the number of diabetics will double in the coming decade compounds the importance of this risk.

Given these statistics, prevention of diabetic complications is of utmost importance. Activation of the RAAS seems to play a crucial role in development and progression of diabetic nephropathy. Angiotensin II affects several aspects of renal structure and function, including the vascular component, sodium and bicarbonate handling, mesangial cell function, and development of fibrosis. For these reasons, inhibition of the RAAS remains the cornerstone of treatment—coupled with overall blood pressure control and glycemic control.

Evidence from large clinical trials such as the Captopril Trial in type 1 diabetics and RENAAL and IDNT trials in type 2 diabetics with macroalbuminuria suggest that RAAS blockade significantly slows the rate of decline of renal function. In the Captopril Trial, type 1 diabetics had a 50% lower risk of the combined endpoint of death, dialysis, and transplantation if they were in the ACE inhibitor treatment arm compared to placebo. This improvement was independent of blood pressure control.

The use of ARBs has similarly proven beneficial in type 2 diabetics. The use of losartan or irbesartan reduces the risk of progression to ESRD by 20% over 3 years. A post hoc analysis of the RENAAL data showed that the reduction of albuminuria was present in all ethnic groups studied. Several other studies (including the HOPE, LIFE, ABCD, and CHARM trials) revealed improved cardiovascular outcomes in diabetics treated with ACE inhibition or ARBs. Because there appears to be combined renal and cardio-

vascular benefits, quality care requires early and aggressive treatment with RAAS blockade.

The ARB class of medications appears relatively safe and well tolerated. The overall risk of adverse effects in the IDNT trial was lower in the irbesartan treatment arm than the placebo or calcium channel blocker arm. Less than 2% of patients in the ARB treatment cohort developed clinically significant hyperkalemia.

Improved glycemic control is another goal in diabetic patients of all types. The Diabetes Control and Complications Trial showed that intensive insulin therapy and more frequent blood glucose monitoring resulted in glycosylated hemoglobin (HbA1c) levels less than 7%, reducing the occurrence of microalbuminuria by 39% and macroalbuminuria by 54% compared to the cohort with worse glycemic control (HbA1c >9%). The authors concluded that tight glycemic control delays the onset and can slow the progression of many diabetic complications, including nephropathy. However, intensive treatment is not without risk. Aggressively treated diabetics tend to gain more weight and have a two- to threefold increased risk of hypoglycemic events.

In regard to glycemic control, peroxisome proliferators–activated receptor (PPAR) agonists may have several beneficial effects on the kidneys. The PPARs belong to a family of ligand-activated transcription factors with a wide repertoire of actions, including regulation of insulin sensitivity, lipid metabolism, adipogenesis, and inflammation. In type 2 diabetics, certain isoforms of this transcription factor are involved in preventing development of nephropathy. This evidence has led to a potential therapeutic role of PPAR modulators in the treatment of diabetic nephropathy beyond their effects on glycemic control. Thiazolidinediones are PPAR gamma agonists that improve serum glucose levels and may retard the rate of renal fibrosis. Further studies, however, are necessary to elucidate the exact role of these drugs as agents in protecting against the progression of diabetic nephropathy.

Access Issues

Arteriovenous (AV) fistulas are preferable to synthetic grafts and vascular catheters in all hemodialysis populations because fistula survival is double that of graft survival in the diabetic population. However, due to the high likelihood of vascular calcification and other blood vessel abnormalities fistula formation and maturation may be difficult to achieve. The rate of primary fistula failure remains high in diabetics. AV fistula formation 3 to 6 months prior to the anticipated need for dialysis helps

ensure adequate hemodialysis access and may reduce the use of venous catheters.

Preoperative evaluation with duplex ultrasonography improves overall access outcomes in diabetics. Several parameters (including distensibility of the veins, measurement of the arterial lumen diameter, and resistive indices) predict successful fistula maturation. Vein mapping via ultrasound often aids the surgeon in finding the highest-quality vascular location. In addition, blood volume expansion prior to surgery increases venous distension and may improve surgical outcome—although this practice can lead to volume overload in a pre-ESRD patient with limited capacity to excrete the extra fluid.

Despite higher morbidity, mortality, and cost associated with hemodialysis catheters, many diabetic patients will require this type of vascular access at some point during their hemodialysis course. Use of catheters for AV access is higher among diabetics than the general hemodialysis population. Per the 2003 USRDS database, the insertion rate of catheters in diabetics on hemodialysis reached 520 per 1000 patient-years versus 473 insertions per 1000 patient-years in the overall hemodialysis population.

Dialysis Options and Complications

Diabetic patients nearing ESRD have the same options for renal replacement therapy as other ESRD patients. Similar to other ESRD patients, transplantation offers the most long-term benefits. Unfortunately, the cadaveric waiting list exceeds 5 years on average—limiting preemptive transplantation.

Diabetics face unique obstacles associated with all types of renal replacement therapy. Therefore, the ideal form of treatment is a highly individualized decision. Hemodialysis and PD have comparable long-term survival rates in the diabetic population. However, as previously stated diabetics suffer greater mortality risk than nondiabetics on dialysis and complications associated with renal replacement therapy are commonplace.

With regard to hemodialysis, intradialytic hypotension, left ventricular hypertrophy (LVH), and vascular access problems remain particularly difficult to overcome. Even though 50% of diabetics require antihypertensive therapy, intradialytic hypotension (IDH) causes significant morbidity and may lead to catastrophic consequences—including cerebral and cardiac ischemia. IDH occurs more frequently in diabetics than nondiabetics for several reasons, including autonomic insufficiency, impaired left ventricular func-

tion, vascular calcification, and increased susceptibility for intradialytic fluid gain.

As a consequence of long-standing hyperglycemia, autonomic insufficiency is present in a substantial portion of diabetics on dialysis. In the setting of autonomic dysfunction, the usual compensatory responses to decreased circulating volume (such as splanchnic and dermal vasoconstriction, increased arterial tone, and elevated heart rate) are diminished. When a patient experiences recurrent IDH, the first step is to avoid antihypertensive medications on the morning of dialysis. In addition, treatment with certain medications can augment the body's response to hypotension. For example, midodrine (a selective alpha-1 adrenergic receptor agonist) successfully counteracts IDH in a substantial percentage of diabetics. This medication raises blood pressure through constriction of both arterial and venous blood vessels. Typically, this drug is prescribed to treat orthostatic hypotension but has proven useful for intermittent dosing prior to hemodialysis. A single dose between 2.5 and 10 mg usually suffices because the medication's half-life during dialysis reaches 3.5 hours. In a meta-analysis of nine studies, midodrine improved postdialysis systolic blood pressure 12.4 mmHg and diastolic pressure 7.3 mmHg. In this publication, the treated cohort had a nadir dialysis systolic blood pressure 13.3 mmHg higher than the control group.

Other drugs reported as reducing the risk of intradialytic hypotension include caffeine 250 mg (equivalent to the amount in about five soft drinks), L-carnitine (a cofactor required for mitochondrial transport of fatty acids), sertraline (a selective serotonin reuptake inhibitor), and fludricortisone (an oral mineralocorticoid). The antihypotensive effects of fludrocortisone in renal failure may be mediated through extrarenal mechanisms rather than the usual method of increased sodium reabsorption in the distal tubule.

Other strategies for minimizing hypotension on dialysis include modification of dialysate temperature or sodium profile. Small changes in temperature may impact largely on the body's hemodynamic responses. Cooling dialysate to 34.4 to 35ºC results in substantially fewer episodes of IDH and improved mean arterial pressure. One study reported sevenfold fewer hypotensive occurrences compared to standard temperature. No studies to date have reported reduction in dialysis adequacy when using lower temperatures. Alternatively, sodium modeling—the practice of initiating dialysis sessions with a relative hypertonic solution (sodium concentration of about 150 mEq/L) and decreasing tonicity in a stepwise or linear fashion over several hours—may also reduce

episodes of intradialytic hypotension while reducing side effects such as dizziness, muscle cramps, and headaches.

In addition to the previously cited drugs and maneuvers, minimizing hourly ultrafiltration (less than 500–600 ml per hour) reduces the likelihood of IDH. Diabetic patients require extensive counseling to limit interdialytic fluid gains, and those patients who do gain more than 2 L between dialysis sessions might require longer or more frequent hemodialysis and ultrafiltration sessions.

Despite efforts to limit a patient's fluid gains between dialysis sessions, poorly controlled hyperglycemia augments the thirst sensation through increased osmotic forces. Anecdotally, the thirst sensation may be partially quenched with glucose-free hard candies throughout the day. Limited studies have also suggested that ACE inhibitors may decrease thirst via an effect mediated by the central nervous system. However, this treatment effect lasts only a short time. After 4 to 6 weeks of treatment, the thirst sensation equalizes between ACEi-treated and non-ACEi cohorts.

In addition to its association with IDH, autonomic dysfunction has also been linked to the development of LVH. LVH is a substantial risk factor for development of congestive heart failure and shortened survival. In an echocardiography study of hemodialysis patients from Japan, diabetic patients had greater mean left ventricular mass index (LVMI) than nondiabetics. The authors commented that the coexistence of autonomic insufficiency and LVH factors into the large number of cardiac events in this patient population.

PD serves as a viable alternative to hemodialysis for diabetics. PD offers several advantages over hemodialysis for diabetic patients, including reduced cardiac stress, less hypertension and improved volume control, steady metabolite removal, and slower loss of residual renal function. In addition, patients can administer insulin via the peritoneal route if desired. The overall incidence of peritonitis is not greater in the diabetic population compared to their nondiabetic counterparts.

Over time, however, the peritoneal membrane of diabetics on PD becomes permeable to small solutes—leading to loss of ultrafiltration capability and eventual development of peritoneal fibrosis. The precise etiology of this phenomenon has not been elucidated, but likely results from glucose degradation products generated during heat sterilization of the dialysate.

Perhaps this anatomic change leads to the metabolic differences observed between diabetics and nondiabetics on PD. One study comparing these two groups on continuous ambulatory PD found that diabetics had lower serum albumin (3.0 mg/dL versus 3.5 mg/dL,

respectively) and greater dialysis protein loss than nondiabetics. Regardless of the cause, these changes ultimately lead to increased rates of technique failure in diabetics over time.

Another concern for diabetics undergoing PD involves systemic glucose uptake from dialysate. This increase in simple carbohydrate absorption ultimately leads to an increase in serum glucose levels and weight gain. Over time, as the ultrafiltration coefficient of the peritoneal membrane decreases patients require higher concentrations of dextrose—further complicating serum glucose control. A potential solution to this problem may reside in the use of glucose-free dialysate solutions, such as icodextran (discussed later in the chapter).

PD patients have slower loss of residual renal function than hemodialysis patients. Residual renal function is a positive prognostic indicator of survival and well-being among all dialysis patients. Among incident dialysis patients, diabetics are at greater risk of declining renal function. However, both diabetic and nondiabetic PD patients had a 65% lower risk than the hemodialysis cohort for losing residual renal function.

Diabetic end-stage renal patients spend more time in the hospital compared to the nondiabetic group. ESRD patients average slightly less than 14 days per year in the hospital. Diabetic hemodialysis patients average 17 days per year, whereas diabetic PD patients average more than 19 days yearly.

Among both HD and PD patients, cardiovascular disease accounts for the majority of hospitalizations. As predicted, mortality in the diabetic dialysis population remains higher than the general dialysis cohort. The mortality rate among both groups is about 25% per year.

Glycemic Issues

Increased peripheral insulin resistance and decreased insulin degradation accompany the progression of chronic renal failure. The balance between these two changes often leads to an overall decreased insulin requirement as glomerular filtration declines. Although instituting dialysis may reverse some of these effects, ESRD patients tend to require less insulin than non dialysis-dependent diabetics.

Evaluation of glycemic control may not be straightforward in patients with renal failure. Hemoglobin A1c measurements are less accurate in renal failure patients for several reasons. The average red blood cell life span dips to 90 days in dialysis patients, compared to 120 days in the general population—falsely elevating

the hemoglobin A1C level. In addition, elevated urea corrupts certain HbA1c assays—leading to an overestimation of hyperglycemia. Regardless, many experts target HbA1c level below 7% to reduce the risk of diabetic-associated complications. Alternatively, measurement of fructosamine may better represent overall glycemic control. Similar to hemoglobin, several other proteins undergo nonenzymatic glycosylation in the setting of hyperglycemia. Some of these proteins, including albumin, are measured collectively and are defined as fructosamine. In the non dialysis-dependent patient, fructosamine correlates better with glycemia over the previous 3- to 6-week period compared to HbA1c. Serum fructosamine levels do require adjustment for serum albumin levels, however.

Oral hypoglycemic agents remain the mainstay of therapy for type 2 diabetics on dialysis. Metformin is contraindicated in patients with moderate renal insufficiency due to the risk of lactic acid production. In addition, certain sulfonylureas (such as glyburide and glimeprimide) are highly renally cleared and have prolonged half-lives in the setting of renal insufficiency and their use may lead to profound hypoglycemia. The majority of glipizide metabolism occurs in the liver and can be used in renal insufficiency. The class of PPAR gamma agonists medications known as thiazolidinediones (discussed previously) also undergo liver metabolism, and therefore accumulation does not appear to occur in renal failure.

For insulin-dependent patients on PD, intraperitoneal insulin administration provides an alternative to more traditional routes. This treatment has the benefit of continuous insulin infusion and may provide more physiologic levels of insulin compared to intermittent subcutaneous treatment. However, several disadvantages to intraperitoneal insulin administration exist, including an increased risk of bacterial contamination of dialysate during the injection process. Higher doses of insulin, sometimes a fourfold increase, are necessary for adequate glycemic control when insulin is delivered by a peritoneal route. Furthermore, intraperitoneal insulin administration has been associated with greater risk of peritoneal fibroblast proliferation and hepatic steatosis—because the insulin quickly enters the splanchnic and then the portal circulation rather than being absorbed slowly from the peripheral circulation.

The use of icodextran-containing dialysate solution has several potential benefits compared to dextrose-based solutions, including better ultrafiltration and reduced systemic and peritoneal glucose exposure. Icodextran, an iso-osmotic glucose-free polymer, provides sustained ultrafiltration during long PD dwells. Small studies have

confirmed that the use of this solution enhances ultrafiltration and convective clearance when used during daytime dwells. It also improves glycemic control in insulin-dependent diabetics without increasing the risk of peritonitis. Short-term use of icodextran does not cause hyperglycemia or hyperinsulinemia. In addition, one randomized controlled trial revealed that patients treated with traditional dextrose-containing solutions gained weight—whereas those who received icodextran in their daytime dwell lost weight. Improvement of morbidity and mortality remains unknown, as do the long-term effects of icodextran and systemic accumulation of its by-product maltose.

Hemodialysis also exposes patients to glucose-containing solution. Unlike PD, however, the goal is not ultrafiltration but the minimization of hypoglycemia during the procedure. Without glucose in the dialysate, patients lose up to 30 g of sugar during each treatment. In general, hemodialysis solution contains approximately 100 to 200 mg/dL dextrose.

General Diabetic Care

Minimizing the extrarenal risks of hyperglycemia remains an important aspect of the overall care of diabetics. The American Diabetic Association (ADA) recommends routine eye and foot examinations. This is exceedingly pertinent to the diabetic ESRD population, as these patients already have known micro- and macrovascular compromise. Guidelines from the ADA vary slightly between type 1 and type 2 diabetics, but in essence all patients should undergo ophthalmologic evaluation annually (more frequently if retinopathy already exists).

Proper care of the diabetic patient also includes examination of the feet and legs for neuropathy, vascular insufficiency, and nonhealing lesions. Annual evaluation of the lower extremities via a Semmes-Weinstein 5.07 monofilament is useful for detecting loss of sensation. Assessment of pedal pulses and risk of claudication is also valuable, and according to the ADA even patients with asymptomatic peripheral artery disease should undergo testing with ankle brachial index.

General care for dialysis-dependent diabetic patients also includes assessment for cardiovascular disease. Ischemic heart disease and myocardial infarction in new dialysis patients in the United States is significantly more common in diabetic dialysis patients compared to nondiabetics. The ADA recommends cardiac stress testing for any patient with typical or atypical cardiac symptoms and an abnormal electrocardiogram.

The UKPDS trial demonstrated benefit of blood pressure control for improving cardiovascular outcomes in diabetics. The benefit of HMG-Co A reductase inhibitors (statins), on the other hand, remains controversial in all diabetic dialysis patients. The 4D study, which compared atorvastatin to placebo in more than 1200 patients, did not show improvement of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke. This medication did, however, have a small but significant benefit on all cardiac outcomes combined. Contrary to the findings of this trial, several observational studies have documented a cardiovascular benefit of statins in this population.

Currently, no specific studies of aspirin or other antiplatelet therapy exist in this patient population. Although the risk of bleeding at hemodialysis access sites increases when patients use platelet inhibitors, the benefits of daily aspirin (75–325 mg) likely outweigh the risks. Similarly, smoking is an exceedingly important modifiable risk factor for at-risk patients. In the United States, tobacco exposure among diabetics is greater than nondiabetics and smoking cessation is paramount to improving outcomes.

Whereas cardiovascular disease accounts for a large portion of mortality in diabetic dialysis patients, peripheral neuropathy remains a significant cause of morbidity and decreased quality of life. In 2005, the ADA recommended glycemic control as the initial step toward treatment of peripheral neuropathy. Improvement in blood sugar alone may fail to improve a patient's symptoms. Several options now exist for neuropathic pain relief, although some have not yet gained FDA approval for use in ESRD. Providers have traditionally prescribed gabapentin and tricyclic antidepressants as first-line therapy for this disorder, despite lacking specific FDA approval.

Newer drugs, such as pregabalin (a drug structurally similar to gabapentin and duloxetine, a dual-serotonin and norepinephrine uptake inhibitor) have proven efficacious in non dialysis-dependent patients for treatment of diabetic peripheral neuropathy. Pregabalin requires dose reduction in dialysis-dependent patients, and a supplemental dose is recommended after hemodialysis sessions. This medication can cause sedation and may be habit forming. In the setting of renal failure, dosing of the other new medication (duloxetine) remains undefined. Major metabolites of this drug accumulate seven- to ninefold greater in dialysis patients compared to patients with normal GFR.

Another treatment option for diabetic peripheral neuropathy includes topical capsaicin cream, produced from hot peppers.

Capsaicin acts locally to deplete substance P and through this mechanism produces local pain relief. Anecdotal experience with topical lidocaine suggests that it too may reduce symptoms, likely as adjunct therapy.

Gastroparesis occurs less commonly than peripheral neuropathy in diabetics, but still affects a substantial proportion of patients. This entity of delayed gastric emptying afflicts more than 25% of type 1 diabetics and more than 50% of type 2 diabetics. In addition, recurrent nausea and vomiting may contribute to an already poor nutritional status of diabetics on dialysis. These patients have increased susceptibility to electrolyte abnormalities, acid/base disturbance, volume problems, variable serum glucose levels, and vitamin deficiencies. Symptom improvement requires both behavior modification and medications, but even with proper treatment gastroparesis may be difficult to control. Because solid foods, large meals, and fat all delay gastric emptying, dieticians and providers should counsel patients to eat smaller and more frequent meals with less fat content. In this situation, liquid dietary supplements help maintain adequate nutrition.

Both antiemetic and prokinetic medications play a substantial role in the treatment of symptomatic gastroparesis episodes. IV erythromycin, cisapride, and metoclopramide improve gastric emptying time. All of these medications have substantial potential side effects. Erythromycin decreases gastric retention to a greater degree than placebo but can be associated with ototoxicity, prolonged QT syndrome, and pseudomembranous colitis. Cisapride, which acts as a serotonin 5HT4 receptor agonist, leads to acetylcholine release in the myenteric plexus. This drug has been used successfully in the past, but access is now severely limited due to propensity for deadly arrhythmias. Metoclopramide acts as a prokinetic agent and as an antiemetic. This medication works better in IV form than oral, but adverse effects such as tardive dyskinesia limit its use.

A relatively new drug, tegaserod, has a mechanism of action similar to that of cisapride. This medication acts as a partial 5HT4 agonist and was first used as treatment for irritable bowel syndrome. In clinical studies, this drug reduces orocecal transit time. In one study, gastric emptying normalized in 80% of treated patients compared to only about half of untreated patients. When behavior changes and medications fail to control symptoms, more invasive procedures (such as pyloric botulinum toxin injection and gastric pacemakers) may be employed. These alternatives remain investigational, however—limiting their use to date.

Transplantation

The National Kidney Foundation recommends that patients whose GFR drops below 30 mL/minute be referred for evaluation of renal transplant. Earlier referral for diabetics helps ensure adequate time for proper workup. According to the most recent USRDS database, the national transplant waiting list contained more than 16,500 diabetics awaiting cadaveric renal transplantation—a fourfold increase over the past decade. Diabetics, who previously accounted for only 15 to 20% of those awaiting cadaveric transplant, now comprise more than 30% of the waiting list. Despite this growth, diabetics are still underrepresented with regard to transplantation. This discrepancy is often attributed to the overall co-morbidities associated with diabetes mellitus.

In recent years, the gap between allograft survival in diabetics and nondiabetics has decreased. One-year graft survival rate for patients who received a kidney from a deceased donor is nearly equivalent between the groups (approximately 89%). Nearly equivalent 2-, 3-, and 5-year survival rates also exist. Diabetic transplant patients do spend on average 2 days more in the hospital each year than the nondiabetic group (9.2 versus 7.2 days, respectively), but this is still nearly a 50% reduction compared to diabetics receiving dialysis.

Recurrent diabetic nephropathy tends to occur in the allograft within a few years of transplantation. Hallmarks of disease recurrence include thickening of the basement membrane, hyalinization of the arterioles, and mesangial expansion. These pathologic findings aid in differentiating diabetic causes of rising creatinine from chronic allograft nephropathy and calcineurin inhibitor toxicity.

Type 1 diabetics should consider a pancreatic transplant at the time of kidney transplant. When successful, the tandem allocation of these two organs to an individual greatly improves health status and quality of life. Patients who receive simultaneous kidney/pancreas transplants have improved overall survival and better graft survival than those diabetics who receive only a kidney. However, adjusting for age of donor and recipient and other factors may attenuate some of this benefit. Regardless, type 1 diabetics who do not receive a pancreas at the time of cadaveric renal transplant (or those who undergo transplantation from a living donor) should remain listed with the United Network of Organ Sharing for a pancreas.

Recommended Reading

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular

outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345(12):861–69.
This study and the study by Lewis et al. and IRMA II (published simultaneously in the NEJM) provide unequivocal proof that certain ARBs are beneficial in reducing progression of various stages of diabetic renal disease.
Davies SJ. Exploring new evidence of the clinical benefits of icodextrin solutions. Nephrol Dial Transplant 2006;21(2):ii47–50.
This meta-analysis evaluates the use of icodextrin and reports increased ultrafiltration and better glycemic control compared to glucose-contating solutions.
Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977–86.
This is a large randomized controlled trial that assesses the beneficial effects of intensive glycemic control versus usual care in insulin-dependent patients. Long-term follow-up (6.5 years) resulted in reduced risk of developing or slowing progression retinopathy and decreased occurrence of microalbuminuria and neuropathy. Treatment was not without risk, however.
Gaston RS, Basadonna G, Cosio FG, Davis CL, Kasiske BL, Larsen J, et al. for the National Kidney Foundation Task Force on Diabetes and Transplantation. Transplantation in the diabetic patient with advanced chronic kidney disease: A task force report. Am J Kidney Dis 2004;44(3):529–42.
This task force report discusses the state of transplantation for diabetic patients. It provides an excellent overview of topics uniquely important to the subset of diabetic patients awaiting transplant and those who have received a kidney or kidney-pancreas transplant.
Hilsted J, Parving HH, Christensen NJ, Benn J, Galbo H. Hemodynamics in diabetic orthostatic hypotension. J Clin Invest 1981;68(6):1427–34.
This is a small study evaluating the difference in hormonal response to standing in diabetics with and without neuropathy compared to healthy controls. In diabetics with severe neuropathy, orthostatic hypotension was likely due to impaired sympathetic activity.
Krishnan M, Tam P, Wu G, Breborowicz A, Oreopoulos DG. Glucose degradation products (GDPs) and peritoneal changes in patients on chronic peritoneal dialysis: Will new dialysis solutions prevent these changes? Int Urol Nephrol 2005;37(2):409–18.
This review article describes the formation of glucose degredation products and their potential role in altering the peritoneum, ultimately leading to ultrafiltration failure.
Lemley KV. A basis for accelerated progression of diabetic nephropathy in Pima Indians. Kidney Int Suppl 2003;(83):S38–42.
In this small study of Pima Indians who underwent renal biopsy, the author puts forth a hypothesis for the phenomenon of accelerated rate of diabetic nephropathy.
Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993 Nov 11;329(20):1456–62.
A landmark randomized controlled study evaluating the use of ACE inhibitor versus placebo for patients with diabetic nephropathy.
Mason NA, Bailie GR, Satayathum S, Bragg-Gresham JL, Akiba T, Akizawa T, et al. HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. Am J Kidney Dis 2005;45(1):119–26.
Unlike the results of the previously cited randomized controlled trial, this observational study of patients prescribed statins showed improved overall

survival. Cardiac and noncardiac causes of death were both lower in patients who received a prescription for one of these lipid-lowering agents.

Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. Diabetes 1992;41(6):736–41.

This prospective observational study links microalbuminuria to risk of death, especially cardiovascular-associated death in non insulin-dependent diabetics.

Nelson RG, Newman JM, Knowler WC, Sievers ML, Kunzelman CL, Pettitt DJ, et al. Incidence of end-stage renal disease in type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. Diabetologia 1988;31(10):730–36.

This epidemiology article investigates the etiology of ESRD among Pima Indians, a population with exceedingly high rates of diabetes and renal failure.

Parving HH, Smidt, B. Friisberg B, et al. A prospective study of glomerular filtration rate and arterial blood pressure in insulin-dependent diabetics with diabetic nephropathy. Diabetologia 1981;20:457–61.

This prospective study documents the natural history of GFR decline in untreated type 1 diabetics.

Parving HH, Tarnow L, Rossing P. Genetics of diabetic nephropathy. J Am Soc Nephrol 1996;7(12):2509–17.

This article reviews genetics and family clustering of diabetic nephropathy. It also discusses confounding pieces of evidence regarding the role of ACE inhibitor gene deletion polymorphisms.

Ritz E, Strumpf C, Katz F, Wing AJ, Quellhorst E. Hypertension and cardiovascular risk factors in hemodialyzed diabetic patients. Hypertension 1985;7:118–24.

This paper is a retrospective analysis of cardiovascular risk factors and likelihood of death in diabetics compared to nondiabetics. Sudden death was far more common in this study than nonfatal myocardial infarction and stroke combined.

Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial 2004;17(5):365–70.

This review article discusses metabolism and dosing requirements of typical drugs used for diabetic glycemic control.

U.S. Renal Data System. USRDS 2005 annual data report. Bethesda, Maryland, U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005. Available at *http://www.usrds.org*. Accessed July 2006.

This site provides information on ESRD epidimology and patterns over the past two decades. It is published yearly by the National Institutes of Health.

Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353(3):238–48.

Also known as the 4D study, this is a large randomized double-blind placebo-controlled trial that evaluated the benefits of Atorvastatin. The treatment arm did not show a better outcome despite dramatically improved cholesterol profiles.

CHAPTER 82

Choice of Insulin Administration Route in Diabetic Peritoneal Dialysis Patients

José A. Diaz-Buxo, MD, FACP, and
Terri L. Crawford-Bonadio, RN, CNN

Many clinicians consider peritoneal dialysis (PD) the preferred modality of therapy in the treatment of diabetics with end-stage renal disease. The potential advantages of PD in the treatment of diabetic patients (Table 82.1) include the use of intraperitoneal (IP) insulin to provide a more physiologic route of administration[1] (Figure 82.1). Extensive clinical experience during the last two decades with this practice has improved our understanding of the effects of IP insulin on certain metabolic processes, but has also generated many conflicting results. Simultaneously, new insulin preparations and an emerging class of compounds that elicit gluco-regulatory actions (such as the incretin mimetics) has made improved glycemic control possible in these patients.[2]

Insulin Absorption

The IP administration of insulin results in absorption into the portal circulation, mimicking endogenously secreted insulin. From the portal circulation it is transported to the liver, where approximately 50% of the insulin is bound to receptors in a single pass and the remainder reaches the systemic circulation. Intrahepatic insulin concentration is regulated depending on the concentration of glucose and amino acids in blood. Insulin inhibits hepatic glycogenolysis, gluconeogenesis, and ketogenesis and enhances glycogen and fatty acid synthesis. Insulin clearance during the first pass through the liver regulates its plasma concentration and reduces hyperinsulinemia.

With IP insulin use, lower basal insulin levels and faster insulin release and peaks are obtained in response to acute glucose loads. Several studies have shown lower mean plasma glucose and lower peripheral free-insulin levels with IP insulin compared to subcuta-

Table 82–1

Potential Advantages of PD in the Treatment of Diabetic Patients

- No need for vascular access
- Continuous solute removal and ultrafiltration
- More stable volume control and blood pressure
- Better preservation of residual renal function
- Lower blood losses and improved control of anemia
- No need for systemic anticoagulation
- More liberal diet
- Continuous administration of insulin (IP)
- Lifestyle advantages

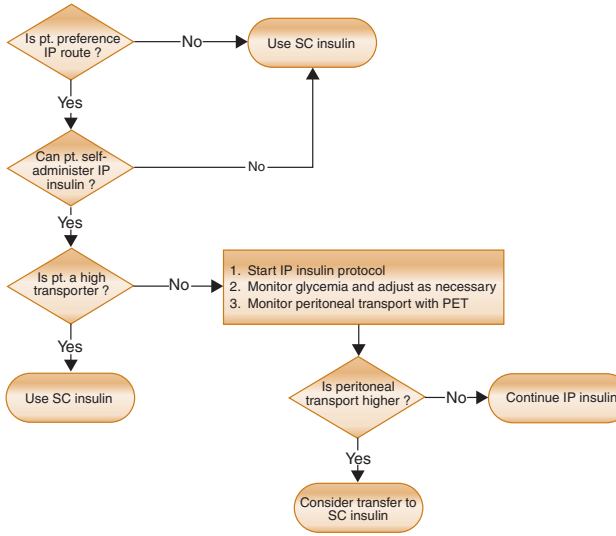


Figure 82–1

Algorithm for selection of insulin administration route for diabetic patients undergoing peritoneal dialysis.

neous (SC) insulin. IP insulin administration is also associated with quicker serum peak levels after administration into an empty peritoneal cavity than when mixed with PD solution. Insulin kinetics has demonstrated better and more predictable absorption of IP insulin.

SC administration is affected by tissue degradation of insulin and regional variations in absorption due to fluctuations in tissue perfusion or sequestration.

Glycemic Control

Glycemic control in diabetic patients undergoing PD can be facilitated by the constant infusion of glucose and insulin into the peritoneal cavity and their gradual absorption. Maintenance of a balanced glucose-insulin administration via the IP route can theoretically result in better glucose utilization, more physiologic insulin administration, and avoidance of wide fluctuations in the plasma concentration of both substances.

The expected end results are improved glycemic control and nutrition, reduction of hyperinsulinemia, and elimination of multiple daily injections. The effects on lipid metabolism and the ultimate influence on clinical outcomes are more difficult to assess. Excellent glycemic control is possible in diabetic patients undergoing PD with divided doses of insulin administered SC, IP, or with insulin pumps. The available clinical data have not provided proof of superiority of one method over another in terms of glycemic control.

Lipid Metabolism

Hyperinsulinemia has been associated with a high risk of atherosclerosis. Reducing the circulating levels of insulin should reduce atherogenic risk. However, the literature offers conflicting results. The effects of IP insulin on serum lipids have been reported to be beneficial by some and detrimental by others. The confusing interpretation of the available data may be related to methodologic variances among the studies, poor understanding of the ultimate effects of specific lipid profiles on clinical outcome, lack of adjustment for co-morbid conditions, and incomplete databases. Nevalainen et al. studied type 1 diabetics before and after treatment with continuous ambulatory PD (CAPD).[3]

During CAPD, all patients were first treated with SC insulin and then transferred to IP insulin. Better glycemic control and insulin sensitivity were observed with IP insulin. After switching from SC to IP insulin, the peripheral insulin profile and portal/peripheral insulin gradients were normalized. Initiation of CAPD did not affect serum lipids, but IP insulin administration significantly reduced HDL cholesterol and increased the LDL/HDL (low density lipoprotein) (high density lipoprotein) ratio. In a subsequent study, these investigators characterized the reduction in HDL as

mainly in the HDL_3-cholesterol fraction and to a lesser extent in the HDL_2-cholesterol fraction, suggesting no major change in the size of the HDL.[4] The most prominent change was a reduction of ApoA-I, the principal protein component of HDL. Although both reduced HDL cholesterol and ApoA-I are considered high risk factors for atherogenesis, the potential may be less than expected if the relative size of HDL remains unchanged. The clinical significance of these effects on lipid profiles remains unclear.

More recently, Torun et al. evaluated the association of hepatic subcapsular steatosis (HSS) with clinical parameters in nondiabetic CAPD patients and diabetic patients receiving IP or SC insulin in a cross-sectional study.[5] HSS was only detected in five of the eight diabetic patients receiving IP insulin. None of the diabetics receiving SC insulin and none of the nondiabetic patients developed HSS. Comparison of diabetic patients receiving IP insulin who had HSS with those without HSS showed higher daily insulin dosage ($p = 0.02$), body mass index (BMI, $p = 0.02$), serum triglycerides ($p = 0.04$), and $D/P_{creatinine}$ at 4 hours ($p = 0.02$)—as well as a lower D_0/D_4 ($p = 0.04$).

No differences in dialysate-glucose load was found between diabetic patients receiving IP insulin who had HSS and those who did not, but mean daily insulin dosage among those receiving IP insulin who had HSS was approximately twice as high as those without HSS. We may infer from these data that IP insulin plays a more important role in the pathogenesis of HSS than glucose levels in diabetic patients and that HSS is associated with higher daily insulin requirements, obesity, hypertriglyceridemia, and high peritoneal transport in diabetics receiving IP insulin. However, this was a cross-sectional study with observations made at a single moment in the patient's lifetime, allowing the possibility that HSS was due to increased peritoneal transport rather than to the dose or route of insulin administration.

High peritoneal transport rates increase insulin absorption and glucose absorption, which in turn may lead to obesity, hyperinsulinemia, and hypertriglyceridemia. Thus, we are left with the important question: Is IP insulin responsible for the development of HSS and increased peritoneal transport, or are patients with increased peritoneal transport more likely to develop HSS? Further prospective long-term studies are required to provide an answer. In the meantime, it is reasonable to avoid the use of IP insulin in patients with high peritoneal transport and to monitor all patients undergoing IP insulin therapy with periodic peritoneal equilibrium tests.[6] If there is evidence of increased peritoneal transport, as reflected in an increase in $D/P_{cretinine}$ or a decrease in

$D_0/D_{Glucose}$, strong consideration should be given to discontinuance of IP insulin.

Advantages and Disadvantages of IP Insulin Administration

Table 82.2 summarizes the potential advantages and disadvantages of IP insulin administration in PD patients.[7] Aside from the improved glycemic control, a more physiologic route of absorption through the portal circulation, and avoidance of insulin injections associated with IP insulin, some interesting observations have been made related to other metabolic processes. Hepatic functions unrelated to carbohydrate or lipid metabolism have been reported to improve with IP insulin administration. Likewise, higher levels of plasma hydroxy-vitamin D have been observed with IP insulin compared to SC administration in patients with comparable glycemic control.

There are few disadvantages to the use of IP insulin in PD. The need for higher total insulin doses adds to the cost of therapy. As previously mentioned, the development of HSS (particularly among patients with high transport rates) is a concern. A rare instance of malignant omentum syndrome, whereby insulin is trapped in the omentum in response to a foreign protein, has also been reported.

Based on the available literature, the incidence of peritonitis in diabetic patients is not significantly different than in nondiabetics,

Table 82–2

Advantages and Disadvantages of IP Insulin over SC Insulin in PD

Advantages	Disadvantages	No difference
• Better glycemic control	• Higher total insulin doses	• Peritonitis rates
• More physiologic absorption	• Higher cost	• Protein losses
• Avoidance of injections	• Subcapsular steatosis and focal necrosis	• Lipid profiles
• Higher vitamin D levels	• Malignant omentum syndrome	
• Less hyperinsulinemia (in the absence of high peritoneal transport)		

and the use of IP or SC insulin does not seem to influence peritonitis rates. Protein losses are not affected by the addition of insulin to the dialysate. As previously discussed, the effect of IP insulin on lipid profiles and their clinical consequences remains controversial.

Determinants of Insulin Dose

The total dose of IP insulin is significantly higher than the previous SC total dose required for adequate control of glycemia prior to initiation of PD. The reasons for this increment in insulin dose are multiple. Insulin doses increase by approximately 15% after initiation of PD, probably due to the increased glucose load resulting from absorption of glucose from PD solutions (90 to 150 g/day).

The total caloric load varies with the patient's specific transport rate, ultrafiltration requirements, and the use of hypertonic exchanges. In addition, the total IP insulin dose increases by 100 to 200% over the total previous SC dose due to hepatic binding, adsorption to the solution bags and tubing, and unabsorbed insulin discarded in the peritoneal effluent. It is estimated that 50 to 60% of the insulin is discarded in the peritoneal effluent unused. Another 15% is bound to the plastic bag and administration tubing.

Effect of PD Prescription on IP Insulin Requirements

It is easier to achieve good glycemic control with CAPD than with automated PD (APD) because the exchanges of CAPD are well spaced throughout the day, providing the opportunity to adjust the insulin dose according to the caloric load and glucose monitoring. However, simple and reliable methods of IP insulin administration in continuous cycling peritoneal dialysis (CCPD) or in nightly intermittent peritoneal dialysis have been in use for many years with remarkably good results (vide infra).

It is imperative to equally divide the nocturnal dose among the various bags to avoid accidental hypoglycemia if the bags drain unevenly. Furthermore, if the patient uses a single diurnal exchange additional SC insulin may be required to accommodate the caloric loads associated with midday feedings. Regular glucose monitoring is essential, particularly during the initial period when the proper dose is being determined. In our experience, most CCPD patients (>85%) have benefited from IP insulin administration and more than 60% enjoyed tight glycemic control without additional SC administration using the guidelines discussed in the following section.

Recommended Regimens for IP Insulin Administration

The goal of IP insulin administration is to maintain fasting blood glucose levels near 100 mg/dL, with postprandial sugars of <200 mg/dL and HbA1c as close to normal as possible. It is generally recommended to mix insulin with the dialysis solution before delivery into the peritoneal cavity. This way the insulin is diluted, resulting in a very low concentration in the solution—causing the insulin diffusion to be slow and continuous. Alternatively, when insulin is injected into the connecting tube through the medication/sample port a high concentration of insulin is achieved in the first 50 mL of dialysis solution that gets infused into the peritoneal cavity—which reduces the total amount of insulin required.

The amount of insulin needed depends on the patient's insulin sensitivity, the peritoneal transport rate, and the amount of glucose absorbed from the dialysate. During the first few treatments, blood sugar levels are checked often and the insulin dose is adjusted to maintain the desired serum glucose level. Several treatment days are usually required to determine the exact amount of insulin needed by an individual patient. Once stable, blood sugar should be checked periodically during the treatment. The procedure is as follows. Table 82.3 outlines general management recommendations for diabetic patients on PD.

1. Total the previous daily SC insulin dose, including all NPH and regular doses.
2. Multiply by 2 for the total initial IP dose using regular insulin only. Subsequent adjustments will probably result in three times the total previous SC dose.
3. For CAPD: divide 85% of the total dose into the diurnal exchanges and the remaining 15% in the nocturnal exchange(s). Perform exchanges 0.5 hour prior to meals.
4. For CCPD: place 50% of the total dose in the nocturnal cycles (equally divided among the bags) and 50% in the diurnal exchange.
5. For CCPD with additional daytime exchanges: divide the insulin equally among all exchanges.
6. If a 2.5% solution is used, increase the base insulin by approximately 10%. If a 4.25% solution is used, increase by approximately 20%.
7. Adjustments to the amount of insulin added to the dialysate bags should be made according to glycemic control. CAPD patients should check their blood glucose prior to each exchange to determine the dose of IP insulin to be

Table 82–3

Managing the Diabetic Patient

- Only use regular insulin IP. Do not use NPH insulin because it precipitates and is poorly absorbed across the peritoneal membrane.
- Blood sugar monitoring at HS, morning, midday, and PRN may be necessary for tight blood sugar control.
- Patients should adjust insulin doses only after consultation with a nurse or physician.
- Additional monitoring is generally required during episodes of peritonitis.
- If the facility has a policy to change needles prior to injecting medication into the dialysis solution, a slight increase in the amount of insulin may be necessary to compensate for medication that remains in the discarded needle.
- Longer needles (1.5 inches or 3.8 cm) are preferred to ensure that the full dose of insulin is injected into the solution container rather than being trapped in the injection port of the bag.
- Inversion of the bag several times is recommended to ensure proper mixing.
- Controlling the use of 4.25% and 2.5% solution is important in decreasing the patient's serum glucose levels.

administered. APD patients require diligent monitoring to achieve blood glucose control.

8. A sliding scale can be used based on blood glucose monitoring; for example:
   - Increase insulin: 2 U for blood glucose >200
   - 4 U for blood glucose >400
   - 6 U for blood glucose >600
   - Decrease insulin: 2 U for blood glucose <100

Peritonitis, Other Infectious Processes, and Hypercatabolic States

Glycemic control is difficult in diabetic patients during episodes of peritonitis, infectious processes, and other catabolic states. Peritonitis is often associated with significant increases in peritoneal transport rates, resulting in rapid absorption of glucose from the peritoneum as well as reduced ultrafiltration. The consequences are hyperglycemia and the need for more hypertonic PD solutions, thus perpetuating hyperglycemia.

Hypercatabolism also requires higher caloric and protein administration, and in extreme cases the use of total parenteral nutrition—dictating the need for more ultrafiltration and higher insulin doses. Regular and frequent monitoring of blood glucose; frequent and effective adjustment of IP insulin doses, supplemented with SC or intravenous (IV) doses; and early diagnosis and treatment of the intercurrent illness often allow the continuation of PD and IP insulin administration. However, if glycemia becomes difficult to control, temporary discontinuation of PD, transfer to hemodialysis, and SC or IV sliding scale insulin are recommended.

Hospitalizations and Change of PD Prescription

Well-controlled diabetic patients are prone to experience wide glycemic fluctuations during hospitalizations. These fluctuations may occur in both directions, ranging from hyperosmolar states to frank hypoglycemia. The most common causes are changes in dietary intake (increased intake due to IV solutions or reductions in intake/NPO), changes in PD prescription (transfer from CAPD to APD, or vice versa), inactivity, administration of drugs that affect glucose metabolism, and inadvertent or inappropriate change in insulin dose. Under any of these circumstances, frequent monitoring of blood sugar is mandatory. Once the patient becomes stable, it is imperative to resume the patient's IP insulin regimen under strict supervision using frequent monitoring.

Summary

The route of insulin administration for diabetic patients undergoing PD should be based on patient preference, patient ability to comply with therapy, peritoneal transport status, coexisting co-morbid conditions, and cost of therapy.

References

1. Diaz-Buxo JA. Peritoneal dialysis prescriptions for diabetic patients. Adv Perit Dial 1999;15:91–95.
   Reviews pertinent pathophysiology in diabetic uremic patients and offers specific therapeutic recommendations based on clinical evidence whenever possible.
2. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. Ann Intern Med 2005;143:559–69.

Comparison of exenatide (an incretin mimetic) and insulin glargine (an analogue of human insulin designed to have an extended duration of action) performance among poorly controlled adult-onset diabetics.

3. Nevalainen P, Lahtela JT, Mustonen J, Pasternack A. The influence of peritoneal dialysis and the use of subcutaneous and intraperitoneal insulin on glucose metabolism and serum lipids in type I diabetic patients. Neprhol Dial Transplant 1997;12:145–50.
4. Nevalainen PI, Lahtela JT, Mustonen J, Taskinen MR, Pasternack A. The effect of insulin delivery on lipoproteins in type I patients on CAPD. Perit Dial Int 1999;19:148–53.
   Review of the literature and observations of the effect of IP and SC insulin on lipid and carbohydrate metabolism in CAPD diabetic patients.
5. Torun D, Oguzkurt L, Sezer S, Zumrutdal A, Singan M, Adam FU, et al. Hepatic subcapsular steatosis as a complication associated with intraperitoneal insulin treatment in diabetic peritoneal dialysis patients. Perit Dial Int 2005;25:596–600.
   Evaluation of hepatic subcapsular steatosis and its association with clinical parameters in nondiabetic and diabetic CAPD patients receiving IP or SC insulin.
6. Thorp ML, Wilks TS. Three diabetic peritoneal dialysis patients receiving intraperitoneal insulin with dosage adjustment based on capillary glucose levels during peritoneal equilibrium tests. Am J Kidney Dis 2004;43:927–29.
   This article discusses adjustment of IP insulin dosage based on capillary glucose levels during the peritoneal equilibration test.
7. Scarpioni L, Ballocchi S, Scarpioni R, Cristinelli L. Peritoneal dialysis in diabetics. Optimal insulin therapy on CAPD: Intraperitoneal versus subcutaneous treatment. Perit Dial Int 1995;16(1):S275–78.
   Review of the comparative advantages and disadvantages of IP and SC insulin administration in CAPD patients.

CHAPTER 83

Principles of Drug Usage in Dialysis Patients

Ali J. Olyaei, PharmD, and William M. Bennett, MD

Evolution of the field of dialysis and advances in surgical procedures and access placement have made it possible to treat patients with end-stage renal disease (ESRD) with dialysis therapy for more than 50 years. Improvements in pharmacotherapy and pre- and postdialysis management have contributed to these remarkable advancements. However, uremia may directly or indirectly affect different aspects of drug pharmacokinetics or pharmacodynamics. Most therapeutic agents or their metabolites are completely or partially eliminated by the kidneys.

In patients with chronic renal failure, this route of elimination is impaired. In addition, uremia may alter extrarenal drug metabolism. Depending on various factors (such as the size of the drug molecule and degree of protein binding), a significant amount of drug removal may occur during dialysis. To prevent toxicity and optimize efficacy, it is critical that these factors be taken into account and appropriate dosage adjustments made when prescribing drugs for dialysis patients. This chapter discusses pharmacologic principles for prescribing drugs in this population and references specific dosage recommendations.

Pharmacologic Principles and Alterations in Uremia

Dosage modification in dialysis patients must take into account the effects of uremia and other factors on a variety of pharmacokinetic parameters, such as drug absorption, volume of distribution, protein binding, and drug metabolism. Drug absorption may be impaired due to delayed gastric emptying or edema of the gastrointestinal tract, particularly in diabetic patients with gastroparesis. Medications commonly prescribed in dialysis patients may alter drug absorption.

Gastric pH is frequently high due to the use of antacids or H_2 blockers, which may result in decreased absorption of medications requiring an acid milieu. Aluminum- or calcium-containing phosphate-binding antacids may form nonabsorbable chelation

products with certain drugs, such as digoxin or tetracycline, with impairment of their absorption.

Following absorption and equilibration, individual drugs distribute throughout the body in a characteristic manner. The apparent volume of distribution (V_d) is the quantity of drug in the body (L/kg body weight) divided by the plasma concentration at equilibrium. V_d represents that amount of water in which the drug must have been dissolved to render the observed plasma concentration. Drugs that are highly tissue bound or lipid soluble usually have a large V_d, whereas drugs that are highly bound to circulating proteins are largely confined to the vascular space and therefore usually have a V_d of <0.2 L/kg. A variety of disease states, including uremia, may alter the V_d of therapeutic agents. From a practical standpoint, the changes in V_d are usually not clinically significant except for those drugs that have a small V_d (>0.7 L/kg) under normal circumstances.

The degree of drug protein binding may be altered in uremia, with potentially important pharmacologic consequences. It is the unbound or free drug that is pharmacologically active and available for metabolism or excretion. Decreased binding of various drugs has been demonstrated in patients with renal failure. As a result, for any given drug level (bound plus unbound) the proportion of free or active drug is increased. Because both drug elimination and pharmacologic activity are increased for any given dose, the clinical consequences are difficult to predict.

The metabolic biotransformation of drugs to another chemical form may be altered in uremia. Drug metabolism by reduction, acetylation, or ester or peptide hydrolysis may be delayed—whereas metabolism by hepatic microsomal oxidation is usually normal.

The kidney is the most common route of drug excretion. Drug removal rate is typically expressed as elimination half-life ($t^1/_2$), the time required for the plasma concentration to decrease by 50%. The half-life is dependent on V_d and clearance (renal, hepatic, or other) as expressed by the following formula.

$$t^1/_2 = 0.693 \times V_d/\text{clearance}$$

As the renal clearance decreases, $t^1/_2$ will increase (assuming that V_d is unchanged). It should be noted that active drug metabolites may also be excreted by the kidney and therefore have a prolonged half-life in renal failure.

Drug Administration

Drugs or their metabolites that are normally excreted by the kidney require dosage modification in advanced renal failure. In general, the loading dose of a drug does not need to be changed unless the V_d is significantly altered. The maintenance regimen may be modified by the interval extension method or dosage reduction. The interval extension method uses the same dose at greater intervals and is useful for drugs with long half-lives. The dosage reduction method reduces the dosage and leaves the interval between doses unchanged. This method generally leads to more constant serum levels.

Monitoring of drug levels can be very useful in guiding drug therapy and in preventing toxicity. Interpretation of drug levels must be made in light of the amount of drug administered, the time elapsed since the last dose, and the route of administration.

After steady-state levels are reached, peak drug levels occur 30 to 60 minutes following parenteral administration or 1 to 2 hours after oral ingestion—and trough levels are drawn immediately prior to the next dose. In general, peak levels tend to correlate with drug efficacy—whereas trough levels are used as indicators of toxicity. Drug level monitoring can be expensive and is not always available. Drug level monitoring does not always reduce the incidence of toxicity. Ongoing clinical assessment is important even when drug levels are within the established therapeutic range. Most assays do not distinguish between free and protein-bound drug in the plasma. An increase in unbound drug is common in patients with renal failure. Table 83.1 summarizes the therapeutic drug monitoring in renal insufficiency for drugs for which monitoring of drug levels is routinely recommended.

Renal Function Assessment

The glomerular filtration rate (GFR) is closely correlated with unchanged drug elimination through the kidney and is useful in determining dosage adjustments. The Cockcroft and Gault formula is the most commonly used method of calculating the creatinine clerarance (Clcr), which has traditionally been used to approximate the GFR. Both blood urea nitrogen (BUN) and serum creatinine (Scr) are, at best, crude markers of renal function. The Cockcroft and Gualt formula (as follows) includes the variables of age (years), ideal body weight (IBW) (kg), and Scr (mg/dL) and calculates the Scr (mL/minute).

Table 83–1

Therapeutic Drug Monitoring

Drug name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Aminoglycosides (conventional dosing) Gentamicin, Tobramycin, Amikacin	Gentamicin and Tobramycin: • Trough: 0.5–2 mg/L • Peak: 5–8 mg/L Amikacin: • Peak: 20–30 mg/L • Trough: <10 mg/L	• Trough: Immediately prior to dose • Peak: 30 min after a 30- to 45-min infusion	Check peak and trough with 3rd dose. For therapy less than 72 h, levels not necessary. Repeat drug levels weekly or if renal function changes.
Aminoglycosides (24-h dosing) Gentamicin, Tobramycin, Amikacin	0.5–3 mg/L	Obtain random drug level 12 h after dose	After initial dose. Repeat drug level in 1 wk or if renal function changes.
Carbamazepine	4–12 mcg/mL	Trough: Immediately prior to dosing	Check 2–4 d after first dose or change in dose.
Cyclosporin	150–400 ng/mL	Trough: Immediately prior to dosing	Daily for first week, then weekly.
Digoxin	0.8–2.0 ng/mL	12 h after maintenance dose	5–7 d after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients.
Lidocaine	1–5 mcg/mL	8 h after IV infusion started or changed	

Table 83–1

Therapeutic Drug Monitoring—Cont'd

Drug name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Lithium	Acute: 0.8–1.2 mmol/L Chronic: 0.6–0.8 mmol/L	Trough: Before a.m. dose at least 12 h since last dose	[????????]
Phenobarbital	15–40 mcg/mL	Trough: Immediately prior to dosing	Check 2 wks after first dose or change in dose. Follow-up level in 1–2 months.
Phenytoin	10–20 mcg/mL	Trough: Immediately prior to dosing	5–7 d after first dose or after change in dose.
Free Phenytoin	1–2 mcg/mL		
Procainamide NAPA (n-acetyl procainamide) a procainamide metabolite	(A) 4–10 mcg/mL • Trough: 4 mcg/mL • Peak: 8 mcg/mL (B) 10–30 mcg/mL	(A) Trough: Immediately prior to next dose or 12–18 h after starting or changing an infusion (B) Draw with procainamide sample	
Quinidine	1–5 mcg/mL	Trough: Immediately prior to next dose	
Sirolimus	10–20 ng/dL	Trough: Immediately prior to next dose	

Table Continued

Table 83–1

Therapeutic Drug Monitoring—Cont'd

Drug name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Tacrolimus(FK-506)	10–15 ng/mL	Trough: Immediately prior to next dose	Daily for first week, then weekly.
Theophylline p.o. or Aminophylline IV	15–20 mcg/mL	Trough: Immediately prior to next dose	
Valproic acid (divalproex sodium)	40–100 mcg/mL	Trough: Immediately prior to next dose	Check 2–4 d after first dose or change in dose.
Vancomycin	• Trough: 5–15 mg/L • Peak: 25–40 mg/L	• Trough: Immediately prior to dose • Peak: 60 min after a 60-min infusion	With 3rd dose (when initially starting therapy, or after each dosage adjustment). For therapy less than 72 h, levels not necessary. Repeat drug levels if renal function changes.

$$\text{Clcr}^* = \frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{Scr}}$$

* Multiply result by 0.85 in women

Patients with acute renal failure should have an assumed Clcr of <10mL/minute and it should be remembered that Clcr overestimates the GFR. A new marker of GFR, iohexol, is currently being utilized in both the research and clinical setting to more accurately measure renal function without exposing the patient to radiolabeled material. In addition, the Modification of Diet in Renal Disease (MDRD) study recently reported a new formula for estimating renal function. The formula approximates GFR rather than Clcr, and therefore may be a more accurate estimate of renal function. The formula uses a creatinine assay (the kinetic alkaline picrate reaction), which is the least subject to artifact interference. GFR was predicted over a wide range of values, including variables for ethnicity and serum albumin concentration, and did not rely on timed urine collections. The MDRD study equation is as follows.

$$\text{GFR} = 170 \times [\text{Scr}]^{-0.999} \times [\text{age}]^{-0.176} \times [0.762 \text{ if female}] \times [1.180 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \times [\text{albumin}]^{-0.318}$$

Effects of Dialysis on Drugs

Drug removal during dialysis is an important factor to consider when prescribing drug therapy for the patient with ESRD. A variety of factors affect dialysis drug clearance, including molecular weight, water solubility, degree of protein binding, and membrane clearance. Drugs with a molecular weight of >500 daltons are poorly cleared by conventional hemodialysis membranes. In addition, drugs that are highly protein or tissue bound or that are highly lipid soluble are not dialyzed to a significant extent because of their large V_d. The clearance of some molecules of molecular weight of >500 daltons may be greater with peritoneal dialysis than with hemodialysis. From a practical standpoint, however, it is unusual for peritoneal dialysis to remove drugs that are not also removed by hemodialysis.

The use of more permeable membranes, such as polysulfone, is becoming more common. Removal of drugs with relatively low molecular weights and small V_d could conceivably be enhanced with the use of these membranes. Vancomycin, for example, significantly increases removal of low-molecular-weight drugs when used with polysulfone membranes compared to cuprophane membranes. Thus, supplemental vancomycin administration is

Table 83–2

Antimicrobial Dosing in Renal Failure

Oral Cephalosporin									
Cefaclor	250–500 mg tid	70%	100%	100%	50%		250 mg after dialysis	250 mg q8–12h	N/A
Cefadroxil	500 to 1 g bid	80%	100%	100%	50%		0.5–1.0 g after dialysis	0.5 g/d	N/A
Cefixime	200 to 400 mg q 12 h	85%	100%	100%	50%		300 mg after dialysis	200 mg/d	Not recommended
Cefpodoxime	200 mg q12 h	30%	100%	100%	100%		200 mg after dialysis	Dose for GFR <10	N/A
Ceftibuten	400 mg q24 h	70%	100%	100%	50%		300 mg after dialysis	No data: Dose for GFR <10	Dose for GFR 10–50
Cefuroxime axetil	250–500 mg tid	90%	100%	100%	100%	Malabsorbed in presence of H2 blockers. Absorbed better with food.	Dose after dialysis	Dose for GFR <10	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Cephalexin	250–500 mg tid	95%	100%	100%	100%	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis.	Dose after dialysis	Dose for GFR <10	N/A
Cephradine	250–500 mg tid	100%	100%	100%	50%	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis.	Dose after dialysis	Dose for GFR <10	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

IV Cephalosporin									
Cefamandole	1–2 g IV q6–8 h	100%	q6 h	q8 h	q12 h		0.5–1.0 g after dialysis.	0.5–1.0 g q12 h	Dose for GFR 10–50
Cefazolin	1–2 g IV q8 h	80%	q8 h	q12 h	q12–24 h		0.5–1.0 g after dialysis.	0.5 g q12 h	Dose for GFR 10–50
Cefepime	1–2 g IV q8 h	85%	q8–12 h	q12 h	q24 h		1 g after dialysis.	Dose for GFR <10	Not recommended
Cefmetazole	1–2 g IV q8 h	85%	q8 h	q12 h	q24 h		Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Cefoperazone	1–2 g IV q12 h	20%	No renal adjustment is required.			Displaced from protein by bilirubin. Reduce dose by 50% for jaundice. May prolong prothrombin time.	1 g after dialysis.	None	None

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Cefotaxime	1–2 g IV q6–8 h	60%	q8 h	q12 h	q12–24 h	Active metabolite in ESRD. Reduce doses further for combined hepatic and renal failure.	1 g after dialysis.	1 g/d	1 g q12 h
Cefotetan	1–2 g IV q12 h	75%	q12 h	q12–24 h	q24 h		1 g after dialysis.	1 g/d	750 mg q12 h
Cefoxitin	1–2 g IV q6 h	80%	q6 h	q8–12 h	q12 h	May produce false increase in serum creatinine by interference with assay.	1 g after dialysis.	1 g/d	Dose for GFR 10–50
Ceftazidime	1–2 g IV q8 h	70%	q8 h	q12 h	q24 h		1 g after dialysis.	0.5 g/d	Dose for GFR 10–50
Ceftriaxone	1–2 g IV q24 h	50%	No renal adjustment is required.				Dose after dialysis.	750 mg q12 h	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Cefuroxime sodium	0.75–1.5 g IV q8 h	90%	q8 h	q8–12 h	q12–24 h	Rare allergic interstitial nephritis. Absorbed well when given intraperitoneally. May cause bleeding from impaired prothrombin biosynthesis.	Dose after dialysis.	Dose for GFR <10	1.0 g q12 h
Penicillin						Bleeding abnormalities, hypersensitivity. Seizures.			
Oral Penicillin									
Amoxicillin	500 mg tid	60%	100%	100%	50–75%		Dose after dialysis.	250 mg q12 h	N/A
Ampicillin	500 mg q6 h	60%	100%	100%	50–75%		Dose after dialysis.	250 mg q12 h	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Dicloxacillin	250–500 mg q6 h	50%	100%	100%	50–75%		None	None	N/A
Penicillin V	250–500 mg q6 h	70%	100%	100%	50–75%		Dose after dialysis.	Dose for GFR <10	N/A
IV Penicillin									
Ampicillin	1–2 g IV q6 h	60%	q6 h	q8 h	q12 h		Dose after dialysis.	250 mg q12 h	Dose for GFR 10–50
Nafcillin	1–2 g IV q4 h	35%	No renal adjustment is required.				None	None	Dose for GFR 10–50
Penicillin G	2–3 million units IV q4 h	70%	q4–6 h	q6 h	q8 h	Seizures. False-positive urine protein reactions. Six million units/d upper-limit dose in ESRD.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Piperacillin	3–4 g IV q4–6 h		No renal adjustment is required.			Specific toxicity: sodium, 1.9 mEq/g.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Ticarcillin/ clavulanate	3.1 g IV q4–6 h	85%	1–2 g q4 h	1–2 g q8 h	1–2 g q12 h	Specific toxicity: Sodium, 5.2 mEq/g.	3.0 g after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Piperacillin/ tazobactam	3.375 g IV q6–8 h	75–90%	q4–6 h	q6–8 h	q8 h	Specific toxicity: sodium, 1.9 mEq/g.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Antimicrobial Dosing in Renal Failure									
Quinolones						Photosensitivity, food, dairy products, tube feeding and Al $(OH)_3$ may decrease the absorption of quinolones.			
Cinoxacin	500 mg q12 h	55%	100%	50%	Avoid		Avoid	Avoid	Avoid
Fleroxacin	400 mg q12 h	70%	100%	50–75%	50%		Dose for GFR<10	400 mg/d	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Ciprofloxacin	200–400 mg IV q24 h	60%	q12 h	q12–24 h	q24 h	Poorly absorbed with antacids, sucralfate, and phosphate binders. Intravenous dose 1/3 of oral dose. Decreases phenytoin levels.	250 mg q12 h (200 mg if IV)	250 mg q8 h (200 mg if IV)	200 mg IV q12 h
Lomefloxacin	400 mg q24 h	76%	100%	200–400 mg q48 h	50%	Agents in this group are malabsorbed in the presence of magnesium, calcium, aluminum, and iron. Theophylline metabolism is impaired. Higher oral doses may be needed to treat CAPD peritonitis.	Dose for GFR<10	Dose for GFR <10	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Levofloxacin	500 mg qd	70%	q12 h	250 q12 h	250 q12 h	L-isomer of ofloxacin: appears to have similar pharmacokinetics and toxicities.	Dose for GFR<10	Dose for GFR <10	Dose for GFR 10–50
Moxifloxacin	400 mg qd	20%	No renal adjustment is required.				No data	No data	No data
Nalidixic acid	1.0 g q6 h	High	100%	Avoid	Avoid	Agents in this group are malabsorbed in the presence of magnesium, calcium, aluminum, and iron. Theophylline metabolism is impaired. Higher oral doses may be needed to treat CAPD peritonitis.	Avoid	Avoid	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Norfloxacin	400 mg q12 h	30%	q12 h	q12–24 h	q24 h	See above.	Dose for GFR <10	Dose for GFR <10	N/A
Ofloxacin	200–400 mg q12 h	70%	q12 h	q12–24 h	q24 h	See above.	100–200 mg after dialysis.	Dose for GFR <10	300 mg/d
Pefloxacin	400 mg q24 h	11%	100%	100%	100%	Excellent bidirectional transperitoneal movement.	None	None	Dose for GFR 10–50
Sparfloxacin	400 mg q24 h	10%	100%	50–75%	50% q48 h		No data: Dose for GFR <10	No data	Dose for GFR 10–50
Trovafloxacin	200–300 mg q12 h	10%	No renal adjustment is required.				No Data	No Data	No Data

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Miscellaneous Agents							
Azithromycin	250–500 mg qd	6%	No renal adjustment is required.	No drug-drug interaction with CSA/KF.	None	None	None
Clarithromycin	500 mg bid			20%	No renal adjustment is required.	None	None
Clindamycin	150–450 mg tid	10%	No renal adjustment is required.	Increase CSA/FK level.	None	None	None
Dirithromycin	500 mg qd		No renal adjustment is required.	Nonenzymatically hydrolyzed to active compound erythomycylamine.	None	No data: None	Dose for GFR 10–50
Erythromycin	250–500 mg qid	15%	No renal adjustment is required.	Increase CSA/FK level, avoid in transplant patients.	None	None	None

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Imipenem/ Cilastatin	250–500 mg IV q6 h	50%	500 mg q8 h	250–500 q8–12 h	250 mg q12 h	Seizures in ESRD. Nonrenal clearance in acute renal failure is less than in chronic renal failure. Administered with cilastin to prevent nephrotoxicity of renal metabolite.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Meropenem	1 g IV q8 h	65%	1 g q8 h	0.5–1 g q12 h	0.5–1 g q24 h		Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Metronidazole	500 mg IV q6 h	20%	No renal adjustment is required.			Peripheral neuropathy, reaction with beverages.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Pentamidine	4 mg/kg/d	5%	q24 h	q24 h	q48 h	Inhalation may cause bronchospasm, IV administration may cause hypotension, hypoglycemia and nephrotoxicity.	None	None	None
Trimethoprim/ Sulfamethoxa-zole	800/160 mg bid	70%	q12 h	q18 h	q24 h	Increase serum creatinine. Can cause hyperkalemia.	Dose after dialysis.	q24 h	q18 h
Vancomycin	1 g IV q12 h	90%	q12 h	q24–36 h	q48–72 h	Nephrotoxic, ototoxic, may prolong the neuromuscular blockade effect of muscle relaxants. Peak 30, trough 5–10.	500 mg q12–24 h (high FLX).	1.0 g q24–96 h	500 mg q12 h

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Vancomycin	125–250 mg qid	0%	100%	100%	100%	Oral vancomycin is indicated only for the treatment of C. diff.	100%	100%	100%
Antituberculosis Antibiotics									
Rifampin	300–600 mg qd	20%	No renal adjustment is required.			Decrease CSA/FK level. Many drug interactions.	None	Dose for GFR<10	Dose for GFR <10
Antifungal Agents									
Amphotericin B	0.5– 1.5 mg/kg/d	<1%	No renal adjustment is required.			Nephrotoxic, infusion related reactions, give 250 cc NS before each dose.	q24 h	q24 h	q24–36 h
Amphotec	4–6 mg/kg/d	<1%	No renal adjustment is required.						

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Abelcet	5 mg/kg/d	<1%	No renal adjustment is required.						
AmBisome	3–5 mg/kg/d	<1%	No renal adjustment is required.						
Azoles and other Antifungals						Increase CSA/FK level.			
Fluconazole	200–800 mg IV qd/bid	70%	100%	100%	50%		200 mg after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Flucytosine	37.5 mg/kg	90%	q12 h	q16 h	q24 h	Hepatic dysfunction. Marrow suppression more common in azotemic patients.	Dose after dialysis.	0.5–1.0 g/d	Dose for GFR 10–50
Griseofulvin	125–250 mg q6 h	1%	100%	100%	100%		None	None	None
Itraconazole	200 mg q12 h	35%	100%	100%	50%	Poor oral absorption.	100 mg q12–24 h	100 mg q12–24 h	100 mg q12–24 h

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Ketoconazole	200–400 mg qd	15%	100%	100%	100%	Hepatotoxic.	None	None	None
Miconazole	1200–3600 mg/d	1%	100%	100%	100%		None	None	None
Terbinafine	250 mg qd	>1%	100%	100%	100%	May cause CHF.			
Antiviral Agents									
Acyclovir	200–800 mg 5x/d	50%	100%	100%	50%	Poor absorption. Neurotoxicity in ESRD. Intravenous preparation can cause renal failure if injected rapidly.	Dose after dialysis.	Dose for GFR <10	3.5 mg/kg/d
Amantadine	100–200 mg q12 h	90%	100%	50%	25%		None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Cidofovir	5 mg/kg weekly x2 (induction); 5 mg/kg every 2 weeks	90%	No data: Avoid	No data: Avoid	No data: Avoid	Dose-limiting nephrotoxicity with preteinuria, glycosuria, renal insufficiency; nephrotoxicity and renal clearance reduced with coadministration of probenecid.	No data	No data	Avoid
Delavirdine	400 mg q8 h	5%	No data: 100%	No data: 100%	No data: 100%		No data: None	No data	No data: Dose for GFR 10–50
Didanosine	200 mg q12 h (125 mg if <60 kg)	40–69%	q12 h	q24 h	50% q24 h	Pancreatitis.	Dose after dialysis.	Dose for GFR <10	Dose for GFR <10

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Famciclovir	250–500 mg po bid to tid	60%	q8 h	q12 h	q24 h	VZV: 500 mg po tid HSV: 250 po bid. Metabolized to active compound penciclovir.	Dose after dialysis.	No data	No data: Dose for GFR 10–50
Foscarnet	40–80 mg IV q8 h	85%	40–20 mg q8–24 h according to ClCr			Nephrotoxic, neurotoxic, hypocalcemia, hypophosphatemia, hypomagnesemia and hypokalemia.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Ganciclovir IV	5 mg/kg q12 h	95%	q12 h	q24 h	2.5 mg/kg qd	Granulocytopenia and thrombocytopenia.	Dose after dialysis.	Dose for GFR <10	2.5 mg/kg q24 h

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Ganciclovir po	1000 mg tid	95%	1000 mg tid	1000 mg bid	1000 mg qd	Oral ganciclovir should be used ONLY for prevention of CMV infection. Always use IV ganciclovir for the treatment of CMV infection.	No data: Dose after dialysis.	No data: Dose for GFR <10	N/A
Indinavir	800 mg q8 h	10%	No data: 100%	No data: 100%	No data: 100%	Nephrolithiasis; acute renal failure due to crystalluria, tubulointerstitial nephritis.	No data: None	No data: Dose for GFR <10	No data
Lamivudine	150 mg bid	80%	q12 h	q24 h	50 mg q24 h	For hepatitis B.	Dose after dialysis.	No data: Dose for GFR <10.	Dose for GFR 10–50
Nelfinavir	750 mg q8 h	No data	No data	No data	No data		No data	No data	No data

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Nevirapine	200 mg q24 h x 14 d	<3	No data: 100%	No data: 100%	No data: 100%	May be partially cleared by hemodialysis and peritoneal dialysis.	Dose after dialysis.	No data: Dose for GFR <10	No data: Dose for GFR 10–50
Ribavirin	500–600 mg q12 h	30%	100%	100%	50%	Hemolytic uremic syndrome.	Dose after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Rifabutin	300 mg q24 h	5–10%	100%	100%	100%		None	None	No data: Dose for GFR 10–50
Rimantadine	100 mg bid	25%	100%	100%	50%				
Ritonavir	600 mg q12 h	3.50%	No data: 100%	No data: 100%	No data: 100%	Many drug interactions.	No data: None	No data: Dose for GFR <10	No data: Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Saquinavir	600 mg q8 h	<4%	No data: 100%	No data: 100%	No data: 100%		No data: None	No data: Dose for GFR <10	No data: Dose for GFR 10–50
Stavudine	30–40 mg q12 h	35–40%	100%	50% q12–24 h	50% q24 h		Dose for GFR <10 after dialysis.	No data	No data: Dose for GFR 10–50
Valacyclovir	500–1000 mg q8 h	50%	100%	50%	25%	Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome.	Dose after dialysis.	Dose for GFR <10	No data: Dose for GFR 10–50
Vidarabine	15 mg/kg infusion q24 h	50%	100%	100%	75%		Infuse after dialysis.	Dose for GFR <10	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Zanamivir	2 puffs bid x 5 d	1%	100%	100%	100%	Bioavailability from inhalation and systemic exposure to drug is low.	None	None	No data
Zalcitabine	0.75 mg q8 h	75%	100%	q12 h	q24 h		No data: Dose after dialysis.	No data	No data: Dose for GFR 10–50
Zidovudine	200 mg q8 h, 300 mg q12 h	8 to 25%	100%	100%	100 mg q8 h	Enormous interpatient variation. Metabolite renally excreted.	Dose for GFR <10.	Dose for GFR <10	100 mg q8 h

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Analgesic Dosing Analgesics	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Narcotics and Narcotic Antagonists									
Alfentanil	Anesthetic induction 8–40 g/kg	Hepatic	100%	100%	100%	Titrate the dose regimen	N/A	N/A	N/A
Butorphanol	2 mg q3–4 h	Hepatic	100%	75%	50%		No data	No data	N/A
Codeine	30–60 mg q4–6 h	Hepatic	100%	75%	50%		No data	No data	Dose for GFR 10–50
Fentanyl	Anesthetic induction (individualized)	Hepatic	100%	75%	50%	CRRT-titrate	N/A	N/A	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Meperidine	50–100 mg q3–4 h	Hepatic	100%	75%	50%	Normeperidine, an active metabolite, accumulates in ESRD and may cause seizures. Protein binding is reduced in ESRD. 20–25% excreted unchanged in acidic urine.	Avoid	Avoid	Avoid
Methadone	2.5–5 mg q6–8 h	Hepatic	100%	100%	50–75%		None	None	N/A
Morphine	20–25 mg q4 h	Hepatic	100%	75%	50%	Increased sensitivity to drug effect in ESRD.	None	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Naloxone	2 mg IV	Hepatic	100%	100%	100%		N/A	N/A	Dose for GFR 10–50
Pentazocine	50 mg q4 h	Hepatic	100%	75%	75%		None	No data	Dose for GFR 10–50
Propoxyphene	65 mg q6–8 h	Hepatic	100%	100%	Avoid	Active metabolite norpropoxyphene accumulates in ESRD.	Avoid	Avoid	N/A
Sufentanil	Anesthetic induction	Hepatic	100%	100%	100%	CRRT-titrate	N/A	N/A	N/A
Nonnarcotics									
Acetaminophen	650 mg q4 h	Hepatic	q4 h	q6 h	q8 h	Overdose may be nephrotoxic. Drug is major metabolite of phenacetin.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Acetylsalicylic acid	650 mg q4 h	Hepatic (renal)	q4 h	q4–6 h	Avoid	Nephrotoxic in high doses. May decrease GFR when renal blood flow is prostaglandin dependent. May add to uremic GI and hematologic symptoms. Protein binding reduced in ESRD.	Dose after dialysis.	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antihypertensive and Cardiovascular Dosing

Antihypertensive and Cardiovascular Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
				GFR >50	*GFR 10–50*	*GFR <10*				
ACE-Inhibitors							Hyperkalemia, acute renal failure, angioedema, rash, cough, anemia and liver toxicity.			
Benazepril	10 mg qd	80 mg qd	20%	100%	75%	25–50%		None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Captopril	6.25–25 mg tid	100 mg tid	35%	100%	75%	50%	Rare proteinuria, nephrotic syndrome, dysgeusia, granulocytopenia. Increases serum digoxin levels.	25–30%	None	Dose for GFR 10–50
Enalapril	5 mg qd	20 mg bid	45%	100%	75%	50%	Enalaprilat, the active moiety formed in liver.	20–25%	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Fosinopril	10 mg qd	40 mg bid	20%	100%	100%	75%	Fosinoprilat, the active moiety formed in liver. Drug less likely than other ACE inhibitors to accumulate in renal failure.	None	None	Dose for GFR 10–50
Lisinopril	2.5 mg qd	20 mg bid	80%	100%	50–75%	25–50%	Lysine analog of a pharmacologically active enalapril metabolite.	20%	None	Dose for GFR 10–50
Pentopril	125 mg q24 h		80–90%	100%	50–75%	50%		No data	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Perindopril	2 mg q24 h	<10%	100%	75%	50%	Active metabolite is perindoprilat. The clearance of perindoprilat and its metabolites is almost exclusively renal. Approxi-mately 60% of circulating perindopril is bound to plasma proteins, and only 10–20% of perindoprilat is bound.	25–50%	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Quinapril	10 mg qd	20 mg qd	30%	100%	75–100%	75%	Active metabolite is quinaprilat. 96 % of quinaprilat is excreted renally.	25%	None	Dose for GFR 10–50
Ramipril	2.5 mg qd	10 bid	15%	100%	50–75%	25–50%	Active metabolite is ramiprilat. Data is for ramiprilat.	20%	None	Dose for GFR 10–50
Trandolapril	1– 2 mg qd	4 mg qd	33%	100%	50–100%	50%		None	None	Dose for GFR 10–50
Antihypertensive and Cardiovascular Dosing in Renal Failure										
Angiotensin-II-Receptors Antagonists							Hyperkalemia, angioedema (less common than ACE inhibitors).			

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Candesartan	16 mg qd	32 mg qd	33%	100%	100%	50%	Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastro-intestinal tract to candesartan.	None	None	None
Eprosartan	600 mg qd	400–800 mg qd	25%	100%	100%	100%	Eprosartan pharma-cokinetics more variable in ESRD. Decreased protein binding in uremia.	None	None	None

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Irbesartan	150 mg qd	300 mg qd	20%	100%	100%	100%		None	None	None
Losartan	50 mg qd	100 mg qd	13%	100%	100%	100%		No data	No data	Dose for GFR 10–50
Valsartan	80 mg qd	160 mg bid	7%	100%	100%	100%		None	None	None
Telmisartan	20–80 mg qd		<5%	100%	100%	100%		None	None	None
Beta Blockers							Decrease HDL, mask symptoms of hypo-glycemia, bronchospasm, fatigue, insomnia, depression and sexual dysfunction.			

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Acebutolol	400 mg q24 h or bid	600 mg q24 h or bid	55%	100%	50%	30–50%	Active metabolites with long half-lives.	None	None	Dose for GFR 10–50
Atenolol	25 mg qd	100 mg qd	90%	100%	75%	50%	Accumulates in ESRD.	25–50 mg	None	Dose for GFR 10–50
Betaxolol	20 mg q24 h	80–90%	100%	100%	50%	50%		None	Dose for GFR 10-50	Dose for GFR 10–50
Bopindolol	1 mg q24 h	4 mg q24 h	< 10%	100%	100%	100%		None	None	Dose for GFR 10–50
Carteolol	0.5 mg q24 h	10 mg q24 h	<50%	100%	50%	25%		No data	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Carvedilol	3.125 mg tid	25 mg tid	2%	100%	100%	100%	Kinetics are dose dependent. Plasma concentrations of carvedilol reported to be increased in patients with renal impairment.	None	None	Dose for GFR 10–50
Celiprolol	200 mg q24 h		10%	100%	100%	75%		No data	None	Dose for GFR 10–50
Dilevalol	200 mg bid	400 mg bid	<5%	100%	100%	100%		None	None	No data
Esmolol (IV only)	50 mcg/kg/min	300 mcg/kg/min	10%	100%	100%	100%	Active metabolite retained in renal failure.	None	None	No data

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antihypertensive and Cardiovascular Dosing in Renal Failure										
Labetalol	50 mg PO bid	400 mg bid	5%	100%	100%	100%	For IV use: 20 mg slow intravenous injection over a 2-min period. Additional injections of 40 or 80 mg can be given at 10-min intervals until a total of 300 mg or continuous infusion of 2 mg/min.	None	None	Dose for GFR 10–50
Metoprolol	50 mg bid		100 mg bid	<5%	100%	100%		None	None	None

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Nadolol	80 mg qd	160 mg bid	90%	100%	50%	25%	Start with prolonged interval and titrate.	40 mg	None	Dose for GFR 10–50
Penbutolol	10 mg q24 h	40 mg q24 h	<10	100%	100%	100%		None	None	Dose for GFR 10–50
Pindolol	10 mg bid	40 mg bid	40%	100%	100%	100%		None	None	Dose for GFR 10–50
Propranolol	40–160 mg tid	320 mg/day	<5%	100%	100%	100%	Bioavailability may increase in ESRD. Metabolites may cause increased bilirubin by assay interference in ESRD. Hypoglycemia reported in ESRD.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Sotalol	80 bid	160 mg bid	70%	100%	50%	25–50%	Extreme caution should be exercised in the use of sotalol in patients with renal failure undergoing hemodialysis. To minimize the risk of induced arrhythmia, patients initiated or reinitiated on BETAPACE should be placed for a minimum of three days	80 mg	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

							(on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring.			
Timolol	10 mg bid	20 mg bid	15%	100%	100%	100%		None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Calcium Channel Blockers							Dihydropyridine: headache, ankle edema, gingival hyperplasia, and flushing. Non-dihydropyridine: bradycardia, constipation, gingival hyperplasia, and AV block.			
Amlodipine	2.5 qd	10 mg qd	10%	100%	100%	100%	May increase digoxin and cyclosporine levels.	None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Bepridil	No data	<1%	No data	No data	No data		Weak vasodilator and anti-hypertensive.	None	No data	No data
Antihypertensive and Cardiovascular Dosing in Renal Failure										
Diltiazem	30 mg tid	90 mg tid	10%	100%	100%	100%	Acute renal dysfunction. May exacerbate hyperkalemia. May increase digoxin and cyclosporine levels.	None	None	Dose for GFR 10–50
Felodipine	5 mg bid	20 mg qd	1%	100%	100%	100%	May increase digoxin levels.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Isradipine	5 mg bid	10 mg bid	<5%	100%	100%	100%	May increase digoxin levels.	None	None	Dose for GFR 10–50
Nicardipine	20 mg tid	30 mg tid	<1%	100%	100%		Uremia inhibits hepatic metabolism. May increase digoxin levels.	None	None	None
Nifedipine XL	30 qd	90 mg bid	10%	100%	100%	100%	Avoid short-acting nifedipine formulation.	None	None	None
Nimodipine	30 mg q8 h		10%	100%	100%	100%	May lower blood pressure.	None	None	Dose for GFR 10–50
Nisoldipine	20 mg qd	30 mg bid	10%	100%	100%	100%	May increase digoxin levels.	None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Verapamil	40 mg tid	240 mg/d	10%	100%	100%	100%	Acute renal dysfunction. Active metabolites accumulate, particularly with sustained-release forms.	None	None	Dose for GFR 10–50
Diuretics							Hypokalemia/ hyperkalemia (potassium-sparing agents), hyperuricemia, hyper-glycemia, hypomag-nesemia, and increased serum cholesterol.			

