COMMUNITY-ACQUIRED PNEUMONIA

EDITED BY THOMAS J. MARRIE

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Edited by

Thomas J. Marrie
University of Alberta
Edmonton, Alberta, Canada

KLUWER ACADEMIC PUBLISHERS
NEW YORK, BOSTON, DORDRECHT, LONDON, MOSCOW

eBook ISBN: 0-306-46834-4
Print ISBN: 0-306-46432-2

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Contributors

Stephen A. Berger Departments of Geographic Medicine and Clinical Microbiology, Tel Aviv Medical Center, Tel Aviv, Israel

Steven L. Berk James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee 37614

Robert F. Breiman National Vaccine Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia 30333

Jay C. Butler Arctic Investigations Program, Centers for Disease Control and Prevention, Anchorage, Alaska 99508

Thomas R. Cate Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030-3498

Dennis James Cleri Internal Medicine Residency, St. Francis Medical Center, Trenton, New Jersey 08629

Burke A. Cunha State University of New York School of Medicine, Stony Brook, New York 11790

Ross J. Davidson Division of Microbiology, Queen Elizabeth II Health Sciences Centre, and Departments of Medicine, Pathology, and Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4H7

Christopher W. H. Davies Osler Chest Unit and Department of Raidology, The Churchill Hospital, Oxford Radcliffe Hospitals, Headington, Oxford OX3 7LJ, England

Herbert Dele Davies Child Health Research Unit, Alberta Children's Hospital and University of Calgary, Calgary, Alberta, Canada T6G 2B7

Robert J. O. Davies Osler Chest Unit and Department of Radiology, The Churchill Hospital, Oxford Radcliffe Hospitals, Headington, Oxford OX3 7LJ, England

Scott F. Davies University of Minnesota, School of Medicine and Pulmonary Service, Hennepin County Medical Center, Minneapolis, Minnesota 55415

Santiago Ewig Medizinische Universitätsklinik und Poliklinik Bonn, Innere Medicin-Pneumonologie, Sigmund Freud Str. 25, 53105 Bonn, Germany

Ann. R. Falsey Department of Medicine, Rochester General Hospital, University of Rochester School of Medicine and Dentistry, Rochester, New York 14621

Alan Fein Columbia University College of Physicians & Surgeons, St. Luke's-Roosevelt Hospital Center, New York, New York 10025

Barry S. Fields Division of Bacterial and Mycotic Disease, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C02, Atlanta, Georgia 30333

Thomas M. File, Jr. Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272 and Summa Health Systems, Akron, Ohio 44304

Jay A. Fishman Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02114

Kevin Forward Department of Medicine, Division of Infectious Diseases, Dalhousie University and Queen Elizabeth II Health Centre, Halifax, Nova Scotia, B3H 2Y9 Canada

Keiji Fukuda Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Altanta, Georgia 30333

Fergus V. Gleeson Osler Chest Unit and Department of Radiology, The Churchill Hospital, Oxford Radcliffe Hospitals, Headington, Oxford OX3 7LJ, England

David J. M. Haldane Department of Pathology and Laboratory Medicine, Queen Elizabeth II Health Sciences Centre, and Departments of Microbiology and Immunology and Pathology and Medicine, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4H7

Todd F. Hatchette Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada

Diane H. Johnson Infectious Disease Division, Winthrop University Hospital, Mineola, New York 11510

B. Lynn Johnston Department of Medicine, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada B3H 4H7

Jay S. Keystone Tropical Disease Unit, Division of Infectious Disease, The Toronto Hospital, University of Toronto, Toronto, Ontario, Canada M5G 2C4

Steven H. Kirtland Section of Pulmonary and Critical Care Medicine, Virginia Mason Medical Center, Seattle, Washington 98111

Natalie C. Klein Infectious Disease Division, Winthrop University Hospital, Mineola, New York 11510

Irma Helena Koivula Department of Medicine, Division of Infectious Disease (4620), Kuopio University Hospital, SF-70211, Kuopio, Finland

Joanne M. Langley Community Health and Epidemiology, Dalhousie University, and Infection Control Services, Izaak Walton Killam Grace Health Centre for Children, Women and Families, Halifax, Nova Scotia, Canada B3H 4H7

Richard W. Light Saint Thomas Hospital and Vanderbilt University, Nashville, Tennessee 37205

Mark Logan Department of Diagnostic Imaging, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, B3H 2Y9 Canada

Kelly S. Macdonald Mount Sinai and Princess Margaret Hospitals, and Department of Medicine, University of Toronto, Toronto, Ontario, Canada M5G 1X5

Thomas J. Marrie Department of Medicine, Walter C. Mckenzie Health Sciences Centre, Edmonton, Alberta, Canada T6G 2B7

Randy Marton St. Joseph's Hospital and Medical Center, Paterson, New Jersey 07501

David G. McCormack London Health Sciences Centre, Victoria Campus, London, Ontario N6A 4G5, Canada

Dick Menzies Montreal Chest Institute, McGill University, Montreal, Quebec, H3A 1A3 Canada

Claudia Molina University of Texas Medical Branch, Galveston, Texas 77555-0609

Julio S. G. Montaner British Columbia Centre for Excellence in HIV/AIDS and Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada V6E 1B2

Valentina Carla Montessori British Columbia Centre for Excellence in HIV/AIDS and Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada V6E 1B2

Jock Murray MS Research Unit, Dalhousie University, Halifax, Nova Scotia, B3H 4H7, Canada

James W. Myers James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee 37614

Åke Örtqvist Department of Infectious Diseases, Karolinska Institutet, Karolinska Hospital, S-171 76, Stockholm, Sweden

David Ost Columbia University College of Physicians & Surgeons, St. Luke's-Roosevelt Hospital Center, New York, New York 10025

Ward Patrick Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, B3H 2Y9, Canada

Masis Perk Department of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 4H7 Canada

Joseph F. Plouffe Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio 43210

Colin Powell Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 4H7 Canada

Mohammed Rabbat St. Joseph's Hospital and Medical Center, Paterson, New Jersey 07501

Julio A. Ramirez Division of Infectious Diseases, Department of Medicine, School of Medicine, University of Louisville, Louisville, Kentucky 40202

Jordi Rello Critical Care Department, Hospital Univeristy Joan XXIII, Univeristy Rovira & Virgili, Carrer Dr. Mallafre Gausch, 43007 Tarragona, Spain

Kenneth Rockwood Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 4H7 Canada

Anna Rozenshtein Columbia University College of Physicians & Surgeons, St. Luke's-Roosevelt Hospital Center, New York, New York 10025

Robert H. Rubin Center for Experimental Pharmacology and Therapeutics, Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02114

Marcio Sa-Borges Intensive Care Department, Hospital Doce de Octubre, 28009 Madrid, Spain

George A. Sarosi Indiana University School of Medicine, and Roudebush VA Medical Center, Indianapolis, Indiana 46202

Gerry Schaller Department of Diagnostic Imaging, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, B3H 2Y9 Canada

Walter F. Schlech III Division of Infectious Diseases, Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada

Stephen D. Shafran Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada T5A 1BO

Andrew E. Simor Department of Microbiology, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, North York, Ontario M4N 3M5, Canada

Steven Q. Simpson Division of Pulmonary and Critical Care Medicine, University of Kansas, Kansas City, Kansas 66160

Larry J. Strausbuagh Infectious Diseases Section, Medical Service, Veterans' Affairs Medical Center, and the Division of Infectious Diseases, Department of Medicine, School of Medicine, Oregon Health Sciences, University, Portland, Oregon 97201

Henry Su Section of Pulmonary and Critical Care Medicine, Virginia Mason Medical Center, Seattle, Washington 98111

Kathryn N. **Suh** Infectious Diseases, Department of Medicine, Queen's University, Kingston, Ontario, Canada K7L 3N6

James T. Summersgill Division of Infectious Diseases, Department of Medicine, School of Medicine, University of Louisville, Louisville, Kentucky 40202

James S. Tan Infectious Disease Section, Department of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272 and Department of Medicine, Summa Health Systems, Akron, Ohio 44304

Antoni Torres Hospital Clinic I Provincial, Servei de Penumologia I Allergia Respiratoria, Villarroel 170, 08036 Barcelona, Spain

Claire Touchie Division of General Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada K1H 8L6

John Vernaleo Western Queens Community Hospital, Astoria, Queens, New York 11102

David H. Walker University of Texas Medical Branch, Galveston, Texas 77555-0609

Elaine E. Wang Department of Pediatrics, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, M5S 1A8 Canada

Richard H. Winterbauer Section of Pulmonary and Critical Care Medicine, Virginia Mason Medical Center, Seattle, Washington 98111

Mark Woodhead Department of Respiratory Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom

Dick Zoutman Infection Control Service, Kingston General Hospital, and School of Medicine, Faculty of Health Services, Queen's University, Kingston, Ontario K7L 2V7, Canada

Preface

Pneumonia is a formidable challenge for both the patient and the physician. For the patient, it is a life-threatening illness. Indeed, for many of us who may be fortunate enough to live to an old age (80 or more years), pneumonia is often the final common pathway for a number of illnesses that can result in one's demise. In this setting, we must hope that our physician will be able to integrate both the art and science of medicine. For the physician, the challenge is that the causative agent of the pneumonia is often unknown and that there are a large number of agents that could be causing the pneumonia.

This book is an attempt to meet the challenge posed by pneumonia. As such, there are chapters on its history, on end-of-life decision making, empiric therapy, critical pathways for its treatment, as well as on pneumonia in specific populations and pneumonia due to specific microorganisms.

This book will be a success if it stimulates at least one reader to study pneumonia, in hopes of answering some of the many questions that still remain.

Thomas J. Marrie

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The Captain of the Men of Death

The History of Pneumonia

JOCK MURRAY

"Diseases are not immutable entities but dynamic social constructions that have biographies of their own."

—Robert Hudson, *Disease and Its Control: The Shaping of Modern Thought,* 1983

"In the mortality bills, pneumonia is an easy second, to tuberculosis; indeed, in many cities the death-rate is now higher and it has become, to use the phrase of Bunyan, 'the Captain of the men of death.'"

—Sir William Osier (1849-1919), "Medicine in the Nineteenth Century," *Aequanimitas*

The Earliest Records

Pneumonia has been known since the earliest records of medicine and is one of the oldest diseases to have a specific diagnosis and name (Major, 1932). The Greeks gave the name pneumonia, meaning "condition about the lung" (Duffin, 1993b). Pulmonary diseases have been found in Egyptian mummies from the period 1250–1000 BC, including silicosis, anthracosis, a case of pneumonia that contained a bacillus that resembled plague, and pneumonia with hepatization (Ruffier, 1921; Heffron, 1939; Janssens, 1970; Ackerknecht, 1973, 1977).

JOCK MURRAY • Dalhousie University, Halifax, Nova Scotia, B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

The Early Descriptions

Although Hippocratic physicians tended to identify *dis-ease* rather than specific conditions, some patterns were known clearly, and pneumonia was one of these (Porter, 1997).

> Peripneumonia and pleuritic affections, are to be thus observed: If the fever be acute, and if there be pains on either side, or in both, and if expiration be attended with pain, if cough be present, and the sputa expectorated be of a blonde or livid color, or likewise thin, frothy, and florid, or having another character different from the common ... (Francis Adams, 1856)

Hippocrates (460–370 BC) recommended bleeding and clysters for pneumonia with pleurisy, depending on the location of the pain, the age and color of the patient, and the season of the year (Hippocrates, 1859). The various clinical features of the stages of pneumonia were recognized and treatments were designed for each. Physicians recognized that the "crisis" represented a crucial and dramatic point, indicating a victory over the disease. If there was pain, hot water in a bottle or bladder, a sponge of hot water, or a cataplasm of linseed was applied to the hypochondrium. The bowels were opened with a clyster or by a purge when the fever was at its peak. The patient would be given a linctus containing galbanum and pine fruit in Attic honey, or southernwood in oxymel. Other medicines thought to be beneficial were opoponax, a bitter resin with a garlic taste, mixed in oxymel, and a drink of ptisan, made from husked barley, also mixed with oxymel. The features that allowed a prognosis of worsening or cure were recognized by Hippocrates:

> When pneumonia is at its height, the case is beyond remedy if he be not purged and it is bad if he has dyspnea, and the urine is thin and acrid and if sweat comes out about the neck and head, for such sweats are bad as proceeding from the suffocation, rales, and the violence of disease which is obtaining the upper hand, unless there be a copious evacuation of thick urine, and the sputa be concocted; when either of these come on spontaneously, that will carry off the disease.

Aretaeus of Cappadocia (*fl* AD 140) in the second century also recognized the seriousness of pneumonia and noted, as had Hippocrates, that death often came on the seventh day (Aretaeus, 1856). After explaining how crucial the lungs are to life, he discussed pneumonia.

> But if the lungs be affected, from a slight cause there is difficulty breathing, the patient lives miserably, and death is the issue, unless some one effects a cure. But in a great affection, such as inflammation, there is a sense of suffocation, loss of speech and breathing, and a speedy death. This is what we call Peripneumonia, being an inflammation of the lungs, with acute fever, when they are attended with heaviness of the chest, freedom from pain, provided the lungs alone are inflamed.

Aretaeus spoke of the membrane around the lung, and an inflammation of it called pleurisy, which "if it takes a favorable turn ... the resolution occurs on the fourteenth day. But if not so, it is converted into empyems." Although Aretaeus recommended a treatment for pneumonia similar to that recommended by Hippocrates, he advocated even more copious bleeding from both arms, in an attempt to avoid unconsciousness. He also used purging, attenuant and diluent drinks, rubefacients containing mustard applied to the chest, hyssop, and wine (Bett, 1954). Although Hippocrates, Celsus, and Galen called this disease peripneumonia, it was shortened to pneumonia by Plutarch.

Galen of Pergamon (120–210 AD) was able to differentiate pneumonia from pleurisy (Ackernecht, 1977). He treated pneumonia in a manner that remained little changed for the next 1700 years. He recommended venesection if the pneumonia was "primary" and clysters, cupping, and scarification if it was "secondary." This was not unlike the recommendations of Hippocrates 600 years earlier or the advice of physicians in the 19th century.

The methods of Soranus of Ephesos, a prominent physician of the sect of Methodists, were recorded by Caelius Aurelianus in a Latin text that is one of the most comprehensive and systematic ancient medical texts (Ackernecht, 1977). Soranus treated pneumonia by having the patient lie in a comfortable position, fasting the patient for 3 days, and preventing sleep by repeated massage. The Methodist theory was that pneumonia is a "status strictus" and as sleep is also strictus, it must be prevented as well. He recommends cataplasms and after 3 days allows the patient to sleep, prescribes warm water, and, if the patient is strong enough to withstand it, bleeding. This is followed by groats, warm cataplasms, cupping of the chest, soft electuaries of pine kernels, fennel seeds, boiled honey, and egg yolk. Then the patient was subjected to gentle swinging, a pattern of therapeutic passive movement. When the patient improved the therapy continued with more food and wine, baths, and rubbing of the body with wax ointments and softening plasters (Ackernecht, 1977). Soranus objected to the oxymel of Hippocrates, the clysters and oxymel of Diocles, and other "sharp" medicaments. He was confident enough to object to the famous Asklepiades who advised against venesection and poultices, but agreed with his warnings against clysters. He also objected to the numerous medicines recommended by the empiricists and listed 18 that they recommended.

For thousands of years the elaborate theories of disease resulted in equally elaborate polypharmacy to counteract or bolster any factor that was out of balance. Some patients lived or died despite the treatment, others were discomforted and inconvenienced, and some seriously harmed.

Although Celsus (25 BC–50 AD) was active at the beginning of the Christian Era, his work was unknown until his text *De Re Medica* was recognized and made widely known by Pope Nicholas V (1397–1455) in the 15th century. It was the first medical text to be printed by the new movable type. Celsus had accurately described pneumonia and for its treatment recommended bleeding, a light diet, exposure to bright light, and frequent changes of the room air (Castiglione, 1947).

Until the 17th century and even beyond, the approach to treating pneumonia continued to follow the general approach of Hippocrates and Aretaeus. Assessing information about pneumonia during

these centuries is difficult as the terminology was vague and often the general area of acute pulmonary infections was included in the general term peripneumonia (Bett, 1954). A clearer view began to emerge in the 17th century when the anatomists examined the structure of the lung in health and disease and physicians applied new approaches to clinical observation (Epifano & Brandstatter, 1993). Marcello Malpighi (1628–1694) demonstrated the pulmonary circulation and the anastomosis between the pulmonary arteries and the veins. Thomas Sydenham (1624–1689) gave the best early English description of the disease, but felt that peripneumonia and pleurisy were just variants of the same condition. He also described a variant he called "bastard peripneumony" which affected older obese persons who indulged in strong liquors, especially brandy (Bett, 1954). Hermann Boerhaave (1668–1738) wrote in *Aphorisms* (1709) that lobar pneumonia could be separated from other pulmonary infection. Giovanni Battista Morgagni (1682–1771) described the postmortem appearance of lobar consolidation and pleural adhesions. In 1793, Matthew Baillie (1761–1823) described hepatization of the lung in pneumonia and correlated the pathological findings with the clinical picture. Other therapies were developed. John Huxham (1692–1768) was able to differentiate pleurisy, peripneumonia, and pleuroperipneumonia. He was an inveterate challenger to quacks and developed a compound tincture of cinchona, called Huxham's tincture, for the treatment of pneumonia. He also favored wet cupping over the shoulders and the use of setons and issues. He examined the blood drained from the patients at various stages of the disease to determine course and treatment.

Clinical Examination of Pneumonia

In records from earlier centuries there is little comment on the physical examination of the patient since most diagnoses and prognoses were based on observation of breathing, pulse, fever, and body fluids such as blood and urine. In 1761, the clinical examination of pneumonia was advanced by the observation of Leopold Auenbrugger (1722–1809) that a different percussion note was evident over the consolidated lung. As the son of an innkeeper, he noted that the level of wine in a barrel was determined by listening to the changing sound as one tapped above and below the level. He applied this to percussion over the lung and noted different sounds over consolidation. His 1761 text on using percussion to diagnose lung diseases was largely criticized and then ignored until his student, Jean-Nicolas Corvisart, then the physician to Napoleon, made it known. In turn, his student Laennec would use percussion to support his stethoscopic observations (Laennec, 1830).

Rene Theophile-Hyancinthe Laennec (1781–1826) wrote about pneumonia, and in 1819 described the use of the stethoscope to make the diagnosis (Duffin, 1998). He indicated that although it was one of the internal conditions best known among the ancients it was only easily recognized in its typical form. He went on to describe the features of the disease, including the crepitus rattle at the onset of the disease and the gradual disappearance of the rattle when hepatization occurred. He described moist rales, puerile breathing, pectoriloquy and aegophony in the diagnosis of pneumonia and other respiratory diseases. He added further to the differentiation of pneumonia from pleurisy, which he recognized as an inflammation of the pleural membranes rather than the lung tissue. Laennec advocated the use of high-dose therapy with tartar emetic (antimony potassium tartrate), which despite its toxicity was widely used for another century. He later combined tartar emetic in lower doses with bloodletting and "his success was most marked" (Routh, 1855). Laennec said that before 1824 he did not keep exact accounts but did not remember losing a single patient. In that year he had only one death in 28 severe cases—a man of age 70. Louis objected to Laennec's figures as he felt some were not pneumonia cases and the number of venesections was not indicated (Routh, 1855). Although Laennec advocated bloodletting only in strong and robust cases, Louis felt that bloodletting was an error if used at all. Despite this debate, the brilliant descriptions of Laennec were very influential in the approach to pulmonary diseases and also in the development of the concepts of physical examination for internal disease. We owe our modern concept of pneumonia to the descriptions of Laennec.

Advances in the understanding of pneumonia continued during the mid-19th century. Josef Skoda

(1805–1881) was an excellent diagnostician and advanced the observations of Auenbrugger and Laennec in a treatise on percussion and auscultation in 1839, describing the drum-like sound heard with pneumonia and pericardial effusion (skodaic resonance). Thomas Addison (1793–1860) wrote a treatise on pneumonia, *Observations on Pneumonia,* in 1843 and noted that the pneumonia originated in the air cells of the lungs rather than in the parenchyma. Carl von Rokitansky (1804–1897) in 1849 distinguished lobar pneumonia from bronchopneumonia.

To Bleed or Not to Bleed?

From earliest times physicians have felt that vigorous measures were needed to cure pneumonia. For 2500 years, bleeding was the main approach. By the late 18th and early 19th centuries, bleeding became widespread and aggressive in the treatment of many diseases, especially pneumonia. When the great Boerhaave died, the mantle of leadership in clinical medicine passed to William Cullen (1712–1790) and his colleagues in Edinburgh. Cullen felt that there was really only one condition of pneumonia, and separation of types was of little practical use; the treatment in each case was aggressive bleeding (Bett, 1954). Cullen's copious bleeding would obviously weaken and endanger these very ill individuals, and the sicker they were the more he bled them.

A younger Edinburgh faculty member, John Hughes Bennett (1812–1875), had trained in many European centers and taught his students that they should base their understanding of disease on pathological observation, and not on clinical observation alone. He challenged a number of standard dogmas of his teachers and the senior faculty at the university. In one lecture he questioned bloodletting for pneumonia as advocated by Cullen, Alison, Gregory, and others, a challenge that was seen as an affront to Edinburgh greats and the national pride of Scotland (King, 1982). King (1982) has reconstructed the arguments from the published articles and reports in the medical society transactions of the times. Both sides agreed on the high mortality of pneumonia and that the practice of bloodletting was decreasing among practitioners. Where they differed was their concept of pneumonia. Bennett was one of the leading microscopists of the day and he understood that in pneumonia there was an exudate from the blood into the lung tissues, filling the air spaces and coagulating. If recovery occurred the exudate softened and was reabsorbed into the blood. Bennett argued that bloodletting could not aid this process. Indeed, it would further weaken the patient, and thus cause harm. He believed that the decrease in mortality from pneumonia was due to the decrease in the practice of venesection in recent years. William Pultney Alison (1790–1859) was a leading senior faculty member at Edinburgh but had no experience with pathology. His knowledge was clinical and he felt the severe pneumonia seen earlier in the century, a lobar pneumonia which was aided by bloodletting, was being replaced with more cases of a milder form (that we would recognize as bronchopneumonia), which was not aided by bloodletting. He felt the new diagnostic aids and skills of auscultation and percussion allowed the clinician to decide when bloodletting would be helpful. The prevailing argument seemed to be about the benefit of bloodletting in pneumonia, but Bennett and Alison were arguing from different platforms (King, 1982). By this time bloodletting was on the wane in England and North America, although there would be a brief increase at the end of the century, but it did not disappear until the advent of antibiotics in the mid-20th century.

Bleeding was often combined with other therapies. An unusual pneumonia therapy of German origin was the use of chloroform, keeping the patient just above unconsciousness, and repeating inhalations every 2 to 4 hours. A minimum of 21 and a maximum of 162 inhalations were used in the reports of this therapy. This therapy was criticized by Routh (1855), who reviewed the treatment of pneumonia and advocated a more cautious and mild approach. He noted that mortality was higher if bleeding and tartar emetic were used together, and condemned these methods and the new chloroform therapy. He indicated that the treatment with homeopathy and by those "devoted to this delusion" were getting better results, as were those who employed cold water therapy, simply because they refrained from the harsher therapies of his colleagues.

Although bleeding was on the wane in some

countries, it was becoming more aggressive in others. Bouillard in Paris and Rasori in Pavia used aggressive "bleeding blow upon blow" for pneumonia, taking five to ten pounds of blood by what they called the "strangling method," and even Laennec had experimented with different bleeding methods (Sturges, 1876). Routh (1855) addressed the Medical Society of London and said, "this treatment, besides, is far too energetic, too antiphlogistic, and I fear, often founded on erroneous principles and theories." He said he did not wish to impugn the skill of his colleagues and went on to do so, indicating that the figures on pneumonia were incorrect, poorly defined, and reported differently. For example, healthy persons usually survived, and cases involving the elderly and "complicated" cases were not separated, resulting in conflicting mortality rates between London and the country and England and the Continent. He felt that the use of aggressive bleeding and tartar emetic together probably increased mortality.

Pierre Louis (1787–1872) championed the use of numerical methods, what we would now call statistics, to examine whether treatments actually worked, and his most dramatic example was with venesection in pneumonia. He demonstrated that it made no difference in the outcome of pneumonia whether venesection was done early or late, or whether small or large amounts of blood were let.

Walter B. Cheadle (1835–1910) advocated moderation in bleeding and indicated that even Celsus was concerned about excessive bleeding. Cheadle castigated the copious bloodletting common at the turn of the century, especially by the Italians who were the "most bloodthirsty," indicating that Frank of Pavia would bleed people 12 times for pneumonia, with mortality rates that were said to be enormous. Although bloodletting was dying out in Vienna, it came back in favor in the mid-19th century, and the tendency was to "bleed remourseFully," on a schedule to remove ten pounds of blood. Two pounds were bled on the first day after three bleedings, two pounds on the second day after two bleedings, and smaller amounts on the next few days to remove the remaining six pounds. Cheadle suggested that many mild cases of pneumonia would fail to survive under this form of therapy (Cheadle, 1900).

Pneumonia in the American Civil War

During the American Civil War (1861–1865) more troops fell to infection and other illness than to enemy bullets. Of all the respiratory problems that ravaged the troops from time to time, the most deadly was pneumonia (Cunningham, 1958). It was estimated that between January 1862 and August 1863 the number of cases increased as the temperature increased, causing the deaths of between 17,209 and 21,474 on the Southern side alone, one fourth of deaths from all causes. Of 6752 Confederate troops operating in the Gulf of Mexico area, 1161 came down with pneumonia over an 18-month period but the number of deaths was unusually low, at 151. However, a third of the 979 cases of pneumonia in the infamous Andersonville prison were fatal. It was thought that prior to the war the predominant type of pneumonia was the sthenic type, treated with antimony and bleeding with few deaths. During the war the predominant form seemed to be a more severe asthenic type that was resistant to such treatment and had a higher mortality rate. A replenishing regimen was then used, with a carefully regulated diet, and liberal use of brandy or whiskey, opium, and quinine. Some physicians recommended cupping plus expectorants, such as snakeroot. Another treatment was local mustard seed applications, stramonium leaves, or hickory leaves, along with butterflyroot and sanguinaria (Cunningham, 1958).

Pneumonia in Hospital and in General Practice

In the mid-19th century the usual treatment for pneumonia, whether in a child or an adult, by civilian physicians rested on three elements: depletion, calomel, and tartar emetic. If this was not successful, doses of Dover's powders or Dr. James' Fever Powder were added. Wine was also thought to be indispensable in both adults and children, and even in breastfeeding infants.

Signs of better results with milder therapies were becoming evident. Fleichman achieved good results, with a mortality of only 6% with homeopathy (Cheadle, 1900). Hughes Bennett recommended

a restorative therapy of wine and beef tea and claimed a mortality rate of 3%, and Cheadle (1900) suggested that children left untreated had a mortality rate of only 2%. It was noted that those who attacked the disease with aggressive therapies were obtaining mortality rates much higher than those who used more moderate approaches, and Cheadle and others noted that homeopathy was lowering mortality, not due to the homeopathic remedy, but by setting aside the physician's bleeding and high doses of tartar emetic. The homeopathy adherents did advocate aconite as an important agent and reported 7.4% mortality compared to 20.4% when bleeding was used by the physicians or 20.7% when high doses of tartar emetic were used (Russell, 1863).

So much of the documentation of medical progress comes from journal articles written by prominent consultants or at metropolitan hospitals or medical schools that it is instructive to examine the experience of a country practitioner. Duffin (1993a) has contributed to our understanding of practice in the mid-19th century with her careful documentation of the life and notes of Dr. James Miles Langstaff (1825–1889) of Richmond Hill, Ontario. He carefully recorded his cases over 40 years of practice and 10% of the 535 deaths in 1849 to 1889 were due to pneumonia. He noted that it was more common in the period between October and March and felt many cases were due to exposure to cold. Some years there was more pneumonia but of a less virulent type and other years the pneumonia was less frequent but deadly. He was able to use his skills of percussion and auscultation to delineate the pneumonia and to also identify pleurisy and pericarditis. His sole publication was on pneumonia involving the entire lung of a young girl, who responded to therapy with cupping and tartaric emetic, but developed a lung abscess that drained spontaneously 2 months later. Duffin describes the scene of the doctor entering the room of a pneumonia patient showing the signs of medical efforts: "... Langstaff would have entered a darkened room, possibly smoky from stramonium, to attend his breathless and often blue patient, confused with fever, wet and bald from showering and shaving of the head, and lying nearly motionless so as not to disturb the mustard plasters on her feet."

Sir James MacKenzie (1919), writing about one of his teachers in the 1870s, described a strong young man admitted to the Royal Infirmary in Edinburgh with high fever and rigors. The cause of his illness was not apparent to the housestaff but the professor glanced at his face, felt his pulse, and as he walked away said, "Going to have pneumonia," then quietly, "He will do no good." The young man was dead a few days later, and MacKenzie said it was long experience that allowed him to see the "slight dusky tinge of the countenance, with a faint blueness of the lips, and the pulse is large, with no sustained force, and rapid—a pulse difficult to describe ..."

The Advent of Serotherapy

Advances in microbiology and the development of germ theory began to explain some of the features of pneumonia. Jurgenses in 1874 noted the infectious nature of pneumonia, and Klebs in 1877 found the microorganism in the lungs of pneumonia patients. Sternberg found *Diplococcus pneumonia* in his own saliva in 1880. That year Pasteur isolated from saliva and described an organism that caused septicemia in rabbits and described the morphological characteristics of *D. pneumonia.* In 1881 Pasteur isolated the pneumococcus but it was Frankel who connected this organism with pneumonia 3 years later. Carl Freidlander, Anton Weichselbaum, and others began to note that other organisms were sometimes involved. George and Felix Klemperer produced a vaccine in 1891 that would produce immunity to pneumococci in rabbits, setting the stage for the development of vaccines that would resurface periodically over the next century. Neufeld in 1902 noted that the pneumococcal capsule would swell when the organism came in contact with a specific antiserum—the Quellen reaction.

Osier's Approach to the Captain of the Men of Death

Sir William Osier referred to a quotation of John Bunyan when he called pneumonia the captain of the men of death. In his 1892 textbook of medicine he provided a dramatic picture of the feared pneumonia and a graph of the temperature, pulse, and respirations during the course of the disease. He

demonstrated the "crisis" so well portrayed in novels and on the stage. The scene of the doctor by the bedside cautioning the worried family that the crisis would come that night, ending either in recovery or death, was well known to attendees of Victorian theater and readers of pulp fiction. Moreover, the fear was not theatrics, although the stage version often was, as the public was aware that a third of pneumonia sufferers would die.

Osier (1892) noted that pneumonia was prevalent among the poor, especially in crowded cities, and among those debilitated by other conditions such as Bright's disease, diabetes, and alcoholism, but also noted that immigrants were more resistant to the disease. He observed that no acute disease recurred with such frequency, and some individuals had had ten or more attacks. Although more cases occurred in winter months he felt it was not the cold but the changeability of the weather that had the greatest effect. The agent was not known but it was becoming regarded as an infectious disease due to an organism, most likely *Diplococcus pneumonia.* Although found in 20% of normal people, his colleague Welch had found the agent in all ten pneumonia cases he examined. The infectious cause was supported by the observation of Laennec and others who noted that pneumonia could occur in epidemics. Osier himself had seen three cases in the same family, and noted that epidemics occurred in crowded penitentiaries with a high mortality. The mortality ranged from 20.4% seen at the Montreal General Hospital to 40% in some epidemics. It was noted that the mortality varied with age, from 3.7% among those under age 20 years to 65% among those over age 60. Although he noted that antipneumotoxins were under study, the most effective regimen was diet and good nursing care, perhaps with Dover's powder to help sleep, opium for cough, and waiting for the crisis in the third or fourth day. Although often called a therapeutic nihilist, Osier (1892) had some surprisingly aggressive approaches if the patient appeared to be failing, emphasizing his concern about this dreaded and often fatal illness. If the patient had severe pain, likely pleurisy, cupping or leeching may help, but he favored morphia. Surprisingly, Osier favored bleeding in severe cases, indicating that although previous generations of physicians had bled too often, the current generation was bleeding too little, and timely bleeding could save the life of a pneumonic patient. He recommended it freely in earlier stages, saying that only one of 12 cases he had seen survived when bleeding was done later. When the heart seemed to be failing he gave alcohol, beginning with 4 to 6 ounces but increasing to 16 to 20 ounces later. He also felt strychnine was the most effective cardiac tonic and expressed some uncertainty and caution about the use of digitalis in fever. Some cases justified injection of antiseptic into the lung tissue itself.

It is difficult these days to recognize just how pneumonia was feared by the population in the preantibiotic era, but it can be imagined by the grim mortality statistics: In England and Wales in 1893 more than 40,725 deaths occurred due to pneumonia and it was said in that year to be even more prevalent and fatal in America. At the turn of the century the respected London physician Walter B. Cheadle addressed the students of St. Mary's Medical School saying, "There is probably no disease which yields to treatments, as it is styled, less than pneumonia, and there is no disease in which more harm can be done by wrong treatment; and yet no disease perhaps has been, and still is, so overtreated as pneumonia; every drug almost, and every possible therapeutic device, have been tried in this disease and vaunted as successful." He castigated the copious bleeding and the vigorous and harsh therapies of the past century, and felt aggressive therapy should be reserved for three groups of patients—those who had problems breathing, those who were in cardiac failure, and those with very high fever—although he felt the last condition was more benign than most believed and should not be overtreated. Cardiac failure would be treated with digitalis, moderate venesection, or leeches, and the fever by ice packs, cold baths, or sponges. He said pneumonia was simpler than bronchopneumonia, which he referred to as "that curious creeping mixed form which accompanies influenza." That form needed the addition of ipecacuanha, iodides, and alkaloids in full dose.

World War I and the Influenza Pandemic

Despite the gloomy regard for pneumonia therapy, important steps were being made. In 1891

Klemperer showed that the serum of convalescent patients possessed properties that could cure laboratory animals, and this led to the development of antisera therapy. In 1911, attempts to immunize gold and diamond miners in South Africa were made by Sir Almroth Wright using whole killed pneumococci, but with inconclusive results. They did not recognize that antibodies to one strain might not be effective against another. It was this activity that led George Bernard Shaw to make Wright a central character in his critical play on the exaggerated claims and the arrogance of physicians in "The Doctor's Dilemma." Dochez and Gillespie published in 1913 the features of three main antigenic types, types I, II, III, and an ill-defined type IV. Oswold Avery would further subdivide types and worked with his team at the Rockefeller Institute for Medical Research to develop specific serums, and by 1932 there were 32 types described (Spink, 1978).

As World War I was beginning there was great concern about pneumonia and other infections as these felled more soldiers than bullets in recent wars. Osier speculated that in this war battlefield wounds would cause less deaths because of advances in management, but pneumonia would continue to be "the best war killer" (Osier, 1916). Osier himself died of pulmonary disease, not the acute pneumonia he regarded as a great scourge, but of a chronic *H. influenza* infection with pleurisy and empyema, which brought him much pain and debilitation, requiring aspiration of fluid and pus from his pleural cavity.

Prior to the Great War, oxygen therapy was little used for pneumonia, even though it had been suggested by Wells in 1904, until Haldane advocated its use for soldiers who were gassed. It then entered common use for respiratory diseases and was used by William C. Stadie during the 1918 flu epidemic in New York City.

As World War I came to an end and troop ships moved along the Atlantic seaboard, a rapidly spreading pandemic of influenza traveled with the troops, causing more than 30 million deaths worldwide, three times the number that fell in the war. The origin is unclear but army records suggest it may have been seen first at Fort Riley, Kansas, in March 1918 (Spink, 1978). Although it appeared in different countries, widely separated, most of those involved in the war did not release mortality figures on the epidemic because of morale concerns, but Spain was neutral and mortality numbers from that country gave rise to the term "Spanish flu." There were waves of illness. The first influenza epidemic in August 1918 was mild. The second was deadly and involved a virulent pneumonia that killed 20% to 60% of those affected. This was followed by encephalitis lethargica, a sleeping sickness that would cause a form of postencephalitic parkinsonism in many who survived.

One strange feature of this influenza was the predilection for young healthy adults. Because young adults were affected more, a feature that has not been explained, the crowded barracks with returning soldiers would be an obvious target. By October 1918, 20% of the U.S. Army was ill. Of the 4 million in the military, 1 million would eventually come down with influenza and 99% of the deaths were due to pneumonia, including pneumococcal lobar pneumonia, hemolytic streptococcal, *H. influenza,* and staphylococcal infection. There were 76,000 cases of lobar pneumonia, many resulting in empyema (Spink 1978). Half a million American civilians died. In Britain, 200,000 died, and a quarter of the population of Samoa died. The deaths mounted in countries all over the world—Spain, France, South Africa, Sierra Leone, Canada—the largest pandemic ever known, greater than the Black Death, or any of the famous epidemics of earlier centuries.

The efforts to reduce the deaths from pneumonia were reviewed by Wetmore (1919). Vaccines prepared against many of the suspected organisms were used in conjunction with general measures such as gargles, cathartics, a milk and lime water diet, and placement of the bed between two open windows. A last wave of influenza occurred in 1920 and then the disease disappeared as quickly and mysteriously as it had appeared. There were efforts in 1998 to retrieve the virus from victims of the 1918 pandemic who were buried in permafrost but these were unsuccessful.

After the War

During these years, Rufus Cole, Raymond Dochez, and Oswald Avery (Avery, 1917) contin-

ued work on the typology of the pneumococcus. In 1929, Rene Dubos made the important discovery of a bacterial enzyme that decomposed the polysaccharide of the capsule of type III pneumococci.

In 1919, Loomis reviewed the treatment of pneumonia at the major New York hospitals and found a uniformity of approach, giving calomel on admission, saline the next morning, local applications to the chest if there was pain, and a thin milk diet (Campbell, 1919). If there was a high fever the patients were given cold packs to the chest, alcohol sponging, and cold baths, and if there was a cough, codeine, heroin, or morphine was administered. If pulmonary edema occurred, patients were given atropine and injections of adrenaline, and cupping was performed. Oxygen was administered if cyanosis was present, and if cardiac stimulation was indicated the order of preferred medications was alcohol, strychnine, and digitalis. Although he recognized the consistency of approach he cautioned that "more patients are harmed than helped by promiscuous drugging which is prevalent." He believed that iron acetate and strychnine had "surprisingly good results" in children (Campbell, 1919).

By the late 1920s the mortality from pneumonia in general hospitals in England was 25% and in private hospitals, 20%. The higher rates in the general hospital were felt to be due to overwork, poor nutrition, fatigue, and alcoholism which were greater problems there than in private hospitals. Recommendations for care included specific serum therapy, but also good nursing care, morphine for pain, digitalis, optochin, and avoidance of therapies such as alcohol, hydrotherapy, and venesection.

Although many variations on elaborate treatments prevailed over the centuries, the most common patterns were cupping, venesection, leeches, counterirritation, setons, issues, cautery and moxa. Cupping was an ancient treatment but continued to be used.

In 1927 Casper and Schiemann noted that antibodies could form to the polysaccharides in the bacterial capsule. By 1938, Finland showed that immunization with the polysaccharide material protected against pneumonia. That year Felton reported a trial with antibodies to two strains in 60,000 men, who were protected against those two strains. Work on vaccines continued over the next decade but interest waned when penicillin became available, as it was thought to have solved the problem of pneumonia.

The Development of Penicillin

In August 1928, a momentous event in the treatment of pneumonia occurred, although it would not come to fruition for 15 years. Alexander Fleming had identified penicillin in a laboratory mold that contaminated his petri dishes containing staphylococci (MacFarlane, 1984). He noted that the mold had destroyed the colonies of staphylococci. Rather than discard the ruined bacterial colonies, he studied the phenomenon. As Pasteur said, chance favors the prepared mind, and Fleming, who had been a student of Sir Almroth Wright, had already studied antiseptics in war wounds in World War I, and when researching defenses against infection discovered the enzyme lysozyme in 1921. Little attention was given to his publications on both lysozyme and penicillin and he was repeatedly turned down for election to the Royal Society when nominated by Sir Almroth Wright. Fleming himself saw little potential for penicillin which was so difficult to produce and had no effect against gram-negative organisms. It remained for the team of Florey and Chain at Oxford to rediscover his publication, and to begin a major effort to characterize and produce penicillin in large quantities.

The Development of Sulfa Drugs

Many forms of pneumonia therapy were developed in the 1930s. Antiserum research led to the production of a number of antisera, including Klemperer's convalescent serum, immune chicken serum, rabbit antiserum, Huntoon's antibody solution, and immune horse serum. As the antisera were being developed other more drastic treatments were being used, including roentgen-ray therapy and heavy doses of quinine, used for its "pneumococcidal powers."

By this time, however, the new drug prontosil, discovered by Domagk in 1935, was showing promise. Sulfanilamide became available in 1937 and ushered in a new era in the treatment of infections,

and although effective against streptococcal infections and pneumonia due to Group A hemolytic streptococci it was ineffective against other forms of bacterial pneumonia. After a less than dramatic beginning, the benefits of the drug and its successor prontylin, changed the treatment of pneumonia completely. Soon after, sulfapyridine was developed and was credited with saving the life of Winston Churchill at a crucial point in the war. Many more sulfa drugs were later developed.

Due to the increasing interest in a new agent for serious infections, and the minimal regulation of new drugs, sulfa began to be used widely, which led to many complications and restricted the ability to collect accurate data on the results (Lerner, 1991). Many were skeptical of the results with prontosil because there were so many claims for miracle drugs that came to naught during this era. Sulfa became readily available when it was discovered that the active component of prontosil was sulfanilamide, which was in the public domain and cheaper. Soon many sulfonamides were produced. Although enthusiasm grew for the new drugs, the results were conflicting, and it was difficult to contemplate clinical trials with placebos or untreated groups.

In 1938 a prospective controlled trial in pneumococcal pneumonia was carried out and demonstrated a mortality rate of 8% in the treated group compared with 27% in the untreated group (Evans & Gaisford, 1938). Despite wide overuse and inappropriate use of the drugs, a major step towards more effective treatment for pneumonia had been taken. However, just as investigators were finding the benefits and the limitations of the various sulfa drugs, penicillin was becoming available and was found to be effective against pneumococcal, streptococcal, and staphylococcal pneumonia.

The Massachusetts Pneumonia Study and Service

An excellent review of pneumonia is contained in the classic text by Heffron (1939), and a review of sulfonamides in a treatise Lerner (1991). Heffron's text (1939) was the outcome of the Massachusetts Pneumonia Study and Service, inaugurated by Dr. George H. Bigelow and carried out between 1931 and 1935 to organize statewide use of antipneumococcal serum as a community project. Spink (1978) mentions his experience treating patients as part of this program when he was housestaff at a Boston hospital. Pneumonia programs were begun as early as 1904 to provide antisera typing and production of specific antisera. The programs also included training of physicians, educational materials for health professionals, public health programs, and public education.

Mycoplasma Pneumonia (Primary Atypical Pneumonia)

Reimann (1938, 1971) described an atypical form of pneumonia that he initially thought was due to a virus, in which the severe symptoms seemed out of keeping with the few abnormal physical findings, and which had a low mortality and a prolonged convalescence. The disorder was reviewed by Spink (1978) when he recovered from the disease. The work of the Commission on Acute Respiratory Diseases at Fort Bragg during World War II showed that bacteria-free nasal washings from patients could transmit the disease, which seemed to confirm that the disease was due to an unidentified virus. After independent isolation by Eaton and colleagues in 1944, this agent was referred to as "Eaton's agent" until it was shown to be a unique microorganism, *Mycoplasma,* by Couch in 1973, and later found to be responsive to tetracycline.

Recent Events in Pneumonia

Interest in pneumococcal vaccines resumed when Austrian and Gold (1964) noted that many patients were being admitted with pneumococcal pneumonia at the Kings County Hospital in New York over a 10-year period and that the mortality was 18%, and as high as 25% in older patients and those with underlying disease, similar to the rates before the advent of antibiotics. Although his work was greeted with skepticism, efforts were beginning in the late 1960s by the Infectious Disease Branch of the National Institute of Allergy and Infectious Diseases, and by Merck, Sharp and Dohme to develop an effective vaccine. Harkening

back to Sir Almoth Wright's experiments in 1911, the research was carried out on miners in South Africa, and then later in the United States, Chile, and New Guinea in groups who had a high risk of developing pneumonia. Pneumovax was licensed in November 1977 (Steege, 1979).

Although pneumonia was thought to be pneumococcal, it became evident in the 1970s through reports from Austrian and Gold (1964), Foy (1970), and others that different organisms were often involved and that therapy had to be specific for the organism. Transtracheal aspiration showed that the organisms were often mixed in the pneumonia, and that aspiration of organisms in the oropharynx was an important factor. Although penicillin was the drug of choice in aspiration pneumonia, in 1983 a multicenter study showed that clindamycin, a broad-spectrum drug that was active against oropharyngeal organisms, was more effective than penicillin.

Much publicity and public fear was generated when following a 1976 convention of Legionnaires at the Bellevue-Stratford Hotel in Philadelphia, 182 came down with a respiratory illness that caused the deaths of 29. Various theories on the cause of the outbreak appeared in the media, including Communists from the Polish tall ship anchored in the Delaware River coming ashore at night to spread germs; magicians who were at a convention there before the Legionnaires; and drug companies who hoped the epidemic would increase sales of their vaccines (Karetzky et al., 1993). The illness was called Pontiac fever when it occurred in a milder form in workers and visitors to the health department in Pontiac, Michigan. Other instances were traced back to 1959. Although the organism was unidentified, it became evident that guinea pigs would develop the disease if exposed to the air conditioning system or injected with the water from the condenser, with a nodular lobar pneumonia developing in the animals. Although many worked on the identification of the organism, it was the efforts of Joseph McDade that led to the identification of the bacterium in December 1976, and the organism and disease were named after the Legionnaires.

Other organisms have come into prominence in recent decades, including *Chlamydia pneumoniae, Pneumocystis carinii,* and *Moraxella catarrhalis,* which was originally called *Neisseria catarrhalis* and then *Branhamella catarrhalis.*

In the summer of 1981 in San Francisco 5 young men came down with a rare pneumonia—pneumocystis pneumonia. A study by the Centers for Disease Control and Prevention revealed that all were homosexuals and had an unusual pattern of immunological deficiency. Soon similar cases occurred in homosexual young men in other cities, and an epidemic of what became known as gay-related immune disease (GRID) was under way. It later was called acquired immunodeficiency syndrome (AIDS), and by 1984 Montagnier discovered that a transmissible virus, the human immunodeficiency virus, was the cause.

Since 1985 there have been many studies that have described the nature of community-acquired pneumonia (Woodhead et al., 1987; Marrie et al., 1989; Fang et al., 1990). The developments in microbiology and therapy since 1975 have been reviewed by Fass (1993). It is clear that although most cases were thought to be due to *Diplococcus pneumonia* 50 years ago, there are now many organisms involved, and efforts have to be made to categorize the disease in each patient and in the community at large. Although a few decades ago many felt the mortality of pneumonia had been eliminated by the era of antibiotics, people still die of this disease and the mortality among hospitalized cases can be as high as 20%, a rate similar to that reported in the last century.

In the early part of this century the mortality rates from tuberculosis and pneumonia were similar. After 1950 tuberculosis deaths continued to decrease whereas the pneumonia mortality rate initially plateaued, then varied year to year, and increased in the last two decades (Armstrong et al., 1999).

Although new therapeutic agents are becoming available, microbial resistance challenges these therapeutic efforts, and the approach to community-acquired infections is clearly a work in progress.

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2

Epidemiology of Community-Acquired Pneumonia

IRMA HELENA KOIVULA

Introduction

Pneumonia continues to be a major cause of illness and death worldwide in children and adults, but there still is no general definition of pneumonia. In most studies the diagnostic criteria include acute systemic and lower respiratory symptoms and signs, as well as pulmonary infiltrates identified by radiology, but classic symptoms, signs, and radiological findings are rare, especially in elderly individuals with underlying cardiac or pulmonary disease (Macfarlane, 1994; Metlay et al., 1997). The simple definition for community-acquired pneumonia (CAP) is pneumonia that was not acquired in a hospital or other institution. Some CAP studies have, however, included patients who acquired pneumonia from nursing homes. Other cases of pneumonia, for example, those occurring in immunosuppressed patients, are frequently excluded from the definition of CAP.

Pneumonia causes excess morbidity, hospitalization, and mortality, especially among the elderly, the fastest growing sector of the population. According to first- or second-listed diagnosis, approximately 1 million persons were discharged from short-stay hospitals after treatment for pneumonia in the United States in 1990, and elderly persons aged 65 years or more accounted for 52% of all pneumonia discharges (Fedson & Musher, 1994). According to a national hospital discharge register in Finland, annual hospital treatment periods for all cases of pneumonia increased between 1972 and 1993 from 15.5 to 23.9 per 1000 individuals aged 65 years or more (Säynäjäkangas et al., 1997). Hospital treatment costs are more than 10 times higher per episode of pneumonia than the costs of treatment at home (Mäkelä et al., 1993). Despite major improvements in diagnostic techniques and antimicrobial therapies, pneumonia and influenza are still one of the six leading causes of death in developed countries (Macfarlane, 1987; Research Committee of the British Thoracic Society and the Public Health Laboratory Service, 1987; Central Statistical Office of Finland, 1985–1988, 1989; Örtqvist et al., 1990; Centers for Disease Control and Prevention, 1995). The impact of pneumonia on the healthcare system is even greater because of associated effects such as excess hospitalization for certain underlying chronic conditions (e.g., heart failure) and longstanding deterioration of health. These effects should be taken into account when estimating cost-effectiveness of preventive measures, but unfortunately, data on their frequency and magnitude are lacking. However, the healthcare system should prepare for the increasing need for prevention of pneumonia.

The main causative agent of pneumonia is *Streptococcus pneumoniae,* but estimates of the incidence of pneumococcal pneumonia among the elderly vary widely due to differences in establishing the etiological diagnosis (Bentley et al., 1981; Fedson et al., 1989; Fedson & Musher, 1994; Jokinen et al., in press). Information on the incidence, etiology, and prognosis of pneumonia and on the

IRMA HELENA KOIVULA • Department of Medicine, Division of Infectious Diseases (4620), Kuopio University Hospital, SF-70211 Kuopio, Finland.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

efficacy of the vaccines are essential for designing rational prevention programs. The pneumococcal vaccine has been shown to be effective against invasive pneumococcal infections, but there is less evidence of its efficacy in preventing pneumonia, especially in the elderly (Austrian et al., 1976; Smit et al., 1977; Riley et al., 1977; Shapiro & Clemens, 1984; Bolan et al., 1986; Sims et al., 1988; Fair et al., 1995; Shapiro et al., 1991; Austrian, 1980; Simberkoff et al., 1986; Leech et al., 1987; Gaillat et al., 1985; Koivula et al., 1997; Örtqvist et al., 1998; Honkanen et al., 1999).

Incidence of Community-Acquired Pneumonia

The high incidence of pneumonia in young children and elderly people has been a general feature in pneumonia incidence studies (Table 1). Detailed data on the incidence of all cases of pneumonia in the population with age- and gender-specific figures are rare because most of the epidemiological studies of CAP have been carried out in patients treated in hospitals. In industrialized countries, the annual incidence of CAP in adults and

TABLE 1. Incidence of Community-Acquired Pneumonia in Industrialized Countries[a]

Study	Study period	Population	Identification of population	Number of pneumonia cases	Age (years)	Incidence per 1000 per year
Foy et al. (1979)	1964–1975	Seattle, WA: 64,000–180,000 HMO members	Diagnoses reported by physicians	15,141	<5	34
					5–9	16
					15–59	5–8
					60–69	10
					≥70	18
					All ages	12
Groop et al. (1979)	1975–1977	Närpiö, Finland: 13,000	Patients in a health center	124	All ages	8
Austrian (1980)	1974–1976	San Francisco, CA: 6818 HMO placebo recipients	Vaccination trial	542	≥45 years	16
Murphy et al. (1981)	1965–1975	Chapel Hill, NC: Children among a total population of 30,000	Patients in a group practice	1483	≤5	15–40
					5–9	22
					9–12	11
					12–14	7
Patrick & Woolley (1981)	1977–1978	Salt Lake City, UT: 9500 HMO members	Diagnoses reported by physicians	173	≥18	12
Woodhead et al. (1987)	1984–1985	Nottingham, UK: population of 53,137	Patients seen by general practitioners	251	15–79	5
McConnochie et al. (1988)	1971–1975	Monroe County, NY: 3930 child-years	Patients in a pediatric practice	61	<3	17
Gable et al. (1990)	1986–1988	Minnesota: Blue Cross/Blue Shield	Data on file	26	≥50	11
Jokinen et al. (1983)	1981–1982	Four municipalities in Finland: population of 46,979	Patients reported by all physicians working in the area or at the referral hospitals	546	<5	36
					5–9	17
					10–14	16
					15–59	6
					60–69	15
					70–79	21
					≥80	42
					All ages	12

HMO, health maintenance organization.
[a]Reproduced, with permission, from Jokinen et al., 1993.

adolescents older than 13 to 15 years has varied from 2.6 to 9.0 per 1000 persons, with age and socioeconomic factors the strongest determinants of the incidence (Riley et al., 1977; Oseasohn et al., 1978; Fay et al., 1979; Woodhead et al., 1987; LaCroix et al., 1989; Gable et al., 1990; Almirall et al., 1993; Jokinen et al., 1993; Marston et al., 1997).

In the 1960s and 1970s, the incidence of pneumonia among members of a health maintenance organization in Seattle was found to be 12.5 per 1000 members overall and 18 per 1000 members aged 70 years or more (Foy et al., 1979). In Nottingham, United Kingdom, the annual incidence of CAP seen by general practitioners in the mid-1980s was 4.7 per 1000 persons aged 15 to 79 years; pneumonia was found to account for only 5.6% of all community-acquired lower respiratory tract infections (LRTI) for which antibiotics were prescribed (Woodhead et al., 1987). In a more recent study the annual incidence of all acute LRTI was found to be 44 per 1000 persons; the incidence was 2 to 4 times higher in persons aged 60 years or more (Macfarlane et al., 1993). In Maresme, Spain, the annual incidence of CAP in 1990–1991 was found to be lower than in previous studies: 2.6 per 1000 in a population of 39,733 persons aged 13 years or more (Almirall et al., 1993). A detailed population-based study of approximately 47,000 persons living in eastern Finland determined the overall incidence of CAP with age- and gender-specific data in the total population of a defined geographic area (Table 2). In this study, the incidence was 9 per 1000 per year at ages 15 years or more despite the almost complete absence of influenza; the incidence increased rapidly after the age of 50 years, to as high as 20 per 1000 per year in persons aged 60 years or more (Jokinen et al., 1993). In a Finnish pneumococcal vaccination trial, the incidence of pneumonia was 17.4 per 1000 person-years in a population of persons aged 60 years or more at baseline, and the incidence of CAP was 12.3 per 1000 person-years; of these 39% were treated at home, and 61% in hospitals, health center wards, or facilities for chronic care (Koivula et al., 1997).

Although peak incidences of pneumonia in areas with a temperate climate have been described in winter and spring, with the highest peaks associated with influenza epidemics, especially among the elderly (Barker, 1986; Chakraverty et al., 1986; Glezen et al., 1987), more recent work has suggested that pneumonia occurs throughout the year, and there is no "pneumonia season" (Marrie et al., 1989; Donowitz & Mandell, 1995). However, in a 12-month study in Nottingham, United Kingdom, 53% of pneumonia cases in the elderly were seen in December and January (Venkatesan et al., 1990). Because the majority of pneumococcal bacteremias in adults are associated with pneumonia, the sea-

TABLE 2. Incidence of Community-Acquired Pneumonia by Age and Sex in Four Municipalities in Eastern Finland, September 1, 1981 to August 31, 1982[a]

Age (years)	Population			Incidence per 1000 inhabitants per year					
				Males		Females		Total	
	Males	Females	Total	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI
<5	1520	1397	2917	47.4	36.7–58.0	23.6	15.7–31.6	36.0	29.2–42.8
5–14	3024	2910	5934	16.2	11.7–20.7	16.2	11.6–20.7	16.2	13.0–19.4
15–29	6187	5452	11,639	4.2	2.6–5.8	4.6	2.8–6.4	4.4	3.2–5.6
30–44	5031	4409	9440	5.6	3.5–7.6	5.9	4.6–7.2	5.7	4.2–7.2
45–59	4273	4403	8676	9.8	6.9–12.8	7.0	4.6–9.5	8.4	6.5–10.3
60–74	2564	3789	6353	25.0	18.9–31.0	9.0	6.0–12.0	15.4	12.4–42.1
≥75	644	1376	2020	65.2	46.1–84.3	19.6	12.3–27.0	34.2	26.2–42.1
All ≥60	3208	5165	8373	33.0	26.9–39.2	11.8	8.9–14.8	19.9	17.0–22.9
Total	23,243	23,736	46,979	13.9 (mean)	12.4–15.4	9.4 (mean)	8.2–10.6	11.6 (mean)	10.7–12.6

CI, confidence interval.
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sonal variation in the incidence of invasive pneumococcal infections reflects the seasonal variation of pneumonia. In Finland between 1983 and 1992 there was a marked seasonal variation every year in the number of invasive pneumococcal isolates among adults, with a major peak occurring in December–January (mean 11.3 cases per month) and a trough in July–August (mean 4.4 cases per month); these figures are based on a prospective surveillance of all invasive pneumococcal isolates in the microbiology laboratories of three geographical areas covering 29% of the total adult population in Finland (Sankilampi et al., 1997). This seasonal variation was also observed in a 12-month study in south and west England (Smith et al., 1998), where a distinct peak of invasive pneumococcal infections occurred in December (16.5% of all cases), and the lowest number of cases occurred in July–September (average 3.5% of all cases per month).

Despite the many uncertainties and differences in catchment population, case definition, and patient selection, some general conclusions of the incidence of CAP can be made. The overall incidence is likely between 5 and 20 per 1000 per year, with a higher incidence in young children and elderly persons, in closed communities, in winter and spring than in summer, and in developing than in industrialized countries.

Hospitalization Rate and Incidence of CAP Requiring Hospitalization

There is a wide geographic variation in the incidence of pneumonia treated in hospitals, which only partially reflects the incidence of severe cases because local patterns of admitting patients to hospitals largely contribute to the hospitalization rate. These include outpatient medical care systems, treatment recommendations and practices, and availability of ambulatory diagnostic and therapeutic facilities, as well as cultural and socioeconomic factors. In addition, physicians rely on their impression of the clinical status of a pneumonia patient rather than on specific prognostic factors when they decide on hospitalization (Fine et al., 1990, 1993, 1997). The decision to admit a pneumonia patient is economically very important because treatment in hospitals causes the heaviest burden to the health-care system from this illness. In Finland a large number of pneumonia patients (70% of those aged 60 years or more) are referred to hospitals, and as mentioned previously hospital treatment costs are 10 times higher per episode of pneumonia than the costs of treatment at home (Mäkelä et al., 1993). Elderly persons aged 65 years or more have accounted for 37% (Research Committee of the British Thoracic Society and the Public Health Laboratory Service, 1987) to 86% (Marrie et al., 1989) of adults hospitalized due to CAP.