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Acetazolamide	125 mg tid	500 mg tid	90%	100%	50%	Avoid	May potentiate acidosis. Ineffective as diuretic in ESRD. May cause neurologic side effects in dialysis patients.	No data	No data	Avoid
Amiloride	5 mg qd	10 mg qd	50%	100%	100%	Avoid	Hyperkalemia with GFR <30 mL/min, especially in diabetics. Hyper-chloremic metabolic acidosis.	N/A	N/A	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antihypertensive and Cardiovascular Dosing in Renal Failure										
Bumetanide	1–2 mg qd	2–4 mg qd	35%	100%	100%	100%	Ototoxicity increased in ESRD in combination with aminoglycosides. High doses effective in ESRD. Muscle pain, gynecomastia.	None	None	N/A
Chlorthalidone	25 mg q24 h	50%	q24 h	q24 h	Avoid	Ineffective with low GFR.		N/A	N/A	N/A
Ethacrynic Acid	50 mg qd	100 mg bid	20%	100%	100%	100%	Ototoxicity increased in ESRD in combination with aminoglycosides.	None	None	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Furosemide	40–80 mg qd	120 mg tid	70%	100%	100%	100%	Ototoxicity increased in ESRD, especially in combination with amino-glycosides. High doses effective in ESRD.	None	None	N/A
Indapamide	2.5 mg q24 h	<5%	100%	100%	Avoid	Inef-fec-tive in ESRD.		None	N/A	None
Metolazone	2.5 mg qd		10 mg bid	70%	100%	100%	High doses effective in ESRD. Gynecomastia, impotence.	None	None	None

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Piretanide	6 mg q24 h	12 mg q24 h	40–60%	100%	100%	100%	High doses effective in ESRD. Ototoxicity.	None	None	N/A
Spironolactone	100 mg qd	300 mg qd	25%	100%	100%	Avoid	Active metabolites with long half-life. Hyperkalemia common when GFR <30, especially in diabetics. Gynecomastia, hyperchloremic acidosis. Increases serum by immunoassay interference.	N/A	N/A	Avoid

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Thiazides	25 mg bid		50 mg bid	>95%	100%	100%	Avoid	Usually ineffective with GFR <30 mL/min. Effective at low GFR in combination with loop diuretic. Hyperuricemia.	N/A	N/A
Torasemide	5 mg bid	20 mg qd	25%	100%	100%	100%	High doses effective in ESRD. Ototoxicity.	None	None	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Triamterene	25 mg bid	50 mg bid	5–10%	q12 h	q12 h	Avoid	Hyperkalemia common when GFR <30, especially in diabetics. Active metabolite with long half-life in ESRD. Folic acid antagonist. Urolithiasis. Crystalluria in acid urine. May cause acute renal failure.	Avoid	Avoid	Avoid

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antihypertensive and Cardiovascular Dosing in Renal Failure: Miscellaneous Agents										
Amrinone	5 mg/kg/min daily dose <10 mg/kg	10 mg/kg/min daily dose <10 mg/kg	10–40%	100%	100%	100%	Thrombocytopenia. Nausea, vomiting in ESRD.	No data	No data	Dose for GFR 10–50
Clonidine	0.1 bid/tid	1.2 mg/d	45%	100%	100%	100%	Sexual dysfunction, dizziness, portal hypotension	None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Digoxin	0.125 mg qod/ qd	0.25 mg qd	25%	100%	100%	100%	Decrease loading dose by 50% in ESRD. Radioimmunoassay may overestimate serum levels in uremia. Clearance decreased by amiodarone, spironolactone, quinidine, and verapamil. Hypokalemia and hypomagnesemia enhance toxicity. Vd	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

							and total body clearance decreased in ESRD. Serum level 12 h after dose is best guide in ESRD. Digoxin immune antibodies can treat severe toxicity in ESRD.			
Hydralazine	10 mg qid	100 mg qid	25%	100%	100%	100%	Lupus-like reaction	None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Midodrine	No data	No data	75–80%	5–10 mg q8 h	5–10 mg q8 h	No data	Increased blood pressure	5 mg q8h	No data	Dose for GFR 10–50
Minoxidil	2.5 mg bid	10 mg bid	20%	100%	100%	100%	Pericardial effusion, fluid retention, hypertrichosis, and tachycardia.	None	None	Dose for GFR 10–50
Nitroprusside	1 mcg/kg/min	10 mcg/kg/min	<10%	100%	100%	100%	Cyanide toxicity	None	None	Dose for GFR 10–50
Dobutamine	2.5 mcg/kg/min	15 mcg/kg/min	10%	100%	100%	100%		No data	No data	Dose for GFR 10–50
Milrinone	0.375 mcg/kg/min	0.75 mcg/kg/min		100%	100%	100%		No data	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Endocrine and Metabolic Dosing in Renal Failure

Hypoglycemic Agents	Normal Dosage		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
				GFR >50	*GFR 10–50*	*GFR <10*				
							Avoid all oral hypoglycemic agents on CRRT.			
Acarbose	25 mg tid	100 mg tid	35%	100%	50%	Avoid	Abdominal pain, N/V, and flatulence.	No data	No data	Avoid

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Acetohexamide	250 mg q24 h	1500 mg q24 h	None	Avoid	Avoid	Avoid	Diuretic effect. May falsely elevate serum creatinine. Active metabolite has $T_{1/2}$ of 5–8 hours in healthy subjects and is eliminated by the kidney. Prolonged hypoglycemia in azotemic patients.	No data	None	Avoid
Chlorpropamide	100 mg q24 h	500 mg q24 h	47%	50%	Avoid	Avoid	Impairs water excretion. Prolonged hypoglycemia in azotemic patients.	No data	None	Avoid

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Glibornuride	12.5 mg q24 h	100 mg q24 h	No data	No data	No data	No data		No data	No data	Avoid
Gliclazide	80 mg q24 h	320 mg q24 h	<20%	50–100%	Avoid	Avoid		No data	No data	Avoid
Glipizide	5 mg qd	20 mg bid	5%	100%	50%	50%		No data	No data	Avoid
Glyburide	2.5 mg qd	10 mg bid	50%	100%	50%	Avoid		None	None	Avoid
Metformin	500 mg bid	2550 mg/d (bid or tid)	95%	100%	Avoid	Avoid	Lactic acidosis	No data	No data	Avoid
Repaglinide	0.5–1 mg	4 mg tid								

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Tolazamide	100 mg q24 h	250 mg q24 h	7%	100%	100%	100%	Diuretic effects.	No data	No data	Avoid
Tolbutamide	1 g q24 h	2 g q24 h	None	100%	100%	100%	May impair water excretion.	None	None	Avoid
Troglitazone	200 mg qd	600 mg qd	3%	100%	Avoid	Avoid	Decrease CSA level, hepatotoxic.			
Parenteral agents							Dosage guided by blood glucose levels.			
Insulin	Vari-able		None	100%	75%	50%	Renal metabolism of insulin decreases with azotemia.	None	None	Dose for GFR 10–50
Lispro insulin	Vari-able		No data	100%	75%	50%	Avoid all oral hypoglycemic agents on CRRT.	None	None	None

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Endocrine and Metabolic Dosing in Renal Failure

Hyperlipidemic Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Atorvastatin	10 mg/d 80 mg/d	<2%	100%	100%	100%	Liver dysfunction, myalgia, and rhabdomyolysis with CSA/FK.	No data	No data	No data
Bezafibrate	200 mg bid-qid 400 mg SR q24 h	50%	50–100%	25–50%	Avoid		No data	No data	No data
Cholestyramine	4 g bid 24 g/d	None	100%	100%	100%	No data	No data	No data	No data
Clofibrate	500 mg bid 1000 mg bid	40–70%	q6–12 h	q12–18 h	Avoid	No data	No data	No data	No data

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Colestipol	5 gm bid	30 g/d	None	100%	100%	100%	No data	No data	No data	No data
Fluvastatin	20 mg daily	80 mg/d	<1%	100%	100%	100%	No data	No data	No data	No data
Gemfibrozil	600 bid	600 bid	None	100%	100%	100%	No data	No data	No data	No data
Lovastatin	5 mg daily	20 mg/d	None	100%	100%	100%	No data	No data	No data	No data
Nicotinic acid	1 g tid	2 g tid	None	100%	50%	25%	No data	No data	No data	No data
Pravastatin	10–40 mg daily	80 mg/d	<10%	100%	100%	100%	No data	No data	No data	No data
Probucol	500 mg bid		<2%	100%	100%	100%		No data	No data	No data
Rosuvastatin	5–40 mg daily	40 mg/d	10%	100%	100%	50%	5 mg qd; maintenance, not to exceed 10 mg qd.	50%	50%	50%
Simvastatin	5–20 mg daily	20 mg/d	13%	100%	100%	100%	No data	No data	No data	No data

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antithyroid Dosing in Renal Failure

Antithyroid Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Methimazole	5–20 mg tid	7	100%	100%	100%		No data	No data	Dose for GFR 10–50
Propylthiouracil	100 mg tid	<10	100%	100%	100%		No data	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Gastrointestinal Dosing in Renal Failure

Gastrointestinal Agents	Normal Doses		% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments
	Starting Dose	*Maximum Dose*		*GFR >50*	*GFR 10–50*	*GFR <10*	
Anti-ulcer Agents							
Cimetidine	300 mg tid	800 mg bid	60%	100%	75%	25%	Multiple drug-drug interactions; beta blockers, sulfonylurea, theophylline, warfarin, etc.
Famotidine	20 mg bid	40 mg bid	70%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Lansoprazole	15 mg qd	30 mg bid	None	100%	100%	100%	Headache, diarrhea
Nizatidine	150 mg bid	300 mg bid	20%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Omeprazole	20 mg qd	40 mg bid	None	100%	100%	100%	Headache, diarrhea

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Rabeprazole	20 mg qd	40 mg bid	None	100%	100%	100%	Headache, diarrhea
Pantoprazole	40 mg qd	80 mg bid	None	100%	100%	100%	Headache, diarrhea
Ranitidine	150 mg bid	300 mg bid	80%	100%	75%	25%	Headache, fatigue, thrombocytopenia, alopecia
Cisapride	10 mg tid	20 mg qid	5%	100%	100%	50–75%	Avoid with azole antifungal, macrolide antibiotics and other P450 3A-4 inhibitors
Metoclopramide	10 mg tid	30 mg qid	15%	100%	100%	50–75%	Increase cyclosporine/tacrolimus level, neurotoxic
Misoprostol	100 mcg bid	200 mcg qid		100%	100%	100%	Diarrhea, nausea, vomiting, abortifacient agent
Sucralfate	1 gm qid	1 gm qid	None	100%	100%	100%	Constipation, decreased absorption of MMF

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Neurologic/Anticonvulsant Dosing in Renal Failure

Anticonvulsants	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Carbamazapine	2–8 mg/kg/d; adjust for side effect and TDM	2%	100%	100%	100%	Plasma concentration: 4–12, double vision, fluid retention, mylosuppression.	None	None	None
Clonazepam	0.5 mg tid 2 mg tid	1%	100%	100%	100%	Although no dose reduction is recommended, the drug has not been studied in patients with renal impairment.	None	No data	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

							Recommendations are based on known drug characteristics not clinical trials data.			
Ethosuximide	5 mg/kg/d; adjust for side effect and TDM		20%	100%	100%	100%	Plasma concentration: 40–100, headache.	None	No data	No data
Felbamate	400 mg/tid	1200 mg/tid	90%	100%	50%	25%	Anorexia, vomiting, insomnia, nausea.	Dose after dialysis	Dose for GFR < 10	Dose for GFR 10–50
Gabapentin	150 mg tid	900 mg tid	77%	100%	50%	25%	Less CNS side effects compared to other agents.	300 mg load, then 200–300 after hemodialysis.	300 mg qod	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Lamotrigine	25–50 mg/d	150 mg/d	1%	100%	100%	100%	Autoinduction, major drug-drug interaction with valproate.	No data	No data	Dose for GFR 10–50
Levetiracetam	500 mg bid	1500 mg bid	66%	100%	50%	50%		250–500 mg after dialysis.	Dose for GFR <10	Dose for GFR 10–50
Oxcarbazepine	300 mg bid	600 mg bid	1%	100%	100%	100%	Less effect on P450 compared to carbamazapine.	No data	No data	No data
Phenobarbital	20 mg/kg/d; adjust for side effect and TDM		1%	100%	100%	100%	Plasma concentration: 15–40, Insomnia.			

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Phenytoin	20 mg/kg/d; adjust for side effect and TDM	1%	Adjust for renal failure and low albumin.			Plasma concentration: 10–20, nystagmus, check free. phenytoin level.	None	None	None
Primidone	50 mg 100 mg	1%	100%	100%	100%	Plasma concentration: 5–20.	1/3 dose	No data	No data
Sodium valproate	7.5 to 15 mg/kg/d; adjust for side effect and TDM	1%	100%	100%	100%	Plasma concentration: 50–150, weight gain, hepatitis, check free valproate level.	None	None	None

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Tiagabine	4 mg qd, increase 4 mg/d, titrate weekly	2%	100%	100%	100%	Total daily dose may be increased by 4–8 mg at weekly intervals until clinical response is achieved or up to 32 mg/d. The total daily dose should be given in divided doses two to four times daily.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Neurologic/Anticonvulsant Dosing in Renal Failure										
Topiramate	50 mg/d	200 mg bid	70%	100%	50%	Avoid		No data	No data	Dose for GFR 10–50
Trimethadione	300 mg tid-qid	600 mg tid-qid	None	q8 h	q8–12 h	q12–24 h	Active metabolites with long half-life in ESRD. Nephrotic syndrome.	No data	No data	Dose for GFR 10–50
Vigabatrin	1 g bid	2 g bid	70%	100%	50%	25%	Encephalopathy with drug accumulation.	No data	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Zonisamide	100 mg qd	100–300 mg qd-bid	30%	100%	75%	50%	Manufacturer recommends that Zonisamide should not be used in patients with renal failure (estimated GFR <50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity. The initial dose should be 100 mg daily. After 2 weeks, the	Dose for GFR <10	Dose for GFR <10	Dose for GFR <10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

			dose may be increased to 200 mg/d for at least 2 weeks. It can be increased to 300 mg/d and 400 mg/d, with the dose stable for at least 2 weeks to achieve steady state at each level. Evidence from controlled trials suggests that Zonisamide	

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

			doses of 100–600 mg/day are effective for normal renal function. Dose recommendations for renal impairment based on clearance ratios.	

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Rheumatologic Dosing in Renal Failure

Arthritis and Gout Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Allopurinol	300 mg q24 h	30	75%	50%	25%	Interstitial nephritis. Rare xanthine stones. Renal excretion of active metabolite with $T_{1/2}$ of 25 h in normal renal function; $T_{1/2}$ one week in patients with ESRD. Exfoliative dermatitis.	½ dose	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Auranofin	6 mg q24 h	50	50%	Avoid	Avoid	Proteinuria and nephritic syndrome.	None	None	None
Colchicine	Acute: 2 mg; then 0.5 mg q6 h Chronic: 0.5–1.0 mg q24 h	5 to 17	100%	50–100%	25%	Avoid prolonged use if GFR <50 mL/min.	None	No data	Dose for GFR 10–50
Gold sodium	25–50 mg	60–90	50%	Avoid	Avoid	Thiomalate proteinuria; nephritic syndrome, membranous nephritis.	None	None	Avoid
Penicillamine	250–1000 mg q24 h	40	100%	Avoid	Avoid	Nephrotic syndrome.	1/3 dose	No data	Dose for GFR 10–50
Probenecid	500 mg bid	<2	100%	Avoid	Avoid	Ineffective at decreased GFR.	Avoid	No data	Avoid

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Nonsteroidal anti-inflammatory drugs						Decrease renal function and platelet aggregation, nephrotic syndrome, interstitial nephritis, hyperkalemia, sodium retention, and increased risk of CVD, MI, and stroke.			
Diclofenac	25–75 mg bid	<1	50–100%	25–50%	25%		None	None	Dose for GFR 10–50
Diflunisal	250–500 mg bid	<3	100%	50%	50%		None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Etodolac	200 mg bid	Negligible	100%	100%	50%		None	None	Dose for GFR 10–50
Fenoprofen	300–600 mg qid	30	100%	100%	50%		None	None	Dose for GFR 10–50
Flurbiprofen	100 mg bid-tid	20	100%	100%	50%		None	None	Dose for GFR 10–50
Ibuprofen	800 mg tid	1	100%	100%	50%		None	None	Dose for GFR 10–50
Indomethacin	25–50 mg tid	30	100%	100%	50%		None	None	Dose for GFR 10–50
Ketoprofen	25–75 mg tid	<1	100%	100%			None	None	Dose for GFR 10–50
Ketorolac	30–60 mg load; then 15–30 mg q6 h	30–60	100%	50%	25–50%	Acute hearing loss in ESRD.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Meclofenamic acid	50–100 tid-qid	2 to 4	100%	100%	50%	None	None	Dose for GFR 10–50
Mefanamic acid	250 mg qid	<6	100%	100%	50%	None	None	Dose for GFR 10–50
Nabumetone	1.0-2.0 g q24 h	<1	100%	50–100%	50%	None	None	Dose for GFR 10–50
Naproxen	500 mg bid	<1	100%	100%	50%	None	None	Dose for GFR 10–50
Oxaproxin	1200 mg q24 h	<1	100%	100%	50%	None	None	Dose for GFR 10–50
Phenylbutazone	100 mg tid-qid	1	100%	100%	50%	None	None	Dose for GFR 10–50
Piroxicam	20 mg q24 h	10	100%	100%	50%	None	None	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Sulindac	200 mg bid	7	100%	100%	50%	Active sulfide metabolite in ESRD.	None	None	Dose for GFR 10–50
Tolmetin	400 mg tid	15	100%	100%	50%		None	None	Dose for GFR 10–50

Rheumatologic Dosing in Renal Failure

Biologic agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Etanercept	50 mg SC weekly	Hepatic	100%	100%	100%	Increased risk of TB and other infections.	100%	100%	100%
Infliximab	3 mg/kg IV at 0, 2, and 6 weeks; then q 8 weeks + methotrexate	Hepatic	100%	100%	100%	Increased risk of TB and other infections.	100%	100%	100%

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Adalimumab	40 mg SC qow	Hepatic	100%	100%	100%	May be continued during therapy; may increase to 40 mg SC q week in patients not receiving concomitant methotrexate. May cause glomerulonephritis.	100%	100%	100%

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Anakinra	100 mg/d SC	Renal	100%	50%	Avoid	Renal impairment: plasma clearance is reduced up to 75% in patients with severe or end-stage renal disease (CrCl less than 30 mL/min); no formal studies have been conducted.	100%	50%	Avoid
Rituximab	375 mg/mm every other week	Hepatic	100%	100%	100%	Increased risk of TB and other infections.	100%	100%	100%

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Sedative Dosing in Renal Failure Sedatives	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure *GFR >50*	*GFR 10–50*	*GFR <10*	Comments	HD	CAPD	CVVH
Barbiturates						May cause excessive sedation. Increased osteomalacia in ESRD. Charcoal hemoperfusion and hemodialysis more effective than peritoneal dialysis for poisoning.			

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Pentobarbital	30 mg q6–8 h	Hepatic	100%	100%	100%		None	No data	Dose for GFR 10–50
Phenobarbital	50–100 mg q8–12 h	Hepatic (renal)	q8–12 h	q8–12 h	q12–16 h	Up to 50% unchanged drug excreted with urine with alkaline diuresis.	Dose after dialysis.	1/2 normal dose	Dose for GFR 10–50
Secobarbital	30–50 mg q6–8 h	Hepatic	100%	100%	100%		None	None	N/A
Thiopental	Anesthesia induction (individualized)	Hepatic	100%	100%	100%		N/A	N/A	N/A
Benzodiazepines						May cause excessive sedation and encephalopathy in ESRD.			
Alprazolam	0.25–5.0 mg q8 h	Hepatic	100%	100%	100%		None	No data	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Clorazepate	15–60 mg q24 h	Hepatic (renal)	100%	100%	100%		No data	No data	N/A
Chlordiazepoxide	15–100 mg q24 h	Hepatic	100%	100%	50%		None	No data	Dose for GFR 10–50
Clonazepam	1.5 mg q24 h	Hepatic	100%	100%	100%	Although no dose reduction is recommended, the drug has not been studied in patients with renal impairment. Recommendations are based on known drug characteristics not clinical trials data.	None	No data	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Diazepam	5–40 mg q24 h	Hepatic	100%	100%	100%	Active metabolites, desmethyl-diazepam, and oxazepam may accumulate in renal failure. Dose should be reduced if given longer than a few days. Protein binding decreases in uremia.	None	No data	None
Estazolam	1 mg qhs	Hepatic	100%	100%	100%		No data	No data	N/A
Flurazepam	15–30 mg qhs	Hepatic	100%	100%	100%		None	No data	N/A
Lorazepam	1–2 mg q8–12 h	Hepatic	100%	100%	100%		None	No data	Dose for GFR 10–50
Midazolam	Individualized	Hepatic	100%	100%	50%		N/A	N/A	N/A

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Oxazepam	30–120 mg q24 h	Hepatic	100%	100%	100%		None	No data	Dose for GFR 10–50
Quazepam	15 mg qhs	Hepatic	No data	No data	No data		Unknown	No data	N/A
Temazepam	30 mg qhs	Hepatic	100%	100%	100%		None	None	N/A
Triazolam	0.25–0.50 mg qhs	Hepatic	100%	100%	100%	Protein binding correlates with alpha-1 acid glycoprotein concentration.	None	None	N/A
Benzodiazepines: Benzodiazepine Antagonist						May cause excessive sedation and encephalopathy in ESRD.			
Flumazenil	0.2 mg IV over 15 sec	Hepatic	100%	100%	100%		None	No data	N/A

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Miscellaneous Sedative Agents									
Buspirone	5 mg q8 h	Hepatic	100%	100%	100%		None	No data	N/A
Ethchlorvynol	500 mg qhs	Hepatic	100%	Avoid	Avoid	Removed by hemoperfusion. Excessive sedation.	Avoid	Avoid	N/A
Haloperidol	1–2 mg q8–12 h	Hepatic	100%	100%	100%	Hypertension, excessive sedation.	None	None	Dose for GFR 10–50
Lithium carbonate	0.9–1.2 g q24 h	Renal	100%	50–75%	25–50%	Nephrotoxic. Nephrogenic diabetes insipidus. Nephrotic syndrome. Renal tubular acidosis. Interstitial fibrosis.	Dose after dialysis.	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

			Acute toxicity when serum levels >1.2 mEq/L. Serum levels should be measured periodically 12 h after dose. $T_{1/2}$ does not reflect extensive tissue accumulation. Plasma levels rebound after dialysis. Toxicity enhanced by volume depletion, NSAIDs, and diuretics.	

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Meprobamate	1.2–1.6 g q24 h	Hepatic (renal)	q6 h	q9–12 h	q12–18 h	Excessive sedation. Excretion enhanced by forced diuresis.	None	No data	N/A

Antiparkinson Dosing in Renal Failure

Antiparkinson Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Carbidopa	1–2 tab tid/qid (30–200 mg qd)	30	100%	100%	100%	Require careful titration of dose according to clinical response.	No data	No data	No data

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Levodopa	1–2 tab tid/qid (300–2000 mg qd)	None	100%	50–100%	50–100%	Active and inactive metabolites excreted in urine. Active metabolites with long T1/2 in ESRD.	No data	No data	Dose for GFR 10–50
Rasagiline (mao-b inhibitor)	1 mg qd	<1%	100%	100%	100%				

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Antipsychotic Dosing in Renal Failure

Antipsychotics	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Phenothiazines						Orthostatic hypotension, extrapyramidal symptoms, and confusion can occur.			
Chlorpromazine	300–800 mg q24h	Hepatic	100%	100%	100%		None	None	Dose for GFR 10–50
Promethazine	20–100 mg q24 h	Hepatic	100%	100%	100%	Excessive sedation may occur in ESRD.	No data	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Thioridazine	50–100 mg PO tid. Increase gradually. Maximum of 800 mg/d.	Hepatic	100%	100%	100%		No data	No data	Dose for GFR 10–50
Trifluoperazine	1–2 mg bid. Increase to no more than 6 mg.	Hepatic	100%	100%	100%		No data	No data	Dose for GFR 10–50
Perphenazine	8–16 mg PO bid, tid, or qid. Increase to 64 mg daily.	Hepatic	100%	100%	100%		No data	No data	Dose for GFR 10–50
Thiothixene	2 mg PO tid. Increase gradually to 15 mg daily.	Hepatic	100%	100%	100%		No data	No data	Dose for GFR 10–50
Haloperidol	1–2 mg q8–12h	Hepatic	100%	100%	100%	Hypotension, excessive sedation.	No data	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Loxapine	12.5–50 mg IM q4–6 h		100%	100%	100%	Do not administer drug IV.	No data	No data	Dose for GFR 10–50
Clozapine	12.5 mg PO 25–50 daily to 300–450 by end of 2 weeks. Maximum: 900 mg daily.	Metabolism nearly complete	100%	100%	100%		No data	No data	Dose for GFR 10–50
Risperidone	1 mg PO bid. Increase to 3 mg bid.		100%	100%	100%		No data	No data	Dose for GFR 10–50
Olanzapine	5–10 mg	Hepatic	100%	100%	100%	Potential hypotensive effects.	No data	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Quetiapine	25 mg PO bid. Increase in increments of 25–50 bid or tid. 300–400 mg daily by day 4.	Hepatic	100%	100%	100%	No data	No data	Dose for GFR 10–50
Ziprasideone	20-100 mg q12h	Hepatic	100%	100%	100%	No data	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Miscellaneous Dosing in Renal Failure

Corticosteroid Dosing in Renal Failure

Corticosteroids	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
						May aggravate azotemia, Na^+ retention, glucose intolerance, and hypertension.			
Betamethasone	0.5–9.0 mg q24 h	5	100%	100%	100%		No data	No data	Dose for GFR 10–50
Budesonide	No data	None	100%	100%	100%		No data	No data	Dose for GFR 10–50
Cortisone	25–500 mg q24 h	None	100%	100%	100%		None	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Dexamethasone	0.75–9.0 mg q24 h	8	100%	100%	100%	No data	No data	Dose for GFR 10–50
Hydrocortisone	20–500 mg q24 h	None	100%	100%	100%	No data	No data	Dose for GFR 10–50
Methylprednisolone	4–48 mg q24 h	<10	100%	100%	100%	Yes	No data	Dose for GFR 10–50
Prednisolone	5–60 mg q24 h	34	100%	100%	100%	Yes	No data	Dose for GFR 10–50
Prednisone	5–60 mg q24 h	34	100%	100%	100%	None	No data	Dose for GFR 10–50
Triamcinolone	4–48 mg q24 h	No data	100%	100%	100%	No data	No data	Dose for GFR 10–50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Anticoagulant Dosing in Renal Failure

Anticoagulants	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure			Comments	HD	CAPD	CVVH
			GFR >50	*GFR 10–50*	*GFR <10*				
Alteplase	60 mg over 1 h; then 20 mg/h for 2 h	No data	100%	100%	100%	Tissue-type plasminogen activator (tPa).	No data	No data	Dose for GFR 10–50
Anistreplase	30 U over 2–5 min	No data	100%	100%	100%		No data	No data	Dose for GFR 10–50
Aspirin	81 mg/d 325 mg/d	10%	100%	100%	100%	GI irritation and bleeding tendency.	No data	No data	Dose for GFR 10–50
Clopidogrel	75 mg/d 75 mg/d	50%	100%	100%	100%		No data	No data	Dose for GFR 10–50
Dalteparin	2500 U SQ/d 5,000 U SQ/d	Unknown	100%	100%	NA	Check anti-factor Xa activity	No data	No data	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

							4 hours after 2d dose in patients with renal dysfunction.			
Dipyridamole	50 mg tid		No data	100%	100%	100%		No data	No data	No data
Enoxaparin	20 mg/d	30 mg bid	8%	100%	75–50%	50%	1 mg/kg q12 h for treatment of DVT. Check antifactor Xa activity 4 h after 2d dose in patients with renal dysfunction. Some evidence of drug accumulation in renal failure.	No data	No data	Dose for GFR 10-50

Table Continued

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Fondaparinux	2.5 mg SQ daily	10 mg SQ daily	No data	100%	75–50%	Avoid	Half-life increases with renal failure. Should be used for patients with HIT only.	No data	No data	Avoid
Heparin	75 U/kg load then 15 U/kg/h		None	100%	100%	100%	Half-life increases with dose.	None	None	Dose for GFR 10–50
Iloprost	0.5–2.0 ng/kg/min for 5–12 h		No data	100%	100%	50%		No data	No data	Dose for GFR 10–50
Indobufen	100 mg bid	200 mg bid	<15%	100%	50%	25%		No data	No data	N/A
Streptokinase	250,000 U load then 100,000 U/h		None	100%	100%	100%		N/A	N/A	Dose for GFR 10–50
Sulfinpyrazone	200 mg bid		25–50%	100%	100%	Avoid	Acute renal failure. Uricosuric effect at low GFR.	None	None	Dose for GFR 10–50

Table 83–2

Antimicrobial Dosing in Renal Failure—Cont'd

Sulotroban	No data		52–62%	50%	30%	10%		No data	No data	No data
Ticlopidine	250 mg bid	250 mg bid	2%	100%	100%	100%	Decrease CSA level and may cause severe neutropenia and thrombocytopenia.	No data	No data	Dose for GFR 10–50
Tranexamic acid	25 mg/kg tid-qid		90%	50%	25%	10%		No data	No data	No data
Urokinase	4400 U/kg load then 4400 U/kg qh		No data	No data	No data	No data		No data	No data	Dose for GFR 10–50
Warfarin	5 mg/d	Adjust per INR	<1%	100%	100%	100%	Monitor INR very closely. Start at 5 mg/d. 1 mg Vit. K IV over 30 min or 2.5–5 mg PO can be used to normalize INR.	None	None	None

required following each dialysis session with a polysulfone membrane in order to maintain therapeutic vancomycin levels.

Continuous hemofiltration modalities are gaining popularity in the intensive care unit for the management of acute renal failure. In this procedure, convective mass transfer removes solutes and drugs. In general, a drug is significantly removed if it is primarily distributed in the plasma water and is not highly protein bound. Measurement of serum drug levels may be helpful in guiding the need for supplemental dosing with these modalities.

Dosing Tables

Table 83.2 presents key information required for prescribing drugs in dialysis patients. Table 83.2 provides information on drugs that require dosing adjustment for patients with ESRD and on the half-life of the drugs (hours). The adjustment for ESRD applies to those patients with renal function poor enough to require maintenance dialysis (GFR generally <10 mL/minute). In patients with renal failure, a careful pharmacotherapeutic plan pertinent to each patient's situation should be applied. When the method of adjustment is interval extension (I), the number of hours that should elapse between doses is indicated in the table previously cited.

The quantity of the dose should be the same as that given to a patient with normal renal function. On the other hand, when the dose reduction method (D) is recommended the adjustment refers to the percentage of the dose given to a patient with normal renal function. This dose should be given at the usual dosing interval. Brackets in the previously cited table indicate the dosage formulation and currently available formulations. However, like any clinical guideline patient-specific factors such as age, disease state, nutrition, and body fluid should be considered during the dosage adjustments.

Recommended Reading

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31.
First reliable method for estimating renal function for patients with chronic kidney disease.
Gaspari F, Perico N, Remuzzi G. Application of newer clearance techniques for the determination of glomerular filtration rate. Curr Opin Nephrol Hypertens 1998;7:675.
Comprehensive review of newer clearance techniques for determination of GFR.
Levey AS, Bosch JP, Lewis JB, et al. for the Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular

filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 1999;130:461.

The article challenges the view that the Cockcroft and Gault formulation should be based on estimating renal function and instead proposes a new method of estimating a more accurate renal function for patients with chronic kidney disease.

Olyaei AJ, Bennett WM. Drug dosing in dialysis and renal failure. Comprehensive Clinical Nephrology 2006 (in press).

Comprehensive review of drug-induced nephropathy and nephrotoxins.

Olyaei AJ, deMattos AM, Bennett WM. Drug dosing in dialysis and renal failure. Clinical Nephrology 2003;[volume]:[pages].

A simple method to estimate renal function and adjust drug dosing according to renal function.

Olyaei AJ, deMattos AM, Bennett WM. Drug induced renal dysfunction in diabetes patients. In Harold, Lebowitz (eds.), *Therapy for Diabetes Mellitus and Related Disorders*. 2004:358–68.

Comprehensive review of drug-induced nephropathy.

Olyaei AJ, deMattos AM, Bennett WM. Drug-drug interactions and most commonly used drugs in renal transplant recipients. In Weir M (ed.), *Medical Management of Kidney Transplantation*. Philadelphia: Lippincot, William & Wilkins 2005:512–32.

Recent update to guidelines for prevention of drug-drug interaction in transplant patients.

Olyaei A, deMattos AM, Bennett WM. Drug usage in dialysis patients. In Nissenson, Fine (eds), *Clinical Dialysis*. New York: McGraw-Hill 2005:891–926.

Clinical guidelines for screening and assessing renal function and adjustment of drug dosage in renal failure.

Swan SK, Halstenson CE, Kasiske BL, et al. Determination of residual renal function with iohexol clearance in hemodialysis patients. Kidney Int 1996;49:232.

The renal clearance of iohexol was evaluated in 42 hemodialysis patients to determine residual renal function. This study provides reliable evidence of the safety and efficacy of iohexol in the accurate and safe measurement of residual renal function in hemodialysis patients.

CHAPTER 84

Physical Activity and Functioning in Dialysis Patients

Patricia Painter, PhD

The miraculous technologies of dialysis and transplantation have certainly improved survival of patients with renal failure. Federal legislation providing payment for end-stage renal disease (ESRD) treatment was passed by Congress in 1972 with the expectation that those receiving these life-saving treatments would be able to "get on with life." This expectation has been fulfilled for many of the younger and healthier patients. However, the increasing age and increasing co-morbidities of those receiving treatment have resulted in few patients actually returning to productive and fulfilling lives. Rehabilitation, meaning recovering or restoring what is necessary to get on with living, is now required for most patients. Unfortunately, rehabilitation efforts have been a low priority in most dialysis facilities—and necessary psychosocial and physical interventions have not been uniformly offered.

The Life Options Advisory Council, a multidisciplinary work-group addressing rehabilitation issues for renal patients, states that the ideal rehabilitation opportunity for a dialysis patient is "a coordinated program of medical treatment, education, counseling and dietary and exercise regimens designed to maximize the vocational potential, functional status and quality of life of dialysis patients." The main goals for rehabilitation include employment for those able to work, including patients over age 65 who wish to work; enhanced fitness to improve physical functioning for all patients; improved understanding of adaptation and the options for living well with dialysis; increased control over the effects of kidney disease and dialysis; and resumption of activities enjoyed prior to dialysis.

The Council has identified five "bridges" to rehabilitation that will lead to these desired outcomes. These five bridges (core principles) are identified as the five Es: education, encouragement, employment, exercise, and evaluation. The specifics of these bridges are well described in the publication *Renal Rehabilitation: Bridging the Barriers*. The Council has continued to develop materials related to rehabilitation for use by nephrologists, dialysis providers, health care workers, and patients and families. These

materials are available at *www.lifeoptions.org*. The focus of this chapter is on the core principle of exercise for reversing the effects of physical deconditioning and for optimizing physical functioning and quality of life in patients on dialysis (Table 84.1).

Definitions

Physical Functioning

Physical functioning is often used as a term to encompass many concepts. Physical functioning is best defined as an individual's ability to perform activities required in their daily lives. Physical functioning is determined by many factors, including physical fitness (cardiorespiratory fitness, strength, and flexibility), sensory function, clinical condition, environmental factors, and behavioral factors. *Physical fitness* is a set of attributes people have or achieve that relates to the ability to perform physical activity. One of these attributes is *cardiorespiratory fitness* (often referred to as *exercise capacity*), which relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained physical activity.

Physical functioning can be improved with regular physical activity or exercise training. *Exercise* (physical activity) is defined as bodily movement produced by the contraction of skeletal muscle that substantially increases energy expenditure. *Exercise*

Table 84–1

Definition of Terms Related to Physical Functioning

- *Physical functioning:* An individual's ability to perform activities required in daily life
- *Physical fitness:* A set of attributes that relates to the ability to perform physical activity (e.g., cardiorespiratory fitness, muscle strength, flexibility)
- *Exercise capacity (cardiorespiratory fitness):* Attribute that relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained physical activity
- *Exercise (physical activity):* Bodily movement produced by muscle movement that substantially increases energy expenditure
- *Exercise training:* Planned, structured, and repetitive bodily movement done to improve physical fitness or to obtain other health benefits

training is planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness or to obtain other health benefits. Increased *physical activity* can be considered exercise training, although increased physical activity can also result from unstructured increases in movements throughout the day. The use of the term *physical activity* may be less intimidating to dialysis patients who are typically elderly and often frail or chronically fatigued. However, exercise training is appropriate and recommended for dialysis patients due to their extremely low levels of physical functioning and exercise capacity.

Assessment of Physical Functioning

Given the multiple determinants of physical functioning (i.e., cardiorespiratory fitness, strength, sensory function, clinical status, and environmental and behavioral factors), no one measure can cover all areas. Assessment of functioning can range from objective laboratory measures of cardiorespiratory fitness to questionnaires of self-reported physical functioning that include questions relating to the ability to perform activities that range from basic self-care to household activities and more strenuous tasks (Table 84.2).

Cardiorespiratory fitness (exercise capacity) is objectively measured using laboratory estimates or actual measures of oxygen uptake during a maximal exercise test performed on a cycle ergometer or treadmill (VO_{2max}). There are objective criteria for achievement of VO_{2max}, many of which are not achieved by patients with chronic disease (who are often limited by symptoms such as skeletal muscle weakness or shortness of breath). In such cases, the measure of exercise capacity should be referred to as VO_{2peak}, or symptom-limited VO_{2peak}. Because of the expertise and technical requirements of exercise testing, it may not be practical for routine clinical evaluation of physical functioning. Thus, other measures are available for assessment.

The growing interest in physical functioning in older and diseased populations has led to development of tests that measure physical performance of standardized tasks such as walking (6-minute walk, gait speed), balancing, reaching, rising from a chair, and climbing stairs. These tests are more realistic for the majority of patients, are less expensive, do not require specialized equipment or testing personnel, and are easily performed in a clinical setting. These tests are referred to as physical performance tests. They are not direct measures of cardiorespiratory fitness,

Table 84–2

Measurement of Physical Functioning

Test Type	Measurement	Comments
Laboratory exercise testing	Estimated or measured peak oxygen uptake (VO2peak)	• Few dialysis patients able to perform test • Limited diagnostic utility in dialysis patients • Expensive; requires specialized equipment • Predictive of outcomes in dialysis patients
Physical performance tests	• Gait speed • Timed sit to stand • Standing balance test • 6-min walk	• Most patients able to perform tests • Inexpensive • Practical for use in clinical setting • Well standardized by national studies in gerontology population • May have ceiling effect in higher-functioning patients
Self-reported physical functioning	• Limitations in performance in activities of daily living • Limitations in performance of variety of activities	• Easily administered in the clinic • Documented to be predictive of outcomes in dialysis patients

strength, or flexibility but are indicators of these physical fitness measures. Self-reported physical functioning can also be evaluated using questionnaires, such as the SF-36 Health Status questionnaire—which assess level of difficulty performing activities of daily living, instrumental activities of daily living, and more strenuous activities.

Physical Functioning in Dialysis Patients

Physical functioning is low in patients treated with dialysis, whether measured by objective laboratory measures (exercise testing), performance-based measures, or self-report. In patients who are able to perform symptom-limited maximal exercise testing, the values for peak oxygen uptake (VO_{2peak}) are severely reduced—averaging about 60% of age-predicted values (ranging from 17.0 to 28.6 mL/kg/minute). The specific limitations of VO_{2peak} in patients treated with dialysis have not been identified and are potentially numerous.

Painter et al. showed significant improvement in VO_{2peak} within 8 weeks after successful transplant. This improvement occurred without exercise training or significant improvements in hematocrit, suggesting that other physiologic limitations may be present in the uremic state. Anemia associated with renal disease has always been implicated in the limited VO_{2peak}, and in the early trials of r-Hu-erythropoeitin treatment several studies measured VO_{2peak}. When increasing hematocrit from 17 to 20% to 30 to 33% there is a corresponding increase in VO_{2peak}. However, the increase in VO_{2peak} per increase in hematocrit is blunted compared to that observed in normal healthy subjects whose hematocrit was manipulated through phlebotomy and/or reinfusion of packed red cells (Figure 84.1).

In another study by Painter et al., in which hematocrit was increased using r-HuEPO from 33% to 40 to 42%, there was no change in VO_{2peak} unless the patients were involved in exercise training (Figure 84.2). In fact, even with this near-normalization of hematocrit plus exercise training, VO_{2peak} remained surprisingly low compared to age-predicted values (average 56.8 ± 20.6% of age- and gender-predicted levels).

The factors limiting exercise capacity in uremic patients are many (Figure 84.3). It is documented that these patients have low cardiac output responses to exercise, primarily due to a blunted heart rate. They also may be limited by endothelial dysfunction, which may affect the ability to divert cardiac output to the working muscles during exercise. The blunted heart rate response and/or

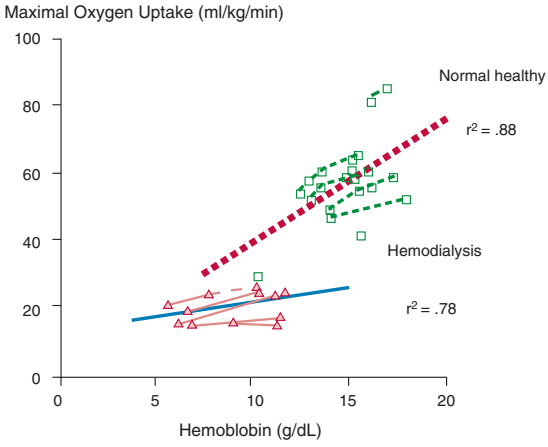


Figure 84–1

Changes in maximal oxygen uptake with changes in hematocrit from various studies of normal subjects (broken lines) and hemodialysis patients treated with r-Hu erythropoetin. *(From Painter P, Moore GE. Adv Renal Replacement Thera 1994;1:55–65.)*

endothelial dysfunction may be related to autonomic dysfunction, which may be related to oxidative stress and/or inflammation. However, these mechanisms have not been well documented.

It is also evident that these patients have abnormal muscle function due to metabolic and structural factors. Thus, although anemia may be the most obvious contributor to the limited VO_{2peak}, once hematocrit is treated to levels above 30% there is no further benefit in normalizing it in terms of exercise capacity. In this case, other interventions (particularly exercise training) may be needed to improve muscle function to optimize utilization of the increased oxygen delivery resulting from the increased hematocrits.

The reported values for VO_{2peak} are for those patients physically capable of performing the test. Although there are many patients who have co-morbid medical conditions that may contribute to limited exercise capacity, the markedly low functioning in the best of the patients indicates that there is a need to intervene to increase functioning. To put these levels of VO_{2peak} in perspective, patients with congestive heart failure are classified as moderate

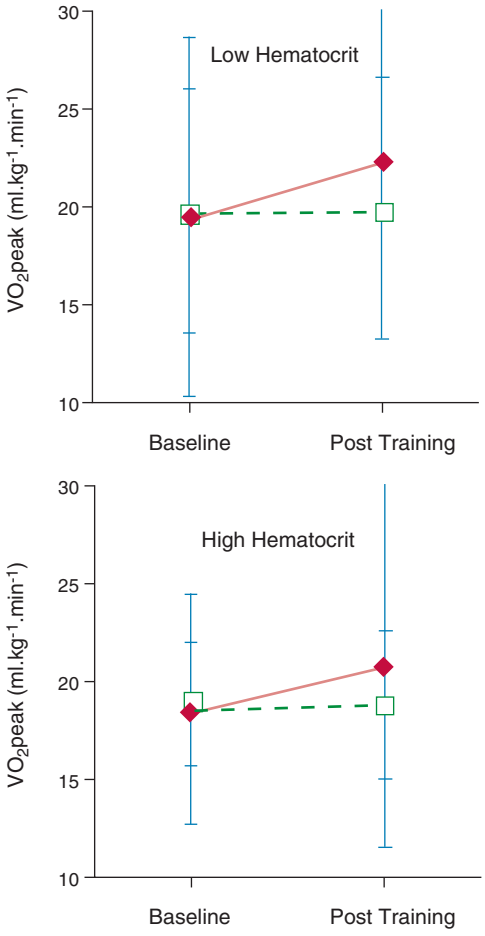


Figure 84–2

Changes in exercise capacity with exercise training in patients with usual-care hematocrit (30–33%) and those with near-normal hematocrit (40-42%). Closed diamonds represent the exercise-trained group. *(From Painter P, et al. Am J Kidney Dis 2002; 39:257–65.)*

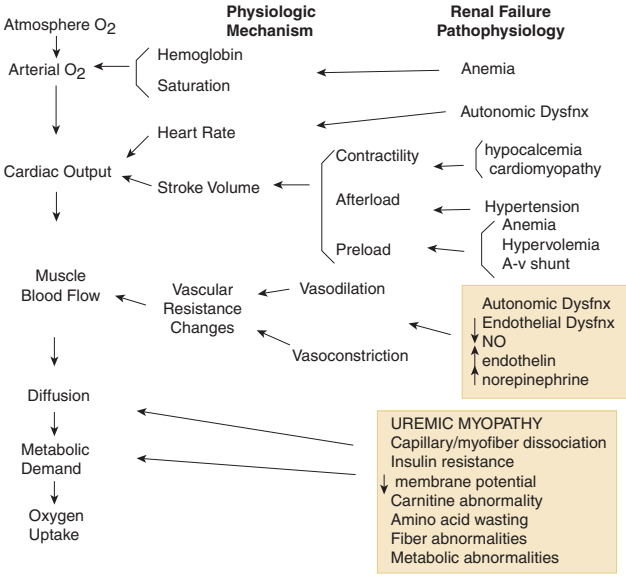


Figure 84–3

Determinants of oxygen uptake and factors that may limit oxygen uptake in patients with renal failure.

severity if the VO_{2peak} levels are between 16 and 20 mL/kg/minute. It is possible that more than 50% of patients are physically not capable of performing a symptom-limited exercise test—having physical functioning levels similar to or less than those of patients with congestive heart failure.

In patients who may not be able to perform symptom-limited exercise testing, physical performance testing may provide an indication of levels of functioning. Physical performance testing results are low in dialysis patients with gait speed averaging 66 to 77% of age-expected values. Lower extremity function as measured by sit-to-stand testing is reported to be severely limited, averaging less than 25% of normal age-predicted values.

Self-reported physical functioning is the most commonly used assessment in dialysis patients and is also severely limited. The Physical Function (PF) scale on the SF-36 Health Status Questionnaire and the Composite Physical Component (PCS) scale are both significantly below reported age norms in dialysis patients.

Levels of self-reported physical functioning in dialysis patients are lower than those reported for patients with congestive heart failure and similar to those reported for patients with chronic obstructive pulmonary disease.

Low self-reported physical functioning has been shown to predict outcomes of hospitalization and death in large populations of dialysis patients. Higher self-reported functioning scores result in significant improvement in the odds of death, and declines in physical composite scores over 1 year increase mortality risk. Objective laboratory measurement of oxygen uptake is also identified as an independent predictor of death over 3.5 years of follow-up. The predictive value of these measures of physical functioning remains even when corrected for case mix, contributing co-morbidities, and contributing factors.

Physical Activity in Dialysis Patients

Most dialysis patients are sedentary. Data from the Renal Exercise Demonstration Project showed that 59% of 286 hemodialysis patients participated in no physical activity beyond basic activities of daily living. Data from the USRDS Dialysis Morbidity and Mortality Study survey indicate that 12.4% were unable to ambulate or transfer and 35% were categorized as sedentary. Two studies using the USRDS data have reported that patients classified as sedentary show significantly greater risk of mortality over 1 year compared with nonsedentary patients with adjustment for other variables associated with survival in this group (Table 84.3).

Exercise Training in Dialysis

Dialysis patients will increase their physical activity if given specific information and encouragement to do so. Increasing physical activity and participation in exercise training will improve physical functioning (with increases in VO_{2peak} ranging from 5 to 42%) and will improve performance-based measures and self-reported functioning measures. The changes are most pronounced in patients who have low self-reported physical function scores on the SF-36 (PCS scale). Because the natural course of physical functioning in dialysis patients is deterioration of physical functioning over time, even *maintenance* of functioning is a positive outcome that can certainly be achieved by increasing physical activity. Reported benefits of exercise training in dialysis patients are outlined in Table 84.4.

Table 84–3

Studies Relating Physical Functioning and Physical Activity to Outcomes

Measure	Findings	Citation
VO_{2peak}	VO_{2peak} <17.5 mL/kg/min had greater deaths compared to those with VO_{2peak} >17.5 mL/kg/min. Exercise capacity was the strongest predictor of survival over the 3.5-year follow-up.	Sietsema K, et al. Kidney Int 2004; 65:719–24.
Self-reported functioning	Patients with PCS score (SF-36) below the median (<34) were twice as likely to die and 1.5 times more likely to be hospitalized. For every 5-point increase in the physical composite score (PCS), there was a corresponding 10% increase in the probability of survival.	De Oreo P. Am J Kidney Dis 1997; 30:204–12.
	Compared with patients with a PCS score (SF-36) >50, those with PCS score <20 had a hazard ratio of 1.97; those with PCS = 20–29 had a hazard ratio of 1.62; and those with a PCS score = 30–39 had a hazard ratio of 1.32. A decline in PCS over 1 year resulted in additional mortality and increased risk of mortality: hazard ratio of 1.25 per 10-point decline in PCS score.	Knight [initial], et al. Kidney Int 2003;63:1843–51.
	PF scale on Duke Health Profile was predictive of survival: difference of 10 points results in 63% greater chance of survival over 1 year.	Parkerson [initial], et al. Health Care Financing Review 2001;21:171–84.
Physical activity (from USRDS wave 2 form)	Patients who were sedentary at study initiation of dialysis had a 62% greater risk of mortality over 1 year compared with nonsedentary patients.	O'Hare A, et al. Am J Kidney Dis 2003;41:447–54.
	Mortality risk was lower for patients who exercised 2–3 times/week (RR 0.74) or 4–5 times/week (RR 0.70).	Stack A, et al. Am J Kidney Dis 2005;45:690–701.

Table 84–4

Counteracting the Impact of ESRD with Intradialytic[a] Exercise Training

Impact of CKD	Impact of Intradialytic Exercise
Physiologic/Clinical Impact	
• Reduced VO2peak	• Increased VO2peak
• Elevated submaximal exercise heart rate	• Reduced submaximal exercise heart rate
• Poor control of blood pressure	• Improved blood pressure control
• Increased use of antihypertensive medications	• Decreased requirement of antihypertensive medications
• Increased adiposity	• Favorable adaptation of body composition
• Reduced oxidative metabolism	• Increased phosphofructokinase activity
• Exacerbated malnutrition-inflammation complex	• Reduced C-reactive proteins and increased albumin
• Uremia and elevated solute concentrations	• Improved removal of toxins by dialysis
Functional Impact	
• Reduced muscular strength	• Increased muscular strength
• Reduced exercise capacity	• Increased 6-min walk
• Functional limitations in daily tasks	• Improved gait speed and sit-to-stand testing
Psychological Impact	
• Increased subjective fatigue symptoms	• Reduced subjective fatigue symptoms
• Poor perception of physical functioning	• Improved perception of physical functioning
• Poor perception of general health	• Improved perception of general health
• Increased anxiety	• Reduced anxiety
• Poor mental health	• Improved mental health
• Greater experience of bodily pain	• Reduced experience of bodily pain
• Reduced vitality	• Increased vitality

a. Most of these benefits are also documented in nondialysis exercise training. Adapted from Cheema et al. with permission.

Recommendations for Exercise Training for Dialysis Patients

Flexibility and Strengthening Exercises

Most patients are able to do *something* more than they are currently doing. For many, the most appropriate starting point may be stretching and strengthening exercises. This will improve range of motion to assist with performance of self-care and activities of daily living. Strengthening exercises may facilitate ambulation, allowing the patient to progress to some form of cardiovascular exercise—which will provide health benefits.

Stretching exercises throughout the dialysis treatment may prevent the troublesome stiffness experienced in sitting in one place for 3 to 4 hours, and may counteract the negative and painful effects of cramping that may be experienced during the treatment. Stretching and strengthening exercises should be progressed slowly. Sample exercises with descriptions and progressions can be found in the document *Exercise for the Dialysis Patient* available at *www.lifeoptions.org*.

Cardiovascular Exercise Training

Exercise that uses large muscle groups in a rhythmic manner (as in walking, cycling, rowing, and swimming) elicits health benefits in the general population and in patients with renal disease. The typical exercise prescription includes recommendations on the type, frequency, duration, intensity, and progression of exercise. The key is for patients to start exercise slowly and progress gradually.

Initial levels and progression will be highly individual, depending on starting physical condition and medical conditions. Details for prescribing exercise for dialysis patients can be found in the document *Exercise for the Dialysis Patient: A Prescribing Guide* available at *www.lifeoptions.org*. The recommendation for exercise does not have to be detailed, because for most patients just increasing their physical activity throughout the day may be beneficial. Changing activity patterns such as parking further away from the clinic or the store, or walking to the corner and back, may be helpful.

For many patients, exercise training with more structure may be recommended. Although there are no known contraindications to any type of exercise for dialysis patients, many patients experience some musculoskeletal discomfort. Thus, activities that minimize jarring on the joints may be most appropriate—

specifically, walking, cycling, or swimming. Exercise should be encouraged on most days of the week. However, nondialysis days may be most convenient for exercise due to excessive fatigue experienced following the dialysis treatment—as well as the time required for the treatment.

Patients initiating cardiovascular exercise should start with a duration of exercise that is comfortably tolerated (i.e., 5 or 10 minutes). Duration should gradually increase by 2 to 5 minutes per session each week as tolerated to a goal of 30 to 45 minutes per session. Some patients may need to do intervals, meaning that the exercise is performed for 1 to 2 minutes followed by 1 to 2 minutes of rest (repeated as tolerated). Gradually the rest intervals will be decreased so that the patient works up to a continuous session of 30 to 45 minutes.

Although the intensity of exercise is usually gauged by heart rate, this is not recommended for dialysis patients due to blunted chronotropic response to exercise, changing fluid status, and irregular medication regimens that may change the heart rate on a given day. Thus, with dialysis patients intensity of exercise is gauged by a subjective scale called the Rating of Perceived Exertion—which is a scale from 0 to 10 (or 6–20) with descriptors of "fairly light," "light," "somewhat hard," "hard," and "very hard" (Figure 84.4). The exercise session should begin with a warm-up or activity at a low intensity of "fairly light" increased in intensity to a subjective level of "somewhat hard" or "hard." Use of this subjective scale to gauge intensity allows for the changing physiology and fatigue experienced from day to day between and after dialysis treatments (Table 84.5).

Delivery of Exercise Counseling

Nephrologists could provide most dialysis patients the opportunity to gain strength and endurance and improve activity tolerance by referring them to physical therapy or cardiac rehabilitation. More proactively, these services could be easily provided within the dialysis center. Exercise during the treatment is safe and convenient and allows for easy supervision by health care personnel. It has also been shown that intradialytic exercise improves clearance of toxins through increasing blood flow through the leg muscles, thus exposing greater tissue area to dialysis. Even if exercise is not feasible during the dialysis treatment, patients should be regularly encouraged by dialysis staff to exercise on their nondialysis days by including such encouragement and monitoring as part of the routine pre-dialysis assess-

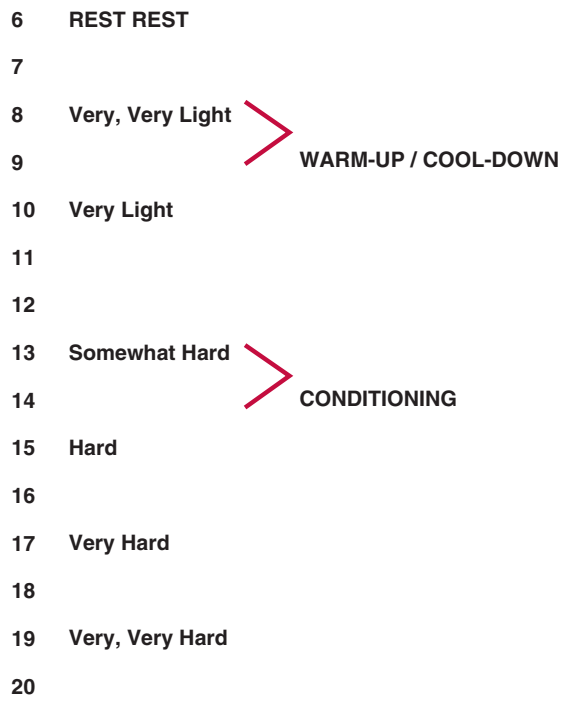


Figure 84–4

Subjective ratings of perceived exertion for recommending intensity of exercise.

ment—and by including it as part of the patient care plan, which is regularly reviewed and addressed by the care team.

Risks of Exercise

Exercise has two general types of risk: disease dependent and disease independent (the latter being the most common). Musculoskeletal injury and muscle soreness are the most common. In dialysis patients, muscle and joint soreness will be experienced because most patients have been sedentary for a long time. These are usually minor and transient. More serious disease-dependent

Table 84–5

Basics of Exercise Recommendations

Type of Exercise	Frequency	Starting Level	Goal	Progression
Resistance or strengthening	3 times per week	Using amount of resistance that can comfortably be lifted 10–12 times, perform one set of 10–12 repetitions of exercises for all major muscle groups.	3 sets of 10–12 repetitions of exercises for major muscle groups	Start with low weights (or Therabands) at 1 set of 10–12 repetitions and increase the number of sets to 3 sets; then increase the weight.
Flexibility	4 times per week	• Perform stretching around each major group. • Hold each stretch for 10–15 seconds.		• Move into stretch position gradually until a stretch is felt. • Do not bounce. • Be sure to breathe throughout the stretch.

Cardiovascular exercise	4–7 times per week	5–10 min as tolerated.
		• May be intervals of work/rest.
		• Low-level intensity.
			30–45 min per session (includes warm-up, conditioning time, and cool-down)
			• Duration:
			  • Warm-up: 3–5 min
			  • Conditioning: 20–35 min
			  • Cool-down: 3–5 min
			• Intensity:
			  • Warm-up: RPE of 9–10
			  • Conditioning: RPE of 12–15
			  • Cool-down: RPE 9–10
				Increase duration by 2–5 min per session each week.
				• Once 30 is achieved, increase intensity to 12–15.
				• For intervals, gradually decrease the rest interval.

risks include stress fractures and tendon avulsions, which may be possible in dialysis patients who have had uncontrolled secondary hyperparathyroidism for more than 4 years. Large powerful muscles such as the quadriceps can generate force that exceeds bone strength.

Screening for osteodystrophy with questions about bone pain, fractures, and laboratory evidence of osteodystrophy should be considered. Patients with evidence of bone pain or with X-ray or laboratory evidence of osteodystrophy should participate in non weight-bearing exercise and only low-level strengthening exercises. Patients allowed to become deconditioned through inactivity experience significant muscle weakness, making them more susceptible to falls. Improved muscle strength may reduce the risk of falls and associated orthopedic injury.

In the majority of dialysis patients who have diabetes, loss of blood glucose control during or after exercise is a risk. Diabetic patients can safely exercise and are encouraged to do so by most diabetes care guidelines. To prevent hypoglycemia, careful blood glucose monitoring is required. Patients must learn their own glucose response to exercise and adjust their diet and insulin accordingly. If exercise is performed during the dialysis treatment, the blood glucose will be maintained by the dialysate glucose concentration—which acts as a sort of glycemic clamp.

Cardiac events such as myocardial infarction and sudden death are the most feared risks of exercise, in that cardiovascular disease is prevalent in the dialysis population. In the non-dialysis population of people at high risk and/or persons suspected of having cardiac disease, the reported cardiac risks during exercise *testing* (i.e., pushing patients to near-maximal levels) are fewer than one death per 10,000 exercise tests, 4 or fewer non-fatal myocardial infarctions per 10,000 exercise tests, and approximately 5 hospitalizations per 10,000 exercise tests.

The risk of exercise *training* in cardiac patients participating in cardiac rehabilitation is most recently reported to be 1 cardiac arrest per 112,000 patient-hours of exercise, 1 death per 790,000 patient-hours of exercise, and 1 myocardial infarction per 300,000 patient-hours of exercise. Thus, the relative risk of exercise training in patients with *known cardiac disease* (1 arrest per 112,000) is actually lower than the risk of cardiac arrest during hemodialysis—which has been reported to be 1 per 11,570 dialysis sessions.

To put the cardiac risks of exercise training into perspective, two studies have reported that 4 to 7% of 1000 nondialysis patients who presented with acute myocardial infarction acknowledged

strenuous physical exertion preceding the event. Although the relative risk of myocardial infarction during or soon after unaccustomed exertion (i.e., in sedentary individuals) was 2 to 6 times higher than at other times, regular exercise participation attenuates the risk of cardiovascular event during strenuous exercise. When patients in the previously mentioned studies were stratified according to frequency of regular exercise, the relative risk of a cardiac event was clearly higher in those who were sedentary.

Likewise, the relative risk of cardiac arrest during exercise compared to risk at other times was 56 times greater in men with low levels of habitual physical activity and only 5 times greater among men with high activity levels. Thus, it is possible that dialysis patients are actually at greater risk by *not* being physically active because the risk of cardiac events are so much higher in less active or sedentary individuals (Table 84.6).

Minimizing Risks

Several steps can be taken to minimize risks associated with exercise (Table 84.6). All dialysis patients should be adequately dialyzed. Frequent assessments of dry weight should be made to

Table 84–6

Minimizing Risks of Exercise

Minimizing overall risk:
- Provide guidelines and assess regularly
- Start slowly and progress gradually
- Monitor (assess) patient responses to increasing levels of activity

Minimizing cardiovascular risk:
- Facilitate and encourage regular participation
- Provide adequate dialysis
- Manage ongoing medical concerns
- Control hypertension
- Respond to symptoms suggestive of cardiac disease

Minimizing musculoskeletal risk:
- Ensure adequate calcium/phosphorous balance
- Avoid high-impact activities
- Ensure appropriate warm-up and cool-down
- Ensure use of appropriate footwear
- Avoid use of maximal efforts

avoid volume overload. Co-morbidities such as metabolic bone disease, diabetes mellitus, arthritis, infection, anemia, and hypertension should be addressed and aggressively managed. Hypertension must be controlled and patients must be educated about the identification and management of signs and symptoms related to cardiovascular disease.

Exercise should be individualized and started at low intensity, with initial increases in duration rather than intensity. A low-impact (non–weight-bearing) type of exercise should be recommended to minimize musculoskeletal stress. Prolonged warm-up and cool-down times are important to enhance redistribution of blood flow and reduce the possibility of postexercise hypotension (especially important for those using stationary cycles during the dialysis treatment).

The Need for Exercise Testing

Although exercise testing is recommended prior to initiating exercise training for individuals at high risk for cardiovascular disease, the recommendation is dependent on the level of intensity of training expected. According to the American College of Sports Medicine, for those in the increased risk category with no symptoms who plan to initiate a program of moderate exercise (i.e., intensity of 40–60% of maximal capacity) no exercise test is recommended. To recommend pre-participation exercise testing for moderate increases in physical activity presents a significant barrier to participation in regular exercise. For dialysis patients, many barriers to initiating exercise already exist (e.g., socioeconomic, fatigue, and time factors).

Because dialysis patients have such low exercise capacity, the recommended intensity of exercise is usually very low (typically less than or equal to the intensity required for most activities of daily living) and does not put patients at a substantially higher risk than their daily living activities. Thus, it is questionable whether pre-participation exercise testing is necessary for dialysis patients. The diagnostic utility of the standard exercise test in dialysis patients may be limited for several reasons. The sensitivity of the exercise electrocardiogram (ECG) ranges from 50 to 90%, and specificity ranges from 60 to 98%.

Test sensitivity is decreased by inadequate stress (<85% of age-predicted maximal heart rate) and by drugs (or conditions) that alter the cardiac work responses to exercise. In dialysis patients the following may limit the diagnostic utility of the test: skeletal muscle limitations preventing achievement of adequate

stress; long-standing hypertension with LVH and strain patterns on the ECG, and electrolyte abnormalities that mask changes in S-T segments; and blunted chronotropic response to exercise (most patients achieve approximately 75% of age-predicted values) limiting cardiac stress. Thus, if the goal of exercise for the dialysis patients is to increase the frequency and duration of activity and to maintain function and prevent deterioration rather than elevate the patient to an arbitrary fitness and activity level less rigid guidelines for pre-participation exercise testing may be appropriate.

Although there are no data on adverse events experienced during exercise in dialysis patients, there have been no adverse events reported in any exercise testing or training study in dialysis patients. In our experience of more than 400 exercise tests in hemodialysis patients, there have been no cardiac events. Likewise, the author has extensive experience in exercise training hemodialysis patients in both clinical programs and research studies—including those with multiple co-morbidities. In more than 600 patients involved in cycling exercise during the dialysis treatment or participating in independent home exercise, there have been no adverse cardiac events or other untoward events.

The lack of adverse events is probably reflective of the low level of exercise hemodialysis patients are able to sustain during training. Because of their extreme deconditioning, typical exercise training programs for these patients start at levels that are very low and are similar to the energy expenditure of many activities of daily living. For "low fit" patients, this level of sustained physical activity is well tolerated. Routine training even at this level, with gradual increases in duration and sometimes in intensity, results in significant improvements in physical functioning and quality of life.

For dialysis patients who are exceptionally healthy, even strenuous exercise is well tolerated. In fact, there are reports of patients participating in athletic competitions such as open-water swimming, long-distance cycling, Olympic and Iron-man triathlons, and bodybuilding competitions. Thus, we feel that for patients who are adequately dialyzed with well-controlled hypertension and anemia exercise is safe and is an important part of overall medical management.

Incorporation into Routine Care

The first official statement recommending regular assessment of physical functioning and encouragement of physical activity for

dialysis patients is found in the recently published Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines on management of cardiovascular disease (guideline 14). The published guideline (guideline 14.1) states, "All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity."

The NKF-K/DOQI recommendations are for counseling and encouragement by nephrologists and dialysis staff in regard to identification of unique challenges to exercise in order to refer patients appropriately (i.e., to physical therapy or cardiac rehabilitation), measurement of physical functioning every 6 months using physical performance testing or questionnaires, identification of barriers to participation, and appropriate referral to cardiac rehabilitation or physical therapy. The goal of activity is to achieve cardiovascular exercise at a moderate intensity for 30 minutes on most, if not all, days of the week. Patients with low functioning should start at very low levels and durations and gradually progress to this level.

The NKF-K/DOQI guidelines also recommend that assessment and encouragement of physical activity participation should be a part of the routine patient care plan, which includes regular review that includes assessment of changes in activity patterns and physical functioning levels. It remains to be seen whether these NKF-K/DOQI guidelines will be implemented, and the question of the optimal method of incorporating exercise counseling into nephrology practice remains to be addressed. It is probable that the most effective way to motivate and encourage patients to increase physical activity and participate in regular exercise training is through changes in the routine care within dialysis clinics.

It is feasible that pretreatment patient assessment include activity participation at home since the last treatment. Documentation of this can be tracked and reviewed as a part of the patient review. The goals for each patient's exercise can be included into the short- and long-term patient care plan, with subsequent regular review. Assessment of physical functioning can be performed by a patient care technician prior to the dialysis treatment every 6 months. Information of these tests and information on physical activity participation can provide the nephrologist valuable information of a change (deterioration) in physical functioning that may indicate a change in clinical status that might not otherwise be detected.

Whether the NKF-K/DOQI guidelines are adopted or not, it seems reasonable for nephrologists to adopt guidelines of practice for conditions common in CKD patients. Many of these practices

include regular physical activity. Specifically, national guidelines for the treatment of hypertension (JNCVII), hyperlipidemia (NCEP Adult Treatment Panel III), and diabetes include regular physical activity as a first-line recommendation for treatment. Likewise, for individuals at high risk for cardiovascular disease or with known disease regular physical activity is recommended as a part of a comprehensive treatment program. The U.S. Surgeon General's report on physical activity and health states that "Regular physical activity can help people with chronic, disabling conditions improve their stamina and muscle strength, improve psychological well-being and quality of life by increasing the ability to perform activities of daily life."

Summary

Now that the lifesaving/life-sustaining potential of dialysis for CKD patients has been established, it is time to address the issue of quality of life. Providing information and encouragement, increasing physical activity, and participating in regular exercise training are necessary in optimizing physical functioning—which will contribute to enhanced quality of life and may optimize outcomes.

Recommended Reading

Cheema B, Singh MAF. Exercise training in patients receiving maintenance hemodialysis: A systematic review of clinical trials. American Journal of Nephrology 2005;25:352–64.

Meta-analysis of exercise training studies performed in patients with end-stage renal disease.

Cheema BSB, Smith BCF, et al. A rationale for intradialytic exercise training as standard clinical practice in ESRD. Am J Kidney Dis 2005;45:912–16.

Editorial providing documenation of research findings that justify the practice of intradialytic exercise training.

Copley JB, Lindberg JS. The risks of exercise. Advances in Renal Replacement Therapy 1999;6(2):165–71.

Discussion of the risks of exercise training in hemodialysis patients, with a presentation of existing guidelines for exercise testing and the differences in hemodialysis patients in terms of the diagnostic utility of exercise testing hemodialysis patients.

Moore GE. Selecting dialysis patients for an exercise program. Seminars in Dialysis 1995;8:42–44.

Thorough discussion of clinical risks of exercise training in patients with chronic kidney disease. Includes discussion of disease-dependent versus disease-independent risks, factors, and practices that can minimize risks.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines: Cardiovascular Disease in Dialysis Patients. American Journal of Kidney Diseases 2005;45(4):l3.

Guideline 14 includes recommendations for practice related to increasing physical activity in patients on dialysis.

Oberley E (ed). *Renal Rehabilitation: Bridging the Barriers*. Madison, WI: Medical Education Institute 1994.

This publication presents a comprehensive discussion on the status of rehabilitation in dialysis patients and factors ("bridges") that can improve rehabilitation for these patients.

Office of the U.S. Surgeon General. *Physical Activity and Health: A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, 1996.

Presentation of data on the benefits of physical activity in the general population and people at high risk for cardiovascular disease. Includes a chapter on "special populations" that indicates benefits in ability to perform daily activities and improvements in psychological health and quality of life.

Painter P. Physical functioning in end-stage renal disease patients: Update 2005. Hemodialysis International 2005;9:218–35.

Comprehensive and up-to-date literature review of physical functioning, exercise training, and the importance of exercise training in patients with renal disease.

Painter P, Blagg C, et al. *Exercise for the Dialysis Patient: A Comprehensive Program*. Madison, WI: Medical Education Institute 1995.

This document is a product of the Life Options Renal Rehabilitation Advisory Council which includes several separate documents: Exercise: a Guide for the Dialysis Patient, *which provides instruction on starting and maintaining a comprehensive exercise program (including diagrams and information on stretching and strengthening exercises and examples of a progressive cardiovascular exercise training program)*; Exercise: A Prescribing Guide, *which is a resource for recommending exercise for dialysis patients geared toward exercise professionals who need to know what considerations or modifications need to be made for prescribing exercise for patients with renal disease; and* Exercise for the Dialysis Patient: A Guide for the Nephrologist. *This provides information on exercise benefits and risks, and on how to select patients for exercise and how to minimize risks of exercise*.

Painter P, Stewart AL, et al. Physical functioning: Definitions, measurement, and expectations. Advances in Renal Replacement Therapy 1999;6(2):110–23.

This is a review of definitions related to physical functioning and of determinants of physical functioning—as well as a discussion of expectations for exercise training in patients with renal failure. It is part of an entire issue focusing on physical functioning issues in renal patients.

CHAPTER 85

Physical, Psychosocial, and Vocational Rehabilitation of Adult Dialysis Patients

John H. Sadler, MD

Whatever the cause of chronic renal failure, for most patients the effects are the same. The insidious progression of symptoms parallels the slow worsening of blood chemistries as glomerular filtration declines. Many patients fail to recognize the change in their vigor and well-being, and simply adjust to serial changes. This allows marked losses in exercise capacity and endurance to occur as deconditioning proceeds. Similar slowing of mental processes impairs relationships and communication. Dialysis removes most of the accumulated metabolites, but does not restore lost abilities. Those require, at least, exercise and stimulation to recover. This chapter addresses the additional efforts needed to rehabilitate dialysis patients and the reasonable expectations for improvement.

Background

Concern for rehabilitation has a long history in chronic renal failure. Advocates for Medicare benefits for dialysis and transplantation before the 1972 legislation made public assurances of the restored productivity of successfully treated patients, predicting that benefits provided would be returned in part by taxes paid by reemployed patients. Such enthusiasm was appropriate to the patients of that era of severely limited resources: each was carefully reviewed and accepted because of his or her ability to resume an active life with correction of uremia. Nephrologists reporting these results to encourage funding for dialysis and transplantation did not project what would ensue with open enrollment of all comers into end-stage renal disease (ESRD) therapy.

After implementation of the Medicare ESRD Program in 1973, the dialysis population rapidly expanded—and just as rapidly ceased to be a uniform, motivated, youthful population with little co-morbidity. As well, return to productive employment ceased

to be the norm. Because the only definition of rehabilitation used was vocational rehabilitation, there was a widely perceived failure of the ESRD Program to fulfill its promise. Many in Congress and elsewhere felt betrayed. Nephrologists were embarrassed, and rehabilitation dropped from the ESRD vocabulary.

In place of rehabilitation, the focus turned to mortality and hospitalization (which also got worse with older, sicker patients)—and to the development of improved technology. By the time the United States Renal Data System (USRDS) was developed, using the Medicare database to shine a unique spotlight on ESRD care, the emphasis had changed from the large numbers of people who survived chronic renal failure with treatment to the number of dialysis patients who had short survival and/or poor health.

Redefining Rehabilitation

The initial definition of rehabilitation addressed only the restoration of gainful employment, partly because of its potential economic consequences and partly because it was hard data easily used for assessment of outcome. It was widely remarked that in the absence of employment as the standard no one knew how to define rehabilitation.

Despite those remarks, other medical communities recognized that there are also psychosocial rehabilitation and physical rehabilitation in addition to vocational rehabilitation. Efforts to improve and monitor outcomes in those areas were often used by general internists, physiatrists, social workers, exercise therapists, and others. Cardiac rehabilitation has become nearly universal following cardiac injury or surgery.

The ESRD community has many clinicians who always sought to understand the lifestyle and problems of their patients and to help them cope with and improve their lives, but this was individual effort—with no systematic structure, no standards or guidelines, and no national or regional recognition. The results were reported as anecdotes of fulfilling experiences for professionals, as well as successes for patients—but not as clinical trials in medical journals. The impact of these experiences was quite limited.

In 1993, with support from Amgen, the Life Options program was started—and the Life Options Rehabilitation Advisory Council (LORAC), composed of experts in dialysis care and psychosocial research, was established to lead it. The Council's members set out to define an orderly structure for rehabilitation

efforts that would include physical, psychosocial, and vocational rehabilitation arenas—and that would provide guidance to clinicians and facilities undertaking it. This program is not the only such effort, but the organization of ideas and the subsequently reported successful programs make it an easy model for application to most ESRD treatment sites—as well as to other chronic disease settings.

Life Options begins with the "five Es" of renal rehabilitation (Table 85.1). The approach starts with *encouragement*, believing that the person can do better and that everyone involved will be gratified by the accomplishment—gently (or forcefully, if necessary) stimulating the patient to make the effort to be healthier. The *evaluation* that individualizes the approach can be included in the clinical planning for each patient, required by regulations and routinely documented. This includes education, work history, former and recent activity levels, physical capacity, social support, interests and hobbies, and hopes for the future. Patients need to know that this is happening, need to be informed, and need to make some choices in their plan. Interval reevaluation is important both to adjust the program and to provide everyone involved with a means of measuring what has been accomplished. Recognition of even small steps forward can mean a great deal. Setting a goal individualized to each patient's needs and capacities in clear and measurable terms, and noting milestones as each is reached, will ensure that all participants are rewarded.

Education begins with each patient learning about renal failure and the dialysis regimen; follows with health improvement goals, functional expectations, and exercise methods; and

Table 85–1

Life Options Definition of Renal Rehabilitation

- *Encouragement:* Surrounding the patient with a positive attitude.
- *Education:* Learning about kidney disease and dialysis, and about opportunities and interests.
- *Exercise:* Essential to recover and maintain physical capacity; improves cardiovascular health.
- *Employment:* Maintain or return quickly where possible; understand barriers and benefits.
- *Evaluation:* Repeated assessment of status and changes; important for factual reinforcement (along with regular assessment of functional status and health-related quality of life).

continues through specific learning to enable progress toward specific goals. Self-management of this regimen and direction is encouraged. Subsequently, this may include outside agencies or individuals. Some patients may not progress past the simplest grasp of their situation, but every patient needs enough knowledge to minimize fear of their disease and its treatment and to lessen dependence on staff and family. The opportunity to learn about subjects of interest may activate patients who have been self-absorbed and passive.

Almost every patient needs *exercise*, because most undergo significant physical deconditioning with loss of capacity and endurance as disease progresses. The "spiral of deconditioning" described by exercise physiologist Patricia Painter is quickly recognized by most patients and clinicians as accurate. Loss of vigor is so gradual the patient often does not recognize it. Exercises to reverse this decline need to be light but regular, composed of repetitions capable of being counted so that there will be a tangible reward through achieving higher counts, which reveal improved physical capacity. Most patients can train themselves to physical capacity near premorbid levels. Painter's work in active dialysis facilities demonstrates improved peak oxygen uptake after successful physical training, an objective measure of improved functioning. A booklet on ESRD-specific exercises is available through Life Options Renal Resource Center, Medical Education Institute, 414 D'Onofrio Dr., Madison WI 53719 (800-468-7777) or *www.lifeoptions.org*.

Stationary bicycles, treadmills, and other exercise devices are effective, and have been installed in a number of dialysis facilities. Some are used before dialysis; others have been adapted for use during the usually boring time spent on dialysis. Exercises during dialysis are usually well tolerated, without disrupting the procedure.

Everyday objects may also be used for exercise. A chair can be used for bracing during movement or for seated leg exercises. Canned goods can be used as dumbbells. Large rubber bands (Therabands) are used as a resistance to pull against. A sandbag can serve as a flexible weight that can be held on a foot to exercise a leg or in a hand to exercise a shoulder. Walking is always a good exercise for those who can. Walking indoors works when weather or neighborhoods discourage going outside. A few steps up and down the stairs are easy to repeat and count, with numbers increasing as exercise builds endurance.

Most of these simple actions build strength for activities of daily living. Periodic reassessment provides the patient a

satisfying reinforcement of accomplishment. It is important to promote expectations of well-being sufficient for continued productive living and independence, and then to demonstrate that ability. Counting repetitions is simple. When more quantitative results are sought, the standard 6-minute walk, stand-sit-stand test, or measured grip strength may be used. Loss of confidence may be as limiting as the loss of physical strength. Repeated reinforcement of progress through objective measurements can rebuild confidence.

The goal of *employment* is not realistic for most dialysis patients. Published reports confirm that those already employed can often retain employment or return to it promptly with less difficulty than trying to place an individual in a new job. Success is also related to education level. Vocational rehabilitation (VR) agencies or private employment companies can provide evaluations, arrange some types of training, and make potential employment contacts. The enthusiasm for such services must often come from the patient or the dialysis staff assisting the patient. VR offices are more accustomed to amputees, persons impaired in vision or hearing, or others with more obvious physical deficiencies—and some workers there may be ill at ease with a dialysis patient's problems. The pool of those who want to work or who can realistically become employable may be small, but for those few even a part-time job can be a great advantage. Working produces income and provides tangible evidence of recognition and personal worth, sets a framework for living through a regular schedule, and helps maintain physical capacity.

A survey of dialysis patients 18 to 55 years old found that more than 30% believed themselves able to work, but less than 20% were able to be employed. A favorable economy may improve that situation. The clinical team must realize the potential for employment and support the effort if patients are to succeed. In addition, a number of patients are known to work part-time or "off the books" in order to avoid loss of disability benefits—which compete well with what many can earn. Those unreported jobs are usually out of the ESRD professionals' awareness as well.

Other life-enhancing activities are more widely available than returning to employment. The mean age of dialysis patients is over 60, and many are beyond employability. However, some of them can discover useful and rewarding roles as volunteers or as members of other community activities that engage them in life outside their home—distracting them from focusing on

health problems. These activities meet a broad definition of rehabilitation. Not just the elderly but the majority of dialysis patients can improve physical, social, and intellectual functioning through education (in living with dialysis, in crafts, in history, arts, or specific interests) and through exercise during, before, or after dialysis in an entertaining way.

With encouragement, most patients can find ways to incorporate simple physical conditioning into daily activities. Encouragement from many sources (family, staff, volunteers, other patients, and so on) underlies the patient's acceptance and promotion of his or her own health. The clinical team's evaluation of results and feedback to patient and family of the findings can reinforce the rewards of self-improvement efforts on a number of levels. All of these can aid in establishing groups for shared activity, increasing social interaction, and avoiding isolation.

Every renal clinician can relate stories of individual patients who are not responsive to any effort at motivation, whose noncompliant behavior and self-destructive lifestyle frustrates everyone who comes in contact with them. Such individuals should not be accepted as the norm. Positive support for good habits and visible recognition of self-improvement achieved by other patients help to prevent bad habits from becoming contagious. These failures do not merit emphasis, but sometimes can be seen as an object lesson for other patients who would avoid their fate. Expecting effective rehabilitation will not always succeed, but expecting failure fulfills itself easily. For clinicians, the success of some patients can make tolerable the frustration caused by those who are unresponsive, undisciplined, determinedly pessimistic individuals.

Prerequisites to Effective Rehabilitation

Adequate Dialysis and Anemia Control

Fundamental to the promotion of health for dialysis patients is an adequate dose of dialysis. Monitoring to ensure this is routine. The mean measured dose of dialysis as Kt/V or urea reduction ratio is increasing every year. Higher blood and dialysate flows and more powerful dialyzers produce much of the increase, but many patients have to dialyze longer—never a welcome change. Motivation to accept longer treatment must come from learning the importance of good lab values and seeing the results in improving health. Learning is a central part of any successful dialysis regimen, and renal clinicians must teach.

Nephrologists must lead this effort. Informed patients can accept the choices needed for health and rehabilitation.

Correction of anemia is equally essential to health promotion. Achieving adequate red blood cell mass requires sound nutrition, conserving blood in procedures, adequate iron replacement, vitamin supplements, and (for most patients) regular administration of recombinant erythropoietin (EPO) to promote erythropoiesis. Increased red blood cell mass is important to strength and endurance, general well-being, and relief of some symptoms once thought to be the result of uremia. Exercise capacity improves. Average hematocrits rose sharply when EPO became available, and have continued to rise slowly since. That continued rise may be partly due to better monitoring and maintenance of iron stores, to promotion of better nutrition, or to higher doses of EPO. Much of this effort is made pursuing the raised expectations of the clinical renal community. Patients have become more aware of their hematocrit levels and their goal. That awareness provides patients with another milestone of achievement.

Co-morbid Conditions and High-Risk Lifestyles

Control of co-morbid conditions such as hypertension and heart failure is a routine consideration for the dialysis population because these conditions are frequent in renal failure. Rehabilitation requires each individual to reach his or her optimal health and to realize adequate stability for the confidence to try to expand capabilities. Medications are usually effective for these conditions, but effective sodium and volume restriction and regular physical activity, such as some of the exercises previously mentioned, promote cardiovascular health.

Systematic monitoring of cardiac function through periodic echocardiograms and other testing can guide clinical management, and recognize new problems in established cardiac disease. For diabetics, better control of glucose and blood pressure help preserve vision and cardiovascular function even after the onset of renal failure. For those with demonstrated vascular disease, control of serum lipids is important to preserve circulatory function. This often requires cholesterol-lowering medication as well as lifestyle modification. All of these factors merit attention as part of the health plan that underlies rehabilitative efforts. In these days of NKF-K/DOQI guidelines, there is always external monitoring of most of these factors.

Beyond specific diseases, many patients are obese, use tobacco, abuse alcohol or drugs, and are passive and inactive. All such behaviors are difficult to change, but a supportive and consistent group of dialysis clinicians, assisted by successful patients, can often motivate change. Repetitive contact makes this encouragement more effective through reinforcement. Specific instruction, counseling, or focused group therapy may be needed outside dialysis. The final responsibility is the patient's, who must make the change effective. These high-risk behaviors are common across the entire population, but when added to the risks of renal failure and its treatment they pose even greater potential harm to ESRD patients. Clinicians must seek effective messages that help change patient behavior to promote health.

Diet and activity are cultural practices. Changing them requires patients to learn the reason for changes. Repetitive monitoring and reinforcement aid motivation. Damaging habits seen as pleasures are given up more easily with some compensating enrichment of relationships, surroundings, or other pleasures that reward compliance. This is often beyond the reach of dialysis clinicians, but there are some conditions we can change (such as schedule and companions during treatment). Other conditions only need to be pointed out emphatically (such as weight loss, improved exercise capacity, and better laboratory values).

Depression is common in ESRD patients. It is probably a normal response to having to start dialysis, and often dissipates as symptoms clear. If exercise can restore vigor, spirits often rise as well. Clinicians need to be sensitive to clues to mood change and depression, because these can affect compliance, nutrition, activity, and survival. Patients with physical disease and depression often respond well to antidepressant medication as well as to improved circumstances.

Family Participation

Families may be protective of patients to the point of promoting dependence or preventing activities that can improve their functioning. The family needs to be included in learning and reinforcement of desirable behavior. Families need reassurance that denying a wish that adds to disease is the right thing to do, even if it causes friction. Patients regress behaviorally as they become limited by disease, acting more childlike in many ways. Families have to deal with that behavior more than clinicians, and their easiest coping mechanism may be to yield to requests

that break the regimen and promote co-morbidity. Older patients in particular may retreat and withdraw, making it difficult to engage them in the social and physical activity necessary to promote health. Family members need to make efforts to break this pattern, but many find it difficult to exercise authority over parents. Support and education from the clinical team can help them understand and act appropriately.

Implementing Renal Rehabilitation

Effective rehabilitation efforts require that everyone endorse the concept and commit to the program. Administration must commit resources of staff time and space to enable these activities. They have to value the goal or they will not invest to reach it. The medical director and other nephrologists must accept the idea and promote it, because attitudes and values often come from the doctors.

Nurses and clinical technicians must consistently reinforce the goal of rehabilitation and encourage the activities leading toward it in their repeated contacts with patients. Consistent positive attitudes move the program forward, and improve the atmosphere in the facility at the same time. Social workers can coordinate outside agencies and contacts to assist patients, and their contacts with patients can be most effective in building a positive attitude in them. Because nutrition is fundamental to gaining strength and feeling better, dietitians have opportunities to show patients how learning and following a regimen makes them healthier.

Some individual on the staff, often a social worker or dietitian but also frequently a nurse, must be named responsible for coordinating the rehabilitation program and for monitoring outcomes accomplished. The coordinator must be supported by all staff, not abandoned in the position, because patients often need help from multiple sources to succeed.

The coordinator may lead groups of patients in exercise activities or designate another person to do so if exercise in the facility is undertaken. Any staff member can teach simple exercises for patients to do independently, at home or in dialysis. All staff can help with education and all staff must consistently encourage patients to make the effort—then cheer the results. Rehabilitation is a team effort. These steps can be a by-product of existing practices and contacts. The theory is simple: a group of people consistently believing that trying will accomplish something good for patients can convince patients to make the

effort. Then everyone can enjoy the results, and the facility is a more pleasant place.

Evaluation of Outcomes

Employment, as noted in the historical review, is readily documented. Physical improvement is less so. Self-reports from patients are valuable, but it may be useful to observe and count repetitions of simple exercises or to use a standard measurement such as stand-sit-stand (as many times as possible in 30 seconds), the 6-minute walk (probably too time consuming to do for a group), or measured grip strength. Attitudes and increased knowledge are subjective but definite, and merit notation.