In a 7- to 12-year follow-up of a cohort representative of the population aged 55 to 74 years in the United States, the incidence of pneumonia requiring hospitalization was 5 per 1000 person-years in persons aged 55 to 64 years (5.9 in men and 4.2 in women), and 9.9 in those aged 65 to 74 years at baseline (11.9 in men and 8.3 in women) (LaCroix et al., 1989). In the Nottingham study, 22% of patients with CAP aged 15 to 79 years were hospitalized, corresponding to an annual incidence of 1 per 1000 persons (Woodhead et al., 1987). In Nova Scotia, Canada, the annual incidence of CAP requiring hospitalization increased markedly with age from 0.50 per 1000 persons aged 15 to 54 years to 3.6 per 1000 persons aged 55 or more, and 11.6 per 1000 persons aged 75 or more; the hospitalization rate was very high in nursing home residents—33 per 1000 (Marrie, 1990). The incidence of CAP requiring hospitalization in Ohio in 1991 was found to be 2.7 per 1000 persons aged 18 years or more, and 10 per 1000 persons aged 65 years or more (Marston et al., 1997). In the Spanish study the overall incidence of CAP in persons aged 13 years or more was lower than in previous studies, but the hospitalization rate was 50%, corresponding to an annual incidence of CAP requiring hospitalization of 1.3 per 1000 (Almirall et al., 1993). A high hospitalization rate was also found in the Finnish study, in which 42% of CAP patients of all ages were hospitalized; among persons aged 60 years or more the hospitalization rate was as high as 67%, corresponding to an annual incidence of 13.4 per 1000 persons (Jokinen et al., 1993). In Sweden, the hospitalization rate for pneumonia was 68% among immunocompetent persons aged 50 years or more who had been previously treated in hospitals for pneumonia (Hedlund et al., 1997; Örtqvist et al., 1998).

Incidence of Pneumococcal CAP

The microbial etiology of pneumonia has been intensively studied, but there still is uncertainty about the roles of the various causative agents. *S. pneumoniae* is the most important etiological agent of pneumonia. The precise incidence of pneumococcal pneumonia is, however, difficult to define because of the lack of reliable methods for the routine evaluation of patients. In addition, it is difficult to estimate the incidence of pneumococcal pneumonia among patients who are managed without hospitalization (Fedson & Musher, 1994; Jokinen et al., in press). The different microbiological methods used for etiologic diagnosis of CAP are largely responsible for the diverging results found in the literature. Geographical variation in the etiology of CAP further undermines the reliability of the results. Methods used for detection of pneumococcal etiology have included blood and sputum cultures and tests for detection of pneumococcal antigens and antibodies. Because of the low sensitivity and controversies associated with culture methods, improved methods are needed in both etiologic and epidemiological studies of pneumococcal pneumonia.

Pneumococci have been implicated in approximately 25% to 55% of CAP cases requiring hospitalization (Berntsson et al., 1985; Macfarlane et al., 1982; Kerttula et al., 1987; Holmberg, 1987; Örtqvist et al., 1990; Kauppinen et al., 1995; Lieberman et al., 1996), and according to population-based studies in 12% to 41% of all CAP cases in adults depending on the diagnostic panel used. In these population-based studies other common etiological agents of CAP have been *Chlamydia pneumoniae* (10%–15%), *Mycoplasma pneumoniae* (1%–10%), *Haemophilus influenzae* (0%–27%), and other viruses (5%–11%) (Dulake & Selkon, 1982; Woodhead et al., 1987; Almirall et al., 1993; Jokinen et al., in press).

The incidence of pneumococcal pneumonia determined in studies of members of health maintenance organizations in the United States are of the same order of magnitude: 1.3 per 1000 members of all ages in Seattle (Foy et al., 1979), 1.2 per 1000 controls aged 45 years or more in a vaccination trial in San Francisco (Austrian, 1980), and 2.3 per 1000 members aged 18 years or more in Salt Lake City (Patrick & Woolley, 1981). In Nottingham, the annual incidence of pneumococcal pneumonia seen by general practitioners was 1.6 per 1000 inhabitants aged 15 to 79 years; a pathogen was identified in 55% of the episodes of pneumonia (Woodhead et al., 1987). A much lower incidence—0.3 per 1000 inhabitants over 13 years of age—was found in Maresme, Spain (Almirall et al., 1993); however, the overall incidence of pneumonia was low, and the microbial etiology was identified in only 44% of the pneumonia patients. In a population-based Finnish study, microbial etiology was identified in 60% of the episodes of CAP. The annual incidence of pneumococcal pneumonia was higher than in previous studies: 3.3 per 1000 inhabitants aged 15 years or more, and 8.0 per 1000 at ages 60 years or more, with pneumococci being the single most frequent cause (41%) of CAP based on a wide array of serological methods (Jokinen et al., in press). In a Finnish pneumococcal vaccination trial the overall incidence of serologically diagnosed pneumococcal pneumonia was 7.0 per 1000 person-years, and the incidence of pneumococcal CAP was 5.3 per 1000 person-years in the elderly population aged 60 years or more in a defined geographic area followed prospectively from 1983 to 1985 (Koivula et al., 1997). In another Finnish pneumococcal vaccination trial conducted in northern Finland in 1993-1994, the incidence of pneumococcal pneumonia was lower: 2.4 per 1000 person-years among persons aged 65 years or more (Honkanen et al., 1999). In a recent Swedish pneumococcal vaccination trial, the annual incidence of pneumococcal pneumonia among patients previously treated in hospitals for CAP was as high as 20 per 1000 persons aged 50 to 85 years (Örtqvist et al., 1998).

Incidence of Invasive Pneumococcal Disease

The incidence of invasive pneumococcal disease (IPD) can be more clearly defined than that of pneumococcal pneumonia, and it is strongly influenced by the socioeconomic situation of the population being studied (Table 3). Age is another important factor determining the incidence of IPD, which is high in children under 2 years of age, low in adolescents and young adults, and higher among

TABLE 3. Incidence of Invasive Pneumococcal Disease in the Whole Population in the the Elderly[a]

Location of population, period	Incidence/100,000/year		Reference
	All ages	Elderly	
Finland, 1976–1980	3	NA	Virtanen & Peltola (1982)
Sweden, 1976–1980	8	15 (≥60 years)	Burman et al. (1985)
Sweden, 1992	10	NA	Hudlund et al. (1995)
Denmark, 1994	18	55 (>60 years)	Nielsen & Henrichsen (1992)
England and Wales, 1982–1992	9	19 (≥75 years)	Aszkenasy et al. (1995)
Israel, 1977–1985	12	39 (≥65 years)	Kramer et al. (1987)
United States			
West Virginia, 1978–1981	8	15 (≥75 years)	Mufson et al. (1982)
Oklahoma, 1984	16	87 (≥80 years)	Istre et al. (1987)
Hawaii, 1986–1987	9	22 (≥65 years)	Campbell et al. (1989)
South Carolina, 1986–1987			Breiman et al. (1990)
Blacks	29	85 (≥65 years)	
Whites	12	37 (≥65 years)	
New York, 1985–1989			Bennett et al. (1992)
Blacks	49	162 (≥65 years)	
Whites	14	59 (≥65 years)	
Oklahoma, 1990	17	42 (≥65 years)	Haglund et al. (1993)
Alaska, 1986–1990			Davidson et al. (1994)
Natives	74	186 (≥65 years)	
Non-natives	16	90 (≥65 years)	
Ohio, 1991–1993	NA	83 (>65 years)	Plouffe et al. (1996)
California, 1992–1995	13	32 (≥65 years)	Zangwill et al. (1996)
Australia, 1992–993			Trotman et al. (1995)
Aborigines	297	194 (>50 years)	
Non-aborigines	9	10 (≥50 years)	

NA, not analyzed.
[a]Reprinted with permission from Sankilampi, 1997.

the elderly (Sankilampi et al., 1997). In adults, bacteremic pneumonia is the most common clinical manifestation of IPD, accounting for 70% to 90% of cases (Ruben et al., 1984; Burman et al., 1985; Kramer et al., 1987; Kuikka et al., 1992). In Figure 1, age- and gender-specific incidences of IPD over a 10-year period from 1983 to 1992 are compared with corresponding data on CAP in Finland in 1981–1982, showing similar increases with advancing age and male predominance. The overall incidence of pneumonia (pneumococcal in 40% by a wide pattern of serological and antigen detection tests) was 100 times higher than that of IPD (bacteremia in 90%) (Jokinen et al., 1993; Sankilampi et al., 1997; Jokinen et al., in press).

Among the elderly (60–65 years or older) the annual incidence of pneumococcal bacteremia has ranged from 22 to 60 per 100,000 persons during the 1980s in the United States, depending on the characteristics of the population; among the native population of Alaska it was as high as 186 per 100,000 (Davidson et al., 1994). More recently the incidence of IPD among persons aged 65 years or more in the United States was 83 per 100,000 persons (Plouffe et al., 1996) and 80 per 100,000 persons (Pastor et al., 1998). Annual incidence figures among the elderly have been reported also from other countries: 39 per 100,000 in Israel (Kramer et al., 1987), 55 per 100,000 in Denmark (Nielsen & Henrichsen, 1992), 15 per 100,000 in Sweden (Burman et al., 1985). In Finland the annual incidence of IPD is much higher in the elderly than in younger adults: 27 per 100,000 persons aged 65 years or more versus 6.2 per 100,000 persons aged 16 to 64 years (Sankilampi et al., 1997). The overall incidence (9.1 per 100,000) in Finland is comparable to

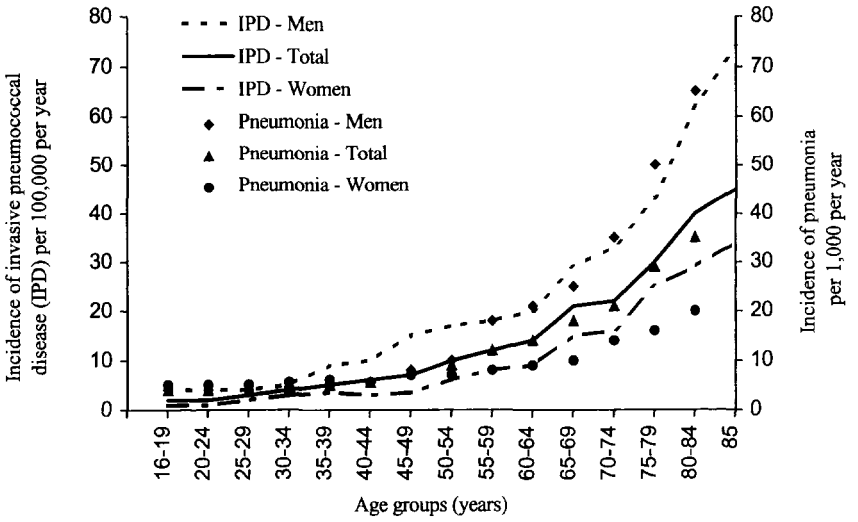

FIGURE 1. Age-specific incidences of invasive pneumococcal disease (IPD) per 100,000 per year in Finnish men and women, and age- and gender-specific incidences of community-acquired pneumonia per 1000 per year (Sankilampi et al., 1997; Jokinen et al., 1993). Reprinted, with permission, from Sankilampi et al., 1997.

that reported from several countries (Table 3), and most recently from south and west England, where the overall incidence of IPD in 1995 was 10.3 per 100,000 persons (12.0 in men vs. 8.9 in women); the incidence was very high (33.2 per 100,000) in infants under 1 year of age, and lowest (1.9 per 100,000) in the 15–24-year age group, increasing rapidly after the age of 45 years to peak at 44.7 per 100,000 in persons aged 75 years or more (Smith et al., 1998).

Risk Factors for Pneumonia

Several studies indicate that age and underlying diseases are the most important risk factors for contracting pneumonia, and that elderly persons with high-risk conditions have excess rates of hospitalization and death from pneumonia (Dorf et al., 1973; Macfarlane et al., 1982; Berntsson et al., 1985; Lipsky et al., 1986; Woodhead et al., 1987; LaCroix et al., 1989; Marrie et al., 1989; Granton & Grossman, 1993; Jokinen et al., 1993). However, most of this information is based on hospitalized patients or other selected patient groups, and prospective, population-based studies are rare (LaCroix et al., 1989; Salive et al., 1993; Lange et al., 1995; Woodhead et al., 1987; Jokinen et al., 1993). Chronic cardiovascular and lung diseases are generally regarded as predisposing factors for pneumonia because of their frequent occurrence in patients hospitalized for pneumonia (Research Committee of the British Thoracic Society and the Public Health Laboratory Service, 1987; Venkatesan et al., 1990; Marrie, 1990; Macfarlane et al., 1993). In addition, old age, male gender, diabetes, alcoholism, renal failure, cancer, dementia, seizure disorders, smoking, and previous hospitalization are listed as risk factors for pneumonia requiring hospital treatment (Fekety et al., 1971; Lipsky et al., 1986; Farr et al., 1988; LaCroix et al., 1989; Marrie, 1990).

Although the prevalence and severity of chronic conditions increase with age, age itself has consistently been found to be an independent risk factor for contracting pneumonia and for pneumonia-related death (Lipsky et al., 1986; LaCroix et al., 1989; Fine et al., 1990, 1996; Jokinen et al., 1993; Salive et al., 1993; Lange et al., 1995). In several studies male gender has been associated with higher rates of death from pneumonia (Burman et al., 1985; LaCroix et al., 1989; Salive et al., 1993; Jokinen et al., 1993; Gilbert & Fine, 1994; Fine et al., 1996; Hedlund et al., 1997). Congestive heart failure and chronic bronchopulmonary diseases have

also been strongly associated with pneumonia (Lipsky et al., 1986; Farr et al., 1988; LaCroix et al., 1989; Zweig et al., 1990; Lange et al., 1995; Fine et al., 1996). Conditions that generally compromise host defenses, such as neoplastic disease, use of corticosteroid or other immunosuppressive agents, or institutionalization, have been identified as risk factors for a complicated course of pneumonia (Lipsky et al., 1986; Fine et al., 1990; Hedlund et al., 1993; Salive et al., 1993). The role of diabetes or alcoholism as a risk factor for pneumonia is more controversial (Moss, 1980; Filice et al., 1980; Lipsky et al., 1986; Kramer et al., 1987; LaCroix et al., 1989; Diepersloot et al., 1990; Bouter et al., 1991). Most of the cited studies are, however, based on selected series of patients treated in specialist-level hospitals, and population-based information is available from only a few studies (Woodhead et al., 1987; Jokinen et al., 1993; Koivula et al., 1994), and four study groups have reported data for unaffected controls (Lipsky et al., 1986; Farr et al., 1988; LaCroix et al., 1989; Koivula et al., 1994). Lipsky and coworkers studied risk factors for acquiring pneumococcal pneumonia among elderly men; statistically significant, independent risk factors were dementia, seizure disorders, current smoking, congestive heart failure, cerebrovascular disease, institutionalization, and chronic obstructive pulmonary disease, but not alcoholism or diabetes. The incidence of pneumococcal infections increased linearly with age: the risk of pneumonia was 2.2 times higher among persons aged 71 to 80 years than among those 50 years or younger (Lipsky et al., 1986). Farr and coworkers (1988) conducted a case–control study of risk factors for CAP treated in hospitals in England and identified age, heart disease, cancer, diabetes, renal failure, lifetime smoking history, and chronic obstructive pulmonary disease or asthma as independent risk factors for CAP. LaCroix and coworkers (1989) carried out a prospective study of risk factors for hospitalization and death associated with CAP and found rates for pneumonia-related death to be 3-fold higher for men than for women, with hospitalization rates showing a similar difference. The risk of hospitalization for pneumonia was higher among persons with chronic obstructive pulmonary disease and currently smoking men, and the risk of pneumonia-related death was higher among persons with congestive heart failure, stroke, cancer, or diabetes. Koivula and coworkers (1994) analyzed the prevalence of medical conditions included in most risk group-based recommendations for influenza vaccination among 4167 inhabitants aged 60 years or more at baseline in a small town in eastern Finland. That population was then followed prospectively for 3 years, and all patients with pneumonia were registered. One could then identify which elderly persons had an increased risk for contracting pneumonia, for hospitalization because of pneumonia, and for pneumonia-related death. The following conditions were significantly more common at baseline in persons who subsequently developed pneumonia than in the rest of the study population: heart diseases (38.4% vs. 23.0%), chronic obstructive lung diseases (13.0% vs. 3.8%) and bronchial asthma (11.9% vs. 3.1%), immunosuppressive therapy (2.7% vs. 0.8%), alcoholism (2.2% vs. 0.3%), and permanent institutionalization (8.6% vs. 3.9%) (Fig. 2). Each year of age increased the risk of contracting pneumonia by a factor of 1.07; the risk of developing pneumonia was 1.5 times higher among persons aged 70 years or more than among those 60 to 69 years of age, but male gender was not an independent risk factor for pneumonia. The highest risk for acquiring pneumonia was associated with alcoholism: alcoholics had a 9-fold higher risk than nonalcoholics. Heart disease, bronchial asthma, and other lung diseases were the most prevalent medical conditions, which increased the risk of contracting pneumonia 2- to 4-fold. Immunosuppressive therapy increased the risk of contracting pneumonia 3-fold. Approximately one third of the elderly population had at least one of these conditions (Fig. 3). Diabetes, chronic pyelonephritis, and extra pulmonary malignancies were not associated with an increased risk for pneumonia. The diseases shown to be risk factors for contracting pneumonia were also associated with a significantly higher risk of hospitalization for pneumonia, with the exception of alcoholism. Patients 70 years of age or more were approximately two times more likely to require hospitalization or die because of pneumonia than those aged 60 to 69 years. Pneumonia patients had a 5- to 13.5-fold increased risk of fatal outcome if they had heart disease, were receiving immunosuppressive therapy, or were institutionalized at baseline. However, bronchial asthma and other chronic obstructive

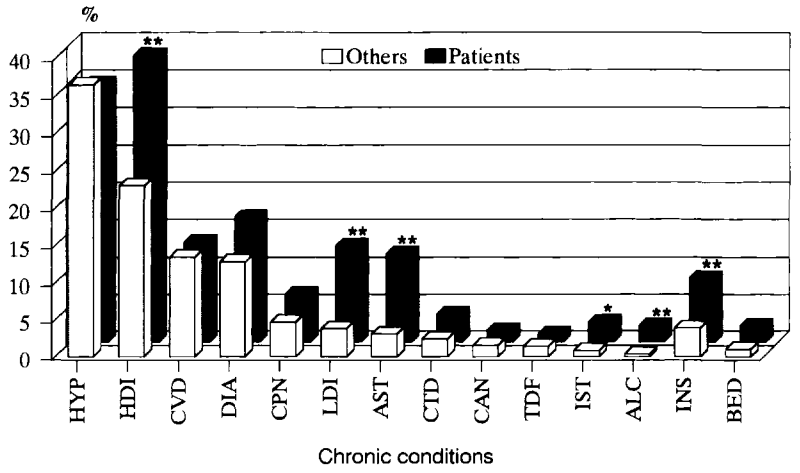

FIGURE 2. Prevalence of chronic medical conditions at baseline among persons who subsequently developed pneumonia (patients, n = 185) compared to that in the rest of the study population (others, n = 3982). Statistical significance was calculated using the chi-square analysis: $*P < 0.05$, $**P < 0.001$. HYP, hypertension (only hypertension requiring medication considered); HDI, heart disease (aortic, mitral, or pulmonary stenosis; cor pulmonale; congenital heart disease with pulmonary hypertension; chronic compensated heart failure with medication [96% of heart disease]; chronic congestive heart failure [1.6% of heart disease]); CVD, other cardiovascular disease (coronary artery disease or arrhythmia without heart failure, obliterative arteriosclerosis); DIA, diabetes (includes all diabetics, also those treated with diet alone); CPN, chronic pyelonephritis (renal parenchymal disease diagnosed radiologically, by biopsy or by functional tests); LDI, lung disease (chronic bronchitis, pulmonary emphysema, chronic interstitial lung disease, sequelae of tuberculosis, bronchiectases, lung cancer); AST, bronchial asthma (only asthma requiring medication considered); CTD, connective tissue disease (rheumatoid arthritis, other connective tissue diseases); CAN, cancer (only malignancies diagnosed during the last 5 years); TDF, thyroid dysfunction (hyperthyreosis or hypothyreosis); IST, immunosuppressive therapy (cytostatics, radiation or corticosteroids currently or within 1 year); ALC, alcoholism; INS, institutionalization (resident in hospital or home for the elderly); BED, permanently bedridden. Reprinted, with permission, from Koivula et al., 1994.

lung disease, which were important risk factors for contracting pneumonia and for hospitalization due to pneumonia, did not increase the risk of death. Of interest to the discussion of pneumonia prevention is the fact that 45% of the pneumonia patients had no identified medical risk factor. This means that a risk factor-oriented vaccination strategy would fail to cover almost one half of potential pneumonia cases (Fig. 3).

Previous hospital care for any reason has been found to be a risk factor for pneumonia (Fedson & Baldwin, 1982), and the incidence of pneumonia has been found to be more than five times higher in persons previously treated in hospitals for pneumonia than in persons treated for other infections (Hedlund et al., 1992). The findings were similar in a recent Swedish prospective study covering approximately 3 years: the incidence of CAP was as high as 98 per 1000 person-years in middle-aged and elderly persons previously treated in hospitals for CAP (Hedlund et al., 1997). It was almost five times higher than the overall incidence of pneumonia in persons over 60 years of age in Finland (Jokinen et al., 1993). Hospital-based pneumococcal immunization has been proposed as capable of reaching patients most likely to develop pneumococcal disease (Fedson et al., 1990), but there are no prospective studies that have demonstrated the effectiveness of pneumococcal vaccination in CAP patients. In fact, a recent Swedish trial showed that the 23-valent vaccine was not effective in preventing pneumococcal pneumonia among patients aged 50 to 85 years who had been previously treated as inpatients for CAP. Despite the immunization the annual incidence of pneumonia treated in hospitals was found to be very high: 40, 54, and 116 per 1000 person-years in the 50–65 years, 66–75 years, and 76–85 years age groups, respectively (Örtqvist et al., 1998). Thus, efforts should be taken to prevent the first episode of pneumonia.

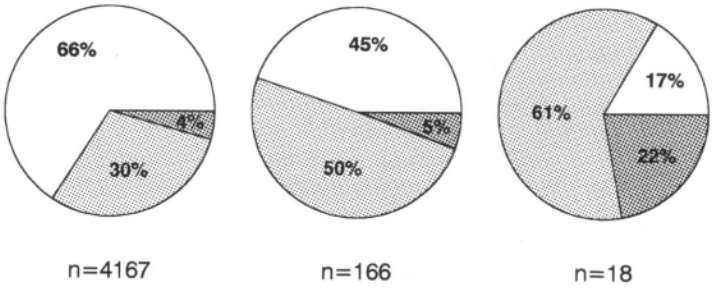

FIGURE 3. Proportions of the whole study population (left) and the pneumonia patients at baseline (one pneumonia episode, middle; two or three pneumonia episodes, right) in three different strata concerning the degree of risk for pneumonia. The whole study population included inhabitants aged 60 years or older in one township (population 24,716) in eastern Finland. All pneumonia patients in the same population were prospectively identified over a period of three years from 1983 to 1985. High risk stratum (dark shadowed): immunosuppressive therapy, cancer, or connective tissue disease. Increased risk stratum (light shadowed): heart disease, bronchial asthma, lung disease, alcoholism, or institutionalization. Low risk stratum (white): diabetes, hypertension, other cardiovascular disease, chronic pyelonephritis or thyroid dysfunction; also includes persons without any defined chronic diseases. Reprinted, with permission, from Koivula et al., 1994.

Death from Pneumonia

Despite improved diagnostic and therapeutic methods, pneumonia continues to be the fifth or sixth leading cause of death in the United States, United Kingdom, and Scandinavian countries (Macfarlane, 1987; Research Committee of the British Thoracic Society and the Public Health Laboratory Service, 1987; Central Statistical Office of Finland, 1989; Örtqvist et al., 1990; Centers for Disease Control and Prevention, 1995). Influenza epidemics strongly increase the incidence of and death rates from pneumonia (Centers for Disease Control and Prevention, 1995; Nichol et al., 1994).

Mortality figures are strongly influenced by the study design, especially the exclusion criteria. For example, in some studies the very elderly, immunocompromised patients, patients from nursing homes, and those with pneumonia as a terminal illness are often excluded. Pneumonia-related mortality during 12 years of follow-up among elderly persons in the United States was 2.5 per 1000 person-years among men aged 55 to 64 years and 5.9 among men aged 65 or more; respective figures among women were markedly lower: 0.46 and 1.8 (LaCroix et al., 1989). In a 6-year study of risk factors for pneumonia-related mortality among persons aged 65 years or more in the United States, the pneumonia mortality rate using the underlying cause of death only was 4.3 per 1000 person-years in men and 1.4 in women; when all deaths with pneumonia were grouped together the rate was 7.3 per 1000 person-years in men and women together (Salive et al., 1993). Very similar figures were found in the Finnish 1-year prospective pneumonia incidence study: the mortality rate in men aged 60 years or more was 4.4 per 1000 inhabitants per year and 0.8 in women (Jokinen et al., 1993). In another Finnish study, the pneumonia-related mortality rate was 8.7 per 1000 person-years among persons aged 60 years or more at baseline during a mean follow-up period of 9.2 years and a total of 38,170 person-years; this study was based on a central register of death certificates, and all deaths with pneumonia were grouped together, whether it was an underlying, immediate, or contributing cause of death (Koivula et al., unpublished data). In England and Wales the pneumonia-related death rate in 1985 was 3.2 per 1000 men and 3.7 per 1000 women aged 65 years or more (Cullinan, 1988).

The case–fatality rate of all cases of pneumonia in the general population was 2% (all ages) in a study of Native Americans (Oseasohn et al., 1978) and 3% in adults aged 16 to 79 years with CAP seen by general practitioners in Nottingham (Woodhead et al., 1987). The rate was 14% among members of a health maintenance organization aged 45 years or more in San Francisco (Austrian, 1980). In a population-based study in Finland the case–fatality rate was 0.6% at ages 15–59 years and

11% in persons aged 60 years or more (Jokinen et al., 1993). Case–fatality rates between 4% and 29% have been found in studies of adults requiring hospitalization for CAP, the varying figures reflecting differences in patient selection and study design. The case–fatality rate was 4% in adults with a mean age of 62 years in Sweden (Örtqvist et al., 1990), 15% in adults with a mean age of 51 years (Macfarlane et al., 1982), 5.7% in adults with a mean age of 48 years, and 12% in those aged 60–74 years in the United Kingdom (Research Committee of the British Thoracic Society and the Public Health Laboratory Service, 1987); 29% in persons over 60 years of age in Halifax County, Nova Scotia, Canada (Marrie et al., 1989); 18% in persons aged 65 years or more in Shenandoah, Virginia (Fedson et al., 1990); and 12.5% in persons aged 65 years or older in Ohio (Marston et al., 1997). The overall death rate in elderly patients admitted to an intensive care unit because of CAP was recently found to be as high as 40%, but not associated with age or comorbid illness other than immunosuppressive therapy (Rello et al., 1996).

Progress in antibiotic therapy and advances in intensive care have apparently not improved the outcome of pneumococcal bacteremia, because case–fatality rates among the elderly (60–65 years of age or more) have been reported to be 30% to 40% in the United States and Canada, similar to the rate determined by Austrian and Gold in the 1960s (Austrian & Gold, 1964; Mufson et al., 1982; Finkelstein et al., 1983; Murphy & Fine, 1984; Fedson & Musher, 1994; Afessa et al., 1995; Plouffe et al., 1996). Case–fatality rates of the same order have been reported from the United Kingdom (37%, Gransden et al., 1985) and Israel (43%, Kramer et al., 1987); lower rates have been reported from Sweden (7%, Örtqvist et al., 1988 and 25%, Burman et al., 1985). In two Finnish studies the mortality rate has been 18% (Kuikka et al., 1992) and 34% (Lääveri et al., 1996).

Several studies have evaluated prognostic factors that can be identified during the acute phase of CAP; mortality has varied by etiology and by several other factors depending on the study design and the catchment population (Fine et al., 1996); fatal outcome of pneumonia is almost confined to the elderly, patients admitted from a nursing home, patients with underlying diseases or vital-sign abnormalities, and bacteremic patients (Research Committee of the British Thoracic Society and Laboratory Service, 1987; LaCroix et al., 1989; Marrie et al., 1989; Brancati et al., 1993; Salive et al., 1993; Lange et al., 1995; Fine et al., 1993, 1997; Lieberman et al., 1997). Bilateral pleural effusions at presentation were also found to be an independent predictor of short-term mortality (Hasley et al., 1996). In some studies, however, death has not been related to age (Levy et al., 1988; Zweig et al., 1990; Venkatesan et al., 1990; Örtqvist et al., 1990; Farr et al., 1991; Brancati et al., 1993; Rello et al., 1996) or to underlying diseases (Levy et al., 1988; Venkatesan et al., 1990; Örtqvist et al., 1990; Farr et al., 1991; Rello et al., 1996).

Although pneumonia continues to be a leading cause of illness and death, there are only few reports of long-term effects of CAP, and these studies have focused on cases treated in hospitals (Zweig et al., 1990; Hedlund et al., 1992, 1993, 1997; Brancati et al., 1993). In one study 32% of the 119 patients aged 18 to 92 years who survived hospital treatment for CAP died within the next 24 months; mortality was related to severe or moderate comorbidity but not to age (Brancati et al., 1993). In a Swedish study the risk of subsequent death during 2.5 years of follow-up after hospital-treated pneumonia was twice (1.43-3.20) as high in the pneumonia patients as in the general population (Hedlund et al., 1993). A similar result was found in a Finnish population-based study (Koivula et al., 1999). The subsequent pneumonia-related mortality over 9 years was twice as high in patients who had survived CAP (in 57% of cases treated in hospitals) as in other inhabitants of the same area aged 60 years or more at baseline, although comorbidities present at baseline were included in the risk analysis. If the CAP episode was caused by *S. pneumoniae,* the risk was three times higher. Subsequent total and cardiovascular mortality was also increased in CAP patients. Thus, CAP was found to be an independent risk factor for mortality and to have predictive value even many years later.

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3

Clinical Features and Outcomes of Community-Acquired Pneumonia

THOMAS J. MARRIE

Introduction

This chapter gives an overview of the clinical features of community-acquired pneumonia (CAP) using data from two studies. Marrie and colleagues (1989) studied all patients with CAP admitted to an acute-care hospital in Halifax, Nova Scotia, from November 1, 1981, to March 15, 1987. Fine and coworkers (1998) studied 944 outpatients and 1343 inpatients with CAP at two hospitals in Pittsburgh, Pennsylvania; one hospital and one health maintenance organization in Boston, Massachusetts; and one hospital in Halifax, Nova Scotia. The study was conducted from October 1991 through March 1994. More than 12,502 patients with a diagnosis of pneumonia were screened to enroll these 2287 patients.

Symptoms at Presentation

Table 1 presents the symptoms for three groups of patients with pneumonia. Patients from the Halifax study (Marrie et al., 1989) are divided into those with CAP and those with nursing home-acquired pneumonia (nursing homes are part of the community). There is a wide spectrum of physical impairment among residents of nursing homes, from full function to an incapacitated state. The nursing home setting closely mimics the hospital setting and for this reason some authorities do not consider nursing home-acquired pneumonia as being community-acquired.

From a review of Table 1 it is evident that despite temporal, geographic, and some methodological differences in the studies, the symptoms recorded for patients with pneumonia are remarkably similar. The nursing home patients have much lower incidence of most symptoms except myalgia. Also noteworthy from the data in Table 1 is the number and frequency of extrarespiratory symptoms. About 25% of the patients complained of vomiting. This may preclude treatment with oral antibiotics and necessitate hospital admission or home intravenous therapy until vomiting subsides. Fatigue was a prominent symptom (90.1%) in the study by Fine and co-workers (1998). Age has a considerable influence on symptoms at presentation. Metlay et al. (1997c) divided 1812 patients with CAP into four age groups: 18 through 44 years (43%), 45 through 64 years (25%), 65 through 74 years (17%), and 75 years or older (15%). For 17 of the 18 recorded symptoms there were significant decreases in reported prevalence with increasing age ($p < .01$). For example, the prevalence of cough was 90% in the youngest age group and 84% in the oldest. Other symptoms that differ in prevalence in the youngest and oldest age groups, respectively, include dyspnea (75% and 64%); sputum production (64% and 64%); pleuritic chest pain (60% and 31%); hemoptysis (19% and 12%); fatigue (83% and 84%); fever (85% and 53%); chills (85% and 52%); anorexia (77% and 64%); sweats (83% and

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Symptoms of Patients with Community-Acquired Pneumonia Requiring Hospitalization

	Marrie et al., 1989 (n = 588)	Marrie et al., 1989 (n = 131)[a]	Fine et al., 1998 (n = 1343)
Cough	82%	62%	78.8%
Productive cough	60%	34%	59.7%
Fever	68%	64%	71.4%
Anorexia	61%	43%	70.2%
Chills	51%	16%	64.1%
Pleuritic chest pain	39%	18%	39.4%
Headache	29%	10%	44.1%
Nausea	29%	15%	41.8%
Myalgia	27%	43%	39.9%
Vomiting	22%	18%	28.5%
Sore throat	19%	8%	NS
Arthralgia	16%	3%	NS
Abdominal pain	12%	11%	23.8%
Diarrhea	11%	7%	25.3%
Dyspnea	NS	NS	75.2%
Hemoptysis	NS	NS	14.4%
Fatigue	NS	NS	90.1%

NS, not stated
[a]Patients with nursing home-acquired pneumonia.

45%); headache (72% and 36%); myalgia (67% and 25%); nausea (48% and 31%); sore throat (45% and 27%); inability to eat (31% and 14%); vomiting (29% and 21%); diarrhea (29% and 21%); and abdominal pain (27% and 18%).

Table 2 presents the physical signs recorded for these three groups of patients. No comparisons can be made with Fine's 1998 data, since the same parameters were not reported for both studies. Hypothermia and hyperthermia were present in only 1% and 1.3% of the patients, respectively. About 80% of the patients had an oral temperature reading of >37°C at presentation. Crackles were present on auscultation in 80% of patients, and rhonchi in 34% to 47% (more common in the nursing home patients). About 25% had the physical findings of dullness to percussion, bronchial breathing, whispered pectoriloquy, and aegophony. Alteration in mental status was common. Marrie and coworkers (1989) reported confusion in 48% of the patients with nursing home-acquired pneumonia and in 30% of the other patients with CAP. Fine and colleagues (1998) define altered mental status as stupor, coma, or confusion representing an acute change from the usual state prior to presentation with pneumonia. This was present in 17.3% of the hospitalized patients. The marked difference in mental status change found in the two studies likely reflects differences in study design.

In contrast to a decrease in symptoms with increasing age, tachypnea increased with increasing age (Metlay et al., 1997c). Thirty-six percent of 780 patients with CAP in the 18–44 year age group had tachypnea on admission versus 65% of the 280 patients who were ≥75 years old. There were minimal differences in the proportion of patients with tachycardia and hyperthermia in the different age groups.

Accuracy of Clinical Findings for Diagnosing CAP

Metlay et al. (1997b) searched the English-language medical literature from 1986 through October 1995 to try and answer the question posed above. From previous studies it is known that there is considerable variation in the recording of symptoms (Cochrane et al., 1951). This variation can be eliminated by use of standardized questionnaires for documenting symptoms. Studies of reliability among 24 physicians in the examination of 24 pa-

TABLE 2. Signs in Patients with Community-Acquired Pneumonia Requiring Hospitalization

	Marrie et al., 1989 (n = 588)	Marrie et al., 1989 (n = 131)[a]	Fine et al., 1998 (n = 1343)
Temperature >37°C	78%	80%	NS
Temperature <35°C	NS	NS	1.0%
Temperature ≥40°C	NS	NS.	1.3%
Crackles	78%	80%	NS
Rhonchi	34%	47%	NS
Consolidation	29%	24%	NS
Respiratory rate ≥30/min	NS	NS	23% (305/1328)
Heart rate ≥125/min	NS	NS	13% (174/1338)
Systolic blood pressure <90 mm Hg	NS	NS	3.4% (45/1337)
Confusion	30%	48%	NS
Altered mental status	NS	NS	17.3%

NS, not stated
[a]Patients with nursing home-acquired pneumonia.

tients with a variety of respiratory conditions revealed poor inter-observer agreement (Spiteri et al., 1988). For example, there was 75% agreement on the finding of dullness to percussion, 79% for wheezes (rhonchi), 72% for crackles, 85% for increased tactile fremitus, and 63% for tachypnea. The next question is, can a combination of symptoms and signs reliably predict the presence or absence of pneumonia? Metlay et al. (1997b) reviewed three prediction rules for pneumonia diagnosis. These rules did not perform well. They concluded that a chest radiograph must be performed if diagnostic certainty is required in the management of a patient with suspected pneumonia. However, even the gold standard of chest radiography is somewhat tarnished in that there is 79% agreement among radiologists on the presence of pneumonia (Albaum et al., 1996). Agreement on the pattern of infiltrates and the presence of air bronchogram was also poor.

Comorbid Illnesses in Patients with CAP Who Require Admission to Hospitals

Patients who require admission to hospitals for treatment of CAP are generally older adults. Marrie et al. (1989) reviewed 19 studies published from 1960 through 1989 of patients with CAP requiring hospitalization; 14 of these studies provided the mean age of the patients studied. The mean age ranged from 40 years to 80.8 years. Many of the older patients were from a nursing home. Chronic obstructive pulmonary disease was present in 33.9% of the patients studied by Fine et al. (1998). Other comorbidities included coronary artery disease, 25%; alcohol or intravenous drug abuse, 25%; cancer, 17.8%; congestive heart failure, 16.8%; neuromuscular or musculoskeletal disorder, 16.3%; diabetes mellitus, 14.7%; cerebrovascular disease, 14.2%; immunosuppression, 12.1%; renal disease, 10.4%; dementia, 10%; and seizure disorder, 5.6%. Indeed, in this study only 14.4% of the patients had no comorbidity. Many of these comorbidities, such as chronic obstructive pulmonary disease, congestive heart failure, and coronary artery disease, are aggravated by pneumonia. In turn, many of the comorbidities may result in more severe manifestations of pneumonia such as chronic obstructive pulmonary disease, immunosuppression, cancer, and diabetes mellitus. A large administrative database study of patients with CAP admitted to 193 Pennsylvania hospitals in 1991 by Lave et al. (1996) gives a good overview of patient demographics in this population of 36,222 patients: 52.3% were female and 69.9% were aged > 65 years; 10.7% were admitted from nursing homes and 73.9% were admitted through the emergency room; and 26% had three or more concomitant illnesses.

The white blood cell count was increased to

$>11{,}000 \times 10^9$/L in 57.2% of patients with CAP requiring admission to hospitals (Fine et al., 1998). Just over 10% were thrombocytopenic (platelet count $<150 \times 10^9$/L); 6.9% had serum glucose elevated to ≥13.9 mmol/L; 6.2% had a serum sodium <130 mmol/L; 27.6% had a serum creatinine level aggravated by pneumonia (≥133 μmol/L); 914 of 1343 patients (68.1%) had a blood gas analysis at the time of presentation; 36.7% were hypoxemic with a $PO_2 \leq 60$ mm Hg. Pulse oximetry was carried out in 914 patients; 26.9% had an oxygen saturation of ≤90%. Only three patients (0.2%) admitted to hospitals for treatment of CAP had no laboratory tests. In contrast, 47.8% of patients treated on an ambulatory basis had no laboratory tests performed.

Seventy-one percent of the inpatients had blood cultures performed prior to antibiotic therapy; 8.6% were positive for a pathogen (Fine et al., 1998). Just over half the patients, 58%, had a sputum specimen processed for culture within 48 hours of presentation. Acute- and convalescent-phase serum samples were collected from 13.5% of the patients. Pleural fluid was obtained for culture in 61 of 1343 (4.6%) patients—5 of the 61 patients (8.2%) had a positive culture.

Outcomes

The mortality rate for CAP requiring hospitalization ranged from 2% to 40% in the 14 studies reviewed by Marrie et al. (1989). The 40% mortality rate was reported for patients with nursing home-acquired pneumonia. The 2% rate was reported in a study of 100 patients with pneumonia, but the mortality rate was given for 188 patients (Fekety et al., 1971). The mortality rate in published studies is a function of the patient population, which, in turn, depends on the inclusion and exclusion criteria used in the study. In the study by Marrie et al. (1989) the mortality rate was 21.1%, whereas in Fine's 1998 study it was 8%. It is noteworthy that there was no difference in site-specific mortality in the Fine study; in Halifax, the mortality rate was similar to the rates reported in Boston and Pittsburgh. However, all patients admitted with CAP were included in Marrie's study whereas in Fine's study, only 2287 of the 12,502 patients with an admission diagnosis of pneumonia were enrolled in the study.

A pneumonia-specific severity of illness score would allow for comparison among cohorts of patients with CAP. Fine et al. (1997) described such a scoring system; this system stratified patients into one of five risk classes, Class I being the lowest risk group and class V being the highest risk group. Classes I, II, and III had a mortality rate of 1.2% ranging from 0.5% for class I patients to 1.2% for class III patients. In contrast the mortality rate for class IV patients was 9% and for class V patients it was 27.1%. The mortality rate in Lave's study of 36,222 patients was 11.6% (Lave et al., 1996).

Complications

The major complications occurring in patients with CAP who require admission to hospitals are respiratory failure, congestive heart failure, shock, anemia, *Clostridium difficile*-associated diarrhea and colitis, pneumothorax, nosocomial pneumonia, renal insufficiency, rash, and stroke or transient ischemia attack (Fine et al., 1998). Thirty-one percent of patients who were admitted with pneumonia had no complications (Fine et al., 1998).

Resolution of Symptoms

Metlay et al. (1997a) studied 576 adults with CAP. They noted the presence and severity of cough, fatigue, dyspnea, sputum, and chest pain at presentation and again at 7, 30, and 90 days after presentation. Ninety days after presentation, 57% of the patients reported fatigue, 32% cough, 28% sputum production, and 8% pleuritic chest pain. The percentage of patients who had those symptoms prior to onset of pneumonia were 29%, 16%, 10%, and 3%, respectively. It is evident that symptom resolution occurs only slowly in patients with CAP.

Pneumonia Syndromes

Atypical versus Typical Pneumonia

Atypical pneumonia is a term that arose in the 1930s to distinguish a milder form of pneumonia

that was not due to *Streptococcus pneumoniae,* the etiological agent of almost all cases of pneumonia at that time. It is likely that the atypical pneumonia cases were due to *Chlamydia psittaci.* Other causative agents include *Mycoplasma pneumoniae, Coxiella burnetii, Legionella pneumophila,* other *Legionella* species, *Chlamydia pneumoniae,* and respiratory viruses (e.g., influenza viruses A and B; parainfluenza viruses 1, 2, and 3; adenovirus; respiratory syncytial virus). Initially, atypical pneumonia was thought to be distinguishable from typical pneumonia in that the former was a milder illness with a much lower mortality rate; the prodromal illness was longer than that of typical pneumonia, and extrapulmonary manifestations such as confusion, central nervous system involvement, diarrhea, cardiac involvement, and certain laboratory findings such as hyponatremia were more common. Unfortunately none of these features can reliably differentiate pneumonia due to *S. pneumoniae* (typical pneumonia) from atypical cases.

Community-Acquired Pneumonia

Community-acquired pneumonia can be divided into a number of discrete categories that have different prognoses and a difference in the rank order of the causative pathogens: (1) nursing home-acquired pneumonia; (2) Pneumonia in the patient with human immunodeficiency virus infection; (3) Pneumonia in the immunocompromised patient (other than those with HIV infection); (4) Pneumonia in children and adolescents; (5) Pneumonia during pregnancy; (6) Pneumonia requiring admission to the intensive care units; and (7) Pneumonia due to a specific microorganism.

Cost of Treating Community-Acquired Pneumonia

Niederman et al. (1998) conducted a retrospective analysis based on national incidence data and paid claims data for patients treated for CAP to assess the frequency of services rendered and the recruiting costs. They found that the total cost of treating CAP in the United States was $8.4 billion; $4.8 billion was spent treating patients aged $\geqslant 65$ years or older. Room and board represented the largest percentage of hospital charges—26.3%; pharmacy accounted for 19.9%; laboratory services 13.2%; respiratory services 10.6%, and medical/surgical supplies 9%. The average CAP outpatient costs per visit, including diagnostics and radiology, were $74, $76, and $159 for physicians' offices, emergency departments, and outpatient departments, respectively. They also found that 71.9% of patients 64 years or younger with CAP were seen in physicians' offices, and 23.5% in emergency rooms. The corresponding percentages for those 65 years or older were 53.8% and 41.8%.

Summary

Community-acquired pneumonia is an illness with a wide diversity of clinical presentations. These presentations continue to evolve because of changes related to the host (increasing age; more people living in nursing homes; increasing numbers of immunosuppressed persons living in the community) and changes related to the causative microorganisms, including increasing prevalence of penicillin- and multidrug-resistant subspecies of *S, pneumoniae,* and the discovery of new pathogens such as Hantavirus, *C. pneumoniae,* and *Legionella* species.

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4

Laboratory Diagnosis of Community-Acquired Pneumonia

ROSS J. DAVIDSON AND KELLY S. MACDONALD

Introduction

Despite our increased understanding of the disease processes that cause community-acquired pneumonia (CAP) and recent technological advances in the laboratory, an etiological diagnosis is not determined in almost 50% of patients with CAP (Burman, 1991). Notwithstanding poor isolation rates, reasons exist for pursuing specific information about the causative process. In the face of increasing antimicrobial resistance, the identification of a specific pathogen allows the physician to better target antimicrobial therapy and ensures that inappropriate therapy is avoided. Failure to make an etiologic diagnosis may translate into increased hospitalization and morbidity due to inappropriate therapy and may contribute to antimicrobial resistance due to the use of broad-spectrum antimicrobials. These arguments, however, are countered by valid concerns that the most useful diagnostic tests are often invasive and may ultimately be nondefinitive, thus incurring both expense and patient morbidity without altering the physician's management plan. Thus, it is a challenge to both the clinician and laboratory scientist to develop diagnostic strategies that are rational in their approach to minimize both unwarranted testing and patient morbidity while at the same time maximizing information relevant to the physician's management plan.

Although a number of molecular diagnostic techniques are now available or are in development, conventional microbiological techniques such as the gram stain and culture are the mainstay of most laboratories. Regardless of the technique used for the isolation and identification of potential pathogens, several important issues must be considered. These include, but are not limited to, the sensitivity and specificity of each test, whether the morbidity that some procedures entail warrant their use, and the impact of a test result on patient management.

Sputum Gram's Stain and Culture

Traditionally, the evaluation of a Gram's stained sputum specimen has served to both identify potential pathogens and to guide the initial selection of antimicrobial therapy for patients with suspected bacterial pneumonia. The collection and microscopic examination of sputum has been used to diagnose pneumonia for decades. It remains popular today for several reasons. Sputum collection involves little risk to patients, an assessment can be completed in the laboratory within several minutes, and it is a relatively inexpensive test to perform. However, the reliability of the sputum Gram's stain and culture has been repeatedly challenged due to its relative lack of specificity and sensitivity (Neiderman et al., 1993).

Several problems are inherent to the sputum

ROSS J. DAVIDSON • Division of Microbiology, Queen Elizabeth II Health Sciences Centre, and Departments of Medicine, Pathology, and Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, B3H 1V8, Canada. **KELLY S. MACDONALD** • Mount Sinai and Princess Margaret Hospitals, and Department of Medicine, University of Toronto, Toronto, Ontario M5G 2M9, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

Gram's stain and culture. Unlike some specimens, such as a blood culture, patient cooperation is required to obtain a specimen. Many elderly and very young patients cannot produce adequate specimens. Several studies have demonstrated that almost half of patients enrolled in pneumonia trials cannot produce adequate specimens unless extraordinary methods are used to ensure its collection (Fine et al., 1991). Techniques for the induction of sputum specimens have been employed for more than 40 years. Studies have been performed to identify whether the process of induction alters the microscopic detection of potential pathogens. No statistically significant differences have been found between the microbiologic yields of induced and spontaneous sputum specimens (Fishman et al., 1994; Plouffe et al., 1998). Secondly, the quality of sputum as a specimen is highly variable. Attempts have been made to improve the clinical relevance of sputum cultures by preliminary gram stain to determine the extent of oropharyngeal contamination (Bartlett, 1974; Murray & Washington, 1975). The degree of contamination can be estimated from the proportion of leukocytes and squamous epithelial cells in the Gram's stain. The presence of neutrophils are indicative of active infection, whereas the presence of epithelial cells indicates oropharyngeal contamination. In laboratories where the screening of sputum specimens is performed, 40% to 75% of specimens are rejected (Bartlett, 1974; Lentino & Lucks, 1987).

Perhaps the biggest criticism of sputum Gram's stain or culture is that these tests cannot differentiate between potentially pathogenic organisms and the normal flora. In isolation, this criticism would appear to be valid. Critics may argue that *Streptococcus pneumoniae* is capable of colonizing the nasopharynx of otherwise healthy individuals and thus demonstration of this pathogen in sputum cannot be reliably correlated with disease. However, colonization of the upper respiratory tract of adults with *S. pneumoniae* has been relatively difficult to demonstrate in recent times (Plouffe et al., 1996). Foy and coworkers (1975) were able to isolate *S. pneumoniae* from only 1 of 63 adults older than 40 years. Thus, fear of the carrier-state should not be a deterrent in obtaining a sputum specimen. Furthermore, carriage, which is associated with a lower total number of organisms, is unlikely to result in a gram stain with more than minimal numbers of gram-positive diplococci.

Gleckman and colleagues (1988) demonstrated that a physician, when aided by the morphology of a Gram's stained sputum, could select appropriate monotherapy 94% of the time when selective, defined criteria for the microbiology of valid sputum are met. Furthermore, the negative predictive value of a Gram's stain compared with sputum culture in a study by Glaister (1991) was found to be 78%. However, a number of studies have demonstrated that the sensitivity and specificity of a sputum gram stain can range widely, from 15% to 100% (Boerner, 1982; Kalin et al., 1983; Lentino & Lucks, 1987; Thorsteinsson et al., 1975). The sensitivity and specificity of the sputum gram stain have been found to be highly operator-dependent (Kalin et al., 1983; Xiaoping et al., 1988). In addition, a significant degree of inter- and intra-reader variability exist when interpreting sputum gram stains (Cooper et al., 1998). Cooper and coworkers (1998) demonstrated that interpretation of sputum gram stain quality was highly dependent on the operator.

Taken together, the use of both a Gram's stain and culture may be useful. The Gram's stain allows a judgment about the acceptability of the specimen for culture, may provide a presumptive identification of a pathogen, and can confirm whether organisms subsequently isolated on culture correspond with those observed (Hirschman & Everett, 1979). A preliminary report of sputum gram stain findings should be communicated to the physician as soon as possible as the results may affect the choice of initial therapy. Sputum gram stains are most helpful when the results are available soon enough to influence empiric therapy. It should be noted that this is not the case in most outpatient practice settings.

When sputum culture is performed, both blood and chocolate agar media should be used. Chocolate agar will facilitate the isolation of *Haemophilus influenzae* and other fastidious pathogens. In severely ill patients admitted to hospital, the use of MacConkey agar may be warranted to aid in the isolation of gram-negative organisms.

Culturing of sputum for *Legionella pneumophila* should not be routinely performed on immunocompetent patients with CAP. Specialized media (buffered charcoal yeast extract) is required and the low pre-test probability should preclude its routine use. *Legionella* culture should be reserved for patients requiring admission to the intensive care unit (ICU); for patients whose sputum Gram's stain reveals polymorphonuclear (PMNs) but no visible

bacteria, immunocompromised patients, and patients from institutions such as nursing homes, particularly if previous cases of *Legionella* pneumonia have been identified. However, even in proven cases of *Legionella* pneumonia, the recovery rate by sputum culture is low and bronchoscopy or urine antigen detection tests for *L pneumophila* are more sensitive and specific than sputum culture (Koler et al., 1984; Stout & Yu, 1997).

For any test to be useful and cost-effective, the results of the test must have some impact on patient management. Given this, the use of the sputum Gram's stain and culture is not appropriate in all settings. Patients diagnosed with CAP, but who are otherwise healthy are generally treated in the outpatient setting, usually with a macrolide. Rarely do even the most basic investigations alter management in these patients. Marrie (1994) has demonstrated that almost 50% of patients in this group will harbor an atypical pathogen such as *Mycoplasma pneumoniae.* These agents cannot be visualized on a Gram's stain, and few laboratories have the ability to culture these organisms. Therefore the use of the Gram's stain and culture should be reserved for situations where the results will influence management decisions such as hospital admission or antibiotic choice.

Blood Cultures

For those patients sick enough to require admission to a hospital, blood cultures can be useful in establishing an etiologic diagnosis. Marrie (1994) demonstrated that approximately 10% of patients admitted to hospitals with CAP will have a positive blood culture. Similarly, Bartlett and Mundy (1995) found that 11% of patients admitted to hospitals with CAP were bacteremic. In both studies, *S. pneumoniae* accounted for 60% and 67% of positive blood cultures, respectively. In patients admitted to the ICU, the incidence of positive blood cultures ranges from 10% to 27% (Leroy et al., 1995; Moine et al., 1994). Little data exists on the incidence of bacteremia among patients with CAP treated in the outpatient setting. However, one study examined the incidence of bacteremia in outpatients diagnosed with CAP in the emergency room (Sturmann et al., 1996) and reported an overall incidence of 1.8%.

A positive blood culture in patients with CAP can establish a definitive etiologic diagnosis, particularly for *S. pneumoniae.* Thus, blood cultures should be obtained in all patients requiring admission to a hospital. For patients with CAP who are treated in the outpatient setting, blood cultures are of limited diagnostic value and are not warranted.

Bronchoscopic Methods

The introduction of the flexible bronchoscope in the late 1960s allowed direct access to the lower airway (Torres et al., 1998). Bronchoscopy is considered an invasive technique; however, retrospective surveys of more than 72,000 procedures show a low mortality rate of 0.015%, usually occurring in people with severe underlying cardiovascular disease (Hayner & Baughman, 1995). Although direct access to the lower airway can be obtained using this technique, routine bacterial cultures of secretions obtained by suction through the inner channel of the bronchoscope or by use of an unprotected brush are no more reliable than cultures of expectorated sputum (Bartlett et al., 1976; Jordan et al., 1976). Several opportunities exist for contamination of the specimen including aspiration of oropharyngeal contents related to laryngeal anesthesia, contamination of the suction channel during passage through the upper airway, and mobilization of oropharyngeal flora to the lower airway concurrent with advancement of the bronchoscope (Hayner & Baughman, 1995; Torres & EI-Ebiary, 1998). The technique of direct bronchial washing has been used in an attempt to improve the yield of bronchoscopy; however, significant growth of normal flora was still observed in volunteers (Kirkpatrick et al., 1989).

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL), in which a segment of the lung is washed with sterile fluid is a valuable diagnostic technique in certain clinical settings. The most consistent results have been obtained in the diagnosis of *Pneumocystis carinii* pneumonia in patients with AIDS. Several studies have reported diagnostic yields as high as 89%–98% (Broaddus et al., 1986; Jules-Elysee et al., 1990). Conventional histochemical stains such as methenamine silver, toluidine blue, or Giemsa are commonly used. The use of BAL in AIDS patients and in bone marrow and solid organ recipients to

diagnose cytomegalovirus (CMV) pneumonia has also been very successful (Crawford et al., 1988; Emmanuel et al., 1986; Pisani & Wright, 1992). The use of BAL has also proven to be extremely useful in diagnosing patients with mycobacterial pneumonia (Baughman et al., 1987; Xavier et al., 1990). Even in patients with negative mycobacterial sputum cultures, BAL has been reported to have a sensitivity of 85% (Xavier et al., 1990).

The use of BAL for the diagnosis of pneumonia in other settings has been less well defined. The specimen obtained from BAL may be contaminated with oropharyngeal flora when performed in nonintubated patients (Kahn & Jones, 1988; Kirkpatrick et al., 1989). In addition, standard criteria for the diagnosis of bacterial pneumonia have not been established for BAL. However, the use of cytologic screening and quantitative bacterial cultures of BAL fluid significantly increase the specificity of a diagnosis of bacterial pneumonia using BAL (Kahn & Jones, 1988; Martin et al., 1995; Meduri & Chastre, 1992; Thorpe et al., 1987). Specimens containing less than 1% squamous epithelial cells are thought to be representative of the lower airway with minimal oropharyngeal contamination. Quantitative cultures yielding greater than 10^4 cfu/mL of a microorganism are thought to be significant and indicative of a true infection rather than colonization. If gram stain criteria are used, the observation of 25% of neutrophils with intracellular organisms or more than one organism seen on cytocentrifuged BAL material at 1000 × magnification have correlated well with quantitative culture for detecting pneumonia (Chastre et al., 1995; Thorpe et al., 1987). The use of quantitative cultures from BAL specimens can be misleading since these are actually semi-quantitative in nature, and controversy exists over the appropriate cutoff to maximize sensitivity and specificity based on the organism found. Furthermore, the addition of quantitative cultures is very labor-intensive and dramatically increases the cost of culture. Since the utility of quantitative cultures has predominantly been to differentiate colonization versus infection (primarily a problem in gram-negative, nosocomial pneumonia), many laboratories do not perform quantitative BAL cultures except under defined circumstances.

The sensitivity of BAL in diagnosing pneumonia varies considerably from study to study. In a retrospective analysis of studies examining the utility of BAL for diagnosing nosocomial pneumonia, Cook and colleagues (1991) reported the sensitivity of BAL to vary between 53.3% and 100%. Based on 24 studies, the overall sensitivity of BAL was reported to be 69% ± 22%. The wide range of reported sensitivities is due in large part to differences in study design, patient populations, prior antimicrobial treatment, and the threshold value of quantitative cultures used to diagnose pneumonia. Specificity also varies widely from study to study; however, based on 22 studies, Cook and colleagues (1991) calculated a specificity of 88% ± 14%.

Protected Specimen Brush

The use of the protected specimen brush (PSB) was first reported in 1979 (Wimberly et al., 1979). This technique uses a series of cannulas to shield the PSB from oropharyngeal contamination during insertion and removal from the lower airway. A series of reports have clearly demonstrated that using the PSB technique allows the recovery of high concentrations of bacterial pathogens in most patients with clinical evidence of bacterial pneumonia, provided the patients were not receiving antibiotics at the time of the procedure (Wimberly et al., 1979, 1982). However, few studies have addressed the diagnostic value of PSB in CAP. Of the few studies that have evaluated PSB as a diagnostic tool for CAP, the results have been encouraging. Ortqvist and colleagues (1990) evaluated the diagnostic utility of PSB in 24 patients with CAP. They found that the use of the PSB significantly affected the management of this group of patients. When results of the PSB were obtained, antimicrobial therapy was modified in 19 of the 24 patients. In this study, the positive predictive value was 100% and the negative predictive value was 81%. In a separate study, the results of PSB were compared with those of BAL in 40 patients with CAP before they began antimicrobial therapy (Jimenez et al., 1993). Of the 38 organisms isolated in this study, PSB and BAL agreed on the identity of 32. The sensitivity of PSB was calculated at 70%. In a study of severe CAP, Leroy and colleagues (1995) found that the etiologic diagnosis of CAP in intubated patients was made in most cases with the aid of PSB.

Torres and coworkers (1988) found a sensi-

tivity of only 22% for PSB and BAL in CAP, compared to 72% for patients with ventilator-associated pneumonia. For patients with severe CAP, a specific microbiological diagnosis using PSB resulted in the modification of empiric therapy in only 6% of cases (Pachon et al., 1990). PSB has not been systematically compared to BAL in pneumonia due to *Pneumocystis carinii* or CMV, where BAL has been found to have particular utility. Thus, PSB cannot currently be recommended over BAL in most circumstances. Lastly, a number of reports have suggested that the use of aggressive bronchoscopic techniques does not significantly alter patient mortality (Pachon et al., 1990; Sorensen et al., 1989; Torres et al., 1991). Given the good response to empiric therapy of CAP in immunocompetent hosts, bronchoscopy should be reserved for the diagnosis of pneumonia in patients with underlying immunosuppression, in severely ill patients failing to respond to antimicrobial therapy or if the local epidemiology or patient's history leads to a suspicion of unusual pathogens (Torres & El-Ebiary, 1998).