An overall assessment through self-report of a standard Health Status/Functional Status questionnaire or Health Related Quality of Life form is now a frequent practice in dialysis, and the results correlate well with survival and hospitalization, and predict behaviors that may affect the course of dialysis. These self-reported data demonstrate good correlations with more conventional clinical outcomes, and offer interval assessment of health status that can guide clinicians' efforts to improve functioning and well-being.

Applying these instruments and using the scores obtained to assess progress toward rehabilitation has been recommended as the single most useful indicator of an effective approach to renal rehabilitation in a facility. There are accepted, recognized instruments of considerable experience that may be valuable to a facility in assessing the patient's perception of progress. Used semiannually, such reports give a numerical score that can be followed as an integrated evaluation by the patient of the outcome of care. These results can point out aspects of care that need attention, just as lab results and physical findings can guide the dialysis prescription.

As ESRD patients become "older and sicker," it is easy to give up hope of improvement or accomplishment for many. However, when the five Es are applied as part of dialysis care every patient has an opportunity to improve him- or herself and become rehabilitated in terms specific to them. The results reported in a number of facilities confirm that as attitudes and communication improve demonstrably improved functioning occurs, and the staff share in the rewards they have helped patients achieve. When rehabilitation is defined as helping each patient reach his or her highest level of functioning and satis-

faction, the goal is reasonable, individually achievable, and beneficial.

Conclusions

The amount of time dialysis patients and staff spend together invariably exerts influence. It can be an opportunity to enrich one another's lives in ways that encourage and reward healthy behavior, leading to rehabilitation as defined here. All such endeavors take time, and current constrained finances in ESRD care make this difficult because time is in short supply. Using milestones and giving guidance toward rehabilitation have to be incorporated into the obligatory contacts of treatment or there will not be time to do these things. Health promotion and rehabilitation have to be a central part of therapy, not an additional or peripheral aspect of care that receives attention only after other steps are complete. When physical, social, and sometimes vocational rehabilitation are the goals of treatment, dialysis can become holistic therapy.

Expecting people on dialysis to return to active lifestyles, whether employed or not, is not always successful. However, expecting passivity, depression, and progressive physical deterioration will usually lead to just those outcomes. The social environment in a dialysis facility is conditioned by the expectations of clinicians and their response to good results. Rehabilitation will not occur passively. The matrix of adequate use of effective technology, good nutrition, appropriate medication, and medical monitoring is fundamental to dialysis care and essential for effective rehabilitation. A conscious, organized plan to help each patient improve according to individual capability is the next step toward improved health. Working partnerships between patients and clinicians can succeed in promoting greater health, confidence, and positive attitudes. Those attributes are themselves one level of rehabilitation for many patients.

Rehabilitation, and the promotion of optimal health accompanying it, is best seen as the central goal of treatment—not as an addition to treatment. Incorporated into the framework of care in this fashion, it is effectively addressed as part of routine care as much as dialysis, medication, and diet. Once clinicians are comfortable with their knowledge of renal rehabilitation, the contact with patients includes observations, recommendations, instructions, and assessments of their health status without a great increase in contact time.

Programmed exercise before, during, or after dialysis requires some oversight, which will consume time for a staff member able to supervise exercise. Surveys for health and functional status and quality of life measurement are largely self-administered, but scoring and handling requires some staff effort. Analyzing and using these results in focusing attention and improving care takes thought and practice. Helping patients to make themselves well is achievable. The rewards of improved productive living for patients, improved satisfaction for staff, and stabilizing the patient population (which preserve facility income) make renal rehabilitation a positive experience for all concerned.

Recommended Reading

Capelli J. Implementing organizational systems to measure outcome-related processes of end-stage renal disease care. Am J Kidney Dis 1994;24:346–54.
Practical and detailed report of developing systematic assessment of operations and outcomes, including aspects of rehabilitation and associated characteristics. Provides guidance in systematic analysis and use of operational data to improve care.
DeOreo P. Patient assessed functional health status (FHS) predicts survival in hemodialysis (hd) patients as well as Kt/V and nPCR do. J Am Soc Nephrol 1996;7(9):1444.
DeOreo P. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. Am J Kidney Dis 1997;30(2):204–12.
Important article demonstrating the importance of functional status/QOL assessment. Based on data from a multicenter program with good data collection and analysis.
Gutman R, Stead W, Robinson R. Physical activity and employment status of patients on maintenance dialysis. New Engl J Med 1981;304:309–13.
Broad survey of poor employment and physical capacity results of maintenance dialysis. The first attempt at objectivly defining results for dialysis patients under Medicare.
Kurtin PS, Davies AR, Meyer KB, et al. Patient-based health status measures in outpatient dialysis: Early experiences in developing an outcomes assessment program. Medical Care 1992;30(5):MS136–49.
Details of how to use these questionnaires, patient acceptance, and use of results. Good example for planning such a program. Critical, objective description.
Kutner N, Brogan D, Fielding B. Employment status and ability to work among working-age chronic dialysis patients. Am J Nephrol 1991;11:334–40.
This review provides much of the basic approach to the problem, and remains valid. Describes obstacles and methods to promote employment.
Life Options Rehabilitation Advisory Council. *Renal Rehabilitation: Bridging the Barriers*. Madison, WI: Medical Education Institute, 1994.
Life Options Rehabilitation Advisory Council. *Exercise for the Dialysis Patient: A Comprehensive Program*. Madison, WI: Medical Education Institute, 1995.
Life Options guide for programs setting up exercise for patients.
Life Options Rehabilitation Advisory Council. *Building Quality of Life: A Practical Guide to Renal Rehabilitation*. Madison, WI: Medical Education Institute, 1997.

Reports fundamental to the Life Options rehabilitation strategy. Good starting points for those starting a program of rehabilitation. Provides context and rationale.

Lowrie EG. Chronic dialysis treatment: Clinical outcome and related processes of care. Am J Kidney Dis 1994;24:255–66.

Lowrie EG, Lew NL. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990;15:458–82.

These three papers use a simple but large corporate dialysis database to analyze outcomes and relationship of lab values, test results, practices, and outcomes. Confirms value of functional status measures in assessment.

Lowrie EG, Zhang H, LePain N, Lew N, Lazarus JM. SF-36 and mortality. CQI Memorandum. Fresenius Medical Care North America, 16 January 1998; Reference No. 98 - 01-16.

Painter P. The importance of exercise training in rehabilitation of patients with end-stage renal disease. Am J Kidney Dis 1994;24(1/1):S2–9.

Painter P, Carlson L, Carey S, Paul SM, Myll J. Low-functioning hemodialysis patients improve with exercise training. Am J Kidney Dis 2000;36(3):600–08.

Reports the experience of a pioneering exercise physiologist with dialysis patients. Clear, detailed, and persuasive findings.

Rasgon S, James-Rogers A, Chemleski B, Ledezma M, Mercado L, Besario M, et al. Maintenance of employment on dialysis. Adv Ren Replace Ther 1997;4(2):152–59.

Reports efforts to maintain and restore employment in a dialysis population.

Rettig RA, Levinski NG. *Kidney Failure and the Federal Government*. Washington, DC: National Academy Press, 1991.

Comprehensive assessment of Medicare ESRD Program and results. Initiated efforts to assess quality of care and functional status. A landmark report by a genuinely expert group of professionals from several fields.

Rettig RA, Sadler JH, Meyer KB, Wasson JH, Parkerson GR, Kantz B, et al. Assessing health and quality of life outcomes in dialysis: A report on an Institute of Medicine workshop. Am J Kidney Dis 1997;30(1):140–55.

Follow-up to IOM ESRD Study, promotes functional status measures. First broad review of methods and meaning. Provides broad background in these measures, and a context in which results can be evaluated.

van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: Results of a randomized clinical trial. Nephrol Dial Transplant 2005;20(1):141–46. E-pub 2 Nov 2004.

Careful trial of exercise in dialysis with objective test results.

CHAPTER 86

Ethical Considerations in the Care of Dialysis Patients

Charles Jerome Foulks, MD

The 1973 implementation of the federal ESRD (end-stage renal disease) program brought life to many who previously would have died from uremia. Before 1973, selection committees chose those who would receive the scarce dialysis resources that were available. Following the implementation of the ESRD program in July of 1973, dialysis was offered to nearly all patients with chronic kidney disease (CKD) regardless of the nature of their underlying medical disorders. As experience with ESRD outcomes has increased, it has become clear that not all patients with CKD will benefit from dialysis therapy.

Many patients with stage 5 CKD who have severe, debilitating, or rapidly progressive diseases might sustain a greater burden of suffering while undergoing dialysis that may be physiologically successful but that prolongs only the patient's misery. The National Kidney Foundation responded to the need for guidelines that could assist renal professionals in dealing with the ethical problems of the initiation and withdrawal from dialysis by convening the Controversies in the Quality of Dialysis Care Consensus Conference (Scottsdale, Arizona, 14–16 March 1994).

A broad group of renal professionals—including nephrologists, nurses, social workers, religious leaders, and transplant patients (both transplant patients also represented dialysis patients since they individuals had previously required dialysis prior to transplantation)—was convened to develop appropriate guidelines for the initiation and withdrawal from dialysis. The author was fortunate to have participated in this conference. The work of this panel resulted in the 1996 publication by the National Kidney Foundation of *Initiation or Withdrawal of Dialysis in End Stage Renal Disease: Guidelines for the Health Care Team.* In addition, the Renal Physicians Association and the American Society of Nephrology collaborated in developing a clinical practice guideline concerning the initiation and withdrawal from dialysis.

Tenets of Ethical Decision Making

Physicians have traditionally used the Hippocratic Oath to guide them in making decisions and recommendations for their patients. However, profound changes in the technology and knowledge of medicine have placed upon the physician the burden of possessing a practical ability to apply ethical standards to the clinical practice of medicine. The ability to know what is best for the patient has become an impossible pipe dream.

Even with the use of APACHE scores, multivariate analyses of co-morbidities, and other functional or physiologic scoring systems, physicians remain unable to predict the future. This is compounded by a lack of information on the part of the patient, family, or surrogate; unrealistic expectations by the same groups; and inadequate communication by everyone. The physician is left to deal with these problems and still to act in the patient's best interests. Without a structure to formalize decision making, the physician, patient, family, and others may be providing improper care or not providing needed care.

Autonomy is the foremost ethical principle to be followed in deciding to treat or not to treat. For a patient to fully exercise his or her rights of individual autonomy and self-determination, the physician must provide the patient with the data necessary to allow informed consent to be present. Informed consent has three components: disclosure, competency, and free will. Physicians must provide diagnoses, prognosis, benefits, and risks of therapy to meet the burden of disclosure. To be competent for medical decision making, patients must possess the mental ability to understand relevant information, to understand the medical situation, to apply these facts to their personal situation, and to communicate a treatment decision.

Preventing the patient from being subject to undue coercion by family or caregivers ensures free will. Because autonomy and informed consent mean that the patient can make decisions about their care, they can withdraw permission for treatment at any time they wish. A problem in dealing with autonomy occurs when the patient is not competent to make medical decisions. In this circumstance, the physician must turn to a surrogate decision maker who is tasked with acting in the patient's interests as if the patient were making the decision. In the absence of previous discussions or of an advanced directive or living will, the surrogate decision maker is often unsure and may tend to want everything possible done for the patient. The physician has the burden of

educating the surrogate by providing the facts necessary for the surrogate to meet the burdens of informed consent.

An advanced directive or living will serves to guide a surrogate decision maker in carrying out the patient's wishes. It is very valuable to point out that the surrogate is merely ensuring that the patient's wishes are carried out. The surrogate is not making a life or death decision. They are acting as a legal agent of the patient. In the absence of previous discussions, an advanced directive, or living will, the surrogate should make decisions based on an estimation of what that individual patient might decide under the current circumstances. Last, if this fails because there is insufficient knowledge to guide the surrogate concerning the patient's values and probable decisions, the surrogate has the burden to act in a manner in which a reasonable individual could be expected to act under the circumstances. In this situation, the education of the surrogate in diagnosis, prognosis, benefits, and risks of therapy by the physician is the most important element.

The physician is bound to act to improve patient well-being (beneficence). The physician is also tasked with doing no harm (nonmaleficent). Full disclosure that allows true informed consent will promote beneficence and nonmalfeasance. The principle of justice (or equitable use of resources) requires that the patient receive necessary health care resources on an equitable basis (*i.e.,* discrimination in the application of health care resources cannot occur). Certainly, there are times when scarce health care resources might exist and rationing of these resources must occur. However, discrimination in the rationing cannot occur.

Institutions should have already established policies that explicitly describe the manner in which scarce or expensive resources would be provided under conditions of shortage. Under these circumstances, the physician must continue to act as the patient's advocate in trying to obtain these resources if the use is truly in the patient's best interests and informed consent has been ensured. The physician is responsible for the proper use of scarce resources, but the decision should be based on medical facts—including the likely response to treatment and outcomes based on the treatment—not on discriminatory criteria such as lifestyle, sex, age, ethnic background, or other nonmedical characteristics.

The professional integrity of the health care professional must be maintained. By virtue of education and experience, health care professionals have an ethical obligation not only to patients but to their profession and to their personal, conscientious, and

religious beliefs. Health care professionals are not obligated to participate in care to which they object. Policies on the use of life-continuing treatments must allow the health care professional to withdraw from the case and for the patient to receive appropriate care from another medical professional.

Guidelines for the Initiation and Withdrawal of Dialysis

The National Kidney Foundation Initiation and the document *Withdrawal of Dialysis in End Stage Renal Disease: Guidelines for the Health Care Team* are very thorough and were developed with great attention to the ethical principles of autonomy, beneficence, nonmalfeasance, and justice—and to the duty of the health care team to maintain professional standards. The ideal process for making these decisions comes from shared decision making between the physician (the medical expert) and the patient or surrogates (the patient expert).

The physician supplies the data for informed consent and the patient applies these data to his or her circumstances. This does not mean that the physician merely acts as a fact giver. The physician is also obligated to act as a guide and advisor in the application of these facts by the patient. It is inappropriate to list a smorgasbord of options and expect the patient to fill his or her plate from it. On the other hand, it is also inappropriate for the physician to act in a paternalistic manner by making the choice for the patient. In a medical emergency, when there is no advanced directive or living will the physician obviously has to act in a paternalistic manner and should act to maintain or preserve life.

After the patient has survived the acute resuscitation, the process of informed consent can begin with the patient or the surrogate decision maker. Unfortunately, nephrologists see many patients for the first time in the intensive care unit—and not surprisingly often initiate "Do Not Resuscitate" discussions. Patients are often referred to a nephrologist when they become overtly uremic and decisions have to be made quickly under less than ideal circumstances. In this scenario, it is often wise to initiate dialysis while buying time for shared decision making. Decisions to initiate or withdraw dialysis are very patient specific and must incorporate the patient's cultural, religious, ethnic, and personal beliefs.

In the event that quality of life or intellectual capacity is invoked as a reason to not initiate or to withdraw dialysis therapy,

it is only the patient's or surrogate's perception or opinion about the quality of life or intellectual functioning that matters. The personal values of the health care team are of no importance to the decision unless the caregiver has an ethical, professional, or religious objection to the patient's or surrogate's decision. The provision of dialysis therapy is not legally or ethically mandated when the health care team believes that the therapy will offer no substantive benefit to the patient.

The members must be very careful when this is invoked and must ensure that they are using patient-centered values and not their own personal values. Very specific examples of not offering dialysis include the persistent vegetative state, the irreversible and severe mental disorder that precludes the patient from interacting with the environment (*e.g.,* advanced Alzheimer's disease or severe anoxic encephalopathy). In general, patients who are thought to have a life expectancy less than 60 days secondary to a nonrenal disorder should not be offered dialysis. Uncommonly, dialysis might be offered such a patient to allow the attainment of some short-term goal: the birth of a grandchild, wedding of a child, or other similar occurrences.

There are times when the benefits of dialysis cannot be predicted. In this situation, a trial period of 30 days of dialysis is reasonable—with the expectation that a reevaluation of the benefits and burdens will occur at the end of the 30-day trial. Sometimes this technique is useful in the acute setting of the hospital (typically the intensive care unit)—the only difference being that a shorter timeline is used. All patients who are committed to chronic dialysis should undergo a complete reevaluation by the renal caregivers after 90 days to determine if alterations in therapy or even alterations in the original decision to dialyze are needed. When a trial of dialysis is chosen, the care team and the patient or surrogate decision maker must clearly define the exact criteria that will be used to define success or failure. To not define these parameters on the front end invites confusion, misunderstandings, and mistrust when the evaluation of the trial of therapy comes about.

Withdrawal should not be considered euthanasia. It represents the appropriate withdrawal of care that is interfering with the process of death. In these circumstances, it is useful to remember the medical proverb "When God lays his hands on the patient, the doctor should remove his." Of utmost importance when dialysis is withdrawn is the necessity for the physician and the other care providers to uphold the section of the Hippocratic Oath that advises the physician to always provide

comfort. The patient and family must continue to receive care, comfort, and support during the dying process. They cannot be abandoned. Hospice referral is very appropriate and helpful to the patient and all of the caregivers when dialysis is withdrawn.

Infrequently, competent patients will wish to discontinue dialysis—often feeling that the burden of continued dialysis is excessive. The health care team must prove that the patient is not depressed or suicidal, is not being coerced by external forces, is not uremic, and does not suffer from an acute but very reversible illness. It is very useful for the physician, primary nurse, social worker, chaplain or other religious advisor, and others (family or important friends) to have a conference with the patient so that these acute problems can be identified and treated. It is also important to receive a psychiatric consultation if the patient is felt to be depressed. After this is completed and acute problems rectified, patients have the right to discontinue therapy.

This situation is very difficult for the family and considerable social and religious support for them is proper and necessary. Patients often wish to die at home, although occasionally patients prefer the hospital. It is important to reassure the patient and family that the death from uremia is marked by the gradual onset of somnolence, followed by coma, and that there is no pain involved. On the rare occasion, the nephrologist may have to bring such a patient back to the dialysis unit for isolated ultrafiltration to relieve pulmonary congestion or pulmonary edema. When dialysis is withdrawn voluntarily, the patient and family must be assured that the decision is reversible and that dialysis therapy can be reinstituted. Dialysis cannot unilaterally be withdrawn by the physician except when continued dialysis is not physiologically or mechanically possible, such as in the patient who is actively dying and vital signs are insufficient to support dialysis.

The Unrecognized Dilemma

The currently unrecognized problem facing the U.S. medical community, including nephrologists, is that we are not prepared to take care of the hordes of dialysis patients expected by 2010 (going from 375,00 in 2000 to >610,000 in 2010) or to even begin to evaluate and care for the numbers of CKD patients in the U.S. population. Depending on the geographic area of the United States, between 7 and 11% of the population has CKD. This percentage will undoubtedly rise because we are facing a

pandemic of obesity, metabolic syndrome, diabetes mellitus, and hypertension. At Scott & White, since 2002 we have seen the diagnostic causes of ESRD in our patient population change: diabetes mellitus has risen from 38 to 58% and hypertension from 54 to 88%. We do not believe we are unique in these observations.

We believe that there may be about 3500 to 4900 practicing nephrologists in the United States out of the 5500 nephrologists listed as Board Certified in Nephrology or whom the AMA lists as nephrologists (6800). We only graduate about 340 new nephrologists per year and we are faced with the increasing numbers of retirements and deaths of practicing nephrologists. It has been estimated that the United States is losing about 75 nephrologists annually or may be gaining about 100 annually. Even if the number of nephrologists is increasing, the rate is only 2% per year.

Currently, the ratio of dialysis patients per nephrologist is 76–102:1—and if the predictions are correct the ratio may be 115–174:1 by 2010. These numbers of nephrologists that are predicted do not account for an increasing number of female nephrologists, nephrologists who must return to their native countries, the increasing importance that newly or recently graduated U.S. physicians place on personal time, and the increasing popularity of interventional nephrology as a career choice. Some nephrology practices are refusing to see new CKD patients and are accepting new dialysis patients only.

Not only are there too few nephrologists, there are few physician assistants (PAs) and nurse practitioners (NPs) who work in nephrology. Although there is a greatly increased interest of PAs and NPs in nephrology, there are no nephrology educational programs available. Each nephrologist is left to train a PA or an NP on the job without benefit of prior nephrology education, educational materials and resources, or educational objectives. The demands of practice and of federal reimbursement of professional services do not permit nonacademically based nephrologists the freedom to develop these critical resources. Without sound evidence based medical resources, the training of PAs and NPs is apt to be spotty—and this method of training will perpetuate, if not exacerbate, the variations in practice and care that lead to less than optimal outcomes.

These shortcomings in our nephrology care system can be overcome. There is a need for a central, unified, distance education curriculum that is designed to educate nephrology PAs and NPs. This program would supply the supervising nephrologist with

educational materials and objectives and supply the PA or NP with the objectives, educational materials, and case examples. This would allow the supervising nephrologist to use his or her practice as the living classroom and to take advantage of patients to depict the pertinent portions of the curriculum currently being taught.

In this manner, the nephrologist can gain productivity from the PA or NP and can teach a well-prepared curriculum that is supported with up-to-date evidence-based material. Experience and teaching both prepare the candidate for appropriate testing of the material. Such a curriculum will decrease variability in practice and will improve outcomes. Without a dedicated effort to ensure that we properly educate PAs or NPs and integrate them into the care system now, outcomes in dialysis and CKD will deteriorate and we will have permitted an ethical lapse to occur: to know the problems, see a solution, and to not act.

It has been clearly documented that early referral of CKD patients to a nephrologist confers a survival advantage, improves the likelihood of home dialysis, increases the chances for an arteriovenous fistula, decreases catheter use, improves metabolic disorders, decreases hospitalizations, and decreases cost of care. The number of patients who need evaluation and care is far greater than our current capacity to care for them. Our practices are simply not set up to evaluate and treat this huge number of patients.

We believe that a CKD clinic staffed by a nephrologist, PA/NP, RD, MSW, and RN represents a model for the care of large numbers of patients with a chronic disease such as CKD. We propose that primary care referral physicians should focus on the prevalence, causes, and medical needs of CKD patients. They will need educational resources such as CME (continuing Medical Evaluation) conferences and focused educational materials that can be merged into a busy private practice and enhance the flow of patients through the practice. An evaluation of the cause of a patient's CKD could be initiated prior to referral to a CKD clinic.

Group visits could be used for the educational portions of CKD management such as dietary, social, home dialysis, access care, bone disease, anemia, and diabetic management. Strict outcomes criteria for management such as a hemoglobin A1c <6.5%, LDL <70 mg/dL, average blood pressure of 125/75, and a MAP mean arterial pressure <92 mmHg could be used, and diagnostic and treatment algorithms could be used to attain these goals and to reduce variation. We are concerned that most private practices do not have the resources to initiate and manage such

clinics, and although the NKF KEEP initiative is a wonderful start it is not designed to actually focus on the management of the CKD patients who are found.

It will fall to nephrologists, working with primary care physicians and PAs and NPs trained in nephrology, to manage and care for these patients. Although nephrologists recognize that these patients must be identified and cared for, there is little they can do to address the needs of this vast number of patients in addition to caring for their already existing dialysis patients and those who are soon-to-be dialysis patients.

Nephrologists will have to learn to manage large numbers of patients by treatment algorithm and by extending their medical management through the use of physician extenders. In addition, the national and international renal organizations must recognize that the magnitude of the problem dwarfs our currently designed medical model. With this in mind, these organizations should be at the forefront of designing the CKD care system that will be needed to properly address the problem of a ballooning CKD population.

The ethical dilemma is to recognize the need and to not act (beneficence and nonmalfeasance, professional duties and obligations). Unless we intervene quickly we may well face rationing (justice, autonomy, and informed consent) in the provision of dialysis services. It is better to act to decrease the number of patients who might require dialysis than it is to do nothing and hope for the best (nonmalfeasance).

Summary

In the end, patients and their surrogates have total authority over the care they wish to receive. Principles of autonomy, beneficence, nonmalfeasance, and justice must be utilized and tempered by informed consent, shared decision making, and professional duties and obligations.

Patients with a life expectancy greater than 60 days, who possess the ability to meaningfully interact with the environment, and who are not in the process of dying from a nonrenal cause should be offered dialysis. In situations that are not clear, short-term dialysis should be offered and the patient fully reassessed at that time. Patients may withdraw from dialysis or surrogates may request their withdrawal. Acute illnesses (including under-dialysis and depression) must be eliminated, coercion must be excluded, and patients must be reassured that they can return to dialysis if they change their mind.

A greater threat to ethical conduct in nephrology is to recognize that a true disaster is coming and to not act. The increase in dialysis patients and CKD patients, the stagnant output of nephrologists, a lack of nephrology educated PAs and NPs, and the lack of an educational process for nephrology PAs and NPs—if not faced—will cause rationing of resources that will cause a collapse of the ESRD system and will shorten the lives of millions of patients. The scarce resources that will be rationed are the nephrologists and their knowledge.

Recommended Reading

Galla JH. Clinical practice guidelines on shared decision-making in the appropriate initiation of and withdrawal from dialysis. J Am Soc Nehprol 2000;11:1340–42.

Hastings Center. *Guidelines on the Termination of Life-Sustaining Treatment and the Care of the Dying: A Report of the Hastings Center*. Briar Cliff Manor, NY: The Hastings Center, 1987.

This is a superb discussion on the application of ethical principles in decision making for the use of life-sustaining treatment. There is a specific discussion about the use of dialysis.

National Kidney Foundation. *Initiation or Withdrawal of Dialysis in End Stage Renal Disease: Guidelines for the Health Care Team.* New York: National Kidney Foundation, 1996.

An excellent discussion of ethical principles and a complete discussion of the specific guidelines.

Osinski M, Wish J. Physician workforce: Coming up short. Nephrology News and Issues 2005;19(4):58–59. Also available at *http://www.nephrologyusa.com/article5.html*.

Excellent discussion of the nephrologist shortage and the reasons it has occurred.

Secure MA, Moss HA. Withholding and withdrawing dialysis: The role of physician specialty and education and patient functional status. American J of Kidney Diseases 1998;31(3):464–72.

This is a study that examined the role of physician specialty and education in principles of ethics in deciding to withhold or withdraw dialysis therapy. It is a thoughtful discussion and recommends remedies for improving care.

CHAPTER 87

Vascular Access in Children

Darrell L. Cass, MD, and Jed G. Nuchtern, MD

For children who require renal replacement therapy, peritoneal dialysis is the preferred choice for dialysis and early renal transplantation is the ultimate goal. In pediatric patients, hemodialysis has particular inherent disadvantages: it is technically difficult in small patients, it is not conducive to full-time school attendance, and for children with arteriovenous fistulas the psychological burden associated with painful needle sticks can be overwhelming. Despite these limitations, when emergent dialysis is indicated hemodialysis or continuous hemofiltration may be the only forms of therapy available.

Hemodialysis is also indicated for those children with more chronic renal disease who are not candidates for peritoneal dialysis, including those with chronic peritonitis, loss of membrane function, or caretakers who are unable or unwilling to perform the rigorous procedures of peritoneal dialysis at home. Because children with end-stage renal disease have a relatively longer life span compared to adults, it is likely they will require many courses of dialysis. Therefore, the critical issue for these patients is to provide adequate vascular access for the current need while minimizing compromise to future access sites. Because this requires a different surgical philosophy, it is important to develop a team composed of surgeons and nephrologists interested in these unique challenges.

Children, like all patients with potentially progressive renal disease, should have the nondominant arm protected from the time of diagnosis. A single venipuncture or placement of an intravenous catheter into the cephalic vein at age 2 can render the vein useless at age 10, making it impossible to create a primary fistula. The incidence of subclavian stenosis following insertion of even a small single-lumen catheter in the subclavian vein can be significant, and in pediatric patients this incidence may be as high as 80%.[1] Subclavian catheters should never be placed in children with progressive renal disease unless there is truly no other option.

Acute Hemodialysis Access

At times, vascular access for hemodialysis is required immediately in children with acute renal failure and in those with end-stage renal disease. Acute hemodialysis access is obtained by placing an uncuffed nontunneled dual-lumen polyurethane catheter into the femoral or internal jugular veins using the Seldinger technique. In small infants, single-lumen catheters may occasionally be used. The length of catheters placed via the neck or groin should be chosen so that the tip resides in the superior or inferior vena cava, respectively. The size of catheter used must be individualized to each patient. Larger catheters are more effective for dialysis, but carry a higher risk of thrombosis, vessel damage, and subsequent stenosis.

The goal is to select the smallest catheter that will provide adequate dialysis (a flow rate of 3 to 5 mL/kg/minute is acceptable in most patients). The femoral route is preferred in settings where dialysis will be needed for less than a few weeks, in order to preserve all future routes of access to the superior vena cava. Under no circumstances should the subclavian vein be the initial vein used for dialysis access. This is important because future forearm fistulae in the ipsilateral extremity can fail from the outflow obstruction associated with a "minor" stenosis in the subclavian vein. When use of the femoral vein is not possible, a puncture of the internal jugular is the next preferred option (Seldinger technique)—followed by a cut-down on the external, then internal, jugular vein.

Insertion-related complications of acute catheters include arterial puncture, local bleeding, pneumothorax, hemothorax, air embolism, and retroperitoneal bleeding. Table 87.1 lists the incidence of these complications compiled from several adult studies. On the basis of catheter to patient-size ratio alone, it is likely that several of these complications are more common and potentially more serious in infants and children. Real-time ultrasound guidance during cannulation of central veins may decrease the incidence of complications compared to anatomic landmark cannulation techniques, particularly in that 1/4 of patients referred for central access have variations in their internal jugular vein anatomy.[2]

In addition to central vein stenosis, late complications of acute catheters include central vein thrombosis, vessel perforation, cardiac tamponade, hemomediastinum, catheter malfunction, and infection. Acute catheter thrombosis can be treated with intralumenal thrombolytics (t-PA or urokinase) or catheter exchange. Catheter malfunction (insufficient blood flow for adequate

Table 87–1

Incidence of Complications During Acute Catheter Insertion

Complication	Incidence (Range)
Arterial puncture	4.4% (0–12%)
Local bleeding	4.0% (0–16%)
Pneumo/hemothorax[a]	2.0% (1–3%)
Air embolism	0.6% (1–1.3%)
Retroperitoneal bleeding[b]	0.6% (1–1.3%)

a. Primarily reported for acute catheters inserted in subclavian vein. The incidence in studies, including internal jugular catheters, is approximately 0.6%.
b. Acute dialysis catheters inserted in the femoral vein.
Data from Oliver MJ. Acute dialysis catheters. Semin Dial 2001;14:432–35.

dialysis) may be due to malposition or kinking of the catheter. A right internal jugular catheter with its tip in the distal superior vena cava is ideal. Left internal jugular and femoral catheters are more likely to malfunction, due to side-hole occlusion or high recirculation, respectively.

Unlike the clinical picture in adults, kinking is a major cause of removal of acute hemodialysis catheters in children, particularly when using catheters less than 9 French in diameter. In a report from Goldstein and colleagues, 59% of uncuffed catheters were removed for complications—of which 61% failed because of kinking.[3] Only 12% developed infection necessitating removal, and all catheters with intralumenal thrombosis were salvaged. The 1- and 2-month actuarial survival for uncuffed catheters was 69% and 48%, respectively.

Infection is a relatively rare cause of failure in uncuffed nontunneled temporary catheters. Exit-site infections should be treated with removal and replacement of the catheter in an alternate site. Patients with positive blood cultures require 3 weeks of therapy with culture-specific antibiotics. In patients with end-stage renal disease who develop catheter-related bacteremia without exit-site infection, it is reasonable to perform initial catheter exchange over a guidewire 24 to 48 hours after initiation of antibiotics—followed by 3 weeks of culture-specific therapy. Patients who do not become afebrile within 48 hours should have the catheter removed and replaced at a new site.

Chronic Hemodialysis Access

In children, as in adults, vascular access for long-term hemodialysis may be provided by creation of a native arteriovenous fistula (AVF), creation of an AVF with synthetic graft (AVG), or placement of a cuffed central venous catheter. Unfortunately, none of these options provides a perfect solution, and all have limitations with regard to rate of flow, long-term patency and use-life, or complication rates. Deciding which access is best for an individual patient is based on considerations of the patient's diagnosis, likelihood of transplant, risk of the procedure, home environment, and probability of long-term patency. In particular, teams who treat children with chronic renal failure must consider the size of the patient in order to select the best access option. For infants and small children, cuffed catheters may be the only hemodialysis access option. On the other hand, larger children and teenagers may be approached similar to the algorithm described in the NKF-K/DOQI Guidelines (2001).

As with all patients undergoing evaluation for permanent hemodialysis access, the assessment starts with a history and physical examination. Particular attention should be paid to a history of congenital heart and vascular malformations, other nonrenal disease, previous central lines, and long hospitalizations with poor peripheral intravenous access sites. In addition, it is important to know the handedness of the child. Upon physical examination, the presence of scars from previous vascular access, extremity edema, collateral veins, and pulses should be noted. An Allen's test should be performed. Diagnostic tests (including Doppler ultrasound, magnetic resonance venography, and conventional venography) may be required for patients with an abnormal vascular examination, a history of multiple previous vascular accesses, or the presence of edema, collateral veins, or differential size in the ipsilateral extremity.[2]

Whenever feasible, the first choice for long-term hemodialysis access in children is an autogenous AVF. Primary fistulas in general, and the radiocephalic fistula (Brescia-Cimino) in particular, have been shown to have longer patency and lower complication rates than expanded polytetrafluoroethylene (ePTFE) bridge grafts or external catheters.[4] However, arteriovenous grafts or cuffed catheters may be appropriate or required for some children.

Primary Arteriovenous Fistula

The first subcutaneous AVF was described by Brescia and Cimino in 1966, and involved the anastomosis of the radial artery to

the largest available vein at the wrist. Although there have been slight technical modifications since, the Brescia-Cimino fistula remains the first choice for long-term dialysis access. It is simple to create, preserves more proximal vessels for future access, has the highest patency and lowest complication rate, and it does not interfere with future kidney transplantation. Following surgery, the cephalic vein gradually increases in diameter and flow.

Whereas a minimum of 6 weeks is recommended for maturation of AVF in larger children and adults, up to 4 months may be required for fistula maturation in younger children. Temporary access provided during this time should be placed in the femoral or contralateral jugular veins to avoid any outflow obstruction. No venipunctures or blood pressure measurements should be performed in the ipsilateral extremity of a patient with a primary fistula (or AVG). In some instances, the fistula may never "mature" (known as primary failure) and alternative dialysis access will be required.

The advantages of these fistulae are that they are easy to create and have excellent patency once established; have lower incidences of conduit stenosis, infection, pseudoaneurysm, and vascular steal; and have improved flow over time. The principal disadvantages are that they have relatively long maturation times, lower flow rates, and higher primary failure rates. In addition, in some patients the veins may be more difficult to cannulate than a graft and may become quite engorged—resulting in a less desirable cosmetic appearance.

Although Brescia-Cimino fistulae can be constructed with high success rates in adults, numerous technical difficulties are encountered in creating these fistulae in small children. Smaller vessel size, higher propensity for vessel spasm, and poor venous outflow lead to higher primary failure rates in children. In adults, some argue that autogenous fistulas should be created whenever a cephalic vein is visible—whereas others feel that the vein must be 3 to 5 mm in diameter in order to provide adequate flow. Lumsden has defined an "adequate" vein in children as one that is greater than 1.5 mm in diameter when a sphygmometer is inflated to greater than 40 mmHg pressure.[5]

Many pediatric centers limit creation of primary fistulae to patients who weigh more than 25 kg. However, several authors have reported excellent results in smaller children using microsurgery techniques—with respective 1-, 2-, and 5-year patency rates of as high as 79, 75, and 70%.[6] Although the Brescia-Cimino fistula may fail at times to provide adequate flow for dialysis, the presence of a functioning fistula may promote dilatation of

the proximal veins to facilitate the creation of a prosthetic fistula using ePTFE.

If a radiocephalic fistula cannot be created, an ulnar-cephalic, brachio-cephalic, or brachio-basilic fistula should be considered. Primary AVFs in the thigh (saphenous vein to femoral artery) may be appropriate for some patients. Brachio-cephalic fistula are slightly more difficult to create surgically, have a higher incidence of steal syndrome, and may result in more arm swelling than radiocephalic fistulae. Brachio-basilic fistula can be created using a transposed basilic vein, in which the vein is tunneled into a subcutaneous position.[7]

The leading cause of primary failure is venous outflow obstruction, usually caused by stenosis or thrombosis from previous venous access. It is important to prevent venous outflow occlusion when possible, but also to recognize it *before* (not after) creation of a primary fistula. A venogram is mandatory in any child who has collaterals present upon physical examination, or who has a negative or equivocal "tap test" for patency of the target vein (placing a tourniquet, tapping the vein distally, and feeling the transmitted wave proximally). Venography may be indicated for children who have had a central venous line or multiple intravenous accesses in the extremity chosen for the primary fistula, even if the vein appears to be patent by physical examination.

Arteriovenous Grafts

When a primary AVF has failed, or is not technically possible, the alternative is to create an AVF with an interposition graft (bridge fistula). Prosthetic conduits can be placed from any artery to any vein of sufficient size to permit an anastomosis, and are readily available in various lengths, diameters, and configurations. In the past, bridge fistulas have been constructed from bovine carotid artery heterografts, human umbilical vein, and cryopreserved human saphenous or femoral veins. However, today most surgeons favor ePTFE in the construction of these fistualae.

PTFE has many advantages: it comes in various diameters and lengths; it is microporous, flexible, and easily packaged and stored; it is easy to sew; and it withstands repeated needle punctures. The most common site for placement of an AVG is the forearm, with straight grafts (radial artery to brachial vein) more common in smaller children and loop grafts (brachial artery to brachial vein) used in larger children. Alternate sites for AVG include the upper arm (brachial artery to distal brachial or axillary

vein) and the thigh (femoral artery to femoral vein). In general, smaller tapered grafts are used (4–6 mm taper) in children.

Although AVFs remain the first choice for permanent hemodialysis access, there are some advantages to AVGs when they are used. In general, they provide a larger surface area available for cannulation. In addition, they are technically easier to cannulate; they have a shorter lag time from insertion to maturation (at least 14 days should be allowed for incorporation of the graft into local tissues); and they are technically easy to repair surgically. In addition, the short-term primary patency rate of AVGs is higher than that for AVFs (96 versus 67%, respectively, at our institution; $p < 0.01$).[8]

Overall, the long-term complications of AVG (including infection, stenosis, thrombosis, and steal syndrome) are much greater than those for AVF. Infection in dialysis access prosthetics, such as PTFE, may be as high as 11 to 35% during the lifetime of the graft—which is significantly greater than the 2 to 3% reported for autogenous AVF. *Staphylococcus aureus* is the most common causative organism, accounting for 70 to 90% of infections. Other common infection-causing organisms include *Staphylococcus epidermidis*, *Streptococcus viridans*, *Enterococcus faecalis*, and Gram-negative bacilli such as *Pseudomonas aeruginosa*. Local signs of infection include erythema, induration, tenderness, wound breakdown, and purulent drainage, but systemic symptoms and life-threatening sepsis may result.

The treatment depends on the clinical presentation, degree of incorporation of the graft, and course of the patient—and involves a combination of intravenous antibiotics, possible surgical drainage, and/or graft removal. If the infection involves the anastomosis, a pseudoaneurysm may result that is at risk for rupture and life-threatening hemorrhage. When infection occurs in well-incorporated grafts, segmental bypass may yield graft salvage rates of 50 to 60%. In our own institution, infection has been reported to occur in 0.48 AVG per 12 access-months (compared to 0.11 AVF; $p = .03$).[8]

Stenosis, usually near the venous anastomosis, is common and essentially universal in these grafts given enough time. At our center, stenosis occurred in 1.06 AVG per 12 access-months, (compared to 0.33 for AVF). Because stenosis eventually leads to thrombosis, all patients with dialysis grafts must have surveillance to look for this complication. Most monitoring modalities (such as venous Doppler ultrasound, MRI, venous pressure monitoring, and fluoroscopic venography) have significant drawbacks that prevent their widespread application. More recently, the ultra-

sound dilution (UD) technique has been proposed as a practical noninvasive and reliable indicator of vascular access flow.

Several studies suggest that it is effective at identifying venous stenosis in adults receiving hemodialysis. Goldstein and Allsteadt at our institution showed very good correlation between low access flow as assessed by UD and angiographically proven venous stenosis in AVG.[9] In AVG, mean flow was 1027 mL/minute/1.73m^2 when no stenosis was present, compared to 401 mL/minute/1.73m^2 when greater than 50% stenosis was found. Access flows less than 700 mL/minute/1.73m^2 correlated strongly with AVG stenosis and may represent a critical minimum value below which access thrombosis may occur. There is insufficient data to address the role of UD in children with AVF.

When graft or venous stenosis is suspected, either by ultrasound dilution or other technique, angiography is indicated to define the stenosis prior to graft thrombosis. In this setting, balloon angioplasty can successfully extend the life of the graft and avoid surgical revisions. In the setting of acute thrombosis due to stenosis, a thrombectomy is performed. If flow can be restored, the patient undergoes angiography with balloon dilatation—either in the operating room or early the next day in the angiography suite. If flow cannot be restored, surgical revision of the graft is undertaken. Effective maintenance of dialysis grafts requires a coordinated effort between catheter-based and open surgical approaches.

Rarely, steal syndrome, heart failure, and limb hypertrophy may occur in children with AVF. All patients with AVF have some degree of steal, which refers to the fact that the fistula diverts blood flow from distal tissues. However, in children it is uncommon that steal becomes clinically significant—likely due to a relative absence of underlying atherosclerotic peripheral vascular disease. In children that have a Brescia-Cimino fistula or forearm AVG created, the ipsilateral hand is often cooler than the contralateral one in the early postoperative period. However, it is rare for the patient to develop pain, parasthesias, or other signs of significant tissue ischemia.

It is not uncommon that Branham's sign (slowing of the pulse by greater than 10% when the fistula is occluded by manual pressure) may be present in children with AVF. However, it is rare that cardiac failure occurs—likely due to better cardiac reserve in these patients. Children with high-flow AVF, particularly PTFE femoral grafts, may develop limb hypertrophy. In one series, 3 of 5 children with 6-mm PTFE thigh AVG developed

leg hyper-trophy—whereas none of 21 patients with arm grafts developed this complication.

What little data that is available suggests that AVG in children have similar patency and complication rates as those in adults. Brittinger reviewed results of 102 children with AVGs. For those with interposition grafts in the arm (n = 15), the "complication-free" function at 1 year was 73%, compared to 65% for those with thigh grafts (n = 46).[7] In the review from Sheth, the primary patency rate was only 41% at 1 year—whereas secondary patency rates were better (96, 69, and 40% respectively at 1, 3, and 5 years[8]). Complications occurred at a rate of 2.9 per 12 access-months, which was significantly greater than for patients with AVF (1.3 per 12 access-months; p = 0.02). Many more interventions were required in the cohort with AVG compared to those with AVF (2.8 interventions per 12 access-months compared to 1.4, respectively).

In this program, careful attention was paid to maintenance of systolic blood pressures and to avoidance of dehydration and high hematocrit in the immediate postoperative period. Routine anticoagulation after access thrombectomy was not used. However, aspirin was often prescribed for those patients with recurrent access thrombosis. Surveillance venograms were performed at 3-month intervals in patients with recurrent thromboses, and at 6-month intervals in patients with no clinical problems. Other indications for venograms included clinical parameters such as an abnormal physical exam of the access, high dialyzer venous pressure, prolonged bleeding after needle removal at the end of dialysis, and a measured increase in access recirculation.

Cuffed Catheters

Cuffed catheters are the most common form of chronic hemodialysis access in infants and children. The most recent North American Pediatric Renal Transplant Cooperative Study reported that 79% of children had access via external catheters (both cuffed and uncuffed types) at the initiation of hemodialysis. In our institution, 64% of hemodialysis patients dialyzed exclusively through a cuffed catheter. Although AVF and grafts have better long-term patency than catheters, certain technical and logistical concerns often favor catheter access in children. Children less than 20 to 30 kg can pose insurmountable technical challenges to permanent access creation due to the small size of their native vessels.

Permanent access should not be attempted in these small children if there is a high likelihood of primary failure, and thus wastage of the most desirable sites. Other reasons for catheter use include immediate need for dialysis with inadequate time to allow an AVF to mature, developmental delay and/or behavioral problems which preclude needle use, parent refusal of permanent access, and the relatively shorter time to transplant in children.

Cuffed tunneled catheters are made from silicone or silastic elastomer, which is softer than the polyurethane material commonly used for short-term dialysis catheters. The softer material permits placement of relatively larger catheters with less vessel injury, and safe tip placement in the right atrium (a position that is not advisable for the stiffer acute catheters). This lack of rigidity requires placement via a peel-away sheath that has been inserted in the vein using a modified Seldinger technique. Tunneling and use of a bonded Dacron cuff help to anchor the catheter in place, and prevent migration of bacteria from the exit site to the vessel lumen.

A variety of cuffed catheters are available for use in children (Table 87.2). These include standard 8- and 10-F round double-lumen catheters, the 7- and 10-F Tesio catheter systems (Medcomp, Harleysville, PA), and 10- and 12-F Ash split catheters (Medcomp, Harleysville, PA). Standard catheters are easiest to insert but have inherent problems with occlusion from the vessel wall and high recirculation. These problems have been partially mitigated by newer designs in which the two ends are offset by a few centimeters.

The Tesio system directly addresses the shortcomings of the standard double-lumen catheter by completely separating

Table 87–2

Estimate of Catheter Size Based on Patient Weight

Patient Size (kg)	Catheter Options
<10	7 or 8 Fr dual lumen
10–20	8 Fr dual lumen
20–25	7 Fr Tesio
	10 Fr dual lumen
20–40	10 Fr Ash-split
	10 Fr Tesio
>40 kg	10 Fr Tesio
	11.5 or 12. 5 Fr dual lumen

the device into twin single-lumen catheters that lie in parallel in a single vein. This allows for circumferential placement of side holes to decrease vessel wall occlusion and good tip offset for less recirculation. The Ash split design is a double-lumen catheter that splits into two separate single-lumen tubes at its distal end. It can be inserted via a single venipuncture-wire-dilator-introducer maneuver and represents a compromise between the ease of insertion of a single catheter and the efficient function of the Tesio design. Unfortunately, the relatively large size of the available Ash devices decreases their utility in the pediatric dialysis population.

Cuffed tunneled catheters are placed under sterile conditions in a dedicated operating room. Fluoroscopy is mandatory for placement of the distal tip in the right atrium. The right internal jugular vein is the preferred site, although the left internal jugular and femoral veins are workable alternatives if the former is occluded. The subclavian veins are scrupulously avoided unless there are absolutely no other sites available, permanent access placement in the upper extremity has failed, or it is required for some other reason.

The insertion-related complications associated with placement of cuffed tunneled catheters (such as pneumothorax, hemothorax, and air embolus) are identical to those seen with acute percutaneous catheters (as described previously). Catheter malfunction can be broken down into acute and chronic problems. Acute malfunction is synonymous with malposition of the device. In children, internal jugular catheters should be positioned with the distal tip within the right atrium and the proximal end in the superior vena cava just above the cavoatrial junction. The tips of femoral devices should lie in the inferior vena cava above the iliac bifurcation. The surgeon can perform a practical test of adequate flow in the operating room using a 10-mL syringe. If the catheter is properly placed, one should be able to fill the syringe from either lumen by rapidly withdrawing the plunger without encountering any hard resistance or "stutter" from the catheter.

At least two studies have addressed outcomes of cuffed tunneled catheters in children. Lumsden reported the results of 29 tunneled cuffed double-lumen catheters placed in children over an 8-year period.[5] The mean duration of access was 8.1 + 6.9 weeks. Eight catheters were removed for infection and eight secondary to trauma, and five required removals for thrombosis not responsive to lytic therapy. We reviewed our single institution experience with traditional double-lumen catheters as well as

with Tesio twin catheters over a 2-year period.[10] Median duration of access was significantly longer with the Tesio catheters (322 catheter days, compared with 91 catheter days for double-lumen tubes; $p = 0.003$). Catheter-related sepsis occurred less frequently with Tesio catheters: one episode per 20 catheter-months versus one episode per 5 catheter-months with the double-lumen catheters. Adequate dialysis (single-pool $Kt/V > 1.2$) was delivered with the same frequency and for a longer duration with the twin catheter system.

Long-term catheter malfunction is caused by thrombosis and/or infection. The incidence of total catheter failure requiring replacement because of thrombosis is approximately 2.2 episodes per 1000 catheter days. Intralumenal thrombosis, the formation of a thrombus within the lumen of the catheter, is caused by inadequate heparin flushing after use of the catheter, heparin leaking from the catheter between uses, or the presence of blood within the catheter. This type of thrombosis is normally amenable to treatment with recombinant tissue plasminogen activator (rt-PA, Alteplase). All hemodialysis catheters should be packed with a heparin solution (2000 units/mL) following each dialysis run. However, specific precautions must be taken to prevent flushing the packing solution into the intravenous circulation—especially in infants and small children.

Formation of a fibrin sheath is a less tractable form of intrinsic thrombosis. Autopsy studies report that 100% of long-term catheters will develop a fibrin sheath. However, the rate of catheter dysfunction associated with these coverings is estimated to be between 13 and 57%. Fibrin sheaths are treated with rt-PA infusion, percutaneous transfemoral sheath extraction, and catheter exchange.

Central vein thrombosis is a potential complication of central venous catheterization, with a reported incidence of between 2 and 63.5%. For symptomatic patients, treatment consists of catheter removal and systemic anticoagulation. Although there is not an extensive experience, rt-PA has been used successfully in children with symptomatic superior vena cava syndrome. In cases where there are very few options for alternative sites of dialysis, the catheter may be left in place and the patient followed closely on systemic anticoagulation plus thrombolytic therapy if the clinical circumstances permit this approach. This same general approach applies to asymptomatic patients with central vein thrombosis or mural thrombus, with the exception that thrombolytic therapy is not indicated in this circumstance.

Infection is the most common and serious complication of hemodialysis catheters. The estimated rate of catheter-related

bacteremia (CRB) in long-term tunneled cuffed catheters is 1 episode per 252 catheter days. The most common organism isolated in CRB is *Staphylococcus aureus*, followed by coagulase-negative *Staphylococcus* and Gram-negative species. The most important strategies for preventing these infections include full barrier precautions during catheter insertion, meticulous exit-site care, and minimization of contamination of the catheter hubs in the dialysis unit.

Established catheter infections include exit-site and tunnel infections and catheter-related bacteremia. Exit-site infection is defined as infection localized to the exit site (external to the anchoring cuff) and is characterized by localized redness, crusting, and exudate. Minor exit-site infections can be treated with topical disinfectants and antibiotic ointment, with systemic therapy added in severe or recalcitrant cases. Tunnel infections involve the external surface of the catheter, proximal to the anchoring cuff. These infections have a high rate of associated bacteremia because the involved portion of the catheter moves in and out of the accessed vein. Catheter removal is mandatory and the tunnel should not be reused for the next catheter. Patients with bacteremia are treated with intravenous culture-specific antibiotics for 21 days, whereas those with negative cultures and localized symptoms and signs can only be treated with shorter courses based on clinical judgment.

Treatment for catheter-related bacteremia is tailored to the clinical setting and the overall status of the patient. Although immediate removal of the catheter would allow most rapid clearing of the bacteremia, evidence continues to accumulate that this approach is neither necessary nor prudent in some clinical situations. Patients with clear signs of sepsis and positive blood cultures should have their catheters removed promptly after initiation of empiric antibiotics. Those with mild symptoms and without exit-site or tunnel infections are candidates for catheter exchange over a wire after 24 to 48 hours of antibiotics, whereas patients with exit-site and/or tunnel involvement require catheter removal after initial antibiotic treatment and replacement at another site. Initial empiric antibiotic coverage should include vancomycin and an aminoglycoside, with substitution of culture-specific medications as soon as the infectious agent is known, for a total antibiotic course of 3 weeks.

Summary

Pediatric vascular access for hemodialysis presents special surgical challenges due to the smaller size of the vessels and the changing

size and physiology of the patient. Primary AVF, with the lowest rate of secondary failure and complications, are preferable for long-term hemodialysis access in children. The decision of which patients are "too small" for this surgical approach will vary from institution to institution based on the experience of the surgeon and the availability of microsurgical techniques.

Ultimately, the decision is between the risk of primary failure (and subsequent loss of that site for a future fistula) and the complications of central venous access (which may also prevent creation of effective future access). Placement of an AVG should be considered only when all options for an adequate primary AVF have been exhausted. The use of a central venous catheter via a jugular or femoral vein approach should be reserved as a "bridge" to a more permanent access, or reserved for children so small that the risk of primary failure of an AVF is unacceptably high.

The subclavian vein should be avoided. In all cases, access must be planned *before* the procedure with the long-term need for dialysis in mind. In most centers, the nephrologist must choose between a vascular surgeon (who may not be aware of the special issues associated with children) and a pediatric surgeon, who may not be aware of the special vascular issues of pediatric access surgery. In either case, it is imperative that the surgeon providing the access be an active participant in the decision-making process, be educated about the special needs of children in renal failure, and be aware of the issues surrounding the choice of access for each patient.

References

1. Clinical practice recommendations 8: Vacular access in pediatric patients. Am J Kidney Dis 2006;48:S274–76.
   Provides up-to-date overview of clinical practice recommendations for pediatric vascular access.
2. Juno RJ, Knott AW, Racadio J, et al. Reoperative venous access. Semin Pediatr Surg 2003;12:132–39.
   Review article discussing issues related to central venous access in children.
3. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. Pediatr Nephrol 1997;11:74–77.
   Review of hemodialysis catheter outcomes in 23 children treated at Children's Hospital, Boston.
4. Ramage IJ, Bailie A, Tyerman KS, et al. Vascular access survival in children and young adults receiving long-term hemodialysis. Am J Kidney Dis 2005;45:708–14.
   Twenty-year retrospective review of long-term hemodialysis access and outcomes in 114 pediatric patients treated at St. James's University Hospital in Leeds, UK.

5. Lumsden AB, MacDonald MJ, Allen RC, et al. Hemodialysis access in the pediatric patient population. Am J Surg 1994;168:197–201.
Review of hemodialysis access in 24 children treated at Emory University in Atlanta.
6. Bourquelot P, Cussenot O, Corbi P, et al. Microsurgical creation and follow-up of arteriovenous fistulae for chronic haemodialysis in children. Pediatr Nephrol 1990;4:156–59.
Review of one surgeon's series of arteriovenous fistula in 380 children treated at Clinique Jouvenet in Paris (long-term patency of 60% at 10 years).
7. Brittinger WD, Walker G, Twittenhoff WD, et al. Vascular access for hemodialysis in children. Pediatr Nephrol 1997;11:87–95.
Review of outcomes of arteriovenous fistulas and grafts in 784 children treated in Germany.
8. Sheth RD, Brandt ML, Brewer ED, et al. Permanent hemodialysis vascular access survival in children and adolescents with end-stage renal disease. Kidney Int 2002;62:1864–69.
Review of outcomes for 47 children with AVF or AVG treated at Texas Children's Hospital.
9. Goldstein SL, Allsteadt A, Smith CM, et al. Proactive monitoring of pediatric hemodialysis vascular access: Effects of ultrasound dilution on thrombosis rates. Kidney Int 2002;62:272–75.
Pediatric study that suggests that ultrasound dilution monitoring and early referral for angioplasty decreases graft thrombosis and costs associated with access care.
10. Sheth RD, Kale AS, Brewer ED, et al. Successful use of Tesio catheters in pediatric patients receiving chronic hemodialysis. Am J Kidney Dis 2001;38:553–59.
Review of outcomes of children with Tesio and conventional double-lumen tunneled hemodialysis catheters.

CHAPTER 88

Infant Hemodialysis

Eileen N. Ellis, MD

Both peritoneal dialysis and hemodialysis are reliable options in the infant who requires renal replacement therapy either for acute renal failure or end-stage renal disease. However, hemodialysis is the treatment chosen for less than 14% of patients aged 0 to 5 years with end-stage renal disease according to the North American Pediatric Renal Transplant Cooperative Study Dialysis Registry. The reasons for the more limited use of hemodialysis in infants are multiple and include technical difficulties of vascular access and equipment, distance of the infant from a pediatric dialysis center, the perception that growth is better on peritoneal dialysis compared to hemodialysis, and the more limited fluid removal possible with hemodialysis compared to continuous peritoneal dialysis in the infant who requires high fluid intake to provide adequate calories for growth.

Hemodialysis is more often the treatment modality of choice for acute or chronic renal failure in those infants who have other complicating medical conditions such as omphalocele, gastroschisis, diaphragmatic hernia, peritoneal-pleural leaks, recent abdominal surgery or other intra-abdominal processes, chronic pulmonary disease, bladder extrophy, or recurrent peritonitis on peritoneal dialysis.[1] The goal for pediatric nephrologists providing hemodialysis to infants with either acute renal failure or end-stage renal disease is to overcome the technical difficulties associated with this technique (Table 88.1) and to provide optimal management of the many complications associated with renal replacement therapy.

Vascular Access

Delivery of hemodialysis therapy in infants is complicated by smaller vascular caliber and the potential for the lifelong need for hemodialysis access. Central venous catheters constitute the most common hemodialysis vascular access in children, and essentially all infants are currently dialyzed though such central venous lines.[2-4] In newborns, the umbilical vessels can be used to insert catheters for adequate acute dialysis but often require two catheter insertions for blood flow to the dialyzer and return

Table 88–1

Infant Hemodialysis Issues

Requirement	Details
Vascular Access	• Usually double-lumen central venous catheter
Equipment	• Dialysis machine with low-volume blood flow and precise ultrafiltration • Dialyzer bloodlines with small volume for infant size • Dialyzer with small surface area and small priming volume for infant size
Management	• Consider prime for dialyzer bloodlines and dialyzer: blood, albumin, or saline • Blood flow to obtain adequate urea clearance for infant size • Ultrafiltration based on accurate weight and careful monitoring of clinical parameters • Temperature regulation of infant • Anticoagulation • Length and frequency of hemodialysis treatments dependent on metabolic needs of the infant

to the infant. Hemodialysis through the ECMO (extracorporeal membrane oxygenation) circuit may also be utilized in infants treated with ECMO. Femoral, subclavian, or internal jugular venous catheterizations are commonly used in infants.

Femoral catheters are used for acute dialysis, with subclavian or internal jugular catheters used more commonly for chronic hemodialysis. Long-term subclavian central venous line placement has led to stenosis of the subclavian vein and ultimate loss of this site for future hemodialysis access. Therefore, in infants for whom hemodialysis access may be needed for many years to come, internal jugular venous placement for chronic use or femoral venous placement for acute use should be considered first.

In the past, single-lumen catheters (e.g., Hickman catheter) were commonly used—but the wide availability of double-lumen 5 Fr and larger central venous catheters (manufactured by various vendors, including Quinton, Arrow, MedComp, Vascath and others) make use of the single-needle technique obsolete. The blood flow achieved from the access is determined by the internal diameter of the lumen and the catheter length, and thus shorter catheters with larger internal luminal diameters result in

the best blood flow for hemodialysis. For chronic hemodialysis, use of cuffed and tunneled double-lumen catheters should be considered for more long-term usage. Assurance of correct catheter placement is critical in achieving adequate blood flow for hemodialysis, and thus demonstration of adequate flow during the placement procedure and radiographic confirmation of tip placement are necessary.

The complications of vascular access for hemodialysis through a central venous line include clotting of the access, malfunction of the access, and infection. For these reasons, the hemodialysis catheter should be used exclusively for hemodialysis and only experienced dialysis nurses specially trained in the use of the hemodialysis catheter should access this central venous line. To maintain intradialytic patency for the hemodialysis catheter, the catheter is flushed with heparin solutions of 1000 U/mL of an equivalent volume to fill the internal diameter of the catheter. Care must be taken in use of these heparin solutions because inadvertent systemic anticoagulation and bleeding have been reported in children on hemodialysis and it is doubtful that heparin concentrations above 1000 U/mL provide any increased catheter patency.[5]

If line clotting is detected at the beginning of the hemodialysis session, urokinase or Altepase at the volume of the internal diameter of the catheter may be required to restore catheter patency. Again, care must be taken to avoid systemic anticoagulation. Exit-site infections and central venous catheter sepsis, most commonly with staphylococcal organisms, occur and prevention requires careful aseptic technique by all involved in the care of the hemodialysis catheter and use of cuffed catheters when possible. Longevity of hemodialysis catheters is short in infants and young children, lasting only a few months on average before access revision is required secondary to nonfunction or infection.[4]

Equipment

To provide safe and effective hemodialysis for infants, the dialysis machine, bloodlines, and dialyzer must meet certain requirements different from hemodialysis in larger children or adults. This equipment must allow for small blood volumes out into the extracorporeal circuit, allow small-volume blood flow through the dialysis machine, and provide precise ultrafiltration while on hemodialysis. Few manufacturers provide such appropriate equipment for infant hemodialysis compared to dialysis

equipment for adult hemodialysis. Pediatric nephrologists providing hemodialysis for infants must carefully investigate these special equipment needs for infants.

The hemodialysis machine used for infants must provide low-volume blood flow through the machine. Such hemodialysis machines available include the Fresenius 2008 series, Gambro Phoenix and CentrySystem 3 machines, and the Baxter Tina or Arena (lowest blood flow is 50 mL/minute with Baxter). Each of these hemodialysis machines provides precise ultrafiltration control, which is required especially in infants for whom small volume changes may precipitate changes in vital signs. The dialysis machine must be calibrated according to the manufacturer's instructions for the diameter of the blood pump segment in the bloodlines for infant hemodialysis, and special pediatric low-volume blood lines are often required.

The bloodlines must allow for small blood volumes out into the extracorporeal circuit, with ideally the blood lines and dialyzer volume containing no more than 10% of the infant's blood volume (80 mL/kg body weight). Medisystems manufactures low-volume dialysis bloodlines for use in the Fresenius and Baxter machines, and Gambro provides pediatric low-volume bloodlines for the Phoenix and CentrySystem 3. In the infant bloodlines, the typical blood volume is about 40 to 44 mL in the smallest lines available. Because of the unique requirements in infant hemodialysis, a special technique for hemodialysis in very small (less than 6 kg) infants has recently been developed and reported.[6]

The goal of each hemodialysis session is to provide a urea clearance of 3 to 5 mL/kg/minute. This can be achieved by selecting a dialyzer with appropriate urea clearance characteristics for the size of the infant, which usually requires a dialyzer with a small surface area of less than 0.5 m^2. All dialyzers currently available for infant dialysis are hollow-fiber in type (Table 88.2). The priming volume of the dialyzer must be added to the volume of the bloodlines to ideally contain no more than 10% of the infant's blood volume in the total circuit. High-flux dialyzers should not be used in infant hemodialysis because dialysate backflow with low ultrafiltration rates can occur.

Management of Hemodialysis

The management of each hemodialysis session should be designed based on the size of the infant, the clinical and metabolic status of the infant, and the infant's tolerance of the dialysis

Table 88–2

Examples of Dialyzers Currently Available for Use with Infants

Dialyzer	Membrane Type	SA (m^2)	Priming Volume (mL)	Urea Clearance at Q_B = 50 mL/min	Urea clearance at Q_B = 100 mL/min	Urea clearance at Q_B = 200 mL/min	UF at 100 mmHg (mL/min/mmHg)
Gambro HG 100	Hemophan	0.22	18	50	82	106	2.0
Fresenius F3	Polysulfone	0.4	28	45	80	125	1.7
Baxter CA .50	Cellulose acetate	0.5	54	NA	NA	128	2.4

Abbreviations: SA = surface area, Q_B = blood flow, UF = ultrafiltration rate, NA = not applicable.

procedure. The smaller the infant, especially those infants weighing less than 10 kg, the more vulnerable the infant is to complications during the hemodialysis procedure. The bloodlines and dialyzer priming volume should be carefully chosen to provide an extracorporeal blood volume of less than 10% of the infant's blood volume (80 mL/kg).

If the infant weighs less than about 8 kg, the extracorporeal volume will be greater than 10% of the infant's blood volume with the currently available equipment. In this case, the bloodlines and dialyzer should be primed with packed red blood cells. Pediatric nephrologists should be aware that the use of banked blood for priming the hemodialysis circuit carries certain risks, including high potassium content of the banked blood, which may give the infant a high potassium load at the initiation of hemodialysis; high viscosity of the banked blood, which may result in high circuit resistance; higher heparinization needs so that it is sometimes recommended that anticoagulation with heparin of the banked blood be done before priming the circuit; and decreased oxygenation of banked blood, which may result in hypoxia in infants with compromised respiratory status.

In larger infants with less than 10% of blood volume in the extracorporeal circuit, the circuit should be primed with 5% albumin or normal saline—depending on the clinical status of the patient. At the end of the treatment, the extracorporeal blood is transfused back to the infant unless the circuit was initially primed with blood, and then the circuit and content can be discarded at the end of the treatment.

The dialyzer must be chosen to provide a urea clearance of 3 to 5 mL/kg/minute and small priming volume (as described previously). The urea clearance is determined by the characteristics of the dialyzer and the blood flow. Therefore, the urea clearance desired for the individual infant determines the blood flow rate needed for the hemodialysis treatment (Table 88.1). If the infant has a very high blood urea nitrogen (BUN) level (>100 mg/dL), the dialyzer urea clearance should be reduced to 1.5 to 2 mL/kg/minute by reducing the blood flow for the first few treatments until control of BUN has been accomplished.

In the situation with high BUN, mannitol (20%, 1 g/kg body weight) can be given through the dialysis circuit during the hemodialysis procedure to minimize the osmotic changes in the infant and help prevent cerebral edema and dysequilibrium. Because an infant's metabolic needs to achieve normal growth are great, high urea clearance (about 5 mL/kg/minute), longer hemodialysis treatments (about 5 hours for each treatment), and

more frequent hemodialysis treatments (4 or 5 times weekly) are often needed for optimal chronic hemodialysis.

The dialysate concentration can be modified based on the infant's chemistries. A variety of dialysate solutions are available and are chosen in a similar fashion as in adult hemodialysis. All dialysate solutions should be bicarbonate based. The dialysate flow rate should be set at 400 to 500 mL/minute and is not based on the infant's size.

Fluid removal by ultrafiltration during the hemodialysis treatment must be carefully planned and executed to maintain stable clinical status in the infant throughout the treatment. A realistic estimate of dry weight and an accurate measurement of current weight of the infant are needed before treatment in order to program the desired ultrafiltration volume removal into the hemodialysis machine. In general, the total ultrafiltration during a hemodialysis treatment should not exceed 5% of the infant's body weight to avoid circulatory collapse. It is better to repeat the treatment the next day rather than to attempt to remove excessive fluid volume in one treatment.

The ultrafiltration volume control on the hemodialysis machine is only approximate, especially in the small infant for whom small volume differences can make large clinical differences. The clinical status of the infant must therefore be monitored on a minute-by-minute basis by an experienced pediatric dialysis nurse. This monitoring must include blood pressure, pulse, respiration, temperature, color, mental status, capillary refill, weight, and any additional loss or intake of fluids. Changes in mental status, especially agitation, or vomiting may precede changes in vital signs. If hypotension is present, the infant must be treated promptly with normal saline or 5% albumin and ultrafiltration stopped until the infant is stabilized.

Because the infant on hemodialysis has a large extracorporeal blood volume, temperature regulation is very important. To help with temperature regulation in infants, the dialysate bath temperature should be carefully chosen and the infant's temperature monitored frequently. For very small or ill infants, a radiant heater over the infant may be required to maintain proper temperature control during the hemodialysis treatment.

Adequate anticoagulation is essential to prevent clotting of the extracorporeal circuit. This can be accomplished by administration of heparin at 10 to 20 U/kg body weight at the beginning of the hemodialysis treatment and followed by a constant infusion of heparin at 10 to 30 U/kg/hour. The anticoagulation must be monitored with activated clotting times during the treatment and

the heparin infusion modified based on the results. Activated clotting times should be kept in the range of 100 to 200 seconds based on the clinical status of the patient.

Use of the newer, more biocompatible, dialyzer membranes may allow for dialysis without anticoagulation—although the extracorporeal circuit must be monitored very carefully for clotting, and frequent flushing of the bloodlines with normal saline may be required to maintain patency. Depending on the clinical situation of the infant, the residual heparin effect can be terminated at the end of the hemodialysis treatment by infusion of protamine over 15 to 20 minutes. The dose of protamine required is calculated to neutralize 1/2 of the total heparin dose administered during the treatment, at a ratio of 1 mg protamine for each 100 units of heparin to neutralize.

Adequacy of Hemodialysis

In adults, many studies have demonstrated a strong correlation between hemodialysis dose and clinical outcome—especially mortality. These studies have resulted in guidelines from the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-K/DOQI) prescribing a minimal functional clearance of urea as a function of its distribution volume (Kt/V) of 1.2 measured monthly in hemodialysis patients. Until recently, however, little has been known about dialysis adequacy in children—and in view of the unique physiology, dietary needs, and complications in children more appropriate outcome measures should be considered (such as growth, attainment of developmental milestones, and sexual maturation).

A recent study has shown improved growth without the use of growth hormone in a group of pediatric hemodialysis patients who were treated with longer-duration hemodialysis at about 5 hours three times a week—providing a Kt/V of 2.0 and improved caloric intake above the recommended daily allowance.[7] Others have reported similar results in pediatric patients treated with peritoneal dialysis. A recent North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) showed that inadequate hemodialysis dose was associated with male gender, black race, larger body surface area, and treatment in a center with few reported Kt/V measurements.[8]

Taken together, these studies indicate that infants on hemodialysis should have Kt/V measured monthly with the aim of providing dialysis adequacy of Kt/V above 1.2 and with evaluation of clinical parameters of dialysis such as growth and

development.[9,10] Although hemodialysis has not been the first line of renal replacement therapy in most infants with end-stage renal disease, this form of therapy can be used safely and effectively with the proper equipment and understanding of the described principles.

References

1. Donckerwolcke RA, Bunchman TE. Hemodialysis in infants and small children. Pediatr Nephrol 1994;8:103–06.
2. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Internat 1994;45:903–06.
3. Al-Hermi BE, Al-Saran K, Secker D, Geary DF. Hemodialysis for end-stage renal disease in children weighing less than 10 kg. Pediatr Nephrol 1999;13:401–03.
4. Shroff R, Wright E, Ledermann S, Hutchinson C, Rees L. Chronic hemodialysis in infants and children under 2 years of age. Pediatr Nephrol 2003;18:378–83.
5. Moritz ML, Vats A, Ellis D. Systemic anticoagulation and bleeding in children with hemodialysis catheters. Pediatr Nephrol 2003;18:68–70.
6. Everdell NL, Coulthard MG, Crosier J, Keir MJ. A machine for haemodialysing very small infants. Pediatr Nephrol 2005;20:636–43.
7. Tom A, McCauley L, Bell L, Rodd C, Espinosa P, Yu G, et al. Growth during maintenance hemodialysis: Impact of enhanced nutrition and clearance. J Pediatr 1999;134:464–71.
8. Leonard MB, Stablein DM, Ho M, Jabs K, Feldman HI. Racial and center differences in hemodialysis adequacy in children treated at pediatric centers: A North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) report. J Am Soc Nephrol 2004;15:2923–32.
9. Sharma A. Reassessing hemodialysis adequacy in children: The case for more. Pediatr Nephrol 2001;16:383–90.
10. Goldstein SL. Adequacy of dialysis in children: Does small solute clearance really matter? Pediatr Nephrol 2004;19:1–5.

CHAPTER 89

Urea Kinetic Modeling for Hemodialysis Prescription in Children

Avram Z. Traum, MD, and Michael J. G. Somers, MD

Chronic Hemodialysis in Children

Hemodialysis is the most commonly used modality of chronic renal replacement therapy, utilized in nearly 2/3 of Americans with end-stage renal disease (ESRD). In children with ESRD, hemodialysis use is less common—with peritoneal dialysis and renal transplantation being the treatment modalities used more frequently in children. Recent registry data from the United States Renal Data System (USRDS) and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) suggest, however, that the proportion of children with ESRD receiving hemodialysis has been increasing. As a result, clinicians caring for these children are now faced more often with the need to assess the adequacy of the dose of dialysis delivered to this population.

Unfortunately, there are very limited data focused on pediatric hemodialysis adequacy or long-term outcomes of dialyzed children analyzed in the context of certain standards of adequacy. The original and the updated National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines for hemodialysis adequacy address this topic for children. They also specify that due to limited specific pediatric data many recommendations are based on extrapolation from experience in adults. Moreover, many outcome measures looking at dialysis adequacy in adults are focused on narrowly assessing mortality rates or specific organ system morbidity over time and do not consider additional clinical variables of special import to assessing the adequacy and effectiveness of renal replacement therapy in children (such as somatic growth and development, cognitive and emotional maturation, and school attendance and performance).

As the NKF-K/DOQI dialysis adequacy guidelines are applied to a broader population of children with ESRD, it is incumbent on pediatric clinicians to continue to try to determine whether

adult standards really do define a proper dose of dialysis for children and to then assess further the applicability of these current standards to appropriate long-term outcome measures.

The Dialysis Prescription in Children

Because the clinician caring for children with ESRD will be prescribing dialysis to patients whose size and weights may vary 20- or 30-fold, there is much more of an individualized focus on the dialysis prescription in children. Certainly, the hemodialysis prescription for an 85-kg adolescent will differ dramatically from the treatment given to a 5-kg baby—which will in turn be quite different than the prescription for a 25-kg elementary school student. Because pediatric patients on dialysis are more likely than adults to have such broad variations in size and total blood volume (which in turn affect many technical aspects of safe and successful hemodialysis provision), the quantity of dialysis a child receives is much more likely to be precisely calculated and readjusted than in adult patients. Moreover, the prescription must be formulated cognizant of ongoing changes in total body water and evolving nutritional requirements as the child grows and gains appropriate weight.

Similar to trends in adults with ESRD on chronic hemodialysis, urea kinetic modeling has become more commonly used in pediatric patients not only to serve as an objective measure of hemodialysis adequacy but to monitor nutritional adequacy by allowing the determination of the protein catabolic rate (PCR). With this approach, urea and its clearance are used as a surrogate to reflect clearance of low-molecular-weight uremic toxins—and the interdialytic rise in urea levels can be used to estimate protein catabolism. The choice of urea as a marker stems from its relatively even distribution over the total body water, its low molecular mass (allowing ready dialysis clearance), and its status as the principal constituent of waste nitrogen that accumulates in body water. The extent of clearance of urea from body water has been correlated with morbidity and mortality outcomes.

The advantages of urea kinetic modeling center on it providing reproducible quantitative data that can guide individualization of a dialysis prescription. Moreover, modeling results can check for disparities between expected or calculated doses of dialysis and actual delivered dialysis. The major disadvantage of kinetic modeling is the need to coordinate obtaining all of the necessary data at the proper time. Depending on local resources, these maneuvers may be relatively labor and time intensive and may

add cost to the chronic therapy. Although the calculations for kinetic modeling are complicated, various programs are readily available to assist with rapid compilation of data.

There has also been controversy as to whether the adequacy of dialysis is best measured using a single-pool or double-pool model of estimated volume. In a single-pool model, the clearance of urea from the blood volume may overestimate the dose of dialysis measured by kinetic modeling because blood measurements are performed prior to effective reequilibration of urea from the intracellular space into the intravascular space (urea rebound). This concern is especially true in children with smaller distributions of urea who are dialyzed with filters with the capability of high rates of solute clearance.

On the other hand, the need for patients to remain for a substantial period after the dialysis treatment is completed to draw a reequilibrated postdialysis BUN (blood urea nitrogen) adds another layer of logistical complexity to utilization of a double-pool model. There are some data suggesting that for the majority of children generally able to achieve relatively high levels of Kt/V the discordance rate between single-pool and equilibrated values does not impact the ultimate management of adequate dialysis prescriptions in most cases.

Principles of Urea Kinetic Modeling in Children

The theoretical principles of urea kinetic modeling are identical in children and adults. The rate of removal of any solute from the intravascular space using hemodialysis can be modeled by considering the permeability properties of the dialyzer used, circuit specifics such as blood and dialysate flow, and physical and biochemical properties of the solute to be removed. The dialyzer's most important characteristic is its permeability surface area product (generally abbreviated as K_0A)—which dependent on the blood flow delivered through the dialyzer defines its potential clearance of the solute in question (K_D). This variable defines the dialyzer's ability to remove the solute in question. The following mass transfer equation can be set up and solved to quantify the physical removal of any solute in question during dialysis.

$$C_T = C_0(e^{-Kt/V}) + G/K(1 - e^{-Kt/V})$$

Here, C_T is the solute concentration at any given time during the dialysis treatment, C_0 is concentration of the same solute at

time 0 or dialysis initiation, K is the dialyzer clearance of the solute for the blood flow through the circuit, t is the duration of dialysis in minutes, V is the volume of distribution of the solute, and G is the ongoing generation rate of the solute. Whereas this equation can be applied to any solute of interest, its application to urea removal is the underpinning of urea kinetic modeling—and the calculated Kt/V has been utilized as the measure of the dose of dialysis delivered or the fractional clearance of urea for the patient's volume of distribution.

There are a number of applications of this equation toward changes in metabolic balance. If all variables are known, BUN concentration can be calculated for any time point during the dialysis session. Similarly, if the remainder of the variables is known V and G can be calculated using several different BUN measurements acquired at varying time points during the dialysis treatment. Once G is known, the PCR can be calculated using the equation

$$PCR = 6.5G + 0.17(Wt),$$

where PCR is expressed as grams of protein/day, G is grams of BUN/day, and Wt is the patient's weight in kilograms. The PCR can be used along with clinical variables such as growth (and other laboratory parameters, such as serum albumin) to help assess nutritional adequacy. A PCR near 1 is considered ideal for most children. Although adequate dialysis helps improve appetite and nutritional intake in patients receiving chronic hemodialysis, there is no evidence that higher doses of dialysis improve nutritional status.

Data Collection

Generally, data is collected over a number of hemodialysis sessions to calculate V and G. The remaining variables in the equations are known or can be easily determined. For instance, BUN is measured at the start of a hemodialysis session (C_0) and at the end (C_T or C_1), and again at the start of the next session (C_2). This pattern helps to define the intradialytic and interdialytic fluxes in BUN, which provide information as to urea reduction rate (URR) during dialysis, residual renal function with accompanying clearance of the solute in question during and between dialysis sessions, and ongoing generation of urea from protein catabolism. The following variables make it possible to predict BUN at any point in time.

- K_D, *dialyzer clearance:* This is a function of the dialyzer (K_0A), blood flow (Q_B), and dialysate flow (Q_D). The measured rather than the prescribed blood flow should be used for calculations.
- K_R, *residual renal function:* This variable is generally measured once and at regular intervals unless a change occurs that would impact otherwise, such as nephrectomy. An adequate urine collection is important to ensure a reliable calculation for this measure, and can be done over the interdialytic interval.
- *T (dialysis time) and U (interdialytic interval):* Both of these variables are measured in minutes and the actual, rather than prescribed times should be used.

Along with the volume of distribution (V) and the urea generation rate (G), these variables can be used to calculate BUN. Because the times and clearances are either predetermined variables or are easily measured, these can be entered into the appropriate equations to generate V and G. Alternatively, commercial software or Internet-based shareware exists to perform these calculations (Figure 89.1). These resources greatly facilitate monitoring dialysis adequacy over time in large numbers of patients.

Common Errors in Calculations

As described previously, V is derived using serial measurements of BUN with respect to multiple hemodialysis sessions. Whereas there may be great variability in V between patients, V should remain fairly consistent for calculations on any individual patient. Thus, errors in calculations may be seen when V calculated for any given month or session varies greatly with respect to previous measurements. Common errors impacting estimate of V include the following.

- *T is misreported:* The duration of the hemodialysis session is actually shorter or longer than that prescribed or utilized for the equation.
- *K is erroneous:* The blood flow (Q_B) actually delivered for the treatment being modeled is different than reported, often related to problems with dialysis access such as stenosis, clotting, or recirculation.
- *Measured BUN is wrong:* Either pre- or post-BUN samples are erroneous, generally related to incorrect timing of the samples or incorrect technique obtaining the samples.

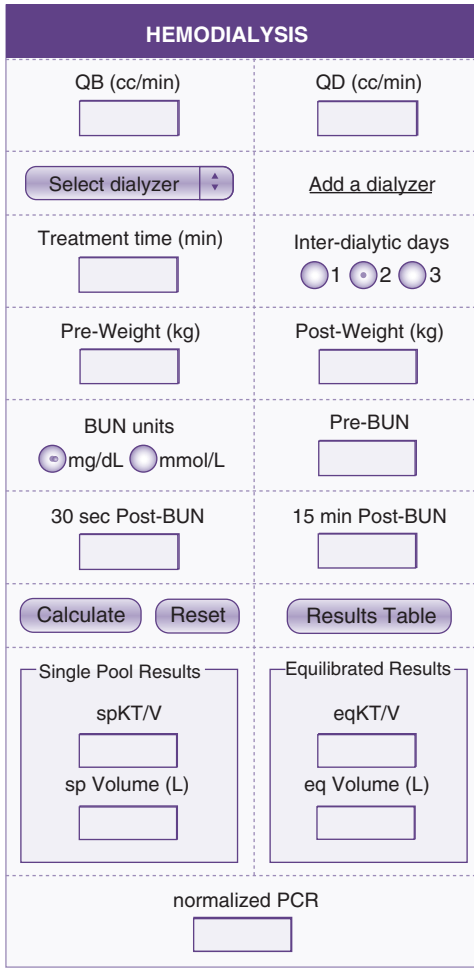


Figure 89–1

Sample dialysis adequacy calculator available as freeware at *www.kt-v.net*. Similar commercial programs are available for purchase and not only facilitate the calculation of Kt/V but greatly reduce the time and effort needed to track doses of dialysis.

Application of Urea Kinetic Modeling

Urea kinetic modeling can provide data about estimated adequacy of hemodialysis and nutrition. Although the data can then be used to adjust the dialysis prescription or dietary intake to improve the child's metabolic and clinical state, it must be remembered that the calculated Kt/V is only an estimate of adequacy and that Kt/V within the target range may not necessarily denote optimal dialysis for all children. As with many therapies in children, a better overall measurement of adequacy would be consideration of the child's composite health, growth, and development while the therapy is ongoing.

Unfortunately, given the need to adjust hemodialysis treatments over short spans of time, such long-term global measures of adequacy become supplemental to more immediate assessments such as Kt/V or PCR calculations. The data, nonetheless, can be quite useful and can impact significantly patient management. For instance, a child found to have a PCR equal to her protein intake would be in neutral nitrogen balance. For an adult this balance might be acceptable, but for a growing child this would impact somatic growth and would represent nutritional deficiency.

Conversely, a child found with what appears to be high predialysis BUN levels could have high dietary protein intake or may be inadequately dialyzed from previous sessions. In this case, assessing the PCR and Kt/V would differentiate between these situations. A high PCR could be modified by decreasing the protein intake to a more appropriate level, whereas a low Kt/V could be adjusted by increasing the dialysis time, increasing the blood flow, or assessing the patient's access for technical complications.

NKF-K/DOQI Pediatric Recommendations for Dialysis Adequacy

NKF-K/DOQI guidelines suggest that the delivered dose of dialysis should be measured routinely by formal urea kinetic modeling using a single-pool model. The dose of dialysis (Kt/V) should accurately describe the fractional clearance of urea corrected for volume of distribution. These guidelines apply to children with a residual GFR <5 mL/minute on a chronic hemodialysis regimen of three treatments weekly. The recommendations do not apply to children receiving dialysis at a different frequency, children with greater residual renal

function, children who are hospitalized and receiving dialysis, or children with acute renal failure who are thought to be on dialysis transiently.

The NKF-K/DOQI guidelines specify that the minimum Kt/V should be 1.2, based on uncontrolled and retrospective reports that point toward improved patient survival with dialysis doses up to Kt/V of 1.2. There have, however, been few studies of the dose of hemodialysis as a predictor of outcome in children. One report did suggest that higher Kt/V values in children may facilitate growth, whereas another looked at mortality and hospitalization rates for dialyzed adolescents and found that teens with Kt/V <1.2 had higher hospitalizations rates and that rates higher than 1.4 had no added benefit.

To account for variability between prescribed and delivered dialysis doses, the NKF-K/DOQI adequacy guidelines suggest that the prescribed Kt/V be 1.3 and that blood sampling be done precisely and in a fashion to minimize recirculation or urea rebound. The same methodology should be used for all patients in any single dialysis unit to facilitate equivalent levels of care.