Antigen Detection Methods

Antigen detection methodologies are commonly used in the laboratory for the diagnosis of many infections, including those of the respiratory tract. These methods have the potential to rapidly diagnose and identify potential pathogens and can be used to identify noncultivatable pathogens. Their utility is tempered however by several issues. First, several reports have suggested that both the sensitivity and specificity of some direct assays are too low to be clinically relevant (Boersma et al., 1991; Capeding et al., 1991). Secondly, the interpretation and reliability of a positive result is wholly organism-dependent. The reliability of the test depends on whether one is detecting a pathogen that may exist as commensal flora (e.g., *S. pneumoniae)* or one that is always considered pathogenic such as *L. pneumophila.* Finally, these tests can be time-intensive and costly, and so for practical purposes many laboratories resort to batching specimens, thus converting a relatively rapid procedure into one that is no more timely than conventional culture.

Antigen detection methods are available for several respiratory tract pathogens. Several methods are available for the detection of *S. pneumoniae,* including counterimmunoelectrophoresis (CICE), coagglutination (CoA) to capsular or pneumococcal C antigens, latex agglutination, and enzyme immunoassay (EIA). Antigen detection can be performed on sputum, sera, or urine. The sensitivity of these tests has been shown to range from approximately 40% to greater than 90% (Boersma et al., 1991; Capeding et al., 1991; Holmberg et al., 1985; Holmberg & Krook, 1986; Ortqvist et al., 1989). EIA has been shown to be no more sensitive than other methods, and many investigators have concluded that the complexity of the test mitigates its routine use in the clinical laboratory. The high cost of sputum pneumococcal antigen detection systems and the lack of studies showing a clear benefit in patient outcome should preclude their routine use for the diagnosis of CAP (MacDonald et al., 1994). In addition, detection of *S. pneumoniae* antigens in sera and urine by CICE, latex, or CoA have not shown adequate sensitivity to be considered clinically useful at this time (Boersma et al., 1991; Capeding et al., 1991).

For *H. influenzae,* antigen detection methods have only been developed for type B *H. influenzae* (Hib). Several factors argue against the routine use of this test. Detection methods for Hib have been subject to many of the problems associated with *S. pneumoniae.* Secondly, Hib is responsible for a very small minority of pulmonary infections in adults, and with the introduction of the Hib vaccine, this number has been reduced even further. Thus, antigen detection of Hib in sputum cannot be recommended as a routine test.

Antigen detection systems for diagnosis of respiratory tract disease are probably best suited for the detection of *L. pneumophila.* Several commercially available kits are available to detect *L. pneumophila* serogroup 1 antigen in urine. Depending on the locale, serogroup 1 is responsible for 70% to 90% of all cases of Legionnaires' disease (Reingold et al., 1984). Radioimmunoassay (RIA), EIA, and latex kits have been developed. RIA, although reported to have a sensitivity of 80% to 99% and a specificity of 99%, relies on the use of radioisotopes and thus has limited popularity. A commercially available EIA method reportedly has a sensitivity of 98% and a specificity approaching 100% and is capable of detecting soluble antigen in urine ap-

proximately 3 days after onset of symptoms. The high specificity is absolutely essential for *L. pneumophila* as this organism is relatively uncommon and even a low percentage of false positives would greatly reduce the positive predictive value. Use of a urinary antigen detection system for *L. pneumophila* such as EIA offers several advantages over other conventional methods. Culture, while relatively sensitive in experienced hands, is fraught with quality-control problems in laboratories with less experience. Urinary antigen detection for *L. pneumophila* using EIA can be automated, eliminating many quality-control concerns; it is relatively rapid; and it only involves obtaining urine, a noninvasive specimen. More importantly, the sensitivity, specificity, and rapidity of the urinary antigen detection method for *L. pneumophila,* unlike those for *S. pneumoniae* or *H. influenzae,* may affect patient outcome by reliably detecting or excluding *L. pneumophila* infection. Direct fluorescent antigen (DFA) kits for detection of *Legionella* spp. in sputum reportedly lack sensitivity (25% to 75%), and their specificity is highly operator-dependent (Edelstein, 1993). Their sensitivity is extremely dependent on a high microbial load, they are time-consuming, and they require technical expertise to perform. Their primary advantage is speed. In areas of low disease prevalence, the positive predictive value of these tests is unacceptably low and the routine use of sputum antigen detection for the diagnosis of CAP should be avoided (Edelstein et al., 1980; Pasculle et al., 1989).

Routine antigen detection for *Chlamydia pneumoniae* in respiratory specimens is still in its infancy, although promising results are obtained using an EIA system. The sensitivity and specificity of one EIA method are reported to be 91% and 99%, respectively (Sillis et al., 1992). A major drawback to this system is the lack of a genus-specific EIA, so *C. trachomatis* and *C. psittaci* may be detected in addition to *C. pneumoniae* if present in respiratory secretions. EIA systems have not yet been widely studied and so cannot be recommended for routine diagnosis of *C. pneumoniae* at present.

DFA kits with monoclonal antibodies specific for *P. carinii* are commercially available for use with either BAL or sputum specimens. These tests have the advantage of being rapid and highly sensitive (90% to 97%). The sensitivity of the DFA is greater in BAL than sputum specimens. Their specificity is operator-variable and a high degree of technical expertise is required to avoid false-positive results. They may be more sensitive than conventional histochemistry in diagnosing *Pneumocystis* pneumonia in settings with a lower load of organisms such as patients on chemoprophylaxis or in bone marrow transplant patients (Cregan et al., 1990).

Serology

The serological diagnosis of CAP is primarily retrospective and plays a limited role in establishing an etiology during the acute illness. The primary use of serology in the setting of CAP is to confirm a diagnosis and for epidemiological studies.

Several serologic assays have been developed for the detection of antibodies against four pneumococcal antigens, including pneumococcal C polysaccharide, capsular polysaccharide, phosphorylcholine, and pneumolysin. Sensitivities of 89% and 97% for the capsular and pneumococcal C polysaccharides have been reported (Burman et al., 1991).

Serologic assays have also been developed to detect an immune response to other respiratory pathogens such as *L. pneumophila* and *L. micdadei, M. pneumoniae, Chlamydia* spp., and *Coxiella burnetii.* The sensitivities and specificity of these serological assays vary significantly and many have not been standardized. Thus these assays should be reserved for epidemiological studies or to confirm a diagnosis of CAP and should not routinely be employed to diagnose acute illness.

The most widely used test to diagnose *C. pneumoniae* is the microimmunofluoresence (micro-IF) assay. The test is considered positive when a 4-fold rise in titer (acute vs. convalescent serum) is seen, or a single IgM titer of $\geqslant$16, or a single IgG titer of $\geqslant$512 is observed (Grayston, 1989). Care should be taken in the liming of retrieval of the convalescent serum specimen. The micro-IF assay may not show an increase in titer until 4 weeks' duration (Ekman el al., 1993). Depending on the gold standard used as a comparison, the sensitivity and specificity of the micro-IF can vary between 39% to 100% and 94% to 100%, respectively (Verkooyen et al., 1998). Complement fixation (CF) methods and EIA have

also been developed for the diagnosis of C. *pneumoniae.* The CF test is considered positive when a 4-fold rise in titer (acute vs. convalescent serum) is observed; however the test lacks the sensitivity of the micro-IF assays. Experience with EIA is limited. The major drawback for the use of EIA in the diagnosis of *C. pneumoniae* is their limited reliability in measuring IgM.

Several methods have been developed for the serological diagnosis of *M. pneumoniae.* CF is often considered a reference method for serological diagnosis of *M. pneumoniae* infections. However, CF suffers from the major disadvantage that it cannot distinguish between antibody classes. The demonstration of seroconversion with paired sera collected 2 to 4 weeks apart provides the optimum diagnostic accuracy by CF (Fedorko et al., 1995; Sillis, 1990). The indirect hemagglutination assay has proven to be consistently more sensitive for the diagnosis of *M. pneumoniae* than CF, however, specificity remains a problem (Kok et al., 1989). Early-generation EIAs proved to be superior to CF in both sensitivity and specificity; however, they could still not differentiate among antibody classes (Fedorko et al., 1995; Thacker & Talkington, 1995). Recently, several newer-generation immunoglobin class-specific EIAs have been developed (Cimolai & Cheong, 1996; Thacker & Talkington, 1995). The immunocard (Meridian Diagnostics, Cincinnati, OH) is a simple and rapid assay; however, in some adults with a minimal IgM response, the sensitivity of the assay may not be adequate enough to detect a *M. pneumoniae* infection (Alexander et al., 1996). From a serological standpoint, the only test for *M. pneumoniae* capable of influencing patient care is IgM detection. From a practical standpoint, a positive test assists diagnosis, but a negative test does not rule out infection. Therefore this test should be ordered only in situations where the results will influence therapy.

In summary, the laboratory of the 21st century is faced with an expanding menu of rapid and molecular diagnostic tests for diagnosing pneumonia, but fiscal resources have not expanded and in some cases have contracted. As such, a more rational approach to the use of the laboratory and the diagnosis of CAP must be employed. In cases of mild illness, the most valid approach may be little or no microbiological work-up and empiric treatment, reserving scarce resources for more expensive procedures and diagnostic assays when warranted by the patient's underlying immunological profile, severity of illness, or response to empiric therapy.

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5

Polymerase Chain Reaction Techniques in the Diagnosis of Pneumonia

BARRY S. FIELDS

Introduction

Approximately one half of the cases of pneumonia and lower respiratory infection are treated empirically, and no etiologic agent is identified (Bartlett et al., 1998). This represents approximately 250,000 cases of pneumonia annually in the United States for which treatment is not pathogen-directed (Centers for Disease Control and Prevention, 1997). Unfortunately, pneumonia is often treated empirically to prevent delays in the initiation of treatment and because an adequate diagnostic test is not available. This practice is partly responsible for the marked increase in penicillin-resistant *Streptococcus pneumoniae* in the last 10 years (Hofmann et al., 1995). These factors illustrate the need for rapid diagnostic tests to identify the etiologic agents of pneumonia. Currently, the laboratory test most likely to allow rapid diagnosis is polymerase chain reaction (PCR). Although PCR is routinely used in most medical laboratories for various procedures, this technique is not relied upon for diagnosis except for a few agents. This is partly due to the lack of studies that thoroughly evaluate PCR and compare the procedure to gold standard tests. PCR is particularly appealing as a potential diagnostic test for the "atypical" agents of pneumonia, namely, *Chlamydia, Legionella,* and *Mycoplasma pneunumiae.* Historically, a pneumonia patient's illness has been categorized as typical or atypical to characterize the presentation of disease. This diagnostic approach generally led to the prescribing of β-lactam antimicrobial drugs for the treatment of typical pneumonia and macrolides for the treatment of atypical pneumonia. This practice is no longer encouraged and the Infectious Disease Society of America (IDSA) has recently published more specific guidelines for patient management (Bartlett et al., 1998). These organisms are extremely fastidious and may be considerably underdiagnosed. The specific difficulties in the diagnosis of each of the agents are discussed in the following sections.

BARRY S. FIELDS • Division of Bacterial and Mycotic Disease, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Chlamydia pneumoniae

C. pneumoniae is now recognized as an important cause of respiratory infections including pneumonia, bronchitis, and sinusitis (Kou et al., 1995). More recently the bacterium has been associated with bronchial asthma and coronary artery disease based on serologic and PCR data. *C. pneumoniae* is implicated in 5% to 15% of cases of community-acquired pneumonia (CAP) although the prevalence is reported to vary from year to year (Marrie et al., 1989; Fang et al., 1990; Marston et al., 1997). Diagnosis of *C. pneumoniae* infection is usually

based on serologic evidence while PCR and culture are used less frequently. The recommended serologic test is a microimmunofluorescence (MIF) test (Kauppinin & Saikku, 1995). This assay has replaced the cumbersome complement fixation (CF) test, but MIF remains labor-intensive and is associated with problems in interpretation and specificity.

C. pneumoniae is an intracellular pathogen and must therefore be grown in cell culture. A nasopharyngeal swab is the preferred specimen for the isolation of these bacteria although they have been isolated from pharyngeal swabs and respiratory secretions (Kauppinin & Saikku, 1995). The procedure entails inoculation of a cell line (usually HEp-2 cells) with the patient specimen in a medium containing selective antibiotics to suppress overgrowth by normal flora and to inhibit HEp-2 cell protein synthesis (Wong et al., 1992). This procedure requires 3 to 7 days' incubation and frequently requires that the material be subcultured (blind passes) multiple times. Positive cultures must be visualized by direct fluorescent antibody staining. Because these techniques can be cumbersome, only a limited number of research laboratories routinely culture for *C. pneumoniae.*

A number of PCR assays have been described for the detection of *C. pneumoniae.* This partly reflects the difficulty in diagnosing this infection by other techniques and a general lack of rapid, sensitive, or specific tests. Most of the published PCR assays target either 16S rRNA, the major outer membrane protein (MOMP), or a 437-bp target sequence of unknown function (Cambell et al., 1992; Gaydos et al., 1992; Sillis et al., 1992; Gaydos et al., 1993, 1994; Pruckl et al., 1995; Dalhoff & Maass, 1996; Khan & Potter, 1996; Wilson et al., 1996; Boman et al., 1997; Gnarpe et al., 1997; Messmer et al., 1997). The PCR assays vary in the use of nested primers and the method of amplicon detection. Gaydos and coworkers (1993) described a method to detect the PCR amplicon based on an enzyme-linked detection system (PCR-EIA). Modifications involving a nested, single-tube PCR assay have been subsequently published (Gaydos et al., 1994). Boman et al. (1997) described the use of nested, touchdown PCR to detect *C. pneumoniae* and *C. psittaci.* A 1994 comparison of culture, PCR-EIA, and single-point (acute) serology indicated that the sensitivity of PCR-EIA was 76.5% and the sensitivity of culture was 87.5% with both procedures far superior to single-point serology (Gaydos et al., 1994). Other reports on the sensitivity and specificity of PCR assays have varied widely, ranging as high as 100%. Unfortunately many of these studies have incorporated small populations or limited numbers of control patients, and a thorough evaluation of the PCR assays has not been completed. The difficulties and approaches to such evaluations will be discussed later in this chapter.

Legionellae and *Legionella pneumophila*

Legionella species cause two forms of respiratory disease in humans—Legionnaires' disease and Pontiac fever—that are collectively termed legionellosis (Helms et al., 1979). Legionnaires' disease is a pneumonic infection and is implicated in 2% to 6% of CAP cases (Fine et al., 1996; Marston et al., 1997). Because the routine use of diagnostic tests is not advocated and the tests that are available are primarily specific for *L. pneumophila* serogroup 1, these figures may underestimate the number of legionellosis cases. *L. pneumophila* serogroup 1 is implicated in approximately 80% of legionellosis cases; however, this figure may be high since other species of legionellae are more fastidious and there are limited diagnostic reagents specific for these organisms (Marston et al., 1994).

Legionellae are facultative intracellular bacteria that multiply within freshwater protozoa in the environment and within phagocytic cells of humans (Fields, 1996). Although the bacteria are considered fastidious, they grow on a complex agar medium and are the least difficult atypical agents to isolate from clinical specimens. Legionellae are cultured on buffered charcoal-yeast extract agar enriched with α-ketoglutarate both with and without selective agents (Edelstein, 1981). Culture diagnosis remains the gold standard for legionellosis and is a sensitive procedure when appropriately performed early in the course of disease (Edelstein, 1993). The bacteria survive poorly in respiratory secretions, and immediate culture of these specimens is critical. The reported sensitivity of culture isolation from respiratory secretions ranges widely, from 20% to 80%, reflecting the perishable nature of

these specimens and the expertise required to isolate them (Roig et al., 1994). Legionellae can be isolated from a number of specimens including blood, tissue, respiratory secretions (sputum or bronchial alveolar lavage [BAL]), and stool (Edelstein, 1993; Rowbotham, 1998). Respiratory secretions are considered the specimens of choice. Culture of the organism requires up to 10 days and is not appropriate for acute diagnosis.

Diagnosis of acute legionellosis can be accomplished using either direct fluorescent antibody staining (DFA) or testing for *L. pneumophila* serogroup 1 antigenuria. The sensitivity of DFA ranges from 25% to 70% (Edelstein, 1993). The specificity of this test is reported to be approximately 99%, although a number of other bacteria have been shown to cross-react with anti-*L. pneumophila* serum. The *Legionella* urine antigen test has proven to be an extremely valuable test for the diagnosis of acute *L. pneumophila* serogroup 1 infections (Kohleretal., 1981,1985;Plouffe et al., 1995). The test is commercially available as either an enzyme immunosorbent assay (EIA) or as an immunochromatographic test (ICT). The EIA has a sensitivity of 97% and a specificity of 100% and requires 3 hours to complete (Plouffe et al., 1995). The ICT has a sensitivity of 95% and specificity of 95% and can be performed in 15 minutes and requires no specialized equipment or expertise. Both tests are limited to detecting infections due to *L. pneumophila* serogroup 1. Use of the urine antigen tests has led to more efficient diagnosis of legionellosis as well as more rapid detection of outbreaks of this illness (Lepine et al., 1998).

PCR represents one of the few diagnostic tests with the potential to detect infections caused by all of the known species of legionellae. Currently there are 42 species representing 64 serogroups of legionellae (Benson & Fields, 1998). Approximately one half of these have been associated with human disease. Since most conventional tests only detect infections due to *L. pneumophila* serogroup 1, an accurate PCR test would greatly enhance the ability to diagnose these infections. PCR tests have been developed for legionellae that target random DNA sequences, 5S rRNA genes, 5S tRNA genes, 16S rRNA genes, and the *mip* gene (Starnbach et al., 1989; Mahbubani et al., 1990; Ramirez et al., 1996). The most widely used test has been a commercially produced kit designed to detect legionellae in the environment (EnviroAmp kit, Perkin-Elmer, Inc., Foster City, California). This test was removed from the market in 1997. It simultaneously amplified two targets: a 5S rRNA target specific for the *Legionella* genus and a portion of the *mip* gene specific for *L. pneumophila.* The kit was designed for testing environmental samples, and the manufacturers did not attempt to have it approved for clinical use. Nevertheless, several researchers successfully used these kits to detect legionellae DNA in human specimens. A very limited number of laboratories test for legionellae by PCR at this time. The few studies that have been conducted indicated that the PCR detection of legionellae infections has a moderate sensitivity and a high specificity. Legionellae DNA has been detected in respiratory secretions, pharyngeal swabs, nasopharyngeal swabs, peripheral blood mononuclear cells (PBMC), urine, and serum (Murdoch et al., 1996; Ramirez et al., 1996; Matsiota et al., 1997). Ramirez and coworkers (1996) reported a sensitivity of 83% for throat swabs tested by PCR to detect legionellae.

Mycoplasma pneumoniae

M. pneumoniae is a common cause of respiratory tract infections including pharyngitis, tracheobronchitis, and pneumonia. The percentage of hospitalized cases of CAP due to *M. pneumoniae* infection is reported to range from 2% to 30%, with most reports citing rates between 12% and 19% (Foy et al., 1979; Marston et al., 1997; Bartlett et al., 1998). Although this infection occurs most commonly in children aged 5 to 9 years, recent studies have shown a higher prevalence than predicted in older adults. There appears to be a seasonal distribution, with most cases occurring in spring (March-April).

M. pneumoniae infections are particularly difficult to diagnose due to the lack of reliable tests. An IDSA expert panel concluded that treatment of these infections usually must be empirical because there is no test that will reliably and rapidly detect *M. pneumoniae* infection (Bartlett et al., 1998). Diagnosis usually is based on serologic tests which can require from 3 to 4 weeks for elevation of antibody titers. Traditionally, serologic diagnosis of

M. pneumoniae was accomplished by the CF test and cold agglutinin titers (Taylor-Robinson et al., 1996). The tests are not sensitive or specific, and the CF test is labor-intensive. Several rapid commercial serologic tests are now available (Thacker & Talkington, 1995). These tests are faster and less technically demanding, but it is not evident that they offer improved sensitivity or specificity.

Culture for *M. pneumoniae* is not sensitive and is time-consuming (Ieven et al., 1996). The procedure entails serial passes, and dilution of the specimen and the result cannot be labeled negative until after 3 to 9 weeks' incubation. PCR is promising as a diagnostic test for *M. pneumoniae* given the inadequacy of the traditional tests (Ieven & Goossens, 1997). PCR tests have been developed for *M. pneumoniae* that target the P1 adhesion protein, the 16S rRNA gene, and a DNA sequence specific for *M. pneumoniae* (Inamine et al., 1988; Van Kuppeveld et al., 1994; Ieven et al., 1996; Gnarpe et al., 1997; Luneberg et al., 1993). These assays have been either single-step or nested protocols and some procedures have employed probes to confirm the amplified products. Studies evaluating PCR versus other diagnostic tests are limited. Several studies report high sensitivity (90%–94%) and specificity (97%-100%) for PCR (Skakni et al., 1992; Van Kuppeveld et al., 1994; Ievens et al., 1996; Ievens & Goossens, 1997; Luneberg et al., 1993). As with the other atypical agents, there is a striking paucity of data on the utility of PCR in detecting *M. pneumoniae* in a clinical setting.

PCR-Based Epidemiology of Community-Acquired Pneumonia

The NAPES Project

Much of the data discussed in the remainder of this chapter are derived from the North American Pneumonia Etiology Study (NAPES). The goal of this study is to obtain information to characterize the epidemiology, geographical distribution, and the value of newer diagnostic tests for etiologies of CAP in North America. Results of this joint effort between Pfizer, Inc., and the CDC will provide important information on the etiology of CAP. Pfizer, Inc.. established access to a network of clinics and providers with a large patient population across North America. The study uses 38 of these investigational sites in the United States and Canada and has enrolled approximately 1000 patients. Clinical samples and specimens obtained from 1000 patients who participated in the study were forwarded to the CDC for testing. Demographic and medical history data were collected and will be merged with laboratory data generated at the CDC. The first 800 patients who presented with clinical and radiographic documentation of CAP, who were at least 16 years of age, required initial hospitalization for the treatment of pneumonia, had not been hospitalized within the preceding 14 days, and gave written informed consent to the study were enrolled. Baseline respiratory specimens, sera, blood, and urine from each patient were collected and forwarded to the CDC (Table 1).

Sputum (or other deep respiratory specimen and/or pleural fluid), nasopharyngeal (NP) swabs, oropharyngeal (OP) swabs, and whole blood were obtained at baseline from all patients and tested by PCR for *M. pneumoniae, C. pneumoniae,* and *L. pneumophila.* Sputa or other deep respiratory specimens were cultured for *Legionella.* Acute and convalescent sera from all patients were tested to detect antibodies to *M. pneumoniae, C. pneumoniae,* and *L. pneumophila.* The Remel serological test (Thacker & Talkington, 1995) was used to deted antibodies to *M. pneumoniae,* MIF testing (Kauppinen & Saikku, 1995) was used to detect antibodies to *C. pneumoniae,* and indirect IFA testing (Wilkinson, 1988) was used to detect antibodies to *L. pneumophila* serogroup 1. Urine specimens were tested using the Binax *Legionella* urinary antigen radioimmunoassay or E1A (Equate test). Sputum specimens were frozen as soon as possible after collection and shipped on dry ice to the CDC laboratory for testing. Both NP and OP swabs were placed in M4-3 medium for the transport of viruses, *Chlamydia, Mycoplasma,* and *Ureaplasma* (Micro Test, Inc.). Whole blood was collected in EDTA tubes containing ethylenediaminetetraaceticacid (Becton Dickinson Vacutainer Systems). Whole blood, NP swabs, and OP swabs were shipped to the CDC laboratory at 4°C and were tested within 72 hours of collection. Serum and urine specimens were shipped frozen on dry ice for subsequent testing at the CDC laboratory.

TABLE 1. Specimens and Transport Used in the North American Pneumonia Etiology Study

Specimen	Test	Organism	Collection	Transport
Whole blood (for harvesting buffy coat)	PCR	*C. pneumoniae* *Legionella* spp. *M. pneumoniae*	5 mL collected in a purple top (EDTA) tube	Overnight at 4°C
Serum	Serology—MIF IFA Remel	*C. pneumoniae* *L. pneumophila* serogroup 1 *M. pneumoniae*	5 mL acute 5 mL convalescent red top tube	Frozen on dry ice
Sputum	PCR Culture	*C. pneumoniae* *Legionella* spp. *M. pneumoniae* *Legionella spp.*	Freeze at bedside	Frozen on dry ice
Nasopharyngeal swab	PCR	*C. pneumoniae* *Legionella* spp. *M. pneumoniae*	M4-3 transport medium (MicroTest, Inc.)	Overnight at 4°C
Pharyngeal swab	PCR	*C. pneumoniae* *Legionella* spp. *M. pneumoniae*	M4-3 transport medium (MicroTest, Inc.)	Overnight at 4°C
Urine	Urine antigen test (Binax Inc.)	*L. pneumophila* serogroup 1	Refrigerate	Overnight at 4°C

PCR, polymerase chain reaction; EDTA, ethylenediaminetetraacetic acid; MIF, microimmunofluorescence; IFA, immunofluorescence assay.

Criteria for establishing infection with a specific etiologic agent were as follows: for *L. pneumophila* and *C. pneumoniae,* a 4-fold rise in IgG was considered diagnostic. In addition, a standing IgM titer of 1:16 or more was considered indicative of *C. pneumoniae* infection. The Remel serologic test for *M. pneumoniae* is an immunoblot test and only gives a positive or negative result. The serologic definition of infection with *M. pneumoniae* was a negative acute test accompanied by a positive convalescent test. For *Legionella,* a positive urine antigen test or a positive culture was considered evidence of infection. For all three pathogens, PCR-amplified DNA was visualized using ethidium bromide labeling of DNA after electrophoresis in an agarose gel. A positive PCR test was indicated by the presence of a band of the appropriate molecular weight.

Factors in the Design and Selection of PCR Assays

The information presented here is not intended to address general approaches to PCR but issues specific to PCR for agents of CAP. The genomic targets used in the PCR assays of the NAPES project are the P1 protein for *M. pneumoniae* and a portion of the 16S rRNA gene for both *C. pneumoniae* and *L. pneumophila* (Messmer et al., 1997; Talkington et al., 1998). No studies have compared the efficacy of the various DNA targets reported in the literature to date. 16S rRNA targets were selected because there appear to be at least two copies of this gene in most bacteria and because an abundance of DNA sequence data are available on these genes. Targeting genes with a high copy number should theoretically increase the sensitivity of a PCR assay. Primer length, annealing temperature, and primer sequence affect the specificity and efficiency of the PCR. Primer length typically ranges from 15 to 30 bp and has a direct effect on the ability of the reaction to tolerate mismatches. Primers selected for assays used in the NAPES project were 18 to 23 bp in length. The annealing temperature should be similar for all primers used in the reaction. The NAPES PCR assays were performed with a standard buffer composition of 1.5 mM Mg^{2+}, 10 mM Tris, and 50 mM KCl.

The PCR assays for the detection of *Legionella* and *Chlamydia* were designed as nested PCR assays with a second (nested) set of primers that anneal internally within an amplified fragment. In a typical nested PCR protocol, a first round of amplification is performed with a single set of a primer

pair for 20 to 30 cycles. This amplified product is then transferred to a new reaction tube for a second round of amplification using a second pair of primers. The second round of amplification is performed with increased stringency in the cycling parameters. Nested PCR can offer extremely high sensitivity. However, this procedure involves open transfer of pre-amplified product and leads to periodic contamination of the second amplification. This approach is not recommended as a diagnostic procedure unless great care is taken to avoid contamination. Additional negative controls may be necessary to monitor for false-positive results.

The legionellae and *C. pneumoniae* PCR assays were combined in a single reaction, or "multiplexed." These two sets of primers require similar annealing temperatures, work within the same buffer conditions, and amplify two different bacterial DNA sequences with the same cycling parameters. This approach saves time and effort and can be advantageous when there is a small quantity of clinical specimen available. However, some experts discourage the use of multiplex PCR for clinical diagnosis because of its low sensitivity (Rolfs et al., 1992). This is the result of compromised optimization of the assay conditions to accommodate the multiple primers. In addition, inhibitory factors can have different effects on the amplification products, leading to increased false-negative results (Rolfs et al., 1992). The *M. pneumoniae* PCR assay was neither nested nor multiplexed with the assays for the other pathogens.

All of the PCR assays contained two negative controls. In one, water replaced the DNA template to ensure that no contamination was present in any of the reagents. In the second negative control, water was processed through the DNA extraction procedure and all amplification steps to ensure that no contamination occurred due to processing of the specimen. Positive controls consisted of DNA or killed cells of the representative organisms. One positive control was run with each PCR process. Specifically, the controls were 50 fg of extracted *Legionella* DNA (Qiagen, Inc.) per reaction tube, 5 fg of extracted *Mycoplasma* DNA (Qiagen, Inc.) per reaction tube, and five *Chlamydia* elementary bodies (heat-killed) per reaction tube. A separate reaction contained both *Legionella* and *Chlamydia* DNA to ensure that both products were amplified simultaneously in the multiplexed reaction.

Incidence of Pneumonia by Agent

A number of studies have investigated the incidence of pneumonia due to specific etiologic agents (Marrie et al., 1989; Fang et al., 1990; Fine et al., 1996; Marston et al., 1997). Most of these studies use serology and culture to confirm diagnosis of the specific agent. NAPES was preceded by another CDC study of pneumonia in 1991. In the 1991 study, Marston and colleagues reported the following diagnoses for these agents based on serologic testing for all three pathogens in addition to culture and urine antigen testing for *Legionella: C. pneumoniae,* definite 2.4%, total 8.9%; *Legionella* species, definite 2.4%, total 3.0%, and *M. pneumoniae,* definite 5.4%, total 32.5% (Marston et al., 1997). Preliminary analysis of the NAPES data indicates that while the percentage of pneumonia cases attributable to these pathogens by serology is comparable to that found in the previous CDC study, PCR appears to detect two to three times as many infections for each of these three organisms. More pneumonia patients had detectable DNA of these three pathogens than had detectable antibody to these same organisms. Additional analysis is ongoing which will help determine whether the higher percentage of PCR positives reflects carriage of these bacteria or whether a significant proportion of the patients fail to exhibit a detectable immune response. In addition, carriage of these organisms needs to be defined. It is possible that DNA of these bacteria could be transient in nature and not represent subclinical infection or colonization.

PCR has the capacity to detect DNA representing very low numbers of organisms and it is possible that some patients positive for *Legionella* species by PCR had low levels of the bacteria present due to recent ingestion of contaminated water. However, this would not explain the presence of *Legionella* DNA in specimens such as buffy coat. The percentage of patients positive for *Legionella* species by PCR is more than three times that detected by serology in this study and previously published investigations of pneumonia (Marrie et al., 1989; Fang et al., 1990; Fine et al., 1996; Marston et

al., 1997). However, serology is limited by the number of different legionellae antigens which can be evaluated. Most laboratories only test for antibodies to *L. pneumophila* serogroup 1 or a limited number of other serogroups of this species. The PCR assay used in this study can detect DNA from all 64 species/serogroups of legionellae and would be expected to detect more cases than the serologic test. Further analysis is required to determine whether the discrepancy between serology and PCR represents infection due to legionellae other than *L pneumophila* or false-positive PCR tests. The percentage of patients positive for *C. pneumoniae* and *M. pneumoniae* by PCR is similar to previously reported figures based on serologic testing (Foy et al., 1979; Marrie et al., 1989; Fang et al., 1990; Fine et al., 1996). The number of PCR-positive patients is approximately twice the number of patients determined to be positive by serology for *C. pneumoniae* and *M. pneumoniae* in the NAPES. Carriage of both *C. pneumoniae* and *M. pneumoniae* has been reported and may account for some of these PCR-positive patients (Hyman et al., 1995).

Comparison of DNA Detection with Gold Standard Tests

Traditionally, new diagnostic tests are compared to a gold standard test to determine the sensitivity and specificity of the new test. The problem with this approach to the evaluation of new diagnostic tests for the atypical agents is that the gold standard tests themselves suffer from poor sensitivity or specificity. In such situations, the disease status is unknown and evaluating PCR by comparing it to an imperfect gold standard will skew the results and magnify the error or bias (Elder et al., 1997). Preliminary analysis of the PCR assays used in the NAPES project suggests that this procedure has a low sensitivity and a high specificity. Other studies have reported higher sensitivity and specificity for PCR detection of *Legionella* species, *C. pneumoniae,* and *M. pneumoniae,* however, these specimens were collected in the same hospital as the testing laboratory and the lack of time in transport may greatly improve the sensitivity and specificity of PCR in clinical specimens (Ramirez et al., 1996). In the NAPES project specimens were transported from hospitals throughout North America and tested within 72 hours of collection. Further analysis should determine the effect of extended transport time on the sensitivity and specificity of PCR.

Approaches other than traditional comparison to gold standard tests may be more appropriate for the evaluation of new diagnostic tests such as PCR. One emerging approach to the evaluation of new diagnostic tests is discrepant analysis (Green et al., 1998). This form of analysis involves a new test that is to be evaluated, a gold standard or reference test that is imperfect, and an arbiter or additional test. Frequently, the arbiter test is another PCR assay using different primers. Discrepant analysis is designed to calculate the sensitivity and specificity of a new test more accurately but has some disadvantages. First, one must assume that the new test is correct and should take precedence over the gold standard test, and second, bias may be introduced depending on the degree of relatedness (termed "dependency") of the new test and the arbiter test (Miller, 1998; Schachter, 1998). An editorial on the use of discrepant analysis summarized this approach with two points of view: (1) Biologists argue that new tests are so superior that they cannot be evaluated against standard technologies; and (2) Statisticians argue that superior performance is a hypothesis and must be tested with an appropriately designed study (Miller, 1998). Currently, incorporation of PCR into the standard diagnostic repertoire is blocked by this paradox of analysis.

Data from the NAPES project will be evaluated by alternative approaches such as discrepant analysis or latent class analysis. The approach would attempt to use the same PCR test on a different specimen from the same patient as the arbiter test. For example, PCR of sputum (new test) could be evaluated against serology (imperfect gold standard test) with PCR of buffy coat as the arbiter test. However, these PCR tests are closely related and this may introduce such extreme bias that these calculations cannot be used. Another approach to the comparison of tests is to display the information graphically or in tables for a more accurate representation (Elder et al., 1997). This type of analysis (broken down by month of enrollment) showed

some agreement between *C. pneumoniae* PCR and serology, but little agreement between these 2 tests for the detection of *Legionella* and *M. pneumoniae.* Again, it is not surprising that the *Legionella* serology and PCR did not agree since the serology is specific for *L. pneumophila* serogroup 1 whereas the PCR test can detect all species of legionellae.

Additional interim analysis showed that of the 532 patients analyzed, 77 had evidence of infection with two of these three pathogens, and eight patients had evidence of infection with all three organisms. Previous studies of pneumonia have varied widely on the reported numbers of patients with evidence of infection with multiple pathogens. It is not clear if such data reflect secondary infection by multiple pathogens or false-positive test results.

Another goal of the NAPES project is to evaluate the utility of PCR on a variety of specimens to determine which, if any, are best for clinical diagnosis. Carriage of *C. pneumoniae* and *M. pneumoniae* is generally accepted, suggesting that detecting pathogen DNA in clinical specimens should not necessarily imply clinical disease due to that organism (Hyman et al., 1995). Positive results on certain specimens or combinations of specimens may or may not be indicative of infection. A list of the most frequently positive specimens for each organism is listed in Table 2. Complete analysis of the NAPES data should indicate which specimens are most valuable for diagnosis.

Conclusions

A number of PCR assays have been developed for detecting the majority of bacterial pathogens. Only a limited number of these assays have been subject to stringent evaluation for clinical diagnosis. Those that have, such as tests for *Mycobacteria* and *Chlamydia trachomatis,* are available commercially and are accepted diagnostic tests (Ieven & Goossens, 1997). The bacteria once referred to as the atypical pathogens of pneumonia are fastidious and difficult to detect. The treatment of pneumonia would greatly benefit from tests that could rapidly detect infection due to these organisms. PCR may represent such a test, but there is an overwhelming lack of data on the efficacy of PCR as a diagnostic tool for infections due to *C. pneumoniae, Legionella* species, and *M. pneumoniae.* Limited studies and preliminary data suggest that PCR may add to the diagnostic repertoire, but this procedure may lack the sensitivity and specificity to provide anything other than supplemental data for the clinician. Biologists and statisticians need to work together to develop mathematical procedures that will allow the effective evaluation of promising new molecular techniques that can replace imperfect reference tests. Additional studies are needed to evaluate the applicability of PCR to the diagnosis of pneumonia.

TABLE 2. Most Frequently Positive Specimen by Polymerase Chain Reaction

C. pneumoniae	*Legionella* species	*M. pneumoniae*
NP swab	Sputum	Sputum
OP swab/Buffy coat	NP swab	Pharyngeal swab
	OP swab	Buffy coat
Sputum	Buffy coat	NP swab

NP, nasopharyngeal, OP, oropharyngeal.

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6

Imaging Community-Acquired Pneumonia

GERRY SCHALLER AND MARK LOGAN

Introduction

Community-acquired pneumonia (CAP) is defined as pneumonia* that developed either outside the hospital or within the first 48 hours after admission (Areno et al., 1996). A chest radiograph is often included in the initial work-up of suspected pneumonia. If the imaging facility is hospital-based it is likely that a radiologist will be available to examine the films and provide a timely report. However, often the attending physician must examine the chest radiographs and rely on her or his own interpretation as part of the diagnostic work-up. Thus it is essential that every physician who treats patients with pneumonia know how to interpret a chest radiograph.

This chapter discusses diagnostic imaging as it applies to CAP. The majority of the discussion relates to standard chest radiographs as virtually all patients who require imaging require only chest radiography. It is important to note that the radiologist does not distinguish CAP from hospital-acquired pneumonia on the basis of the chest radiographs. That distinction is made on a clinical and epidemiological basis; the imaging features of pneumonia are similar for both.

*Terminology used in this chapter is in accordance with Fraser, R. G., Paré, J. A. P., Pare, P. D., Fraser, R. S., & Genereux, G. P. (1988) Glossary of words, terms and symbols in chest medicine and roentgenology, In: *Diagnosis of Diseases of the Chest,* 3rd ed. Philadelphia: W. B. Saunders Co., pp. xiii–xxx.

GERRY SCHALLER AND MARK LOGAN • Department of Diagnostic Imaging, Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, B3H 2Y9, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

The Role of the Chest Radiograph

When the clinical findings suggest that the patient has CAP, a chest radiograph enables the attending physician to confirm the clinical suspicion of pneumonia, assess the extent of the infection, detect concurrent conditions that may complicate diagnosis or management, and expedite empiric therapy decision-making (Torres et al., 1996; Conces, 1994).

In the outpatient setting some patients are mildly ill and are often treated entirely on the basis of a clinical diagnosis of CAP (Areno et al., 1996). It is important to note that the diagnosis of pneumonia based on symptoms and signs is not reliable (Metlay et al., 1997). If CAP is suspected clinically, in most patients a chest radiograph should be obtained at the time of the initial work-up. Generally, the radiographic manifestations of pneumonia will appear within 12 hours of the onset of clinical symptoms (Herold, 1997). In the outpatient setting, patients typically will have been ill for several days before presentation. Therefore, most ambulatory patients with pneumonia will have radiographically visible evidence of their disease. Hospitalized patients will often, however, be imaged more promptly and may not have yet developed radiographic evidence of pneumonia at the time of their chest radiograph. Close follow-up of these patients will be necessary to detect or to exclude pneumonia. The

sensitivity of the chest radiograph will also be lower, especially in the elderly, when there is dehydration or other debilitating illness (Ely & Haponik, 1991) that delays the development of a pulmonary inflammatory response sufficient to cause visible opacities on the films. In these cases, as the concurrent illness is brought under control, imaging should be repeated to detect developing radiographic evidence of clinically suspected pneumonia.

Radiographic evidence of comorbid illness (e.g., carcinoma) may be obscured by an acute pneumonia on a chest radiograph obtained at the initial work-up. If a patient presenting with CAP requires chest radiographic screening for comorbid illness the initial chest radiograph might not be of any benefit in that regard. Under such circumstances a follow-up chest radiograph would be indicated when treatment of the pneumonia can be expected to have reduced the extent of the pneumonia enough to adequately assess the chest x-ray for underlying abnormality.

Patients presenting with symptoms consistent with a lower respiratory tract infection may not have pneumonia. In fact, studies suggest that from 8% to 30% of patients clinically suspected of having CAP actually have another diagnosis (Areno et al., 1996). The clinical diagnosis of pneumonia is best confirmed by a chest radiograph showing new or progressive findings that are consistent with pneumonia and that correlate with the patient's signs and symptoms (Areno et al., 1996; Herold, 1997).

Imaging is useful and necessary to assess the extent of the infection and to detect complications in those patients who appear clinically to be more seriously ill, those who are at risk for complications, those who require hospitalization (Areno et al., 1996), and those suspected of having severe CAP. Severe CAP is defined as a life-threatening pneumonia, acquired in the community by a nonimmunocompromised patient, that requires admission to the intensive care unit (ICU). The American Thoracic Society Guidelines for the classification of CAP as severe include radiographic criteria. In addition to the clinical criteria, a chest radiograph showing bilateral pneumonia or pneumonia involving multiple lobes or an increase in the size of the pneumonia of 50% or greater within the preceding 48 hours justifies defining a case of CAP as severe and requiring ICU admission (Torres et al., 1996). Patients most at risk for severe CAP and for other complications include those with chronic underlying cardiopulmonary disease, e.g., chronic obstructive pulmonary disease [COPD] and those with chronic conditions such as diabetes mellitus, alcoholism, and neuromuscular disorders (Torres et al., 1996).

As will be discussed later, some patterns of pneumonia on the chest radiograph can be associated with certain causative organisms or groups of organisms. However, there is a great deal of overlap between the various infectious and noninfectious causes of pulmonary infiltrates and opacities. Chest radiography is therefore no more able than other noninvasive clinical tests to provide a specific etiologic diagnosis in the majority of cases of pneumonia. In fact, both sputum culture and radiology are able to identify the correct etiology in less than 50% of patients (Areno et al., 1996; Bowton & Bass, 1991; Fein, 1996).

On the other hand, analysis of the radiographic pattern in the context of the patient's clinical and epidemiological circumstances (Conces, 1994; Fein, 1996; Herold, 1997) will often enable the clinician to narrow the list of probable causes and thereby facilitate empirical therapy decisions.

Technical Considerations

Standing posteroanterior and lateral views of the chest in full inspiration comprise the usual and the best initial radiologic examination of a patient suspected of having pneumonia (Conces, 1994; Milne & Pistolesi, 1993; Novelline, 1997). Orthogonal views (i.e., views at right angles to each other) are essential (Freundlich & Bragg, 1992) to enable the viewer to examine regions that would be obscured if only a single view had been obtained and to better localize and characterize detected abnormalities. A posteroanterior radiograph places the patient with his or her chest against the film, minimizing the magnification of the heart and the mediastinum on the image, which minimizes the amount of lung obscured by these structures. Similarly, on the lateral view the size of the heart on the image is minimized if the left side is against the film. The *left-lateral* is therefore the preferred position for the

lateral view. The right side will be magnified slightly more than the left. Therefore, on a well-positioned left-lateral the right ribs are larger and project behind the left ribs.

A high-voltage technique (130 kVP-140 kVP) is preferred to the lower voltage techniques (60 kVP to 80 kVP) because there is better penetration of the bones and mediastinum. This results in both a more useful image of the central structures as well as better depiction of the lungs and pulmonary markings due to the lowered contrast and decreased density of the overlying skeletal structures. However, the low-voltage technique can be used when one is examining for bone detail or wants to assess calcific densities (Freundlich & Bragg, 1992).

There are many situations in which the standard views cannot be performed. These occasions are not restricted to the very ill patients. If an otherwise well patient is unable to stand, the examination must be done with the patient seated or lying down. A posteroanterior view is virtually impossible in these patients and one must accept the limitations of the anteroposterior view. Similarly, the lateral view will be less than optimal but nevertheless should be obtained.

In the hospital setting, it may be necessary to bring the equipment to the patient. Portable x-ray units are versatile but cannot produce the quality of stationary units. They use lower voltage and longer exposure times. Equipment limitations are further compounded by patient factors. The patients must be examined while supine or seated on the bed. They are frequently unable to cooperate fully with the technologist. The portable frontal view is therefore virtually always an anteroposterior view with compromised resolution. For the severely ill patient, portable chest radiography, despite its shortcomings, is extremely useful to assess tubes and lines and their complications, to look for complications of the pneumonia, and to assess its response to treatment.

In some cases special views must be obtained (Novelline, 1997). A portable lateral view is technically more difficult to obtain and not routinely obtained in most settings. It is, however, the most sensitive view to detect pleural fluid (Novelline, 1997). Decubitus views with a horizontal beam are useful to detect pleural effusions and to assess their mobility. Decubitus views are frontal views performed with the patient lying on one side. If a high diaphragm is suspected to be due to a subpulmonic pleural effusion the patient lies on the side of the suspected effusion. A mobile subpulmonic effusion will flow along the dependent aspect of the ipsilateral chest wall and thicken the lateral pleural stripe. On the other hand, if there is a thickened lateral pleural stripe consistent with pleural effusion and loculation needs to be ruled out, a decubitus view should be obtained with the abnormal side up. If the fluid is mobile it will flow down to the now dependent medial aspect of the ipsilateral chest wall and clear the previously thickened pleural stripe. A decubitus view is also sometimes helpful to detect air fluid levels. Traditionally inspiration/expiration frontal views have been used to detect or exclude a pneumothorax. It is now generally accepted that expiration frontal views do not significantly add to the diagnostic information afforded by the inspiration views and need not be done as an initial examination for that purpose (Seow et al., 1996). When the patient suspected of having a pneumothorax is unable to stand or sit, a decubitus view, with the abnormal side up, or a supine horizontal beam lateral view may be helpful (Novelline, 1997). Lordotic views afford a clear view of the lung apex by elevating the overlying clavicle. Oblique views are sometimes helpful to determine the location of an opacity.

Systematic Approach to the Chest Radiograph

Initially, radiographs should be assessed for technical quality. The majority of technically suboptimal chest radiographs are a result of rotation and poor exposure technique. Rotation my be assessed by locating the spinous process at the level of the clavicular heads and measuring the distance from the process to the medial end of the clavicle on either side.

Studies have shown that it is better to first do a routine systematic search of the chest radiograph before doing a specific examination for the suspected abnormality. A routine undirected search has been shown to yield fewer false-positive findings, with no detrimental effect on sensitivity (Swennson et al., 1985). Radiologists are taught,

when shown a film, to do a routine, systematic, and undirected search with no history before examining the film specifically to answer the clinician's question.

Whenever possible previous films should be obtained for comparison. Both the current and the previous chest radiographs should be critically evaluated for positioning and technique before attempting to evaluate the thorax. This allows one to take these factors into account as possible reasons for new or altered findings and thereby improve specificity. For example, an increased size or prominence of a feature compared to the previous study may be due to patient rotation. A change in density may be due, for example, to a difference in the kVP. To the extent that it is possible and practical one should ensure that follow-up films match the previous examinations in positioning and technique.

The film reader should then perform a systematic search of the chest radiograph. Experienced chest radiologists recommend a search based on the body systems (Freundlich & Bragg, 1992). A mnemonic can be used to guide the search. For example, the acronym LAMPS denotes Lungs, Airways, Arteries (pulmonary vessels and mediastinal cardiovascular structures), Adenopathy (examine the hila), Mediastinum, Pleural margins and surfaces, Soft tissues of the abdomen, chest, shoulders and neck, and Skeletal structures. A separate and complete perusal of the chest radiograph should be carried out for each of these headings so that one is examining only the structures specified by the heading with each pass. When a significant abnormality has been found, the search should not be stopped immediately since there may be other possibly very significant abnormalities elsewhere on the film.

Radiographic Appearance of Pneumonia

On the normal chest radiograph, air spaces and most airways are not visible; one sees only well-defined pulmonary blood vessels, major and minor fissures, and the walls of the larger bronchi. A radiographic diagnosis of pneumonia is possible only when the pathophysiologic response to the infection renders the disease visible by altering the appearance of normal structures or by the addition of new, abnormal opacities. The radiographic images of pneumonia are composed of patterns of air space or interstitial opacification alone or in combination.

The terms air space opacification, air space disease, and alveolar consolidation are virtually synonymous and are used to describe the presence of a purulent exudate or other material of similar density that fills alveolar spaces and displaces alveolar air to cause homogeneous opacification, usually with ill-defined margins, in the affected region or regions (Webb et al., 1996; Freundlich, 1992). Pneumonia can therefore be mimicked when edema fluid, hemorrhage, inflammation, neoplastic infiltration, pulmonary alveolar proteinosis, or fluid aspiration displaces and replaces alveolar air.

Interstitial lung disease refers to conditions causing fluid and inflammation to enter and enlarge the interstitial compartments. Together the axial, subpleural, and intralobular interstitium form a continuous fiber skeleton that supports the lung (Webb et al., 1996). Internally the axial interstitium is composed of the central peribronchovascular interstitium which merges peripherally with the centrilobular peribronchovascular interstitium. Externally the subpleural interstitium courses beneath the visceral pleura and envelops the lung in a continuous fibrous sac. Fibrous septa project from the subpleural interstitium into the lung parenchyma between secondary lobules. These projections are known as interlobular septa and define the boundaries between the secondary lobules. Within the secondary lobules there is a system of very fine fibers supporting the walls of the alveoli. These alveolar septal fibers collectively form the intralobular interstitium which links the axial interstitial compartment to the subpleural interstitial compartment. On a chest radiograph the lung interstitium is normally invisible. Interstitial lung disease will be seen on the radiograph when it enlarges and opacifies the interstitial compartments in the affected region and renders them visible. Whereas air space consolidation (Fig. 1) produces homogeneous opacification due to displacement of air from the alveolar spaces, interstitial disease does not (Fig. 2). Alveolar air remains within the alveolar spaces in the affected area and the interfaces between alveolar air and the interstitial opacities may be seen on the radiograph. As a result, purely interstitial opaci-

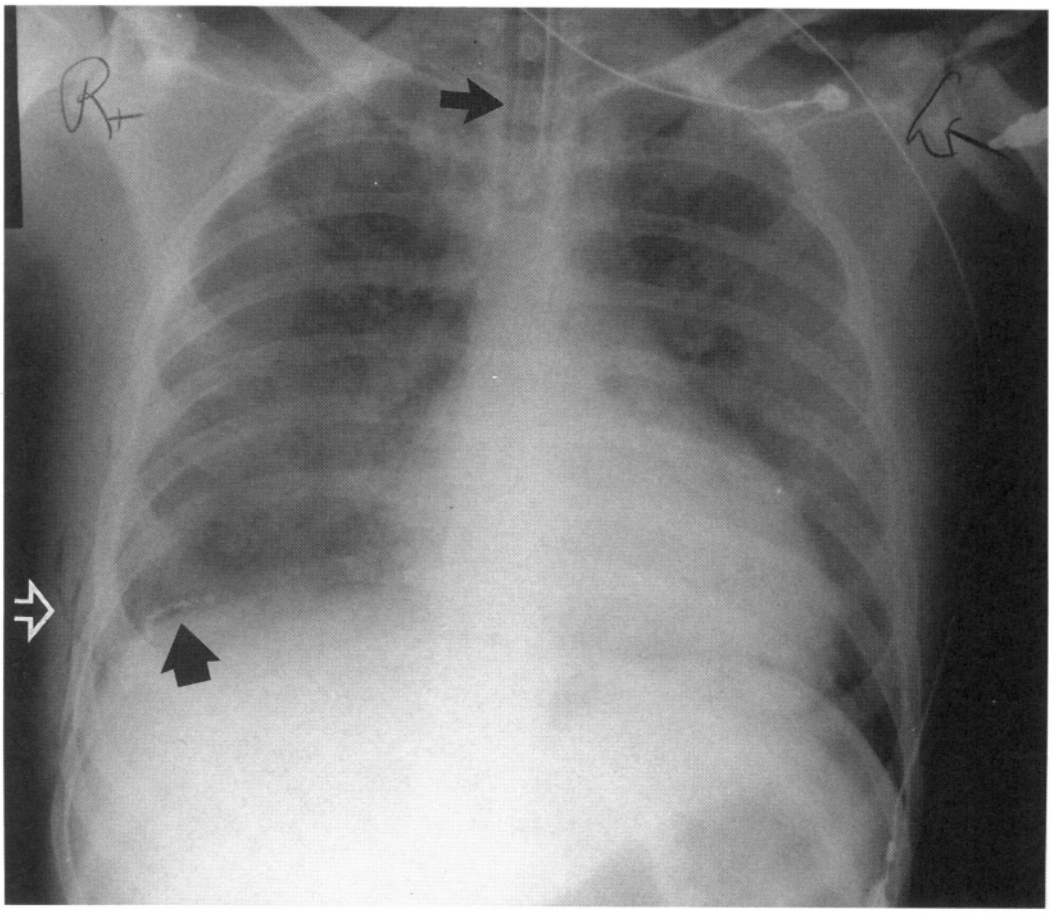


FIGURE 1. Diffuse air space opacification in a patient with adult respiratory distress syndrome. The patient has had a recent lung biopsy as indicated by the surgical clips (wide arrow) and the small collection of subcutaneous air (open white arrow). Note the presence of the endotracheal tube (thin arrow).

ties are relatively discrete with lack of confluence and preservation of lung margins. For practical purposes, the only acute interstitial lung disease that mimics acute interstitial pneumonia is pulmonary edema, usually due to congestive heart failure or fluid overload (Müller, 1992). Subacute conditions mimicking interstitial pneumonia include pulmonary lymphangitic carcinomatosis and interstitial pneumonitis due to drug or treatment reactions. Chronic interstitial lung diseases may have a similar appearance on chest radiograph.

Pneumonia occurs when a sufficiently large inoculum of infected material gains access to the lower airways and alveoli and is not promptly neutralized and cleared. For most patients with CAP the initiating event is aspiration of pathogens that have colonized the upper respiratory mucosa. Aspiration may occur more readily when there is a neuromuscular disorder or when there is alteration or depression of consciousness, as for example, with alcohol use. The pathogens will have entered the nose or mouth either by direct introduction of infected material or by the inhalation of an infected aerosol. Direct inhalation of a contaminated aerosol into the lower tract is a much less common cause of CAP. It is associated particularly with viruses, fungi, tuberculosis (Arunabh & Niederman, 1996), and *Legionella* and the other atypical organisms (Mason & Nelson, 1996).

When airborne aerosolized infected material is

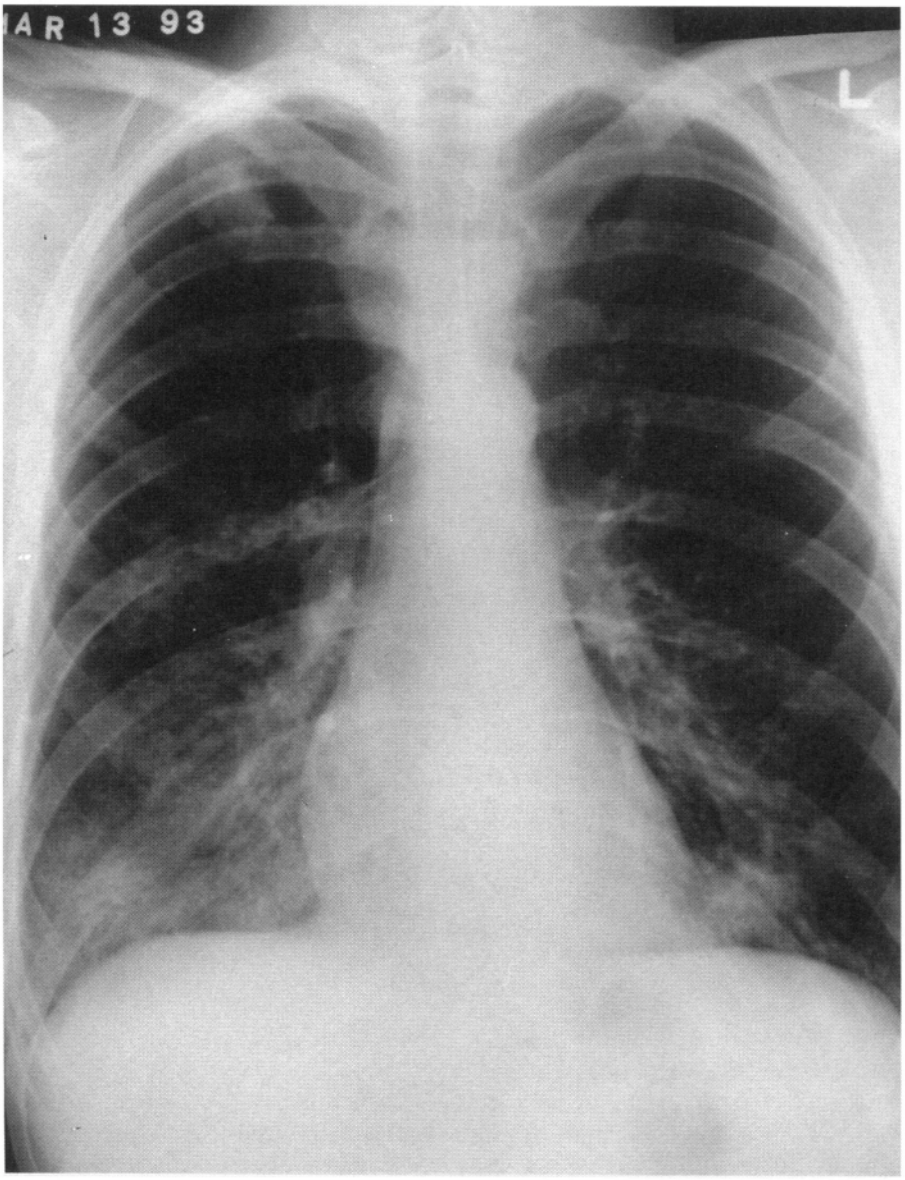
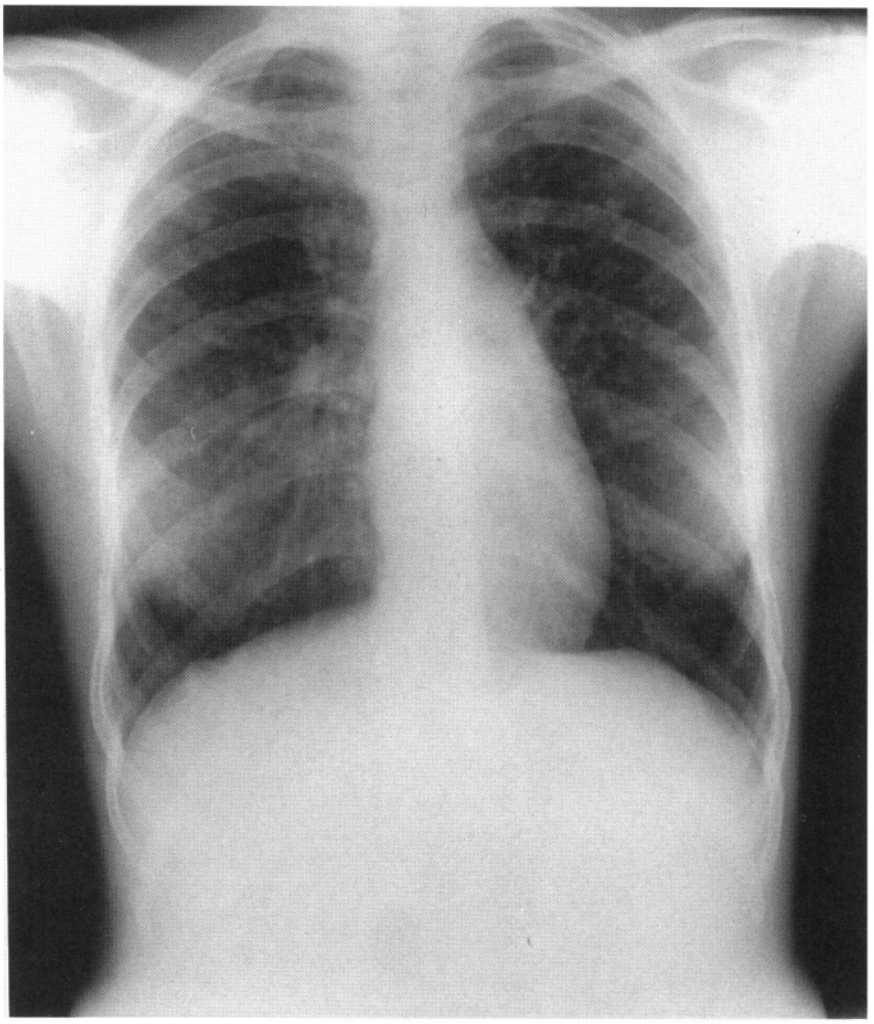


FIGURE 2. Example of predominantly interstitial opacification in a patient with *Pneumocystis carinii* pneumonia.

inhaled, heavier droplets and particles are deposited earlier in the larger, more proximal airways and may not reach the lower airways. Lighter ones are carried further into the lower respiratory tract and may reach the bronchi and more peripheral bronchioles. Only the smallest airborne droplets or particles, less than 5 μm in diameter (McCloud, 1992), will actually reach the alveoli. Once deposited on the walls of the lower airways or alveoli, the pathogens are either cleared or cause infection.