These guidelines have been promulgated with the understanding that they may not represent optimal dialysis but are serving as benchmarks for minimal dialysis dose delivery. Especially in children with the added physiologic burden of ongoing growth and development, the delivered dose of dialysis should at least meet these standards. Because achieving higher levels of Kt/V is often easier to reach in small children with lower volumes of distribution than large adults, many in the pediatric hemodialysis community aim for a single-pool Kt/V of 1.4.

Recommended Reading

Bell L, Espinosa P. Intensive in center hemodialysis for children: A case for longer dialysis duration. Hemodial Int 2003;7:290–95.

This report detailing a single-center experience looks at the benefits of longer dialysis duration on clinical outcomes (especially growth and cardiac function) and concludes that traditional thrice-weekly hemodialysis for children is a less optimal therapy than more frequent and longer-duration therapy.

Fishbach M, Edefonti A, Schroder C, et al. Hemodialysis in children: General practical guidelines. Pediatr Nephrol 2005;20:1054–66.

Guidelines published on behalf of the European Pediatric Dialysis Working Group covering general aspects of pediatric hemodialysis. Guideline 10 (covering urea kinetics) gives an especially clear review of urea rebound. Guideline 11 (on dialysis dose and outcome) gives a more cursory summary of pertinent pediatric data.

Goldstein SL. Adequacy of dialysis in children: Does small solute clearance really matter? Pediatr Nephrol 2004;19:1–5.

In this editorial commentary, the role of small-solute clearance and current standards of dialysis adequacy are explored, with emphasis on the few large prospective trials assessing dialysis dose and patient morbidity and mortality in adults and their relevance to pediatric dialysis patients.

Goldstein SL, Brem A, Warady BA, et al. Comparison of single-pool and equilibrated Kt/V values for pediatric hemodialysis prescription management analysis from the Centers for Medicare and Medicaid Services Clinical Performance Measures Project. Pediatr Nephrol 2006;21:1161–66.

Utilizing data supplied to the 18 ESRD networks that oversee dialysis services in the United States, the authors compare single-pool urea kinetic modeling to equilibrated Kt/V values to discern if a clinically significant difference in provision of dialysis would frequently ensue from the use of double-pool kinetics. Setting an expected discordance rate of 0.2 between single-pool and equilibrated Kt/V, the authors conclude that greater than expected discordance rates varied minimally (0.3 to 5.5%) and would suggest that single-pool Kt/V measurements can be used for clinical screening in children and adolescents.

Gorman G, Furth S, Hwang W, et al. Clinical outcomes and dialysis adequacy in adolescent hemodialysis patients. Am J Kidney Dis 2006;47:285–93.

Analysis of 613 adolescent hemodialysis patients from data supplied to ESRD networks. Patients with Kt/V <1.2 are much more likely to be hospitalized than teens with greater doses of dialysis. No increased benefit was found with levels >1.4.

Marsenic O, Peco-Antic A, Jovanovic O. Effect of dialysis dose on nutritional status of children on chronic hemodialysis. Nephron 2001;88:273–75.

This report looks at the effect of different hemodialysis doses on protein intake and nutritional status in a cohort of 15 children undergoing chronic hemodialysis. Although the data demonstrate that adequate dialysis helps ensure good nutritional intake, the nutritional status of dialyzed children did not benefit from high doses of dialysis (Kt/V >1.6).

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines for Hemodialysis Adequacy, 2000. Am J Kidney Dis 2001;37(1):S7–64.

Updated version of original NKF-K/DOQI guidelines for hemodialysis adequacy with comprehensive discussion of topic and clear delineation of evidence-based recommendations compared to consensus clinical practice. Very limited pediatric-specific information, although guidelines were composed to apply to children undergoing chronic hemodialysis as well as to adults.

CHAPTER 90

Anticoagulation in Children on Hemodialysis

Daljit K. Hothi, MBBS, MRCPCH, and
Elizabeth Harvey MD, FRCPC

Various anticoagulant strategies are employed in pediatric dialysis but all are guided by two principles: maintenance of the patency of the hemodialysis (HD) access and prevention of clots within the extracorporeal circuit (in that clotting leads to blood loss and reduced dialysis efficacy).

Maintaining Hemodialysis Access Patency

Central Venous Line Locks

With the improved survival of pediatric dialysis and transplant patients into adulthood, preservation of native access is a challenge pediatricians must take seriously. The use of prophylactic measures to prevent access thrombosis is considered the standard of care worldwide. Almost universally, central venous lines (CVLs) have been locked with unfractionated heparin (UFH) in children. This inactivates thrombin and inhibits fibrin formation and thrombin-induced platelet activation. At the Hospital for Sick Children, Toronto, for children weighing less than 10 kg we lock each lumen of the CVL with a heparin concentration of 50 μ/kg/lumen. For children weighing between 10 and 20 kg we use a heparin concentration of 1000 μ/mL, and for those weighing greater than 20 kg we use a heparin concentration of 2500 μ/mL—adjusting the volume according to that of the lumen.

Our safety record with this regimen has been excellent, with no evidence of prolonged elevation of the activated partial thromboplastin time (aPTT) in the interdialytic period and no serious bleeding events. However, the lock does place the patient at an increased risk of bleeding due to systemic infiltration of part of the anticoagulant. We have documented systemic anticoagulation transiently for several hours after flushing the CVL. In addition, there have been a number of reports of accidental flushing of the lock (causing serious bleeding).

Locking with alternatives such as recombinant tissue plasminogen activator (rTPA), sodium citrate, and polygeline is gaining popularity within the adult population due to the suggestion that they may be superior to heparin in catheter life, clot volume, and complication rate (flow problems, clotting, and the need for fibrinolysis). The main disadvantage of these newer products is cost, which at the moment precludes their routine use—with the exception of citrate, which offers additional benefits (discussed in material following). Of note, we have encountered significant falsely elevated phosphate concentrations in blood drawn through lines locked with rTPA compared with samples obtained simultaneously peripherally.

It is thought that trisodium citrate (TSC), through chelation of calcium and magnesium, may prevent biofilm formation and bacterial colonization—resulting in antimicrobrial activity against staphylococcal strains at low concentrations (2.2–15%) and Gram-negative bacteria combined with an anti-yeast property at concentrations of 30%. In a direct comparison of TSC 30% with heparin 5000 μ/mL as catheter locking solutions in adult HD patients, 46% of catheters in the heparin group had to be removed because of complications compared to 28% in the TSC group.

Catheter-related bacteremia rates were 1.1 per 1000 catheter days for TSC versus 4.1 in the heparin group, resulting in a risk reduction for catheter-related bacteremia of 87% for tunneled cuffed catheters and 64% for untunneled catheters. There was no difference in catheter flow problems and thrombosis between the two groups. Major bleeding episodes were significantly lower in the TSC group. The adverse effects reported included thrombocytopenia, paresthesias, a metallic taste in the mouth, and tingling in the fingers immediately after locking. These results appear conclusive in support of citrate as effective monotherapy in preventing both catheter-related infections and thrombosis. However, citrate use is not without risk.

There have been reports of fatality thought to be related to patients receiving a bolus of TSC causing sudden and severe hypocalcaemia and subsequent cardiac events. Currently, there are no pediatric safety data on citrate locks in the literature. However, anecdotal single-center experience with 4% TSC is slowly emerging. Until more stringent population-based research is available, citrate locks should only be considered in specific pediatric cases under close monitoring.

Oral Therapy

Oral anticoagulants or antiplatelet agents have been used in those with fistulas or in combination with locks in patients with CVLs. Evidence is generally positive but largely adult based. In a multivariate analysis there was no benefit of low-dose warfarin (1 mg/day) on thrombosis-free, tunneled, cuffed catheter survival time. In contrast, dose-adjusted warfarin (maintaining an INR between 1.4 and 1.9) improved catheter-malfunction-free survival from 8.1% in those with inadequate anticoagulation to 47.1% in patients with adequate anticoagulation. Compared to warfarin, aspirin may be superior in maintaining catheter patency (but at an increased bleeding risk).

In fistulae and shunts, warfarin has been shown to offer little benefit in preventing thrombosis. However, a meta-analysis was favorable toward aspirin, ticlodipine (a platelet aggregation inhibitor), and dipyridamole (a platelet inhibitor) therapy—albeit with a possible increased risk of bleeding. Apart from the obvious risk in diseases associated with a prothrombotic state, one study found an association between late catheter malfunction and low hemoglobin (Hb, <10.5 g/dL), low INR (<1.0), and diabetes.

The morbidity from thrombosis is a concern in pediatrics, but currently there is no evidence to guide the use of these agents in children and therefore practice is based on personal beliefs and anecdotal experience. In a recent audit of warfarin use in our HD unit, we found that 70% of the total INR values fell above or below the desired range (INR of 2–3)—highlighting the difficulty of maintaining therapeutic INR levels with warfarin in children on HD. Warfarin use did not lower the requirement for rTPA doses to restore catheter patency or the need for catheter revisions for catheters obstructed by clots, and its use contributed to gastrointestinal bleeding in two patients. The audit results led to a change of long-standing practice within our unit, with discontinuation of routine warfarin prophylaxis.

Treatment of a Thrombosed Catheter

The standard practice to restore the patency of blocked HD catheters is to lock the lumens with rTPA, but the sustained success rate is poor regardless of the duration of rTPA instillation. Contrary to prior belief, it is now thought that the primary reason for the catheter blockage is not an intraluminal clot but thrombosis occurring primarily around the outside of the catheter. Therefore, a systemic infusion may be more useful than

a lock. In adults, the use of a maximum of three consecutive urokinase infusions (25,000 units in 48 mL of normal saline, infused at 4 mL/hour, followed by warfarin therapy maintaining an INR of 2–2.5) was attempted in 41 episodes of catheter dysfunction for which a urokinase lock had failed to restore patency.

A total of 48 infusions were used, with 37 episodes responding to a single infusion, 2 to two infusions, and 2 to three consecutive infusions—achieving a 95% success rate (with only one catheter requiring replacement and no adverse effects reported). Unfortunately, urokinase is not currently available in North America. An alternative strategy is stripping catheters of fibrin sheaths. With both methods there is a high clot recurrence rate, which is improved by starting warfarin therapy.

The efficacy of short-term intra-catheter infusion of rTPA in restoration of patency of occluded CVLs in adults and pediatric hematology/oncology patients has been demonstrated by a number of authors recently. In six pediatric HD patients with seven episodes of occluded CVLs, low-dose rTPA infusion (2.5 mg rTPA in 25 mL 0.9% saline at 10 mL/catheter port over 2 hours) was shown to be efficacious in restoring catheter patency. Eighty-five percent of catheters had adequate function at the study end, with a 60% probability of primary catheter patency at 32 weeks post-rTPA therapy.

Prevention of Clots in the Extracorporeal Circuit

Traditionally in pediatrics, UFH remains the agent of choice in anticoagulation during dialysis. In adults, low-molecular-weight heparin (LMWH) use is rising and gaining favor—particularly due to its ease of administration. Both agents, however, cause systemic anticoagulation and therefore carry a bleeding risk. Citrate, known more for its use in continuous renal replacement therapy, is being utilized in conventional HD because it offers the option of regional anticoagulation of the extracorporeal circuit and is thus advantageous in those with an increased risk of bleeding.

Unfractionated Heparin

UFH is a mixture of polyanionic-branched glycosaminoglycans with a wide range of molecular weights (between 6000 and 30,000 daltons) and is found in human mast cells and basophilic granulocytes. In addition, heparin-like anticoagulants are expressed

on the surface of endothelial cells. By interacting with components of hemostasis—such as antithrombin (AT) III and von Willebrand factor—these anticoagulants modify the hemostatic response. UFH binds with high affinity to AT, causing a structural change and converting AT to a very rapidly acting inhibitor of thrombin. AT also interacts with other components of the coagulation cascade, such as factors Xa, IXa, XIa, XIIa, and plasmin and kallikrein trypsin. The net result is inhibition of fibrin formation, thrombin-induced platelet activation, and increased vessel wall permeability.

The key binding component in heparin is a pentasaccharide, but for the heparin-AT complex to inhibit thrombin the UFH molecule must consist of at least 18 monosaccharides. Its polyanionic nature allows nonselective binding to other proteins and cell membranes. It is these interactions that mediate additional adverse effects. Heparin activates lipoprotein lipase, causing enhanced degradation of triglycerides and increased generation of free fatty acids. It also augments the clearance of histamine and suppresses aldosterone synthesis. In very high doses, heparin can induce platelet aggregation and with prolonged treatment can lead to a loss of bone mass and osteoporotic fractures.

UFH has to be administered intravenously because intestinal absorption from oral therapy is poor. Following a bolus injection, the nonspecific interactions reduce the anticoagulant bioavailability to approximately 30%—and although this effect is saturable it is also highly variable. As a consequence, an initial bolus is usually recommended to saturate these nonspecific binding sites because the dose-response relationship is almost linear thereafter. UFH is metabolized by the liver, with renal clearance of desulfated fragments.

The half-life varies from 30 to 90 minutes, but is comparable in uremic and normal individuals. Marked inter-individual pharmacokinetics produces a variable sensitivity to heparin. In addition, the dialysis procedure itself is thought to cause heparin inactivation in the extracorporeal circuit—presumably varying with the type of dialyzer used and the length and internal diameter of the blood tubing. In consideration of these confounding factors, it is crucial that heparin requirements during dialysis be individualized and reassessed over time.

As general rule, the starting dose of heparin required to achieve anticoagulation in children is arrived at by scaling down adult protocols—and experience has shown that such protocols are satisfactory for most children. The desired degree of anticoagulation varies among different dialysis units, ranging between

25 and 300% above the baseline. Our goal at the Hospital for Sick Children is to maintain the activated clotting time (ACT) at 20 to 50% above baseline, with a maximum ACT of 220 seconds—using the Medtronic ACT Plus (Medcompare, San Francisco, CA). A bolus dose of 15 to 20 μ/kg of heparin is administered at the start of dialysis, followed by a continuous infusion of 15 to 20 μ/kg/hour.

The heparin infusion is stopped over the last 30 minutes of dialysis. We have set a maximum heparin dose of 100 μ/kg per dialysis session. ACTs are routinely measured once a month, and the heparin dose is adjusted accordingly. Our experience over many years in a large number of patients using double-lumen central venous lines and both single-needle and double-needle fistula access has demonstrated the safety and efficacy of this protocol. Of note, these recommendations are based on the use of hollow-fiber dialyzers (not the less biocompatible Cuprophane membranes associated with increased platelet activation and higher heparin requirements).

Low Molecular Weight Heparin

LMWH consists of smaller molecules (with a mean molecular weight of 3000 to 9000 daltons) prepared from UFH through enzymatic or chemical depolymerization. They are universal in containing the antithrombin-binding pentasaccharide, but their action is predominantly through inhibiting factor Xa (to an extent greater than UFH). The degree of thrombin inactivation varies among the various LMWHs but is less than that of UFH. Following a single subcutaneous injection, bioavailability reaches 100% due to less nonspecific binding to platelets, endothelial cells, and osteoblasts. This also results in a lower incidence of heparin-induced thrombocytopenia type II (HIT-II), platelet activation, and osteopenia. Prolonged treatment with LMWHs has been reported to produce a sustainable lipid-lowering effect on triglycerides, total cholesterol, and apoprotein.

In a normal individual, the more predictable anticoagulant effect reduces the requirement for routine laboratory monitoring. However, variable inter-individual sensitivity makes fixed dosing inappropriate. LMWHs have a longer dose-independent half-life but are principally cleared by the kidney. This results in unpredictable pharmacokinetics in chronic renal disease stages IV and V and a prolonged half-life in patients with renal impairment. Furthermore, no antidote is available that can easily reverse the anticoagulant effects. Conversely, LMWH can provide

adequate anticoagulation during a 3- to 4-hour dialysis treatment with a single bolus dose at the start. In addition, despite being of low molecular weight no relevant elimination of LMWH occurs through either HD or hemofiltration—even with high-flux membranes. This is thought to relate to the negative charge of the LMWH-AT–factor Xa complex, which reduces membrane permeability.

Efficacy and safety of LMWHs compared with UFH is limited and adult based. Despite initial reservations, results have been promising. A randomized crossover trial compared tinzaparin injected in the arterial line at the beginning of HD versus unfractionated heparin anticoagulation. In the tinzaparin group, anti-Xa activity was not routinely measured and the doses were adjusted in 500-IU increments based on the presence of insufficient anticoagulation of the circuit and excessive bleeding. In the heparin group, ACTs were maintained between 150 and 200 seconds. The results demonstrated an increased clotting rate in the arterial and venous bubble traps with tinzarparin, but a greater risk of excessive bleeding with heparin.

The time for compression of the vascular access at the end of the HD session was not significantly different between the two groups. However, most patients reported less bleeding or oozing from their access within the first few hours postdialysis with tinzarparin. Nurses also reported a preference for tinzarparin because of the simplicity and rapidity of its administration. One meta-analysis comparing the safety and efficacy of LMWH and UFH for HD showed no difference in preventing extracorporeal thrombosis and comparable bleeding risks between the groups.

Whether LMWH offers any advantage compared with UFH in providing anticoagulation in dialysis has not been conclusively established. Evidence is being diluted by data on a number of different LMWHs with different pharmacokinetic properties, whereas direct comparative information in patients with end-stage renal failure is limited. LMWH appears to be a highly convenient anticoagulant with benefits that will likely have a positive impact on HD patients. The lack of published pediatric safety data, combined with the lack of an antidote, has precluded its routine use in pediatric HD.

Citrate Regional Anticoagulation

In patients at risk of bleeding, “regional heparinization” was historically achieved by using protamine to reverse the effects of heparin after the blood left the dialyzer and before it was

returned to the patient. This technique fell out of favor because of the difficulty in manipulating the protamine infusion rate to achieve the desired therapeutic effects. In addition, protamine is known to have anticoagulant properties and was thus an independent risk factor for bleeding. The concept of regional anticoagulation has not been abandoned, but is currently practiced using the alternative agent citrate.

Citrate exerts its anticoagulant effect by chelating ionized calcium ions, thus preventing activation of calcium-dependent procoagulants. Regional anticoagulation of the extracorporeal circuit without systemic anticoagulation is achieved by infusing a citrate solution through the arterial limb of the circuit and then both removing citrate through dialysis and neutralizing its anticoagulant effect by infusion of calcium into the venous end of the circuit. A calcium-free dialysate was originally used, but newer simplified protocols employing regular calcium-containing dialysate have been published. Citrate is a small molecule and is dialyzable with an extraction coefficient similar to that of urea, estimated at 60%.

Any unneutralized citrate that escapes into the systemic circulation is rapidly cleared by the tricarboxylic acid pathway—primarily in the liver and skeletal muscle. One molecule of trisodium citrate is metabolized to three molecules of bicarbonate. In high-risk patients, citrate anticoagulation in adults is associated with a lower bleeding risk, negligible dialyzer clotting, and a lower activation of the coagulation system compared to conventional UFH, LMWH, and regional heparinization. However, the incidence of clotting in the venous bubble chamber and tubing is increased. In addition to its anticoagulant effects, citrate is also thought to improve HD biocompability by attenuating complement activation and unfavorable calcium- and magnesium-dependent cellular and humoral events caused by blood/dialyzer membrane interactions.

To make citrate anticoagulation more acceptable for routine daily practice, attempts have been made to simplify protocols without compromising efficacy. However, they have only been validated in adult HD patients. The use of hypertonic trisodium citrate (1.035 mol/L), infused at 75 mL/hour combined with a conventional dialysate containing 1.5 mmol/L calcium and 0.5 mmol/L magnesium has been reported with success. The plasma citrate concentration remained below 2.2 mmol/L in a 4-hour HD session, and an overall clotting rate of 8.87% was achieved—with only 1.48% of clotting resulting in early termination of dialysis. Patients became hypocalcemic at the

start, but levels stabilized at 120 minutes and no other electrolyte disturbances or biochemical evidence of citrate toxicity was observed.

Our personal unpublished experience with regional citrate anticoagulation in nine pediatric HD patients used a similar method. We employed the commercially available solution ACD-A (Baxter, Deerfield, USA, containing 74.8 mmol/L trisodium citrate and 38 mmol/L citric acid) at an infusion rate of 1.875 times blood flow (mL/hour), resulting in a mean pre-dialyzer blood citrate concentration of 3.9 ± 0.5 mmol/L and a pre-dialyzer ACT of 265 ± 17 seconds. The systemic ACT remained unchanged throughout all treatments, but hypocalcemia was common. Clotting did not interfere with HD in any of the patients, but clots were seen in the dialyzer filaments in all patients at the end of the dialysis session.

Using a higher-than-standard dialysate calcium concentration of 1.75 mmol/L, we observed no fall in serum ionized calcium. The only adverse event witnessed was the occurrence of alkalosis in three patients, which could potentially be ameliorated by using a lower dialysate bicarbonate content. The likelihood of clotting can be lowered by combining a lower citrate infusion with a calcium- and magnesium-free dialysate, using a high-flux membrane, and infusing calcium in the venous end. This more complicated method would be the preferred option for patients with evidence of liver impairment because it places less reliance on dialysis to remove citrate and maintains normal plasma calcium levels.

Complications reported with citrate dialysis include citrate intoxication with hypocalcemia, arrhythmias, and paresthesias; hypernatremia; volume overload; aluminum intoxication (if sterilized in glass bottles); and metabolic alkalosis. Patients on mechanical ventilation are more prone to significant alkalosis due to lack of respiratory compensation, and such patients may benefit from a lower bicarbonate dialysate. Citrate anticoagulation can cause an increased anion gap acidosis, especially in patients with liver failure when citrate is not metabolized and accumulates in the patient's circulation. The increased citrate concentration in the blood depresses the ionized calcium and increases the calcium chloride requirement. However, the calcium that is chelated with citrate is still included when measuring the plasma total calcium concentration. The clinical picture is characterized by an increased total calcium and low ionized calcium, the so-called "citrate lock." One recent publication highlighted the importance of an elevated serum total to

ionized calcium ratio greater than 2.5 as indirect evidence of citrate toxicity.

Citrate anticoagulation provides true regional anticoagulation, thus reducing the risk of bleeding. It attenuates the chronic inflammatory response to HD, its actions are easily neutralized, and it has no known chronic adverse effects as are seen with heparin. This makes it a very attractive option in adults, but at present there is no published data of citrate anticoagulation in pediatric HD patients and thus its use in children remains experimental.

Special Considerations

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is mediated by heparin-dependent IgG antibodies that bind to platelets, causing platelet activation and subsequent thromboembolic events—characterized by markedly increased thrombin levels. The risk factors for developing HIT are duration of heparin therapy and the type of heparin being used (bovine lung UFH > porcine intestine UFH > porcine intestinal LMWH). In adult patients undergoing chronic HD, the prevalence is 2.8 to 12% (the prevalence in children may be as high).

There are many commercially available products that can replace heparin and provide effective anticoagulation, but once again data in children are limited. In one series the heparinoid danaparoid sodium achieved remission or stabilization of the thrombocytopenia and control of the degree of thromboembolism in 77% of adults. Successful treatment of HIT with danaparoid in two pediatric patients has been reported, using a single bolus dose of 1000 units plus 30 units/kg for <10 years of age and 1500 units plus 30 units/kg for 10 to 17 years of age. Unfortunately, danaparoid has up to 30% cross-reactivity with platelet-heparin antibodies.

The direct thrombin inhibitor hirudin is efficacious enough to prevent clotting, but its half-life is prolonged in renal failure and therefore carries the risk of bleeding in addition to anaphylactic reactions in patients with renal failure. Nafamostate, a short-acting serine protease inibitor, causes anaphylactic reactions. Argatroban, a synthetic direct thrombin inhibitor, shows promise. It inhibits free and clot-bound thrombin without the need for a cofactor in a dose-dependent manner. Its onset of action is rapid and it is metabolized by the liver, with a half-life ranging from 39 to 51 minutes.

There is no need for dose adjustment in patients with renal impairment or dialysis. Even with high-flux dialysis, only a 20% systemic clearance is seen. Doses are adjusted using activated partial thromboplastin time for low doses and the activated clotting time for high doses. Adequate anticoagulation is achieved by a bolus dose and continuous infusion. Treatment is tolerated well, and until now there have been no reports on new antibody formation. One problem that remains with argabatran and all of these agents is the lack of available antidote.

Infants

In children weighing less than 10 kg, the likelihood of clotting is increased due to small-caliber lines and slow blood flows—and may be further increased during single-needle dialysis or if single-lumen catheters are used for vascular access. We have successfully used a tight heparin regimen, which allows us to aim for higher ACTs in a controlled and supervised manner (see Figure 90.1 for details).

In an attempt to minimize the risk of bleeding in the interdialytic period, we also use a reduced heparin lock concentration of 50 μ/kg/lumen (as previously discussed). Finally, if blood transfusion is necessary during heparin-free HD we recommend infusing it through a peripheral IV line or via a Y-connection at the venous return site—to reduce the possibility of clotting in the dialysis circuit.

Bleeding Tendency

In high-risk groups there is a 10 to 30% risk of bleeding with UFH. Alternative options for reducing the risk in high-risk groups include regional anticoagulation with citrate, prostacyclin infusion, and modification of the standard regimen. Low-dose UFH and heparin-free treatments with regular intermittent saline flushes and high flow rates are viable options, with good success rates in children without compromising solute clearance.

Based on our own experience, from 28 heparin-free HD treatments in children we achieved a 75% success rate—with major clots developing during four treatments and minor clots during three treatments. Using tight heparin regimens and maintaining ACTs below 170 seconds, no clotting was observed in 90% of the treatments—and a minor clot occurred in just one patient (who weighed 8.5 kg). Selecting the appropriate regimen to achieve the balance between preventing clot formation and

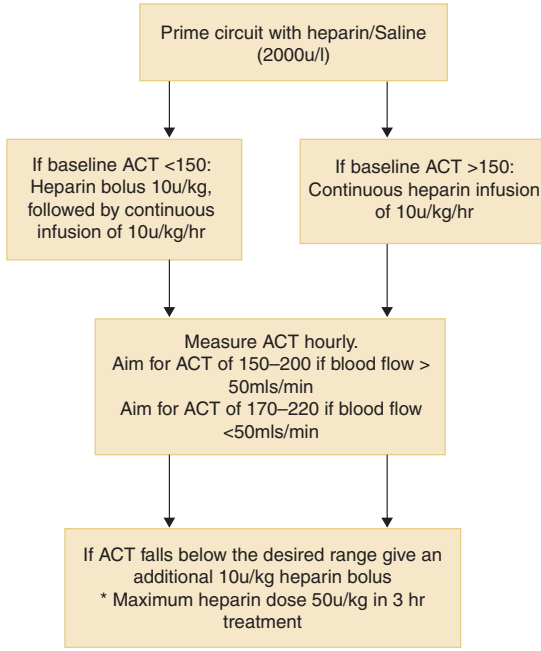


Figure 90–1

Tight heparin regimen.

bleeding can be difficult, but one study reported the benefit of measuring plasma thromboxane B2 as it correlated with platelet activation and the increased risk of incipient clotting during heparin-free dialysis.

Acute HD

Heparinization of children undergoing acute HD may be prescribed along the same guidelines as those described for maintenance dialysis. However, because uremia produces an unpredictable effect on the coagulation system combined with a degree of platelet dysfunction the baseline risk of bleeding is unknown in acute HD patients. Therefore, we recommend a

baseline coagulation assessment prior to starting dialysis—as well as continuous monitoring of the ACT during dialysis to establish the appropriate heparin dose. More often than not, because a new dialysis catheter will have been recently inserted a heparin-free or tight heparin regimen is used in the first dialysis treatment.

Future Directions

Researchers have sought to find ways of modifying dialysis membranes to improve biocompatibility and to enable them to become a source of anticoagulation within the dialysis circuit—reducing peripheral anticoagulation requirements. By recirculating heparin solution (20 I U/mL saline) through Hemophan for 1 hour, successful HD has been achieved without the need for additional anticoagulants. Binding of polycationic unfractionated heparin onto the modified AN69 polyacrylonitrile reduces systemic anticoagulation needs.

Chitosan/heparin polyelectrolyte complex covalently immobilized onto the surface of a polyacrylonitrile membrane has been shown to improve antithrombogenicity and suppress the proliferation of *Pseudomonas aeruginosa*. Finally a simple modification of vitamin-E-coated dialyzers resulted in significant reduction in clotting and reduced heparin requirement and erythopoeitin dosage. These innovative ideas are currently in their preliminary stage, but in combination with some of the novel adult practices described the future may bring radical change to the practice of pediatric anticoagulation as we currently know it.

Recommended Reading

Bamgbola FO, del Rio M, Kaskel FJ, Flynn JT. Recombinant tissue plasminogen activator infusion for hemodialysis catheter clearance. Pediatr Nephrol 2005;20:989–93.

This is a retrospective study of the safety and efficacy of a 2-hour infusion of recombinant tissue plasminogen activator (2.5 mg in 25 mL normal saline over 2 hours prior to HD) in six children with HD catheter occlusion. At 32 weeks post-treatment there was a 60% probability of primary catheter patency. At study completion, 85% of catheters had adequate function as defined by blood flow greater than 200 mL/minute. No adverse events were documented. Despite the limitations of a retrospective study, this short infusion protocol offers a viable alternative to line replacement in pediatric HD patients.

Da Silva AF, Escofet X, Rutherford PA. Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts. Cochrane Database Syst Rev 2003;2:CD002786.

This Cochrane database review examines the efficacy of various antiplatelet therapies in maintaining patency of arteriovenous fistulae and arteriovenous grafts for HD. Analysis of the results of six randomized control trials using

aspirin, ticlopidine, and dipyridamole or dipyridamole plus aspirin compared to placebo confirms the beneficial short-term effects of antiplatelet therapy in maintaining access patency.

Evenepoel P, Maes B, Vanwalleghem J, Kuypers D, Messiaen T, Vanrenterghem Y. Regional citrate anticoagulation for hemodialysis using a conventional calcium-containing dialysate. Am J Kidney Dis 2002;39(2):315–23.

This study outlines a single-center experience with regional citrate anticoagulation (RCA), using a standard calcium- and magnesium-containing dialysate and a standard citrate infusion rate titrated to the circuit ionized calcium. RCA was compared to conventional heparin in 19 HD patients. Transmembrane pressure was modestly increased during RCA. Clotting and thrombus formation were more common with RCA, resulting in early termination of treatment in two patients. RCA was also performed in 45 high-bleeding-risk patients, and was associated with severe hypocalcemia in 0.3% of treatments and with termination of dialysis due to clotting in 1.4% of dialysis sessions. Regional citrate anticoagulation with this simplified protocol offers a safe and viable alternative to conventional anticoagulation in both high-risk and non-bleeding risk groups, but with an increased risk of hypocalcemia and clotting.

Geary DF, Gajaria M, Fryer-Keene S, Willumsen J. Low-dose and heparin-free hemodialysis in children. Pediatr Nephrol 1991;5(2):220–24.

This study reports the feasibility of heparin-free and low-dose heparin HD in children considered at high risk for bleeding. With heparin-free dialysis, 75% of 28 procedures were successful. An activated clotting time of less than 170 seconds and weight less than 10 kg were identified as risk factors for clotting. Patients at high risk for clotting based on the risk factors were dialyzed with low-dose heparin (10 U/kg/hour) with no clotting observed in 90% of patients. Heparin-free and low-dose heparin HD are successful alternatives for children considered high risk for bleeding.

Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: A meta-analysis of randomized trials. J Am Soc Nephrol 2004;15(12):3192–3206.

This is a meta-analysis of 11 randomized control trials comparing the safety and efficacy of LMWH compared to another anticoagulant. LMWH was comparable to unfractionated heparin with respect to bleeding complications, and was as effective as unfractionated heparin in preventing clotting of the dialysis circuit. The selection criteria were reflective of the usual adult HD population and excluded patients with underlying hypercoagulability. Variability in LMWH doses in each study may account for the heterogenicity of the results.

Lord H, Jean N, Dumont M, Kassis J, Leblanc M. Comparison between tinzaparin and standard heparin for chronic hemodialysis in a Canadian center. Am J Nephrol 2002;22(1):58–66.

Neuhaus TJ, Goetschel P, Schmugge M, Leumann E. Heparin-induced thrombocytopenia type II on hemodialysis: Switch to danaparoid. Pediatr Nephrol 2000;14:713–16.

This article documents the development of heparin-induced thrombocytopenia in two pediatric HD patients, and the successful use of danaparoid as an alternative anticoagulant for chronic HD.

Webb A, Abdalla M, Russell GI. A protocol of urokinase infusion and warfarin for the management of the thrombosed hemodialysis catheter. Nephrol Dial Transplant 2001;16(10):2075–78.

This article documents the efficacy of a 12-hour urokinase infusion followed by therapeutic anticoagulation with warfarin for the treatment of dialysis catheter dysfunction. One to three urokinase infusions restored catheter patency in

95% of episodes. Eighty percent of patients who were not subsequently anticoagulated rethrombosed. No bleeding complications were encountered.

Weijmer MC, Debets-Ossenkopp YJ, Van De Vondervoort FJ, ter Wee PM. Superior antimicrobial activity of trisodium citrate over heparin for catheter locking. Nephrol Dial Transplant 2002;17(12):2189–95.

This study compared the antimicrobial efficacy of four concentrations of TSC with equimolar concentrations of sodium chloride, unfractionated heparin, and 7.5% TSC with 1 mg/mL of gentamicin for locking dialysis catheters. TSC plus gentamicin was superior in inhibiting bacterial growth, but not growth of yeast. Increasing concentrations of TSC were more effective in killing staphylococcal species. Thirty-percent TSC was required for complete killing of E. coli *and* P. aeruginosa, *and was able to significantly inhibit growth of* Candida albicans. *Thirty-percent TSC offers the potential to reduce catheter-related sepsis without increasing the risk of emerging gentamicin resistance.*

Zellweger M, Bouchard J, Raymond-Carrier S, Laforest-Renald A, Querin S, Madore F. Systemic anticoagulation and prevention of hemodialysis catheter malfunction. ASAIO J 2005;51(4):360–65.

This study reports the efficacy of systemic anticoagulation with warfarin in reducing catheter malfunction in 65 patients with tunneled cuffed HD catheters. Criteria for catheter malfunction were applicable to a general HD population. Thirty-five patients considered high risk for catheter malfunction were anticoagulated with warfarin with a target INR of 1.5 to 2.0. Fifty-four percent achieved adequate anticoagulation. A fivefold reduction in catheter malfunction occurred in patients achieving therapeutic anticoagulation versus those receiving either no anticoagulation or those with subtherapeutic INRs (0.75 episodes per year versus 3.95 episodes per year). Systemic anticoagulation is of benefit in reducing catheter malfunction in patients at high risk.

CHAPTER 91

Peritoneal Catheter Placement in Children

Mary L. Brandt, MD, and Eileen D. Brewer, MD

Peritoneal dialysis is the preferred modality of dialysis for most children with end-stage renal disease. Choosing the correct catheter and technique for placement is often more an art form than a science. Because the catheters come in a limited number of sizes and children have a vast range of sizes, it is a challenge to choose and position peritoneal catheters in this patient population. The overall complication rate after placement of peritoneal catheters approaches 70% in some series. A logical and well-thought-out surgical approach may decrease the risk of complications, as many complications can be traced to an error in surgical thinking or technique.

Selecting the Catheter

The variety of available peritoneal dialysis catheter designs suggests that the ideal catheter has yet to be created. In general, peritoneal dialysis catheters can be classified by the shape of the intraperitoneal portion (straight or curled Tenckhoff or Toronto Western disc), the shape of the portion of the catheter positioned in the abdominal wall (straight or swan-neck), the number of cuffs (one or two), and the overall length of the catheter. More than 90% of peritoneal dialysis catheters placed in children in North America are of the Tenckhoff design. Little pediatric data exists for the use of Toronto Western or other catheters, and thus Tenckhoff catheters are the focus of this chapter.

In general, most surgeons and nephrologists feel that less occlusion, inflow pain, and catheter migration occur with curled Tenckhoff catheters than with straight ones—although there are no good prospective trials in children to support this conclusion. Data supporting the use of two cuffs in children is also poor. What data there is suggests that the use of two cuffs may decrease infection rates but increase cuff extrusion. Placing the cuff 1.5 to 2 cm from the exit site may decrease the rate of cuff extrusion. Longer distances, however, may lead to incom-

plete epithelialization of the subcutaneous tract—with increased tunnel infections as a result.

In small children, the distance between the two cuffs makes it difficult to achieve optimal subcutaneous cuff position without compromising the exit site. For this reason, many centers prefer a single cuff in small children. There are conflicting data that the swan-neck (preformed downward curve) catheter aids in decreasing infection rates, but most nephrologists feel the benefit of a downward-positioned exit site warrants the use of the swan-neck catheter in children. Regardless of the individual characteristics of the peritoneal catheter, the following principles of placement should be applied for all pediatric patients.

- The exit site should be away from the diaper line and directed in a lateral or, preferably, downward direction.
- The catheter should be an appropriate length to allow intraperitoneal placement into the most dependent portion of the pelvis, without creating an unnatural bend or kink in the catheter.
- The cuff, if single, should be extraperitoneal and firmly anchored in fascia.
- If a second cuff is present, it should be positioned 1.5 to 2.0 cm from the exit site.

Surgical Technique

The patient is positioned in a supine position on the operating room table. Prior to the skin incision, prophylactic antibiotics should be given. Because of the increasing incidence of methicillin-resistant *Staphylococcus aureus*, vancomycin (given as a single prophylactic dose) may be superior to the use of cephalosporins. Children with gastrostomy tubes or vesicostomy/ureterostomy/nephrostomy also need Gram-negative coverage. Prophylactic antibiotics work best when tissue levels are adequate. The ideal time to give the antibiotics is before surgery in the holding area, which places the dose in the ideal window of 20 to 60 minutes before the incision.

In adults, many peritoneal catheters are placed through a midline approach. With the exception of children with a coagulopathy, this approach is not ideal in the pediatric population due to the thinner dimension of the anterior abdominal wall. In children, a midline incision through the skin with a paramedian fascial incision is more effective than a strictly midline approach. The anterior fascia of the rectus sheath is opened longitudinally and the muscle fibers are spread to expose the posterior fascia. The

catheter is then placed through the posterior fascia, usually through a pursestring suture. For a first-time catheter placement, this incision can be slightly extended in order to grasp and then remove the omentum. Although there are minimal data supporting prophylactic omentectomy in children, data in adult patients suggest that omentectomy is beneficial—and most centers now recommend that prophylactic omentectomy be performed.

Prior to introducing the catheter into the peritoneal cavity, a laparoscopic trocar can be placed through the posterior fascia and the abdomen insufflated. Laparoscopic exploration can then be carried out, looking for significant adhesions in the pelvis or the presence of inguinal hernias. When inguinal hernias are identified, repair is recommended.

The catheter is introduced through the abdominal wall with a stylet in place, usually a urologic catheter guide. The optimal position for the catheter tip is in the most dependent portion of the pelvis, anterior to the rectum in the rectovesical or rectouterine pouch. For straight and curled catheters, placing the catheter absolutely in the midline may result in occlusion when the rectum is full. For this reason, positioning the catheter a few degrees lateral to the midline but well within the pelvic brim may be optimal.

The abdominal wall incision is then closed. The deep cuff of a dual-cuffed catheter or the only cuff of the single-cuffed catheter is positioned between the posterior and anterior rectus fascia in the muscle, allowing these two layers to be closed separately for a more secure closure. The catheter is then tunneled laterally out the anterior fascia. It is very important that this opening be kept at a minimum size so that the catheter fits tightly through it. The use of fibrin glue may also decrease the risk of dialysis fluid leakage.

The catheter is then tunneled through the subcutaneous tissue to the exit site. The tunnel should be created in such a way that the catheter cannot move within it. For this reason, using a hemostat or a larger tunneler is not recommended. A Steinman pin with a hole drilled through one end is an effective alternative. The Steinman pin can be introduced into the lumen of the peritoneal dialysis catheter and a transfixing suture through the hole can be used to secure the catheter to the Steinman pin. Selecting and creating the exit site carefully are critical to the success of the catheter. The exit site should be as far as possible from the fascial opening, but should still remain on the anterior abdominal wall.

The catheter, when possible, should exit facing inferiorly or at least laterally. A superiorly directed exit site results in a "pocket" that collects desquamating skin and dirt and is associated with an increased infection rate. However, trying to direct the exit site inferiorly must be weighed against placing too much torque on the catheter—which will lead to intraperitoneal catheter displacement. In most cases, the tunnel will be a gentle curve from the fascial site—with the exit site inferolateral in its direction. The use of a swan-neck catheter with a preformed bend eliminates this problem. If a dual-cuffed catheter is used, the second or subcutaneous cuff should be located 1.5 to 2 cm from the exit site. The second cuff also has to be taken into account when selecting the appropriate exit site for the patient.

The size of the exit size should be so small that some force is required to pull the catheter through it, creating a snug fit of catheter to skin. No suture fixation should be used at the exit site, as this increases bacterial colonization and the ultimate infection rate. Likewise, an antibiotic ointment should not be used because it will macerate the skin. The best dressing is a dry, very occlusive and very stable, dressing. A catheter retention device or equivalent created with tape may also help immobilize the catheter. In whatever manner the catheter is secured to the skin, the catheter should not be able to move at all for the first 7 to 10 days. If possible, a new peritoneal catheter should not be used for 7 to 14 days to allow ample time for wound healing to prevent leakage.

At the completion of the procedure, with the patient still asleep, sufficient normal saline (usually 10–20 mL/kg body weight) containing 1 to 2 units of heparin per mL is instilled into the peritoneal cavity to obtain free flow of peritoneal fluid by gravity siphon. Failure to see a steady stream of peritoneal effluent returning from the catheter should lead to repositioning of the catheter. This instillation and drainage cycle is continued until the fluid is completely clear. Laparoscopic placement of peritoneal catheters is very successful in adults and has been reported in children. Because children have a thinner abdominal wall, laparoscopic placement of peritoneal catheters may be associated with more complications than in adults.

Complications of Peritoneal Dialysis Catheters

Other than peritonitis, which can occur as a result of a break in exit-site care or dialysis technique, many of the complications associated with peritoneal dialysis catheters can be prevented by

good surgical technique. Dialysis effluent leak usually occurs in the immediate postoperative period. Risk factors for leak include inadequate closure of the layers of the abdominal wall, an inappropriately large subcutaneous tunnel, and early use of a newly placed catheter for dialysis. Once a leak is identified, the peritoneal cavity should be drained and the catheter should be cleaned, fixed securely to the abdominal wall with tape or other fixation devices, and dressed with an occlusive dressing. Application of fibrin glue at the exit site may help salvage the catheter by stopping the leak. Peritoneal dialysis should be suspended for as long as possible, in order to allow the site to heal. If the leak persists, the catheter should be removed and positioned in a new location—with closure of the abdominal wall at the site of the initial insertion.

Catheter migration in the peritoneal cavity usually occurs as a result of too much torque placed on the catheter at the time of surgical placement. Because of "catheter memory," if the angle between the intraperitoneal portion and the extraperitoneal catheter is too acute the intraperitoneal portion will become displaced. In infants who have a very shallow pelvis, catheter displacement is common. Occasionally, catheter migration may be due to constipation or excessive bladder distention. The catheter may return to its normal position after therapy for severe constipation (e.g., oral polyethylene glycol) or bladder drainage. If relief of constipation or bladder drainage is not successful in these rare circumstances, the intraperitoneal portion of the catheter can be repositioned by laparoscopic technique. Particularly if a small (3-mm) camera and grasper are used, dialysis can be resumed without difficulty within a day or two. These cases are the exception rather than the rule. In the vast majority of cases, catheter torque is responsible for catheter migration—and the catheter will have to be replaced.

Cuff extrusion, like catheter migration, is usually caused by too much torque placed on the catheter at the time of placement. Cuff extrusion is more likely to occur if the cuff is placed too close to the exit site or in the presence of an exit site or tunnel infection. If the catheter is a dual-cuffed catheter and if there is no evidence of dialysis effluent leak or peritonitis, it may be possible to shave the extruded cuff from the catheter and continue using the same catheter. More often, extrusion results in irritation at the exit site (with subsequent infection) and requires catheter removal and replacement.

Catheter exit-site and tunnel infections may respond to treatment with appropriate antibiotics and careful exit-site care.

The risk of postoperative peritonitis can be decreased by an initial aseptic flush performed in the operating room and subsequent fastidious exit-site care. In the presence of recurrent peritonitis or persistent exit-site or tunnel infection, catheter removal is required. A new catheter should be placed in a new site after the infection has been adequately treated or controlled. Temporary vascular access may need to be placed to allow sufficient time for complete resolution of infection and for wound healing of the new peritoneal catheter before resuming peritoneal dialysis.

Catheter outflow occlusion is usually caused by omentum (if omentum was left in place at the first procedure) or adhesions to mesentery or other intra-abdominal structures. Laparoscopic evaluation may be able to identify an easily correctable problem, which can be handled without open surgery or removing the catheter. In all cases, free return of peritoneal effluent must be documented in the operating room or the catheter must be replaced.

Careful attention to these technical points will help decrease preventable complications of peritoneal dialysis access in children. In addition, the experience of the team placing these catheters is important. When possible, one or two surgeons in each institution should be responsible for placing peritoneal dialysis access in children to optimize catheter outcome and decrease complications.

Recommended Reading

Daschner M, Gfrorer S, Zachariou Z, et al. Laparoscopic Tenckhoff catheter implantation in children. Perit Dial Int 2002;22(1):22–26.

Eklund BH, Honkanen EO, Kala AR, Kyllonen LE. Peritoneal dialysis access: Prospective randomized comparison of the Swan neck and Tenckhoff catheters. Peritoneal Dialysis International 1995;15(8):353–56.

Gadallah MF, Pervez A, el-Shahawy MA, et al. Peritoneoscopic versus surgical placement of peritoneal dialysis catheters: A prospective randomized study on outcome. American Journal of Kidney Diseases 1999;33(1):118–22.

Harvey EA. Peritoneal access in children. Perit Dial Int 2001;21(3):S218–22.

Jones LL, Tweedy L, Warady BA. The impact of exit-site care and catheter design on the incidence of catheter-related infections. Advances in Peritoneal Dialysis 1995;11:302–05.

Hwang T, Chen M, Wu C, et al. Comparison of four techniques of catheter insertion in patients undergoing continuous ambulatory peritoneal dialysis. Eur J Surg 1995;161:401–04.

Kim D, Burke D, Izatt S, et al. Single or double cuff peritoneal catheter? A prospective comparison. Trans Am Soc Artif Intern Organs 1984;30: 232–35.

Kimmelstiel F, Miller R, Molinelli B, Lorch J. Laparoscopic management of peritoneal dialysis catheters. Surg Gynecol Obstet 1993;176:565–570.

Lewis MA, Smith T, Postlethwaite RJ, Webb NJ. A comparison of double-cuffed with single-cuffed Tenckhoff catheters in the prevention of infection in pediatric patients. Advances in Peritoneal Dialysis 1997;13:274–76.

Lye WC, Kour NW, van der Straaten JC, et al. A prospective randomized comparison of the Swan neck, coiled, and straight Tenckhoff catheters in patients on CAPD. Peritoneal Dialysis International 1996;16(1):S333–35.

Macchini F, Valade A, Ardissino G, et al. Chronic peritoneal dialysis in children: Catheter related complications: A single centre experience. Pediatr Surg Int 2006;22(6):524–28.

NAPRTCS 2006 annual report, *https://web.emmes.com/study/ped/*.

Owens L, Brader A. Laparoscopic salvage of Tenchkoff catheters. Surgical Endoscopy 1994;9:517–18.

Patel UD, Mottes TA, Flynn JT. Delayed compared with immediate use of peritoneal catheter in pediatric peritoneal dialysis. Adv Perit Dial 2001;17:253–59.

Rahim KA, Seidel K, McDonald RA. Risk factors for catheter-related complications in pediatrics. Pediatr Nephrol 2004;19:1021–28.

Rusthoven E, van de Kar NA, Monnens LA, Schroder CH. Fibrin glue used successfully in peritoneal dialysis catheter leakage in children. Perit Dial Int 2004;24(3):287–89.

Smith C. One cuff vs two cuff catheters in reference to incidence of infection. In J Maher, J Winshester (eds.), *Frontiers in Peritoneal Dialysis: Proceedings of the III International Symposium on Peritoneal Dialysis*. Washington DC: Field, Rich 1986:181–82.

Sojo ET, Grosman MD, Monteverde ML, et al. Fibrin glue is useful in preventing early dialysate leakage in children on chronic peritoneal dialysis. Perit Dial Int 2004;24(2):186–90.

Stone M, Fonkalsrud E, Salusky I, et al. Surgical management of peritoneal dialysis catheters in children: Five-year experience with 1800 patient-month follow-up. J Pediatr Surg 1986;21:1177–81.

Strippoli GF, Tong A, Johnson D, et al. Catheter type, placement and insertion techniques for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev 2004;(4):CD004680.

Tapper D, Watkins S, Burns M, et al. Comprehensive managment of renal failure in infants. Arch Surg 1990;125:1276–81.

Twardowski Z, Khanna R. Peritoneal dialysis access and exit site care. In R Gokal, K Nolph (eds.), *The Textbook of Peritoneal Dialysis*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1994.

Twardowski Z, Nolph K, Khanna R, et al. The need for a "Swan Neck" permanently bent, arcuate peritoneal dialysis catheter. Perit Dial Bull 1985;5:219–23.

Washburn KK, Currier H, Salter KJ, Brandt ML. Surgical technique for peritoneal dialysis catheter placement in the pediatric patient: A North American survey. Adv Perit Dial 2004;20:218–21.

White CT, Gowrishankar M, Feber J, Yiu V. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol 2006;21(8):1059–66.

CHAPTER 92

Pediatric Peritoneal Dialysis Orders

Karen B. Tipton, RN, BSN, CPN; Suzanne H. White, RN, CPN; and Mark R. Benfield, MD

Introduction

Peritoneal dialysis (PD) has been an available therapy option for children with end-stage renal disease (ERSD) in the United States since the 1960s. In 2005, 58.6% of the pediatric patients receiving dialysis in the United States were receiving PD. To achieve successful outcomes with PD there must be a dedicated team of care providers, an informed decision by the family, proper PD catheter placement, effective home training, optimal dialysis therapy, and close multidisciplinary follow-up. Standing medical-order sets are a useful tool to incorporate NKF-K/DOQI and Centers for Medicare and Medicaid Services guidelines into patient care (Table 92.1). Standing-order sets standardize patient care, promote safety, increase time effectiveness, and decrease errors. Standing-order sets are used as a template for care and should be tailored to meet each patient's individual needs.

Chronic Kidney Disease Family Orientation

The general evaluation of a child nearing chronic kidney disease stage 5 (CKD-V) should include a nonbiased family orientation to all available end-stage therapy options. Ideally, training for the family of a child nearing CKD stage 5 should occur early enough for the family to choose a dialysis modality, receive the required access in time for proper maturing of the chronic dialysis access, and allow for proper training of the family prior to use of the mature access. There are little data to guide the optimal timing of referral for family orientation, but in order to allow for time to achieve all of the necessary decisions, surgery, and training we initiate referral to the CKD stage 5 Family Orientation class when the glomerular filtration rate (GFR) is between 20 and 30 mL/minute/1.73 m^2.

During the CKD stage 5 orientation process, the family is introduced to the multidisciplinary team. The multidisciplinary

Table 92–1

Peritoneal Dialysis Chronic Care Orders

Initiate Peritoneal Dialysis training.
Training sessions should number between 5 and 15.
Primary dialysis modality (circle one): APD CAPD

APD Home Choice Program Prescription:

_____ % Dianeal.

Fill volume _____ ml, (1100–1300 mL/m^2)

Therapy volume _____ mL,

Treatment time _____ hrs,

Last fill volume _____ mL,

Dextrose: (Last) Same _____ Different _____

Cycles _____ ,

Average dwell time _____

Midday exchange: Yes _____ No _____

_____ L × _____ passes _____ % dianeal

Initial Fill volume _____ mL (250–500 mL/m^2/BSA)
Follow Prescription for PD initiation procedure

CAPD Prescription:

_____ % dextrose,

_____ mL volume,

_____ minute drains,

_____ passes per day,

Dry weight _____ kg. Dry weight evaluated at monthly clinic visit and prn.

Notify MD for BP < _____ / _____ or
BP

> _____ / _____ .

Notify MD for weight gain of _____ kg from one day to the next.

PD transfer set tubing change every 6 months, after an episode of peritonitis or a transfer set contamination.

Anthropometrics: Height q month if <18 years old. Skin-fold thickness & arm circumference monthly except for pts. >95% skin fold for age (>26 mm, males; >35 mm, females). Head circumference q month if < 3 years.
Developmental assessment annually on pts. < 6 yrs of age.
Metabolic bone survey q year.

Table Continued

Table 92–1

Peritoneal Dialysis Chronic Care Orders—Cont'd

Laboratory testing schedule:

Monthly RFP, Hgb, Hct, Fe, TIBC, alk phos, PTH, Tissue Typing – UAB for CAD list if applicable

Quarterly PTH (if not receiving rhGH) and mg.

Bi-yearly (Feb & Aug) for pts. on transplant list: CMV, EBV, VZV, RPR, CBC, SGPT, amylase, PT&PTT.

Hold any viral studies when they are known to be positive.

Hepatitis B Vaccine, VZV vaccine, influenza, and pneumococcal vaccines offered to all patients found to be nonimmune from lab results unless otherwise directly by MD.

Alum, TSH & HIV yearly.

Nasal swab of patient and direct caregiver to determine carrier status of *Staphylococcus aureus* initially.

Treatment regimen for MRSA – intranasal Mupirocin to both nares BID for 5 consecutive days a month during the healing phase of the catheter site. For patients found to be MRSA carriers – Mupirocin to PD exit site daily with each dressing change.

Hepatitis surveillance:

Obtain Hepatitis panel & Anti-HBs (Hep B AB quantitative) at initiation of dialysis.

If HBsAg & Anti-HBs both negative, test for HBsAg, ALT, AST monthly.

If HBsAg & Anti-HBs both negative, test hepatitis panel quarterly. (Jan., April, July, Oct)

If HBsAg negative and Anti-HBs positive (>10), test hepatitis panel and Anti-HBs yearly.

If HBsAg positive, retest for HBsAg. Observe hepatitis precautions.

Hepatitis C every 6 months.

If Anti HBs is less than or equal to 10 or nonreactive, patients will be offered the hepatitis B vaccine series unless otherwise directed by MD.

Dialysis Adequacy Testing

PET (Peritoneal Equilibration Test) – by one month of initiating PD, after the pt reaches full dialysis prescription, annually, and after each episode of peritonitis – 6 weeks after antibiotic therapy is completed.

Kt/V and creatinine clearance (Cl/Cr) measured 2 to 3 times within the first 6 months of initiation (i.e., months 1, 4, and 6). Then every 4 months.

MEDICATIONS:

Nephrovite RX _____ .

PO4 binder _____ .

Rocaltrol: _____ mcg po every _____

Aranesp/Epogen _____ units SQ every _____ .

Nutropin _____ units SQ every day.

Iron supplement: _____ Do not take with PO4 binder.

Table 92–1

Peritoneal Dialysis Chronic Care Orders—Cont'd

Heparin _____ units/L to each dianeal bag prn fibrin

Other: _____

Prophylactic antibiotics for dental procedures:

Amoxicillin

Adults 2.0 g (children 50 mg/kg), 1 hour prior to procedure. The total children's dose should not exceed adult dose. (Maximum dose 2 gm)

In Penicillin allergic patients:

Clindamycin

Adults 600 mg (children 20 mg/kg) 1 hour prior to procedure. The total children's dose should not exceed adult dose.

GENERAL INSTRUCTIONS:

Pt is to weigh and measure BP daily and record on daily flow sheet. Also to record ultrafiltrate on daily flow sheet. Patients are given parameters to call the dialysis personnel based on individual patient size and situation for weight and BP limits.

Heparin may be added to dianeal if fibrin is present or if dialysis drains and fills are unusually slow. Dose not to exceed 1000 U/L of dianeal.

PD system only to be entered by dialysis personnel or trained family members.

Patient and/or family will be trained to do Ultra-bag system if primary modality is APD and the patient's fill volume is >1000 mL in case of power outage or other unforeseen circumstances.

Exit-site care per protocol by dialysis personnel, trained hospital personnel, or trained family members.

☐ Insert exit-site care protocol

MANAGEMENT OF COMPLICATIONS:

Treatment of Exit Site infection:

Obtain culture and gram stain of exit site. Follow exit site protocol.

☐ Insert exit-site infection protocol

Treatment of Peritonitis:

Obtain dialysate culture and sensitivity, cell count, and gram stain.

☐ Insert peritonitis protocol

Treatment of system contamination:

Disconnect at titanium

Tear in tubing

☐ Insert repair of PD catheter protocol

Revised 4/03

11/06

team includes personnel with specialized interests, training, and experience in pediatric ESRD. The team should include the pediatric nephrologist, chronic access surgeon, nutrition services, dialysis staff, unit school teacher, social services, renal pharmacist, and transplant coordinator. It is important for the CKD stage 5 multidisciplinary team and family to assess medical condition, co-morbidities, social barriers, and cognitive barriers to determine if contradictions (relative or absolute) exist for any modality. If no barriers or contraindications are identified and the patient is a candidate for self-therapy, this process should allow for the family to choose their preferred modality—and create an integrated plan of care from CKD through dialysis and transplantation.

Peritoneal Dialysis Catheter Placement

When a family chooses PD as their preferred dialysis modality, an appropriate PD catheter must be placed. It is of great benefit to the multidisciplinary team to have a dedicated pediatric surgeon skilled in dialysis access. The dialysis access surgeon will assist in determining the proper choice of catheter and proper technique for insertion of the catheter. Prior to the PD access placement operation, the family, PD nurse, access surgeon, and nephrologist should determine the optimal location of the PD exit site. Considerations for optimal pediatric PD exit site placement should include limiting the chances of possible infection sources.

Considerations to address in limiting sources of infection include continence (e.g., the patient who wears diapers), proximity to other indwelling devices (e.g., gastrostomy tubes, ostomies, indwelling central venous catheters, and tracheostomies), and the presence of scars, skin folds, belt line, and pressure points from clothing. Another infection risk to evaluate and address preoperatively is the *Staphylococcus aureus* carrier status of the child and dialysis caregivers. This is accomplished by culture of the nares. If the results of the cultures are positive, the child and caregivers should be treated with intranasal mupirocin in both nares twice daily for 5 days monthly. To provide optimal healing and decrease the risk of complications the catheter should be allowed to mature 2 to 6 weeks prior to the initiation of dialysis if patient condition permits.

Although the 2006 NAPRTCS (North American Pediatric Renal Trials and Collaborative Studies) annual report notes that the most common type and placement of the PD catheter placed in pediatric patients was the Tenckhoff curled, single-cuffed, straight tunneled catheter with lateral exit-site orientation (14.7%), Gokal

et al. report a lower incidence of infection problems associated with the Tenckhoff double-cuffed curled catheter with a downward exit-site orientation. The access surgeon faces unique challenges when placing a PD catheter in neonates. The neonate must be evaluated to determine if there is enough subcutaneous tissue for adequate support of the PD catheter. Conversely, the challenges for PD catheter placement in the older obese child may include difficulty related to increased exit-site infections or difficulty healing due to excessive skin folds.

The chronic PD catheter is placed under general anesthesia. When the catheter is placed, the surgeon performs the initial irrigation procedure in the operating suite to evaluate adequate flows, rule out mechanical obstruction or leaks at the exit site,

Table 92–2

Intraoperative Peritoneal Dialysis Catheter Irrigation Orders

Pt wt: _____ kg Pt ht: _____ cm Pt m^2: _____

Irrigation Fluids:

D5NS _____ total volume (250 mL/m^2/BSA or 10–15 mL/kg)

Kefzol _____ (200 mg/L)

Gentamicin _____ (8 mg/L)

Heparin _____ units/L (250–1000 U/L).

Vancomycin _____ (20 mg/L)*
*If the patient is allergic to Kefzol or Gentamicin, use only Vancomycin 20 mg/L.

Intraoperative Irrigation Procedures:
1. Run attached fluids into patient for 5 seconds.
2. Stop.
3. Drain patient.
4. Repeat procedure for a total of 3 times.
5. After the third drain, flush the tubing by running the attached fluids into the patient (approximately 5 seconds) and close the twist clamp on the PD transfer set.
6. Remove irrigation fluids and attach minicap to the PD transfer set.
7. The twist clamp on the PD transfer set should be closed at all times except for irrigations.
8. An occlusive dressing will be placed by the surgical team prior to leaving the operating room.
9. Post-operative exit site care and irrigations will be done per dialysis staff.

Revised 10/2006

bathe the peritoneum with prophylactic antibiotics, and anticoagulate the catheter tract (Table 92.2). Sutures at the exit site should be avoided to decrease infection and to promote tissue granulation for proper healing. Prior to leaving the operating suite, the surgeon caps the PD catheter and places a breathable occlusive dressing over the exit site. Postoperative immobilization is essential to promote proper granulation and healing of the catheter tunnel.

Catheter Care

The PD dressing is inspected postoperatively per renal care team and changed if the dressing is noted to be moist or saturated. A weekly sterile dressing change is done to evaluate the exit site for healing and to rule out signs and symptoms of infection (Table 92.3). The exit site is covered with an occlusive dressing and is immobilized to the patient's abdominal area with tape or gauze netting to prevent trauma at the exit site. The catheter

Table 92–3

Peritoneal Catheter Postoperative Dressing

Purpose: To maintain integrity and sterility of the peritoneal dialysis catheter and decrease the risk of infection and leakage at the PD exit site.

Policy: The chronic peritoneal catheter should be dressed occlusive immediately post catheter placement. An occlusive dressing must be maintained for 2 to 4 weeks post catheter placement. A scheduled dressing change is performed weekly by the dialysis staff. If the dressing becomes wet, soiled, or no longer occlusive the bedside nurse should notify the PD nurse on call and change the dressing using the following procedure.

Procedure:

1. Assemble supplies:
   a. CVL dressing kit
   b. Bactroban cream
   c. Sterile cotton applicators
   d. Extra mask for caregivers and patient
   e. Nonsterile gloves
   f. Sterile saline (if needed)
   g. 4 × 4 gauze sponges (if needed)
2. Clean working area with hospital-grade disinfectant.
3. Provide mask for anyone at bedside and for patient.
4. Close doors or pull curtain to provide barrier.
5. Mask and wash hands.

Table 92–3

Peritoneal Catheter Postoperative Dressing—Cont'd

6. Put on nonsterile gloves.
7. Remove any excessive drainage, old blood, or crustiness using 4×4 gauze soaked in sterile normal saline using aseptic technique.
8. Observe and report any s/s of infection such as redness, tenderness, drainage, or foul odor.
9. Remove and discard nonsterile gloves.
10. Open CVL dressing tray using aseptic technique.
11. Place sterile cotton-tipped applicators onto sterile tray using sterile technique.
12. Place pea-sized amount of Bactroban on the sterile field.
13. Apply sterile gloves.
14. Neonate using alcohol swab stick times 3 followed by Betadine swab stick times 3. Use circular motion around insertion site and out to 1 to 1.5 inches. Allow area to air dry.
    Pediatric (over 2 months of age): Prep site using ChloraPrep swab. Clean the PD exit site using friction and back-and-forth motion. Prep area for a 1.5- to 2-inch perimeter. Allow area to air dry. Does not need to be repeated.
15. Apply a thin layer of Bactroban 2% cream using sterile cotton-tipped applicator to catheter.
16. Fold the 2×2 gauze in half and place under catheter. Place 2×2 gauze on top of catheter to cover site.
17. Apply no-sting skin prep to outer aspects of exit site.
18. Secure an occlusive dressing over site using transparent dressing in CVL kit.
19. Apply a strip of transpore tape along the catheter to secure and immobilize the tubing.
20. Write date, time, and initials on the outside of the transparent dressing.
21. Coil catheter tubing on top of transparent dressing and cover with paper tape strips to immobilize catheter.

Written: 4-99
Reviewed: triennially
Revisions: 8-06

remains secured and immobilized for 2 to 6 weeks. As previously stated, postoperative immobilization of the PD catheter and exit site is essential to promote proper granulation, prevent trauma, and decrease bacterial colonization for proper healing of the PD catheter.

Although the catheter may be used in some patients immediately postoperatively, it may take 2 to 6 weeks for the PD catheter to

heal in obese patients or in the very small infant. The caregiver is instructed to secure the catheter and reinforce the occlusive dressing, and to alert medical staff of evidence of leakage, bleeding, or signs and symptoms of infection. After 4 weeks, the caregiver is instructed to perform daily exit-site care (Table 92.4). Acceptable antiseptics for use at the PD exit site are sodium hypochlorite and chlorhexidine gluconate.

The use of Betadine solution and Betadine ointment is discouraged because it has been found to hinder the tissue

Table 92–4

Peritoneal Dialysis Catheter Daily Exit-Site Care

Purpose: Daily catheter and exit-site care is an important part of your peritoneal dialysis (PD) routine. Taking care of the catheter assists in avoiding infection and will prolong the life of the catheter. Exit-site care should be done daily.

Policy: Routine exit-site care is performed daily after shower or sponge bath. Exit-site care should be done if exit site becomes soiled or wet.

Supplies Needed:
- Mask for pt. and caregiver
- Gloves (non-sterile) 2 pair
- 2 × 2 sterile gauze
- ChloraPrep 3ml single sterile applicator
- Paper Tape
- Neonate: Betadine and Alcohol swab sticks, Primapore

Procedure:
1. Gather supplies.
2. Mask and wash hands.
3. Put on gloves.
4. Remove old dressing.
5. Change gloves.
6. Neonate: Prep site using alcohol swab stick times 3 followed by Betadine swab stick times 3. Use circular motion around insertion site and out 1 to 1.5 inches. Allow area to air dry.
   Pediatric (over 2 months of age): Prep site using ChloraPrep swab. Clean the PD exit site using friction and back-and-forth motion. Prep area for a 1.5- to 2-inch perimeter. Allow area to air dry. Does not need to be repeated.
7. *Neonate:* Apply Primapore dressing over exit site.
   Pediatric: Place dry 2 × 2 gauze under and over site and tape loosely with tape. Use a maximum of 2 strips of tape. Do not occlude air flow to exit site.
8. Coil catheter tubing on top of exit-site dressing and secure with strips of paper tape. Do not pull catheter tight.

Table 92–4

Peritoneal Dialysis Catheter Daily Exit-Site Care—Cont'd

Special instructions:

- Sponge bath only for 6 weeks after placement of peritoneal catheter.
- After 6 weeks, bathe or shower daily.
- *Never* immerse exit site in bath water.
- Use liquid antimicrobial soap at exit site using clean wash rag or 4 × 4 gauze.
- Use clean water from tap to rinse exit site.
- Dry exit site with clean gauze.
- After shower or bath, do exit-site care and change minicap.
- Do not dialyze for 1 hour after minicap change.
- Do routine exit-site care daily, usually after shower.
- Do exit-site care if it becomes soiled or wet.
- Do exit-site care after swimming and change minicap.
- Do not dialyze for 1 hour after minicap change.
- Perfumes, powder, baby oil, and lotions are never to be used on or near the exit site.
- Swimming is allowed in private chlorinated pools where no one is eliminating in pool. (i.e., infants, ostomies, etc.). Swimming is also permitted in salt water. *No* swimming in public pools, lakes, creeks, etc. *No* swimming for 6 weeks after catheter placement.
- For infants, *never* place transfer set in diaper.

Call dialysis nurse for drainage, pus, redness, or foul odor.
Written: 8/96
Reviewed: triennially
Revised: 1/03, 12/04, 8/06

granulation process toward promoting proper healing. Because chlorhexidine gluconate and sodium hypochlorite are not approved for use in infants younger than 3 months, some acceptable non-irritating alternatives for exit-site cleansers are sterile normal saline, ShurClens® (mfr. ConvaTec- a nonionic surfactant poloxamer), and pure soap. There are multiple approaches to topical antibiotic prophylaxis after catheter placement, with only limited data to guide choices. It is important to consider antibiotic choices (gentamicin, mupirocin) and patient selection (nasal carriage of *S. aureus*) when making these decisions.

Family Training

Adequate family training is essential to the success of home PD self-therapy. The goal of home training is for the family to perform safe PD therapy and have the ability to recognize, report, and treat complications appropriately per unit protocol and guidelines. The PD coordinator is responsible for home training and case management of the PD population. PD training is routinely done on an outpatient basis while the PD catheter is maturing. The Centers for Medicare and Medicaid Services allows for 15 training sessions and 5 retrain sessions if the family demonstrates the need for extra training. During the CKD stage 5 family orientation class the caregivers are assessed for barriers to learning—such as language barriers, education level, cultural barriers, social limitations, mental limitations, and physical limitations. The PD training nurse ensures that appropriate interventions are anticipated prior to training for any barriers or limitations identified during the family orientation.

It is preferable to identify and train two caregivers for home PD therapy. This allows for sharing of responsibilities and ensures adequate home care should one of the caregivers become ill. The PD nurse instructs the caregivers to operate the automated PD cycler, proper aseptic technique, exit-site care, recognizing and reporting signs and symptoms of peritonitis, exit-site infection, and changes in hydration status. Ultimately, the parent is responsible for ensuring that home PD therapy is performed properly. However, it is also important to involve the patient in their own care to the degree they are developmentally able.

An example of involving a small child in their own care is allowing the child to help gather supplies and put on their own mask. A school-aged child could wash their exit site with soap when taking a shower and take their digital blood pressure measurement. An adolescent could help organize and put away their PD supplies and perform their own exit-site care. The PD nurse follows families new to PD very closely by telephone and with frequent follow-up clinics until the family is settled into the PD routine. The dialysis unit provides nursing and medical support around the clock.

Initiation of Peritoneal Dialysis in Children

The goal of early referral to CKD stage 5 family orientation class is for the family to choose a dialysis modality, to have the appropriate access placed in time for proper healing of the exit

site and catheter tract, and to minimize exposure to bacterial colonization. Normally, the healing process for a PD catheter takes 2 to 6 weeks. If the patient needs immediate dialysis for advanced uremia after the PD catheter is placed, low-volume dialysis is initiated. The patient remains in the hospital for continuous cycling of low-volume dialysis. Low-volume dialysis is initiated per center preference using 250 to 500 mL/m^2 BSA fill volumes with 12 to 24 daily exchanges. Care is taken to maintain immobilization of the catheter.

The PD exit-site dressing should be inspected frequently for fluid leaks. The abdomen should be assessed for focal edema indicating subcutaneous dissection of dialysate without external drainage. Assess the skin for a dimpled appearance and spongy feeling upon palpation. In addition, assess for decreased exchange drain volume or increasing abdominal girth. The patient's inguinal area should be assessed for development of scrotal, labial, or penile edema.

If there are no complications after seven days of low-volume PD exchanges, the fill volumes can gradually be increased over a 7- to 21-day time frame for a target fill volume of 1100 to 1200 mL/m^2 (Table 92.5). IPP monitoring can be performed to guide the practitioner to establish individual maximum tolerable fill volumes. Patient groups at risk for leakage benefit from IPP monitoring. This group includes neonates, children less than 2 years of age, and patients with increased respiratory effort or who are receiving mechanical ventilation. During the PD initiation phase and throughout chronic PD therapy, the practitioner should be aware of the risks for mechanical and infectious complications associated with the PD therapy. The following are common mechanical complications.

Mechanical Complication	Indicators	Diagnostic Work-up
Occlusions: PD catheter migration	Referred pain to the shoulder, difficult or no in and out flow	Abdominal radiograph to confirm catheter placement
Occlusions: Omental wrap and/or adhesions	Easy inflow without fluid return	Abdominal radiograph or CT with contrast – difficult to visualize
Occlusions: Constipation	Inflow and/or outflow obstruction	Abdominal radiograph to confirm constipation. Treat constipation.

Table 92–5

Initiation of Peritoneal Dialysis Therapy

POLICY:
To provide guidance when initiating peritoneal dialysis therapy.

PROCEDURE:

1. This protocol is to serve as a guide and orders may be individualized as needed.
2. MD to prescribe Dianeal concentration (2.5% is most commonly used).
3. Begin a new patient with a fill volume of 250 to 500 mL/m^2/BSA. Infants to begin at the lower end of the scale.
4. The number of cycles to begin at 10 to 12.
5. The total treatment time at 10 to12 hours.
6. Increase the fill volume by 100 mL/m^2 every 2 to 3 days until the target fill volume is reached.
7. Intraperitoneal pressure (IPP) monitoring can be performed to guide the MD to establish the patient's tolerable fill volume. These patients would be neonates, children less than 2 years old, and patients with increased respiratory effort and/or mechanical ventilation.
8. The target fill volume to be 1100 to 1200 mL/m^2/BSA (as found to be adequate by Kt/V).
9. Last fill volume is to be 50% of fill volume.
10. A peritoneal equilibrium test will be done when the target fill volume is reached. This should be done within 4 to 6 weeks of initiating PD.
11. A midday exchange may be added as needed based on patient's Kt/V.
12. The nursing staff, patient, or caregiver is instructed to notify Nephrologist for leaks, abdominal distention, difficulty breathing, or signs and symptoms of infection.
13. The MD will determine adjustments in the fill volume as needed to meet the individualized needs of the patient.

Written: 8-9-99
Revised: September 11, 2006; November 13, 2006

Occlusions: blood or fibrin clots	Inflow and outflow obstruction	Rule out other reasons for occlusions. Consider forceful 20ml Heparin Flush 10 units/ml). Consider instillation of Alteplase solution

Mechanical Complications	Indicators	Diagnostic work up
Leaks: Exit site	External fluid at exit site	Verify clear fluid contains high glucose concentration using test strip
Mechanical Complications	Indicators	Diagnostic work up
Leaks: Tunnel Incision	External fluid at tunnel incision site	Verify clear fluid contains high glucose concentration using test strip
Leaks: Inguinal – hydrocele	Examine scrotum, penis, or labia for edema	Measure IPP
Dissection: subcutaneous	Decreased exchange volume, increasing abdominal girth, dimpled appearance and spongy feeling of tissues upon palpation	CT with intra-peritoneal contrast or ultrasonography
Dissection: diaphragmatic	Sudden respiratory distress	Chest and abdominal radiograph
Pleuro-peritoneal fistula	Respiratory distress	Chest radiograph

Listed below are infectious complications:

Infectious Complications	Indicators	Diagnostic Work up
Exit Site/Tunnel Infections	Purulent discharge from exit site. Persistent erythema of exit site or tunnel tract. Pain or tenderness at the exit site or palpation of the tunnel tract. Foul odor of exit site or dressing gauzes.	Obtain culture and gram stain of drainage. Initiate empiric therapy as indicated by clinical appearance of the exit site. Increase frequency of dressing changes, recommend BID. Close follow up to evaluate response to therapy. For failed responses despite vigorous treatments for 3 to 4 weeks, consider catheter removal.

Peritonitis Includes culture negative, Fungal, mycobacterium, and relapsing peritonitis	Cloudy effluent Abdominal pain/cramping Fever Vomiting and/or diarrhea	Obtain effluent sample for culture, cell count with differential, and gram stain. Empiric diagnosis for peritonitis should be made if effluent is cloudy and cell counts reveal: WBCs >100/mm^3 of which at least 50% are PMNs. Initiate empiric antibiotic therapy per ISPD guidelines while awaiting sensitivity report. Once sensitivities are reported, alter antibiotic therapy to microbe specific treatment. Maintain close follow-up to monitor response to therapy. If no clinical response after 96 hours consider catheter removal.

Routinely, PD is initiated when the caregivers complete the home training process and are consistently able to perform return demonstration for all aspects of home care. To ensure reliability and to promote comfort levels, the family performs a 3- to 5-hour PD treatment run per center preference. The initial PD treatments performed by the family occur in the outpatient dialysis center for up to three consecutive days. The patient begins with a fill volume of 250 to 500 mL/m^2 BSA per unit-specific preference after assessment of the child's clinical condition. The dextrose concentration is ordered by the nephrologist based on the patient's clinical and biologic indicators.

To allow for gradual stretching of the peritoneum, the fill volumes are increased every third day until the patient reaches a maximum fill volume of 1100 to 1200 mL/m^2 BSA/day. It is the preference of our pediatric dialysis center to use 10 to 12 hourly cycles once maximum fill volumes are achieved. This PD schedule will then be specifically tailored to the patient by gathering and using the peritoneal equilibration test (PET) and adequacy (Kt/V)

Table 92–6

Home Flow Sheet

Date
Pre-weight
Pre-BP
Total UF
Post-weight
Post-BP
Dianeal
Date
Pre-weight
Pre-BP
Total UF
Post-weight
Post-BP
Dianeal
Date
Pre-weight
Pre-BP
Total UF
Post-weight
Post-BP
Dianeal
Date
Pre-weight
Pre-BP
Total UF
Post-weight
Post-BP
Dianeal
Date
Pre-weight
Pre-BP
Total UF
Post-weight
Post-BP
Dianeal

data. IPP monitoring may be indicated in those patients believed to be at high risk for increased abdominal pressures.

IPP monitoring or clinical judgment can assist in determining maximally tolerable fill volumes. Care is taken to follow the

newly trained PD patients to ensure the families are able to recognize and adjust dialysis therapy based on individualized home parameters given to assess fluid volume status. Initiation of home PD therapy can be accepted by the family and managed well when the multidisciplinary team maintains close communication with the family until the therapy is assimilated into their daily lives.

Peritoneal Dialysis Adequacy Measures

The treatment goal for PD is physical and mental well-being, absence of uremic symptoms, and minimal interference with family/social/school life. Indicators that suggest inadequate dialysis are overt uremia, manifest edema, clinical or biochemical signs of malnutrition, congestive heart failure, hypertension, BUN values, hyperkalemia, and hyperphosphatemia. Currently, there are no definitive data to support or suggest that dialysis adequacy in children is predictive of well-being, morbidity, or mortality. However, clinical standards for pediatric PD patients suggest that the target doses of PD meet or exceed the adult weekly delivered target of $Kt/V_{urea} > 2.1$ and CrCl of 63L/1.73 m^2 and be opinion based.

It is suggested that PET and Kt/V values be determined 4 weeks after initiation of PD, when maximum fill volumes are achieved. After determining the transport characteristics of the patient's peritoneum, PD dosing tables or software can be used to maximize PD prescription. This PET is used as the baseline measure of peritoneal membrane transport characteristics, not to determine total solute clearance. The PET is performed to rule out unsuspected problems or deviations from mean transport characteristics. PD therapy can be maximized based on peritoneal membrane transporter status. It is also important to include residual kidney function when assessing Kt/V and issues of PD adequacy. Once the child's transport status has been determined, the practitioner can utilize computer-assisted PD adequacy modeling to maximize effective PD dosing.

Outcomes Evaluation

The goal for peritoneal dialysis follow-up and evaluation is optimizing health and promoting normal growth and development. This requires close collaboration and follow-up between the PD family and the multidisciplinary team members. The child receiving home PD therapy is seen in clinic for follow-up by the

multidisciplinary team on a monthly schedule. More frequent follow-up may be necessary depending on circumstances.

Routine PD clinic visits include physical exam, review of problems, assessment of growth and development (height, weight, and anthropometrics), laboratory tests to assess biochemical control, review of daily flow sheets kept by the family, (Table 92.6) review of computerized PD cycler information cards, nutritional assessment with dietary intake, assessment of dialysis adequacy, and social assessment related to coping, school, and adequate family support. During each clinic session the items on the short-term patient care plan should be addressed and updated with appropriate teaching and/or interventions. The long-term care plan includes ongoing evaluation of suitability for renal transplantation.

Recommended Reading

Bernardini J, Piriano B, Holley J, Johnston JR, Lutes R. A randomized trial of Staphylococcus aureus exit site infections in peritoneal dialysis patients: Mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. Am J Kidney Dis 1996;27:695–700.

Fischbach M, Terzic J, Menouer S, Haraldsson B. Optimal volume prescription for children on peritoneal dialysis. Perit Dial Int 2000;20:603–06.

Gokal R, Ash SR, Helfrich BG, Alexander SR, Chen TW, Danielson A, et al. Peritoneal catheters and exit site practices: Toward optimum peritoneal access. Perit Dial Int 1998;18:11–33.

NKF-K/DOQI Guidelines 2006 – http://www.Kidney.org/professionals/NKF-K/DOQI/

Keane WF, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, et al. ISPD guidelines/recommendations: Adult peritoneal dialysis-related peritonitis treatment recommendations, 2000 update. Perit Dial Int 2000;20:396–411.

NAPRTICS 2006 – http://web.emmes.com/study/ped/ped/index.htm

Prowant BF, Twardowski Z. Recommendations for exit site care. Perit Dial Int 1996;16(3):94–99.

Thodis E, Bhaskaran S, Pasadakis P, Bargman J, Vas S, Oreopoulos D. Deccrease in Staphylococcus aureus exit site infections and peritonitis in CAPD patients by local spplication of mupirocin ointment at the catheter exit site. Perit Dialys Int 1998;18:261–70.

CHAPTER 93

Nutritional Management of Children on Peritoneal Dialysis

Ashley A. Perilloux, MS, RD, and Isidro B. Salusky, MD

Peritoneal dialysis (PD) offers major advantages for children with end-stage renal disease, including fewer diet restrictions, increased capability to attend school regularly, and more effective control of biochemical abnormalities associated with uremia. Despite the liberalized diet, the child's appetite may be insufficient to provide adequate energy and other nutrients required for growth, development, and prevention of malnutrition.

At onset of renal failure, children vary in age, psychosocial status, and achievement of developmental and educational milestones. In addition, their eating patterns can be changeable, requiring frequent monitoring of the adequacy of their food intake. This chapter describes methods of assessing nutritional status and offers recommendations for optimal nutritional management in this patient population.

Assessment of Nutritional Status

Assessment and close monitoring of growth parameters, dietary intake, psychosocial status, and intake of prescribed medications is fundamental in the treatment of this patient population. The data collected in the assessment process should be interpreted according to age, gender, and pubertal stage to determine nutrient recommendations.

Growth Parameters

Measurements for weight, length or height, and head circumference (birth through 36 months) should be obtained monthly in infancy and at least quarterly in children older than age 2 years.[1] These measurements should be compared to values for healthy children. The volume of the daytime dwell of dialysate is subtracted from the measured weight to obtain the actual weight. It is also important to determine an estimated dry weight. This is different from the actual weight and is determined using blood pressure, presence of edema (periorbital, pretibial, ascites),

magnitude of ultrafiltration, daytime dwell of dialysate, and clinical appearance as indicators.

Length should be measured on an infant stature board until the child is able to stand unassisted (about age 2), and should be measured using a fixed stadiometer thereafter. Exact procedures for measuring growth parameters are provided in the Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) clinical practice guidelines for nutrition in chronic renal failure (pediatric guidelines).[1] The data are plotted on gender-specific growth charts published in 2000 by the National Center for Health Statistics (NCHS) in order to determine percentiles for weight for age, length or height for age, weight for length, or body mass index (BMI) for age.

Special consideration should be given to infants when assessing growth parameters, especially related to weight-for-length comparisons. Many of these infants have moderate to severe developmental delays and are therefore not reaching physical milestones such as sitting, crawling, and walking as readily as their healthy counterparts. This leads to significantly less lean muscle mass compared to healthy infants of the same age, which in turn suggests that these infants might plot slightly lower on the weight-for-length chart although actually maintaining an appropriate weight. Subjective data, such as the presence of fat rolls, together with biochemical indices should be considered along with growth measurements. However, any infant whose weight for length plots below the 10th percentile is not thriving and warrants aggressive nutritional intervention.

Anthropometrics

The tricep skin-fold measurement and mid-arm circumference are used to calculate the mid-arm muscle circumference, and all three are compared with age- and gender-specific normal values to evaluate fat and muscle stores in children older than 1 year.[1] Standard deviation scores are used to interpret data in terms of the number of standard deviations above (positive value) or below (negative value) the median (50th percentile) value for normal controls of the same age and gender.

Protocols, tables of normal values, and growth charts are available in the NKF-K/DOQI clinical practice guidelines for nutrition in chronic renal failure (pediatric guidelines) and from the NCHS web site. Increased accuracy is obtained when one person serially measures the patient over time. The NKF-K/DOQI guidelines recommend that anthropometric measurements be obtained at least quarterly for children older than 1 year.

Diet History

Dietary intake can be estimated using a variety of validated techniques, including 24-hour recall, food frequency questionnaire, or 3-day food diary. Output (urine, ostomy, and stool habits) should also be evaluated at least quarterly—especially with regard to decreasing residual renal function. The following list includes important areas of information that should be part of the diet history so that nutrition recommendations can be developed.

- Caregivers involved with feeding child (preparation and offering)
- Facilities for food preparation
- Economic resources for food purchasing
- Current dietary restrictions and/or tube feedings, if any
- Physical eating skills, swallowing difficulties, and enteral feeding devices
- Presence of nausea, vomiting, diarrhea, or constipation
- Change in appetite or taste of food
- Usual body weight and weight gain or loss over the past 6 months
- Frequency of eating away from home (fast food, restaurants, school, secondary caregiver)
- Activity level

Subjective Assessment

Patients should be examined regularly for signs of nutritional deficiency such as dry, brittle, or sparse hair; dry, flaking, or hyperpigmented skin; brittle or misshapen nails; bleeding or hypertrophied gums (side effect of some commonly prescribed medications); and skeletal abnormalities (such as genu valgum of the legs). In addition, edema of the face (especially periorbital), abdomen, and extremities should be assessed routinely to monitor needed adjustments in estimated dry weight, dialysis prescription, and/or dietary prescription.

Dialysis Prescription

It is important to note the unique dialysis prescription of each patient, as variances can impact nutritional status. For example, a child placed on hourly exchanges due to low fill volumes may have different nutritional needs than a child placed on a standard dialysis prescription. In addition, the presence of daily dwell can be a factor in the persistence of anorexia and/or a sensation of fullness.

Current Medications

The multiple and varying medications children take can have significant impacts on nutritional status and should be monitored regularly. Phosphate binders should be reviewed with patients and families at each visit to assess not only current prescriptions but the actual dosages reported by the patients/families. Be sure to include dosages taken with meals versus snacks, as well as any calcium supplements taken between meals or at bedtime.

Similarly, vitamin D dosages should be monitored at each visit—ensuring accuracy in following prescriptions and consistency of compliance with daily or intermittent dosages. Oral iron supplements are generally taken daily along with a renal multivitamin. Other medications may include immunosuppressants, epogen, alkali agents, diuretics, and antihypertensives. Angiotensin-converting enzyme (ACE) inhibitors are especially important to note, as they can have a significant impact on potassium levels. Prolonged antibiotic therapy can also impact nutritional status if diarrhea or vitamin loss becomes a resulting side effect.

Biochemistries

Laboratory results related to mineral metabolism, lipids profile, anemia management, urea kinetics, nutritional intake, and metabolic management should be assessed regularly so that adjustments in related dietary parameters, medications, and dialysis prescription can be made.

Radiologic Assessment

Bone age should be evaluated every 12 months, preferably by the same person, in prepubescent children or patients younger than 16. Radiologic evaluation of hands, hips, and knees are obtained under the standard techniques and compared to published standards.

Pertinent Medical History

A complete medical history should be reviewed to ascertain any events with nutritional significance. Events such as recent hospitalizations, infections (including peritonitis), and surgeries can all contribute to depletion of protein stores and will likely be reflected in serum albumin levels. In addition, certain underlying diseases can contribute significantly to increased nutritional needs—as in patients with severe nephrotic syndrome.

Dialysis Adequacy

Urea kinetic modeling (UKM) is a useful tool in determining optimal delivery of dialysis, although there is limited information on the value of using UKM in pediatric patients with end-stage renal disease. Poor appetite and intake, edema, hypertension, and elevated biochemical values can be the results of inadequate dialysis and these can negatively affect nutritional status. A Kt/V (K = clearance, t = time of treatment, V = urea volume of distribution) of 2.1 to 2.2 is the generally accepted target value for automated PD.

Many dialysis programs evaluate Kt/V on a quarterly basis, and more frequently if the patient's status indicates. Care should be taken to perform 24-hour urine collection concurrently with the dialysate samples—even in those patients with minimal output—to more accurately reflect clearance. There are some limited data suggesting a superior benefit of routine evaluation of nPCR compared to serum albumin as a reliable predictor of nutritional status in adolescents on hemodialysis.[2] However, it is unknown at this time how these data apply to the PD population.

Nutrition Care Plan

After the data are collected and interpreted according to age, gender, and pubertal stage in the assessment process, the nutrition care plan is developed. This plan contains specific nutrient recommendations and is the foundation for patient and caregiver education. Diet restrictions should be minimized as much as possible to encourage adequate energy intake in this patient population in which anorexia and poor appetite are frequently present. When recommendations are initiated, careful monitoring via diet history is important to identify nutrients and practices requiring modification.

Energy

The recommended dietary allowance (RDA) for chronologic age and gender is the initial recommendation, and such value can be increased or decreased as appropriate during the monitoring process—based on the patient's dry weight gain.[1] Calories derived from the dialysate glucose are generally not included in the initial recommendations unless the patient has an elevated weight-for-height ratio or BMI. The age-specific recommendations are outlined in Table 93.1. Infants have high energy requirements for weight gain and growth, often exceeding 120 kcal/kg.

Table 93–1

Estimated Energy Allowances for Children and Infants

	Age (y)	Kcal/kg/d
Infants	0–0.5	108
	0.6–1.0	98
Children	1–3	102
	4–6	90
	7–10	70
Males	11–14	55
	15–18	45
	18–21	40[a]
Females	11–14	47
	15–18	40
	19–21	38[a]

a. Based on recommended dietary allowances and increased physical activity. Reprinted with permission from NKF-K/DOQI. *Nutrition in Chronic Renal Failure*.

These high energy needs, combined with oral delays and poor intake, may often make meeting these goals a considerable challenge.

Protein

The protein recommendation is the RDA for chronological age and gender plus a factor of 0.5 to 0.8 g/kg/day to compensate for dialysate protein losses.[1] The age-specific recommendations are outlined in Table 93.2. There is an inverse relationship between protein loss and body size. Therefore, infants and younger children will require the upper range of the added protein. Protein recommendations may be adjusted upward or downward based on the patient's biochemical levels, dialysis prescription, and medical status.

Carbohydrate and Fat

Elevated lipid profiles have been described in children with end-stage renal disease. Because these patients are at high risk for the development of accelerated atherosclerosis, it is prudent to follow standard pediatric dietary guidelines for reduced intake of saturated fats, trans-saturated fatty acids, and simple sugars. Emphasis should be placed on heart-healthy food practices, such

Table 93–2

Recommended Dietary Protein for Children on Maintenance Dialysis

	Age (y)	RDA	Protein Intake[a] for PD
Infants	0–0.5	2.2	2.9–3.0
	0.6–1.0	1.6	2.3–2.4
Children	1–3	1.2	1.9–2.0
	4–6	1.2	1.9–2.0
	7–10	1.0	1.7–1.8
Males	11–14	1.0	1.7–1.8
	15–18	0.9	1.4–1.5[b]
	19–21	1.2	1.3[b]
Females	11–14	1.0	1.7–1.8
	15–18	0.8	1.4–1.5[b]
	19–21	0.8	1.3[b]

a. Values are expressed in grams of protein per kilogram per day.
b. Based on growth potential.
Reprinted with permission from NKF-K/DOQI. *Nutrition in Chronic Renal Failure*.

as cooking with monounsaturated oils and reducing intake of high-calorie meals and snacks with little nutritional value (such as fast food and processed snacks). Although children on PD are generally not heavy consumers of simple sugars, with the possible exception of sodas, glucose uptake from the dialysate solution may exacerbate hypertriglyceridemia.

Potassium

Children treated with PD generally do not require potassium restriction in the diet if the dialysis prescription is adequate. However, closer monitoring should be performed under the following circumstances: anuric patients, patients treated with ACE inhibitors, patients receiving potassium supplements, and children under 2 years of age. Infants may be able to tolerate breast milk or regular infant formula. However, when potassium levels are high a low-electrolyte formula may be necessary. In addition, low-potassium baby foods are sometimes indicated. In older children, if a potassium restriction is needed it is recommended to begin with 3 mEq/kg/day as a starting point and monitor the response. In contrast, patients treated with long-term PD may

develop hypokalemia and the need for subsequent potassium supplementation.

Sodium

In most patients undergoing PD with adequate ultrafiltration and appropriate dialysate prescription, a sodium restriction is not usually required to maintain optimal blood pressure control. However, updated American Heart Association guidelines recommend sodium intake less than 2300 mg per day (a moderate restriction for healthy adults).[3] Although there are no specific guidelines for children at this time, it seems appropriate to encourage more of a "whole foods" diet with avoidance of heavily processed foods and snacks commonly consumed—especially in the adolescent population.

As an added benefit, decreased consumption of processed foods may also decrease phosphorus intake. It is also important to note that there is a subset of anuric/anephric patients who present with elevated blood pressure and/or fluid overload and therefore require a more significant restriction. One important exception is infants, who tend to be polyuric and frequently require a sodium supplement because additional losses occur through dialysis and these losses may be exaggerated by the use of higher dextrose concentrations.

Phosphorus

High-phosphorus foods, such as milk and dairy products, are traditional favorites of children and provide a significant protein source for many patients. On the other hand, they play an important factor in the development of hyperphosphatemia and subsequent secondary hyperparathyroidism. When phosphorus binders are taken as prescribed, the dietary intake of children and adolescents should be limited to 800 mg/day. This allows for 8 ounces of milk per day or the phosphorus equivalent of cheese (1 oz), pizza (1 slice), or other phosphorus-rich food (such as 1/2 cup beans or lentils). This level is prescribed for patients who have a serum phosphorus <5.5 mg/dL. Higher serum levels require phosphorus to be restricted to 600 mg/day, which excludes dairy products and some other high-phosphorus sources. Patients and families who regularly eat excessively large portions of meat, poultry, fish, or eggs may require extra counseling because such foods are a significant source of dietary phosphorus.

Infants and toddlers may not require a significant phosphorus restriction. In fact, infants on low-electrolyte formula may require phosphorus supplementation to maintain serum levels within the normal-for-age range (4.8–7.4 mg/dL). It is important to maintain serum phosphorus concentrations according to age-appropriate levels, mainly during the first 2 years of life, to avoid the consequences of sustained hypophosphatemia on growth. Table 93.3 outlines the target serum phosphorus levels according to age.

Fluids

In most patients undergoing PD with good ultrafiltration, there is no need for fluid restriction. In fact, patients with polyuria (and infants in general) require fluid supplementation—depending on the magnitude of the residual renal function and the degree of ultrafiltration. It is important to monitor residual renal function at regular intervals because it declines over time and adjustments in the dialysis prescription should be performed accordingly. In the subset of patients who are anuric/anephric with concomitant hypertension and fluid overload, a fluid restriction of =5% estimated dry weight is beneficial.

Vitamins and Minerals

The goal is to achieve 100% of the dietary reference intake (DRI) for thiamin, riboflavin, pyridoxine, vitamin B12, and folic acid; and 100% of the RDA for vitamins A, C, E, and K, and for copper and zinc. This can be a difficult goal to achieve without supplementation due to dialysate losses of B vitamins combined with frequent suboptimal intakes of vitamins and minerals due to individual food preferences and dietary restrictions. Because dialysis patients are at risk for hypervitaminosis A, all vitamin

Table 93–3

Representative Normal Values for Serum Phosphorus

Age (y)	Serum Phosphorus (mg/dL)
0–0.25	4.8–7.4
1–5	4.5–6.5
6–12	3.6–5.8
13–20	2.3–4.5

Table 93–4

Dietary Reference Intakes for Children and Adolescents

Category	Thiamin (mg)	Riboflavin (mg)	Pyridoxine[a] (mg)	Folate (µg)	Vitamin B12 (µg)
Infants					
0–6 mo	0.2	0.3	0.1	65	0.4
7–12 mo	0.3	0.4	0.3	80	0.5
Children					
1–3 y	0.5	0.5	0.5	150	0.9
4–8 y	0.5	0.6	0.6	200	1.2
Males					
9–13 y	0.9	0.9	1.0	300	1.8
14–18 y	1.2	1.3	1.3	400	2.4
Females					
9–13 y	0.9	0.9	1.0	300	1.8
14–18 y	1.0	1.0	1.2	400	2.4

a. Refers to the quantity of free pyridoxine and not pyridoxine hydrochloride. Reprinted with permission from NKF-K/DOQI. *Nutrition in Chronic Renal Failure*.

supplement prescriptions should utilize a formulation excluding vitamin A. Current recommendations are summarized in Tables 93.4 and 93.5.

Renal Osteodystrophy

Renal osteodystrophy encompasses a range of bone disorders, including the high-turnover skeletal lesions of secondary hyperparathyroidism and the low-turnover lesions of adynamic bone. Recent recommendations by the Kidney Disease: Improving Global Outcomes (KDIGO) Mineral and Bone Initiative workgroup suggest that the term *renal osteodystrophy* be applied only when the abnormality has been evaluated and classified with bone biopsy. In contrast, the many clinical, biochemical, and imaging abnormalities that have heretofore been identified as correlates of renal osteodystrophy should be defined more broadly as a syndrome or systemic disorder to be called a "chronic kidney disease mineral and bone disorder."

Vascular calcifications and bone disease are the main hallmarks in patients with CKD and they are associated with significant

Table 93–5

Recommended Dietary Allowances for Children and Adolescents

Category	Vitamin A (μg, RE)	Vitamin E (mg α-TE)	Vitamin K (μg)	Vitamin C (mg)	Zinc (mg)	Copper (mg)
Infants						
0.0–0.5 mo	375	3	5	30	5	0.4–0.6
0.6–1.0 mo	375	4	10	35	5	0.6–0.7
Children						
1–3 y	400	6	15	40	10	0.7–1.0
4–6 y	500	7	20	45	10	1.0–1.5
7–10 y	700	7	30	45	10	1.0–2.0
Males						
11–14 y	1,000	10	45	50	15	1.5–2.5
15–18 y	1,000	10	65	60	15	1.5–2.5
Females						
11–14 y	800	8	45	50	12	1.5–2.5
15–18 y	800	8	55	60	12	1.5–2.5

Reprinted with permission from NKF-K/DOQI. *Nutrition in Chronic Renal Failure.*

morbidity and mortality. Unfortunately, despite advances in the treatment of secondary hyperparathyroidism cardiovascular mortality continues to be the leading cause of death in patients with CKD.[4] Futhermore, therapies used to treat secondary hyperparathyroidism may in themselves promote vascular and skeletal disease by inducing hypercalcemia, hyperphosphatemia, and disregulation of osteoblastic and osteoclastic activity. Although the spectrum and treatment of renal osteodystrophy is described elsewhere, there are some specific issues for pediatric patients. Secondary hyperparathyroidism remains, however, the most common form of renal bone disease in pediatric patients undergoing dialysis despite therapy with oral vitamin D analogues.

Over the last few years, advances have been made toward the prevention of complications associated with the therapeutic interventions utilized to treat secondary hyperparathyroidism. The metal-free/calcium-free phosphate binder sevelamer has been shown to halt the progression of cardiovascular calcifications in adult patients treated with hemodialysis. In addition, it has been shown to be an effective binder in pediatric patients.[5] Newer vitamin D analogues with lower calcemic response have also been introduced. Two such compounds, 1-alpha-hydroxyvitamin D_2 (doxercalciferol) and 19-nor-1,25 dihydroxyvitamin D_2 (paricalcitol), are currently available for clinical use and can be used in oral forms.

Recently, our group has demonstrated that treatment with either calcitriol or doxercalciferol together with sevelamer reduces exogenous calcium load and serum calcium levels while effectively controlling secondary hyperparathyroidism in children undergoing PD.[6] Indeed, bone formation rates were within the normal range in the vast majority of the patients on repeat bone biopsy—and serum calcium levels were higher only in those patients treated with calcium-based binders. In the past, we have demonstrated that the administration of intermittent doses of calcitriol combined with calcium-based binders effectively lowers serum parathyroid hormone (PTH) levels and corrects many of the histologic manifestations of secondary hyperparathyroidism in bone. However, adynamic bone commonly develops in a substantial proportion of patients.

Thus, the use of large doses of oral calcium supplements to manage phosphate retention and hyperphosphatemia and treatment with calcitriol has been implicated in the pathogenesis of adynamic bone. In addition, the development of adynamic renal osteodystrophy has been associated with worsening growth retardation in prepubertal children receiving PD.[7] Thus, the

use of newer therapeutic strategies along with more aggressive monitoring of calcium, phosphorus, and PTH levels (maintaining PTH between 300 and 400 pg/mL while titrating therapy with active vitamin D sterols) prevents the development of adynamic bone.[6] When calcium is utilized, the exogenous calcium from both calcium-based binders and dietary intake should not exceed two times the DRI for age-based calcium—and the total intake of elemental calcium should not exceed 2500 mg/day.[8]

New calcium-free phosphate binders (such as lanthanum carbonate) have been approved, although the long-term safety of such compounds remains to be determined. Animal studies have demonstrated lanthanum accumulation on bone and liver. Furthermore, it has been shown that lanthanum can accumulate at the level of the growth plate in growing animals.[9] Studies performed in adult hemodialysis patients demonstrated that plasma and bone lanthanum increased with such therapy.[10] Studies have not been performed in pediatric patients, but in view of the potential growth plate accumulation such agents should not be used in this patient population.

Calcimimetic drugs have been approved for the control of secondary hyperparathyroidism, and studies have consistently demonstrated suppression of PTH with concurrent reductions of serum calcium and phosphorus levels.[11] Studies in pediatric patients are not currently available. Thus, the availability of new vitamin D analogues and calcium-free/metal-free phosphate binders open the window of safety for the treatment of secondary hyperparathyroidism in children treated with dialysis.

Anemia Management

The specific protocols related to anemia management are addressed elsewhere. However, it is worth mentioning that nutritional status should always be considered when a patient is consistently falling short of outcome goals and all other contributing factors (such as iron stores, epogen dose, and blood loss) have been ruled out. Furthermore, it is important to remember that insufficient B vitamin levels (specifically related to folic acid, B6, and B12) can cause a macrocytic anemia—which is generally reflected in elevated MCV/MCH levels.

Growth Failure

For pediatric patients unable to meet their caloric and/or protein goals for growth due to physical limitations (e.g., developmental

delay), anorexia, or other co-morbid condition, supplemental oral feedings may be necessary.[12] There are a variety of infant, pediatric (nonrenal), and adult renal supplements that can be utilized—depending on the metabolic needs of the patient.

In the infant population, expressed breast milk and/or formula may be concentrated using modular components of carbohydrate, protein, and fat to achieve adequate nutrient levels.[13] Infants frequently need enteral tube placement to achieve optimal growth outcomes. Such therapeutic intervention should be planned in advance if possible because placement of a G-tube requires temporary discontinuation of PD and a switch to hemodialysis in the absence of sufficient residual renal function. One should initiate placement without undue time delay to promote the rapid growth velocity normally seen in the first 2 years of life.[12] Evaluation of gastroesophageal reflux, normally present in a percentage of nondialyzed infants, is important to determine need for a fundoplication.

Special attention must be paid to oral stimulation in patients receiving enteral feedings, in order to preserve oral-motor skills. Likewise, solid foods should be initiated in the normal age-appropriate manner to further facilitate oral-motor development. In those infants and toddlers not reaching developmental milestones, both occupational and physical therapy should be pursued aggressively as a vital part of the overall care plan.

School-age children frequently demonstrate selective food preferences and manipulative behaviors related to food, which may lead to inadequate intake and growth issues. Assisting caregivers in appropriate limit-setting techniques around food allows for carryover into other areas needing structure, such as discipline. Small and frequent feedings; modular components of carbohydrate, protein, and/or fat; and enhanced calorie and protein bars and liquids may be used to meet calorie and protein needs.

In the adolescent population, altered body image and peer pressure may lead to nutritional problems. One should consider the patient's current lifestyle and make as few changes as necessary to meet nutritional goals. It is also important to give the adolescent as many choices as possible to increase adherence with recommendations.

In those patients known to have adequate intake of calories and protein yet who continue to fall short of projected growth expectations, recombinant human growth hormone (r-hGH) may be considered. It is important to rule out uremia, acidosis, and secondary hyperparathyroidism as possible causes of the growth failure before initiating therapy.

Physical Activity

Regular physical activity should be encouraged, especially in those patients with excessive weight gain and/or high BMI. No restrictions are generally necessary, with the exception of contact sports that could cause injury to the PD catheter.

Summary

The nutrition assessment of pediatric patients uses components from the normal pediatric patient and the adult population. One component does not tell the entire story. Many pieces fit together to form a mosaic of the child's nutritional status. Families must be given the educational support to help the child receive appropriate nutrient intake. Frequent monitoring and modification of goals is imperative as their bodies grow, medical status changes, and developmental changes occur.

References

1. [Author]. Clinical practice guidelines for nutrition in chronic renal failure: Pediatric guidelines. Am J Kidney Dis 2000;35(6/2): S105–36.
2. Goldstein SL, Baronette S, Gambrell TV, et al. nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. Pediatr Nephrol 2002;17:531–34.
3. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. Hypertension 2006;47:296–308.
4. Jaradat MI, Molitoris BA. Cardiovascular disease in patients with chronic kidney disease. Semin Nephrol 2002;22(6):459–73.
5. Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB. Sevelamer hydrochloride: An effective phosphate binder in dialyzed children. Pediatr Nephrol 2003;18(12):1260–64.
6. Salusky IB, Goodman WG, Sahney S, et al. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. J Am Soc Nephrol 2005;16(8):2501–08.
7. Kuizon BD, Salusky IB. Growth retardation in children with chronic renal failure. J Bone Miner Res 1999;14(10):1680–90.
8. [Author]. Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis 2005;46(4/1): S32–38.
9. Slatopolsky E, Liapis H, Finch J. Progressive accumulation of lanthanum in the liver of normal and uremic rats. Kidney Int 2005;68(6):2809–13.
10. Spasovski GB, Sikole A, Gelev S, Masin-Spasovska J, Freemont T, Webster I, et al. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. Nephrol Dial Transplant 2006;21(8):2217–24.
11. Torres PU. Cinacalcet HCl: A novel treatment for secondary hyperparathyroidism caused by chronic kidney disease. J Ren Nutr 2006;16(3):253–58.

12. Kuizon BD, Nelson PA, Salusky IB. Tube feeding in children with end-stage renal disease. Miner Electrolyte Metab 1997;23:306–10.
13. Spinozzi NS, Nelson PA. Nutrition support in the newborn intensive care unit. J Ren Nutr 1996;6:188–97.

CHAPTER 94

Infant and Neonatal Peritoneal Dialysis

Alicia M. Neu, MD

Infants with kidney failure present a unique clinical challenge for pediatric nephrologists. Therefore, it is appropriate to address renal replacement therapy for this complicated group of patients separately. Obtaining vascular access and meeting the extracorporeal blood volume requirements needed for hemodialysis (HD) may be difficult in small infants and peritoneal dialysis (PD) is considered by many the dialytic therapy of choice in these patients. This chapter addresses some of the technical considerations for performing both acute and chronic PD in neonates and infants. In addition, a number of special issues that arise when caring for infants on maintenance PD are explored.

Acute Peritoneal Dialysis

Historically, PD has been the modality of choice in the neonate or infant with acute kidney injury. The advantages of PD over HD include the avoidance of vascular access and that PD can be performed in the face of hemodynamic instability, including following cardiac surgery. More recently, continuous renal replacement therapy has proven to be a reasonable and relatively well-tolerated option for the hemodynamically unstable infant with acute kidney injury, but this therapy also requires vascular access and frequently involves anticoagulation administration.

The major disadvantage of PD is the risk for peritonitis. In addition, PD is relatively inefficient at clearance of solute and ultrafiltration, but this can often be overcome by the use of frequent exchanges. Contraindications to performing PD include the presence of abdominal wall defects or draining abdominal wounds.

Dialysis Equipment

The success of PD for acute kidney injury relies on the placement of a reliable PD catheter. Temporary PD catheters appropriately sized for infants and neonates are commercially available

(Cook Inc., Bloomington, IN). These devices are typically placed at the bedside under local anesthesia, using the Seldinger technique. Alternatively, a single-cuff Tenckhoff catheter (Kendall, Tyco Healthcare, Mansfield, MA) may be placed surgically. Historically, catheter choice has largely been influenced by the experience at the treating center. However, a retrospective review of 59 pediatric patients (including infants) who required acute PD at a single center over a 10-year period revealed that patients receiving dialysis through a temporary catheter were significantly more likely to suffer catheter-related complications—including occlusion, leakage and infection—than those patients receiving acute dialysis by way of a Tenckhoff catheter.

After the catheter is in place, a dialysis system capable of delivering small exchange volumes is necessary. An example of a commercially available closed system is depicted in Figure 94.1 (Utah Medical Products, Midvale, UT). This system is preassembled and includes a graduated 150-mL administration burette as well as a graduated dialysate meter for measuring outflow. The total priming volume of the system is 63 mL. This system also includes an inline helical infusate warming coil. This is important because the dialysate must be warmed to body temperature in order to avoid hypotension that can occur in infants with inflow of room temperature dialysate.

Dialysate

Standard dialysis solutions containing dextrose in varying concentrations (in addition to sodium, chloride, lactate, magnesium and calcium) are available from a number of manufacturers. The critically ill infant in whom lactic acidosis is common might not tolerate exposure to lactate-containing dialysis solutions. In this situation, bicarbonate-based solutions may be used. Multichamber bicarbonate/lactate-buffered PD solutions are commercially available in Europe but not the United States. However, bicarbonate-based dialysis solutions without dextrose are commercially available in the United States—and dextrose may be added to these solutions for acute PD in the hospital setting.

Acute Dialysis Prescription

Initial fill volumes should be low, to avoid leaking around the catheter exit site and the associated risk for peritonitis. In infants, an initial fill volume of approximately 200 mL/m^2 body surface area (BSA) or 10 mL/kg may be used—increased gradually

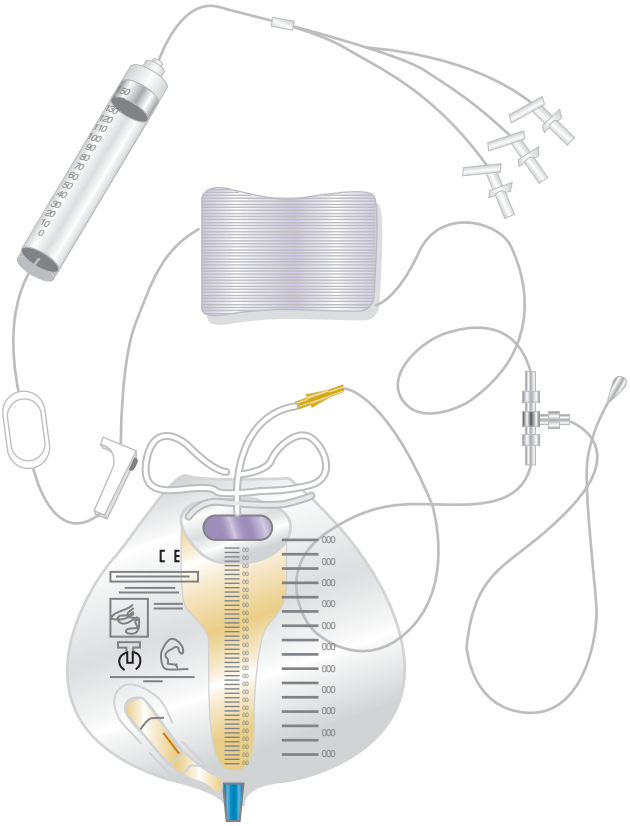


Figure 94–1

An example of a commercially available infant peritoneal dialysis set (Utah Medical Products, Midvale, UT).

after several days, if needed, with a final fill volume of no more than 1000 to 1100 mL/m^2 BSA (40–45 mL/kg). In the first 24 to 48 hours, exchanges may be performed every 30 to 60 minutes to provide the necessary clearance of solute and fluid. Careful monitoring of serum electrolytes and glucose is imperative. In particular, hyperglycemia and hypokalemia are frequently encountered with aggressive PD in infants. If significant hypokalemia develops, potassium chloride (3–4 mEq/L) may be added to the dialysis solution.

Chronic Peritoneal Dialysis

For infants who require chronic dialysis, PD is widely considered the dialysis modality of choice. Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reveal that among infants and toddlers initiating chronic dialysis in North America 96% were treated with PD. Although controlled studies comparing outcomes for infants treated with HD and PD have not been performed, there are reports of improved growth in pediatric patients treated with PD versus HD. In addition, PD allows a more flexible schedule and many patients enjoy a more liberal diet with daily PD compared to thrice-weekly HD. In addition, the issues of extracorporeal blood volume and permanent vascular access for HD remain problematic in the infant who requires chronic dialysis therapy.

Dialysis Equipment

Chronic PD catheters are available in a variety of configurations, including single or double cuff, straight or swan-neck tunnel, and a curled or straight intraperitoneal segment. Use of adult-size double-cuff catheters in infants frequently resulted in cuff extrusion and in increased risk for exit-site infection—prompting primarily use of single-cuff catheters in this population. In addition, data from NAPRTCS reveal that most infants in that registry received catheters with straight tunnels and a curled intraperitoneal segment. In recent years, catheters in appropriate lengths for infants and neonates (31–39 cm) with single and double cuffs and with straight and swan-neck tunnels have become commercially available (Kendall, Tyco Healthcare, Mansfield, MA). Given data from the NAPRTCS that reveal that time to first peritonitis is significantly longer for catheters with

two cuffs compared with one, and for swan-neck tunnels compared to straight, it is possible that use of these configurations in this population will increase.

As with older children on PD, most infants receive automated PD (APD). Only in the last several years, however, have automated cyclers been equipped to provide dialysis to patients under 10 kg. Currently, cyclers with pediatric tubing and programming can provide fill volumes as low as 30 to 60 mL (Fresenius Medical Care, Lexington, MA, and Baxter Healthcare, Deerfield, IL). Because automated cyclers will alarm when the outflow rate falls below a certain rate, very small fill volumes often result in frequent alarms during outflow—making APD impractical with fill volumes under 100 mL.

Chronic Dialysis Prescription

For infants initiating PD, an initial fill volume of 200 mL/m^2 BSA with gradual increase to a volume of approximately 1000 to 1100 mL/m^2 BSA is typically advised. It is important to determine exchange volume based on body surface area rather than weight. This is especially true in infants, as the relationship between peritoneal surface area and weight varies inversely with age. Thus, in the smallest patients an exchange volume based on weight will result in relatively small dialysate volumes and lower solute clearances.

For continuous ambulatory PD, an initial prescription should include three 3- to 5-hour daytime dwells and an overnight dwell lasting 9 to 12 hours. For APD patients, an initial prescription should include five to six 90- to 120-minute cycles plus a daytime dwell. The volume of the daytime dwell is typically half the nighttime volume, to minimize discomfort and reduce the risk of hernias. In anuric infants on APD, manual exchanges during the day may be necessary to maintain euvolemia. Alternatively, a long daytime dwell using icodextrin-containing dialysis solution (Baxter Healthcare, Deerfield, IL) may be used. However, this solution may provide less effective ultrafiltration when used in infants compared to older children.

The final prescription for an individual patient is based on the guidelines cited previously, with an appropriate adjustment based on the patient's peritoneal membrane solute transplant capacity as determined by the performance of a peritoneal equilibration test. In addition, it is recommended that intraperitoneal pressure be monitored and the fill volume adjusted to maintain this pressure below 10 cm H_2O.

Dialysis Adequacy

Previously the National Kidney Foundation's NKF-K/DOQI guidelines recommended that children on PD have measurements of urea and creatinine performed every 4 months with a minimum goal total Kt/V_{urea} between 2.0 and 2.2/week and a minimum total creatinine clearance goal between 60 and 66 L/1.73 m^2/week, depending on whether the patient was on continuous ambulatory PD, APD with a daytime dwell, or APD with a dry day. European studies in young children and infants on PD revealed that these urea clearance targets are typically easily achieved even in infants without residual renal function. However, creatinine clearance goals are rarely reached. Furthermore, reported experience in Europe demonstrated good growth with a Kt/V_{urea} >2.1 and a creatinine clearance of greater than 40 L/1.73 m^2/week.

These data led to suggestions in Europe for a minimum Kt/V_{urea} >2.5 for children under 24 months of age. For children 0 to 12 months of age, the minimum creatinine clearance goal is >40 L/1.73 m^2/week—and for children 12 to 24 months of age the goal is >50 L/1.73 m^2/week. However, the recently updated NKF-K/DOQI guidelines have lowered the minimum Kt/V_{urea} goal to 1.8 for all children on PD.

Growth and Nutrition

In the normal infant, growth and cognitive development occur at a staggering pace in the first few years of life. It is not unexpected, therefore, that the development of chronic kidney disease in infancy may have a profound negative effect on both. To maximize growth and development, it is imperative that the nutritional status of the infant with chronic kidney disease be meticulously monitored. The energy intake for infants on dialysis should be at least 100% of the recommended daily allowance (RDA) for healthy children.

Glucose absorption from peritoneal dialysate should be taken into account because it can contribute 10 to 20% of the total caloric intake per day. Dietary protein requirements are higher for infants on PD than the recommended RDA for healthy children. Current NKF-K/DOQI guidelines recommend an initial dietary protein intake based on the RDA for chronologic age and an additional increment of 0.4 g/kg/day. Unfortunately, many infants with chronic kidney disease will suffer from uremia-induced anorexia, decreased gastric and intestinal motility, and/or gastroesophageal reflux—which may impair voluntary intake of adequate calories and protein.

It is generally held that any patient who is not growing normally and who is unable or unwilling to consume =100% of the RDA for energy intake should be considered a candidate for supplemental tube feedings. Good results with minimal complications have been reported with each of the approaches to tube feedings (i.e., nasogastric tube, gastrostomy tube, and gastrostomy button). If tube feedings are to be given, oral stimulation should be provided at every opportunity and oral intake should continue to be offered.

Other complications of chronic kidney disease (including metabolic acidosis, anemia, renal osteodystrophy, and chronic dehydration) should be aggressively treated to maximize growth. In addition, recombinant human growth hormone therapy should be considered in infants whose length is more than 2 standard deviations below the mean for age or whose growth velocity is more than 2 standard deviations below the mean for age.

Other nutritional problems particular to infants on PD include hyponatremia secondary to dialysate losses of sodium, and sodium supplementation may be necessary. Likewise, losses of phosphorous by the dialysate route can lead to hypophosphatemia—especially when the patient is also on a low-phosphate infant formula. Vitamin supplementation should include water-soluble vitamins and folic acid without fluoride.

Infection

Infection is a significant complication of long-term PD, and infants appear to be especially prone to both peritonitis and sepsis. Although it has been shown that many infants on PD may develop hypogammaglobulinemia, there is no straightforward relationship between low serum IgG and risk for either peritonitis or sepsis in these patients. In addition, most infants on PD are able to respond to and maintain protective antibody levels against routine immunizations, even in the face of low total serum IgG. Nevertheless, because an association between hypogammaglobulinemia and sepsis has by no means been excluded, careful monitoring of the immune status of infants on PD is probably warranted.

Infants on PD should receive all standard childhood immunizations as recommended by the American Academy of Pediatrics, including live viral vaccines. Measurement of serum immunoglobulins as well as antibody levels or titers to these routine childhood immunizations should be considered during

the first few years of life. At present, there are no data to support the routine use of prophylactic immunoglobulin in all infants on PD. However, it may be prudent to consider immunoglobulin therapy in patients with hypogammaglobulinemia who also do not produce protective levels of antibody.

Outcome

Historically, infants who developed ESRD in the first months of life fared poorly—with profound neurologic impairment and high mortality rates. With recent advances in the care of infants on PD (including aggressive nutritional delivery, elimination of aluminum containing phosphate binders, and early intervention with dialysis), cognitive development outcomes have

Figure 94–2

Percent patient survival by age at dialysis initiation: 0–23 months of age, 2–5 years of age, 6–12 years of age, and >12 years of age. *(Reprinted from the North American Pediatric Renal Transplant Cooperative Study 2005 Annual Report, The EMMES Corporation, Potomac, Maryland, web.*emmes.com.*)*

improved. Specifically, in a study of 19 school-age children who required dialysis in early infancy 94% attended school full-time and in age-appropriate classrooms. However, the risk for impairment still exists and further study is needed to develop treatment strategies that optimize neurocognitive development.

In addition, mortality rates remain significantly higher for infants than for older children on PD (Figure 94.2). Studies have linked the presence of anuria and nonrenal abnormalities (such as pulmonary hypoplasia, cardiovascular, or central nervous system disease) with an increased risk for mortality among infants on PD. It is hoped that these and future data will allow identification of patients at high risk for mortality and ultimately allow development of more successful treatment strategies.

Recommended Reading

Chanda V, Warady BA, Blowey DL, et al. Tenckhoff catheters prove superior to Cook catheters in pediatric acute peritoneal dialysis. Am J Kidney Dis 2000;35:1111–16.

A retrospective study comparing outcomes with acute versus Tenckhoff catheters in pediatric patients requiring acute peritoneal dialysis.

Holmberg C, Rönnholm K. Maintenance peritoneal dialysis during infancy. In Warady BA, Schaefer FS, Fine RN, Alexander SR (eds.). *Pediatric Dialysis*. Bodmin: Kluwer Academic Publishers 2004:209–91.

Provides a comprehensive review of the complicated clinical issues encountered in the care of infants on dialysis.

Hölttä T, Rönnholm K, Jalanko H. Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control. Pediatr Nephrol 2000;14:889–97.

Retrospective review of adequacy and clinical outcomes in a cohort of children on peritoneal dialysis.

Neu AM, Warady BA. Special considerations in the care of the infant CAPD/CCPD patient. In Fine RN, Alexander SR, Warady BA (eds.). *CAPD/CCPD in Children, Second Edition*. Boston: Kluwer Academic Publishers 1998:169–79.

Provides a detailed review of the clinical issues encountered in the care of infants on peritoneal dialysis.

North American Pediatric Renal Transplant Cooperative Study 2005 Annual Report. The EMMES Corporation, Potomac, Maryland, *web.emmes.com*.

Large multicenter database containing demographic and clinical characteristics and clinical outcomes on more than 5600 pediatric patients treated with dialysis in North America since 1994.

Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol 1999;13:759–65.

Study evaluating neurologic outcomes in children requiring renal replacement therapy in early infancy.

Wood EG, Hand M, Briscoe DM, et al. Risk factors for mortality in infants and young children on dialysis. Am J Kidney Dis 2001;37:573–79.

Multicenter study evaluating risk factors for mortality in infants on dialysis.

CHAPTER 95

Dialysis in Inborn Errors of Metabolism

Franz Schaefer, MD

Inherited dysfunctions of amino and organic acid metabolism usually become manifest in the early neonatal period by neurologic abnormalities such as irritability, somnolence, and eventually coma. In urea cycle defects or in organic acidemias, these symptoms are mainly due to excessive hyperammonemia—which may cause irreversible neuronal damage. In disorders of branched-chain amino acid metabolism, such as maple syrup urine disease (MSUD), prolonged accumulation of leucine and/or its metabolites (2-ketoisocaproic acid) may lead to severe permanent neurotoxicity.

During the past two decades, the prognosis of these previously lethal disorders has been considerably improved by the introduction of several therapeutical principles. The de novo synthesis of toxic metabolites can be suppressed by high calorie supply inducing a state of anabolism and reduced proteolysis. The physiologic or alternative pathway substrates lacking in hyperammonemic disorders can be infused to reduce ammonium concentrations. In MSUD, a diet low in branched-chain amino acids can be instituted. Finally, and most importantly, the accumulation of the small water-soluble neurotoxic metabolites can be rapidly reversed by dialytic removal. Because the brain damage induced by neurotoxic metabolites is directly correlated with the duration of exposure to neurotoxic metabolites, neonatal metabolic crises are considered emergency dialysis indications requiring use of the most readily available and effective dialysis modality.

A large body of experimental and clinical evidence suggests that the clearance achievable by peritoneal dialysis (PD) is much less than that obtained by hemodialysis (HD). Because technological advances have improved the suitability of extracorporeal blood purification techniques to neonates, they are now the therapy of choice in appropriately equipped and experienced centers.

Techniques of Metabolite Removal

In patients with MSUD, the low endogenous clearance of leucine and other branched-chain keto and amino acids (BCAA) is

insufficient to reverse the accumulation of BCAA that occurs during catabolic states. BCAA clearances several-fold above the endogenous disposal rate are achieved with PD, and continuous extracorporeal blood purification techniques yield even two- to threefold greater metabolite removal rates than PD. Although continuous hemofiltration, HD, and hemodiafiltration have been shown to be feasible, a significant reduction of dialysis time requirements in comparison to PD has been demonstrated for HD only.

In hyperammonemic metabolic crises, experimental evidence suggests that ammonium is more efficiently removed by extracorporeal techniques than by PD. Clinical studies have shown that normalization of blood ammonium levels usually cannot be achieved in less than 24 hours by PD, and dialysis is typically required for 2 to 5 days. Continuous hemofiltration usually reduces blood ammonium concentrations by 90% within 10 to 12 hours. The most efficient toxin removal is clearly achieved by HD. The superiority of HD over hemofiltration is evident from the fact that ammonium clearance with hemofiltration cannot be greater, and is usually considerably less than, the plasma flow rate through the dialyzer.

In contrast, an ammonium clearance close to dialyzer blood flow can be achieved by HD, as shown in Figure 95.1. Inter-

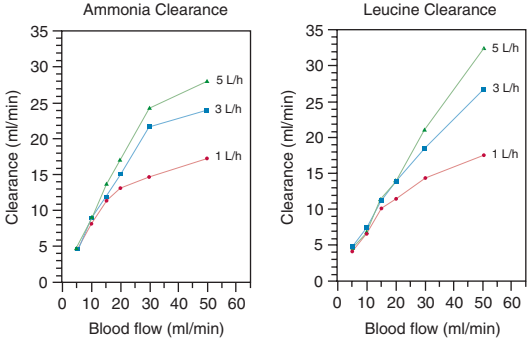


Figure 95–1

Effect of blood and dialysate flow rate on ammonium and leucine removal by HD in a neonatal setting.

mittent HD reliably decreases blood ammonium concentrations by 75% within 3 to 4 hours. However, repeated HD sessions are frequently required due to residual or rebound hyperammonemia. Moreover, the use of intermittent HD in neonates and young infants is usually limited by the size of the extracorporeal volume and the rapid depletion of other small solutes such as phosphate. Hence, continuous venovenous HD (CVVHD) should be considered the treatment of choice until complete normalization of blood ammonium levels has been achieved. The routine use of this technique has become feasible with the advent of extracorporeal devices adapted for use in small children.

Extracorporeal Blood Purification

Dialysis Equipment

Catheter

The choice of catheter has to draw a balance between the aim of achieving an adequate blood flow and the risks of catheter insertion in a newborn. Ideally, a blood flow of 150 mL/minute/m² should be attained (i.e., 30–35 mL/minute in an average neonate). This goal can be reached by inserting a 6.5 French double-lumen catheter (e.g., Gambro 6.5 Fr, 3.5 inch), typically into a femoral vein. This catheter provides excellent blood flow rates (i.e., 30–40 mL/minute), but insertion may be difficult in small neonates. Alternatively, two 5 French single-lumen catheters (e.g., Medcomp 5 Fr, 3.0 inch) can be inserted in different femoral or jugular veins. Whereas umbilical catheters are unsuitable for dialysis because of their high flow resistance, 6.5 French HD catheters have occasionally been inserted into an umbilical vessel in neonates within the first few postnatal days.

Dialyzer

Polysulfone dialyzers are preferred because of their superior biocompatibility and lower anticoagulation requirements. The surface of the dialyzer membrane should approximately match the body surface area of the patient. In neonates, we have had excellent experience with the Spiraflo HFT02 (Bellco, Mirandola, Italy) and recently the FX-paed (Fresenius Medical Care, Bad Homburg, Germany) filters, which have fill volumes of 19 to 24 mL at surface areas fo about 0.24 m². In larger infants, the Fresenius F3 (28-mL fill volume, 0.4 m² surface area) is recommended (Fresenius Medical Care, Bad Homburg, Germany).

Dialysis Device and Tubing

In principle, emergency dialysis in neonates with inborn errors of metabolism can be performed using adjusted tubing systems on standard HD machines—such as the neonatal tubing for the Fresenius 2008 or 4008 devices. These tubing sets have a fill volume of 47 mL. Even when used with a neonatal dialyzer such as the Spiraflo HFT02, the total volume of the extracorporeal system is 72 mL—which is more than 10% of the estimated blood volume of an average neonate. Another disadvantage is that an incorrect blood flow rate is displayed when small-volume neonatal tubes are used. Moreover, due to the fixed high dialysate flow rate of 500 mL/minute with the 2008 device (300 mL/minute with the 4008 machine) critical depletions of phosphate and other solutes not present in the dialysis fluid may occur with prolonged use of this technique.

Devices designed for continuous renal replacement treatment are better suited to acute dialysis in children, such as the BM25 (Edwards Lifesciences) and the PRISMA (Gambro). The BM25 consists of an integrated system of blood pump and two volumetrically controlled peristaltic pumps for filtration and substitution, which can also be used for dialysis. We routinely use the BM25 for continuous venovenous HD in neonatal metabolic crises (see material following). The main advantages of the system are the small volume of the extracorporeal system (tubing volume 29 mL), accurate and fine-scaled setting of blood flow even in the low range typical for neonatal dialysis, precise control and variable choice of dialysate flow, and the mobile reverse osmosis–independent setup of the machine.

The BM25 permits dialysate flow rates of up to 9 L per hour and accommodates the turnover of 15 L of dialysis fluid before bags need to be changed. The PRISMA device has similar properties with respect to the blood circuit, but the efficacy of the system for CVVHD is limited by the maximum dialysate turnover of 2 L per hour. New extracorporeal dialysis devices with enhanced electronic features have recently become available. Both the Aquarius (Edwards Lifesciences) and the PRISMAFLEX (Gambro) device have the potential to further improve the safety and efficacy of extracorporeal blood purification in neonates once adaptations for use in neonates (including appropriate tubing sizes) are provided.

Management Guidelines

To achieve maximal treatment efficacy, blood flow should be set to the maximal value operated by the machine without

alarms—which should be set as wide as possible. The dialysate flow rate required to achieve maximal clearance is determined by the blood flow achieved. In a neonatal dialysis simulation study using the BM25 machine and a Spiraflo HFT02 filter, we found a linear relationship between blood flow and ammonium and leucine clearance up to the maximal blood flow rate usually achievable in neonates (i.e., 30 mL/minute)—with a dialysate flow rate of 5 L/hour (Figure 95.1).

As a rule of thumb, extraction of these metabolites is maximal when dialysate flow exceeds blood flow by at least a factor of 2. This target can easily be achieved by passing bag dialysis fluid along the filter, utilizing the filtration/substitution pump system of a pediatric CRRT (continuous renal replacement therapy) device such as the BM25. The dialysis fluid should contain glucose and potassium at plasma concentrations. During treatment, efficacy can be monitored by measuring metabolite clearance using the formula

$$\text{Clearance (mL/min)} = \text{blood flow (mL/min)} * (C_{pre} - C_{post})/C_{pre},$$

where C_{pre} and C_{post} are the pre- and postdialyzer metabolite blood concentrations. The major complications to consider when dialyzing neonates or small infants with metabolic crises are clotting of the extracorporeal system and hemodynamic instability, each of which can cause treatment interruptions and hence hazardous delays in the removal of toxic metabolites.

To prevent clotting, heparin should be administered at a dose sufficient to increase the activated clotting time to 120 to 150 seconds. We use an initial bolus of 1500 IU/m² followed by continuous infusion of 300 to 600 IU/m²/hour. Anticoagulation should be monitored by hourly ACT measurements. Coagulation requirements are inversely related to the blood flow rate.

Hypotensive episodes and osmotic dysequilibrium occur less frequently than in neonates and infants dialyzed for renal failure because dialysis is usually isovolemic and the accumulated metabolites are osmotically less active than the urea accumulated in uremia. However, hemodynamic instability is common in patients with prolonged duration of hyperammonemia due to urea cycle disorders. This can be minimized by prefilling the system with blood and using appropriate extracorporeal tubing and dialyzer membranes with a total fill volume as small as 35 mL.

Generally, heating of dialysis fluids and bloodlines is necessary in neonatal dialysis to prevent excessive hypothermia. On the other hand, a decrease in plasma ammonia levels was anecdotally

reported in a single infant apparently refractory to hemofiltration when body temperature was cooled to 34°C. This effect was attributed to a slowing of metabolic ammonia generation. However, because no data on hemofiltration efficiency were given in the report, the usefulness of therapeutic hypothermia relative to efficient toxin removal is difficult to judge.

HD should be continued until clinical improvement and complete normalization of the accumulated metabolite levels (ammonium, leucine) have been achieved. Because unknown amounts of pharmacologic scavengers are cleared by a highly efficient extracorporal blood purification, supplemental doses of these substances may be required during or after intermittent HD.

Peritoneal Dialysis

Due to the lower toxin clearance, PD is generally not recommended and should only be considered when extracorporeal techniques are prohibited by vital contraindications.

Catheter

Stylet catheters can be placed immediately but bear a high risk for the subsequent development of leakage or outflow obstruction. Catheter leakage requires a reduction of dwell volumes or catheter replacement, and outflow obstruction may result in an increased intraperitoneal residual volume—both causing a further decrease of the peritoneal clearance. Thus, careful catheter insertion is a prerequisite for successful PD and a slight delay for surgical implantation of a single-cuff Tenckhoff catheter may be justified.

Dialysis Prescription

Prescription of fill volumes must be balanced between maximizing toxin removal and adverse effects of increased intraperitoneal pressure (respiratory problems, catheter leakage). A measure of 15 to 30 mL/kg body weight appears to be an adequate compromise. Short dwell times (30–60 minutes) increase metabolite clearance but also ultrafiltration rates. The use of bicarbonate-buffered dialysate solutions, now commercially available, may help to stabilize acid-base balance and prevent lactacidosis in neonates.

Recommended Reading

Reviews on Most Common Inborn Errors of Metabolism Causing Metabolic Crises

Brusilow SW, Maestri NE. Urea cycle disorders: Diagnosis, pathophysiology, and therapy. Adv Pediatr 1996;43:127–70.

Chuang DT, Shih VE. Disorders of branched chain amino acid and keto acid metabolism. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds.), *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill 1995:1239–77.

Comparisons of Treatment Modalities for Metabolic Crises

Picca S, Dionisi-Vici C, Abeni D, Pastore A, Rizzo C, Orzalesi M, et al. Extracorporeal dialysis in neonatal hyperammonemia: Modalities and prognostic indicators. Pediatr Nephrol 2001;16:862–67.

Ring E, Zobel G, Stöckler S. Clearance of toxic metabolites during therapy for inborn errors of metabolism. J Pediatr 1990;117:349–50.

Rutledge SL, Havens PL, Haymond MW, McLean RH, Kan JS, Brusilow SW. Neonatal hemodialysis: Effective therapy for the encephalopathy of inborn errors of metabolism. J Pediatr 1990;116:125–28.

Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant 1999;14:910–18.

Wiegand C, Thompson T, Bock GH, Mathis RK, Kjellstrand CM, Mauer SM. The management of life-threatening hyperammonemia: A comparison of several therapeutic modalities. J Pediatr 1980;96:142–44.

Large Case Series of Neonatal and Young Infant Hemodialysis

Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int 1994;45:903–06.

CHAPTER 96

Psychosocial Adjustment and Treatment of Children and Adolescents with ESRD

Erik Qvist, MD; Kai Rönnholm, MD; and Christer Holmberg, MD

Introduction

Psychosocial adjustment in end-stage renal disease (ESRD) can be equated with adjustment to any major chronic disease in childhood. Psychiatric morbidity (e.g., severe chronic depression, anxiety, and so on) in the child or in the family may exist independently of ESRD and will certainly not be relieved by its presence or ease adjustment. This needs special attention and expertise that we have to be aware of and capable to identify, but it will not be discussed here.

This chapter focuses on adjustment as a part of normal adjustment to chronic disease and treatment strategies used to facilitate adjustment in children with chronic renal failure. Psychosocial adjustment and well-being of children and their families are important in their own right, but they also have a decisive impact on treatment adherence and thus on physical health, morbidity, and even mortality.

Diagnostic Considerations

Psychosocial adjustment is affected by the severity of the disease. A chronic disease in childhood, particularly a failure of a major organ such as the kidney, may lead to permanent disabilities. Impaired cognitive functioning also affects the child's competence and coping strategies. There has been much progress in the management of children with ESRD, and the outcome (particularly in infants and toddlers) has remarkably improved—and this will also have an impact on adjustment. However, there is considerable individual variation in outcome in cases facing extensive medical problems. This is due to the particular child's and family's coping strategies. The child and the family are also dependent on the social environment and network—consisting of health care

professionals, a peer group of patients and their parents, relatives, and friends.

Adjustment to ESRD is usually facilitated by the fact that the disease progression is mostly slow. There is time to prepare the patient and the family for forthcoming events. On the contrary, a rapid disease progression in acute renal failure is associated with a state of shock—with little opportunity to enhance adjustment (at least in the beginning).

Age at onset of ESRD is crucial. Children with a severe renal disease from birth or early age, affecting the developing brain, are vulnerable to neurological complications. Additional disabilities related to congenital renal diseases are also common. ESRD may also affect cognitive performance in older children and adults, but the possibility of irreversible damage is far less than for infants or toddlers.

The problems related to adjustment also differ with age. An infant or small child is totally reliant on the adjustment of its family. Problems in the relationship with parents or caregivers influence childhood, but the importance of other relationships and individual coping strategies increases in adolescence. Parents and caregivers may be more affected than their children by the anxiety related to a life-threatening disease. Fear of death or the possibility of losing a child is a great stress, although seldom voiced. The awareness of the hazards related to the disease and the treatment may easily lead to overprotection of the child. Avoidance of age-appropriate activities, lack of independence, and failure to place proper limits on behavior impair normal development. The imbalance in family dynamics also involves siblings.

Teenagers do not like to differ from others. Growth problems and delayed puberty are common in ESRD. Adolescence is a sensitive period and even a healthy teenager has to adjust to a changing body image and tackle the fear of not being accepted. A teenager, living in the moment, may be more concerned about his or her body image than about suffering from a serious disease. It takes a lot of self-confidence to show dialysis catheters, scars, or anything that reminds the child or adolescent he or she is different from others. It may be an obstacle to take friends home for a visit because of the questions raised after seeing the dialysis equipment. Nonadherence with medication because of visible side effects has also been shown in many studies, even at the expense of increased mortality. Health professionals have to be aware that medical priority is perhaps not always the patient's main concern.

The burden and stress connected with ESRD are substantial. This is particularly obvious for those involved with infants and small children on dialysis. Despite a great deal of medical and professional assistance, it is parents and caregivers who are involved in a practical everyday sense with treatment around the clock throughout the year. There is limited time to pursue a relationship or to be off-duty. The financial burden of having a child with a chronic illness may also be substantial. A severely ill child may also raise anxiety in the environment.

Problems may not easily be shared with friends and relatives who are not familiar with major illnesses in general, and with ESRD in particular. To spare themselves additional stress, parents often decide to reveal very little of their problems to people outside closest family members. The result may be that the family is left very alone with the burden. It is important that the responsibility rest with more than one person in the family and it is recommended that there be a support person outside the immediate family who can also perform the treatment.

The parents' ambitions to manage may add additional stress. The child's nutrition is a major focus and the nausea and loss of appetite connected with uremia requires considerable effort to overcome. Administration of a nasogastric tube may be perceived as a setback or distrust of the parent's abilities. A child with ESRD may have been regarded as any healthy child, but the presence of the tube will definitively be a reminder that the child is ill.

Psychosocial adjustment may affect the medical or clinical outcome of a treatment or a disease. Nonadherence to medical surveillance and to the prescribed medication is common. It is estimated that up to 50% of patients with chronic diseases may have difficulties in following a prescribed regimen to an extent that such behavior may have some influence on the clinical outcome. ESRD patients are no exception. Such difficulties include adhering to the dialysis regimen, to fluid and diet restrictions, and to medication schedules.

It may also be natural for the parents or the adolescent to actively forget and deny the hard times they have lived through. An older child or teenager who commenced treatment for ESRD as an infant does not have a conception of his or her earliest disease history. The lack of disease history coupled with denial may contribute to poor adherence. However, people are usually very interested in their history. This reflection may also put the adolescent's perception in an appropriate perspec-

tive, increase understanding, and thus even enhance adjustment and adherence.

Treatment

Working with children and families with chronic diseases requires a multidisciplinary approach. The medical decisions lay on the pediatric nephrologists, but during clinical visits significant time is spent with nurses and many topics related to adjustment and treatment are never shared with doctors. It is important that a psychologist (or any mental health professional) be part of the health care team from the beginning. This will enhance the patient's and family's acceptance dealing with emotional and psychiatric aspects of the treatment. A psychosocial case conference at regular intervals is needed to highlight possible adjustment problems and delineate possible treatment strategies to resolve them.

Communication is facilitated if families are given sufficient written material explaining the basics of ESRD, and the need for medical investigations and interventions. It is also beneficial to provide families information on the forthcoming transplantation. Patients and their parents may sometimes have an unrealistic view of the forthcoming transplantation. Although overall well-being is greatly improved, the transition to a kidney transplant recipient does not cure the underlying disease leading to ESRD. Patients require lifelong medication and follow-up after kidney transplantation. The temptation to neglect this fact may lead to nonadherence and a feeling of setback and depression.

Pain is never justified but common to medical interventions. Small children lacking comprehension of medical procedures and their usefulness can easily develop a tremendous fear for everything related to the treatment. Every measure should be taken to diminish pain related to interventions.

To start a home-based dialysis program is highly encouraged. It makes the patients and the families more responsible for their own treatment, with a higher degree of freedom and independence. However, it takes a lot of effort to be familiar with all of the technical and medical details involved. Fortunately, the equipment is today more user friendly and people are in general accepting of technical devices all around them. A home visit from a dialysis nurse is recommended to solve the practical details related to treatment, both before the treatment is commenced and after the patient is discharged from the hospital.

It is important that both parents, if available, are involved and responsible for the treatment. It is recommended that another third party be familiar with the treatment as well, to give parents the possibility of a respite.

Full-time school attendance in combination with a tight dialysis schedule is difficult. However, regular school attendance is one of the main outcome measures of how well children are adjusted and is comparable to employment figures for adults undergoing the same medical scenario. It is of great importance that we do everything to adjust treatment and follow-up schedules to facilitate school attendance. This includes evaluating the child's cognitive abilities, neuropsychological testing, and so on to identify possible needs of remedial teaching and special school services that are required.

Possible problems with friends and schoolmates or a fear of being picked on are most often relieved if knowledge about ESRD and dialysis is shared with peers. A visit to class by a dialysis nurse or someone from the renal team who provides information is usually received favorably. Difficult concepts can be explained at an age-appropriate level, which increases understanding and acceptance of the patient's situation.

There are many organizations, both national and local, that arrange peer group meetings, courses, and educational activities for renal patients and their families. The patients and their families should be encouraged to take advantage of these activities as much as possible. This support from a peer group should be incorporated into clinical visits. Children and their families can be put together during hospital visits to share thoughts and experience. Many things the children or families are reluctant to ask the health professionals may be discussed with other patients and families.

A chronic disease and its treatment may also result in a substantial financial burden to the family. Although the medical aspects and patient well-being are of paramount importance for everyone, a continuous focus on financial issues may impair adjustment and adherence. It is important for the health care team to delineate the family's financial status and Social Security qualifications.

As the children grow up, they should receive more and more responsibility for their own treatment—and should be involved in the decision-making process according to their maturity. Preadolescents (approximately 10 years of age and older) should be encouraged to talk to nephrologists and personnel without parents being present during hospitalizations and outpatient visits.

A list of topics to be discussed with adolescents is helpful on these visits (Table 96.1). The patient receives the list in advance and feels free to pick up any item randomly for discussion and is reassured that even sensitive issues will be discussed.

There is often a feeling of being left alone when children and their families are discharged from the care of a pediatric nephrologist. This should not be seen as distrust of adult caregivers, but more as a reflection of how the transition into adulthood has been handled by the pediatric staff. It is also

Table 96–1

Issues to Discuss with Adolescents/Others with Renal Failure After Transplantation and at Outpatient Visits

- Understanding the disease and knowledge of kidney function and ESRD
- Uremia
  - Diet
  - Medication
- Responsibility of drug administration (who, when, and why)
- Dialysis
  - Peritoneal dialysis
  - Hemodialysis
- Transplantation and the time after transplantation
- Laboratory tests and what they mean (monitoring, disease control)
- Radiological investigations and what they mean
- Biopsies
- Follow-up
  - Outpatient
  - Ward
- Infections
- Vaccinations and traveling
- Life expectancy
- Alcohol, smoking, and drugs
- Making acquaintance with adolescent gynecologist and psychiatrist
- Information of peer and interest group activities, courses, and programs
- Dating, building up a family
- Sex life, prevention, and pregnancy
- Hobbies and sports
- Study and vocational counseling
- School enrollment and joining the military
- Transition from pediatric to adult clinics

a reflection of breaking up a relationship between the patient and the personnel that has developed in some cases for two decades. This transition concept has to be started a long time before the actual transition occurs to make it as smooth as possible. The actual transition should occur when the adolescent has the capability to function as an adult, rather than at a fixed age.

Summary

Health professionals are often impressed how nicely children and their families suffering from ESRD adjust to the demanding treatment. Our task is to support this adjustment and the children's and families' coping strategies. Parents who are satisfied with the medical treatment and the health professionals generally cope well. Adjustment is important for its own sake and for the well-being of patients, but maladjustment and nonadherence have significant medical implications that increase morbidity, mortality, and health care expense.

Recommended Reading

Fielding D, Brownbridge G. Factors related to psychosocial adjustment in children with end-stage renal failure. Pediatr Nephrol 1999;13(9):766–70.
This is one example of a few studies covering risk factors related to inferior adjustment in children with ESRD.
Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev 2003;29(1):55–61.
This article is one example of studies showing that improvement of ESRD treatment has led to better developmental and psychosocial outcome in children with the highest risk for inferior outcome (i.e., suffering from ESRD as infants).
Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(5):487–97.
An extensive review that also has implications for forms of adherence other than just medication.
Soliday E, Kool E, Lande MB. Psychosocial adjustment in children with kidney disease. J Pediatr Psychol 2000;25(2):93–103.
This study compares healthy children with children suffering from kidney disease and underlines the importance of adjustment of the family for a better psychosocial outcome.
Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. J Child Psychol Psychiatry 1998;39(1):29–46.
This is a comprehensive review of the numerous factors affecting a child's adjustment to chronic physical disorders.
Warady BA, Alexander SR, Watkins S, Kohaut E, Harmon WE. Optimal care of the pediatric end-stage renal disease patient on dialysis. Am J Kidney Dis 1999;33(3):567–83.

This is an article that includes guidelines and recommendations of the American Society of Pediatric Nephrology for optimal care of children with ESRD, including rehabilitation and psychosocial adjustment.

Yeo M, Sawyer S. Chronic illness and disability BMJ 2005;330(7493):721–23.

This is a focused review of chronic illness and disability in adolescence. The article also includes recommendations for improving adherence and transition of care to adult health services.

CHAPTER 97

Growth in Children with End-Stage Renal Disease

Steven J. Wassner, MD

Growth is the end result of a complex interplay of nutritional, metabolic, and hormonal forces. Whereas both adults and children with end-stage renal disease (ESRD) experience the same metabolic derangements, in children growth is also affected. Now that survival for children with ESRD is the rule, attention must turn to improving the child's quality of life and ensuring that they achieve their appropriate physical, mental, intellectual, and social potential.

There are both psychological and physical benefits to achieving normal stature. Studies suggest that severe short stature decreases a person's self-image and self-confidence. Taller individuals are seen by others as more competent, and in business surveys increased height is associated with increased earning power. Children with ESRD and significant short stature have an increased risk of both hospitalization and death compared to children of normal height with ESRD—although to date there is no evidence of causation nor direct proof that improving statural growth alters these risks.

Measurement of Growth

In children over 3 years who can stand unaided, height is best measured in centimeters (to the nearest 0.1 cm) using a stationary wall stadiometer. In infants, supine measurements using a sliding-block measuring device should be used. Weight should be determined using a balance beam or electronic scale. Between 2 and 3 years of age, either method is acceptable. Careful measurement of the head circumference using either a fiberglass or steel tape is particularly important in infants with renal failure. Bone age should be determined at 6- to 12-month intervals.

For infants, growth should be assessed at 1-month intervals; for children, at 3-month intervals. In addition to recording the data for height, weight, and head circumference, it is useful to express this information graphically on standard growth charts. Particularly for children with long-standing renal disease, it

is likely that both height and weight will be significantly below normal for chronologic age. Frequently, bone age is also delayed—and some of the disparity between height and chronologic age will be eliminated by plotting height or weight versus bone age. Recent publication of age-/sex-appropriate standards for body mass index (BMI) should allow this measurement to become part of the routine assessment of all patients and should replace the use of weight/height ratios, which are only helpful prior to puberty. A determination that the BMI percentile is decreasing or is less than the 5th percentile requires prompt nutritional assessment and treatment. Conversely, the institution of peritoneal dialysis or renal transplantation can be associated with rapid weight gains and a significant increase in BMI.

For North American infants and children, current growth standards were published in 2000 by the National Center for Health Statistics based on the most recent National Health and Nutrition Examination Study (NHANES) III data. The charts and data are available at *http://www.cdc.gov/growthcharts/* (and programs utilizing the data for the calculation of growth parameters are also available for handheld organizers). The best method for assessing growth, either between the same individual at different ages or between individuals, is through the calculation of standard deviation score (SDS) or Z scores. For any value, such as height or weight, this was originally defined as

$$\text{Z score} = (\text{patient's value} - \text{mean value})/\text{SD of the mean.}$$

Current statistical methods assign three parameters (L, M, and S) based on the individual's age and sex, which are used to directly calculate the Z score. The L, M and S values are available at the same web site as the growth charts. Significant increases in SDS (=1 SDS) imply accelerated ("catch-up") growth, whereas decreases in the SDS reflect losses relative to the normal population.

Use of SDS is important for two reasons. First, it allows accurate assessment of children who fall below the 5th or 3rd percentile on standard growth charts. Second, it allows reporting and comparison between different age groups. Other reporting

---

[The L, M, and S constants are, respectively, the power of the Box-Cox transformation; the median value; and the coefficient of variation. For any given value X the related standard deviation score equals $(((X/M)L) - 1)/(L*S)$. For example, for a boy aged 6 years with a height of 110 cm at age 72 months, the appropriate values are L = 1.137443, M = 115.6609, and S = 0.043673. The SDS is therefore $(((110/115.6609)1.137443) - 1)/1.137443*.043673) = -1.12$.]

measures (such as centimeters grown, percentiles, or percent growth for age) are not normalized and should not be used to report grouped data.

In the first and second year of life, normal infants grow approximately 25 and 15 cm, respectively. Growth rates as high as 80% of normal, although numerically impressive, are quite poor and would still leave a boy at –2.27 SDS for height at the end of the first year. For this reason, particularly in infancy, determination of one additional parameter (the height velocity SDS) is critical because growth velocity will decrease before height SDS becomes abnormal.

For children between 3 years of age and the onset of puberty, height increases an average of 5 to 6 cm/year. Whereas growth velocity measurements are best taken a full year apart, in normally growing North American children there is no seasonal variation noted when height measurements are performed at 6-month intervals.

Growth Prior to End-Stage Renal Disease

At birth, infants with congenital causes of renal failure are on average smaller than expected (mean –1 SDS but worse than –2 SDS in 20%)—and thus at least part of their growth failure is intrauterine. Linear growth and weight gain are particularly problematic during the first 6 months of life, when multiple factors (including poor nutritional intake and abnormal urinary losses) may combine to severely limit growth. There is wide agreement that infants with significant renal impairment grow poorly. During the first 6 months of life they may lose as much as 0.4 to 0.6 height SDS/month of life. Children with congenital disease or those who develop renal failure early in life have a shorter final height than those children whose renal disease begins later.

The most effective intervention is seen when a previously untreated child first begins therapy. In these children, correction of the numerous metabolic problems evident upon presentation is often associated with improvements in the child's state of well-being, the decline in growth rate is halted, and growth SDS often improve. Thereafter, even though therapy is continued growth rates stabilize and further catch-up growth is uncommon. The degree of growth retardation is roughly related to the degree of renal insufficiency, but significant growth failure can be present even in children whose calculated creatinine clearance (Ccr) is greater than 50 mL/minute/1.73 m^2.

Although some reports suggest that the pubertal growth spurt is normal in ESRD, most authorities believe that it appears at a later age than normal; that peak height velocities are decreased; and that the duration is shortened.

It is unclear how long normal growth rates can be maintained in the face of declining renal function. Again, this is of greatest concern during infancy—when growth rates should be highest. In fact, the ability to maintain normal growth rates at low levels of glomerular filtration rate (GFR) may be different at different ages. Currently, the best results reported suggest that in infants GFRs as low as 10 to 15% of normal may be compatible with maintenance of normal heights (>–2 SDS). However, even in well-cared-for patients heights cluster between –2 and 0 SDS—with height SDS averaging –1.4 SDS for the entire cohort.

Growth on Dialysis

Growth rates on dialysis appear to depend on the type of dialysis employed and the child's age. The mean height deficit of children at the start of dialysis is approximately –1.7 SDS, with younger children being more severely affected. For children receiving hemodialysis there is a decline in average height SDS for each year of dialysis. Children who start dialysis with better height SDS grow less well than previously and lose SDS, whereas children with initially poor height SDS remain at those levels. Children on hemodialysis continue to lose approximately 0.2 height SDS/year of dialysis. The pubertal growth spurt is diminished in velocity, and its onset is appropriate for bone age as opposed to chronologic age. On the other hand, growth may continue past age 20, with several centimeters added to final height.

For infants treated with continuous ambulatory peritoneal dialysis–continuous cycling peritoneal dialysis (CAPD/CCPD), the available data appear more promising. Height loss is slightly less for these children, and some studies report that on average they maintain their height SDS. It should be noted, however, that just maintaining the same height SDS is associated with slower-than-average growth velocities. As an example, a 6-year-old male whose height is –2 SDS below the mean will be 9.7 cm shorter than his peers—whereas a 16-year-old male whose height is –2 SDS will be 14.4 cm shorter than other boys his age.

A recent report suggests that catch-up growth may be achievable in infants started on CCPD when strict attention is paid

to providing adequate nutritional support. Although most programs do not report this level of achievement, it does suggest a standard for future efforts. Weight SDS are often lost on hemodialysis but are maintained (or increased) on peritoneal dialysis, at least in part because of the wider diet choices and the daily glucose infusion via the dialysis solution. Weight gain may be a particular problem in adolescents, and the use of BMI measurements is important in documenting the development of obesity and allowing for early intervention.

Growth after Transplantation

The North American Renal Transplant Collaboration Study (NAPRTCS) is the largest database containing growth information on children with chronic renal disease. According to NAPRTCS data, mean height deficits at transplant average –1.85 SDS. This is a reflection of the height deficit of individuals who received preemptive transplantation (approximately 25% of the patient population) and of height potential lost during dialysis. After transplantation, growth appears to be dependent on the presence of a well-functioning graft, the child's chronologic and/or bone age at transplantation, the degree of growth retardation present before transplantation, and the steroid dosage used for immunosuppression.

Growth is most likely to occur in children who receive a kidney transplant before age 7 (some reports suggest 9), when true catch-up growth may occur. It is least likely to occur in children with bone ages over 12 years. It should be noted that the youngest children are usually the same ones with the greatest degree of growth retardation and thus the greatest growth potential. Growth is inversely related to steroid dosage, and is thus improved when alternate-day steroid regimens are utilized or when newer protocols are used that do not utilize chronic steroid therapy.

All available data support the concept that in children, early transplantation is advantageous in attempting to maximize growth potential. A distinction should be made between increments in height and final height. The greatest increments in height are seen in those who were younger and most growth retarded prior to transplantation. However, final height is better related to the patient's height prior to transplantation. Thus, individuals with higher height SDS at time of transplantation reach a higher final height than those whose height at transplant is more significantly retarded. This fact underlies the importance of maintaining normal growth rates in children prior to transplantation.

Correlation of Growth Failure with Renal Disease

Energy Intake

Calorie counts in both children and adults with renal failure reveal that spontaneous energy intakes are low. Numerous investigators have attempted to improve intake and growth by administering dietary energy supplements. A critical evaluation of the data suggests that irrespective of the etiology, energy intakes <70% of the recommended daily allowances (RDAs) for normal children of the same height are associated with poor growth and increasing energy intake can improve growth, that when children ingest >80% of the RDA there is no correlation between growth rates and energy intake, and that given individual variation most would attempt to achieve energy intakes of approximately 100 to 120% of the RDA. Significantly higher caloric intakes may lead to obesity without improvement in height.

Protein Intake

Standard Western diets contain a high percentage of energy intake as protein. Even when total energy intake is low, it is unlikely that protein intake is inadequate. Two exceptions to this statement are infants with congenital nephrotic syndrome who have significant urinary protein loss and infants on peritoneal dialysis who lose significant amounts of protein in the dialysate.

When protein intake is in excess of requirements, the constituent amino acids must be catabolized and the waste products excreted. This is associated with the production of acid equivalents as well as the build-up of urea and possibly other (as yet poorly characterized) metabolic toxins. It appears that very-low-protein diets may limit linear growth in infants without any evidence that they slow the progression of renal failure.

Acidosis

An early study that examined the etiology of growth failure in uremia also noted that metabolic acidosis was common. Because no acidotic child grew normally, these findings suggested that acidosis was an inhibitor of growth in chronic renal disease. Recent studies also suggest that acidosis interferes with growth hormone secretion. Unfortunately, in children with renal failure correction of acidosis has not led to increased height gain. Metabolic acidosis does limit the accretion of body protein mass

due to increased muscle protein catabolism and worsening of nitrogen balance.

Renal Osteodystrophy

Severe renal osteodystrophy associated with skeletal deformity can limit growth and diminish final height. When this situation occurs, vigorous therapy can lead to increased growth and improvement in height SDS. However, when renal osteodystrophy changes are only chemical or histologic there is little relationship between growth failure and the presence of osteodystrophy, elevated parathyroid hormone concentration (PTH) levels, or serum concentrations of vitamin D metabolites. It does appear, however, that high PTH concentrations decrease the growth response to the administration of recombinant human growth hormone (r-HGH).

Hormonal Alterations

Uremia is associated with abnormal plasma levels of numerous hormones generally associated with growth. Plasma growth hormone levels are elevated, but free levels of insulin-like growth factor I (IGF-1) are decreased due to an increase in the serum concentration of IGF-1-binding proteins. Other reports also suggest possible inhibitory actions by some of the binding proteins themselves. Whereas peripheral resistance to insulin is well documented, there is no evidence relating insulin resistance directly to diminished statural growth.

Both children and adults with renal failure are clinically euthyroid, although they may demonstrate decreased thyrotropin reserve. Important exceptions to this observation are children with cystinosis and infants with congenital nephrotic syndrome in whom frank hypothyroidism can develop. Decreasing renal mass leads to diminished production of erythropoietin (EPO) and the development of anemia. Treatment with recombinant EPO is associated with improvement in appetite and multiple aspects of daily living.

Analysis of both NAPRTCS data (for children pre-dialysis) and data from United States Medicare and Medicaid databases (pediatric ESRD) reveal that anemia is associated with decreased growth rates. Cortisol levels are normal, but after renal transplantation a pharmacologic state of hyperglucocorticoidism is maintained so that children maintained post-transplantation who are maintained on steroid-avoidance regimens have better growth

potential. Plasma levels of the sex hormones are diminished, and this may affect these patients' ability to demonstrate an appropriate growth spurt at puberty.

Recommendations

Care of the infant or child with progressive renal disease requires meticulous attention to all known causes of growth failure and prompt intervention to correct or prevent these abnormalities. This is best accomplished in the context of a team approach involving nephrologists, dietitians, nurses, and other staff members interested and experienced in the care of these patients. Because of the low incidence of infants and children presenting with significant renal insufficiency, their care is best carried out in pediatric centers— or where distances are too great by internist nephrologists in regular consultation with pediatric nephrologists.

Appropriate methods and standards for determining growth and growth rates have been noted above. Parents should be trained to help the dietitian obtaining a 3-day diet history so that intake may be monitored. The aim should be to provide energy intakes at 100 to 120% of the RDA for height age. The importance of adequate energy intake should not be overlooked in adolescents on dialysis who require approximately 40 kcal/kg/day. Recommended protein intakes for individuals on peritoneal dialysis are outlined in Table 97.1. Energy supplements in excess of those noted should be limited to infants and children who drop down one growth channel on BMI charts or whose BMI is <2 SD below the mean.

For infants, the need to accurately monitor intake must take preference over the desire to breast-feed, and the mother should

Table 97–1

Recommended Protein Intake for Individuals on Peritoneal Dialysis

Age	Protein Intake (g/kg/d)
<3 years	2.5–3
3 years to puberty	2–2.5
Pubertal children	2
Postpubertal	1.5

be encouraged to either pump her breasts or to use a low-solute humanized infant formula. Either breast milk or commercial formula may need to be supplemented to achieve the caloric and protein intakes noted previously. Energy supplements can be added directly either in the form of glucose polymers or fat supplements.

A significant percentage of infants with chronic renal failure and ESRD are salt losers with an inability to concentrate their urine. In these individuals, concentrated formulas provide high osmolar loads with insufficient free-water intake, leading to azotemia and chronic intravascular dehydration. The use of high-volume low-solute salt- (and bicarbonate-) supplemented formulas are recommended for these infants. Fluid intakes as high as 150 to 200 cc/kg/day are often required.

Pre-ESRD and for those on hemodialysis, protein intake should be limited to the RDA for height age. For individuals receiving peritoneal dialysis, protein intake should be at the levels noted in Table 97.1. Because appetite is decreased in chronic renal failure, it is often necessary to ensure intake by nasogastric, nasojejunal, or gastrostomy feedings. These may be used to deliver the entire dietary allotment, to provide a nighttime supplement, or to supplement when oral intake declines (e.g., during periods of intercurrent illness).

Careful evaluation of electrolyte and mineral status is mandatory. Infants with renal insufficiency secondary to structural abnormalities may require liberal salt intake to prevent chronic volume depletion, a condition that limits growth. The finding of elevated renin levels in normotensive children with structural renal disease may help identify them as salt losers. Serum sodium concentrations should be maintained at between 140 and 145 mEq/L. Because chronic dehydration can be difficult to assess clinically, some have suggested increasing salt supplementation until the infant is either edematous or hypertensive and then dropping back to a lower salt intake.

Sodium bicarbonate cannot be used to improve volume status, and sodium chloride supplements as high as 5 mEq/kg/day are common. Plasma bicarbonate levels should be maintained above 22 mmol/L. In addition to active vitamin D metabolites, calcium supplements are generally required to bind dietary phosphates within the gastrointestinal tract and to keep an appropriate plasma calcium concentration. Phosphate levels should be kept within the normal range for age. This is particularly important in infants on low-phosphate formulas in whom bone calcification can be limited by age-related hypophosphatemia. Phosphate

binders containing aluminum should not be used in pediatric patients because aluminum buildup is associated with progressive neurologic deterioration and bone disease.

The availability of unlimited amounts of recombinant human growth hormone (r-HGH) has allowed pediatric nephrologists to evaluate its use in short children with chronic renal failure as well as children who are growing poorly post renal transplantation. Unfortunately, recent surveys have demonstrated that only a minority of infants and children with significant short stature (height below –1.88 SDS or the 3rd percentile) receive r-HGH. The reasons for this are multiple and include such things as parental refusal, nonresponse to previous use, and children who are severely retarded. The importance of achieving normal growth and the possible use and utility of r-HGH should be discussed with all families early in the course of care of children with chronic kidney disease.

Predialysis, the administration of r-HGH in doses of 0.05 mg/kg/day (0.15 IU/kg/day) is associated with significant improvements in growth velocity and true catch-up growth. Multiple controlled studies have documented that r-HGH improves growth rates in children with renal disease pre-ESRD, while on dialysis, and post-transplantation. Growth hormone is most effective pre-ESRD and in younger patients, and its administration does not speed progression to ESRD. Use of r-HGH in pre-dialysis patients can lead to significant persistent catch-up growth. Administration of r-HGH may be continued after the institution of dialysis. For children on CCPD, r-HGH may be injected intraperitoneally along with a small volume of dialysate each morning. However, patients may require higher doses of r-HGH when this route is chosen. Most centers continue giving r-HGH by subcutaneous injection.

Post-transplant use of r-HGH is less effective than when administered pre-dialysis. Its effect is hindered by concomitant steroid administration. Whether further development of steroid-free antirejection therapy will restore growth rates to normal and eliminate the use of r-HGH post-transplantation is unknown. In most patients, post-transplant use of r-HGH does not lead to renal graft rejection. However, patients who have had multiple prior rejection episodes may be at increased risk for graft loss.

Use of r-HGH should be considered only after other correctable causes of growth retardation (poor calorie intake, salt and water loss, acidosis, and gross renal osteodystrophy) have been addressed. In infants, administration of r-HGH should be delayed until approximately 6 months of age while attention is directed

to the causes of growth failure noted previously. It appears particularly important to control PTH concentrations because severe hyperparathyroidism is associated with a decreased response to r-HGH.

Conclusions

It must be recognized that the aim of these therapies is to promote the growth and well-being of infants and children with chronic renal insufficiency. Rather than any predetermined level of plasma creatinine or GFR, it is the persistence of poor growth rates or abnormal electrolyte and mineral balance that defines the need for r-HGH administration, dialysis, and transplantation. This approach is aggressive and occasionally leads to the institution of peritoneal dialysis in poorly growing infants with significant residual GFR. It can be justified in view of poor growth rates and the lack of catch-up growth noted for conservative therapy in most pediatric programs.

Controversy still exists regarding the most appropriate approach to the timing of renal transplantation in infants. On the one hand, transplant survival is improved when recipients are larger and older than 2 years of age. On the other hand, poor growth and development may delay the time to transplantation and expose the infant to additional complications. In most centers, a consensus seems to be appearing that with current treatment protocols (including the use of recombinant EPO and r-HGH) transplantation may be delayed until 1.5 to 2 years of age or until the infant reaches 10 to 12 kg in weight.

For children on dialysis, early transplantation is recommended. When the transplant is successful, these children have the best growth potential. After transplantation, all agree that administering the lowest effective doses of glucocorticoids promotes growth. The use of newer agents has allowed physicians to administer lower steroid dosages (or none at all), with improved growth rates and probable improvements in final adult height.

Recommended Reading

Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O for the German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Effect of growth hormone treatment on the adult height of children with chronic renal failure..N Engl J Med 2000;343:923–30.

Discusses the utility of r-HGH administration to improve final height SDS in children with chronic renal disease.

Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney International 2000;57:1681–87.

Discusses the special challenges associated with the care of infants with chronic kidney disease.

Märta S, Englund MS, TydénG, Wikstad I, Berg UB. Growth impairment at renal transplantation: A determinant of growth and final height. Pediatric Transplantation 2003;7:192–99.

Discusses the determinants of post-transplant growth as they relate to final adult height.

NAPRTCS. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2006 Annual Report, *https://web.emms.com/study/ped/annlrept/annlrept2006.pdf*.

The largest database of growth in children with chronic kidney disease for predialysis, dialysis, and post-transplantation.

Warady BA, Alexander SR, Watkins S, et al. Optimal care of the pediatric renal disease patient on dialysis. Am J Kidney Dis 1999;33:567–83.

Prepared for the American Society of Pediatric Nephrology, this article covers pediatric dialysis and discusses nutrition.

Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherrard DJ, et al. Anthropometric measures and risk of death in children with end-stage renal disease. American Journal of Kidney Diseases 2000;36:811–19.

Utilizes data from the Pediatric Growth and Development Study from the U.S. Renal Data System to assess height, weight, and BMI in children on dialysis.

CHAPTER 98

Adequacy of Peritoneal Dialysis in Pediatric Patients

Vimal Chadha, MD, and Bradley A. Warady, MD

The provision of dialysis to a child with stage 5 chronic kidney disease (CKD), meaning a glomerular filtration rate (GFR) of <15 mL/minute/1.73m^2, constitutes only one element of the comprehensive management of this debilitating disease. It is apparent that to achieve the best possible outcome, optimal management of anemia, secondary hyperparathyroidism and renal osteodystrophy, acidosis, hypertension, dyslipidemia, nutrition, and growth are equally important. It is also important to recognize that successful management of all of these issues is interdependent. Interestingly, although the therapeutic endpoints of many of these clinical initiatives are relatively well defined there is no consensus on what constitutes adequate dialysis.

The peritoneal dialysis (PD) prescription target has traditionally been derived empirically, with adequacy determined only by the absence of overt symptoms of uremia and the presence of acceptable blood chemistries. In adults, dialysis adequacy is currently characterized by urea removal—with specific quantitative targets based on the evidence of an association between solute clearance and patient morbidity/mortality.

The same cannot currently hold true for children because of the low mortality rate experienced by patients in this age group and the absence of any well-substantiated correlation between their clinical status and the efficiency of dialysis. Furthermore, the provision of evidence-based pediatric PD adequacy guidelines is hampered by a crucial epidemiologic issue: because stage 5 CKD remains a relatively uncommon disease in children and a significant proportion of patients receive a kidney transplant soon after developing end-stage renal disease (ESRD) no long-term pediatric outcome study is adequately powered to detect an effect of the delivered PD dose on pediatric patient outcome.