Pathogens may also reach the lung via the hematogenous route (e.g., septic emboli in drug addicts) or by direct extension. These sources are uncommon etiologies of CAP (Mason & Nelson, 1996; Woodridge, 1992).

Wherever the pathogen becomes established



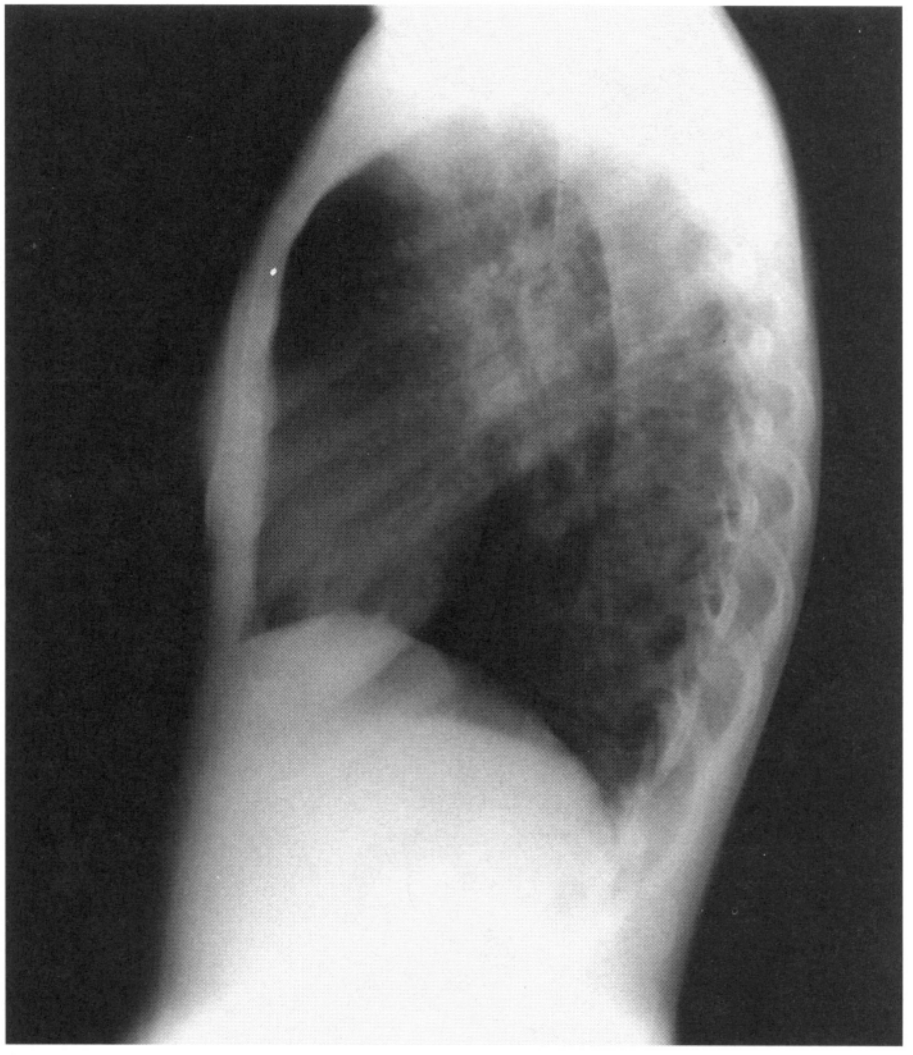
A

FIGURE 3. Diffusely distributed bilateral mid- and upper-lung nodular opacities and prominent peribronchial markings in a patient with bronchopneumonia due to tuberculosis. There is right hilar prominence on a posteroanterior view (A) and hilar density on the lateral view (B) consistent with adenopathy. (*Continued*)

the normal host inflammatory response causes cellular infiltration and edema of the local and adjacent tissue. If the infection progresses the combination of the infective process and the host response will cause an outpouring of purulent, hemorrhagic fluid into adjacent airway lumens and alveolar spaces.

If the pathogen is deposited onto the alveolar epithelium and not cleared promptly the inflammatory response in combination with the infective process results in edema and infiltration of the alveolar wall and an outpouring of fluid into the alveolar spaces, resulting in various patterns of air space opacification on the chest radiograph. If only the centrilobular (peribronchiolar) alveoli of noncontiguous secondary lobules in the region are involved, the pneumonia will be visible as ill-defined micronodules on the chest radiograph (Woodridge, 1992) (Fig. 3). This pattern can be seen in other causes of air space disease such as edema and bronchioloalveolar cell carcinoma. The features may also be consistent with causes of poorly defined pulmonary nodules such as metastases.

If the air space disease spreads, the alveolar micronodules will become confluent and larger

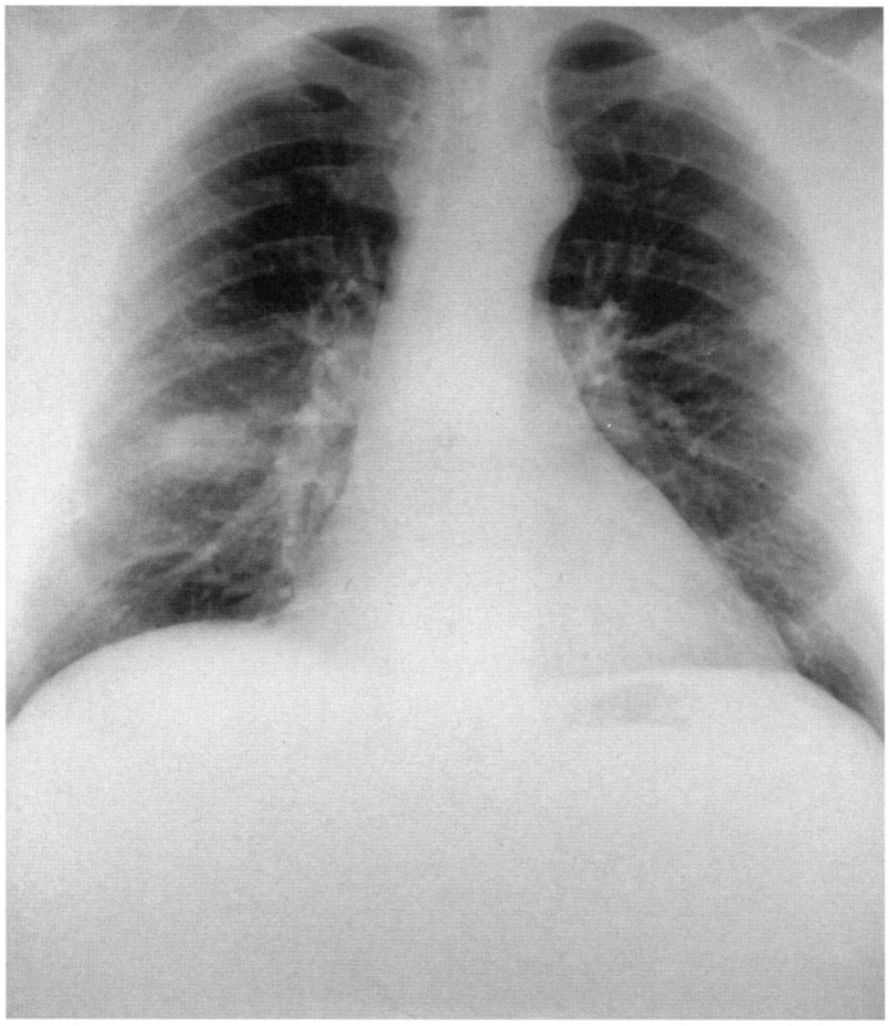


B

FIGURE 3. (*Continued*)

areas of homogeneous opacification may ensue. When only one localized and well-defined opacity ensues it is called round pneumonia (Fig. 4A,B), mimicking a mass. If the infection continues to spread via the pores of Kohn and terminal airways an entire segment or lobe may become opacified to produce the typical lobar pneumonia. Classically the lobe is homogeneously opacified. Radiolucent air bronchograms caused by patent airways within the infected region may be present and will confirm to the reader of the radiograph that the opacification is indeed predominantly pulmonary air space consolidation (Fig 5).

Where air space consolidation abuts the mediastinum, diaphragm, or pleura, the normal margin of these structures is rendered invisible on the radiograph due to loss of the air-soft tissue interface (the silhouette sign) (Fig. 6). It can be a clue to the presence of subtle air space consolidation. Correlating the lobar anatomy with the structure whose silhouette is lost is a major clue to identify which lobe is involved. When air space consolidation is

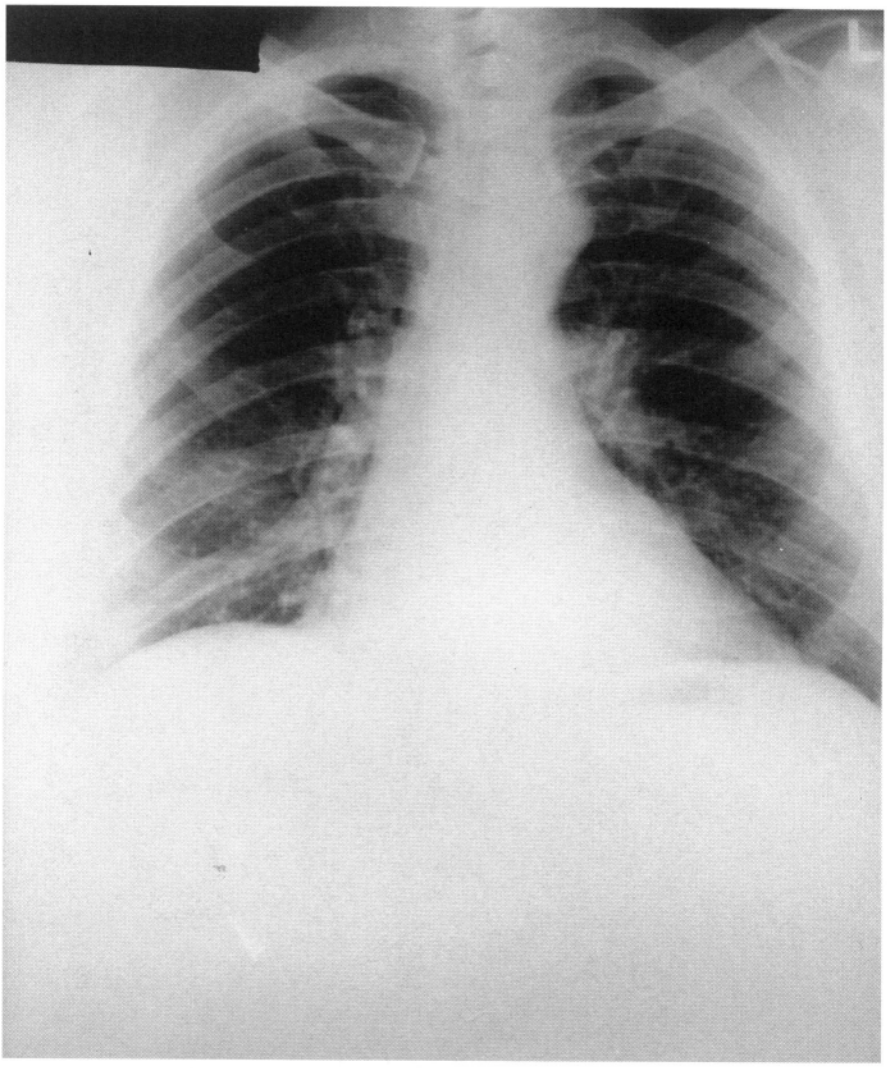


A

FIGURE 4. (A) Round pneumonia in the right lower lung which is resolving on a follow-up examination several weeks later (B). (*Continued*)

behind or in front of a structure its density is added to that of the structure and it can be a clue to its presence. This is called summation (Figs. 6–8). For example, one should see pulmonary markings through the heart. Loss of these markings and an increase in the heart density on the frontal view suggests consolidation in the left lower lobe where it lies posterior to the heart. Another region where summation is often helpful is over the lower thoracic spine on the lateral view. The opacification of the thoracic spine should gradually decrease toward the diaphragm. A lower lobe consolidation increases the density in this region.

Lobar opacification may be incomplete and remain inhomogeneous. This may occur, for example, when the natural history has been altered by antibiotic therapy or when the patient has emphysema. Air space opacification can also be caused by edema, hemorrhage, alveolar proteinosis, and bronchioloalveolar cell carcinoma (Fig. 8) (Freundlich, 1992) and mimicked by pulmonary lymphoma or Kaposi's sarcoma (Goodman, 1992).



B

FIGURE 4. (*Continued*)

There may be an overlap of interstitial and air space pneumonia. The two components may coexist from the start or one may progress to produce the other. For example, segmental or lobar consolidation may develop in a case of primary interstitial pneumonia when there is progression of the original infection or the patient develops a secondary, usually more aggressive, superinfection.

Bronchopneumonia is an example of mixed interstitial and air space pneumonia. It is usually the result of copious aspiration of oropharyngeal secretions or gastric contents containing pathogens which are deposited onto the walls of the airways and subsequently infect them. If the aspirated material or infection reaches the bronchioles the pneumonia spreads rapidly to involve the peribronchiolar alveoli. The earliest phase seen on the chest radiograph consists of peribronchial thickening, increased bronchovascular markings, and acinar nodules (Woodridge, 1992). It is not commonly seen since the infection has usually progressed further by the time a chest radiograph is obtained. The multiple foci of infection usually progress rapidly to produce multiple, frequently bilateral confluent

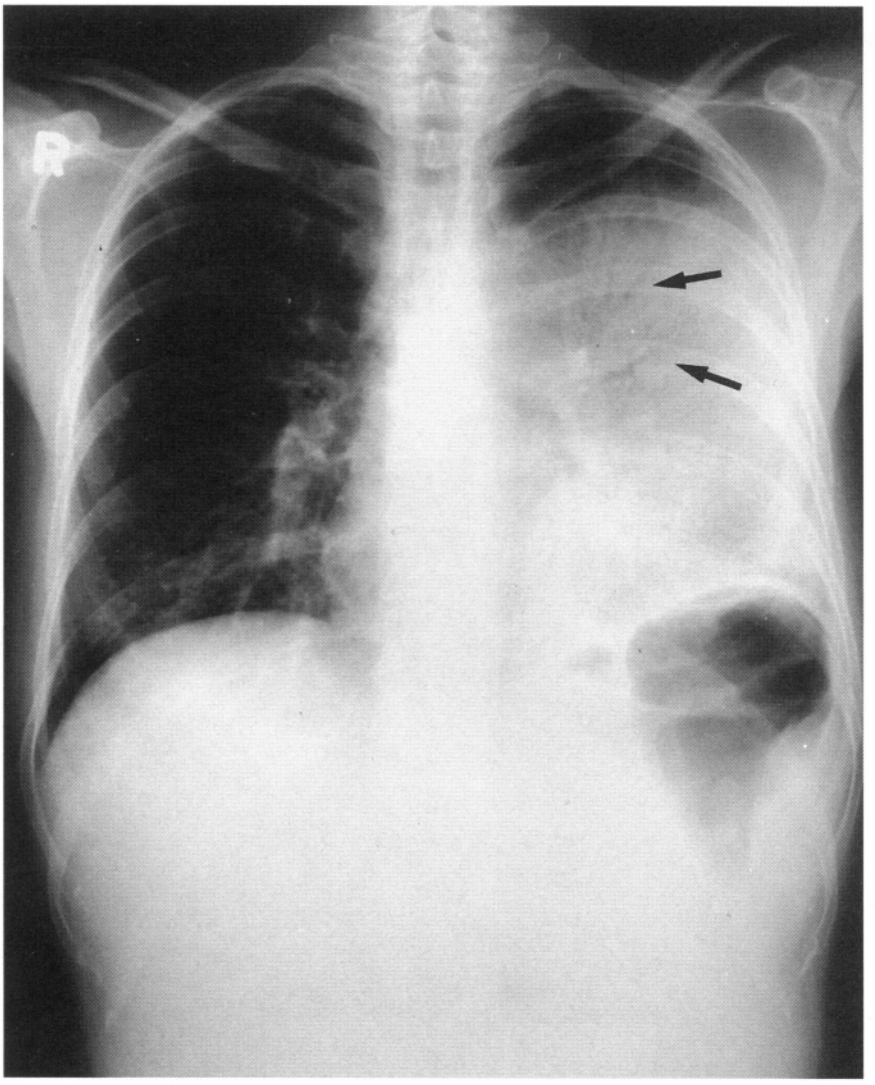
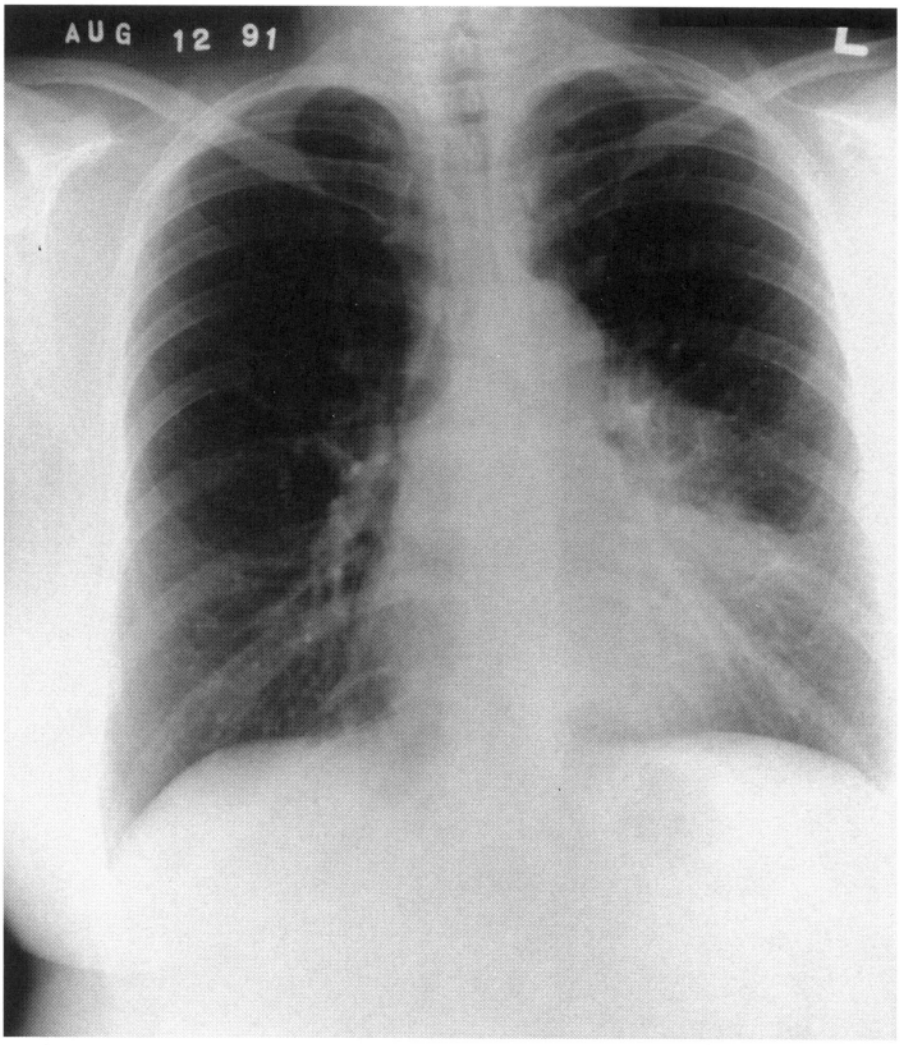


FIGURE 5. Homogeneous air space opacification of the left lower lobe (complete lobar consolidation) in a patient with pneumonia due to *Streptococcus pneumoniae* infection. Air bronchograms are present (arrows). Note also complete loss of the heart and left hemidiaphragm margins.

patches of poorly defined opacification overlying and often obscuring the associated peribronchial disease. If the infection continues to spread the patches coalesce to opacify entire segments or lobes. If unchecked, an entire lung or both lungs may opacify (Fig. 9).

An infectious inflammatory process involving the walls of bronchi and larger bronchioles may spread to the peribronchial and peribronchiolar interstitium. The resulting interstitial edema and infiltration will thicken the walls and margins of the airways. The thickened peribronchial interstitium, when seen end on, will be apparent as peribronchial cuffing. The margins of the companion blood vessels will become indistinct. Inflammation of the smaller bronchioles, especially the intralobular bronchioles, may cause a reticulonodular or micronodular pattern of opacification as they are seen variably *en face* and end on. If the interstitial inflammation spreads to the interlobular septa the



A

FIGURE 6. Silhouette sign. Left lower lobe pneumonia causes loss of the left heart border (A). In (B) the pneumonia has resolved with restoration of the left heart border.

thickened septa may be visible as additional reticulonodular opacities or as septal lines (Kerley B lines). Interstitial pneumonia may, therefore, have an appearance similar to noninfectious interstitial pneumonitis, interstitial edema, and chronic interstitial lung disease (Fig. 2). This is the least common radiographic manifestation of CAP.

In the majority of cases of CAP the tracheobronchial tree is the route of access to the lung and a hematogenous source for the pulmonary infection is much less common. It is virtually always caused by multiple septic bacterial emboli. They are usually widely deposited in a "vascular distribution," which favors the periphery of the dependent regions of the lung. Each focal deposit causes localized hemorrhagic edema, and the pneumonia will typically be seen on the chest radiograph as multiple nodules, often pleural, in the lower two thirds of the lung. They may range from large and poorly defined to small and well defined. Cavitation within the nodules is often seen. If the seeding has been massive and is seen early there may be a miliary pattern of tiny nodules. Nodules in a vascular distribution are also typical in metastatic disease.

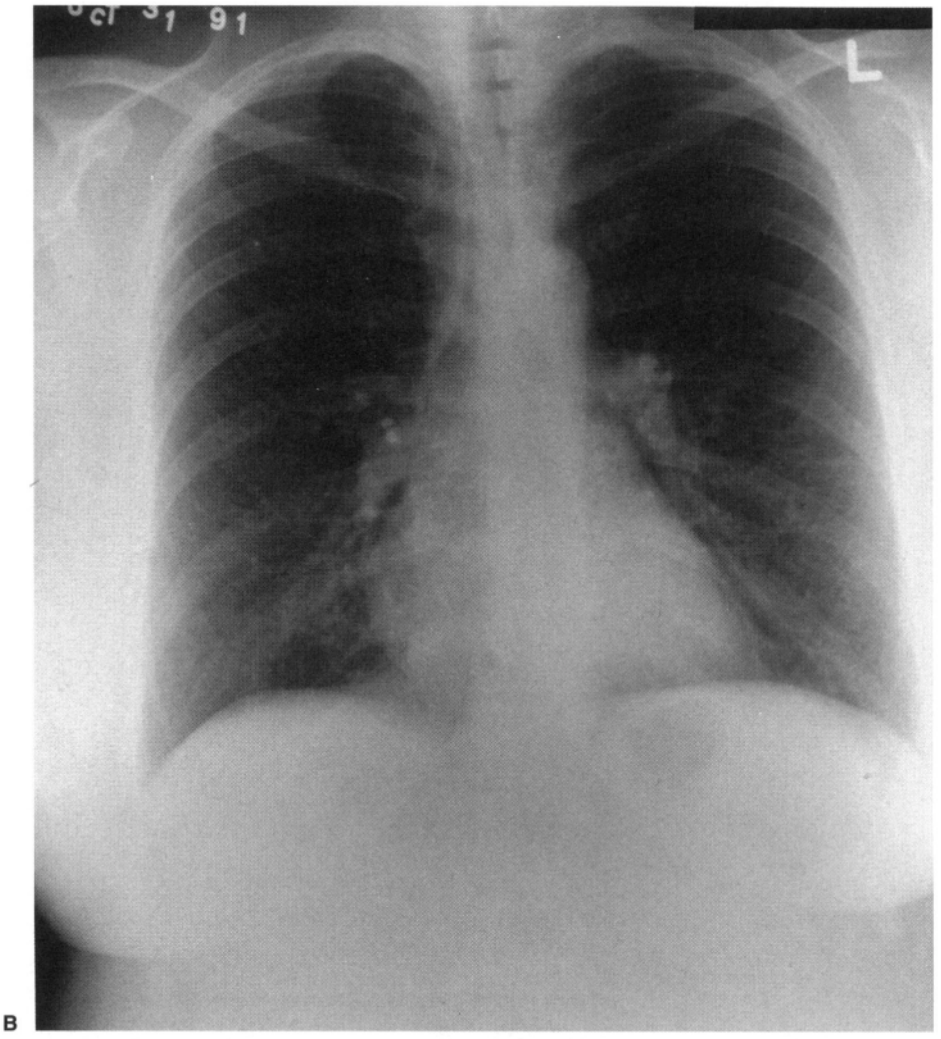
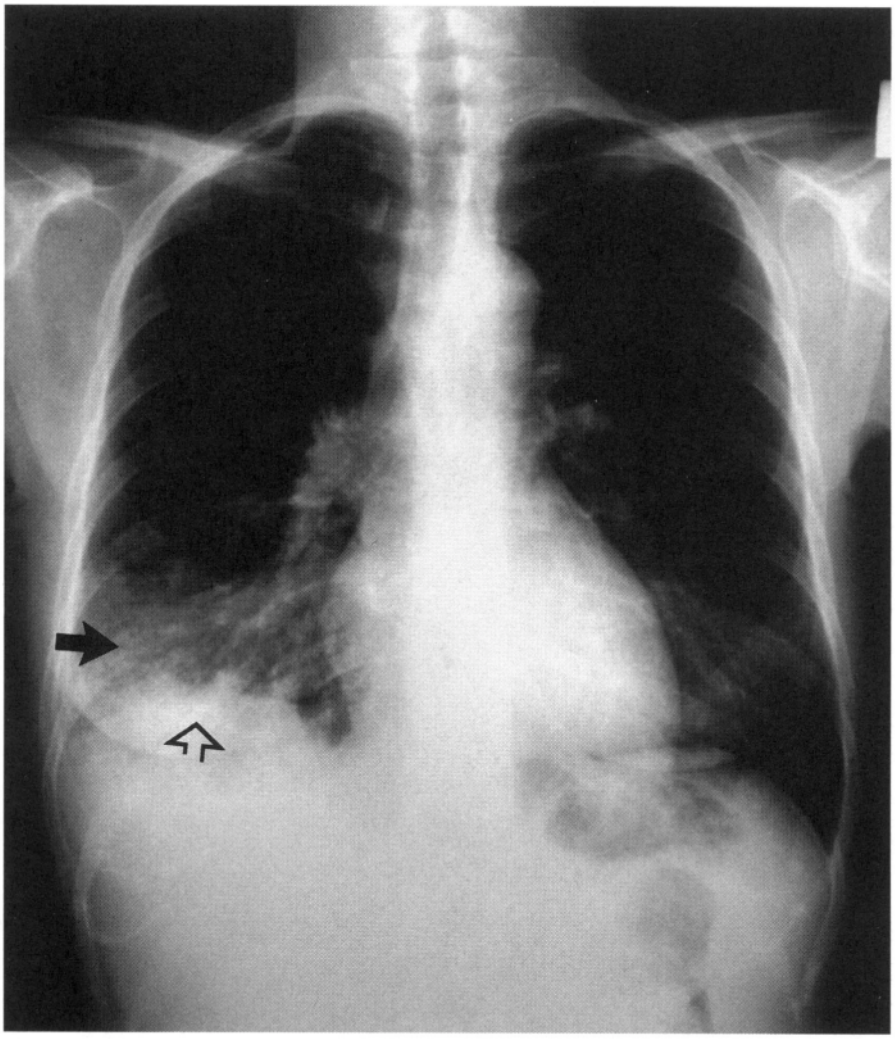


FIGURE 6. (*Continued*)

Pneumonia Pattern Recognition

The sensitivity of the chest radiograph for the detection of pneumonia (and its negative predictive value) depends on the technical quality of the images, the training of the observer, the timing of the examination with respect to the onset of the clinical findings and the degree to which the patient is able to develop an inflammatory response sufficient to render the process radiographically visible. Specificity is primarily dependent on the ability of the observer to minimize false-positive interpretations by recognizing and differentiating the various diseases that produce a radiographic image that can mimic pneumonia.