Accordingly, the revised pediatric component of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Peritoneal Dialysis Adequacy guidelines suggest that the clinical "wellness" of the individual patient should remain an important treatment goal and an important means by which

the adequacy of care should be assessed. An understanding of the basic concepts of dialysis adequacy and key issues from the updated NKF-K/DOQI publication are reviewed in this chapter.

Adequate Versus Optimal Dose of Dialysis

Although an adequate dose of PD might best be defined as the minimum dose, in terms of the quantity of solute removed that achieves a stated outcome measure, the optimal dose of dialysis is that dose above which the incremental clinical benefit does not justify the additional patient burden or cost. Therefore, the optimal dose lies somewhere between the minimal effective (adequate) dose and the maximal dose—or the dose above which there are clearly no additional benefits. However, it is difficult to define the optimal PD dose in children with confidence because of the absence of definitive data correlating dialysis dose to patient outcome. Thus, the recommended clinical practice is in essence to provide the most dialysis that can be delivered to the patient within the constraints of social and clinical circumstances, quality of life (QOL), and cost.

Prescription of Peritoneal Dialysis

Initial Dialysis Prescription

Both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are used by children, although the latter is the preferred PD modality—in large part because its use is characterized by freedom from procedures during the daytime hours. In view of the age-independent relationship between peritoneal surface area and body surface area (BSA), the use of BSA as a scaling factor for the prescribed exchange volume is recommended. Whereas the target range for the exchange volume of patients greater than 2 years is 1000 to 1200 mL/m^2 BSA, the initial prescribed volume should be somewhat lower for smaller infants (approximately 600–800 mL/m^2 BSA) and the exchange volume should be increased in a stepwise manner as tolerated by the patient.

To optimize small-solute clearance, minimize cost, and possibly decrease the frequency of exchanges, one should first increase the instilled volume per exchange (maximum 1400 mL/m^2 BSA) as tolerated by the patient before increasing the number of exchanges per day. The volume of the supine exchange(s) should be increased first because this is the position with the lowest

intra-abdominal pressure. Objective evidence of patient tolerance may require assessment of the intraperitoneal pressure.

The PD prescription process should take into account the peritoneal membrane transport characteristics and the residual renal function (RRF) of the patient (vide infra). It should also be recognized that it is often impractical to consider the provision of a dialysis prescription solely based on kinetic data and achieved solute clearance without reference to social constraints such as school attendance and the working schedule of parents.

Finally, the removal of "middle molecules" and low-molecular-weight proteins should ideally also be taken into account in the prescription process because of the influence it may have on clinical outcome—especially in patients without RRF. In most patients, the PD prescription should be continuous and should preferentially consist of the use of continuous cycling peritoneal dialysis (CCPD) with dwells 24 hours/day or CAPD. This is recommended even if small-molecule clearance is above target without the longer dwell. The use of nightly intermittent peritoneal dialysis (NIPD) without any daytime dwell can be considered in pediatric patients who are clinically well, whose combined dialysis prescription and RRF achieves or exceeds the target solute clearance, and who are without evidence of hyperphosphatemia, hyperkalemia, hypervolemia, or acidosis.

Peritoneal Equilibration Test

The peritoneal equilibrium test (PET) was developed as a clinically applicable means of characterizing solute transport across the peritoneum and is the most common technique used in children to assess the peritoneal membrane transport capacity and guide the prescription process. The procedure yields data necessary to determine the fractional equilibration of creatinine and glucose between dialysate and blood expressed as the dialysate-to-plasma (D/P) ratio for creatinine and the ratio of dialysate glucose to initial dialysate glucose (D/D_O). The test exchange volume should be 1000 to 1100 mL/m^2 when the procedure is conducted in children.

The provision of a smaller volume may result in more rapid equilibration and the artifactual appearance of an inherently more rapid membrane transport capacity. The details of the PET are discussed in another chapter of this book. Here, it is important to highlight the fact that glucose in high concentration (as occurs in dialysis fluid) interferes with the measurement of creatinine by the photometric method. The resulting creatinine value is falsely

elevated. Accordingly, the creatinine concentration in dialysis fluid should be measured by the enzymatic assay method (in which there is no glucose interference) or the creatinine values must be corrected for glucose interference by determining a correction factor for the individual laboratory.

It has been suggested that a patient's initial PET evaluation should be performed approximately 1 month after dialysis initiation to facilitate categorization of a patient's transport capacity in the most accurate manner. Patients are categorized as high, high average, low average, or low solute transporters based on a comparison of their data to reference norms. A child classified as a rapid transporter is likely to dialyze most efficiently in terms of solute and water removal by using short frequent dialysis cycles, as in APD. On the other hand, a low or low average transporter may benefit most from a schedule that includes longer dwell times (as in classical CAPD).

Attention to these prescription issues may be particularly important to children because of the high incidence of cardiac disease and the goal of achieving euvolemia and normotension (vide infra). Whereas routine repetition of the PET evaluation is not indicated, repeat testing should be considered when there is clinical/biochemical evidence of suboptimal dialysis or when clinical events have occurred (e.g., repeated peritonitis) that may have altered the membrane transport capacity.

Mass Transfer Area Coefficient

The mass transfer area coefficient (MTAC) is an additional measure of solute transport capacity and is the most precise means of estimating intrinsic peritoneal membrane permeability to a specific solute. Unlike the D/P ratio determined with the PET, the MTAC is essentially independent of dialysis mechanics such as the exchange volume and the dialysate dextrose concentration. Whereas clinicians have been reluctant to use the MTAC to characterize peritoneal membrane solute transport capacity (largely because of the complexity of the calculations involved), computer technology has now made determination of the MTAC much easier.

Measurement of Peritoneal Dialysis Dose

A valid and reproducible measure of the dose of PD is essential to determine the quantity of dialysis delivered to an individual patient. The total (RRF + dialysis) weekly Kt/V_{urea} and the total

weekly creatinine clearance (C_{Cr}) are the best available measures of PD dose, and both have been used in clinical practice. Nevertheless, determination of dialysis and urine Kt/V_{urea} alone is currently recommended for follow-up based on the simplicity of the calculation and the fact that studies in adult patients on PD have not provided any evidence of a benefit in terms of patient outcome when expressing clearance in any manner other than Kt/V_{urea}. Kt/V_{urea} is a measure of the amount of plasma cleared of urea during the sampling period (K * t) normalized to total body water (TBW) or V, the volume of urea distribution. The total weekly Kt/V_{urea} is calculated as

$$Weekly\ Kt/V = \frac{D_{ur} \times V_D + (U_{ur} \times V_u)}{P_{ur} \times V} \times 7$$

where D_{ur}, U_{ur}, and P_{ur} are (respectively) the dialysate, urinary, and plasma concentrations of urea; V_D and V_U (respectively) the 24-hour dialysate and urine volumes; and V the urea distribution volume.

In the calculation of Kt/V_{urea}, it is most important to use an accurate estimate of V. Traditionally, anthropometric prediction equations based on height and weight (such as those of Mellits and Cheek) have been used to estimate V. However, such equations were established in healthy populations, and recent studies have revealed that the use of these equations routinely overestimates V (or TBW) in pediatric patients receiving PD. In contrast, the recent determination of TBW by heavy water (H_2O-^{18} or D_2O) dilution in 64 pediatric patients receiving PD has allowed for the development of accurate TBW prediction equations. The gender-specific equations are as follows:

$$Males : TBW = 0.010 \times (height \times weight)^{0.68} - (0.37 \times weight)$$
$$Females : TBW = 0.14 \times (height \times weight)^{0.64} - (0.35 \times weight)$$

Gender-specific nomograms for estimating TBW based on these equations are provided in Tables 98.1 and 98.2. Because the (height × weight) parameter also predicts BSA, it has been possible to simplify the prediction equations by utilizing BSA as determined by the Gehan and George equation (vide infra). Although slightly less precise than the best-fitting equations, these equations might be considered more "user friendly."

$$Male : TBW = 20.88 \times BSA - 4.29$$
$$Females : TBW = 16.92 \times BSA - 1.81$$

As noted previously, the measurement of dialysis delivery also requires the determination of RRF and BSA. The RRF is calcu-

Table 98–1

Male Total Body Water (L) Nomograms

Weight (kg) \ Height (cm)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	1.6	1.7	1.8	1.9													
3	1.9	2.1	2.2	2.4													
4	2.2	2.4	2.6	2.8	3.0												
5	2.4	2.7	2.9	3.1	3.3												
6	2.6	2.9	3.1	3.4	3.6	3.9	4.1										
7	2.8	3.1	3.4	3.6	3.9	4.2	4.4	4.7	4.9								
8	2.9	3.2	3.5	3.9	4.1	4.4	4.7	5.0	5.3	5.5	5.8						
9				4.0	4.4	4.7	5.0	5.3	5.6	5.9	6.2	6.5	6.7				
10				4.2	4.6	4.9	5.2	5.6	5.9	6.2	6.5	6.8	7.1	7.4	7.7		
11				4.4	4.8	5.1	5.5	5.8	6.2	6.5	6.8	7.1	7.5	7.8	8.1	8.4	8.7
12				4.5	4.9	5.3	5.7	6.0	6.4	6.8	7.1	7.5	7.8	8.1	8.5	8.8	9.1
13								6.3	6.6	7.0	7.4	7.8	8.1	8.5	8.8	9.2	9.5
14								6.5	6.9	7.3	7.7	8.0	8.4	8.8	9.2	9.5	9.9
15								6.7	7.1	7.5	7.9	8.3	8.7	9.1	9.5	9.9	10.2
16								6.8	7.3	7.7	8.1	8.6	9.0	9.4	9.8	10.2	10.6
17											8.4	8.8	9.2	9.7	10.1	10.5	10.9
18											8.6	9.0	9.5	9.9	10.4	10.8	11.2
19											8.8	9.3	9.7	10.2	10.6	11.1	11.5
20											9.0	9.4	9.9	10.4	10.9	11.3	11.8

Table Continued

Table 98–1

Male Total Body Water (L) Nomograms—Cont'd

Weight (kg) \ Height (cm)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	10.9	11.3	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7										
22	11.4	11.9	12.4	12.8	13.3	13.8	14.3	14.7	15.2	15.7	16.1	16.6										
24	11.8	12.3	12.9	13.4	13.9	14.4	14.9	15.4	15.9	16.4	16.8	17.3	17.8	18.3	18.7							
26	12.2	12.8	13.3	13.9	14.4	15.0	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5							
28	12.6	13.2	13.8	14.4	14.9	15.5	16.0	16.6	17.1	17.7	18.2	18.7	19.3	19.8	20.3	20.8	21.3					
30	13.0	13.6	14.2	14.8	15.4	16.0	16.6	17.1	17.7	18.3	18.8	19.4	19.9	20.5	21.0	21.6	22.1					
32	13.3	14.0	14.6	15.2	15.8	16.5	17.1	17.7	18.3	18.8	19.4	20.0	20.6	21.2	21.7	22.3	22.9	23.4	24.0			
34	13.6	14.3	15.0	15.6	16.3	16.9	17.5	18.2	18.8	19.4	20.0	20.6	21.2	21.8	22.4	23.0	23.6	24.2	24.7			
36	13.9	14.6	15.3	16.0	16.7	17.3	18.0	18.7	19.3	19.9	20.6	21.2	21.8	22.4	23.1	23.7	24.3	24.9	25.5	26.1	26.6	
38	14.2	14.9	15.7	16.4	17.1	17.8	18.4	19.1	19.8	20.4	21.1	21.8	22.4	23.0	23.7	24.3	24.9	25.6	26.2	26.8	27.4	
40			16.0	16.7	17.4	18.1	18.8	19.5	20.2	20.9	21.6	22.3	23.0	23.6	24.3	24.9	25.6	26.2	26.9	27.5	28.1	28.8
42			16.3	17.0	17.8	18.5	19.2	20.0	20.7	21.4	22.1	22.8	23.5	24.2	24.9	25.5	26.2	26.9	27.5	28.2	28.8	29.5
44			16.6	17.3	18.1	18.9	19.6	20.4	21.1	21.8	22.6	23.3	24.0	24.7	25.4	26.1	26.8	27.5	28.2	28.8	29.5	30.2
46			16.8	17.6	18.4	19.2	20.0	20.8	21.5	22.3	23.0	23.8	24.5	25.2	26.0	26.7	27.4	28.1	28.8	29.5	30.2	30.9
48			17.1	17.9	18.7	19.5	20.3	21.1	21.9	22.7	23.5	24.2	25.0	25.7	26.5	27.2	27.9	28.7	29.4	30.1	30.8	31.5
50			17.3	18.2	19.0	19.8	20.7	21.5	22.3	23.1	23.9	24.7	25.4	26.2	27.0	27.7	28.5	29.2	30.0	30.7	31.5	32.2
52						20.1	21.0	21.8	22.6	23.5	24.3	25.1	25.9	26.7	27.5	28.2	29.0	29.8	30.6	31.3	32.1	32.8

Table 98–1

Male Total Body Water (L) Nomograms—Cont'd

54	20.4	21.3	22.1	23.0	23.8	24.7	25.5	26.3	27.1	27.9	28.7	29.5	30.3	31.1	31.9	32.7	33.4
56	20.7	21.6	22.5	23.3	24.2	25.0	25.9	26.7	27.6	28.4	29.2	30.0	30.8	31.7	32.4	33.2	34.0
58	20.9	21.8	22.8	23.7	24.5	25.4	26.3	27.1	28.0	28.8	29.7	30.5	31.4	32.2	33.0	33.8	34.6
60	21.2	22.1	23.1	24.0	24.9	25.8	26.7	27.5	28.4	29.3	30.1	31.0	31.8	32.7	33.5	34.4	35.2
62	21.4	22.4	23.3	24.3	25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7
64	21.7	22.6	23.6	24.6	25.5	26.4	27.4	28.3	29.2	30.1	31.0	31.9	32.8	33.7	34.5	35.4	36.3
66				24.8	25.8	26.8	27.7	28.6	29.6	30.5	31.4	32.3	33.2	34.1	35.0	35.9	36.8
68				25.1	26.1	27.1	28.0	29.0	30.0	30.9	31.8	32.8	33.7	34.6	35.5	36.4	37.3
70				25.4	26.4	27.4	28.4	29.3	30.3	31.3	32.2	33.2	34.1	35.1	36.0	36.9	37.8
72				25.6	26.6	27.7	28.7	29.7	30.7	31.6	32.6	33.6	34.5	35.5	36.4	37.4	38.3
74				25.9	26.9	27.9	29.0	30.0	31.0	32.0	33.0	34.0	34.9	35.9	36.9	37.8	38.8
76				26.1	27.2	28.2	29.3	30.3	31.3	32.3	33.3	34.4	35.3	36.3	37.3	38.3	39.3
78				26.3	27.4	28.5	29.5	30.6	31.6	32.7	33.7	34.7	35.7	36.7	37.7	38.7	39.7
80				26.5	27.6	28.7	29.8	30.9	31.9	33.0	34.1	35.1	36.1	37.1	38.2	39.2	40.2

Table 98–2

Female Total Body Water (L) Nomograms

Weight (kg) \ Height (cm)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	2.0	2.1	2.2	2.4													
3	2.4	2.6	2.8	2.9													
4	2.8	3.0	3.2	3.4	3.6												
5	3.1	3.3	3.5	3.8	4.0												
6	3.3	3.6	3.8	4.1	4.3	4.6	4.8										
7	3.5	3.8	4.1	4.4	4.8	4.9	5.2	5.5	5.7								
8	3.7	4.0	4.3	4.6	4.9	5.2	5.5	5.8	6.1	6.4	6.6						
9				4.9	5.2	5.5	5.8	6.1	6.4	6.7	7.0	7.3	7.6				
10				5.1	5.4	5.8	6.1	6.4	6.8	7.1	7.4	7.7	8.0	8.3	8.6		
11				5.3	5.6	6.0	6.4	6.7	7.1	7.4	7.7	8.1	8.4	8.7	9.0	9.3	9.6
12				5.4	5.8	6.2	6.6	7.0	7.3	7.7	8.0	8.4	8.7	9.1	9.4	9.7	10.0
13								7.2	7.6	8.0	8.3	8.7	9.1	9.4	9.8	10.1	10.4
14								7.4	7.8	8.2	8.6	9.0	9.4	9.7	10.1	10.5	10.8
15								7.6	8.0	8.5	8.9	9.3	9.7	10.0	10.4	10.8	11.2
16								7.8	8.3	8.7	9.1	9.5	9.9	10.3	10.7	11.1	11.5
17											9.3	9.8	10.2	10.6	11.0	11.4	11.8
18											9.6	10.0	10.5	10.9	11.3	11.7	12.2
19											9.8	10.2	10.7	11.1	11.6	12.0	12.5
20											10.0	10.4	10.9	11.4	11.8	12.3	12.7

Table 98–2

Female Total Body Water (L) Nomograms —Cont'd

Weight (kg) \ Height (cm)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7	16.1	16.5										
22	12.3	12.8	13.3	13.7	14.2	14.7	15.1	15.6	16.0	16.4	16.9	17.3										
24	12.8	13.3	13.8	14.3	14.8	15.2	15.7	16.2	16.7	17.1	17.6	18.0	18.5	18.9	19.4							
26	13.2	13.7	14.2	14.8	15.3	15.8	16.3	16.8	17.3	17.8	18.3	18.7	19.2	19.7	20.1							
28	13.6	14.1	14.7	15.2	15.8	16.3	16.8	17.3	17.9	18.4	18.9	19.4	19.9	20.4	20.9	21.3	21.8					
30	13.9	14.5	15.1	15.7	16.2	16.8	17.3	17.9	18.4	18.9	19.5	20.0	20.5	21.0	21.5	22.0	22.5					
32	14.3	14.9	15.5	16.1	16.6	17.2	17.8	18.4	18.9	19.5	20.0	20.6	21.1	21.7	22.2	22.7	23.2	23.7	24.3			
34	14.6	15.2	15.8	16.4	17.0	17.7	18.2	18.8	19.4	20.0	20.6	21.1	21.7	22.3	22.8	23.4	23.9	24.4	25.0			
36	14.8	15.5	16.2	16.8	17.4	18.1	18.7	19.3	19.9	20.5	21.1	21.7	22.3	22.8	23.4	24.0	24.5	25.1	25.6	26.2	26.7	
38	15.1	15.8	16.5	17.1	17.8	18.4	19.1	19.7	20.3	21.0	21.6	22.2	22.8	23.4	24.0	24.6	25.1	25.7	26.3	26.9	27.4	
40			16.8	17.4	18.1	18.8	19.5	20.1	20.7	21.4	22.0	22.7	23.3	23.9	24.5	25.1	25.7	26.3	26.9	27.5	28.1	28.6
42			17.0	17.7	18.4	19.1	19.8	20.5	21.1	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.3	26.9	27.5	28.1	28.7	29.3
44			17.3	18.0	18.7	19.5	20.2	20.9	21.5	22.2	22.9	23.6	24.2	24.9	25.5	26.2	26.8	27.4	28.1	28.7	29.3	29.9
46			17.5	18.3	19.0	19.8	20.5	21.2	21.9	22.6	23.3	24.0	24.7	25.3	26.0	26.7	27.3	28.0	28.6	29.3	29.9	30.5
48			17.8	18.5	19.3	20.0	20.8	21.5	22.3	23.0	23.7	24.4	25.1	25.8	26.5	27.2	27.8	28.5	29.2	29.8	30.5	31.1
50			18.0	18.8	19.6	20.3	21.1	21.8	22.6	23.3	24.1	24.8	25.5	26.2	26.9	27.6	28.3	29.0	29.7	30.4	31.0	31.7
52						20.6	21.4	22.1	22.9	23.7	24.4	25.2	25.9	26.6	27.4	28.1	28.8	29.5	30.2	30.9	31.6	32.2

Table Continued

Table 98–2

Female Total Body Water (L) Nomograms —Cont'd

54	20.8	21.6	22.4	23.2	24.0	24.8	25.5	26.3	27.0	27.8	28.5	29.2	29.9	30.7	31.4	32.1	32.8
56	21.1	21.9	22.7	23.5	24.3	25.1	25.9	26.6	27.4	28.2	28.9	29.7	30.4	31.1	31.9	32.6	33.3
58	21.3	22.1	23.0	23.8	24.6	25.4	26.2	27.0	27.8	28.5	29.3	30.1	30.8	31.6	32.3	33.1	33.8
60	21.5	22.4	23.2	24.1	24.9	25.7	26.5	27.3	28.1	28.9	29.7	30.5	31.3	32.0	32.8	33.5	34.3
62	21.7	22.6	23.4	24.3	25.2	26.0	26.8	27.7	28.5	29.3	30.1	30.9	31.7	32.4	33.2	34.0	34.8
64	21.9	22.8	23.7	24.6	25.4	26.3	27.1	28.0	28.8	29.6	30.4	31.3	32.1	32.9	33.6	34.4	35.2
66				24.8	25.7	26.5	27.4	28.3	29.1	30.0	30.8	31.6	32.4	33.2	34.1	34.9	35.7
68				25.0	25.9	26.8	27.7	28.6	29.4	30.3	31.1	32.0	32.8	33.6	34.5	35.3	36.1
70				25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7	36.5
72				25.4	26.4	27.3	28.2	29.1	30.0	30.9	31.8	32.7	33.5	34.4	35.2	36.1	36.9
74				25.6	26.6	27.5	28.4	29.4	30.3	31.2	32.1	33.0	33.9	34.7	35.6	36.5	37.3
76				25.8	26.8	27.7	28.7	29.6	30.6	31.5	32.4	33.3	34.2	35.1	36.0	36.8	37.7
78				26.0	27.0	27.9	28.9	29.9	30.8	31.7	32.7	33.6	34.5	35.4	36.3	37.2	38.1
80				26.2	27.2	28.1	29.1	30.1	31.1	32.0	33.0	33.9	34.8	35.7	36.7	37.6	38.5

lated as the glomerular filtration rate (GFR) by determining the average of the clearance of urea and creatinine as

$$RRF = \left[\frac{U_{cr} \times V_u}{P_{cr}} + \frac{U \times V_u}{P_{ur}}\right] / 2$$

where U_{cr} and P_{cr} are (respectively) urinary and plasma concentrations of creatinine, U_{ur} and P_{ur} are (respectively) urinary and plasma concentrations of urea, and V_U is 24-hour urine volume. This method mathematically balances the tubular secretion of creatinine and the tubular reabsorption of urea that is characteristic of CKD. During the first few years of dialysis therapy, RRF often contributes appreciably to total solute and water removal. The loss of RRF is a major cause of a decreasing total clearance in PD subjects followed longitudinally and must be compensated for by changes in the dialysis prescription to maintain the desired level of total clearance.

The determination of BSA has been commonly derived using the method of DuBois and DuBois, and most of the currently available data is based on this method. However, in an independent comparison, the Gehan and George method was preferred because more than 400 subjects (including many children) were used to define this formula. In contrast, only 9 subjects were used to define the formula of DuBois and DuBois. The respective formulae are as follows:

$$\textit{DuBois and DuBois method} : BSA(m^2) = 71.84 \times Wt(kg)^{0.425} \times Ht(cm)^{0.725}$$

$$\textit{Gehan and George method} : BSA(m^2) = 0.0235 \times Wt(kg)^{0.51456} \times Ht(cm)^{0.42246}$$

Finally, the solute removal index (SRI) is another measure that has been suggested as a reliable method of determining dialysis adequacy and is especially useful in comparing adequacy of disparate therapies. SRI is calculated by normalizing the solute removed to the amount of solute present at the beginning of treatment. Thus,

$$SRI = \frac{\textit{Solute removed}}{\textit{Solute body content}} = \frac{V_d \times C_d + V_u \times C_u}{V_b \times C_b}$$

where V and C are (respectively) volume and concentration, and subscripts d, u, and b refer (respectively) to dialysate, urine, and body water.

Adequacy Recommendations

Clinical "wellness" of the pediatric patient is an important parameter of PD adequacy, and adequate dialysis is likely pro-

vided if a patient's status is characterized by adequate growth, maintenance of normal serum chemistries, good blood pressure control and nutritional status, and adequate psychomotor development. Despite this fact, solute clearance and ultrafiltration (fluid removal)—only two of the complex functions carried out by the healthy kidney—are the two parameters most commonly utilized to assess dialysis adequacy.

Solute Clearance

As mentioned previously, the latest NKF-K/DOQI guidelines recommend the use of Kt/V_{urea} alone as the solute clearance measurement to characterize dialysis adequacy. Few studies have been conducted with results that have contributed to the establishment of a recommended target clearance. The ADEMEX study, the largest longitudinal study of adult CAPD patients to date, did not demonstrate any clinical benefit associated with a Kt/V_{urea} of >1.7/week—whereas studies by Lo et al. have provided evidence for a recommended minimal Kt/V_{urea} of >1.7/week and an optimal Kt/V_{urea} of 1.8/week based on survival data in anuric adult CAPD patients. Because no similar large-scale studies have been performed in children and clinical experience supports the recommendation that solute clearance targets in children should meet or exceed those of adults, the latest recommendations for children are as follows.

- *For patients with RRF (defined as urine Kt/V_{urea} of >0.1/week):* The minimal dose of total (peritoneal and kidney) small-solute clearance should be a Kt/V_{urea} of at least 1.8/week.
- *For patients without RRF (defined as urine Kt/V_{urea} of <0.1/week) or in those in whom RRF is unable to be measured accurately:* The minimal dose of small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.8/week.

However, regardless of the delivered dose of dialysis if a patient is not doing well and has no other identifiable cause other than kidney failure a trial of increased dialysis is indicated.

Maintenance of Euvolemia

Optimization of TBW requires knowledge and understanding of ultrafiltration capacity and monitoring of a patient's RRF and PD effluent volume. In patients who are hypertensive or in

whom there is evidence of volume overload, ultrafiltration should generally be positive for all daytime or nighttime exchanges. An effort should be made to determine the lowest possible dialysate dextrose concentration required to achieve the desired ultrafiltration volume so as to help preserve peritoneal membrane function.

This is best conducted with knowledge of the patient's peritoneal membrane transport capacity as derived from the PET. If patients are characterized as high/rapid transporters and are unable to achieve the ultrafiltration necessary for blood pressure control with standard dialysis solutions, consideration should be given to the use of an icodextrin-based dialysis solution. Additional factors that may help maintain euvolemia include dietary sodium and fluid restriction, and diuretics in patients with RRF.

Timing and Frequency of Solute Clearance Measurement

For patients initiating dialysis for the first time and/or patients with substantial RRF, the initial measurement of total clearance should be performed within 4 weeks of the initiation of PD. For patients transferring from another renal replacement therapy to PD and/or for patients who do not have substantial RRF, the initial measurement of the delivered dose of PD should be made within 2 weeks of PD initiation to help prevent a prolonged period of underdialysis. The measurement of total Kt/V_{urea} should be performed when the patient is clinically stable (e.g., stable weight, BUN, and creatinine concentrations) and at least 4 weeks after the resolution of peritonitis.

The total solute clearance should be measured once during the first 6 months of therapy and *at least* once every 6 months thereafter. As mentioned previously, modification of the measurement schedule may be necessary if the dialysis prescription has been changed or there have been clinical events (e.g., protracted/repeated peritonitis) that may have altered the function of the peritoneal membrane. The measurement of RRF should be performed a minimum of every 3 months until the residual Kt/V_{urea} is < 0.1, when its contribution to total clearance becomes negligible. Finally, the patient's record of PD effluent volume should be reviewed monthly—with particular attention to the drain volume from the overnight dwell of CAPD and the daytime dwell of CCPD.

Adjusting the Dialysis Prescription By Computer Modeling

Computer-based dialysis modeling may help tailor the PD prescription to the desired solute removal, transport type, body size, lifestyle, and so on. Kinetic modeling programs use peritoneal membrane transport capacity test data from the standard PET (PD Adequest, Baxter Healthcare) and the Peritoneal Dialysis Capacity test (PACK PD, Fresenius; CDC Gambro) to help in prescription management. These have been validated for clinical use in pediatrics. The major advantage of the computer assistance is the flexibility and speed with which prescription options can be determined.

Kinetic modeling may be especially important for APD therapies because of the variety of prescription modifications inherent to this modality. Whereas an increase in the dwell volume is generally the most effective approach to increase the delivered dose of dialysis, computer-assisted kinetic modeling can also be used to determine the likely impact of changes in the exchange frequency or the addition of a daytime exchange—characteristics that influence dialysis adequacy and QOL. It needs to be emphasized that even with the use of computer assistance actual solute clearance measurements are mandatory to confirm the delivered dialysis dose.

Summary

The adequacy of PD is only one aspect of the global management of the stage 5 CKD patient. Clinicians formulating the PD prescription designed to achieve dialysis adequacy in children should be well versed in the properties of CAPD and APD, the value and limitations of Kt/V_{urea} as a measurement of adequacy, the assessment of peritoneal transport characteristics in children, and the use of computer technology to adjust the dialysis prescription. Although the clinical correlates of adequate or optimal dialysis in children are currently not yet defined (as they are in adults), it must be emphasized that the achievement of numeric targets should never be considered the sole determinant of adequate care.

Kt/V_{urea} is only a measure of delivered dialysis dose and cannot and should not be equated to dialysis adequacy. It should be seen as the minimum dose of dialysis required to keep the patient healthy. Dialysis adequacy should rightly be assessed by the patient's well-being. The recent introduction of tools specifically designed to evaluate QOL in children with kidney

disease provide the means of assessing another important outcome parameter. In the patient who is otherwise thriving, failure to achieve specific numeric targets may not be an indication to alter the dialysis prescription or modality.

Alternatively, it is important to recognize that grossly inadequate solute clearance may occur in patients who show only subtle clinical signs of inadequate dialysis (such as a deteriorating nutritional state). Clinical features that may be suggestive of inadequate dialysis and factors that may contribute to this outcome are outlined in Tables 98.3 and 98.4, respectively. In the end, individualizing the prescription is the key to improving patient outcome with long-term PD therapy (Figure 98.1).

Table 98–3

Outcome Measures That May Be Associated with Inadequate Dialysis

- Lack of subjective feeling of well-being
- Clinical or biochemical signs of malnutrition [e.g., low body mass index (BMI), low serum albumin]
- Poor growth or poor response to recombinant growth hormone
- Developmental delay
- Poor school performance
- Poor response to anemia management
- Poor control of renal osteodystrophy
- Excessive calcium × phosphorus product
- Uncontrolled hypertension
- Congestive heart failure

Table 98–4

Factors Contributing to Inadequate Dialysis

- Loss of residual renal function
- Prescription inadequate for peritoneal membrane transport characteristics
- Reduced peritoneal surface area due to extensive intra-abdominal adhesions
- Loss of membrane solute transport and ultrafiltration capacity due to peritonitis
- Noncompliance with PD prescription
- Poorly functioning PD catheter

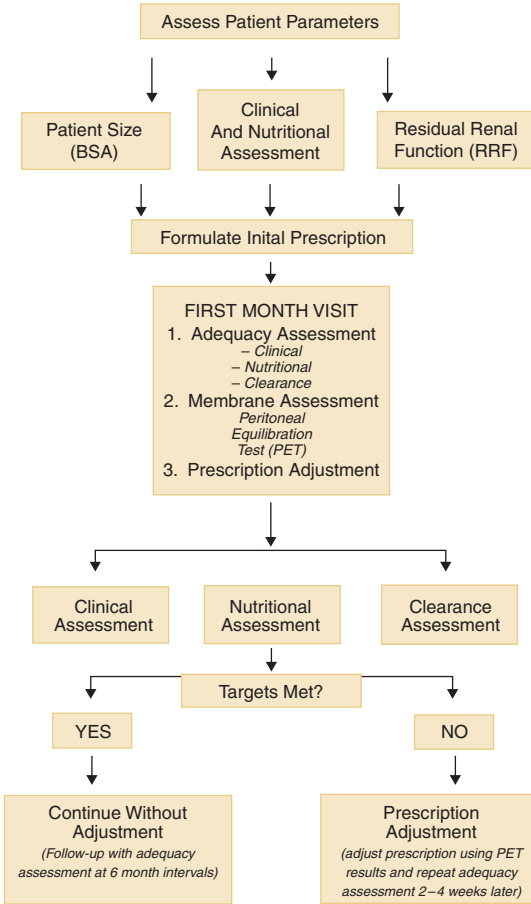


Figure 98–1

Algorithm for PD prescription management.

Recommended Reading

Chadha V, Warady BA. What are the clinical correlates of adequate peritoneal dialysis? *Semin Nephrol.* 2001;21:480–489.

Review article addresses the possible clinical correlates of dialysis adequacy in children.

Fischbach M, Terzic J, Laugel V et al. Measurement of hydrostatic intraperitoneal pressure: a useful tool for the improvement of dialysis dose prescription. *Pediatr Nephrol*. 2003;18:976–980.

Description of measurement of the hydrostatic intraperitoneal pressure as an objective approach to fill volume tolerance.

Goldstein SL, Graham N, Burwinkle T et al. Health Related Quality of Life in Pediatric Patients with ESRD. *Pediatr Nephrol*. 2006;21:846–850.

Study presents results of a pediatric ESRD-specific Health-Related Quality of Life (HRQOL) assessment instrument in 96 pediatric patients with ESRD receiving hemodialysis, peritoneal dialysis or with a renal transplant.

Lo WK, Ho YW, Li CS et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. *Kidney Int*. 2003;64:649–656.

A prospective, randomized control trial examining the effect of Kt/V on continuous ambulatory peritoneal dialysis (CAPD) patients' clinical outcome and nutritional status. 320 patients randomized into three Kt/V targets: group A, 1.5 to 1.7; group B, 1.7 to 2.0; and group C, >2.0. No statistical difference in patient survival, serum albumin, composite nutritional index scores, and hospitalization rate among the three groups. Patients with total Kt/V maintained below 1.7 had significantly more clinical problems and severe anemia.

Mellits ED, Cheek DB. The assessment of body water and fatness from infancy to adulthood. *Monogr Soc Res Child Dev*. 1970;35:12–26.

Anthropometric prediction equations for assessment of body water and fatness derived form healthy population.

Morgenstern BZ, Wühl E, Nair KS et al. Anthropometric prediction of total body water in children who are on pediatric peritoneal dialysis. *J Am Soc Nephrol*. 2006;17:285–293.

Study of total body water (TBW) measurement by heavy water ($H_2^{18}O$) dilution in 64 pediatric patients (aged 1 month to 23 years) receiving chronic peritoneal dialysis to establish and validate anthropometric TBW prediction equations.

National Kidney Foundation. NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. Am J Kidney Dis 48[1 Suppl 1],S1–317. 2006.

Paniagua R, Amato D, Vonesch E et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol*. 2002;13:1307–1320.

A prospective, randomized controlled trial examining the effect of increased peritoneal small-solute clearances on clinical outcomes among patients receiving chronic peritoneal dialysis. A total of 965 subjects were randomly assigned to the intervention or control group. Patient survival was similar for the control and intervention groups in an intent- to-treat analysis.

Warady BA, Alexander S, Hossli S et al. The relationship between intraperitoneal volume and solute transport in pediatric patients. *J Am Soc Nephrol*. 1995;5:1935–1939.

Study demonstrated that exchange volume affects solute transport as determined by the dialysate to plasma (D/P) ratio and emphasized the importance of standardized exchange volume for the reliable interpretation of evaluations such as peritoneal equilibration tests.

Warady BA, Watkins SL, Fivush BA et al. Validation of PD Adequest 2.0 for pediatric dialysis patients. *Pediatr Nephrol*. 2001;16:205–211.

Study evaluated the PD Adequest 2.0 for Windows program (Baxter Healthcare Co., Deerfield, IL) as a prescription aid for the management of pediatric PD patients by comparing the measured and predicted PD clearances, total drain volumes, and net ultrafiltration. There is a basic level of agreement between measured and modeled values for solute removal and total drain volume, but not for net ultrafiltration.

CHAPTER 99

The Peritoneal Equilibration Test in Pediatric Patients

Cornelis H. Schröder, MD, PhD, FASN

Introduction

The prescription of the initial peritoneal dialysis schedule (continuous ambulatory, continuous cycling, or nightly intermittent) is based on an empirically established volume, number, and duration of cycles. The schedule is then fine-tuned based on ultrafiltration and adequacy results. Desired ultrafiltration is dependent on both fluid intake and measured ultrafiltration. Adequacy can be easily determined by measuring urea and creatinine concentrations from 24-hour urine and dialysate collections and a serum sample (Kt/V urea and creatinine clearance).

In the case of inadequate dialysis (both with respect to ultrafiltration and metabolite clearances) the dialysis prescription needs to be adapted. A multitude of choices can then be made by the prescriber (Table 99.1). These can be made on a trial-and-error basis, but it is preferable to use kinetic studies as a guideline for the adaptation of peritoneal dialysis prescription. For this purpose the peritoneal equilibration test (PET) has been most widely applied.

Theoretical Background: Peritoneal Solute and Fluid Transport

The biological character of the membrane used in peritoneal dialysis requires a thorough understanding of the transport pathways in order to achieve an appropriate dose of dialysis for individual patients. Despite extensive studies of the kinetics of solute and fluid removal from the peritoneal cavity during peritoneal dialysis, our understanding of transperitoneal transport is still not complete.

Figure 99.1 summarizes the current understanding of the routes for peritoneal solute and fluid transport. The changes in intraperitoneal volume during peritoneal dialysis are the result of fluid transport from the blood to the peritoneal cavity, and the removal of fluid out of the peritoneal cavity.

Table 99–1

Optimization of Dialysis Schedule in Patients with Inadequate Ultrafiltration/Adequacy

- Dwell volume
- Number of cycles
- Dwell period
- Glucose concentration
- Change peritoneal dialysis modality (e.g., from NIPD to CCPD)
- Addition of daytime icodextrin dwell in NIPD patients
- Convert to hemodialysis

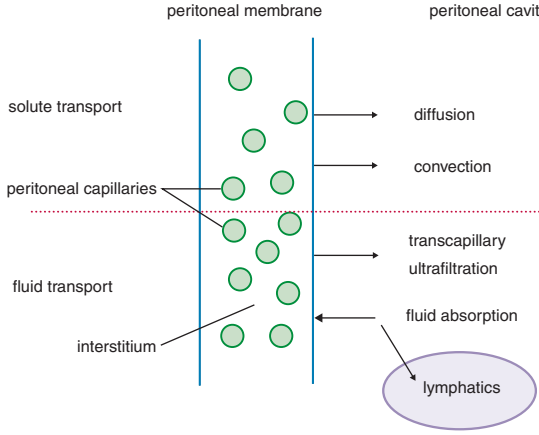


Figure 99–1

Routes for peritoneal transport of solutes and fluid. Solute transport occurs by either diffusion or convection. Fluid transport occurs by either osmotic- or oncotic-induced transcapillary ultrafiltration or by absorption out of the peritoneal cavity directly into the peritoneum or via the lymphatic vessels.

Transport into the Peritoneal Cavity

For transport of fluid from the blood to the peritoneal cavity, osmotic- and oncotic-induced ultrafiltration plays an important role. Removal of uremic toxins across the peritoneal membrane

occurs by two major mechanisms: diffusion and convection. Diffusion is the more important transport mechanism for low-molecular-weight solutes, and is bidirectional depending on the concentration gradient between blood and the dialysis fluid in the peritoneal cavity. The product of the mass transfer area coefficient (MTAC; the maximum theoretical clearance by diffusion at time zero, when no transport has taken place yet) and the concentration gradient between blood and dialysis solution determines the rate of diffusion. Diffusion is a size-selective process, which means that small molecules diffuse at a faster rate than larger molecules due to differences in their free diffusion coefficients.

Convective transport of solutes occurs when equilibrium is present between plasma and the dialysis fluid. Transport of solutes is then determined by the net water transport between plasma and dialysate. The rate of convective transport is limited by two factors: solute sieving and fluid absorption from the peritoneal cavity. The sieving of solutes is determined by the ratio between the dialysate concentration of a solute and its plasma concentration when no transport by diffusion occurs. It can range between 0 (no convective transport at all) and 1.0 (the membrane does not hinder convective transport).

Transport out of the Peritoneal Cavity

During peritoneal dialysis, fluid is lost from the peritoneal cavity into the tissues surrounding the peritoneal cavity and via the lymphatic vessels. The hydraulic pressure within the peritoneal cavity mainly determines the loss of fluid from the peritoneal cavity, which is in contrast to the crystalloid-osmotic- and colloid-osmotic-driven transport into the peritoneal cavity. A hydrostatically driven flux of fluid and solutes occurs into the tissues surrounding the peritoneal cavity, subsequently followed by absorption into the intratissue lymphatics.

In addition to this hydrostatic-pressure-driven transport, fluid is also transported from the peritoneal cavity by subdiaphragmatic lymphatics. The lymphatic openings (also called stomata) permit absorption of intraperitoneal particles, cells, colloids, and fluid. This lymphatic absorption takes place as a result of excursions of the diaphragm during respiration. The majority of investigators agree that fluid absorption directly into the tissues surrounding the peritoneal cavity is the predominant governing influence of fluid loss from the peritoneal cavity.

Based on the current knowledge of peritoneal transport mechanisms, there remains difficulty in understanding how fluid

absorption into peritoneal tissues and transcapillary ultrafiltration can occur at the same time. Knowing that during a normal dwell only a fraction of the anatomic surface area of the peritoneal membrane comes into contact with the dialysis solution, it was suggested that a small amount of fluid will permeate regions of the peritoneum that are not in contact with dialysate—where the fluid will lose its osmotic solutes and will be absorbed due to the hydraulic pressure in the peritoneal cavity.

Several studies concerning peritoneal fluid kinetics refer to the amount of fluid loss from the peritoneal cavity using the term *lymphatic absorption rate*. Because the disappearance of a marker is used to measure fluid loss from the peritoneal cavity (both into the surrounding tissues and by subdiaphragmatic lymphatics), we prefer to use the term *marker clearance* instead of *lymphatic absorption*.

The Three-Pore Model

Although quite simple, the "three-pore model" developed by Rippe et al. is still the most commonly applied mathematical approach to formulation of relationships of intraperitoneal volume versus time under various conditions in peritoneal dialysis. This computer model only takes into account the transport barrier of the peritoneal capillary wall and neglects the mesothelium and the interstitium. Several other published models also take into account the interstitium and the mesothelium, but even though they are more accurate in describing transperitoneal transport their complexity prevents them from being used.

According to the three-pore model, the peritoneum behaves as a membrane having three different types of functional pores: the water-exclusive aquaporins, the small-pore pathways, and the large-pore pathways (Figure 99.2). The frequencies of the pores are inversely related to their pore sizes. Thus, there are approximately 10^6 aquaporins and 10^4 small pores on every large pore.

The small pores represent the major exchange pathway for small hydrophylic solutes and for water. Fluid transport is determined by crystalloid and colloid osmotic pressures. The crystalloid osmotic pressure gradient during peritoneal dialysis with conventional solutions is determined mainly by glucose. Its effectiveness as an osmotic agent depends on the resistance the membrane exerts to glucose transport. This is expressed as the osmotic reflection coefficient, s. It can range from 1 (no passage, ideal semipermeable membrane) to 0 (passage not hindered).

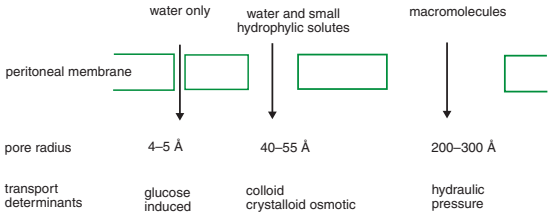


Figure 99–2

Three-pore model of peritoneal transport of solutes and water.

A value of 0.03 for glucose has been calculated in continuous ambulatory peritoneal dialysis (CAPD) patients.

The large pores allow for a slow, unidirectional flux of macromolecules and fluid from the blood to the peritoneal cavity. This transport is driven by hydraulic forces. Computer modeling according to a two-pore formalism of peritoneal transport (taking into account transport across the large and the small pores) allowed for calculation of the individual contribution of each pore system. The large pores are likely to contribute 5 to 6% to transcapillary ultrafiltration. Colloid osmotic forces are negligible across the pore system.

The existence of a third pathway was postulated to be a water-only pathway that rejects solute transport. Computer simulations of peritoneal transport revealed that this water-only transport allows for nearly half the ultrafiltration using conventional glucose solutions. The reflection coefficient of glucose approaches 1.0 across these ultrasmall pores, which might explain why glucose is such an effective osmotic agent despite its small size.

The Peritoneal Equilibration Test

The PET may be performed in several ways. In the literature there is some difference in the glucose concentration chosen, as well as the volume of dialysis solution administered. Although in the original studies by Twardowski et al. a 2.27% glucose solution was used, there are arguments that a 3.86% solution is preferable—particularly if the study of fluid kinetics is included in the PET. Because ultrafiltration is considerably higher using the latter solution, a more detailed and reliable picture of fluid kinetics is obtained.

Presently, it is clear from many studies that the volume prescribed for the PET (as well as for daily clinical practice) should be calculated on the basis of body surface area (not body weight, as was done in the past). Volumes administered in the different studies vary between 800 and 1400 mL/m^2 BSA. In the author's studies, consequently 1200 mL/m^2 are administered (Table 99.2).

The duration of a PET is generally 4 hours, during which period at regular intervals dialysate samples are drawn and compared to one or two serum samples. In this way, dialysate/plasma (D/P) ratios and MTACs can be calculated for urea and creatinine, as well as the D_t/D_0 ratio for glucose. This allows the construction of time/concentration curves, as shown in Figure 99.3. The difference between drained volume and instilled volume (measured ultrafiltration) gives an impression of the ultrafiltration properties of the peritoneal membrane.

Fluid kinetics can be studied in a more accurate way if a large-molecular-weight marker is added to the dialysis solution. This allows calculation of the real transcapillary ultrafiltration (which is higher than the measured ultrafiltration) and of the marker clearance (the disappearance of the dialysis solution in the surrounding tissues; Figure 99.4). The net (measured) ultrafiltration

Table 99–2

Practical Performance of a PET

1. Rinse the peritoneal cavity twice with the regular volume and glucose concentration the patient is treated with.
2. Instill 1200 mL/m2 BSA of a 3.86% glucose solution to which dextran 70 (4 g/L) has been added as a volume marker. During instillation let the patient roll from side to side to promote intraperitoneal mixing of the dialysate.
3. Measure intraperitoneal pressure.
4. Draw dialysate samples for the determination of urea, creatinine, glucose, and dextran 70 at t = 0, 5, 30, 60, 120, 180, and 240 minutes.
5. Draw a serum sample at 120 minutes for the determination of urea, creatinine, and glucose.
   After 240 minutes, measure intraperitoneal pressure and drain the peritoneal cavity. Measure the volume.
6. Instill and drain immediately 1200 mL/m2 of a 1.36% glucose solution. Measure the dextran 70 concentration in the effluent.
7. Resume the normal peritoneal dialysis schedule.

is therfore simply the difference between transcapillary ultrafiltration and marker clearance. In addition, the residual volume (which is approximately 10% of the dialysis volume, but having a large individual variation) can be determined. A full description of the calculations of marker clearance, transcapillary ultrafiltration, net ultrafiltration, and preexchange and postexchange residual volume is found in the section "Formulations" at the end of the chapter.

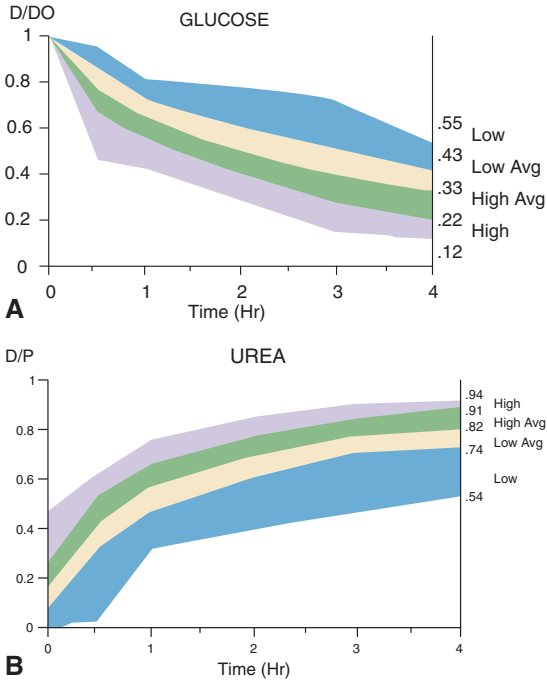


Figure 99–3

A, Dialysate glucose concentration corrected to the initial dialysate glucose (D/DO) in children. The distribution is divided into high, high average, low average, and low equilibration. *B*, D/P blood urea nitrogen ratios in children. The distribution is divided into high, high average, low average, and low equilibration.

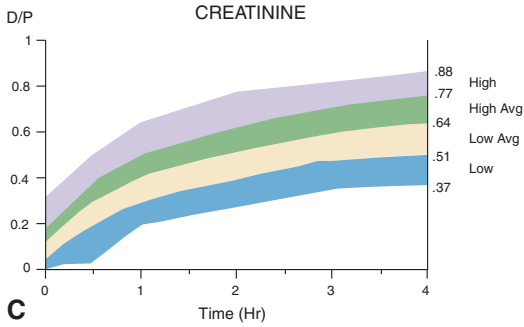


Figure 99–3

Cont'd

C, D/P creatinine ratios in children. The distribution is divided into high, high average, low average, and low equilibration. *(From Warady BA, Alexander SR, Hossli S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol 1996;7:2385–91 with permission.)*

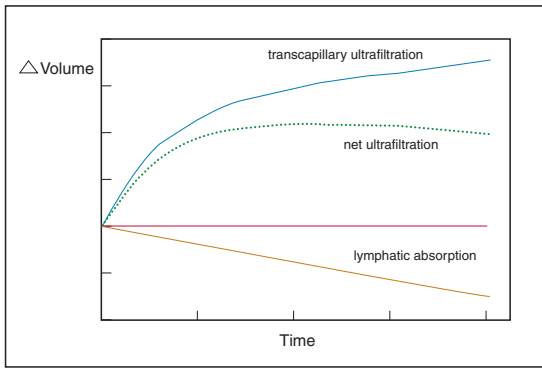


Figure 99–4

Intraperitoneal volume versus time during a PET. Net ultrafiltration is the transcapillary ultrafiltration minus the marker clearance ("lymphatic absorption").

Several macromolecules (human albumin, autologous hemoglobin) have been applied as a volume marker in the PET, but the best results have been obtained with dextran 70 (a 70-kD polyglucose macromolecule). An interesting but less widely applied method of establishing the peritoneal transport characteristics is the determination of the APEX (accelerated peritoneal equilibration examination) time. The APEX time is the moment at which the curves of D/P urea and D_t/D_0 glucose cross. This is approximately after 1 hour. A short APEX time is an indication of a hyperpermeable peritoneal membrane, a long one of a hypopermeable membrane.

If a PET is performed, the measurement of intraperitoneal pressure at the start (just after instillation) and the end (just before drainage) can provide important additional information. Under normal circumstances, intraperitoneal pressure is between 10 and 15 cm H_2O. A low intraperitoneal pressure will hamper ultrafiltration, whereas a high pressure will lead to discomfort.

Interpretation of Results

Normative values for the D/P curves for urea and creatinine and D_t/D_0 curve for glucose in children have been established by several groups, but the most widely applied are those constructed by Warady et al. The values of an individual patient may be plotted against these curves, and hyperpermeability and hypopermeability compared to controls may be established. A patient with a hyperpermeable membrane may benefit from the prescription of shorter dwell times in the daily treatment regimen, whereas a hypopermeable membrane will need longer dwell times. In extreme cases, the patient needs to be converted to hemodialysis.

Equally important is that PET offers the possibility of following long-term peritoneal membrane function, thus giving information on the development of abnormalities with time. Both the development of hyper- and hypopermeability are indications of a deterioration of peritoneal membrane function. It is recommended that a PET be performed every 6 months during treatment with peritoneal dialysis.

Several computer simulation models have been developed to judge fluid and metabolite kinetics, and more importantly to suggest optimization regimens and simulations of effects of changes made in the prescription. Using such a model, the influence of volume increase, number of cycles, change of glucose concentration, and other measures may be predicted in

a more reliable way. The most widely applied computer program is PD Adequest, developed by Vonesh. This program has been validated for pediatric patients and uses the curves of Warady as pediatric norms. In addition, it allows the input of individually calculated figures on marker clearance and residual volume—allowing refining of the predictions.

Use of the PET for Basic Studies of Transport

The PET can be used for more fundamental studies of peritoneal transport mechanisms. Particularly, the peritoneal transport of water through the different types of pores has been the subject of several studies in adults and children. By measuring the sodium concentration in the initial dialysate samples of the PET with a 3.86% glucose solution, a significant decrease of sodium concentration has been observed both in adults and children. This proves a water-only transport to the peritoneal cavity though the ultrasmall pores or aquaporins. If an icodextrin-containing dialysis solution is applied, no decrease in sodium concentration is observed. It is concluded that the high initial ultrafiltration with glucose-containing solutions is mainly through the aquaporins, whereas the slow ultrafiltration with icodextrin-containing solutions is not aquaporin mediated.

The PET also allows the examination of the total peritoneal area available for exchange, indicating the number of capillaries perfused at any given moment and therefore reflecting the peritoneal dialysis capacity. This can be done by the calculation of the steady-state unrestricted area over diffusion distance from the three-pore theory. Using these calculations, it was established that pH-neutral dialysis solutions induce less capillary recruitment than acidic solutions—thus providing new arguments for the better biocompatibility of neutral solutions. This does not, however, result in a difference in transcapillary ultrafiltration (as was shown in another study).

Alternatives to the PET

The Personal Dialysis Capacity (PDC) test is a method to estimate the true peritoneal capacities of individual patients. This method is based on the three-pore model of fluid and solute transport across the peritoneal membrane and was designed to mimic an ordinary dialysis day. The PDC is performed by the patient, following a protocol with five exchanges in 24 hours using

different dwell times and two different glucose concentrations. The PDC is used to calculate 3 parameters: the "area parameter" or unrestricted pore area available for exchange over the diffusion area ($A_0/\Delta X$), which is a fundamental physicochemical parameter for transport across porous membranes determining the diffusion capacities for all solutes; the "absorption" or the reabsorption rate of fluid from the abdominal cavity to the blood, when the glucose gradient has dissipated; and the "large pore flow" representing the flux of plasma through the large pores. In a large multicenter trial it was confirmed that the PDC is a reliable tool for routine evaluation of the peritoneal membrane in adults.

Thus far, only one study has been undertaken to evaluate the effectiveness of PET and PDC in estimating the peritoneal exchange capacity in comparison to each other. It was demonstrated that the unrestricted pore area available for exchange over the diffusion area correlated much better with the plasma appearance rate of intraperitoneally administered iohexol than the PET parameters. As iohexol has proven to be a useful marker of the peritoneal exchange, or the capillary exchange of solutes during dialysis, this study implies that $A_0/\Delta X$ is a better indicator of peritoneal membrane function than are PET parameters. Some data on PDC used with children, is available. It was also confirmed that in children the PDC test was able to model the individual peritoneal membrane function with precision. It was also shown that the test could be performed in APD patients using a simplified study protocol, not requiring a change from an APD to a CAPD regimen, without losing its precision and reliability.

This facilitates the use of a PDC test in most pediatric patients. More recent data obtained in pediatric patients show that $A_0/\Delta X$ can be estimated adequately from the D/P ratios derived from PET analysis. In this study, experimentally determined D/P or D/D_0 concentration ratios for urea, creatinine, phosphate, protein, and glucose were used to estimate $A_0/\Delta X$ for individual patients by using newly developed computer software. This implies that routine performance of PET in combination with the use of adapted computer software will be sufficient to evaluate peritoneal membrane function with more precision.

Formulations

Marker clearance (MC) is defined as the difference between the amount of dextran instilled and the amount recovered, divided by the product of the dwell time and the mean dextran concentration ($v(C_5 \times C_{240})$). It was assumed that MC was a linear process.

The following formula is used. Here, V_i is the volume, C_i is the dextran concentration of the test bag, V_{240} is the drained volume of the test bag, RV_{post} is the calculated postexchange residual volume, C_t is the dextran concentration at time t, and S is the sample volume.

$$\begin{aligned} MC(mL/min) = (C_i \times V_i) - C_{240} \\ \times (V_{240} + RV_{post}) - S \times (C_5 + ...C_{240})\ 240 \\ \times v(C_5 \times C_{240}) \end{aligned}$$

The amount of dextran in the peritoneal cavity is divided by its concentration to calculate intraperitoneal volume (IPV_t). The calculations of IPV_0, IPV_{30}, and IPV_{60} follow. IPV_{120}, IPV_{180}, and IPV_{240} are calculated in a similar way.

$$\begin{aligned} IPV_5\ (mL) = (C_i \times V_i) \\ - MC \times 5 \times v(C_5 \times C_{240}) \end{aligned}$$

$$C_5$$

$$\begin{aligned} IPV_{30}(mL) = C_5 \times (IPV_5 - S) \\ - MC \times 25 \times v(C_5 \times C_{240}) \end{aligned}$$

$$C_{30}$$

$$\begin{aligned} IPV_{60}\ (mL) = C_{30} \times (IPV_{30} - S) \\ - MC \times 30 \times v(C_5 \times C_{240}) \end{aligned}$$

$$C_{60}$$

The theoretical intraperitoneal volume ($TIPV_t$)—that is, the intraperitoneal volume in the absence of MC and sampling—is determined by adding the cumulative sample volume (S_t) and MC:

$$TIPV_t\ (mL) = IPV_t + S_t = MC \times t.$$

Transcapillary ultrafiltration (TCUF) at time t is calculated by subtracting the initial theoretical intraperitoneal volume ($TIPV_5$) from the theoretical intraperitoneal volume at time t:

$$net\ TCUF_t\ (mL) = TIPV_t - TIPV_5.$$

The preexchange residual volume (RV_{pre}) and postexchange residual volume (RV_{post}) are calculated as follows, in which V_r is the inflow volume and C_r the dextran concentration or the rinsing bag after drainage.

$$\begin{aligned} RV_{pre}\ (mL) \\ = V_i \times C_i - V_i \end{aligned}$$

$$C_5$$

$$RV_{post}\ (mL) = V_r \times \frac{C_r}{(C_{240} - C_r)}$$

TCUF and MC are then expressed per $1.73m^2$ body surface area.

Summary

The peritoneal equilibration test is a useful tool for the prescription of the peritoneal dialysis regimen in clinical practice and for the understanding of more basic features of peritoneal permeability. Computer programs for simulation studies are available. It is advocated that a PET be performed every 6 months and that the dialysis prescription be adjusted according to the results.

Recommended Reading

Fischbach M, Lalhou A, Eyer D, Desprez P, Geisert J. Determination of individual ultrafiltration time (APEX) and purification phosphate time (PPT) by peritoneal equilibration test (PET): Application to individual peritoneal modality prescription in children. Perit Dial Int 1996;16:557–60.

The application of the APEX time in children.

Fischbach M, Terzic J, Chauvé S, Laugel V, Muller A, Haraldsson B. Effect of peritoneal dialysis fluid composition on peritoneal area available for exchange in children. Nephrol Dial Transplant 2004;19:925–32.

Study of the peritoneal area available for exchange using different dialysis solutions.

Nourse P, Van de Kar NCAJ, Willems HL, Schröder CH. No significant differences in peritoneal fluid handling in children using pH neutral or acidic solutions. Perit Dial Int 2006;26:587–92.

Study of fluid transport kinetics with pH-neutral biocompatible dialysis solutions.

Reddingius RE, Schröder CH, Willems JL, Lelivelt M, Köhler BEM, Krediet RT, et al. Measurement of peritoneal fluid handling in children on continuous ambulatory peritoneal dialysis using Dextran 70. Nephrol Dial Transplant 1995;10:866–70.

Describes the application of dextran 70 as a volume marker in pediatric PET.

Rippe B, Venturoli D, Simonsen O, De Arteaga J. Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit Dial Int 2004;24:10–27.

Describes the most widely applied mathematical approach to peritoneal transport kinetics.

Rusthoven E, Krediet RT, Willems HL, Monnens LAH, Schröder CH. Peritoneal transport characteristics with glucose polymer-based dialysis fluid in children. J Am Soc Nephrol 2004;15:2940–47.

Study of the aquaporin-mediated water transport with different dialysis solutions by sodium sieving.

Schaefer F, Haraldsson B, Haas S, Simkova E, Feber J, Mehls O. Estimation of peritoneal mass transport by three-pore model in children. Kidney Int 1998;54:1372–79.

Presents the results of PDC testing in children.

Twardowski ZJ, Nolph KD, Khanna R, Prowant B, Ryan LP, Moore HL, et al. Peritoneal equilibration test. Perit Dial Bull 1986;7:138–47.

The original description of the PET in adult patients, using a 2.27% glucose solution.

Vonesh EF, Story KO, O'Neill, PD. Adequest International Study Group: A multinational clinical validation study of PD Adequest 2.0. Perit Dial Int 1999;19:556–71.

The description of PD Adequest, the most widely applied computer model of peritoneal membrane function based on the PET.

Warady BA, Alexander SR, Hossli S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol 1996;7:2385–91.

Presents the most widely used normative values for PET results in children.

CHAPTER 100

Continuous Renal Replacement Therapy in Pediatric Patients

Carl H. Cramer II, MD, and Patrick D. Brophy, MD

Although the basic principles of continuous renal replacement therapy (CRRT) are similar for adults and children, the application of these modalities in children require recognition of the unique properties of pediatric CRRT. Specific attention to detail must be paid to such issues as extracorporeal blood volume and blood priming (especially in patients <10 kg), nutritional issues, etiologic differences in disease processes (i.e., inborn errors of metabolism), access, and line/membrane choice when dealing with problems in this population.

Basic Principles of CRRT

In its various forms, CRRT offers a venue of treatment for pediatric patients requiring renal replacement therapy. This evolving technology represents itself well in the treatment of critically ill children when use of hemodialysis (HD) may not be possible based on patient hemodynamic instability. Further HD may place the patient at risk for potential dysequilibrium, whereas CRRT offers "gentle" fluid and adequate solute removal. CRRT offers an alternative to acute peritoneal dialysis (PD), especially in children with inborn errors of metabolism in whom ongoing PD has been ineffective. PD has been known to cause respiratory compromise by mechanically restricting diaphragmatic movements and increasing the risk of hydrothorax. These concerns are greatly increased in the smallest of our patients, particularly those <3 kg in whom respiratory reserve may already be significantly compromised. Over the past several years, CRRT utilization has increased in the pediatric population. In general, the development of newer technology and appropriate equipment has advanced this modality for use in pediatrics. With the development of more accurate fluid pumps (both blood and ultrafiltration), the error rate associated with the older systems has been decreased significantly. Improved mobility has allowed easier application of this technology in areas it has previously proved cumbersome, such as the operating room.

CRRT is indicated in the pediatric population for a variety of reasons. The "classic" patient would be hypervolemic with anuric acute renal failure (ARF) and electrolyte abnormalities. Under such circumstances, CRRT is the ideal modality because it allows continuous blood purification and volume control even in hemodynamically unstable patients. The Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT) has confirmed previous single-center studies indicating that the degree of fluid overload at time of CRRT initiation inversely correlates with patient survival (i.e., larger fluid overload and higher mortality). This study, as well as others, suggests that patient fluid overload greater than 15 to 20% (above baseline weight) is an independent indication for CRRT initiation. Other indications include catabolic patients with increased nutritional needs, patients with sepsis, poisoning (occasionally in combination with HD), hyperammonemia, inborn errors of metabolism, diuretic unresponsive hypervolemia, and hepatic- or drug-induced coma. In addition, CRRT in conjunction with other therapies [such as plasmapheresis, extracorporeal membranous oxygenation (ECMO), and the newer hepatic support therapies] has proven quite useful.

In general, CRRT may be divided into the following common modalities: continuous venovenous HD (CVVHD), continuous venovenous hemofiltration (CVVH), and continuous venovenous hemodiafiltration (CVVHDF). The historical simultaneous arterial and venous access for CRRT [i.e., continuous arteriovenous hemofiltration (CAVHF)] is seldom used because of complications in maintaining adequate circuit flow and risk to the patient. The employment of these modalities requires an appreciation for some of the basic concepts underlying mechanisms of solute transport across semipermeable membranes (Table 100.1).

Diffusion, which occurs primarily with HD, refers to solute movement across a membrane resulting in the same concentration on either side of the semipermeable membrane. Convection, which occurs primarily with hemofiltration, refers to the movement of solute across a semipermeable membrane. The solute is transported together with solvent [filter replacement fluid (FRF)] by means of filtration, which occurs in response to a transmembrane pressure (TMP) gradient. The ultrafiltrate is the substance generated from crystalloids and plasma water removal from whole blood by crossing a semipermeable membrane in response to a TMP gradient.

Table 100–1

Equations Governing Basic Concepts of CRRT

Diffusion

- Solute transport is governed by Jd = DTA (dc/dx), where:

Jd = solute flux, D = diffusion coefficient, T = solution temperature, A = membrane surface area, dc = concentration gradient between compartments, and dx = membrane thickness.

Convection

- Filtration is governed by Qf = Km TMP, where:

Qf = filtration rate (mL/h), Km = membrane permeability coefficient, and TMP = transmembrane pressure (mmHg). (TMP = Pb – Puf-p, where: Pb = hydrostatic pressure of blood, Puf = hydraulic pressure of the dialysate/ultrafiltrate compartments, and p = protein oncotic pressure.)

- Solute transport is governed by $Jc = UF(x)_{uf}$, where:

UF = ultrafiltrate volume and $(x)_{uf}$ = solute 3 concentration in the ultrafiltrate.

- Convective treatment clearance is represented by $Kc = Qf\ (x)_{uf}/(x)_{Pw}$, where:

Qf = ultrafiltration rate and $(x)_{uf}/(x)_{Pw}$ = ratio of ultrafiltrate and plasma water solute concentrations (or the sieving coefficient).

During ultrafiltration, solutes are carried across the membrane based on their membrane rejection coefficient. The sieving coefficient is equal to 1 minus the membrane rejection coefficient and is clinically represented by the ratio between the concentration of solute in the ultrafiltrate and the plasma water. For molecules such as albumin, the membrane rejection coefficient is 1. Therefore, the sieving coefficient is 0 (whereas the opposite is true for urea).

CVVH uses convection exclusively. In this case, the ultrafiltrate produced is replaced completely or in part by sterile FRF. Solute clearance is dependent on blood flow rate, rate of FRF (mL/hour), and surface area of the membrane used. Convection theoretically has the advantage of increased clearance of "middle molecules" generated during sepsis.

CVVHD offers diffusive solute clearance as occurs in standard intermittent HD. The notable difference is the dialysis solution rate in CVVHD is 2000 mL/hour/1.73m^2 (34 mL/minute) versus 350 to 800 mL/minute of dialysate rate in intermittent HD. CVVHDF offers both convective and diffusive solute clearance. This technique may offer an improved clearance rate of some intoxicants and middle molecules. Again, fluid balance can be maintained or titrated to the desired rate by the administration of a sterile solution. FRF can be administered either premembrane filter (predilutional) or postmembrane filter (postdilutional). For venovenous circuits, predilutional replacement may be preferred because it may decrease blood viscosity and hence improve filter longevity.

Technical Aspects of CRRT

Several commercial CRRT machines are potentially available for use in the pediatric population. The adequacy of their use in smaller children remains to be fully established. In situations in which older hemofiltration systems are used, one must be cognizant that infusion pumps may be off as much as 30%, causing a rapid change in the patient's weight. In these situations, it is imperative that the patient's weight be monitored. It also requires that effluent bags be collected and measured in a graduated cylinder or weighed to determine proper output. The newer pump-dependent machines appear to be safer and offer more accurate ultrafiltration control than past adapted machines. Thus, CVVH(DF)—rather than CAVH(DF)—has become the preferred method of CRRT for pediatric patients at most centers.

These systems offer the advantage of single-, dual-, or triple-lumen access and are effective when the patient is unable to generate a significant arteriovenous pressure difference (i.e., cardiac failure). However, the larger circuit volumes associated with CVVH(DF) can be problematic when initiating therapy in smaller infants or neonates. As a rule, an attempt is made to keep the extracorporeal circulating blood volume <10% of the patient's total blood volume. In these cases, whole-blood priming is often done at the initiation of treatment in order to decrease the potential hemodynamic compromise. These pump-assisted systems do include blood pumps and air leak detectors, as well as venous pressure monitors, which enable relative ease of intervention when required. For example, PrismaFlex (Gambro, Lakewood, CO) and Accura (Baxter Health Care, McGaw, IL) are machines compatible for use in the pediatric patients.

CVVH(DF) can be hindered by increased blood tubing that can increase resistance and decrease effectiveness of ultrafiltration. In addition, efficiency is decreased when the hematocrit is elevated. An optimal hematocrit is usually present between 30 and 35%.

Prescription

Each center has its own rules of thumb for prescribing CRRT. Our standard prescription for CVVH(DF) includes a blood flow rate of 4 to 6 mL/kg/minute, with either the use of pre- or postfilter FRF at a desired rate and/or countercurrent dialysate at 2000 to 4000 mL/hour/1.73 m^2. The goal ultrafiltration is 0.5 to 2 mL/kg/hour in hypervolemic patients. The CRRT circuit volume should ideally be <10% of the intravascular blood volume of the patient. Infants less than 10 kg have a blood volume of approximately 80 cc/kg, which slowly decreases to about 70 cc/kg in adulthood.

Caution needs to be used in circumstances in which the circuit volume is in excess of 10% of the patient's total blood volume. In these cases, blood priming often becomes necessary. The packed red cells obtained from most blood banks have a high hematocrit (about 60%) and need to be reconstituted to about 30% with 0.9% saline in order to avoid clotting the circuit. Attention to the initial clinical response of the child at the initiation of CRRT is required in order to prevent any electrolyte side effects from the high-potassium and low-calcium content found in blood-bank blood.

The potential for the development of hypothermia in youngsters with a significant portion of their blood volume in the extracorporeal space needs to be anticipated. In such circumstances, heating pads may be applied to replacement fluid bags (or the circuit tubing can be heated). In the newer CRRT machines, tubing warmers are a standard feature.

Dialysis/Filter Replacement Solution

The utilization of countercurrent dialysis (CCDx) solution versus FRF is based on a local standard of care. Our general approach is to use CCDx in most patients. The use of FRF may be preferred in sepsis, because it may offer improved clearance/dilution of the toxins associated with sepsis.

Various sterile solutions exist that may be employed as CCDx or FRF. A variety of commercially available FDA-approved

solutions have become available over the past couple of years. Alternatively, pharmacy-prepared bicarbonate-based customized solutions may be employed. These may be phosphorus or calcium based. It makes no difference whether phosphorus or calcium is used. However, with the phosphorus-based solutions calcium must be infused and with the calcium-based solution phosphorus must be infused to the patient (Table 100.2). This approach allows rapid tailoring of therapy to meet the changing requirements of the patient. Its primary drawbacks include its cost, the potential for introduction of infection, and the significant risk of electrolyte composition error leading to morbidity and/or mortality.

Anticoagulation

The clotting system is activated in CRRT circuits because of the circulating blood's contact with artificial surfaces. A low blood-flow rate and a high hematocrit enhance this effect. Individual circumstances dictate anticoagulation requirements. Various methods of anticoagulation have been suggested for CRRT. Low-molecular-weight heparin, prostacyclin, serine protease inhibitors, and regional citrate administration have all been used. Systemic anticoagulation can be hazardous in terms of patient bleeding, and currently in, North America, the predominant method is utilization of regional citrate anticoagulation in pediatric practice.

Various citrate protocols exist with a common theme among them of vigilant monitoring of patient and circuit ionized calcium. One example of a citrate initiation protocol is starting the rate of Baxter ACD (Acid Citrate Dextrose) solution (Baxter Health Care, McGaw, IL) at 1.5 x Qb in mL/hour. In this case, calcium chloride (20 mg/dL) is started at 0.12 x the ACD citrate rate in mL/hr. The targeted CRRT system ionized calcium is between 0.25 and 0.40 mmol/L. This is accomplished and maintained by adjusting the citrate flow rate. Simultaneously, calcium is delivered back into the patient to target the patient's calcium to a physiologic level between 1.10 and 1.30 mmol/L. An example of a heparin protocol is to administer heparin prefilter with a load of 10 to 20 U/kg/dose with a subsequent infusion at 10 to 20 U/kg/hour. The goal activated coagulation time is approximately 200 seconds. Efficient anticoagulation is best reflected in the filter life span. The ppCRRT study group recently published the largest multicenter study comparing heparin, citrate, and no-anticoagulation methods in terms of filter life span. Although no difference was noted in the heparin and citrate groups, the no-anticoagulation method was associated with a significant

Table 100–2

Comparison of Custom-Made Versus Standard, Commercially Available Solutions

Electrolyte (mmol/L)	Normocarb (DSI)	PrismaSate (Gambro)	ACCUSOL (Baxter)	Duosol (Braun)	Ringer's Lactate	Custom (Pharmacy)
Na (mEq/L)	140	140	140	136/140	130	135
Ca (mEq/L)	0	0/2.5/3.5	2.8/3.5	0/3	3	0
K (mEq/L)	0	0/2/4	0/2/4	0/2	4	0–4
Mg (mEq/L)	1.5	1/1.5	1.0/1.5	1/1.5	0	1.5
Cl (mEq/L)	107	108–120	109–116	109–115	109	110
Phos (mmol/L)	0	0	0	0	0	0.75–1.50
Lactate (mEq/L)	0	3	0	0	28	0
Bicarb (mEq/L)	25/35	23/32	30/35	25/35	0	25
Glu (mg/dL)	0	0/110	0/100	0/100	0	0
FDA OK	Y (D&FRF)	Y (D)	Y(D)	Y (D)	Y (FRF)	N (D&FRF)

These are a small representation of the various formulas available and it is recommended that one visit each company's web site or directly contact the company for complete information.
D = dialysate, FRF = filter replacement fluid.

loss of filters. Patients treated with heparin developed more life-threatening complications than the citrate group in these analyses. A large determinant of filter function and duration became apparent in terms of adequacy of access in this analysis. Thus, access became the apparent limiting factor in the pediatric patient population.

Access

Inadequate access often results in being unable to achieve adequate blood flow rates, making CRRT difficult (if not impossible). In general, venous pressure should be maintained less than 200 mmHg. Optimally, access for CVVH(DF) is placed in the right internal jugular vein (the right subclavian vein being somewhat less desirable). As a rule, it is best to optimize the catheter size to provide adequate blood flow rates. This is based on the patient's size (Table 100.3) and clinical status. In the case of the neonate, a 7 French catheter or umbilical vessels can be used.

Table 100–3

Suggested Size and Selection of CRRT Vascular Access for Pediatric Patients

Patient Size	Catheter Size and Source	Site of Insertion
Neonate	Single-lumen 18-, 16-, 14-gauge (Cook)	Femoral artery or vein
	Single-lumen 16-gauge (Argyle)	Femoral artery or vein or umbilical vein
	Dual-lumen 7.0 French (Cook/Medcomp)	Femoral vein
3–6 kg	Dual-lumen 7.0 French (Cook/Medcomp)	Internal/external jugular, subclavian, or femoral vein
6–30 kg	Dual-lumen 8.0 French (Kendall, Arrow)	Subclavian or femoral vein
>15–30 kg	Dual-lumen 9.0 French (Medcomp)	Internal/external jugular, subclavian, or femoral vein
>30 kg	Dual-Lumen 10.0 French (Arrow, Kendall)	Subclavian or femoral vein

CRRT Membranes/Filters

With respect to the hemofilters used in CRRT, the surface area is significantly smaller than the surface area of HD dialyzers. These filter membranes have improved convective water transfer, which enhances middle-molecule clearance. Commercially available hemofilters are chosen based on the equivalent body surface area related to the patient's weight (Table 100.4). As a rule, the filters are permeable to nonprotein-bound solutes with a relative molecular mass less than 40,000 (although this is dependent on the filter fibers of the specific hemofilter).

CRRT membranes have both improved in terms of biocompatibility over the past decades. In 1998, Himmelfarb and colleagues demonstrated a significant difference in that 57% of patients treated with the biocompatible membranes (BCMs)

Table 100–4

Pediatric Circuit Volumes and Hemofilter Properties

Patient Size	Hemofilter	Membrane Material	Surface Area	Filter Priming Volume
<5 kg	M10	AN-69	0.042 m^2	50 mL[a]
<10 kg	Minifilter Plus	Polysulfone	0.07 m^2	15 mL[b]
>5 kg	HF 400	Polysulfone	0.30 m^2	28 mL[b]
	PAN 0.3	Polyacrylonitrile	0.30 m^2	33 mL[b]
	M60	AN-69	0.60 m^2	84 mL[a]
>15 kg	M100	AN-69	0.90 m^2	107 mL[a]
>20 kg	HF 700	Polysulfone	0.71 m^2	53 mL[b]
	PAN 0.6	Polyacrylonitrile	0.06 m^2	63 mL[b]
	HF1000	Polyarylethersulfone	1.15 m^2	165 mL[a]
>30 kg	HF 1200	Polysulfone	1.25 m^2	83 mL[b]
	PAN 1.0	Polyacrylonitrile	1.00 m^2	87 mL[b]
	HF 1400	Polyarylethersulfone	1.40 m^2	186 mL[a]
>35 kg	HF 2000	Polysulfone	1.98 m^2	132 mL[b]

a. These filters come as "sets" that include the filter attached to the bloodlines. The volumes provided include filter and tubing line.
b. The arterial and venous bloodlines are sold separately and volumes vary depending on manufacturer. For example, adult lines (110 mL) and pediatric lines (64 mL) are available for the HF series.
This is a sample of various filters available in the United States.
See manufacturers' filter specification sheet for complete details. AN-69 Membrane (acrylonitrile and sodium methallyl sulfonate co-polymer).

survived versus 46% of patients treated with the bioincompatible membranes (BICMs). In addition, 64% of patients in the BCM group recovered renal function, whereas only 43% of patients in the BICM group did. They further noted that these results were marked in individuals who were nonoliguric at the onset of dialysis.

The increased use of biocompatible membranes such as the AN-69 (MULTIFLO 60 or 100, Gambro, Lakewood, CO) in CRRT—although improving complementation activation and overall patient outcome—led to the recognition of an entity termed the "bradykinin release phenomenon." This occurs in relation to membrane coactivation of prekallikrein and Hageman factor, resulting in production of bradykinin (which is a potent vasodilator). This membrane reaction is potentiated by the presence of angiotensin-converting enzyme inhibitors and is pH dependent. In smaller patients who require blood priming, this presents as a potential cause of hypotension because most blood-bank blood has a pH of about 6.3 and has the bioactive components required to trigger the bradykinin release phenomenon.

Our approach to this reaction is to bypass the hemofilter by giving the blood postfilter and synchronizing a saline prime of the filter at the same time. This, along with judicious use of bicarbonate boluses, has essentially eradicated this phenomenon in our experience. Ionized calcium measurements have been normal in these patients, suggesting that the pH (not electrolyte abnormalities) were responsible for this phenomenon.

Nutrition

Although CRRT readily allows for optimization of nutritional support in patients with high catabolic states (such as ARF), it also contributes to the development of a negative nitrogen balance through loss of free amino acids and peptides across hemofilters. The standard administration of 1.5 g/kg/day of protein is inadequate in most pediatric patients undergoing CRRT. Patient nutrition should be tailored to meet their overall needs with the aim of promoting an anabolic state. It is clear that improved nutrition is associated with decreased morbidity in such patients. Currently, we suggest 2.5 to 3.0 g/kg/day of protein (with a target BUN of aabout 40–60 mg/dL) and a daily caloric intake 20 to 30% above normal resting energy expenditure in the form of total parenteral nutrition (or better yet, enteral feeds).

Special Applications of CRRT

Extracorporeal Membranous Oxygenation

Respiratory failure, as well as cardiac failure, in the pediatric or neonatal intensive care unit may necessitate ECMO. Nearly half of these children undergo CRRT for ARF at some time during their course of ECMO. The ECMO circuit provides heparinization, access, and an ECMO blood flow rate generally in excess of 100 mL/kg/minute. It is imperative that the hemofilter not be placed in series with the oxygenator. A parallel-placed hemofilter may cause the blood to bypass the oxygenator in favor of the lower-resistance circuit of the hemofilter, causing it to rupture and thereby decreasing oxygen to the circuit. The optimal position is to "pull" postoxygenator and return to the bladder of the ECMO circuit.

The blood flow rate across the hemofilter may be 200 to 300 mL/minute. In the small child, this may result in excessive clearance. In the larger child, these blood flow rates may not allow for acceptable clearance. In situations of poor clearance substitution of a larger surface dialyzer (or HD membrane if needed) may overcome these issues. An analysis of 35 patients who underwent CRRT while on ECMO at our center revealed a 43% overall survival rate (to hospital discharge), with a total of 93% of these survivors having full return of renal function after ECMO discontinuation.

Inborn Errors of Metabolism

Utilization of CRRT for treatment of inborn errors of metabolism (such as urea cycle defects) is standard practice. In children with very high ammonia levels, HD should be used first (followed by CRRT) in order to prevent the usual rebound associated with intermittent HD. If a metabolic cocktail such as sodium benzoate is required, the dose may need to be increased in order to accommodate the increased clearance these cocktails have with CRRT. In general, we have found doubling the infusion rate to be adequate.

Intoxications

Use of CRRT in combination with HD for treatment of intoxication (lithium, carbamazepine, and vancomycin) is quite successful, decreasing (and in most cases eliminating) the need for charcoal hemoperfusion.

Hyperosmolar Conditions

Hyperosmolar dialysis solutions and prefilter FRF solutions can be customized by some pharmacies to drive up the serum sodium to150 mEq/L in conditions complicated by elevated intracranial pressure.

Summary

CRRT for the critically ill pediatric patient offers a safe, efficient, and reliable form of renal replacement therapy. The use of this modality is expanding as an increasing number of applications for this modality become apparent. Early intervention with this modality is helping to delineate which groups of patients are best served by it. As the factors that determine survival of critically ill infants and children are better established, it is likely that CRRT will assume a greater role in our overall treatment approach. Cooperative efforts among pediatric critical care physicians, nephrologists, and nurses will enhance the ability to care for sick children with CRRT.

Recommended Reading

Barletta JF, Barletta GM, Brophy PD, et al. Medication errors and patient complications with continuous renal replacement therapy. Ped Nephr 2006:21:842–45.

Provides information supporting commercial-based production of dialysis and FRF solutions.

Brophy PD, Mottes TA, Kudelka TL, et al. AN-69 membrane reactions are pH-dependent and preventable. Am J Kidney Dis 2001;38:173–78.

Describes factors involved in AN-69 (biocompatible) membrane reactions and provides two methods of circumventing the bradykinin release phenomenon in pediatric hemofiltration.

Brophy PD, Somers MJG, Baum MA, Symons JM, McAfee N, Fortenberry JD, et al. Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy. Nephrol Dial Transplant 2005;20:1416–21.

The largest multicenter anticoagulation study published to date. Establishes that no anticoagulation in the pediatric population results in poor filter life span and points to the issues of access in pediatrics as the most problematic area.

Chadha V, Garg U, Warady BA, Alon US. Citrate clearance in children receiving continuous venovenous renal replacement therapy. Ped Neph 2002;17:819–24.

Excellent discussion on the use of citrate in CRRT.

Foland JA, Fortenberry JD, Warshaw BL, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. Ped Crit Care 2004;32:1771–76.

Provides support for initiation of CRRT in children with fluid overload and the overall improved survival in critically ill children on CRRT.

Goldstein SL, Somers MJG, Baum MA, et al. The Prospective Pediatric CRRT Registry Group. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. KI 2005;67:653–58.
Multicenter prospective study demonstrating the importance of initiating CRRT before patients are >20% fluid overloaded.
Himmelfarb J, Tolkoff Rubin N, et al. A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. J Am Soc Nephrol 1998;9:257–66.
Excellent study demonstrating benefits of biocompatible membranes in intensive care unit patients.
Kutsogiannis DJ, Gibney RT, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. KI 2005;67:2361–67.
Discuss the benefits of citrate over heparin on survival of hemofilter and lower risk of bleeding.
McBryde KD, Bunchman TE, Kudelka TL, et al. Hyperosmolar solutions in continuous renal replacement therapy for hyperosmolar acute renal failure: A preliminary report. Pediatr Crit Care Med 2005;6:220–25.
Provides case examples of using CRRT in patients with hyperosmolar conditions.
Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: A prospective comparison between classic hemofiltration and hemofiltration with dialysis. Crit Care Med 2000;28:1161–65.
Provides insightful data regarding nutritional supplementation in pediatric patients on hemofiltration. Also provides quantitative data regarding nitrogenous loss while on hemofiltration.
Symons JM, Brophy PD, Gregory MJ, et al. Continuous renal replacement therapy in children up to 10 kg. Am J Kid Dis 2003;41:984–89.
Retrospective review of the outcome and feasibility of CRRT in children less than 10 kg.

CHAPTER 101

Prevention and Treatment of Bone Disease in Pediatric Dialysis Patients

Cheryl P. Sanchez, MD

Despite improvements in the management of children with kidney disease, impairment of linear growth remains suboptimal—with standard deviation scores for height less than –1.88 at the time of study enrollment according to recent North American Pediatric Cooperative Study (NAPRTCS) data. In addition, renal bone disease can lead to disabling skeletal deformities requiring extensive surgical correction.

Pathogenesis of Bone Disease

Development of High-Turnover Bone

Histologic changes associated with secondary hyperparathyroidism may occur early, without significant elevation in parathyroid hormone (PTH) levels. There are several factors that contribute to the development of bone disease in chronic renal failure. These are discussed in the sections that follow.

Hypocalcemia and Phosphorus Retention

Suboptimal nutrition in children on maintenance dialysis therapy may contribute to low serum calcium levels, which can directly stimulate PTH secretion. Elevated serum phosphorus levels have been associated with hypocalcemia, inhibition of the enzyme 1a-hydroxylase, direct stimulation of PTH secretion, and synthesis independent of calcium and calcitriol levels. Several clinical studies have shown that elevated phosphorus levels and high calcium-phosphorus product increase cardiovascular morbidity and mortality risk in adult dialysis patients.

Decreased Calcitriol (1,25-dihydroxyvitamin D_3) Synthesis

Serum calcitriol levels decline early in the course of chronic renal failure. Circulating small molecular substances in uremia,

including guanidinosuccinic acid, can inhibit renal 1α-hydroxylase activity and inhibit the binding of calcitriol to the vitamin D receptor (VDR). The reduction in calcitriol synthesis can lead to diminished intestinal calcium absorption, hypocalcemia, and secondary hyperparathyroidism.

Parathyroid Gland Hyperplasia

The initial stimulus for the development of parathyroid gland hyperplasia in renal failure is still unclear. Hypocalcemia and high dietary phosphorus content can directly stimulate parathyroid gland synthesis and secretion. The accumulation of the carboxyterminal (C-terminal) and non–1-84 PTH (N-truncated) fragments, which can antagonize the biologic activity of 1-84PTH, can lead to further parathyroid gland enlargement. Nodular areas in the hyperplastic parathyroid gland have poor response to calcitriol due to diminished VDR and calcium receptor expression.

Resistance to Skeletal Actions of PTH

The current recommendation to maintain the serum "intact" PTH levels within 2 to 4 times the upper limits of normal in children on chronic dialysis therapy was based on bone biopsy findings of normal rates of bone formation during treatment with vitamin D. Maintaining a higher target serum intact PTH level may not be satisfactory in the long run because the parathyroid gland continues to function above normal and this may lead to further parathyroid gland hyperplasia. There are several factors that may contribute to the development of skeletal resistance to PTH in renal failure, including the downregulation of PTH/PTHrP receptors in the osteoblast, diminished BMP-7 expression, low vitamin D and calcium receptor expression, and increased FGF-23 and osteoprotegerin levels.

Uncorrected Metabolic Acidosis

Metabolic acidosis promotes bone demineralization, leading to negative calcium balance, movement of inorganic phosphorus from the non-extracellular compartment to the extracellular fluid (worsening hyperphosphatemia), increased PTH levels, and lowered growth hormone secretion.

Possible Role of Fibroblast Growth Factor 23

Fibroblast growth factor 23 (FGF-23) is a newly identified phosphaturic factor that may participate in the development of secondary hyperparathyroidism in renal failure. Serum

FGF-23 levels are elevated in renal failure, highly correlated with serum phosphorus levels and inversely related to levels of calcitriol.

Low-Turnover Bone

Deficiency of 25-hydroxyvitamin D

Defective bone mineralization (osteomalacia) can result from vitamin D deficiency in renal failure. The incidence in children has dramatically declined secondary to the widespread availability of vitamin D and regimens of increased calcium intake and adequate control of dietary phosphorus.

Aluminum Toxicity

Low-turnover bone associated with aluminum is seldom reported because of the judicious use of aluminum binders and the increased use of calcium salts.

Oversuppression of PTH

In the 1990s, high doses of calcium salt, aggressive use of vitamin D to lower PTH levels, and the prevalent use of high-calcium dialysate may have contributed to the increased histologic finding of adynamic or aplastic bone in pediatric patients. The clinical implications of adynamic bone require further investigation in children, but reduction in linear growth and inhibition of cartilage resorption in the growth plate have been described accompanied by hypercalcemia and considerable decline in serum PTH levels.

Clinical Signs and Symptoms

Impairment of Linear Growth

A substantial proportion of pediatric patients with chronic renal failure are growth retarded, especially infants and young children—who have the greatest potential for increase in linear growth. Clinical surveys have shown that adult patients who had chronic renal failure as children associated being taller with a better overall quality of life. Despite normal serum levels of IGF-I, there is considerable reduction in IGF-I availability due to the accumulation of various IGF (insulin growth factor) binding proteins and altered regulation in the hepatic JAK-STAT (Janus Kinase) (signal transducers and activators of transcriptions) signaling pathway.

Skeletal Deformities and Pain

Genu valgum is the most common skeletal deformity in pediatric patients. Young children may exhibit exaggeration of the physiologic varus alignment. Radiographic features associated with vitamin D deficiency include metaphyseal widening of the wrist and ankle, craniotabes, and rachitic rosary. Pathologic or stress fractures may arise if the bones remain bowed and weak. The prevalence of slipped capital femoral epiphysis has declined over the last two decades due to better control of secondary hyperparathyroidism. Skeletal pain can accompany limping or problems with weight bearing.

Myopathy

Muscle involvement can range from muscle wasting, diffuse pain, weakness, and numbness to contracture of the extremities. The exact etiology for the myopathy described in renal failure is still unclear, but rapid fluid removal, electrolyte imbalance, low calcitriol, and the presence of calcific uremic arteriolopathy or calciphylaxis may contribute. There are no diagnostic tests available, and muscle biopsy may show severe atrophy without inflammation or the presence of calcification of small and medium-size vessels.

Extraskeletal Calcification

The prevalence of mineral deposition is higher in patients who had onset of chronic renal failure at a young age, treatment with vitamin D (particularly calcitriol), elevated calcium-phosphorus product, high phosphorus levels, and large doses of calcium salt intake.

Dental Problems

There is limited information on the oral manifestations of bone disease in children with chronic renal failure. Skeletal lesions associated with the development of severe secondary hyperparathyroidism (“brown tumors”) have been demonstrated in some patients. These can lead to facial deformity and jaw enlargement. Children should be evaluated early and followed closely by a pediatric dentist.

Diagnostic Tools

Biochemical Tests

Calcium

Hypocalcemia is a frequent finding in patients with chronic renal failure. Several factors may account for the low serum calcium levels in renal failure, including poor nutrition, inadequate production of calcitriol, and hyperphosphatemia. Calcium can directly regulate PTH gene expression and synthesis. Hypercalcemia has been reported in patients with adynamic bone, aluminum-related bone disease, and secondary hyperparathyroidism. It is also associated with vitamin D therapy, prolonged immobilization, and intake of calcium salts as phosphate binding agents. Serum calcium levels must be maintained within the recommended range for age (Table 101.1).

Phosphorus

Clinical studies have demonstrated that chronic elevation of serum phosphorus level was associated with an increase in cardiovascular morbidity in adult dialysis patients. The clinical implications of these findings require further evaluation in children with chronic renal failure. Serum phosphorus concentration varies widely in children and is age dependent (Table 101.1). Hypophosphatemia occurs infrequently in children with chronic renal failure and is usually seen in patients with some form of tubular problem.

Table 101–1

Range of Normal Values for Serum Calcium, Phosphorus, and Alkaline Phosphatase

Age Group	Serum Calcium (mg/dL)	Serum Phosphorus (mg/dL)	Alkaline Phosphatase (U/L)
Less than 1 year	8.8–11.0	4.0–7.5	145–600
1–5 years	8.8–10.8	3.8–6.5	130–550
5–10 years	8.8–10.8	3.7–5.5	80–450
10–12 years	8.8–10.2	3.7–5.5	60–450
14–19 years	8.4–10.2	2.5–5.5	60–450

Intact Parathyroid Hormone

The majority of the bone biopsy studies performed within the last decade have been correlated with serum PTH levels measured using the Intact PTH assay. Using these histologic studies, the current recommendation is to maintain serum intact PTH level two to four times the upper limit of normal (150–300 pg/mL) in children on dialysis to prevent the development of adynamic bone. Serum PTH values measured using the Intact assay are approximately 30 to 50% higher than PTH levels determined by the newer 1-84PTH assay.

Alkaline Phosphatase

The use of total alkaline phosphatase as a marker for osteoblastic activity has been reported as a poor predictor of bone histology in chronic renal failure compared to PTH. The introduction of the newer immunoassay to measure bone-specific alkaline phosphatase may be a better marker in evaluating bone turnover in patients with renal failure. The bone isoenzyme is specifically derived from osteoblasts expressed during maturation and the early mineralization phase. In conjunction with other biochemical markers, total serum alkaline phosphatase should be monitored during treatment with vitamin D and maintained within the age-appropriate serum level (Table 101.1).

Aluminum

Monitoring of serum aluminum levels is done infrequently in dialysis centers due to a significant decline in the use of aluminum as a phosphate binding agent. Plasma aluminum levels reflect more recent exposure and do not measure aluminum tissue deposition. Bone biopsy specimens with aluminum staining greater than 15 to 25% and an increase in plasma aluminum level greater than 50 μg/L following deferoxamine infusion test are diagnostic.

Radiographic Evaluation

The most common radiographic finding is the presence of subperiosteal resorption in the cortical bone. Intensive cortical resorptive lesions are most likely to occur in the distal ends of the ulna and radius, the neck of the humerus, the phalanges, the medial border of the humerus, at the upper areas of tibia and fibula, at the ends of the clavicles, and in the pelvic bones (Figure 101.1). Widening or fraying of the radiolucent zone in the region of the growth plate (called growth zone lesions or rachitic lesions)

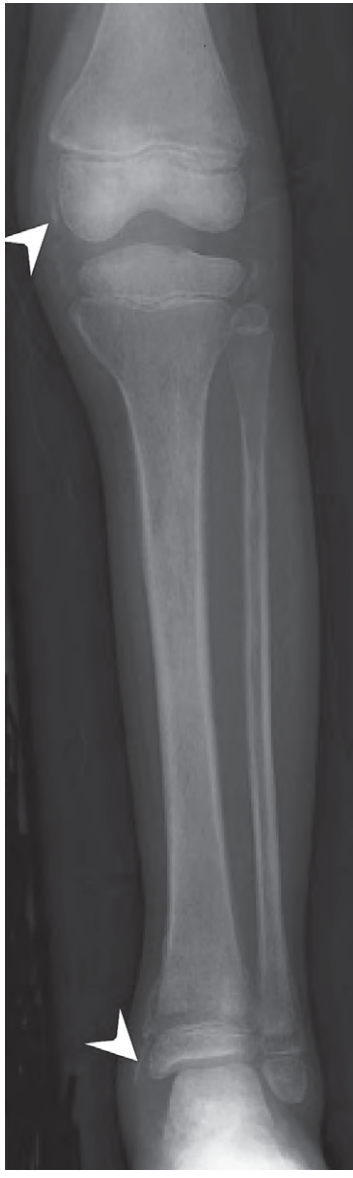


Figure 101–1

Tibia-fibula (AP view) of a child maintained on CCPD with secondary hyperparathyroidism. The arrows denote soft-tissue calcification in the knee and ankle area. Note the cortical tunneling in the tibia and the periosteal reaction in the distal femur and distal tibia.

can be seen by plain radiograph. Progressive bowing of long bones can lead to recurrent stress or pathologic fractures (Figure 101.2). According to Greulich and Pyle, bone age determinations are often below normal relative to chronologic age.

Measurement of Bone Mineral Density

Dual-energy X-ray absorptiometry (DXA), although limited to the two-dimensional assessment of bone, is widely used to diagnose osteoporosis in adults and to identify patients at risk for developing fractures. The WHO (world health organization) classification of osteoporosis is not applicable to children, and similar recommendations are not available in pediatric patients. The interpretation of bone mineral density (including Z-scores) using DXA may be erroneous, particularly in children with chronic renal failure, because the majority of patients are growth retarded (with smaller bone size and delayed skeletal age). Although quantitative computed tomography (QCT) can assess the bone three-dimensionally and differentiate between cortical and cancellous bone, radiation exposure is relatively high. The use of peripheral

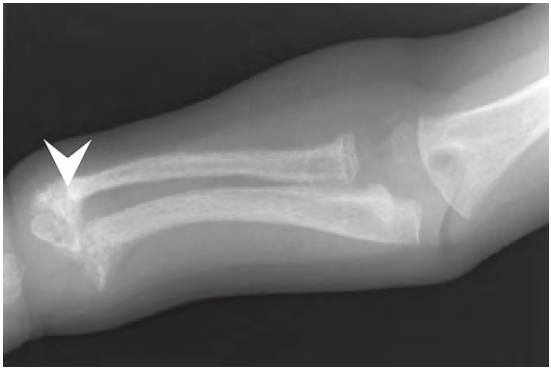


Figure 101–2

Forearm (AP view) in a young child on CCPD. Note that there is significant bowing in the distal part of the radius and ulna, with metaphyseal flaring in the distal part of the humerus. There is mottled and poor definition of the cortical bone, with possible insufficiency fracture in the distal radius (denoted by arrow).

QCT (pQCT) in children is limited by its reproducibility because the appendicular bone changes rapidly during growth. Quantitative ultrasound is not widely used in the pediatric population.

Bone Scintigraphy

Bone scans have limited use in the diagnosis and follow-up of children with chronic renal failure. Various bone scanning agents can be used with technetium-99, including diphosphonates and DMSA (Dimercaptosuccinic acid) to detect soft tissue calcifications (including the lungs and the intestinal tract).

Bone Biopsy

Bone histomophometry remains the gold standard for the diagnosis of the various types of bone disease in patients with chronic renal failure. Although invasive, the bone biopsy procedure has been demonstrated to be well tolerated and safe in children. The indications for bone biopsy in children include unexplained hypercalcemia associated with low PTH levels, previous parathyroidectomy, suspicion of aluminum-related bone disease, and assessment of response to therapy.

Prevention and Treatment

The severity of skeletal complications associated with chronic renal failure and secondary hyperparathyroidism is greatest in very young children. The primary goal of treatment in children with secondary hyperparathyroidism is to maintain serum PTH levels that correspond to a normal rate of skeletal remodeling that will promote growth. Before starting growth hormone therapy, adequate control of secondary hyperparathyroidism must be ensured.

Age-Appropriate Serum Phosphorus and Calcium Levels

Dietary Phosphorus Restriction

Maintaining age-appropriate circulating serum phosphorus levels is difficult solely by dietary phosphorus restriction in children (Table 101.1). Pediatric patients frequently need caloric supplementation, and thus the use of phosphate binding agents has been a necessity. Restriction of dietary phosphorus intake should be lower than the recommended daily allowance, depending on

the age of the child (Table 101.2). Removal of phosphorus by conventional dialysis is inadequate because approximately 240 to 440 mg per day is removed by peritoneal dialysis and 600 to 1000 mg is cleared by hemodialysis. Nocturnal hemodialysis performed six to seven times per week has been shown to significantly lower serum phosphorus levels. This led to discontinuation of phosphate binders. This type of dialysis is not widely used in pediatric patients and the technique may not be feasible in very young children and infants.

Phosphate Binding Agents

Aluminum

In the 1970s and 1980s, aluminum was widely used as a phosphate binder. Although highly effective and unequaled in its potency to bind phosphorus, its long-term use has been associated with toxic effects—including encephalopathy, bone disease, and anemia. Currently, aluminum is only used for a short period of time in patients with elevated phosphorus levels refractory to other binders. In pediatric patients, aluminum should be avoided because of tissue accumulation even at very low doses. Citrate-containing products (e.g., calcium citrate) should never be used concurrently with aluminum because this will increase absorption and enhance the aluminum's toxicity.

Calcium Salts

Various forms of calcium salts are widely used as primary therapy to bind dietary phosphorus and maintain normal calcium levels in children. Calcium salts are most effective as phosphate binders

Table 101–2

Recommended Daily Allowance and Upper Limits of Dietary Intake for Phosphorus

Age Group	Daily Intake (mg)	Upper Limit (mg)
0–6 months	100 mg	Not determined
7–12 months	275 mg	Not determined
1–3 years	460 mg	3000 mg
4–8 years	500 mg	3000 mg
9–19 years	1250 mg	4000 mg

Source: Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington DC: National Academy Press 1997.

if taken immediately before, during, or immediately after a meal. The prescribed dose of calcium salts should be proportional to the estimated amount of phosphorus ingested in each meal. Due to its better solubility compared to calcium carbonate, calcium acetate has been shown to bind a greater proportion of dietary phosphorus at the same amount of calcium absorbed.

According to the Food and Nutrition Board, the upper tolerable limit for oral calcium in children 1 to 19 years of age is approximately 2500 mg daily, and thus the margin of safety between the desired effects and the maximum limit is relatively narrow (Table 101.3). The upper limit of dietary calcium intake in neonates has not been established. Studies have shown that approximately 1 g of elemental calcium can lower serum phosphorus levels by 48% when taken appropriately. Dosages vary widely and are adjusted according to target serum calcium and phosphorus levels, depending on the patient's age (Table 101.1). Complications associated with aggressive use of calcium salts include hypercalcemia and soft-tissue calcification, and the frequency of these problems increases with concurrent use of vitamin D.

Sevelamer Hydrochloride

A newer agent, sevelamer hydrochloride (a tasteless, odorless, calcium- and aluminum-free polymer that binds phosphorus in the gastrointestinal tract through ion exchange and hydrogen binding) may prove to be a safe and effective phosphate binding agent in pediatric patients with chronic renal failure. Clinical studies have demonstrated that sevelamer hydrochloride lowered

Table 101–3

Recommended Daily Allowance and Upper Limits of Dietary Intake for Calcium

Age Group	Daily Intake (mg)	Upper Limit (mg)
0–6 months	210 mg	Not determined
7–12 months	270 mg	Not determined
1–3 years	500 mg	2500 mg
4–8 years	800 mg	2500 mg
9–19 years	1300 mg	2500 mg

Source: Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington DC: National Academy Press 1997.

serum phosphorus and PTH levels without significant changes in serum calcium levels. In addition, there was a considerable reduction in low-density lipoprotein and an increase in HDL levels that may be beneficial in patients with renal failure by lowering the cardiovascular risk related to dyslipidemia.

The dose of sevelamer reported in pediatric clinical studies with stages 3 to 5 chronic renal failure range between 140 ± 86 and 163 ± 46 mg/kg/day or 5380 ± 3240 to 6700 ± 2400 mg/day without considerable changes in serum calcium and bicarbonate levels. Currently, sevelamer hydrochloride is only available in tablet form—which is difficult to crush and mix with food, making it less attractive for infants and young children. Further studies are required to prove its efficacy and tolerability in the pediatric population, including the reported metabolic acidosis that can hinder growth and worsen renal bone disease if used long term and in high doses.

Lanthanum Carbonate

Lanthanum carbonate is a new phosphate binding agent composed of a rare earth metal trace element that contains no calcium or aluminum and exhibits minimal gastrointestinal absorption and low oral bioavailability. Oral doses between 375 and 3000 mg/day have been well tolerated and have been effective in lowering serum phosphorus levels in adult dialysis patients, with few adverse events. The problem of tissue accumulation with long-term lanthanum therapy in renal failure has not been fully evaluated because this drug is relatively new.

Currently, lanthanum carbonate is not widely used in pediatric patients with chronic renal failure due to uncertainty of the possible toxic effects of lanthanum accrual in the skeleton, liver, or brain of growing children. Lanthanum is a trivalent cation that can block calcium binding and inhibit calcium influx in various cells (including chondrocytes). It may also delay skeletal mineralization. Because lanthanum is largely sequestered in tissues, plasma levels may not accurately reflect true body concentration.

Other Phosphate Binding Agents

There are other agents in various stages of development, including iron-containing compounds, colestimide, and magnesium salts. Colestimide is a calcium- and aluminum-free phosphate binder widely used for the treatment of hypercholesterolemia. It has a chemical structure similar to that of sevelamer hydrochloride. Currently, there are no studies available to evaluate the efficacy and safety of these phosphate binding agents in children.

Low-Calcium Dialysate

To avoid hypercalcemia and lower calcium-phosphorus product, the use of low-calcium dialysate at 2.5 meq/L has been recommended—especially in patients receiving both calcium salts and vitamin D. Close follow-up must be done in children to avoid negative total body calcium, which can worsen bone disease in renal failure.

Correction of Metabolic Acidosis

Treatment of metabolic acidosis prevents calcium efflux from the bone, favors the movement of phosphorus intracellularly, restores parathyroid gland sensitivity, normalizes growth hormone secretion, and promotes bone demineralization. The most commonly used alkali in pediatrics includes sodium citrate and sodium bicarbonate. Parents and patients should be advised that the carbonic acid formed from sodium bicarbonate can lead to gastric discomfort.

Clinical studies have shown that patients with secondary hyperparathyroidism respond better to vitamin D therapy when serum bicarbonate levels are above 22 meq/L or mmol/L. It is important to remember that the total CO_2 content in the plasma that most physicians rely on is higher than the serum bicarbonate concentration by 1 to 1.5 mmol/L (meq/L). As previously discussed, any citrate-containing medication or food should not be given concurrently with aluminum binders to avoid toxicity.

Vitamin D Therapy

Ergocalciferol and Cholecalciferol

The current management of secondary hyperparathyroidism in children on maintenance dialysis therapy relies predominantly on the use of vitamin D analogues to lower PTH secretion and prevent bone disease. Ergocalciferol or cholecalciferol can be used to maintain serum 25-hydrovitamin D levels between 25 and 40 ng/mL to maintain adequate skeletal mineralization.

Calcitriol [1,25-$(OH)_2D_3$]

The active metabolite of vitamin D_3 is widely used in the reduction of PTH in renal failure—whether given daily or intermittently or by intravenous, oral, or intraperitoneal route. Calcitriol lowers PTH gene transcription, decreases parathyroid cell proliferation, and increases VDR and calcium receptor expression in the parathyroid gland and in the growth plate cartilage.

Although effective in the treatment of secondary hyperparathyroidism, there is substantial evidence that calcitriol is associated with hyperphosphatemia, hypercalcemia, and elevated calcium-phosphorus product—increasing the risk for cardiovascular mortality and morbidity in dialysis patients (especially in patients taking calcium salts).

Newer vitamin D analogues with low gastrointestinal calcium and phosphorus absorption are currently being used in dialysis patients. Clinical studies have shown that daily or intermittent calcitriol therapy is equally effective in the reduction of PTH in children. The daily dose of oral calcitriol can be initiated at 20 to 50 ng/kg and intermittent therapy can be started at 0.5 to 1.0 microgram per dose given three times weekly and adjusted according to target PTH levels. Calcitriol should be given at night to minimize the gastrointestinal absorption of calcium and phosphorus and to coincide with the nocturnal peak of circulating PTH. Serum intact PTH levels should be maintained within the recommended target levels of 150 to 300 pg/mL, and vitamin D must be lowered when PTH levels decline below 300 pg/mL to prevent adynamic bone.

Paracalcitol [19-nor-1,25-dihydroxyvitamin D_2]

Paracalcitol injection has been approved by the FDA for treatment of secondary hyperparathyroidism in children on dialysis older than 5 years of age. Several studies have shown that paracalcitol is as effective as calcitriol (at a ratio of 3:1) in suppressing PTH synthesis and secretion, with fewer episodes of hypercalcemia and hyperphosphatemia due to reduced stimulation of intestinal calcium transport proteins. Historical cohort studies have reported that PTH-related mortality and morbidity rate significantly decreased in paracalcitol-treated adult hemodialysis patients. Currently, there are no published studies in the use of paracalcitol in pediatric patients. However, two small prospective randomized clinical trials have reported a greater than 30% decline in PTH levels with minimal elevation in calcium and phosphorus in adolescents on hemodialysis.

The initial paracalcitol dose was similar to those used in published adult clinical studies at 40 ng/kg per dose given three times weekly for intact PTH and less than 500 pg/mL and 80 ng/kg per dose for PTH levels higher than 500 pg/mL. Recent clinical reports have demonstrated that daily oral or thrice-weekly intravenous paracalcitol doses were equally effective in the reduction of PTH levels. The initial doses of oral paracacitol as recommended by the manufacturer in adult patients are 1 microgram

daily for iPTH and less than 500 pg/mL or 2 micrograms daily for iPTH higher than 500 pg/mL. The FDA has recommended starting with paracalcitol at 40 ng/kg/dose based on the patient's dry weight.

Doxercalciferol (1a-hydroxyvitamin D_2)

This vitamin D analogue is a prohormone that requires 25-hydroxylation in the liver to be activated. Intermittent intravenous doses of doxercalciferol after each hemodialysis lowered PTH levels with less calcemia and phosphatemia in adult patients with moderate to severe secondary hyperparathyroidism when compared to calcitriol. The dose of doxercalciferol needed to attain an equivalent degree of PTH suppression is approximately 1/2 the dose of paracalcitol. Currently, there are no published pediatric studies. However, a small number of adolescent children on continuous cycling peritoneal dialysis (CCPD) with secondary hyperparathyroidism treated with 2.5 micrograms of doxercalciferol for 8 months demonstrated a decline in intact PTH levels accompanied by improvement in bone histology comparable to 0.5 microgram of calcitriol.

Other Vitamin D Analogues

Multiple vitamin D analogues—including dihydrotachysterol, calcifediol, alfacalcidol (1a-hydroxyvitamin D_3), and 22-oxacalcitriol—have been used in the treatment of secondary hyperparathyroidism in chronic renal failure. Dihydrotachysterol has been available since the 1930s and was used in the treatment of children prior to the availability of calcitriol. Some of these vitamin D analogues are commercially available in Europe and Japan.

Treatment with Cinacalcet HCl

Cinacalcet HCl is a positive allosteric modulator of the calcium receptor that effectively lowers PTH secretion by rendering parathyroid cells more sensitive to the inhibitory actions of calcium. This therapeutic agent is especially useful in the treatment of patients with secondary hyperparathyroidism with elevated serum calcium levels, high calcium-phosphorus product, and greater risk of vascular calcification. Clinical studies have demonstrated a greater than 30% reduction in circulating intact PTH levels in adult patients on dialysis.

There are no published data on the use and safety of calcimimetic agents in children with renal failure. Calcium receptors present in the growth plate cartilage may play a significant role in endo-

chondral bone formation. Animal experiments have shown that treatment with a positive calcium receptor agonist such as cinacalcet can upregulate calcium receptor expression in chondrocytes and enhance bone growth. The use of calcimimetic agents is quite promising, represents an innovative therapeutic approach, and provides an additional option in the management of children with secondary hyperparathyroidism.

Parathyroidectomy

Overall, the number of patients who require parathyroidectomy from advanced secondary hyperparathyroidism has declined over the years with the availability of the various vitamin D analogues, calcium receptor agonists, and other phosphate binding agents. The clinical indications for surgical parathyroidectomy include severe hyperparathyroidism with persistent intact PTH levels greater than 1000 pg/L refractory to medical therapy, persistent hypercalcemia, and uncontrolled hyperphosphatemia with disabling skeletal pain and progressive extraskeletal calcifications. Although the incidence of aluminum toxicity has declined in chronic renal failure, patients should undergo a bone biopsy to ensure the absence of aluminum-related bone disease—which can worsen after parathyroidectomy. The quick PTH (QPTH) assay has grained widespread acceptance among surgeons as an intraoperative adjunct to localize hypersecreting parathyroid glands and measure changes in circulating serum PTH levels.

A majority of patients undergoing parathyroidectomy for severe secondary hyperparathyroidism will develop postoperative hypocalcemia (called "hungry bone syndrome") due to the rapid skeletal uptake of calcium. Intravenous calcium should be started once serum calcium levels are below normal (less than 8.5 mg/dL) and may be required 24 to 48 hours after parathyroidectomy. Calcium supplementation should be started once the patient is able to tolerate oral medication. Vitamin D therapy (preferably calcitriol) should be given 24 hours preoperatively and should be continued post-parathyroidectomy to enhance the gastrointestinal absorption of calcium. Concurrent postoperative hypophosphatemia is usually not treated unless the serum levels are below 2 mg/dL.

Summary

Our understanding of bone disease in renal failure has increased over the years, but the clinical strategies currently employed to

prevent the development of bone disease in children are still evolving. The management of bone disease in children should start early and should include correction of hypocalcemia, maintanence of age-appropriate serum phosphorus, treatment of metabolic acidosis, and maintenance of serum intact PTH levels within the current recommended target ranges. The primary aim in the early treatment of secondary hyperparathyroidism in children with chronic renal failure is to protect the young skeleton against the effects of progressive renal failure and to prevent the development of parathyroid gland hyperplasia.

Recommended Reading

Renal Bone Disease in Children

Andress DL. Vitamin D in chronic kidney disease: A systemic role for selective vitamin D receptor activation. Kidney Int 2006;69:33–43.

An updated basic and clinical review of the available vitamin D analogues currently used in the treatment of renal bone disease.

Food and Nutrition Board, Institute of Medicine, National Academy of Science. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington DC: National Academy Press, 1997.

This handbook provided by the National Academy of Science is an excellent resource for any medical personnel interested in published guidelines on the recommended daily dietary allowance for any nutrient or mineral in children. This reference is also available at http://www.nap.edu.

Klaus G, Watson A, Edefonti A, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol 2006;21:151–59.

Recommendations from the European Pediatric Dialysis Working Group (EPDWG) on the treatment and prevention of bone disease in children with chronic renal failure.

National Kidney Foundation. Clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis 2005;46:S1–119.

A comprehensive publication of the current recommendations for management and treatment of bone and mineral problems encountered in children with various stages of chronic renal failure.

Salusky IB, Ramirez JA, Oppenheim W, et al. Biochemical markers of renal osteodystrophy in pediatric patients undergoing CAPD/CCPD. Kidney Int 1994;45:253–58.

An important clinical study that evaluated the relationship between biochemical parameters (intact PTH levels, calcium, phosphorus, alkaline phosphatase levels) and bone histology in children on dialysis therapy.

Sanchez CP. Renal osteodytsrophy in pediatric patients. In Nissenson A, Fine RN (eds), *Clinical Dialysis, Fourth Edition*. New York: McGraw Hill 2005:1091–1111.

This is a comprehensive review on the pathogenesis, clinical presentation, and management of renal bone disease in children with chronic renal failure and those maintained on dialysis.

Seikaly M, Salhab N, Gipson D, et al. Stature in children with chronic kidney disease: Analysis of NAPRTCS database. Pediatr Nephrol 2006;21:793–99.

This is a thorough evaluation of the factors that can affect linear growth and bone disease in children with chronic renal failure using the NAPRTCS database.

Sheikh MS, Maguire JA, Emmett M, et al. Reduction of dietary phosphorus absorption by phosphorus binders. J Clin Invest 1989;83:66–73.

An important article on the efficacy of aluminum, calcium, and magnesium as phosphate binding agents based on in vitro and in vivo studies.

Vitamin D Analogs in the Treatment of Secondary Hyperparathyroidism in Children on Dialysis

Hernandez J, Wesseling K, Jueppner H, et al. Skeletal response to phosphate binders and intermittent oral vitamin D in dialyzed children with secondary hyperparathyroidism. J Am Soc Nephrol 2005;16:47A.

A prospective randomized clinical study in 40 children on CCPD with histologic findings of secondary hyperparathyroidism treated with either doxercalciferol or calcitriol with sevelamer or calcium carbonate as phosphate binding agent for 8 months.

Kommala D, Benador N, Goldstein S, et al. Paracalcitol (zemplar) injection for the treatment of secondary hyperparathyroidism in pediatric hemodialysis patients. J Am Soc Nephrol 2003;14:199A.

A double-blind placebo-controlled study using intravenous paracalcitol in 29 children on hemodialysis.

Seeherunvong W, Abitbol C, Montane B, et al. Paracalcitol therapy for hyperparathyroidism in children and young adults on hemodialysis. J Am Soc Nephrol 2000;11:582A.

A prospective clinical trial of intravenous paracalcitol in adolescents on hemodialysis.

CHAPTER 102

Management of Anemia in Children on Dialysis

Amira Al-Uzri, MD, MCR

Anemia is defined by low levels of hemoglobin (Hb) and hematocrit (Hct) greater than 2 standard deviations below the mean for healthy children relative to age and gender. The National Kidney Foundation, through its Dialysis Outcomes Quality Initiative (NKF-K/DOQI), has recently published its Pediatric Clinical Practice Guidelines and Recommendations for management of anemia in children with chronic kidney disease (CKD) and on dialysis. The clinical practice guidelines recommend that evaluation of anemia be initiated when the Hb level falls below the 5th percentile for age and sex (Tables 102.1 and 102.2).

Prevalence of Anemia in Children with Chronic Kidney Disease

The incidence of anemia increases as the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2 and is present consistently when the GFR falls below 30 mL/min/1.73 m^2. Therefore, anemia is a frequent finding in children upon the initiation of dialysis therapy. Recent data from the U.S. Renal Data System (USRDS) reveal that the mean Hb level for all children at the start of dialysis therapy is less than 9.9 g/dL regardless of race or cause of renal failure. Surprisingly, less than 40% of those children were actually receiving recombinant human erythropoietin (rHuEPO) therapy.

Chavers et al. reported that children receiving Medicare insurance coverage, whether on hemodialysis (HD) or peritoneal dialysis (PD), had lower mean annual Hb concentration compared to adult dialysis patients. Furthermore, pediatric HD patients received intravenous (IV) iron therapy less frequently than adult patients (66.3% versus 82.5% patient-years; $P < 0.0001$). Causes of undertreatment of anemia in children with CKD and on dialysis may be due to underdosing of EPO in smaller children, less use of IV iron therapy, and the problem of noncompliance associated with subcutaneous (SC) rHuEPO injections. Further studies and

Table 102–1

Hb Levels (g/dL) in Children Between 1 and 19 Years for Initiation of Anemia Workup[a]

All Races/Ethnic Groups	Number of Subjects	Mean	Standard Deviation	Anemia Definition Met if Value is <5th Percentile
Boys				
1 yr and over	12,623	14.7	1.4	12.1
1–2 yr	931	12.0	0.8	10.7
3–5 yr	1281	12.4	0.8	11.2
6–8 yr	709	12.9	0.8	11.5
9–11 yr	773	13.3	0.8	12.0
12–14 yr	540	14.1	1.1	12.4
15–19 yr	836	15.1	1.0	13.5
Girls				
1 yr and over	13,749	13.2	1.1	11.4
1–2 yr	858	12.0	0.8	10.8
3–5 yr	1337	12.4	0.8	11.1
6–8 yr	675	12.8	0.8	11.5
9–11 yr	734	13.1	0.8	11.9
12–14 yr[b]	621	13.3	1.0	11.7
15–19 yr[b]	950	13.2	1.0	11.5

a. Based on NHANES III data, United States, 1988–94. Data abstracted from tables 2 and 3.
b. Menstrual losses contribute to lower mean and 5th percentile Hb values for group.
Published with permission from Elsevier: NKF-K/DOQI; National Kidney Foundation. Clinical practice recommendations for anemia in chronic kidney disease in children. Am J Kidney Dis 2006;47(5/3):S86.

attention to analysis of rHuEPO and iron therapy in pediatric dialysis patients is warranted.

Symptoms

Anemia of chronic renal failure may manifest gradually as fatigue, pallor, loss of appetite, depression, a decrease in cognitive function, tachycardia, tachypnea, and growth retardation. In patients with CKD, correction of anemia improves appetite, utilization of ingested proteins, and cardiac function. Multivariate analysis of more than 5000 children in a recent NAPRTCS survey showed that anemia (Hct <33%) at time of registry has a modest but significant correlation (OR 1.31, $p < 0.01$) with short stature, inde-

Table 102–2

Hb Levels (g/dL) in Children Between Birth and 24 Months for Initiation of Anemia Workup[a]

Age	Mean Hb	–2 SD[b]
Term (cord blood)	16.5	13.5
1–3 d	18.5	14.5
1 wk	17.5	13.5
2 wk	16.5	12.5
1 mo	14.0	10.0
2 mo	11.5	9.0
3–6 mo	11.5	9.5
6–24 mo	12.0	10.5

a. Data taken from normal reference values.
b. Values 2 standard deviations below the mean are equivalent to <2.5th percentile.
Published with permission from Elsevier: NKF-K/DOQI; National Kidney Foundation. Clinical practice recommendations for anemia in chronic kidney disease in children. Am J Kidney Dis 2006;47(5/3):S86.

pendent of other parameters. Anemia is associated with higher morbidity, increased hospitalization days, and mortality in children. Warady and Ho determined that an Hct 33% at dialysis initiation was associated with a greater mean number of hospitalization days within the initial year of dialysis, and an estimated 52% greater risk of death.

A number of studies of adults with CKD have shown a negative impact of anemia on several aspects of health-related quality of life (HRQOL). Children with Hct <36% have greater limitations in domains relating to physical functioning, limitations in school work or activities with friends as a result of physical health, and parental impact in time and family activities compared to children with higher Hct independent of sex, race, and estimated GFR. They also have lower self-esteem and a greater prevalence of behavioral issues compared to adolescents who had an Hct of >36%. The effect of interventions to improve anemia on HRQOL in children with CKD has not yet been assessed.

Tests for Evaluation of Anemia in Children with Dialysis CKD

The etiology of anemia in children with CKD is multifactorial, including a decrease in red blood cell survivability, blood loss

through intestinal losses, frequent blood draws, multiple surgical procedures, and HD sessions. Other factors include malnutrition and the presence of uremic toxins, which inhibit bone marrow erthyropoiesis. However, the principle cause of anemia in chronic renal failure is due to the low production of endogenous EPO. Therefore, the initial workup of anemia in children with CKD should aim at identifying other factors that may contribute to anemia (such as iron deficiency).

The NKF-K/DOQI Clinical Practice Guidelines recommend the following tests as an initial assessment for anemia: CBC, Hb concentration, RBC indices (MCH, MCV, MCHC), white blood cell count with differential and platelet count, and absolute reticulocyte count. These tests will yield important information about the presence of other clinical disorders. For example, the deficiency of vitamin B12 or folate may lead to macrocytosis, whereas iron deficiency anemia or other inherited Hb disorder (such as alpha- or beta-thalasemias) may produce microcytosis. Furthermore, disorders of other cell lines (such as white cells or platelets) may indicate a generalized bone marrow disorder.

Evaluation of iron status in children includes obtaining a serum ferritin to assess iron stores and serum transferrin saturation (TSAT) to assess adequacy of iron for erythropoiesis. Tests other than TSAT included in the recommendation for adults—such as reticulocyte Hb content (CHr) to assess adequacy of erythropoiesis and percentage of hypochromic red blood cells (PHRCs)—are not recommended in children at the present time due to lack of studies in the pediatric dialysis population.

Dose of Erythropoiesis-Stimulating Agents in Children with Dialysis CKD

The erythropoiesis-stimulating agents (ESAs) include all agents that augment erythropoiesis through direct or indirect action on the EPO receptors. These currently include epoetin alfa, epoetin beta, and darbepoetin. The dose of ESA in children varies depending on the mode of dialysis, the route of administration, the age of the child, and the presence of factors that may lower the response to ESA (such as inflammation). Pharmacokinetic studies in adults have shown that SC recombinant human EPO (rHuEPO) has a longer half-life (15–25 hours) than IV rHuEPO (5–9 hours). Therefore, a 30 to 50% reduction in the dosing as well as frequency of administration is possible when using the SC versus IV route. In children, SC injections are uncomfortable and painful and may lead to missed doses. Therefore, the Pediatric

Clinical Practice Recommendations favor the SC administration of rHuEPO and ESAs in general for PD-CKD patients and IV administration for HD patients.

Different studies have shown that children on PD require approximately 225 U/kg/week compared with 300 U/kg/week for children on HD. The reason for the initial dosing difference may be due to blood loss during HD and the use of IV administration in HD patients as opposed to the SC route in PD. This difference in dose was present even when children on both dialysis modalities were given EPO SC, which points toward a greater requirement for ESA in the HD-CKD population.

Age is another factor that determines the dose of ESA in children on dialysis. Younger children require higher doses of rHuEPO, which may be attributed to more rapid clearance and larger volume of distribution when administered either SC or IV. Children younger than 1 year may require 350 U/kg/week. Neonates may require very large doses of rHuEPO of between 500 and 1500 U/kg/week, whereas children older than 12 require 200 U/kg/week at the time of starting EPO.

The NKF-K/DOQI Pediatric Clinical Practice Guidelines recommend close monitoring of blood tests every 1 to 2 weeks after initiating ESA in order to make any necessary adjustments in the ESA dose. The goal for Hb level in children on dialysis is similar to the adult recommendations of 11 to 12 g/dL. No sufficient evidence is present to support Hb levels of >13 g/dL in children. The desired rate of rise of Hb levels in children varies in different studies and ranges between 0.66 and 2 g/dL per month. An average rise of 1 g/dL per month is desirable. Table 102.3 is a proposed table for adjustments in rHuEPO dosing based on the monthly rate of change of Hb levels. Data on adjustments in the Darbepoetin dosing are still under study in children.

Darbepoetin Alpha

Darbepoetin alpha (novel erythropoiesis-stimulating protein) is a new hyperglycoselated form of rHuEPO with a longer half-life than rHuEPO. Kinetic studies in children show that the half-life of darbepoetin in children is similar to adults. The terminal half-life of darbepoetin is reported to be 42.8 hours, with a mean bioavailability of 54% after an SC injection and a terminal half-life of 22.1 hours after IV injection. Darbepoetin alpha can be given once every 1 to 2 weeks SC or IV. The initial starting dose of darbepoetin is 0.45 μg/ kg per week. For children on EPO to

Table 102–3

Proposed Table for Adjustments in the rHuEPO Dose Based on the Monthly Change of Hb Level

Frequency of Blood Test	Hb Level (g/dL)	Percentage Change in Dose
Please see recommendations below*	<10	Increase EPO by 25%
	10–10.9	Increase EPO by 10%
	11–12.5	No change
	12.6–13	Decrease EPO by 10%
	>13	Decrease EPO

*In new patients, monitor Hb every 1–2 weeks until stable; then continue on a monthly basis once target level is reached on a stable dose of EPO. Desired rate of rise in Hb is 1 g/dL per month (range 0.66–2 g/dL). If the rate of rise of Hb exceeds 0.5 g/dL per week, lower the EPO dose by 25–50% but avoid holding the EPO if by 25% possible.

be switched to Darbepoetin, a conversion factor of 0.5 per 200 units of EPO is proposed.

Iron

Iron acts as an active cofactor in multiple metabolic pathways in the body, such as carrying oxygen within the Hb molecule and electron transportation for enzymes involved in the oxidation-reduction reactions. Body iron comes from two sources: dietary iron and the sequestration of Hb molecule in the recituloendothelial system. Ferritin is a protein responsible for short-term iron storage and detoxification of intracellular nonfunctioning iron. Serum ferritin is found to correlate well with tissue ferritin levels. In healthy adults, 1 μg of serum ferritin is equivalent to approximately 8 mg of storage iron. Serum ferritin is an acute-phase reactant that increases with acute inflammation, neoplasia, and other conditions associated with elevated C-reactive protein. Thus, in states of low-grade inflammation (such as CKD) higher levels of serum ferritin (<200 ng/mL in adults and <100 ng/mL

in children) are required to signify the presence of iron deficiency anemia.

Children with CKD have daily iron losses. In children with predialysis CKD and probably PD-CKD, the mean daily intestinal blood losses are 6 mL/m^2 per body surface area. In children with HD-CKD, the mean daily gastrointestinal blood losses increase to 11 mL/m^2—and dialysis-associated blood losses are 8 mL/m^2 per treatment. Therefore, the cumulative annual iron losses approximate 0.9 gm/1.73 m^2 in pre-dialysis CKD and PD-CKD children and 1.6 g/1.73 m^2 in children with HD-CKD. There are no available data on the calculated iron needs in pediatric patients on dialysis, and thus the rationale for iron supplementation is similar to that described in the NKF-K/DOQI for adults.

Diagnosis of Iron Deficiency Anemia

The disturbance in iron metabolism can be measured by the following indices: serum iron, total iron binding capacity, percentage of TSAT, and serum ferritin. The TSAT can be calculated using the following formula:

$$\text{TSAT\%} \frac{\text{Serum iron (µg/dl)}}{\text{TIBC (µg/dl)}} \times 100$$

The NKF-K/DOQI defines absolute iron deficiency anemia in children with CKD and on dialysis as serum ferritin of <100 and TSAT of <20%. Functional iron deficiency anemia occurs when there is failure to meet the demand of iron supply to the reticuloendothelial system in the face of adequate or increased iron stores. Functional iron deficiency anemia develops in instances when there is enhanced erythropoiesis by exogenous EPO administration, after renal transplantation, or when iron release from storage is limited due to inflammatory process in the presence of adequate or even increases in iron stores. Patients with this condition do not meet the laboratory criteria for absolute iron deficiency but may demonstrate an increase in Hb when IV iron is administered.

Differentiation between absolute iron deficiency anemia and functional iron deficiency anemia in CKD is difficult and might not be possible under all circumstances. Other new indices suggested for use in differentiating functional versus absolute iron deficiency anemias are used on a wider scale in Europe than in the United States. These indices include the proportion of PHCRs (proportion of hypochronic red blood cells) in the circulation and the Hb content of CHr hemoglobin content of reticulocytes. The presence of PHCRs of >5% and a CHr of <26 to 28 pg

have been found to be good markers of iron deficiency anemia. However, due to the lack of pediatric data that define these indices the NKF-K/DOQI Pediatric Clinical Practice Guidelines do not recommend the use of such indices to define iron deficiency anemia in children on dialysis.

Oral Iron Therapy

Oral iron therapy is adequate to prevent iron deficiency anemia in children with pre-dialysis CKD and those on PD. However, children on HD require IV iron therapy to provide adequate iron for erthyropoiesis. The dose of oral iron therapy varies between 2 and 6 mg/kg/day. There are many different preparations of iron supplements, such as ferrous sulfate, ferrous gluconate, ferrous fumarate, and polysaccharide iron complexes. Studies have shown equal efficacy among the various preparations. Some of the slow-release iron preparations may be better tolerated.

Adverse effects of oral iron therapy include nausea, vomiting, diarrhea, constipation, bloating, and abdominal pain. Iron suspension given orally in infants may cause discoloration of teeth. Antiacids and phosphate binders interfere with the absorption of oral iron and therefore should be spaced 1 to 2 hours.

Intravenous Iron Therapy

Due to the higher rate of iron loss in children on HD, IV iron therapy is the preferred method of administration during HD sessions (Table 102.4). Adverse reactions to IV iron dextran administration occur in 1.7% of patients and may include nausea, vomiting, hypotension, dyspnea, wheezing, chest pain, headache, dizziness, and even anaphylactic reactions. Other reactions that may occur 24 to 48 hours after the infusion may consist of arthralgias, malaise, and fever. Patients with a history of drug allergies are at higher risk for developing adverse reactions to IV iron. A test dose of iron dextran should be administered prior to the actual infusion (Table 102.4). Patients who develop an allergic reaction to iron dextran can receive other iron preparation safely.

Adverse reactions to iron gluconate include nausea, vomiting, diarrhea, abdominal pain, and hypotension—largely attributed to oversaturation of transferrin with rapid release of free iron in the circulation. Limiting the dose of IV iron gluconate to a maximum of 3 mg/kg/dose usually prevents this complication. Iron sucrose has been generally tolerated well, with rare reports of allergic reactions.

Table 102–4

Intravenous Iron Preparations with Proposed Dosing

Iron Preparation	Dose of Iron (mg/kg)	Repletion Dose	Maintenance Dose
Iron dextran, INFeD DexFerrum	1–4 mg/kg up to 100 mg per dose (test dose required). For child < 40 kg test dose is 12.5 mg; for child ≥ 40 kg, test dose is 25 mg.	Once a week for 6–10 doses	Total of 10–14 weeks by published reports
Sodium ferric gluconate Ferrlecit (62 mg/5 m)	1–3 mg/kg/dose IV up to 125 mg per dose (no test dose required).	With every HD for a total of 8–10 HD sessions	1–2 mg/kg/wk
Iron sucrose Venofer (50 mg/mL)	1–4 mg/kg/dose IV up to 100 mg per dose (no test dose required).	With every HD for a total of 8–10 HD sessions	1–2 mg/kg/wk

Modified from Yorgin P, Al-Uzri A (eds.). *Management of Renal Anemia: Pediatric Dialysis.* [City]: Kluwer Academic Publishers 2004:295–331.

Frequency of Blood Monitoring on EPO and Iron Therapy

The NKF-K/DOQI Pediatric Clinical Practice Guidelines recommend that HD-CKD patients who start on ESA or iron therapy have their Hb and Hct monitored every 1 to 2 weeks, and iron studies every month. After the initial replenishment phase, less frequent monitoring is required in stable dialysis CKD patients. In stable HD-CKD patients, Hb and Hct can be monitored every

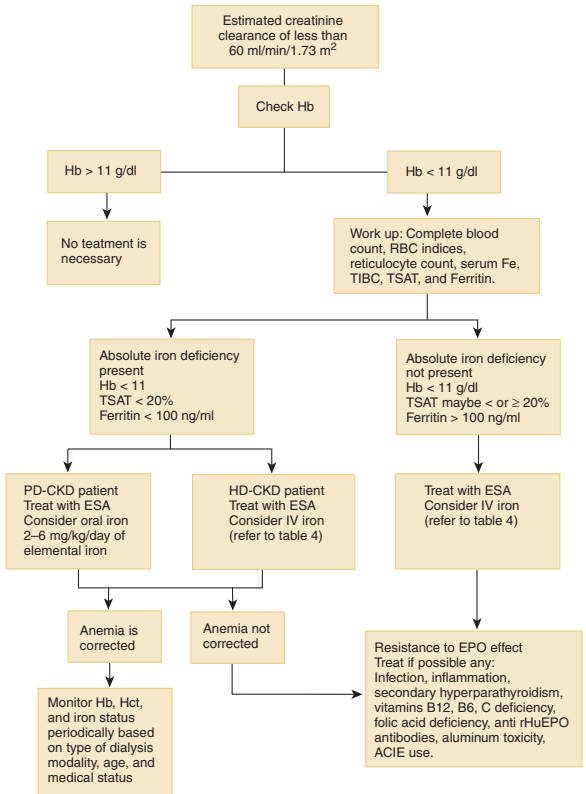


Figure 102–1

A proposed flow chart for the management of anemia in children with CKD.

2 to 4 weeks—and iron studies every 3 months. For PD-CKD patients, Hb and Hct are monitored once every month and iron studies every 3 months—similar to stable HD-CKD patients.

Resistance to EPO Therapy

Failure to respond to ESA therapy is recognized when increased doses of EPO are required to maintain a constant Hb level, or a decrease in Hb levels is observed with the use of a constant ESA dose. A failure to increase the Hb level to more than 11 g/dL despite the use of high doses of EPO in excess of 500 IU/kg/week indicates a state of hyporesponsivenes to ESA therapy. The etiology of ESA resistance includes inflammation, secondary hyperparathyroidism, vitamin B12 and B6 deficiency, folic acid deficiency, vitamin C deficiency, anti rHuEPO antibodies, aluminum toxicity, and the use of angiotensin-converting enzyme inhibitors. Correction of some of these implicating factors will result in improved response to ESA therapy. Rare cases of pure red cell aplasia have been reported due to antibodies formed to rHuEPO therapy.

In summary, anemia is common in children with CKD due to multiple causes, the most important being ESA deficiency. SC or IV dosing of ESA differs by age, and by dialysis modality. Diagnosis and correction of iron deficiency anemia with oral or IV iron is important in the management of anemia. Figure 102.1 is a proposed flow chart for the management of anemia in children with CKD.

Recommended Reading

Chavers BM, Roberts TL, Herzog CA, Collins AJ, St Peter WL. Prevalence of anemia in erythropoietin-treated pediatric as compared to adult chronic dialysis patients. Kidney Int 2004;65:266–73.

This is a retrospective analysis of the USRDS database on the prevalence of anemia in pediatric HD and PD patients compared to adults.

Gerson A, Hwang W, Fiorenza J, et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 2004;44(6):1017.

NKF-K/DOQI. NKF-K/DOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 2006;47(5/3):S11.

Recommendations based on the best evidence available at the time of publication. These guidelines are designed to provide information and assist in decision making.

NKF-K/DOQI. Clinical practice recommendations for anemia in chronic kidney disease in children. Am J Kidney Dis 2006;47(5/3):S86.

Recommendations based on the best evidence available at the time of publication. These recommendations are designed to provide information and assist in decision making.

Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D. Stature in children with chronic kidney disease: Analysis of NAPRTCS database. Pediatr Nephrol 2006;21(6):793.

A retrospective analysis of 1942 patients from the dialysis registry of the North American Pediatric Renal Transplant Cooperative Studies (NAPRTCS) to evaluate risk factors associated with short stature (one of which is anemia).

USRDS. USRDS Annual Data Report: Atlas of End-Stage Renal Disease in the United States 2004. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease 2004.

The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) in the United States. The USRDS publishes the Annual Data Report on End-Stage Renal Disease in the United States for adults and children, which is available online at http://www.usrds.org/.

Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 2003;18(10):1055.

A retrospective analysis of 5615 patients from the chronic renal failure registry of the North American Pediatric Renal Transplant Cooperative Studies (NAPRTCS) to evaluate the association between anemia and patient mortality and prolonged hospitalization.

Warady BA, Arar MY, Lerner G, Nakanishi AM, Stehman-Breen C. Darbepoetin alfa for the treatment of anemia in pediatric patients with chronic kidney disease. Pediatr Nephrol 2006;Aug;21(8):1144–52. Epub 2006 May 25.

This is an interventional open-label trial in children with chronic kidney disease to assess the efficacy of using Darbepoetin alfa in children for the treatment of anemia compared to erythropoeitin therapy.

Warady BA, Schaefer FS, Fine RN, et al. Management of renal anemia. In P Yorgin, A Al-Uzri (eds.), *Pediatric Diaylsis*. Dordrecht, The Netherlands: Kluwer Academic Publishers 2004:295–331.

Comprehensive book about pediatric dialysis. The chapter is a complete and thorough overview of all aspects of anemia in children on dialysis with 266 references.

CHAPTER 103

Assessing Quality of Life in Pediatric Patients Undergoing Dialysis

Stuart L. Goldstein, MD

Introduction

Medical care advancements for children receiving hemodialysis and peritoneal dialysis have resulted in relatively improved long-term patient survival compared to adult patients receiving maintenance dialysis.[1] As a result, more pediatric dialysis patients are reaching adult age. Thus, optimal care for the pediatric dialysis patient requires attention not only to medical management but to the psychosocial and developmental factors that will either ensure or prevent successful transition into adulthood. This chapter discusses the factors that impact, and recent studies that aim to assess, pediatric dialysis patient health-related quality of life (HRQOL).

The Scope of the Problem

No long-term prospective outcome study has been performed for children with end-stage renal disease (ESRD). Lack of long-term outcome data stems from many causes including, most importantly, the need for multicenter study given the low prevalence of children receiving maintenance dialysis. Dialysis imparts significant constraints and restrictions that impact normal psychosocial development. The medical requirements, including dietary restrictions and dependence on a hemodialysis or peritoneal dialysis machine, isolate children from their healthy peers. Such interruptions in the normal daily life of a child are a likely primary cause for the relatively low self-esteem and low rates of independent living, close interpersonal relationships, and employment reported in adult survivors of pediatric ESRD.[2,3] Adolescent and young adult ESRD patients with a renal transplant report lower employment rates and greater concern about body image than a similar cohort of diabetic patients.[4]

The prolonged paternalistic medical team approach to the child with chronic illness differs significantly from the adult medical "subculture" in which patients themselves are primarily responsible for their own health and interactions with the health care system.[5] Pediatric patients with chronic illness usually receive medical care in tertiary care facilities with significant local philanthropic support and a staff that has a disposition to advocate for the child. These factors can prevent development of personal responsibility and independence. Patients and their families should be provided with a transition plan to proceed through a medical adolescence that allows greater personal patient responsibility for care while preventing medical endangerment.

A successful plan requires education not only about medical issues but about health insurance, in that nearly half of young adults who survive childhood with a chronic illness are uninsured.[6] Practical but detailed assessment of pediatric ESRD patient HRQOL will be critical to evaluate any intervention aimed at improving a patient's successful childhood psychosocial development and transition to the adult health care system.

Early Pediatric HRQOL Study

Early research into the HRQOL of pediatric ESRD patients occurring over 10 years ago demonstrates that although pediatric patients with ESRD certainly have some similar developmental and psychosocial issues as children with other chronic illnesses they also have challenges specifically related to ESRD.[7-11] Obstacles common to most chronically ill children include physical changes related to illness, the need to take many medications and undergo medical treatment, and time away from school and peers—all of which can lead to perceived differences and isolation. Children receiving dialysis have additional challenges, such as maintaining a restricted dietary and fluid regimen and the knowledge that they will live their entire lives with the recurrent cycle of dialysis and transplantation. To date, no follow-up from these studies has been published.

The tools used in previous studies were not ESRD specific. Information gathered with these tools illustrated that children with ESRD have psychosocial issues and adjustment problems. Children receiving dialysis demonstrate increased incidences of depression, behavior disturbances, dependency on caregivers, poor school performance, lack of higher education or vocational training, cognitive delays, separation anxiety disorder, and poor social adjustment and peer relationships. Parents of children with

ESRD experience increased stress levels, increased marital strain, decreased support from friends and employers, increased incidences of anxiety and depression, and role confusion related to being both parent and medical caregiver (particularly in the case of parents providing home peritoneal dialysis).

None of the early studies account for the cause of psychosocial issues and differences between the groups of children using different modalities of renal replacement therapy. Lack of information regarding the underlying causes of psychosocial differences results from the fact that these tools were devised without input from patients/parents/caregivers involved in ESRD and the fact that many of these scales focus primarily on cognitive ability and mental health and not on HRQOL per se. The instruments used in these early studies are not suitable for frequent readministration to track a patient's changes in HRQOL over short periods of time.

Specific HRQOL Measurement Instruments for Children with Chronic Disease

HRQOL tools—including the SF-36 (a non ESRD-specific tool) and the KDQOL (an ESRD-specific tool)—have been crucial for evaluation of the impact of medical treatment on adult patients with ESRD.[12-14] Data from adults have shown that the ESRD-specific KDQOL tool offered higher discrimination between dialysis modalities than the SF-36.[15-17] Although standard outcome measures used for adult patients such as death and hospitalization rates are important for children, they are clearly insufficient.

Other factors (including growth, exercise capacity, school attendance and performance, self-reliance and functional development) are crucial components for assessing the pediatric HRQOL. A number of HRQOL assessment tools used in healthy children and those with a chronic illness have recently been studied in children with CKD. Table 103.1 outlines characteristics of HRQOL tools studied in pediatric patients undergoing dialysis.

Child Health and Illness Profile: Adolescent Edition

The Child Health and Illness Profile: Adolescent Edition (CHIP-AE) is a 153-item self-report instrument that assesses six domains of health status. The instrument takes about 20 minutes to complete.[18] The CHIP-AE has been evaluated in a multicenter cross-sectional study of health status in adolescents with chronic kidney

Table 103–1

Characteristics of HRQOL Instruments Studied in Pediatric Patients on Dialysis

Instrument	Parent/Child Forms	Items	Ages	Domains
CHIP-AE	Child	153	11–17	6
CHQ	Both	50	10–19	12
PedsQL	Both	23	2–18	5

disease (CKD). Adolescents with CKD were compared to two control groups of age-, socioeconomic-, and gender-matched peers.[19] One hundred thirteen patients were studied in seven pediatric nephrology centers in the Northeast United States (39 CRI—chronic renal insufficiency, 21 receiving dialysis, 53 with a renal transplant) and compared to 226 control subjects.

Patients with CKD had lower overall satisfaction with health and more restriction in activity. Positively, patients with CKD had more family involvement, better home safety and health practices, better social problem-solving skills, and were less likely to participate in risky social behaviors or socialize with peers who engaged in risky behavior. Patients receiving dialysis were less physically active and experienced more physical discomfort and limitations in activities. Among CKD patients, dialysis patients were found to have the poorest functional health status.

The Children's Health Questionnaire

The Children's Health Questionnaire (CHQ) is generic health status instrument with both parent and child forms. The child version is appropriate for administration to children aged 10 to 19 and takes about 20 minutes to complete. The CHQ measures 12 domains of health status (physical functioning, limitations in schoolwork and activities with friends, general health, bodily pain and discomfort, limitations in family activities, emotional/time impact on the parent, impact of emotional or behavior problems on school work and other daily activities, self-esteem, mental health, behavior, family cohesion, and change in health).

The CHQ has previously been used in a single-center study with children who have kidney disease maintained on hemodialysis,[20] and more recently in a multicenter study of adolescents with CKD.[21] The CHQ was used to demonstrate the negative

impact of anemia on several aspects of HRQOL. This cross-sectional study examined the association between anemia and HRQOL in a prevalent cohort of adolescents with CKD using the parent version of the CHQ (Child Health Questionnaire Parent Form, CHQ-PF50). The study population included 113 CKD patients (mean age 14.4 ± 1.9 years) requiring dialysis, with functioning kidney transplants or with advanced stage 2 or stages 3 to 5 CKD.

Seventy-five patients were anemic, with a hematocrit =36%. Anemic patients scored lower within several categories of HRQOL, specifically in CHQ-PF50 subdomains relating to physical functioning, role-physical, and general health. These findings suggest that correction of anemia in adolescents with CKD may significantly improve long-term health outcomes for children with renal disease and their corresponding HRQOL, and demonstrate that the use of a HRQOL measure can reflect clinical improvement in response to a specific therapy.

The Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) is a 23-item generic health status instrument with parent and child forms that assesses five domains of health (physical functioning, emotional functioning, psychosocial functioning, social functioning, and school functioning) in children and adolescents ages 2 to 18. The inventory takes approximately 5 minutes to complete.[22] An advantage of the PedsQL is its short length, which allows for quick completion by patients and their parents—rendering it ideal for assessing the impact of an intervention on HRQOL and/or for repeated longitudinal assessment. Initial work has been performed with the PedsQL in 85 pediatric patients and 96 parents of children with ESRD receiving dialysis or with a renal transplant.[23] ESRD patient HRQOL scores were significantly lower than healthy controls. Transplant patients reported better physical and psychosocial health than dialysis patients. No difference was noted between HD and PD patients for any PedsQL domain.

Another advantage of the PedsQL methodology is the ability to create disease-specific modules, which can be completed in conjunction with the PedsQL 4.0 Generic Core Scales to provide further insight into the specific issues that impact HRQOL for a particular patient population.[24,25] Currently, a pediatric ESRD-specific PedsQL module is being assessed in four large U.S. pediatric centers.

Conclusions

Research efforts have significantly expanded to determine the state of pediatric dialysis patient HRQOL. As children demonstrate improved survival into adulthood, vigorous attention to pediatric HRQOL will be essential to provide optimal care and the tools needed for successful transition into the adult health care system. The HRQOL assessment instruments and their associated studies described in this chapter represent the first step toward achieving these goals.

References

1. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med 2004;350:2654–62.
2. Reynolds JM, Morton MJ, Garralda ME, et al. Psychosocial adjustment of adult survivors of a paediatric dialysis and transplant programme. Arch Dis Child 1993;68:104–10.
3. Morton MJ, Reynolds JM, Garralda ME, et al. Psychiatric adjustment in end-stage renal disease: A follow up study of former paediatric patients. J Psychosom Res 1994;38:293–303.
4. Henning P, Tomlinson L, Rigden SP, et al. Long term outcome of treatment of end stage renal failure. Arch Dis Child 1988;63:35–40.
5. Reiss JG, Gibson RW, Walker LR. Health care transition: Youth, family, and provider perspectives. Pediatrics 2005;115:112–20.
6. White PH. Access to health care: Health insurance considerations for young adults with special health care needs/disabilities. Pediatrics 2002;110:1328–35.
7. Brownbridge G, Fielding DM. Psychosocial adjustment and adherence to dialysis treatment regimes. Pediatr Nephrol 1994;8:744–49.
8. Fukunishi I, Honda M. School adjustment of children with end-stage renal disease. Pediatr Nephrol 1995;9:553–57.
9. Fukunishi I, Kudo H. Psychiatric problems of pediatric end-stage renal failure. Gen Hosp Psychiatry 1995;17:32–36.
10. Brownbridge G, Fielding DM. Psychosocial adjustment to end-stage renal failure: Comparing haemodialysis, continuous ambulatory peritoneal dialysis and transplantation. Pediatr Nephrol 1991;5:612–16.
11. Rosenkranz J, Bonzel KE, Bulla M, et al. Psychosocial adaptation of children and adolescents with chronic renal failure. Pediatr Nephrol 1992;6:459–63.
12. Johansen KL, Painter P, Kent-Braun JA, et al. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. Kidney Int 2001;59:1121–27.
13. Valderrabano F. Quality of life benefits of early anaemia treatment. Nephrol Dial Transplant 2000;15(3):23–28.
14. Diaz-Buxo JA, Lowrie EG, Lew NL, et al. Quality-of-life evaluation using Short Form 36: Comparison in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 2000;35:293–300.
15. Carmichael P, Popoola J, John I, et al. Assessment of quality of life in a single centre dialysis population using the KDQOL-SF questionnaire. Qual Life Res 2000;9:195–205.
16. Rao PN, Mehta SN, Guleria S, et al. The quality of life in successful live-related renal allograft recipients in India. Natl Med J India 1996;9:118–19.

17. Mapes DL, Bragg-Gresham JL, Bommer J, et al. Health-related quality of life in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2004;44:54–60.
18. Starfield B, Riley AW, Green BF, et al. The adolescent child health and illness profile: A population-based measure of health. Med Care 1995;33:553–66.
19. Gerson AC, Riley A, Fivush BA, et al. Assessing health status and health care utilization in adolescents with chronic kidney disease. J Am Soc Nephrol 2005;16:1427–32.
20. Kurtin PS, Landgraf JM, Abetz L. Patient-based health status measurements in pediatric dialysis: Expanding the assessment of outcome. Am J Kidney Dis 1994;24:376–82.
21. Gerson A, Hwang W, Fiorenza J, et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 2004;44:1017–23.
22. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–12.
23. Goldstein SL, Graham N, Burwinkle T, et al. Health-related quality of life in pediatric patients with ESRD. Pediatr Nephrol 2006;21:846–50.
24. Varni JW, Burwinkle TM, Szer IS. The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: Reliability and validity. J Rheumatol 2004;31:2494–2500.
25. Varni JW, Katz ER, Seid M, et al. The pediatric cancer quality of life inventory-32 (PCQL-32): I. Reliability and validity. Cancer 1998;82:1184–96.

CHAPTER 104

Immunization in Children Undergoing Dialysis

Jodi M. Smith, MD, MPH, and Janet A. Englund, MD

Introduction

Infections are a source of significant morbidity and mortality in the pediatric dialysis population. Despite this, vaccination rates in the end-stage renal disease (ESRD) population are significantly lower than for the general population.[1] To limit vaccine-preventable infections in this high-risk population, it is critical that the pediatric nephrologist monitor the immunization status of his/her patients and maintain compliance with vaccines and new recommendations. This chapter reviews immunization recommendations for patients on dialysis, how to prepare dialysis patients for transplant, and how to maintain readiness for patients on the transplant list. In addition, evidence of vaccine responsiveness in the pediatric population is presented.

Vaccine Schedule: Current American Academy of Pediatrics Recommendations

All patients on dialysis should receive the standard immunizations according to the time frames suggested by the Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP) and the American Academy of Family Physicians.[2] Children receiving dialysis should be immunized against all routine childhood vaccine-preventable diseases: tetanus, diphtheria, pertussis, polio, *Hemophilus influenzae* type B (HIB), *Streptococcus pneumoniae*, *Neisseria meningitides*, varicella, measles, mumps, rubella, influenza, and hepatitis A and B.

Numerous studies document the safety of vaccination of dialysis patients. Killed or component vaccines have not been associated with any deterioration in dialysis efficacy.[3] Live-virus vaccines have also been shown to be safe in the pediatric dialysis population. Table 104.1 summarizes a recent immunization schedule recommended by the AAP.[2] Notable changes included in these recommendations are discussed in the sections that follow.

Table 104–1

Recommended Childhood and Adolescent Immunization Schedule by Vaccine and Age

	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-6 yr	11-12 yr	13-14 yr	15 yr	16-18 yr
Hepatitis B	Hep B	Hep B		Hep B	Hep B				—	—	—	—		
Diptheria, tetanus, pertussis	—	—	DTaP	DTaP			DTaP			DTaP	Tdap[a]			
Hemophilus influenza type b		Hib	Hib	Hib	—	Hib								
Inactivated poliovirus		—	IPV	IPV	IPV					IPV				
Measles, mumps, rubella						MMR								
Varicella						Varicella								
Meningococcal											MCV4[a]			
Pneumococcal			PCV	PCV	PCV	PCV								
Influenza					Influenza (yearly)									
Hepatitis A						Hepatitis A series								
Human papilloma virus											HPV[a] (girls)			

a. New recommendations.

Combination Tetanus-Diphtheria-Pertussis Vaccines

New formulations of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines (Tdap adolescent preparation) were licensed by the United States Food and Drug Administration (FDA) in 2005 (Adacel, Boostrix). The rationale for this addition is that pertussis remains endemic despite universal immunization of young children with multiple doses of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine (DTaP). The Tdap formulation is recommended for adolescents (beginning at 11 years of age) who have completed the recommended childhood DTP/DTaP vaccination series and have not received a recent tetanus-diphtheria toxoids (Td) booster dose. Adolescents who missed the Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series and it has been at least 2 years since receipt of a DT-containing vaccine.

Meningococcal Vaccine

The polysaccharide meningococcal vaccine has been available for children for many years, but a new meningococcal multivalent conjugate vaccine (MCV4, Menectra) was approved by the FDA in January of 2005. The new conjugate vaccine provides protection against meningococcal serotypes A, C, Y, and W135, and provides potential superiority compared to the polysaccharide vaccine because of improved immunologic memory, boostability, and increased potential for reduction of carriage. The new conjugate vaccine is recommended for all children aged 11 to 12 years, as well as to all unvaccinated adolescents at high school entry.

Hepatitis A

Hepatitis A vaccine is universally recommended for all children at age 1 year. The two doses in the series should be given at least 6 months apart.

Human Papilloma Virus

Human papilloma virus (HPV) vaccines have undergone worldwide clinical testing, and the first HPV vaccine was licensed by the FDA in June of 2006 for use in females 9 to 26 years of age.[4] This vaccine consists of only the outer coat of each virus, and is extremely safe and immunogenic. One HPV vaccine (Gardisil,

Merck) contains four types of HPV, and a second vaccine (Cervarix , GlaxoSmithKline) contains two HPV antigens—including the two types that cause most (70%) cervical cancers (types 16 and 18). The Gardisil vaccine also contains the two other viral strains that cause most (90%) genital warts (types 6 and 11). The vaccine is given as a series of three injections over a 6-month period. The second and third doses should be given 2 and 6 months (respectively) after the first dose. The proposed recommendations are to provide routine vaccination for 11- to 12-year-old girls and catch-up vaccination for 13- to 26-year-old females.

Combination Measles-Mumps-Rubella-Varicella Vaccine

A new combination vaccine containing the traditional measles-mumps-rubella (MMR) combined in the same syringe with varicella zoster vaccine (Varivax) is now available, which may be used as the primary dose at 12 months of age and potentially as a booster dose in the future.

Preparing for Transplantation in the Dialysis Patient

Achieving immunity to vaccine-preventable childhood infections prior to renal transplantation is critical. Ideally, routine immunizations should be up to date prior to referral for transplant. If no immunization records are available, routine immunizations should be "caught up" according to the recommendations of the AAP and ACIP guidelines.[2] Special considerations are noted in the sections that follow.

Varicella Vaccine

Antibody to varicella zoster virus (VZV) can be monitored and patients immunized as appropriate prior to transplantation. Although current recommendations include the administration of one dose of VZV vaccine prior to 2 years of age, some experts believe that long-lasting protection could be enhanced by a second dose administered as a preschool booster. VZV vaccine may be given as early as 9 months of age if early transplant is anticipated. It can be given simultaneously with MMR or at least 4 weeks later. It is generally recommended that transplant not occur for a minimum of 6 weeks after immunization with Varivax due to the live viruses it contains.

Measles-Mumps-Rubella Vaccine

Immunity to measles and rubella should be assessed prior to transplantation. Immunity to mumps remains more challenging and potentially concerning in view of recent epidemics of mumps both in Europe and the United States, but in general can be assumed to be present in the face of adequate responses to measles and rubella. Patients can be immunized as appropriate. Two catch-up doses may be given at least 1 month apart. In general, patients should not undergo transplantation for a minimum of 6 weeks after immunization with MMR due to the live viruses it contains.

DTap/dT Vaccine

Children aged 2 months to 7 years should be vaccinated according to the routine immunization schedule. The first two doses should be administered 1 to 2 months apart and the third dose should be administered 6 to 12 months after the second dose. Patients should receive the Tdap booster by age 11 to 16 years, and then every 10 years thereafter. In patients 7 years of age or older, Tdap may be substituted for any dose in a primary catch-up series or as a booster if age appropriate for Tdap. A 2-year interval from the last Td dose is encouraged when Tdap is used as a booster.

Poliovirus Vaccine

A total of four doses of inactivated trivalent polio vaccine are recommended for all children. Oral polio vaccine is no longer recommended in the United States and should not be administered to children awaiting transplantation. The first three doses can be given a month apart in children over 6 years of age who have not received any vaccines.

Hemophilus Influenzae Type B Vaccine

Rapid catch-up immunization with HIB vaccine can be accomplished in children with a minimum of 4 weeks between doses. Children aged 12 to 59 months who are unimmunized or who received only one dose of HIB vaccine prior to 12 months should receive two doses separated by 2 months. Those who received two doses before the age of 12 months should receive one additional dose. At-risk children >59 months of age who have not received HIB should receive two doses at least one month apart.

Pneumococcus Vaccine

Table 104.2 outlines the recommendations for immunization against *Streptococcus pneumonia*, the pneumococcal conjugate vaccine (PCV-7, Prevnar), and the 23-valent pneumococcal polysaccharide vaccine (23PS, Pneumovax).

Hepatitis A Vaccine

A total of two doses given 6 months apart is recommended. This vaccine can safely be given earlier than 24 months of age if transplant is anticipated.

Hepatitis B Vaccine

A total of three doses should be administered to all children beginning at birth and concluding by 6 months of age. Catch-up immunization should be initiated for all children as soon as

Table 104–2

Recommendations for Pneumococcal Vaccination

Age	Previous Doses	Recommendations
<23 mo	None	• PCV7 at 2, 4, 6, 12–15 mo.
24–59 mo	4 doses of PCV7	• 23PS at 24 mo, 6–8 weeks after last dose of PCV7. • Booster: 23PS, 5 y after first dose of 23PS.
23–59 mo	1–3 doses of PCV7	• 1 dose of PCV7, followed 6–8 weeks later with one dose of 23PS. • Booster: 23PS 5 years after first dose of 23PS.
24–59 mo	1 dose of 23PS	• 2 doses of PCV7 (6–8 weeks apart) beginning 6–8 weeks after last 23PS. • Booster: 23PS 5 years after first dose of 23PS.
24–59 mo	None	• 2 doses of PCV7, 6–8 weeks apart. • 1 dose of 23PS, 6–8 weeks after last PCV7.
5–10 y	None	• One dose of PCV7 and one dose of 23PS 6–8 weeks apart.
>10 y	None	• 23PS only. Unless overly immunocompromised; then one dose PCV7 and one dose 23PS 6–8 weeks apart.

possible due to the high risks associated with hepatitis B infection in patients receiving hemodialysis or post-transplant. Response to vaccination can be assessed by determining the antibody level at 1 to 2 months after the third dose, and if < 10 mIU/mL the patient can receive up to three more doses.

Influenza Vaccine

Routine annual influenza vaccination is recommended for all children >6 months of age with significant underlying disease (including those on dialysis or awaiting transplantation) and their close contacts, including siblings, parents, and other caretakers. Trivalent inactivated influenza vaccine without preservatives (FluzoneR, Sanofi Aventis) should be administered intramuscularly as early in the fall season as possible to children awaiting transplantation to offer protection against influenza. Two doses are required if the initial vaccination is occurring at less than 9 years of age. Live attenuated influenza vaccine (FLumist, MedImmune) can be considered for children on dialysis who are not on chronic immunosuppression and for their family members.

Updating Immunizations for the Dialysis Patient Awaiting Transplant

The immunization status of patients on the transplant waiting list should be monitored and updated as appropriate. Hepatitis B antibody status should be assessed with annual antibody testing, and vaccine readministered using either brand of commercially available vaccine (Recombivax HB or Energix) when antibody levels decline below 10 mIU/mL. Recommendations using Recombivax vaccine include a repeat dose 1 to 2 months after the third dose if the antibody levels decline below 10 mIU/mL.

Patients should receive the Tdap booster by age 11 to 16 years, and then every 10 years. The influenza vaccine should be given annually once a year to both the patient and his/her family. Live attenuated influenza vaccine can be given as an intranasal preparation. The new live-vaccine preparation (nose drops) should not be used in immunocompromised patients.

Vaccine Response in the Dialysis Population: What is the Evidence?

Due to multiple disturbances of host defenses, patients with chronic kidney disease (CKD) can demonstrate suboptimal

vaccine responses. Defective host responses can result from the uremic state, the underlying cause of ESRD and its therapy, and/or the dialysis itself. These factors have been demonstrated to impact virtually every aspect of the host immune system.[5] Antibody responses to currently recommended immunizations in pediatric dialysis patients have been monitored, and the results are variable. In general, these studies identify two main issues in the dialysis population: suboptimal antibody response and waning immunity. In the setting of suboptimal antibody responses, repeat vaccinations with an increased dose can be considered. The issue of waning immunity demands rigorous follow-up of patients (with revaccination as indicated).

Diphtheria and tetanus antibody responses to vaccine have been studied by the Pediatric Peritoneal Dialysis Study Consortium in eight infants on peritoneal dialysis. Seven of the eight infants had protective levels of IgG to both of the toxoids for up to 24 months postvaccination.[6]

A less than optimal response to the MMR vaccine was seen in 10 pediatric dialysis patients, with 8 of 10 responding to measles vaccine, 5 of 10 to mumps, and 8 of 10 to rubella.[7] A study of infants immunized while on peritoneal dialysis found that 5 of 8 children demonstrated protective antibody titers to rubella.[6] One center demonstrated that a protocol of early MMR vaccination induced immunity in most infants with chronic renal failure and those on peritoneal dialysis.[8] Due to variable responsiveness to the various elements of the vaccine, it is recommended that antibody titers be verified previous to transplant.

The responsiveness to the conjugate HIB vaccine was studied in 10 children on peritoneal dialysis, with 9 of 10 children ages less than 42 months developing protective antibody levels.[9] Serial measurements did reveal declining antibody levels in 2 subjects. Monitoring of antibody levels in high-risk infants and children should be considered.

An open-label multicenter prospective clinical trial to evaluate the safety and immunogenicity of a two-dose regimen of varicella vaccine was conducted by the Southwest Pediatric Nephrology Study Group in 96 children ages 1 to 19 years with chronic renal insufficiency on dialysis.[10] Nearly all children (98%) seroconverted 1 to 2 months after the second dose of the two-dose regimen. At 1, 2, and 3 years' follow-up all evaluable patients maintained VZV antibody, including 16 who received a transplant. No significant vaccine-associated adverse events were seen. This and other studies[11] confirm that varicella immunization in children on dialysis results in a high rate of seroconversion and persist-

ence of protective antibody titers. More widespread use of the vaccine prior to renal transplantation is recommended.

In the adult CKD population, the poor antibody responses to the hepatitis B vaccine led to the recommendation that these patients receive higher doses of the vaccine. The Southwest Pediatric Nephrology Group evaluated the responsiveness to the hepatitis B vaccine in 78 pediatric patients with CKD (22 pre-dialysis, 42 chronic dialysis, and 14 transplant).[12] Ninety-one percent of 66 patients who received three doses of the vaccine had a protective antibody titer of 10 mIU/mL or more. The seroprotective rates were 100% in the pre-dialysis group, 94% in the dialysis group, and 64% in the transplant population. The conclusion of the study was that a regimen of three 20-mcg doses of Recombivax HB was suitably immunogenic for children not on immunosuppressive therapy. It is recommended that this vaccine be administered prior to the progression to ESRD, if feasible.

The response to the trivalent inactivated influenza vaccine was studied in a group of pediatric patients with CKD (15 pre-dialysis, 10 dialysis, and 17 renal transplant).[13] There was no significant difference in the seroconversion rates and percentage of patients with protective hemagglutination-inhibition titers between study groups and controls, suggesting that CKD patients benefit from influenza immunization.

Pneumococcal infection is an important cause of sepsis during childhood, and responses to the multivalent conjugate pneumococcal vaccine have been studied. The antibody response to pneumococcal serotypes 3 and 14 following administration of the pneumococcal polysaccharide vaccine was evaluated in 10 pediatric patients on peritoneal dialysis.[14] Evaluation of antibody responses at 1 month and 1 year post-vaccination found that the majority of patients retained protective IgG levels. Seven of these 10 patients maintained protective levels at 5 years post-vaccination.[15]

Summary

Morbidity and mortality from vaccine-preventable illness are significant concerns in the pediatric dialysis population. However, children with ESRD are often under the care of numerous physicians at multiple sites where vaccinations are administered, and the vaccine history in these complex patients may be overlooked. Pediatric dialysis patients should receive routine childhood vaccinations on a timely schedule, and every effort should be

made to complete the vaccination program prior to transplantation—using an accelerated schedule if necessary.

Increased compliance with vaccine recommendations has been observed when the nephrologist assumes responsibility for the administration and surveillance of immunizations. In addition, ensuring that family members are up to date with their immunizations will help to maximize the preventive benefits of this intervention. Small studies in pediatric dialysis patients demonstrate vaccine responsiveness, but an important issue still not well studied is the duration of the immunity following vaccination in this patient population. Thus, it is important for practitioners to be diligent, measure titers when possible, and revaccinate to maintain the health of this vulnerable population.

References

1. U.S. Renal Data System. USRDS 2005 Annual Data Report. Bethesda, National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, 2005.
2. Centers for Disease Control and Prevention. Recommended childhood adolescent immunization schedule-United States, 2006. MMWR 2005;54(Nos.51&52):Q1–Q4.
3. Neuhaus TJ. Immunization in children with chronic renal failure: A practical approach. Pediatr Nephrol 2004;19(12):1334–39.
   Review article of immunization recommendations in pediatric patients with chronic renal failure, dialysis, and post-transplant.
4. Centers for Disease Control and Prevention National Immunization Program, *www.cdc.gov/nip/vaccine/hpv*.
5. Pesanti EL. Immunologic defects and vaccination in patients with chronic renal failure. Infect Dis Clin North Am 2001;15(3):813–32.
   Review article of the immune defects associated with chronic renal failure.
6. Neu AM, Warady BA, Furth SL, Lederman HM, Fivush BA. Antibody levels to diphtheria, tetanus, and rubella in infants vaccinated while on PD: A study of the Pediatric Peritoneal Dialysis Study Consortium. Adv Perit Dial 1997;13:297–99.
   Multicenter study of the vaccine response to diphtheria, tetanus, and rubella in eight infants on chronic peritoneal dialysis.
7. Schulman SL, Deforest A, Kaiser BA, Polinsky MS, Baluarte HJ. Response to measles-mumps-rubella vaccine in children on dialysis. Pediatr Nephrol 1992;6(2):187–89.
   A study of the immune response to the MMR vaccine in 10 children on dialysis.
8. Flynn JT, Frisch K, Kershaw DB, Sedman AB, Bunchman TE. Response to early measles-mumps-rubella vaccination in infants with chronic renal failure and/or receiving peritoneal dialysis. Adv Perit Dial 1999;15:269–72.
   Study of a protocol of early MMR vaccination in 9 infants on peritoneal dialysis.
9. Neu AM, Lederman HM, Warady BA, Fivush BA for the Pediatric Peritoneal Dialysis Study Consortium. Haemophilus influenzae type b immunization in infants on peritoneal dialysis. Pediatr Nephrol 1996;10(1):84–85.
   Multicenter study of the vaccine response to hemophilus influenzae type B in 10 peritoneal dialysis patients.

10. Furth SL, Hogg RJ, Tarver J, Mouton LH, Chan C, Fivush BA for the Southwest Pediatric Nephrology Study Group. Varicella vaccination in children with chronic renal failure: A report of the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 2003;18(1):33–38.
Study of the safety and immunogenicity of the varicella vaccine in 96 children with chronic renal insufficiency and on dialysis.
11. Webb NJ, Fitzpatrick MM, Hughes DA, Brocklebank TJ, Judd BA, Lewis MA, et al. for the Trans-Pennine Paediatric Nephrology Study Group. Immunisation against varicella in end stage and pre-end stage renal failure. Arch Dis Child 2000;82(2):141–43.
Study of the seroconversion rate and duration of immunity to varicella vaccination in a group of 32 children with ESRD and pre-ESRD.
12. Watkins SL, Alexander SR, Brewer ED, Hesley TM, West DJ, Chan IS, et al. for the Southwest Pediatric Nephrology Study Group. Response to recombinant hepatitis B vaccine in children and adolescents with chronic renal failure. Am J Kidney Dis 2002;40(2):365–72.
Multicenter study of the vaccine response to the recombinant hepatitis B vaccine in pediatric patients with chronic renal failure, on dialysis and post renal transplant.
13. Furth SL, Neu AM, McColley SA, Case B, Steinhoff M, Fivush B. Immune response to influenza vaccination in children with renal disease. Pediatr Nephrol 1995;9(5):566–68.
Study of the vaccine response to the influenza vaccine in pediatric patients with chronic renal failure, on dialysis, and post renal transplantation.
14. Furth SL, Neu AM, Case B, Lederman HM, Steinhoff M, Fivush B. Pneumococcal polysaccharide vaccine in children with chronic renal disease: A prospective study of antibody response and duration. J Pediatr 1996;128(1):99–101.
Study of the vaccine response to the pneumococcal vaccine in 41 pediatric patients with renal disease.
15. Neu AM, Fivush BA. Immunizations for pediatric dialysis patients. Adv Ren Replace Ther 2000;7(3):239–46.
Review article on immunizations in pediatric dialysis patients with a focus on the evidence of vaccine responsiveness in this population.

CHAPTER 105

Prevention and Treatment of Cardiovascular Complications

Mark M. Mitsnefes, MD, MS

The survival of children with end-stage renal disease (ESRD) in the United States remains low. For children on long-term dialysis, the life span is 40 to 60 years less than that of an age-and race-matched U.S. population (meaning that these children die in young adulthood). The most likely cause is cardiac mortality due to development of accelerated atherosclerosis and premature dilated cardiomyopathy. Cardiac complications in children on dialysis can cause cardiovascular death not only in later life but in childhood. In the general pediatric population, death due to cardiac disease is less than 3%. However, data indicate that in children with ESRD (as in adults), cardiovascular disease (CVD) is one of the leading causes of death—accounting for approximately 20 to 25% of all deaths.

Cardiac death in patients developing ESRD during childhood has a frequency approximately 1000 times greater than in the general pediatric population. Of the specific causes of cardiovascular deaths, cardiac arrest is the most common, followed by arrhythmia and cardiomyopathy. These causes are different from those of adults. In adults, coronary artery disease and congestive heart failure due to cardiomyopathy are two leading causes of mortality from CVD. The mortality from these causes is extremely low in children and in adults younger than 30 years of age.

The high rate of sudden death in children, especially in infants with ESRD, is poorly understood and warrants further investigation. The risk factors and pathogenic mechanisms leading to CVD in adults who had the onset of chronic kidney disease (CKD) in childhood are better understood than are those producing cardiac morbidity and mortality in children. This chapter focuses on prevention of the "classic" form of CVD as seen in adults who developed CKD in childhood.

Development of "Classic" Adult-Type CVD in CKD

The conventional thinking is that two groups of risk factors are responsible for accelerated CVD in adults with CKD. First, compared to the nonuremic population there is an overrepresentation in uremic patients of classical risk factors (e.g., diabetes, hypertension, and hyperlipidemia). A majority of the adults who develop ESRD do so as a complication of diabetes or generalized atherosclerosis.

Often cardiac disease antedates the onset of CKD in these patients. Second, there are numerous uremia-related risk factors (such as dyslipidemia, anemia, hyperhomocysteinemia, alteration of calcium phosphorus metabolism, inflammation, infection, and oxidative stress) that may singly or in concert trigger the development of CVD. For more information, see the extensive review of literature on CVD biomarkers in the Kidney Diseae Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guide-lines for Cardiovascular Disease in Dialysis. As can be seen in Table 105.1, many of the same risk factors are present in high frequency in children on dialysis—making them extremely susceptible to CVD.

There are two parallel processes involved in the development of CVD in children with CKD. The first is cardiomyopathy. It is initially manifest by disorders of the left ventricle (LV), which lead to adoptive LV remodeling. Two types of LV remodeling are recognized. Concentric LV hypertrophy (LVH) results primarily from pressure overload as occurs with hypertension. Eccentric LVH has been related primarily to volume overload, as frequently seen in patients on dialysis or with

Table 105–1

Prevalence of Risk Factors for Cardiovascular Disease in Children with Chronic Kidney Disease

Risk Factor	(%)
Hypertension	52–75
Dyslipidemia	33–87
Anemia	40–67
Hyperparathyroidism	58
Hyperhomocysteinemia	87–92
Chronic inflammation (↑ CRP)	76
Hypoalbuminemia	40–60

anemia. It is likely that the effects of hemodynamic overload on the LV are augmented by nonhemodynamic LVH-generating causes such as hyperparathyroidism, sympathetic hyperactivity, systemic inflammation, local production of angiotensin II, and malnutrition.

With time, a maladaptive phase of LVH develops, which is characterized by decreased capillary density, decreased coronary reserve and subendocardial perfusion, a tendency to arrhythmia, and the development of myocardial fibrosis. All of this leads to myocyte death, and finally to diastolic and systolic dysfunction. Symptomatic cardiomyopathy is very rare in children, but early abnormalities of cardiac structure and function can frequently be seen. LVH develops when renal insufficiency is mild or moderate in children and progresses as renal function deteriorates. About 1/3 of children with pre-ESRD and 2/3 of those who start maintenance dialysis therapy have an increased LV mass (LVM). LVH persists (52–75%) during long-term dialysis. Both concentric and eccentric geometric patterns of LVH are present in these patients, suggesting that as in adults with ESRD the mechanism of LVH in advanced CKD in children is volume and pressure overload.

LVH is prevalent in both children on hemodialysis and peritoneal dialysis. Small retrospective studies suggest that with good blood pressure (BP) control LVH will regress in young patients on dialysis. In contrast to adults, in whom systolic dysfunction is frequently associated with early cardiac failure and decreased survival, in children systolic LV function is usually preserved. On the other hand, these children may develop LV diastolic dysfunction—often the initial manifestation of abnormal cardiac function.

The second process involves accelerated vascular injury. Endothelial dysfunction is followed by arterial hypertrophy and stiffness. This leads to atherosclerosis and to symptomatic (ischemic) coronary artery disease. Young adults who develop ESRD during childhood have a high prevalence of asymptomatic atherosclerosis, as demonstrated by abnormal carotid intimamedial thickness, diminished arterial wall compliance, and coronary artery calcification. Recent studies showed that these arterial abnormalities are already present in children on chronic dialysis, supporting the hypothesis that they have accelerated atherosclerosis. In CKD patients, a variety of factors have been associated with the development of atherosclerosis. Many of these factors are similar to those involved in the development of cardiac hypertrophy and include hypertension, dyslipidemia,

abnormal calcium-phosphorus metabolism, chronic inflammation, and others.

Evaluation and Treatment Recommendations

The overall strategy in prevention of cardiovascular complications in children with advanced CKD is avoidance of long-term dialysis. The goal is to prevent development and delay the progression of cardiomyopathy and atherosclerosis. Even though kidney transplantation poses continuous cardiovascular risk (hypertension, hyperlipidemia, allograft dysfunction), it eliminates many uremia-related risks, reduces risk of cardiac death by approximately 80%, and prolongs life span by 20 to 30 years. Thus, kidney transplantation should be the ultimate goal to minimize cardiovascular morbidity and mortality. For those patients who must have long-term dialysis, the strategy is directly linked to achievement of adequate dialysis outcomes—which include aggressive monitoring and management of hypertension, dyslipidemia, calcium-phosphorus metabolism, anemia, nutrition, systemic inflammation, and other dialysis complications.

Echocardiographic Evaluation

The NKF-K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommend that children have echocardiographic evaluation for the presence of cardiac disease (cardiomyopathy and valvular disease) at the time of initiation of dialysis therapy. As discussed previously, the most common cardiac diagnosis in children on chronic dialysis is hypertrophic cardiomyopathy (LVH). There is no uniform definition of LVH in children, which makes it difficult to establish specific targets for LVM. The most commonly used definition of LVH is based on the 95th percentile of LVM indexed to height raised to the power of 2.7 ($g/m^{2.7}$). For children older than 9 years, the value of the 95th percentile is relatively stable and is 38 to 42 $g/m^{2.7}$.

The fourth NKF-K/DOQI report on BP in children recommends an LVM index value of 51 $g/m^{2.7}$ as a conservative cutoff point for the presence of LVH. This value is above the 99th percentile for children and adolescents. In adults with hypertension, this value is associated with up to a fourfold increase in cardio-vascular morbidity. The use of this value to define LVH in children younger than 5 years is problematic because the normative values for LVM index ($g/m^{2.7}$) in this age range are significantly higher than in older children. In fact, the value

of 51 g/m$^{2.7}$ represents the normal LVM index for children 1 to 5 years of age.

At Cincinnati Children's Hospital, we define LVH based on locally generated normative values obtained from 2704 nonobese children, aged 0 to 18 years, who had normal echocardiograms performed for routine indications (Figure 105.1a and b; presented

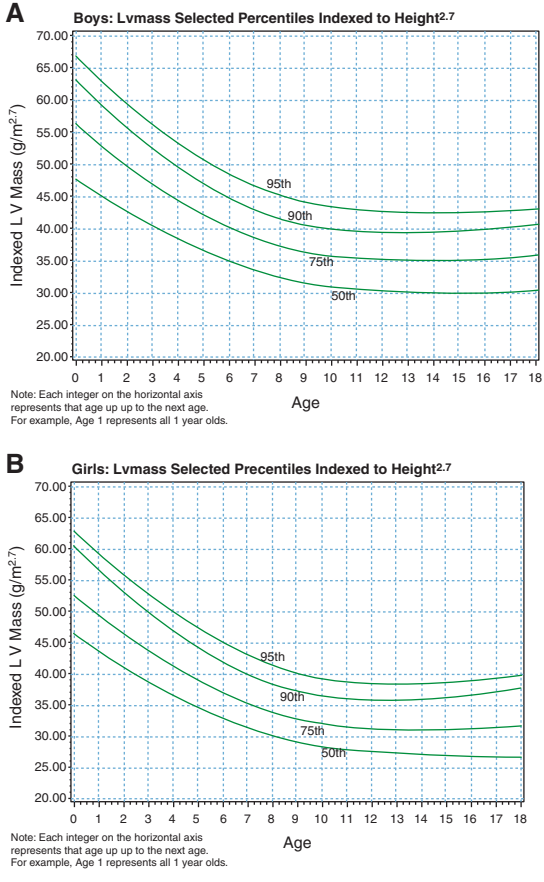


Figure 105–1

LV mass indexed to height.

at the American Society of Echocardiography meeting, 2004, San Diego). If LVH is diagnosed at the initiation of dialysis, routine echocardiographic monitoring every 6 months is recommended. If the initial echocardiogram is normal, yearly echocardiographic follow-up is suggested. Echocardiography is also important in monitoring cardiac function. A shortening fraction (index of systolic function) is routinely calculated from echocardiographic parameters. Systolic dysfunction is rare in children on dialysis, but if discovered the patient should be evaluated by a cardiologist.

Hypertension

As recommended by the Fourth Report on Blood Pressure in Children, the target blood pressure in children with CKD should be less than the 90th percentile—adjusted for age, gender, and height or set at less than 120/80 mmHg, whichever is lower. About 3/4 of children entering maintenance dialysis therapy have a BP above the 95th percentile (uncontrolled hypertension), and in almost all the BP is above the target level of the 90th percentile. It is especially troubling that hypertension is unlikely to improve during long-term dialysis. Hypertension is frequent with both hemodialysis and peritoneal dialysis but is reported to be more frequent in hemodialyzed children. Poor BP control in children on chronic dialysis is multifactorial, but the major cause is chronic hypervolemia. Thus, the first step in the diagnosis and management of hypertension should be evaluation of volume status.

Unfortunately, many children on dialysis do not achieve their dry weight. Volume status assessment in young patients is frequently not accurate. This is one of the reasons the frequency of hypertension is higher in young children. In addition, correct assessment of BP is difficult in small children and is consequently frequently underdiagnosed, and therefore not adequately treated. Another group of children who present with significant fluid overload, and therefore with hypertension, is adolescents who are almost always noncompliant with fluid and salt restriction. Chronic fluid overload with secondary hypertension is the major cause of high prevalence of LVH in children on chronic dialysis. Thus, aggressive management of fluid overload and achievement of dry weight is the most effective treatment of hypertension and LVH in children on chronic dialysis.

For children on hemodialysis, longer and more frequent dialysis sessions (and sometimes intermittent ultrafiltration) might

be needed to improve volume status. Noninvasive hematocrit monitoring—such as the CRIT-LINE instrument (Hemametrics, Kaysville, Utah, USA)—is currently widely used to assess volume status in pediatric dialysis units. To improve ultrafiltration in children on peritoneal dialysis without increasing a glucose concentration in peritoneal solution, a daily long dwell with icodextrin (Baxter, Deerfield, IL, USA) may be considered.

In most children, the achievement of dry weight results in normalization of BP and a significant decrease in the use of antihypertensive medications. If BP remains elevated despite adequate volume control, antihypertensive medications should be optimized. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be considered as a first line of therapy in children on dialysis because of their renal and cardioprotective effects. The addition of calcium channel blockers or beta blockers should be tried next. It is important to remember that if effective dry weight is not achieved antihypertensive medications (especially vasodilators and beta blockers) will likely not work and may further impair the ability to remove fluid. If BP is still inadequately controlled after achieving dry weight and maximizing the use of BP medications, nephrectomies should be strongly considered.

Achievement of normal daytime office BP measurement does not necessarily indicate the absence of hypertension. Patients with CKD frequently have undetected nighttime hypertension. Children who have normal BP in the dialysis unit might benefit from ambulatory BP monitoring to investigate the presence of nighttime hypertension.

Dyslipidemia

Dyslipidemia is very prevalent in children on chronic dialysis and is characterized by low HDL (high density lipoprotein cholesterol) and high triglyceride levels. Many children also have increased total cholesterol and LDL (low density lipoprotein cholesterol). The NKF-K/DOQI guidelines recommend evaluation of dyslipidemias in adolescents upon presentation with CKD stage 5 (GFR <15 mL/min/1.73 m^2 or on dialysis), at 2 to 3 months after a change in treatment or other conditions known to cause dyslipidemias, and at least annually thereafter. Reasons to repeat lipid measurements after 2 to 3 months include changes in kidney replacement therapy modality, treatment with diet or lipid-lowering agents, immunosuppressive agents that affect lipids (e.g., prednisone, cyclosporine, or sirolimus), or other changes that may affect plasma lipids.

The assessment of dyslipidemias should include a complete fasting lipid profile, with total cholesterol, LDL, HDL, and triglycerides. The definition of dyslipidemia differs in children and adults. Hyperlipidemia in children is defined as lipid levels greater than the 95th percentile for age and gender. The normative data for lipids in children and adolescents currently used are from the Lipid Research Clinics Program of the National Institutes of Health, published in 1980. This data can be found in the 2003 NKF-K/DOQI guidelines for management of dyslipidemias in chronic kidney disease.

For adolescents with stage 5 CKD and a level of LDL = 130 mg/dL, NKF-K/DOQI recommends treatment to reduce LDL to <130 mg/dL. If LDL <130 mg/dL, fasting triglycerides equal 200 mg/dL, and non-HDL cholesterol (total cholesterol minus HDL) equals 160 mg/dL, treatment should be considered to reduce non-HDL cholesterol to <160 mg/dL. All children with dyslipidemias should follow the recommendations for therapeutic lifestyle changes (TLC), which include diet modification (reduction in saturated fat intake and increased fiber intake) and moderate physical activity. Adolescents should be counseled about avoiding smoking. Unfortunately, noncompliance with TLC is one of the major problems in the management of dyslipidemia in adolescents. Pediatric nephrologists must also recognize that appropriate caloric intake, including calories from fat, should be emphasized to avoid malnutrition and ensure normal growth and development—especially in young children.

If LDL cholesterol equals 160 mg/dL and non-HDL cholesterol equals 190 mg/dL, statin therapy is recommended in children older than age 10 years. The age limitation is based on the concern that starting statin at a younger age might interfere with sexual maturation because steroid hormones are all derived from cholesterol. Published reports over the last 5 years, largely concerning children with familial hypercholesterolemia, indicate that statins are safe and can be used in children as young as 8 years of age with no impact on sexual development. However, these studies do not provide long-term safety data. The concern for a delayed puberty is one of the reasons the criteria for statin therapy initiation are different from recommendations in adults, for whom statin therapy is initiated at lower levels of LDL cholesterol and non-HDL cholesterol.

Although it is prudent to be cautious, the decision to start drug therapy should be guided by the child's overall cardiovascular risk profile. As discussed previously, children with CKD (especially those on chronic dialysis) are extremely susceptible

to the development of accelerated atherosclerosis and premature coronary artery disease. Because of this risk, the potential benefit from statin therapy might be more important than the risk of delayed puberty. Thus, initiation of statin therapy at lower than currently recommended cholesterol levels might be warranted.

Abnormal Calcium-Phosphorus Metabolism

The Working Group on Cardiovascular Disease in Dialysis Patients recommends maintaining calcium (Ca) and phosphorus (P) levels within the normal range and the Ca × P product <55 mg^2/dL^2 in children on chronic dialysis. These recommendations are based on adult studies, demonstrating that hyperphosphatemia and increased Ca × P product are strongly correlated with cardiac calcification and increased cardiac morbidity and mortality. The majority of children on chronic dialysis are hyperphosphatemic, and as a result require phosphate-binding therapy.

Studies of children and young adults on chronic dialysis determined that the cumulative dose calcium-based phosphate binders and the administration of active vitamin D preparations are strong determinants of arterial stiffness, coronary artery calcification, and metastatic calcinosis. This may represent risk factors for CVD that are even more important than hypertension and dyslipidemia. Therefore, use of non calcium-based phosphate binders, careful monitoring of serum calcium level, and appropriate adjustment of the dose of vitamin D to avoid hypercalcemia are essential in the management of children on dialysis to prevent development and progression of cardiovas-cular abnormalities.

Anemia

Studies in adult dialysis patients have identified anemia as a risk factor for patient morbidity and mortality. The studies from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) indicate that anemia is very common and is frequently under treated in children on chronic dialysis. The NAPRTCS data also showed that anemia is present in more than half the children entering maintenance dialysis and is associated with a 52% higher risk of death in chronically dialyzed children. A few small single-center pediatric studies determined that anemic children more frequently have LVH than those with normal hemoglobin and that treatment of severe anemia with erythropoietin results in a significant reduction of LVM index.

The hemoglobin level of 11.0 g/dL represents the value less than the 5th percentile for boys younger than 5 years, 11.5 g/dL for boys 6 to 8 years old, 12.0 to 12.5 g/dL for boys 9 to 14 years old, and 13.5 for boys 15 to 19 years old. For girls of all ages, the lower limits of normal values are 11 to 12 g/dL. Current NKF-K/DOQI guidelines for treatment of anemia recommend keeping the hemoglobin level above 11 g/dL by using an appropriate iron therapy and recombinant erythropoietin. In the opinion of the Working Group on Cardiovascular Disease in Dialysis Patients, there is insufficient evidence to recommend routinely maintaining hemoglobin levels above 13 g/dL or greater. These target levels are about 2 g/dL less than the mean hemoglobin values for children in each age category. They are based on adult data showing that higher hemoglobin levels in hemodialyzed patients with heart disease were associated with increased rate of nonfatal myocardial infarction.

Because symptomatic CVD (including myocardial infarction) is extremely rare in children, the results from these adult studies (and therefore current hemoglobin targets) might not be applicable to pediatric patients. Unfortunately, for recombinant erythropoietin therapy reimbursement in children with CKD, Medicare and insurance companies follow current NKF-K/DOQI guidelines that establish the upper limit of hematocrit level at 36%. These guidelines apply even to children who are not yet on dialysis, possibly putting them at risk for CVD prior to initiation of chronic dialysis therapy. The appropriate hemoglobin level in children on chronic dialysis is undoubtedly an issue that requires intense investigation.

Malnutrition and Inflammation

Adequate nutrition is an essential part of dialysis care. Malnutrition is frequent in children on chronic dialysis, especially in young patients and those who require long-term dialysis. Failure to thrive and hypoalbuminemia are significant risks of death in pediatric patients with ESRD. Recent studies in adults on chronic hemodialysis place the malnutrition-inflammation complex at the center of a debate about the role of traditional and nontraditional risk factors for poor cardiovascular outcome. This issue emerged after publication of a series of articles describing the phenomenon of “reverse epidemiology.”

The studies have shown that in adults on chronic hemodialysis low blood pressure, low body mass index (BMI), and low serum cholesterol are often correlated with an unfavorable

clinical outcome. Thus, whereas traditional risk factors of CVD are correlated with an unfavorable outcome in the general population and patients with CKD not yet on dialysis in hemodialyzed patients mild hypertension, hypercholesterolemia, and overweight appear to be protective and associated with an improved survival.

It has been speculated that the malnutrition-inflammation-atherosclerosis complex underlies, at least partly, the phenomenon of reverse epidemiology because malnutrition causes a low BMI and hypocholesterolemia. That these results might be applied to pediatric patients is not clear at this time. However, they suggest that more emphasis should be placed on the assessment and management of nontraditional cardiovascular risks in dialyzed children.

Recommended Reading

Greenbaum LA. Anemia in children with chronic kidney disease. Adv in Chronic Kidney Dis 2005;12:385–96.

Full review of current literature on the mechanisms, frequency, consequences, and management of anemia in children with chronic kidney disease.

Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. Advances in Chronic Kidney Disease 2005;12:397–405.

Detailed review on the topic; fully referenced.

National High Blood Pressure Education Program. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004;114:555–76.

Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents that contains the taskforce's current recommendations on the diagnosis, evaluation, and treatment of pediatric hypertension (which updates the group's previous recommendations from 1996).

NKF. Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients: National Kidney Foundation NKF-K/DOQI Guidelines. Am J Kidney Dis 2005;45(3):S10–15.

In addition to practical recommendations, the guidelines include updated review on novel CVD biomarkers.

NKF. Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease: National Kidney Foundation NKF-K/DOQI Guidelines. Am J Kidney Dis 2003;41(3):S22–38.

Review of current literature on the mechanisms and prevalence of dyslipidemia in pediatric patients on chronic dialysis.

CHAPTER 106

Surgery in End-Stage Renal Disease Patients

Michael J. Moritz, MD, and Vincent T. Armenti, MD, PhD

Chronic dialysis and the associated medical treatments for end-stage renal disease (ESRD) patients are life-sustaining but create a state of altered homeostasis. The etiology of renal failure also impacts the degree and type of deviations from normal physiology that can significantly influence the perioperative course of the ESRD patient requiring surgery. This chapter outlines the risks for surgery in ESRD patients and explains how to mitigate these risks.

The most frequent procedures in ESRD patients are those for dialysis access. Two other common problems in this population for which surgery is indicated include atherosclerosis—due to hypertension, hyperlipidemia, hyperparathyroidism, and/or diabetes (cardiac, vascular, and amputation surgery)—and hyperparathyroidism (parathyroid surgery, orthopedic procedures).

ESRD patients are at increased risk for some perioperative complications, particularly bleeding (uremic coagulopathy) and ischemia (arteriosclerosis)—although other co-morbid factors (especially diabetes and hypertension) can overshadow the risks attributable to renal failure. Specifically, after coronary bypass surgery renal failure is an independent risk factor for stroke and is associated with increased short-term and long-term mortality (hospital mortality 14.6%). ESRD patients are at increased risk of developing atheromata of the ascending aorta, which may be responsible for this increased stroke risk.

Similarly, renal failure is associated with a threefold increase in inpatient mortality after elective open abdominal aortic aneurysm surgery (11.8% versus 3.4%). Finally, most studies have not found that renal failure is a risk factor for wound infection, although a minority of studies does show an association. Interestingly, renal failure has been identified as a risk factor for infection of the sternotomy incision but not the saphenous vein incision after coronary bypass surgery.

Preoperative Assessment

Serious attention must be paid to the history and physical examination. Dry weight must be elicited. The medication list must be reviewed in detail, and new or unfamiliar medications must be investigated. The dialysis unit or nephrologist can attest to the patient's compliance with the dialysis prescription, diet, phosphate binders, medications, and other aspects of care. Disease-specific issues are numerous. Diabetes (with its increased risk of vascular disease plus gastroparesis, retinopathy, and neuropathy) is the most common cause of ESRD in the developed world. Patients on dialysis, because of diabetic nephropathy, have a rate of lower extremity amputation 10 times higher than the rate for diabetics not on dialysis and 2 times higher than the rate for patients with other etiologies of ESRD.

Hypertension carries an increased risk of vascular disease, cardiomyopathy, and stroke. Severe or poorly controlled hypertension immediately preoperatively may be due to acute fluid overload, chronic underdialysis and fluid overload, poor control or poor compliance with medications, or rebound hypertension due to nonabsorption or withdrawal of antihypertensives because of gastrointestinal disease or preoperative NPO status.

Depending on the severity of hypertension and the urgency of the surgical procedure, the decision must be made between canceling surgery to improve blood pressure control and proceeding with surgery with parenteral antihypertensives. The increased risk of coronary artery disease must be assessed along with the patient's exercise tolerance and the magnitude of the planned surgery as regards preoperative cardiac evaluation. Other cardiac conditions are also more prevalent in ESRD patients, including arrhythmias, valvular calcification, left ventricular hypertrophy, and cardiomyopathies (uremic, hypertensive, amyloidotic).

Common derangements in this population that require attention perioperatively include fluid and electrolyte abnormalities (hyperkalemia, fluid overload), hypertension, and coagulopathy. Fluid status must be assessed preoperatively, preferably by comparing current weight to dry weight and by physical examination. Potassium rises gradually between dialysis sessions and should be checked immediately preoperatively. Poorly controlled hypertension is most commonly due to fluid overload, and in this event dialysis to remove excess fluid is the best treatment. Most dialysis patients are maintained on antihypertensive medications, which should be continued without interruption through the perioperative period.

Coagulation abnormalities are also common. Aside from the uremic coagulopathy detailed in material following, patients with a history of lupus may have hypercoagulability due to lupus anticoagulant. The partial thromboplastin time (PTT) is prolonged with lupus anticoagulant. In addition, patients may be on anticoagulants [Coumadin (warfarin), heparin, low-molecular-weight heparins, and others] or antiplatelet drugs [aspirin, dipyridamole, Plavix (clopidogrel bisulfate), Ticlid (ticlopidine hydrochloride), and others] for a specific indication or to promote hemoaccess patency. Depending on the indication and the planned procedure, these drugs may need to be suspended for a time. Percutaneous dialysis catheters are prone to cause over-heparinization with catheter use, manipulation, or routine filling with concentrated heparin. Note that for procedures involving hemodialysis accesses (especially thrombectomies) it may be desirable to continue anticoagulants or antiplatelet drugs.

Hyperkalemia

The best treatment for hyperkalemia is hemodialysis. When a patient is known to be hyperkalemic the day prior to surgery, cation exchange resin (Kayexalate) can be given in a dose of 15 to 60 mg orally or by retention enema to remove potassium.

Intraoperatively and postoperatively, potassium can rise abruptly for several reasons. Potassium will redistribute from the intracellular to the extracellular space from metabolic acidosis, tissue trauma, hemolysis, and resorbing hematoma. Neuromuscular blocking agents (one component of general anesthesia) generally cause a small rise in serum potassium. Stored red blood cells leak potassium, which rises from a baseline of 4.5 up to 40 mEq/L for 21- to 30-day-old red cells—and the potassium will be higher (up to 60 mEq/L in irradiated 30-day-old red cells). Each unit of packed red cells for transfusion consists of 200 to 250 mL of volume.

There are at least four treatments that can be used to acutely lower serum potassium in an emergent situation, but these treatments only shift potassium intracellularly to gain time until dialysis can remove the excess potassium. Cellular uptake of potassium is promoted by administering glucose and insulin IV [25 mL of D50 (25 g) plus 5–10 units of regular insulin] or a β_2-adrenergic agonist such as albuterol (150–300 μg/kg by nebulizer) or salbutamol [4–5 μg/kg IV over 15 minutes or 5 mg by nebulizer (2.5 mg for patients less than 25 kg in weight)].

These treatments will lower potassium by 0.6 to 0.9 mEq/L 60 minutes after administration and by 1.4 mEq/L after another hour. Increasing the pH by administering sodium bicarbonate intravenously (1 amp, 44.6 mEq) also forces potassium intracellularly, but may only be effective in patients with metabolic acidosis. When the pH is manipulated, each 0.1-unit rise in pH lowers potassium by 0.5 mEq/L. Calcium gluconate IV (10 mL of 10%) does not change potassium but does acutely antagonize the cardiac effects of hyperkalemia in an emergency. IV calcium can cause metastatic calcification in patients with hyperphosphatemia and can precipitate digoxin toxicity.

In general, a potassium of less than 6 mEq/L will not cause electrocardiogram (EKG) changes and does not require emergent treatment. A potassium of more than 6 mEq/L requires an EKG to interpret its effect on the heart. Tall peaked T waves are a sign of serious hyperkalemia requiring emergent treatment. A potassium level greater than 7 mEq/L requires immediate therapy and results in progressively more serious effects on the EKG (loss of P waves, widened QRS complexes, and ultimately ventricular fibrillation).

Coagulopathy

Uremic coagulopathy is complex and multifactorial. Whereas some elements of the coagulopathy are at least partially corrected by dialysis, others persist. Regardless of the causes and the remedies (outlined in material following), it is critical to remember that the greatest correction of the coagulopathy comes from adequate dialysis.

The formation of clot arises from the interaction of platelets with a damaged vessel wall in the presence of von Willebrand factor (vWF) leading to platelet adherence, platelet aggregation, and the generation of thrombin and fibrin (leading to a fibrin clot). The defects in clot formation in ESRD include altered vessel walls with increased production of prostacyclin, altered platelet function (including reduced platelet generation of serotonin, adenosine diphosphate, and thromboxane A_2), and altered effectiveness of vWF. Additional contributory factors include anemia (which affects both the viscosity of blood and platelet function when the hematocrit is below 30%) and hyperparathyroidism, as the intact parathyroid hormone molecule inhibits platelet aggregation. Now that erythropoietin is in routine use, anemia is seen less often.

Most components of the coagulation system as measured are normal in ESRD patients, including the plasma levels of clotting

factors, the number of platelets, the coagulation tests (prothrombin time and PTT), and the function of the fibrinolytic system. On the other hand, the bleeding time is often abnormally prolonged in dialysis patients, reflecting coagulopathy. However, the bleeding time does not correlate well with clinical bleeding events and is generally not used as a risk assessment measure. It can be used to measure the effect of treating the coagulopathy, which should shorten the bleeding time.

Uremic coagulopathy can be treated prophylactically as part of preoperative preparation or in the face of active bleeding. Other than transfusion of packed red blood cells to correct anemia, the three direct treatments listed in order of rapidity of action are cryoprecipitate, deamino-8-D-arginine vasopressin (DDAVP), and conjugated estrogens. Cryoprecipitate is a pooled plasma fraction enriched in factor VIII and vWF, which is administered in bags of 10 units (i.e., pooled from 10 donors). When its effect is measured via correction of the bleeding time, the bleeding time begins to correct within 1 hour after infusion—with a peak effect between 4 and 12 hours. The effect is gone in 24 to 36 hours. The risk of administration is the risk of transfusion-acquired infections. Desmopressin is the generic name for DDAVP, which induces release of autologous vWF.

When given intravenously (in a dose of 0.3 μg/kg in 50 mL of saline), the bleeding time begins to shorten by 1 hour and the effect lasts 6 to 8 hours. When given subcutaneously (0.3 μg/kg), the same effect is achieved but is delayed and is not seen until 2 hours after administration. Desmopressin can also be administered intranasally at 10 times the parenteral dose (3.0 μg/kg). Intranasal desmopressin has a half-life of 3 hours. When used preoperatively, it should be given 2 hours before the planned procedure. Repeated administration of desmopressin more often than every 48 hours rapidly results in diminished efficacy (tachyphylaxis), presumably because of depletion of endogenous stores of vWF.

Conjugated estrogens can be given intravenously (0.6 mg/kg/day for 5 consecutive days) or orally (25–50 mg). These normalize the bleeding time more slowly than cryoprecipitate or DDAVP, but theie effect is longer lasting. They are typically started 1 week before planned surgery. The mechanism of their effect is unknown. Recombinant factor VIIa has been utilized in the treatment of a variety of bleeding diatheses. Its use in uremic coagulopathy requires further study.

At least two aspects of the dialysis procedure effect coagulation. The first aspect is heparin administered for dialysis. The

half-life of heparin is unchanged in ESRD at 30 to 90 minutes, with considerable inter-individual variation. Postoperatively, dialysis can be performed with no, minimal, or low heparin dosing to minimize the risk of postoperative bleeding consonant with the magnitude of the procedure performed. The second aspect is the effect of the "foreign" surface on activation of blood components. Exposure of blood to the dialysis circuit has many effects, but the most relevant include depletion of complement, a fall in the platelet count, and lowered arterial oxygen. As a consequence of uremic coagulopathy, the risks of postoperative deep venous thrombosis (DVT) and pulmonary embolism are low and the use of pharmacologic DVT prophylaxis (beyond sequential compression devices) is generally not an issue in ESRD patients.

Immune System

Chronic dialysis patients have numerous definable defects in their immune systems involving both the humoral and cell-mediated arms. The most clinically relevant defect in humoral immunity involves the decreased responsiveness of the dialysis patient to immunization. The most relevant defect in cell-mediated immunity involves the increased incidence of malignancy in dialysis patients. Despite these defined deficiencies, there does not appear to be a substantially higher risk of perioperative infections in dialysis patients.

Nutrition

There is clinical evidence of protein-calorie malnutrition in about 20% of ESRD patients definded as hypoalbuminemic, hypoproteinemic, or unusually low in blood urea nitrogen. Malnutrition is multifactorial, including decreased appetite due to azotemia, water-soluble vitamin deficiencies from dialysis losses, and proteinuria. Unrelated to adequacy of protein-calorie nutrition, obesity and lesser degrees of excessive weight are common in this population. Consequently, poor wound healing and dehiscence are more common in ESRD patients.

Intraoperative Considerations

Safe perioperative care requires protection of the patient's current hemodialysis access, and equally importantly protection of veins that may be used in the future for creation of arteriovenous

fistulae for hemoaccess. Therefore, the anesthesia team must be aware of the importance of forearm and upper arm cephalic veins and not use them for IV access except in a critical situation. For patients requiring central venous access, the internal jugular venous route is preferred to the subclavian venous route due to the lower risk of late venous complications. Protection and padding of the current hemoaccess is essential and should be routine, but the patient and physicians must also be aware that the relative hypercoagulability from the trauma of surgery can cause thrombosis of any hemoaccess unrelated to how well it was protected. Prompt recognition and thrombectomy, especially for arteriovenous fistulae, are key.

Regarding anesthetic drugs, neuromuscular blocking agents that are not dependent on renal excretion are widely available. A mild rise in serum potassium associated with general anesthetic induction is common. Although narcotics are not metabolized or excreted by the kidney, dialysis patients are more sensitive to their central nervous system and respiratory depressive effects and the dose used should be lowered both intraoperatively and postoperatively. Meperidine (Demerol) and propoxyphene (Darvon, Darvocet) both have metabolites excreted by the kidney and that accumulate in ESRD. These narcotics should not be used.

Meticulous surgical technique and close attention to hemostasis are essential to the success of even the simplest procedure in these patients. The presence of hematoma, whether deep or superficial, jeopardizes the success of the procedure and is an invitation to infectious problems. Prophylactic antibiotics should be administered as for any surgical patient. Depending on the antibiotic's route of metabolism, the interval between doses may need to be extended.

Management of the peritoneal dialysis catheter during abdominal surgery varies. For relatively "clean" abdominal procedures, the catheter can be left in place and a temporary venous catheter placed for hemodialysis access until the wound is sufficiently healed to resume peritoneal dialysis. For "dirty" cases, in which the catheter is likely to become contaminated, it is best to remove the catheter and start anew after recovery.

Postoperative Considerations

Especially for abdominal surgeries, there should be a low threshold for placement of a nasogastric tube because of the increased incidence of gastroparesis in ESRD patients. This is true for

all ESRD patients, not just diabetics. Gastric emptying will be furthered impaired by narcotics as part of the anesthetic or for postoperative analgesia.

For patients unable to quickly resume oral fluids, IV fluids are generally provided at 500 mL/day plus losses. Mildly hyponatremic solutions are commonly used because of insensible water loss; for example, D5-1/2PSS (5% dextrose in half-physiologic-strength saline). The serum sodium should be followed to watch for hyponatremia. Substantial internal (i.e., third-space) losses after major surgery should be replaced with saline with or without dextrose. Potassium-containing solutions such as lactated Ringer's should be avoided. External losses should be sampled and their electrolyte composition measured so that appropriate replacement can be provided before electrolyte derangements occur.

Postoperative hyperkalemia can result from all of the causes previously noted. Kayexalate enemas must be prescribed with great caution after abdominal surgery, particularly after renal transplantation. In the absence of adequate colonic motility, the hyperosmolar Kayexalate can cause necrosis of the colonic wall. Although temporizing measures can briefly lower serum potassium, only dialysis efficiently removes excess body potassium.

For most postoperative patients, urinary output is used as a measure of adequate circulating volume. For ESRD patients, this is unavailable and thus careful attention to vital signs (and after major procedures, or where any question exists, serial measurements of the hemoglobin and hematocrit) is essential to detect ongoing bleeding. Patients with bleeding postoperatively require appropriate transfusions, measures to address uremic coagulopathy, and careful watch of the serum potassium so that hyperkalemia does not prevent timely reoperation if needed.

The most common causes of postoperative fever are atelectasis, wound or urinary tract infection, and thrombophlebitis. In dialysis patients, urinary infections can still occur—even in the anuric patient, who may develop pyocystis. With fever and suprapubic pain, bladder catheterization is appropriate. Other causes of fever to consider in dialysis patients include dialysis access infections, peritonitis (in peritoneal dialysis patients), and pericarditis.

Postoperative management of hypertension in patients who are NPO requires careful attention. Most medications can be continued orally with a sip of water or via nasogastric tube.

However, controlled-release or sustained-release formulations will have unpredictable effects or be completely ineffective in patients with altered gastrointestinal motility, as commonly occurs postoperatively. Therefore, alternatives must be used for these formulations (either a short-acting formulation or substitution of a different antihypertensive).

Sublingual nifedipine was commonly used, but is associated with increased mortality from cardiac events and should be avoided. Intravenous antihypertensives given by continuous infusion (such as nicardipine) are very effective, but require an intensive care unit setting and may result in excessive fluid administration. The clonidine patch is also an option, but it takes 48 hours from application to be effective. Minoxidil postoperatively or via nasogastric tube works well in the short term and can provide good control until prior medications can be restarted. Abrupt withdrawal of beta blockers must be avoided due to rebound hypertension and tachyarrhythmias (substitution of an IV form is indicated). Abrupt withdrawal of clonidine can also result in rebound hypertension.

Nutritional Support

Careful attention should be paid to the nutritional needs and support of the ESRD patient postoperatively. Their needs are often greater than those of other patients because of the increased incidence preoperatively of protein-calorie malnutrition. However, the requirement to limit fluid intake because of dialysis dependency can hamper the ability to deliver nutrition. Regardless, assessment of nutritional needs and delivery should be part of the perioperative planning. When supplemental nutrition is given, enterally or intravenously, the highest-caloric-density fluid the patient can tolerate should be used. For patients with high caloric needs, increasing the frequency of dialysis sessions to allow greater fluid intake may be necessary. Similarly, continuous hemodialysis modalities may be very useful in allowing provision of nutrition to severely ill patients.

When supplemental feedings are used, the protein intake should be adequate to minimize tissue catabolism (whereas caloric intake should be high). A caloric intake of 30 to 35 Kcal/kg body weight with a protein intake of 1.2 to 1.5 g/kg is optimal for the catabolic patient receiving renal replacement therapy. This ensures adequate delivery and use of protein without imposing the risks of overfeeding to a metabolically compromised group.

As the ESRD patient has other co-morbidities, supplemental nutrition should be administered cautiously—observing for problems with tolerance (i.e., gastroparesis) in the diabetic. Mesenteric ischemia may result in tube feeding intolerance or intestinal angina in these patients. The hemodynamic consequences of hemodialysis generally preclude administration of feedings during dialysis sessions. Obese patients may be maintained on diets that reduce caloric intake but meet protein needs.

Uremic Pericarditis

Uremic pericarditis can occur in dialysis patients presumably because of inadequate removal of uremic toxins. Acutely ill catabolic patients may be relatively underdialyzed and at increased risk for pericarditis. Patients with pericarditis may have chest pain, fever, or a pericardial friction rub—and will usually have a pericardial effusion. The standard treatment is intensive (usually daily) dialysis. Other causes of pericardial effusion include viral and tubercular infections, lupus, drugs such as minoxidil, and malignant pericardial involvement. If the effusion enlarges rapidly or acutely, pericardial tamponade can develop.

Signs that a patient may be progressing toward tamponade include loss of a friction rub (due to increasing size of the effusion) and hypotension with tachycardia in the absence of hypovolemia. This presentation can occur during dialysis from fluid removal (decreasing the high preload needed to maintain acceptable hemodynamics), but with the patient still above their dry weight. A high index of suspicion and prompt echocardiography are vital to make a timely diagnosis. Indications for surgical treatment (pericardial window) include tamponade (i.e., hemodynamic compromise) or failure of a large effusion to improve with intensive dialysis. Any patient with uremic pericarditis is at risk for bleeding into the pericardium. Therefore, anticoagulants should be avoided.

Summary

Dialysis patients are at increased cardiovascular risk for surgery, especially surgery on the vascular tree, related to the increased incidence and progression of atherosclerotic arterial disease. The other risks of surgery are generally controllable with careful attention to the patient's history, ongoing physical examination, medications, operative technique, and laboratory studies.

Recommended Reading

Burke JF, Francos GC. Surgery in the patient with acute or chronic renal failure. In Merli GJ, Weitz HH (eds), *Medical Management of the Surgical Patient, Second Edition*. Philadelphia: W. B. Saunders 1998:326–37.

A good discussion of numerous perioperative issues, particularly electrolyte derangements and dialysis.

Eggers PW, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. Kidney Int 1999;56:1524–33.

Statistical analysis of amputation rates in ESRD patients comparing diabetics and nondiabetics.

Kemper MJ, Harps E, Muller-Wiefel DE. Hyperkalemia: Therapeutic options with acute and chronic renal failure. Clin Nephrol 1996;46:67–69.

Labrousse L, de Vincentiis C, Madonna F, et al. Early and long-term results of coronary artery bypass grafts in patients with dialysis dependent renal failure. Eur J Cardiothorac Surg 1999;15:691–96.

Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: A systematic review. Crit Care Med 2005;33:883–90.

Remuzzi G. Bleeding and coagulation abnormalities. In Glassock RJ, Massry SG (eds), *Textbook of Nephrology, Third Edition*. Baltimore: Williams & Wilkins 1995:1205–09.

Révész T, Arets B, Bierings M, et al. Recombinant factor VIIa in severe uremic bleeding. Thromb Haemost 1998;80:353.

Saimanen E. Risk factors for ascending aortic atheromatosis: A retrospective study of 2,263 patients undergoing coronary artery bypass surgery. Ann Chir Gynaecol 1999;88:280–84.

A concise review of uremic coagulopathy and available treatments.

CHAPTER 107

Pregnancy in Dialysis Patients

Susan Hou, MD

Frequency of Pregnancy in Dialysis Patients

Fertility is markedly reduced in dialysis patients. The only survey with responses from all dialysis units was done in Belgium, which reported pregnancies in 0.3% of women of childbearing age. Surveys done in Saudi Arabia, the United States, and Japan give rates of conception of 1.4%, 0.55%, and 3.4%, respectively. The United States Renal Data System Coordinating Center puts the frequency of conception in U.S. dialysis patients slightly higher (at 1% per year), noting a constant rate of conception over the 10 years from 1991 to 2001. Of note is that the frequency of conception in hemodialysis patients is two to three times higher than in peritoneal dialysis patients (0.55 versus 0.25%, respectively, per year).

None of the surveys take into account whether patients are sexually active or using contraception. They also do not take into account reasons for infertility other than renal failure, such as prior treatment with cyclophosphamide. The likelihood of pregnancy in sexually active women who are not using contraception is higher than indicated by the surveys.

The reasons for the rarity of pregnancy in dialysis patients are not well understood. A recent report indicates that 42% of premenopausal women on dialysis have menses, although their menses are often irregular. Dialysis patients frequently have anovulatory periods, and hyperprolactinemia is common. Careful study of hormonal changes in women dialyzed with current dialysis regimens are needed. It is not clear whether the difference in the frequency of conception between hemodialysis patients and continuous ambulatory peritoneal dialysis patients is the result of endocrine differences or in some way related to peritoneal dialysis itself. It is possible that hypertonic dextrose damages the ovum or that the volume of fluid in the intraperitoneal space interferes with transport of the ovum from the ovary to the fallopian tubes or compresses the fallopian tubes, interfering with movement of the ovum through the tubes. (See Table 107.1)

Table 107–1

Management of Pregnant Dialysis Patients

Hemodialysis
- *Dialysis time:* ≥20 h/wk.
- *Dialysis bath:* 2.5 mEq/L calcium, bicarbonate 25 mEq/L.
- *Potassium:* 3.0–3.5 mEq/liter. May require addition of phosphorus. Adjust based on weekly measurements of electrolytes, calcium, and phosphorus.
- *Heparinization:* Stop heparin only for vaginal bleeding.

Peritoneal Dialysis
- Increase total dialysis by 50%.
- Combine cycler and daytime exchanges.
- Hospitalize patient for bloody dialysate.
- Treat peritonitis with penicillins and cephalosporins.
- Decrease exchange volume for comfort.
- Increase exchange frequency or add hemodialysis if exchange volume is reduced.
- Hold PD 2 d to 2 wk following C section. Restart with small exchange volumes.

Hypertension
- Maintain BP <140/90.
- Home BP twice daily on nondialysis day.
- Assess volume status and treat with a trial of fluid removal.
- Avoid ACE inhibitors and A2 blockers even in the first trimester.
- *First-line drugs:* Alpha-methyl-dopa, labetalol, calcium channel blockers.
- *Second-line drugs:* Other beta blockers, hydralazine, clonidine.

Anemia
- 50% increase in erythropoietin dose.
- Weekly CBC, monthly iron studies.
- Ferric gluconate to maintain iron saturation >15% (pregnancy category B).
- Transfuse for hematocrit <25%.

Diet
- Increase dose of water soluble vitamins fourfold.
- Sodium restriction for weight gain >2L between treatments.
- *Protein:* 1.5 g/kg + 10 g/d.
- Adjust potassium and phosphorus based on chemistries.
- Adjust dry weight after weekly examination of volume status.

Contraception

Although the frequency of conception in dialysis patients is lower than for woman using any type of birth control, sexually active women who have normal periods should use contraception if they do not wish to become pregnant. The use of oral contraceptives is safe in most dialysis patients and may offset the negative effect of estrogen deficiency on the bones, but these drugs should be avoided in patients with lupus and patients with problems of clotting vascular access. There is some concern that intrauterine devices may be associated with increased bleeding because of heparin use with hemodialysis. Commonly used barrier methods of contraception are safe and effective.

Women with regular menses are more likely to conceive, but in at least one instance a woman conceived after 9 years of amenorrhea. Pregnancy has occurred in women who have been on dialysis as long as 20 years, and fully a fourth of the pregnancies reported in the Japanese series occurred after 10 years on dialysis. Repeat pregnancies in women who become pregnant on dialysis are not uncommon. In the 318 women whose pregnancies are recorded by the National Registry for Pregnancy in Dialysis Patients (NPDR), 8 became pregnant twice, 8 became pregnant three times, and 1 conceived four times.

Diagnosis of Pregnancy in Dialysis Patients

A high degree of suspicion is required to make the diagnosis of pregnancy because amenorrhea is frequent in dialysis patients and nausea and fatigue are often attributed to other problems. Soft signs of pregnancy may be an increase in erythropoietin requirements and difficulty with fluid removal. Because beta HCG is removed by the kidney, beta HCG (human chronic gonadotropin) levels are higher at each stage of gestation than in women with normal renal function. Borderline positive HCG levels can be seen in nonpregnant dialysis patients. The stage of gestation must be determined by ultrasound rather than by quantitative beta HCG levels.

Outcome of Pregnancy in Dialysis Patients

In 1980, the European Dialysis and Transplant Association reported 115 pregnancies in dialysis patients. Of those not electively terminated, only 23% resulted in surviving infants. Success rates for pregnancy in dialysis patients have improved somewhat since then. In Saudi Arabia, 30% of pregnancies resulted in surviving infants. The NPDR recorded 222 pregnancies in women

who were receiving dialysis at the time of conception. Of the 165 pregnancies that reached the second trimester, 57% resulted in surviving infants. Sixteen percent of live-born infants died in the neonatal period. A total of 7.2% of pregnancies reaching the second trimester resulted in stillbirth, and 22% resulted in spontaneous abortion.

The four induced abortions done in the second trimester were done for life-threatening maternal problems (three hypertension and one critical aortic stenosis) rather than for social reasons or anticipated problems. Stillbirth appears to be less common in intensively dialyzed patients. Similar outcomes were seen in the Japanese report, with 60% of 60 pregnancies not electively terminated resulting in surviving infants. Prematurity accounted for most of the neonatal deaths. The high frequency of late pregnancy losses is an ongoing source of heartbreak for women who become pregnant and elect to continue their pregnancies.

Infant survival is only one measure of pregnancy success. Many of these infants are premature or small for gestational age. Eighty-five percent of infants born to women who conceived after starting dialysis reported to the NPDR were born prematurely (mean gestational age 32.4 weeks). Thirty-six percent weighed less than 1500 g at birth, and 28% were small for gestational age. Their neonatal course was complicated by respiratory distress and other complications of prematurity. Eleven of 116 live-born infants and 1 stillborn infant reported to the NPDR were noted to have congenital anomalies.

Eleven of 49 infants for whom follow-up data were available had long-term medical or developmental problems, most of which appear to be the result of prematurity rather than an azotemic intrauterine environment. The Japanese survey found a 4.4% rate of cerebral palsy and a 4.4% rate of cerebral atrophy in infants born to dialysis patients. The known increase in developmental abnormalities in very small infants and infants delivered 3 or more months preterm would lead us to expect a large number of problems in follow-up of these infants. The outcome of pregnancy for women who conceive before starting dialysis is better than for those who conceive after starting dialysis, with infant survival being 77.7%.

Maternal Complications

There have been three maternal deaths reported to the NPDR. One death resulted from lupus cerebritis in a woman who started

dialysis after conception. There were two deaths in women who conceived after starting dialysis: one as a result of hypertension and one from unknown causes. All three infants survived.

Hypertension

Approximately 80% of dialysis patients who become pregnant have either a blood pressure greater than 140/90 or require antihypertensive medication at some time during pregnancy. In over half of hypertensive pregnant dialysis patients, the blood pressure exceeds 170/110. In a series of 69 women in whom blood pressure measurements were available, there were 6 intensive care unit (ICU) admissions for accelerated hypertension in addition to the one death. On nondialysis days, the patient should check her blood pressure twice daily. The first line of treatment for hypertension is assessment of volume status and a trial of volume removal. If there is concern that volume removal will compromise uterine blood flow, fetal monitoring can be done during dialysis. Dialysis treatments during which fetal monitoring is done are generally carried out in an inpatient obstetric unit.

Drug Therapy

If volume removal does not control the blood pressure, a wide variety of antihypertensive medications has been used safely in pregnancy. The major groups of drugs contraindicated in pregnancy are angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. ACE inhibitors are associated with renal dysplasia, oligohydramnios, and pulmonary hypoplasia when used in the second and third trimesters. One recent paper reports an increase in congenital anomalies in infants exposed to ACE inhibitors in utero during the first trimester. Alpha methyl dopa and hydralazine have been used in pregnant women for over 40 years and are considered safe. Labetalol and calcium channel blockers are widely used alternatives.

Calcium channel blockers may cause profound hypotension when used in conjunction with magnesium. Dialysis patients are at increased risk for preeclampsia, but the diagnosis is difficult to make because many of the signs and symptoms can be caused by renal failure or distorted by it. Hyperreflexia or only transient response to fluid removal and antihypertensive drugs may signal the development of preeclampsia. The risk of life-

threatening hypertension persists for 6 weeks after pregnancy, with two of the previously mentioned ICU admissions having occurred several weeks postpartum.

Anemia

Normal pregnancy is accompanied by a 40 to 50% increase in plasma volume and a 30% increase in red cell mass, mediated by increased erythropoietin. Normal hemoglobin in a pregnant woman is 11 g/dL. Dialysis patients dependent on exogenous erythropoietin have a more profound drop in hemoglobin as plasma volume increases. Increased doses of erythropoietin are usually necessary, and the dose can be increased by 50% when the diagnosis of pregnancy is made. Further dose adjustments can be made on the basis of weekly hemoglobin and hematocrit. Normal pregnancy requires 700 to 1400 mg of additional iron. Ferric gluconate has been designated category B in pregnancy.

Peritonitis

There are few reports of peritonitis in pregnant PD patients. In three case reports of peritonitis during pregnancy, two resulted in premature labor and one in stillbirth. Of six episodes reported to the pregnancy registry, five pregnancies resulted in surviving infants and one resulted in spontaneous abortion remote from the time of infection. The contact of the fallopian tubes with the peritoneal fluid leads to a high risk of either ascending or descending infection. There is one case report of a postpartum uterine infection resulting in peritonitis requiring catheter removal. Penicillins and cephalosporins are the preferred antibiotics for treating peritonitis. Clindamycin can be used in penicillin-allergic women. Amphoterecin can be used for fungal peritonitis. Other antibiotic and antifungal agents are used if considered necessary for the mother's safety.

Dialysis Regimen

Dialysis Modality

There is no difference in infants survival between hemodialysis and peritoneal dialysis patients (43.9 versus 50%, respectively), but the outcome for hemodialysis patients dialyzed 20 or more hours per week may be better than the outcome for peritoneal dialysis patients. A peritoneal catheter can be placed at any time

during pregnancy, but the increased intra-abdominal pressure may increase the risk of a dialysate leak.

Hemodialysis

It has been common practice to increase the amount of dialysis in pregnant women. Although information on the effect of dialysis regimens on pregnancy outcome is limited, there is increasing evidence that outcome is improved when the amount of dialysis is increased to 20 or more hours per week. Infant survival in women dialyzed more than 20 hours per week was 79% compared to 44% in women dialyzed less than 20 hours per week ($P < .05$). Infants of mothers dialyzed 20 or more hours per week are less likely to be born prematurely. Seventy-seven percent of infants born to mothers dialyzed more than 20 hours per week were born at more than 32 weeks' gestation compared to 37.5% of infants born to women receiving less dialysis. There is one report of 100% fetal survival with 1.5 to 3.5 hours of dialysis daily, but the group contains a large number of women who started dialysis after conception. This group noted an improvement in polyhydramnios with an increased dialysis dose.

The advent of short daily dialysis has made us familiar with some of the electrolyte abnormalities that will be seen with intensified dialysis. Hypokalemia may occur, and a 3- or 3.5-mEq/L bath may be used. Some patients no longer require phosphate binders, and in rare cases phosphorus has to be added to the bath. The target bicarbonate for a pregnant woman is 18 to 20 mEq/L because of the respiratory alkalosis associated with pregnancy. It may be necessary to decrease the dialysate bicarbonate to 25 mEq/L. A dialysate calcium of 2.5 mEq/L is usually enough to provide the 30 g of calcium necessary to calcify the fetal skeleton. All adjustments should be made based on weekly measurements of electrolytes, calcium, and phosphorus.

Heparin does not cross the placenta. The lowest dose of heparin possible should be used, but efforts to dialyze the patient without heparin frequently result in blood loss from clotting of the extracorporeal circuit. It is reasonable to use heparin as long as there is no vaginal bleeding.

Peritoneal Dialysis

Because conception is unusual in peritoneal dialysis patients, there are no data on the efficacy of different dialysis regimens.

It is reasonable to attempt to increase the amount of dialysis delivered by 50%. The increase may require combining a cycler with several daytime exchanges. Maintaining such a dialysis regimen becomes more difficult late in pregnancy because abdominal discomfort may require decreasing the exchange volume. In some instances, peritoneal dialysis has been supplemented by hemodialysis.

If a pregnant woman has blood in the peritoneal fluid, she should be hospitalized to evaluate the cause. Hemoperitoneum may signal an impending spontaneous abortion or placental separation. In one instance, severe blood loss occurred when the peritoneal catheter lacerated a dilated vessel on the surface of the uterus.

Diet

The increase in dialysis time usually allows the pregnant woman to eat without dietary restrictions, but the woman's diet should be reviewed frequently with the renal nutritionist. Early in pregnancy, it may be difficult to maintain adequate calorie and protein intake. Caloric intake should be 35 Kcal/kg plus an additional 300 calories for the pregnancy. Protein intake should be 1.5 g/kg plus 10 g for the pregnancy. The dose of water-soluble vitamins should be increased because of the increased requirements in pregnancy and the increased removal with intensive dialysis. The folate dose should be increased to 4 mg/day because folate deficiency during pregnancy is associated with neural tube defects. Dietary potassium and the use of phosphate binders can be guided by weekly laboratory measurements. Sodium restriction may be necessary if there are excessive weight gains between treatments.

We do not prescribe a specific weight gain because there is a risk that it would be achieved by inadequate fluid removal at dialysis. The best approach is careful assessment of the volume status by a physician on a weekly basis, with adjustment of the dialysis regimen to achieve euvolemia.

Obstetric Considerations

The greatest cause of fetal loss in pregnant dialysis patients is premature delivery. There is a continuum from second trimester

spontaneous abortions to premature births. Frequently, there is cervical dilatation with mild contractions. Beta agonists, indomethacin, calcium channel blockers, and magnesium have been used as tocolytics. Indomethacin is effective, particularly in women with polyhydramnios, but the time the dialysis patient requires treatment for premature labor usually exceeds the recommended time for using the drug. The fetus needs to be monitored for right heart strain. There may be a loss of residual renal function with the use of indomethacin. Magnesium is also suited for short-term use.

If magnesium is used either for premature labor or for pre-eclampsia, the patient should not receive a continuous magnesium infusion. She should be given a loading dose with supplementation after dialysis. In peritoneal dialysis patients, intraperitoneal magnesium has been used to treat premature labor. There is no experience with progestational agents in dialysis patients, but any effective treatment for premature labor that is not contraindicated in renal failure should be attempted in these women because they are at higher risk of premature delivery than almost any other group of pregnant women.

Caesarian delivery need only be performed for the usual obstetric indications. When it is done in a peritoneal dialysis patient, it can be done extraperitoneally. Dialysis has been resumed as early as 24 hours after delivery, but most obstetricians and nephrologist treat the patient with hemodialysis for 2 weeks postpartum to avoid incisional leaking. The baby can be expected to have an osmotic diuresis after delivery and should be monitored in a neonatal ICU and given appropriate fluid and electrolyte replacement.

Summary

Pregnancy in dialysis patients is associated with serious maternal risks and with a high fetal loss rate. With careful monitoring of blood pressure, hemoglobin, and serum chemistries, maternal risk can be minimized. With intensive dialysis and improved treatment for premature labor, the success rate for pregnancy in dialysis patients can be expected to improve. Care of the patient requires close cooperation of obstetricians, nephrologists, and neonatologists, but meticulous observation and care by the dialysis staff is the most important prerequisite for success.

Recommended Reading

Frequency, Outcome, and Complications of Dialysis-Patient Pregnancy 1980 to 2001

Bagon JA, Vernaeve H, De Muylder X, Lafontaine JJ, Martens J, Van Roost G. Pregnancy and dialysis. Am J Kidney Dis 1998;31:756–65.

Collins A, Weinhandl E, Gilbertson D. Pregnancy, antepartum complications, and outcome rates in dialysis and renal transplant populations. United States Renal Data System, *www.usrds.org*.

Okundaye IB, Abrinko P, Hou SH. A registry for pregnancy in dialysis patients. Am J Kidney Dis 1998;31:766–73.

Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. Br J Obstet Gynaecol 1980;87:839–45.

Souqiyyeh MZ, Huraib SO, Saleh AGM, Aswad S. Pregnancy in chronic hemodialysis patients in the Kingdom of Saudi Arabia. Am J Kidney Dis 1992;19:235–38.

Toma H, Tanabe K, Tokumoto T, Kobayashi C, Yagisawa T. Pregnancy in women receiving renal dialysis or transplantation in Japan: A nationwide survey. Nephrology, Dialysis and Transplantation 1999;14:1511–16.

Effect of Peritonitis on Pregnancy

Gadallah MF, Ahmad B, Karubian F, Campese VM. Pregnancy in patients on chronic ambulatory peritoneal dialysis. Am J Kidney Dis 1992;20:407–10.

Jacobi P, Ohel G, Szylman P, Levit A, Lewin M, Paldi E. Continuous ambulatory peritoneal dialysis as the primary approach in the management of severe renal insufficiency in pregnancy. Obstet Gynecol 1992;79:808–10.

Tison A, Lozowy C, Benjamin A, Usher R, Pritchard S. Successful pregnancy complicated by peritonitis in a 35 year old CAPD patient. Per Dial Int 1996;16:S489–91.

Tuncer M, Trak B, Sapan M, Oxcan S, Süleymanlar G, Yakupoglu G, et al. Successful pregnancy complicated with peritonitis in a 25-year-old Turkish CAPD patient. Peritoneal Dialysis International 2000;20:349–53.

Changes in Dialysis Regimen Necessary in Pregnant Women

Cole DE, Hussain SA, Piering WE, Savin VJ. Phosphate enriched hemodialysis during pregnancy. J Am Soc Nephrol 2001;12:263A.

Hou S. Daily dialysis in pregnancy. Hemodialysis International 2004;8:167–71.

Other Topics

Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitor. N Engl J Med 2006;354:2443–51.

This recently published report calls into question the long-standing belief that exposure to ACE inhibitors in the first trimester does not carry any increased risk. It reports congenital anomalies in 7.12% of 209 infants exposed to ACE

inhibitors exclusively in the first trimester, compared to 1.73% of infants exposed to other antihypertensive medications and 2.63% of infants exposed to no antihypertensive medications. A total of 1001 infants whose exposure to antihypertensive medications extended beyond the first trimester were excluded.

Holley JL, Schmidt RJ, Bender FH, Dumler F, Schiff M. Gynecologic and reproductive issues in women on dialysis. Am J Kidney Dis 1997;29:685–90.

This is the most recent survey of menstrual patterns in dialysis patients.

Hou S H, Orlowski J, Pahl M, Ambrose S, Hussey M, Wong D. Pregnancy in women with end stage renal disease: Treatment of anemia and premature labor. Am J Dis Kid 1993;21:16–22.

This article describes the use of erythropoietin to treat anemia in pregnant dialysis patients and the use of indomethacin to treat premature labor.

Sibai BM. Drug therapy: Treatment of hypertension in pregnant women. N Engl J Med 1996;335:257–65.

This is a review of the use of antihypertensive drugs during pregnancy.

CHAPTER 108

Treatment of Poisoning with Extracorporeal Methods

James F. Winchester, MD; Nikolas B. Harbord, MD; and Donald A. Feinfeld, MD

Almost two and a half million poisonings were reported to the American Association of Poison Control Centers in 2004,[1] yet only 1183 patients succumbed to their toxic exposure. Alkalinization of the urine was employed in 8654 patients (additionally 1726 received hemodialysis and 29 received hemoperfusion). This chapter outlines the initial approach to the poisoned subject, and then discusses areas in which the nephrologist may advise alkaline diuresis, dialysis, and related techniques. In addition, criteria for clinical judgment as to when these techniques should be used in the management of poisoning are provided.

Initial Management

Rapid assessment and stabilization of the airway, ventilation, and hemodynamic status are the mainstays of treatment. Hypoglycemia should be ruled out, and unconscious or convulsing patients should receive oxygen, naloxone, and dextrose. Hypothermia may be treated by passive external warming, and hyperthermia by cooling or by peritoneal lavage. Frequently, more than one drug and alcohol may be involved.

Calculation of the anion gap may aid in the diagnosis of salicylate, ethylene glycol, and methanol (high) or lithium (low) poisoning—whereas an osmolal gap [the difference between measured (by freezing point depression) and calculated osmolality] may aid in the identification of an alcohol poisoning (ethylene glycol, methanol, isopropyl alcohol). If the patient has co-ingested ethanol or received therapy, or if the poisoning is well advanced, calculation of anion gap and osmolal gap may give misleading results.

Gastrointestinal Manipulation

Gastric lavage and syrup of ipecacuanha are not as effective as was once thought, and are now recommended only up to 1 hour

after ingestion unless drugs with known delaying effect on gastric emptying have been ingested (e.g., tricyclic antidepressants, aspirin, and barbiturates). Polyethylene glycol solutions, used for preparation of the gastrointestinal tract for endoscopy, have theoretical advantages for whole-bowel elimination of drugs—but no clinical trials have been produced and caution has been advised.[2] Multiple-dose-activated charcoal (50 g q2-6h) has been shown to be effective in patients with a wide range of drug ingestions, but single-dose-activated charcoal is recommended only for barbiturate, anticonvulsant, theophylline, aspirin, quinine, or dapsone ingestion.[3] Oral charcoal significantly shortens drug half-life through interruption of the enterohepatic circulation of some agents (e.g., barbiturates, digitalis preparations, theophylline, and so on).

Altering Urinary pH

The dissociation constant (pKa) for drugs that are weak acids or bases can determine whether they exist in solution as the nonionized or ionized species. The nonionized molecules are lipid soluble and diffuse across cell membranes, whereas the ionized form is unable to penetrate lipid membranes and can be trapped in the renal tubule.

Increasing the pH of tubule fluid increases the degree of ionization of weak acids and reduces passive tubule free-drug absorption by lowering its nonionic diffusion, whereas the reverse occurs with weak bases. In salicylate intoxication, acidemia also increases the amount of nonionized and diffusible salicylic acid in the blood and thereby enhances its accumulation within cerebral tissue. At a pKa equal to the pH, the concentrations of nonionized drug and ionized drug are equal. Elimination of weak acids [salicylate, phenobarbital, 2,4-dichlorophenoxyacetic acid (2,4-D)] by the kidney is increased in alkaline urine for drugs having a pKa in the range of 3.0 to 7.5.

On the other hand, weak base (e.g., quinine and phencyclidine) elimination is increased in acid urine if the pKa is 7.5 to 10. 5. Giving copious amounts of intravenous fluids (300–500 mL/hour) in “forced diuresis” may be complicated by hyponatremia, water intoxication, pulmonary edema, cerebral edema, or hypokalemia. Forced diuresis should be conducted with close vigilance, hourly measurement of urinary pH, and measurement of electrolytes every 1 to 2 hours initially and frequently thereafter. Correction of acidemia may also induce potassium shifts (cellular and renal), and serum potassium should be measured frequently.

Administration of alkali alone, without copious quantities of fluid, results in good quantities of salicylate recovered in urine. Although validated mainly in children with moderate to severe salicylate poisoning, use of the Done nomogram can aid in the decision to institute forced alkaline diuresis. Dialysis should be used when other measures have failed, manifestations of salicylate poisoning persist, or clinical deterioration is seen.

Principles of Dialysis and Hemoperfusion for Poisoning

Peritoneal dialysis and hemodialysis utilize natural and artificial semipermeable membranes, respectively. Drug removal may also be increased by modifications of hemodialysis [CAVH (continuous arteriovenous hemofiltration), CAVHD (continuous arteriovenous hemodialysis), CVVH (continuous venovenous hemofiltration), CVVHD (continuous venovenous hemodialysis); CVVHDF (continuous venovenous hemodiafiltration); see descriptions elsewhere in this book]. Factors governing drug removal are the same for uremic toxins: molecular size, lipid-water partition coefficient, protein binding, the volume of distribution, and maintenance of a concentration gradient. Other factors include blood flow rate, dialysate flow rate, dialyzer surface area, and the characteristics of the specific membrane chosen. The intercompartmental transfer rate of drugs from tissues into plasma may also influence drug removal rates.

Modern dialyzers with highly porous membranes and large surface area may give clearance rates approaching activated charcoal or resin hemoperfusion used to enhance elimination in the era of cuprophane membrane use. Peritoneal dialysis is the least effective method of removing drugs and should not be used for this purpose. Optimal conditions for hemodialysis include high blood flow rates (pressor support of the circulation may be necessary), the use of bicarbonate dialysate, and careful heparinization or avoidance of heparin by saline flushes. Prolonged (or repeat) dialysis may be required in lithium, ethchlorvynol, glutethimide, and midazolam (in dialysis patients) poisoning to avoid large rebounds in drug concentration after the procedure—which might cause a relapse of intoxication. Rebound may also be eliminated by continuous renal replacement therapies. Table 108.1 lists the reported dialyzable drugs.

Hemoperfusion, the passage of blood through a column containing sorbent particles, was used clinically for a wide range of poisonings. Hemoperfusion relies on physical adsorption for

Table 108–1

Drugs Removed with Hemodialysis

Note: ( ) Denotes poor removal. * Denotes substance often reported to require hemodialysis.

Antimicrobials and Anticancer Agents

- cefaclor
- cefadroxil
- cefamandole
- cefazolin
- cefixime
- cefmenoxime
- cefmetazole
- cefonicid
- cefoperazone
- ceforanide
- cefotaxime
- cefotetan
- cefotiam
- cefoxitin
- cefpirome
- cefroxadine
- cefsulodin
- ceftazidime
- (ceftriaxone)
- cefuroxime
- cephacetrile
- cephalexin
- cephalothin
- (cephapirin)
- cephradine
- moxalactam
- amikacin
- dibekacin
- fosfomycin
- gentamicin
- kanamycin
- neomycin
- netilmicin
- sisomicin
- streptomycin
- bacitracin
- colistin
- amoxicillin
- ampicillin
- azlocillin
- carbenicillin

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

- clavulinic acid
- (cloxacillin)
- (dicloxacillin)
- (floxacillin)
- mecillinam
- (mezlocillin)
- (methicillin)
- (nafcillin)
- penicillin
- piperacillin
- temocillin
- ticarcillin
- (clindamycin)
- (erythromycin)
- (azithromycin)
- (clarithromycin)
- metronidazole
- nitrofurantoin
- ornidazole
- sulfisoxazole
- sulfonamides
- tetracycline
- (doxycycline)
- (minocycline)
- tinidazole
- trimethoprim
- aztreonam
- cilastatin
- imipenem
- (chloramphenicol)
- (amphotericin)
- ciprofloxacin
- (enoxacin)
- fleroxacin
- tobramycin
- bacitracin
- colistin
- amoxicillin
- ampicillin
- azlocillin
- carbenicillin
- clavulinic acid
- (cloxacillin)
- (dicloxacillin)
- (floxacillin)

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

- mecillinam
- (mezlocillin)
- (methicillin)
- (nafcillin)
- penicillin
- piperacillin
- temocillin
- ticarcillin
- (clindamycin)
- (erythromycin)
- (azithromycin)
- (clarithromycin)
- metronidazole
- nitrofurantoin
- ornidazole
- sulfisoxazole
- sulfonamides
- tetracycline
- (doxycycline)
- (minocycline)
- tinidazole
- trimethoprim
- aztreonam
- cilastatin
- imipenem
- (chloramphenicol)
- (amphotericin)
- ciprofloxacin
- (enoxacin)
- fleroxacin
- (norfloxacin)
- ofloxacin
- isoniazid
- (vancomycin)
- capreomycin
- PAS
- pyrizinamide
- (rifampin)
- (cycloserine)
- ethambutol
- 5-fluorocytosine
- acyclovir
- (amantadine)
- didanosine
- foscarnet

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

- ganciclovir
- (ribavirin)
- vidarabine
- zidovudine
- (pentamidine)
- (praziquantel)
- (fluconazole)
- (itraconazole)
- (ketoconazole)
- (miconazole)
- (chloroquine)
- (quinine)
- (azathioprine)
- bredinin
- cyclophosphamide
- 5-fluorouracil
- (methotrexate)

Barbiturates
- amobarbital
- aprobarbital
- barbital
- butabarbital
- cyclobarbital
- pentobarbital
- phenobarbital
- quinalbital
- (secobarbital)

Nonbarbiturate Hypnotics, Sedatives, Tranquilizers, and Anticonvulsants
- baclofen
- carbamazepine
- carbromal
- chloral hydrate
- (chlordiazepoxide)
- (diazepam)
- (diphenylhydantoin)
- (diphenylhydramine)
- ethiamate
- ethchlorvynol
- ethosuximide
- gallamine
- glutethimide
- (heroin)
- meprobamate

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

- (methaqualone)
- methsuximide
- methyprylon
- paraldehyde
- primidone
- *valproic acid

Cardiovascular Agents
- acebutolol
- (amiodarone)
- atenolol
- betaxolol
- (bretylium)
- (calcium channel blockers)
- captopril
- (diazoxide)
- (digoxin)
- enalapril
- fosinopril
- lisonopril
- quinapril
- ramipril
- (encainide)
- (flecainide)
- (lidocaine)
- metoprolol
- methyldopa
- (ouabain)
- N-acetylprocainamide
- nadolol
- (pindolol)
- practolol
- procainamide
- propranolol
- (quinidine)
- (timolol)
- sotatol
- tocainide

Alcohols
- ethanol
- *ethylene glycol
- isopropanol
- *methanol

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

Analgesics and Antirheumatics
- acetaminophen
- acetophenetidin
- *acetylsalicylic acid
- colchicine
- *methylsalicylate
- (d-propoxyphene)
- *salicylic acid

Antidepressants
- (amitriptyline)
- amphetamines
- (imipramine)
- isocarboxazid
- MAO inhibitors
- (pargylline)
- (phenelzine)
- tranylcypromine
- (tricyclics)

Solvents and Gases
- acetone
- camphor
- carbon monoxide
- (carbon tetrachloride)
- (eucalyptus oil)
- thiols
- toluene
- trichloroethylene

Plants, Animals, Herbicides, and Insecticides
- (star fruit, Averrhoa carambola)
- alkyl phosphate
- amanitin
- demeton sulfoxide
- dimethoate
- diquat
- methylmercury complex
- (organophosphates)
- paraquat
- snake bite
- sodium chlorate
- potassium chlorate

Miscellaneous
- acipimox
- allopurinol

Table 108–1

Drugs Removed with Hemodialysis—Cont'd

- aminophylline
- aniline
- borates
- boric acid
- (chlorpropamide)
- chromic acid
- (cimetidine)
- dinitro-o-cresol
- folic acid
- mannitol
- methylprednisolone
- potassium dichromate
- sodium citrate
- *theophylline
- thiocyanate
- ranitidine

Modified from Winchester JF. Active methods for detoxification. In LM Haddad, Shannon MW, Winchester JF (eds), *Clinical Management of Poisoning and Drug Overdose, Third Edition*. Philadelphia: Saunders WB 1998:175–87.

its efficiency, and was reported to give better clearances for some substances than conventional hemodialysis or forced diuresis. This difference in efficiency may not hold true for modern polysulfone hemodialyzers, which possess a pore structure capable of removing higher-molecular-weight species than the cuprophane dialyzers to which hemoperfusion was compared in the past.[4] Certain resins have been shown to be most effective for removal of lipid-soluble drugs, with drug clearance rates exceeding those achieved by charcoal hemoperfusion. For example, removal of lipid-soluble drugs such as glutethimide and methaqualone is far more efficient with XAD-4 resin hemoperfusion than with activated charcoal. Activated charcoal hemoperfusion devices are currently still available; resin hemoperfusion cartridges are not. Most charcoal hemoperfusion devices have polymer-coated particles to improve biocompatibility. Hemoperfusion columns usually contain between 100 and 300 g of activated charcoal or 650 g (wet weight) of polystyrene resin, in a circuit resembling that for hemodialysis.

Hemoperfusion can be combined in series with hemodialysis, to increase core temperature, to increase drug removing effi-

ciency, or to correct acidosis. As in hemodialysis, blood flow rates should be maximized to improve efficiency. Because platelets adhere to the sorbents, heparinization is necessary to minimize thrombocytopenia. Even with anticoagulation, the blood may still thrombose in the cartridge. Pressure safety devices can detect rises in interior pressure, which signify thrombosis inside the device. Transient platelet losses of about 30% occur with coated or uncoated charcoal or resin preparations.

With the resin preparations, greater falls in platelet counts have been observed. Small variable reductions in serum calcium and serum glucose, transient falls in white blood cell counts, and reduction of 1 to 2 degrees F in body temperature may also be seen. Pressor agents are removed, and it is recommended that they should be given distal to the devices. Hemoperfusion devices and their contained sorbents are listed in Table 108.2. Table 108.3 lists drugs that have been reported to be removed by various types of hemoperfusion.

Criteria for Consideration of Hemodialysis or Hemoperfusion in Poisoning

The decision to deploy dialysis or hemoperfusion is based on the clinical features of the poisoning, especially if the patient's condition progressively deteriorates despite intensive supportive therapy (correction of fluid balance, acid-base abnormalities, circulatory support, and maintenance of renal function). Suggested clinical criteria are progressive deterioration despite intensive supportive therapy; severe intoxication with depression of mid-

Table 108–2

Examples of Available Hemoperfusion Devices

Manufacturer	Device	Sorbent Type	Amount of Sorbent	Polymer Coating
Asahi	Hemosorba	bead charcoal	170 g	Poly-HEMA
Gambro	Adsorba	Norit charcoal	100 or 300g	Cellulose acetate
Organon-Teknika	Hemopur 260	Norit extruded charcoal	260 g	Cellulose acetate

brain function; development of complications of coma, such as pneumonia or septicemia, and underlying conditions predisposing to such complications (e.g., obstructive airway disease); impairment of normal drug excretory function in the presence of hepatic, cardiac, or renal insufficiency; intoxication with agents with metabolic and/or delayed effects (e.g., methanol,[5] ethylene glycol, and paraquat); and intoxication with an extractable drug or poison, which can be removed at a rate exceeding endogenous elimination by liver or kidney.

A recent report suggests that persistent hyperosmolality may also be a criterion for instituting dialysis. These criteria should be used along with monitoring of elevated plasma concentrations of common dialyzable drugs, although drug concentration data may be misleading because most overdoses involve multiple drugs.

Plasma Exchange and Exchange Blood Transfusion

Both techniques have been used rarely in the treatment of poisoning. The process is largely used for removal of highly protein-bound drugs (e.g., chromic acid and chromate and in small infants). Exchange blood transfusion has been used, especially when hemolysis and methemoglobinemia have complicated the poisoning (e.g., sodium chlorate poisoning).

Table 108–3

Drugs and Chemicals Removed with Hemoperfusion

Barbiturates	**Antimicrobials/ Anticancer**	**Cardiovascular**
amobarbital	(adriamycin) **	digoxin
butabarbital	ampicillin	diltiazem
hexabarbital	carmustine**	(disopyramide)
pentobarbital	chloramphenicol	flecainide
phenobarbital	chloroquine	metoprolol
quinalbital	clindamycin	n-acetylprocainamide
secobarbital	dapsone	procainamide
thiopental	doxorubicin	quinidine
vinalbital	gentamicin	
isoniazid		
(methotrexate)		
(methotrexate)		thiabendazole
(5-fluorouracil)		

Table 108–3

Drugs and Chemicals Removed with Hemoperfusion—Cont'd

Nonbarbiturate Hypnotics, Sedatives, and Tranquilizers	**Antidepressants**	**Miscellaneous**
(tricyclics)	(amitryptiline)	aminophylline
carbromal	(imipramine)	cimetidine
chloral hydrate	(fluoroacetamide)	
chlorpromazine		(phencyclidine)
(diazepam)		phenols
diphenhydramine		(podophyllin)
ethchlorvynol		theophylline
glutethimide	**Plant and Animal Toxins, Herbicides, and Insecticides**	**Solvents and Gases**
meprobamate	amanitin	carbon tetrachloride
methaqualone	chlordane	ethylene oxide
methsuximide	demeton sulfoxide	trichloroethane
methyprylon	dimethoate	xylene
promazine	diquat	
promethazine	methylparathion	
(valproic acid)	**Metals**	
nitrostigmine	(organophosphates)	(aluminum)*
Analgesics and Antirheumatics	phalloidin	(iron)*
acetaminophen	polychlorinated biphenyls	
acetylsalicylic acid	paraquat	
colchicine	parathion	
star fruit, Averrhoa carambola		
d-propoxyphyene		
methylsalicylate		
phenylbutazone		
salicylic acid		

( ) Not well removed, ( )* Removed with chelating agent, ** well removed in regional hemoperfusion.
Modified from Winchester JF. Active methods for detoxification. In LM Haddad, Shannon MW, Winchester JF (eds), *Clinical Management of Poisoning and Drug Overdose, Third Edition*. Philadelphia: Saunders WB 1998:175–87.

Hemoperfusion and Hemodialysis with Chelation

In dialysis patients, aluminum and iron intoxications have been treated with deferoxamine (DFO) in conjunction with dialysis (continuous ambulatory peritoneal dialysis or hemodialysis) or

hemoperfusion for removal of the DFO-Al or DFO-Fe complex. Clinical improvements have been reported. During hemodialysis, heavy metal removal may be enhanced with certain chelating agents—such as n-acetylcysteine, cysteine, or succimer. Many chelating agents appear to offer promise in heavy metal removal.

Immunopharmacology

When injected, Fab fragments of antibodies to drugs combine with a high degree of specificity to antigens (drug). In potentially fatal cases of digoxin poisoning, Fab fragment administration has resulted in a rapid therapeutic response. In renal failure, because digoxin excretion depends on renal elimination the effectiveness of Fab fragment administration may be reduced. Many cases of digoxin poisoning have been treated successfully by Fab antibody fragments, but failures have also been reported and the cost of treatment is high.

In dialysis patients, judgment to use either hemoperfusion or Fab antibody fragments is required—especially because digoxin elimination can be enhanced with the addition of hemoperfusion. In addition, recurrent digoxin poisoning in renal failure patients has been reported 24 to 48 hours after receiving Fab antibodies. There is a single report that plasmapheresis effectively removed digoxin-Fab complexes in a patient with renal failure. Antibodies have been developed for, but not yet used in, colchicine and tricyclic antidepressant drug poisoning.

References

1. Watson WA, Litovitz TL, Rodgers GC, et al. 2004 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2005;13:589–666.
This is a must-read for the latest demographics of poisoning in the United States. The report has been published annually for many years in September.
2. Dargan PI, Colbridge MG, Jones AL. The management of tricyclic antidepressant poisoning: The role of gut decontamination, extracorporeal procedures and fab antibody fragments. Toxicol Rev 2005;24:187–94.
This review points out that hemodialysis, hemoperfusion, or a combination of both do not influence tricyclic antidepressant (TCA) drug removal in poisoned subjects. This citation is included to inform the reader that Fab fragments of IgG antibodies to tricyclic drugs have been developed. It will be interesting to see if they will prove useful for the management of clinical TCA intoxication.
3. Chyka PA, Seger D for the American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: Single-dose activated charcoal. J Toxicol Clin Toxicol 1997;35:721–41.

This is a carefully done committee report using evidence-based medicine to support statements on single-dose orally activated charcoal in the treatment of specific poisons. The committee recommendations do not apply to multiple-dose-activated charcoal (see Chyka PA. Multiple-dose activated charcoal and enhancement of systemic drug clearance: Summary of studies in animals and human volunteers. J Toxicol Clin Toxicol 1995;33:399–405).

4. Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. Am J Kidney Dis 2000;36:640–43.
   This is a case report showing that modern high-flux dialysis achieves drug clearance comparable to charcoal hemoperfusion in phenobarbital poisoning, in contrast to low clearances associated with cuprophane dialyzers.
5. Barceloux DG, Krenzelok EP, Olson K, Watson W for the American Academy of Clinical Toxicology Ad Hoc Committee. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. J Toxicol Clin Toxicol 1999;37:537–60.
   The clinician is often confused whether to use 4-methyl pyrazole alone to block alcohol dehydrogenase in methanol (and ethylene glycol) poisoning or whether to use 4-MP along with ethanol and/or dialysis. Clear guidelines for methanol poisoning are given (and these are applicable to ethylene glycol poisoning).

INDEX

B

C

D

E

F

G

H

I

Au: Pls. check

M

N

O

P

Q

R

S

T

U

V

W

Y

Z