Notwithstanding the ability of the chest radiograph to detect pneumonia and to aid in assessing its severity (Torres et al., 1996) and response to treatment (Fein, 1996), it is unable to provide a specific etiologic diagnosis. It is, however, no worse than the clinical assessment as both are of limited value in this regard. In fact, when multiple clinical and radiologic criteria are combined in the assessment of CAP, the correct etiologic agent is identi-



A

FIGURE 7. Summation sign. Posteroanterior (A) and lateral (B) demonstrate right lower lobe pneumonia. The right lower lobe density (thinner arrow) sums with the heart density to yield a markedly increased density overlying the posterior aspect of the heart on the lateral view (wider arrow) bounded anteriorly by the right major fissure. The retrocardiac density is also greater than normal. There is partial silhouetting of the right hemidiaphragm margin on both views (open arrows).

fied in less than half of the cases (Bowton & Bass, 1991).

Although the chest radiograph cannot specifically diagnose the causative organism, it can nevertheless expedite empiric therapy decision-making by enabling the skilled reader to narrow the list of probable causative organisms through systematic analysis of the radiographic pattern of the pneumonia in conjunction with the clinical and epidemiological circumstances (Bowton & Bass, 1991; Conces, 1993, 1994; Herold, 1997; Freundlich & Bragg, 1992; Torres et al., 1996).

Pneumonia pattern analysis requires that pulmonary parenchymal abnormalities noted on the chest radiograph of the patient suspected of having CAP be analyzed and characterized as air space disease, interstitial disease, or a mixture of the two. If the radiographic pattern is atypical (e.g., a mass),

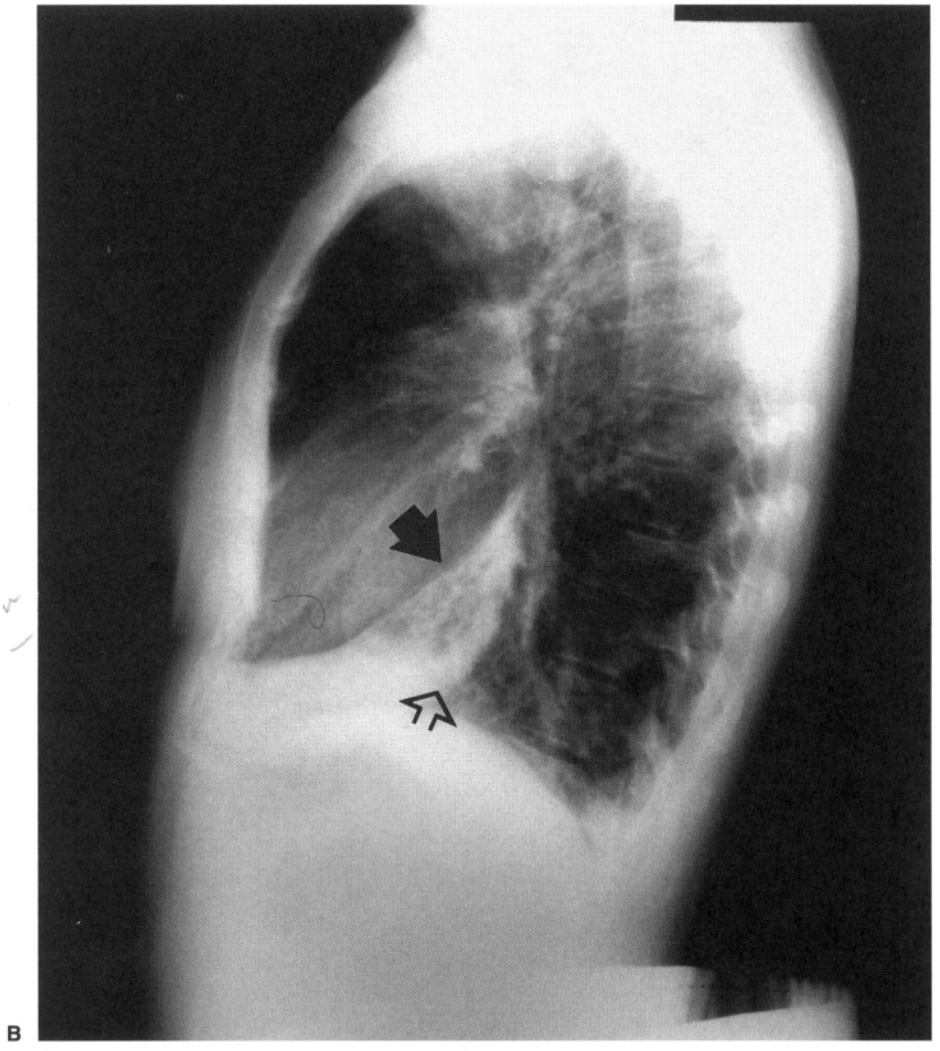
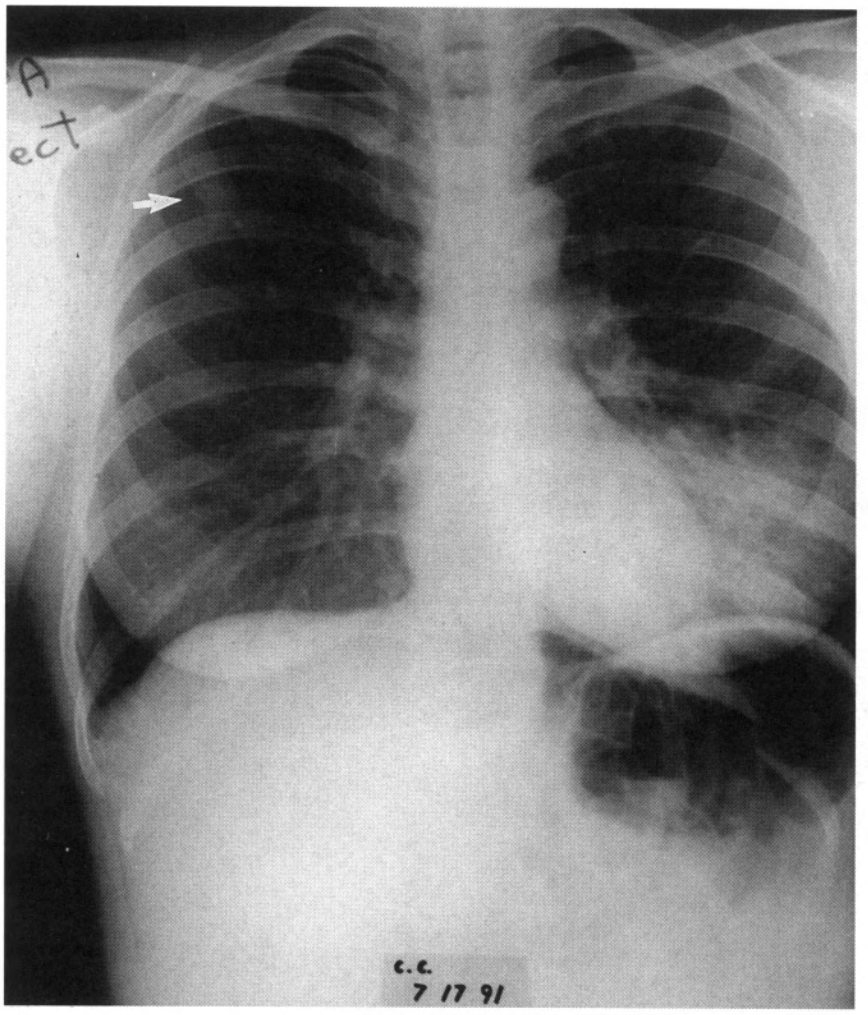


FIGURE 7. (*Continued*)

one should include other conditions in the differential diagnosis. Findings consistent with pneumonia should then be classified according to their location. The pneumonia may be focal, segmental, lobar, multilobar, or diffuse. The area of abnormality can be homogeneous, heterogeneous, or confluent. The pneumonia may have a central or peripheral predominance; have an upper, middle, or basal predominance; or simply be scattered.

The mediastinum and hila should be assessed for adenopathy. The presence of pneumothorax, atelectasis, and collapse need to be noted. Pneumatoceles, cavitation, and abscess formation are associated with more virulent organisms, with varying degrees of necrosis. Pleural effusion is the most common complication of pneumonia (Woodridge, 1992) and it may develop into an empyema. Infrequently the infection can extend beyond the pleural space to involve the heart, mediastinum, or chest wall.

Finally, the reader should assess the films specifically for evidence of comorbid conditions that



A

FIGURE 8. Summation sign. In (A) there is air space opacification in the left lower lobe causing increased density of the cardiac shadow and loss of the lung markings normally seen through the heart. In (B) the pneumonia has resolved restoring the normal cardiac density and the visibility of the lung markings behind the heart. Note the bronchoalveolar cell carcinoma in the right upper lobe (arrows). It has enlarged in the 3-month interval between the examinations.

may complicate the course of the illness or that may actually be mimicking pneumonia, such as a mass or congenital anomaly.

Specific Pneumonia Patterns

Pneumonia patterns on the radiograph can be grouped into four categories: lobar pneumonia, bronchopneumonia, nodular patterns of pneumonia, and diffuse patterns of pneumonia (Conces, 1994).

Lobar Pneumonia

Lobar pneumonia is a primary air space pneumonia that starts as a small peripheral subsegmental opacity that, if unchecked, may spread to involve the entire segment and then, via the pores of Kohn and terminal airways, may spread to homogeneously opacity the entire lobe (Woodridge, 1992). Early recognition and treatment of the lobar pneumonia will modify its progression, and the chest

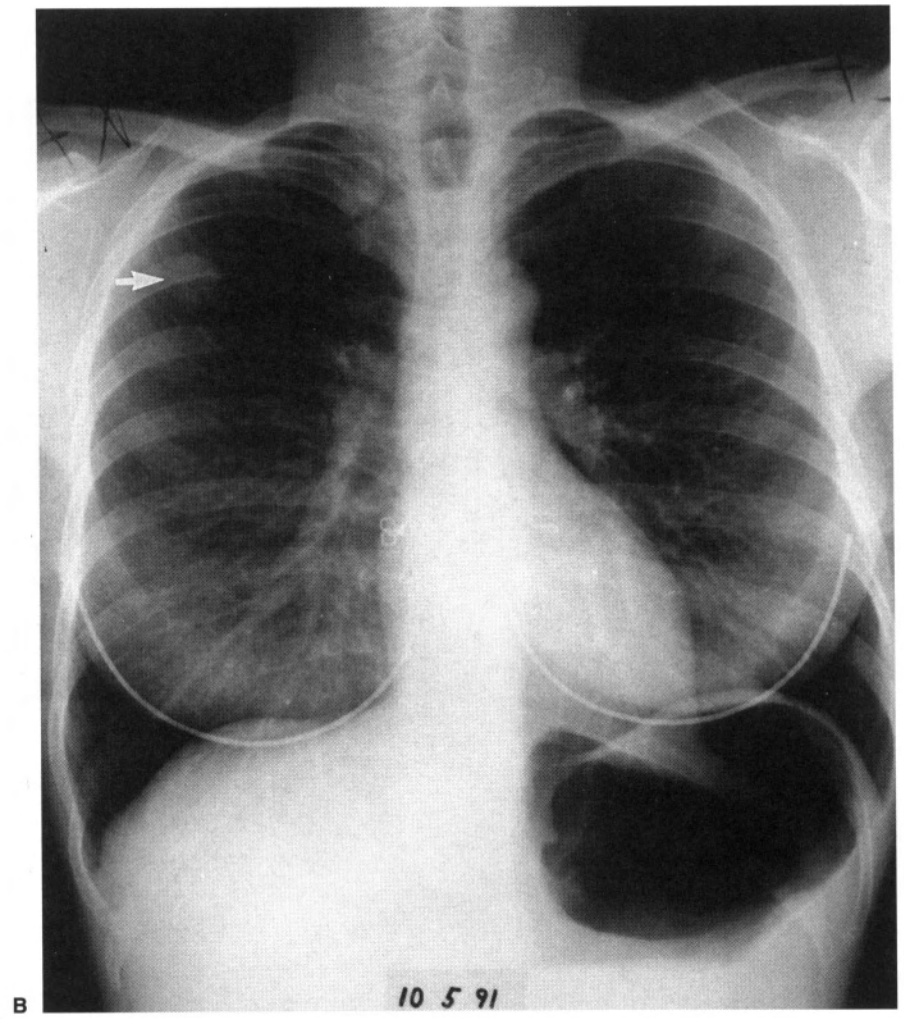


FIGURE 8. (*Continued*)

radiograph may never demonstrate more than patchy subsegmental or segmental opacification within the affected lobe. Since lobar pneumonia does not involve the bronchi, they typically remain open and there is no atelectasis. The patent bronchi within the region or regions of air space opacification may be seen as air bronchograms.

Community-acquired lobar pneumonia is most commonly caused by a bacterial infection (Conces, 1993; Miller 1994) with *Streptococcus pneumoniae* being the most common etiologic agent in normal individuals. *Klebsiella* follows as the next most common. *Klebsiella* is noted to be particularly associated with marked edema that fills and expands the infected lobe causing the fissures to bulge. However, lobar pneumonia with lobar enlargement can be seen with other bacterial infections including *S. pneumoniae, Staphylococcus aureus, Legionella pneumophila, Haemophilm influenzae,* and *Mycobacterium tuberculosis* (Woodridge, 1992) (Fig. 10). The round variety of lobar pneumonia is uncommon. However, it is most frequently located in the superior segment of the lower lobes, most commonly in children. The usual pathogen is *S. pneu-*

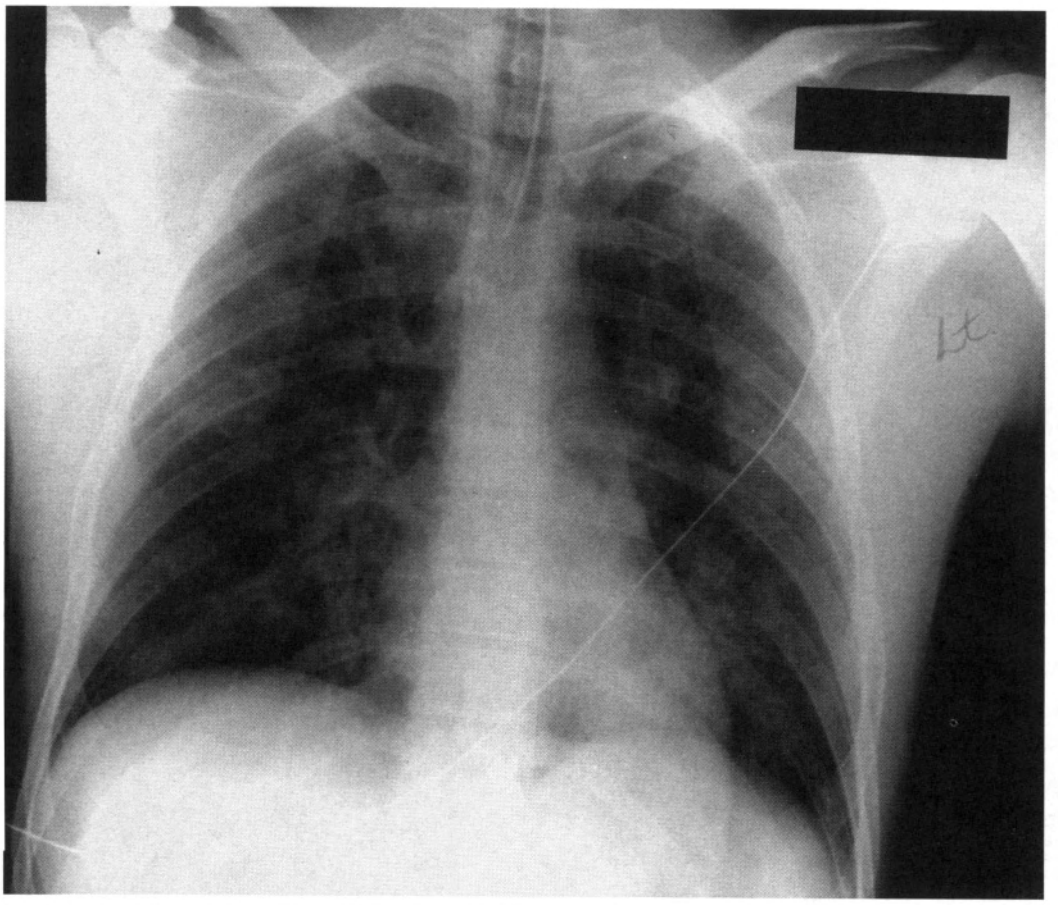


FIGURE 9. Progression of bronchopneumonia over a 2-day period from predominantly peribronchial and nodular opacities (A) to regions of confluent air space opacification in both lungs (B).

moniae (Woodridge, 1992; Singleton, 1992). Primary pulmonary tuberculosis presenting as a segmental or lobar pneumonia is typically in association with adenopathy and occasionally with pleural effusion (Miller, 1992). *L. pneumophila* pneumonia may present as patchy subsegmental air space opacification that spreads to involve an entire lobe. Other bacteria that may cause lobar pneumonia include aerobic gram-negative bacilli and *Mycoplasma pneumoniae.* On occasion, viral pneumonia may mimic a bacterial lobar pneumonia (Woodridge, 1992). A number of pulmonary fungal infections may involve one lobe but usually in a patchy subsegmental distribution. Fungi most closely associated with focal air space disease include *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Cryptococcus neoformans,* and invasive *Aspergillus fumigatus.*

If there is bilateral lobar pneumonia or unilateral multilobar pneumonia it should be classified as severe CAP. The organisms most frequently associated with severe CAP are *S. pneumoniae, L. pneumophila,* gram-negative bacilli, *M. pneumoniae, H. influenzae,* and *S. aureus* (Torres et al., 1996).

Cavitation, necrosis, and gangrene (Fig. 11) frequently occur in pneumonia with lobar enlargement (Woodridge, 1992) and cause lucencies within the consolidated lobe. Lobar pneumonia in a patient with emphysema may have a similar appearance. Comparison with previous films will confirm the preexisting lucencies in this case.

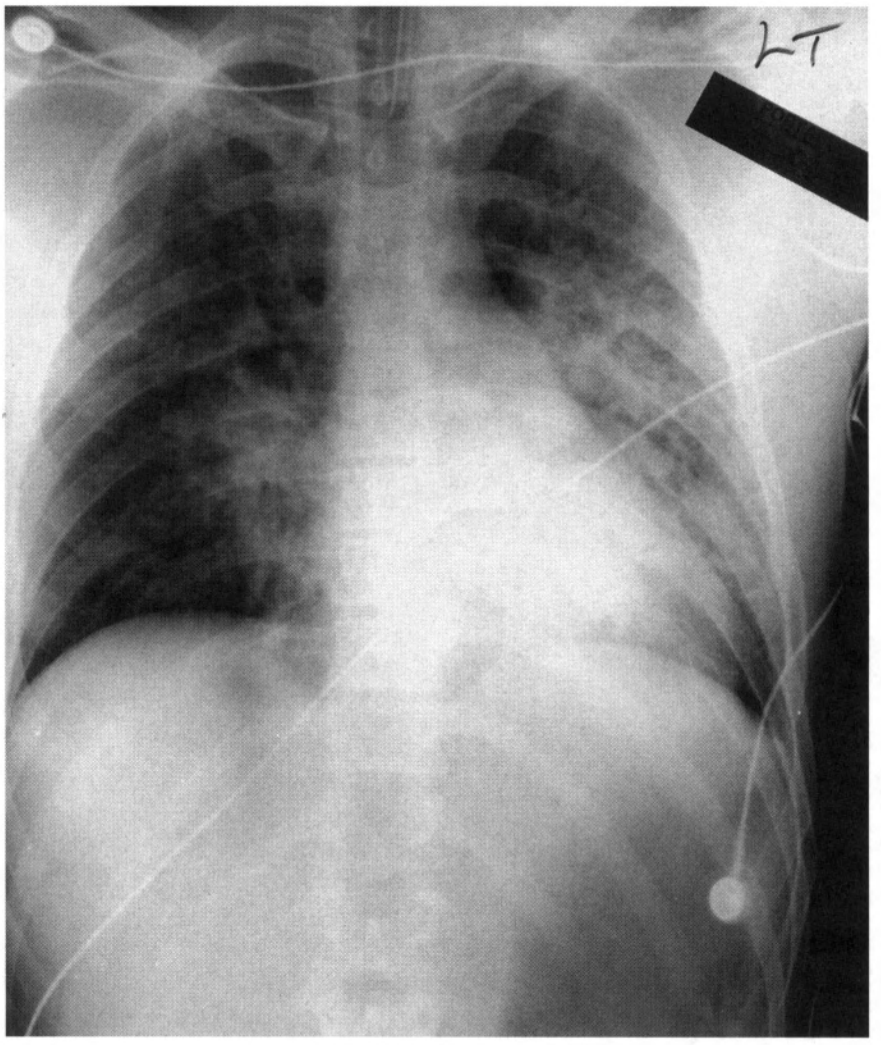


FIGURE 9. (*Continued*)

Bronchopneumonia

Bronchopneumonia initially involves the bronchi and bronchioles but spreads rapidly to involve the peribronchiolar alveoli. In its earliest stage it will be apparent on the chest radiograph as regional, diffuse or bilateral accentuation of the bronchovascular markings and bronchial wall thickening. However, by the time the chest radiograph has been obtained the infection usually has spread to the peribronchiolar alveoli and has begun to opacify multiple noncontiguous secondary lobules and is seen on the film as multiple ill-defined acinar nodules (Fig. 3). As the disease progresses more secondary lobules become involved and the chest radiograph will show multiple regions of patchy air space opacification (Woodridge, 1992; Conces, 1994). The underlying accentuated bronchovascular markings and bronchial wall thickening may be obscured but is typically apparent if sought (Fig. 9). In aggressive bronchopneumonia the patchy air space disease spreads, becoming more confluent, to involve one or more entire lobes and may become indistinguishable from lobar pneumonia. However, atelectasis of the involved lobes is more common in bronchopneumonia due to airway obstruction by

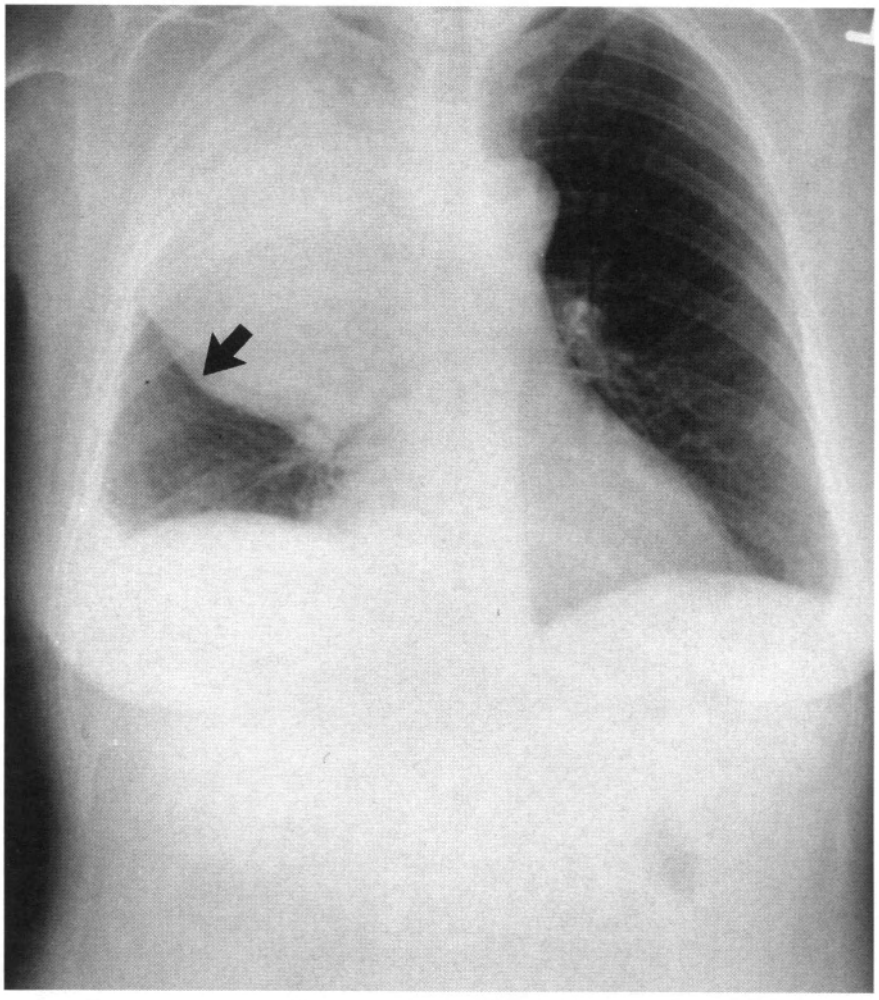


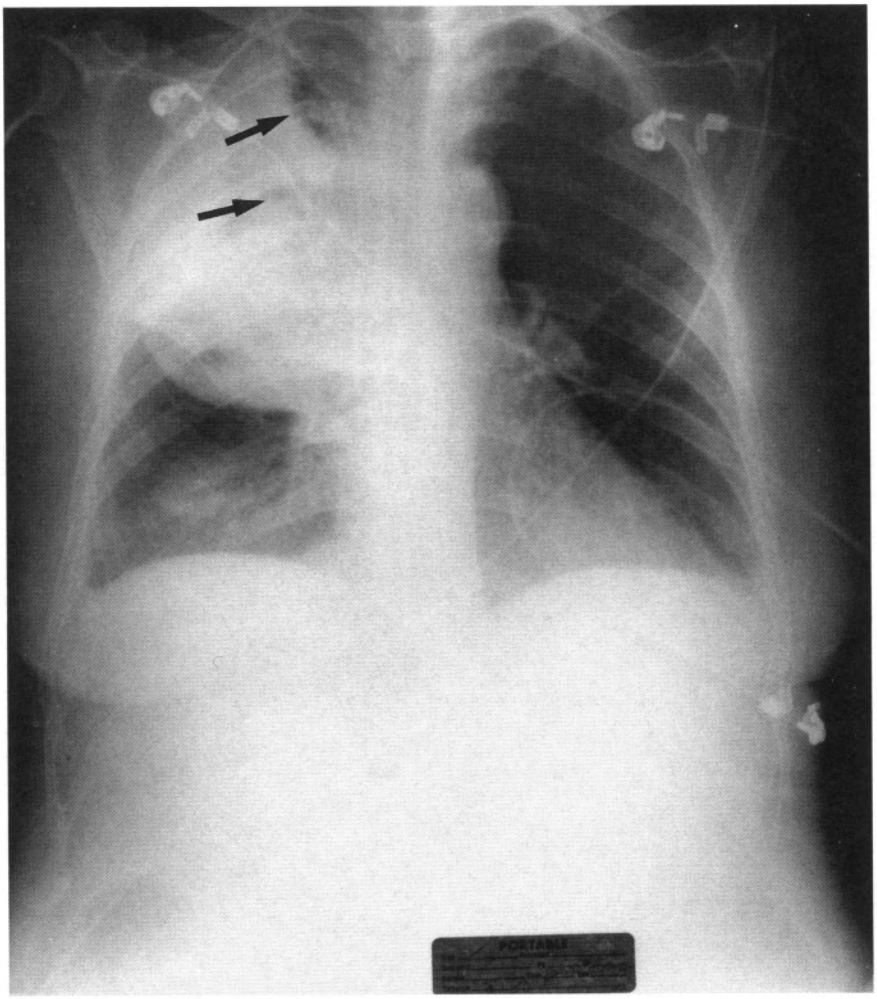
FIGURE 10. *Legionella pneumophila* pneumonia in the right upper lobe causing lobar enlargement as indicated by the bulging minor fissure (arrow).

inflammatory debris. In the most severe cases of bronchopneumonia the patient will develop diffuse bilateral consolidation. Necrosis with formation of pneumatoceles, cavities, and abscesses are frequent complications of bronchopneumonia (Woodridge, 1992) (Fig. 12).

Bronchopneumonia is typically caused by bacterial infection (Conces, 1993) and is most commonly due to *S. aureus, L. pneumophila, S. pneumoniae,* gram-negative bacilli *(Escherichia coli, Proteus, Pseudomonas aeruginosa,* and *Serratia)* and/or anaerobic bacteria. Gram-negative bacilli and anaerobic bacteria are frequent causes of bronchopneumonia in patients who aspirate oral or gastric contents due to neuromuscular dysfunction or loss of consciousness. Aggressive viral pneumonia may cause a bronchopneumonia pattern (Woodridge, 1992).

Nodular Pneumonia

Nodular patterns of pneumonia may range from a single focus of round pneumonia to more numerous and widely distributed nodules. Pneumonia nodules are typically poorly defined and range in size from acinar nodules, measuring less



A

FIGURE 11. Pulmonary gangrene (necrosis). This is the same patient as in Fig. 10. Lucencies (arrows) have developed in the enlarged right upper lobe consistent with necrosis. (*Continued*)

than 1 cm in diameter, to nodules measuring 10 cm or more that resemble masses (Miller, 1992). The nodular opacities can be due to foci of air space consolidation, septic emboli, or granulomas and may have a regional or diffuse distribution.

S. aureus, S. pneumoniae, L. pneumophila, and *Nocardia* and various gram-negative bacilli are foremost among bacterial pathogens that can cause a mass-like round pneumonia. Multiple acinar and larger nodular opacities can be seen in the earliest stages of bronchopneumonia. Reactivation tuberculosis can produce nodular opacities (Fig. 13). Acute fungal infections typically begin as focal areas of air space opacification that may become better defined and take on a nodular or mass-like appearance as granuloma formation develops. Some may cavitate. Fungal infections commonly producing nodular opacities include A. *fumigatus, C. immitis, C. neoformans* and Mucorales. The most common pattern seen with invasive pulmonary aspergilosis (Conces, 1993) is multiple nodules which cavitate due to infarction within the infected regions.

Septic emboli produce focal areas of pneumonitis, predominantly in the dependent regions of the lungs, that are poorly defined and frequently

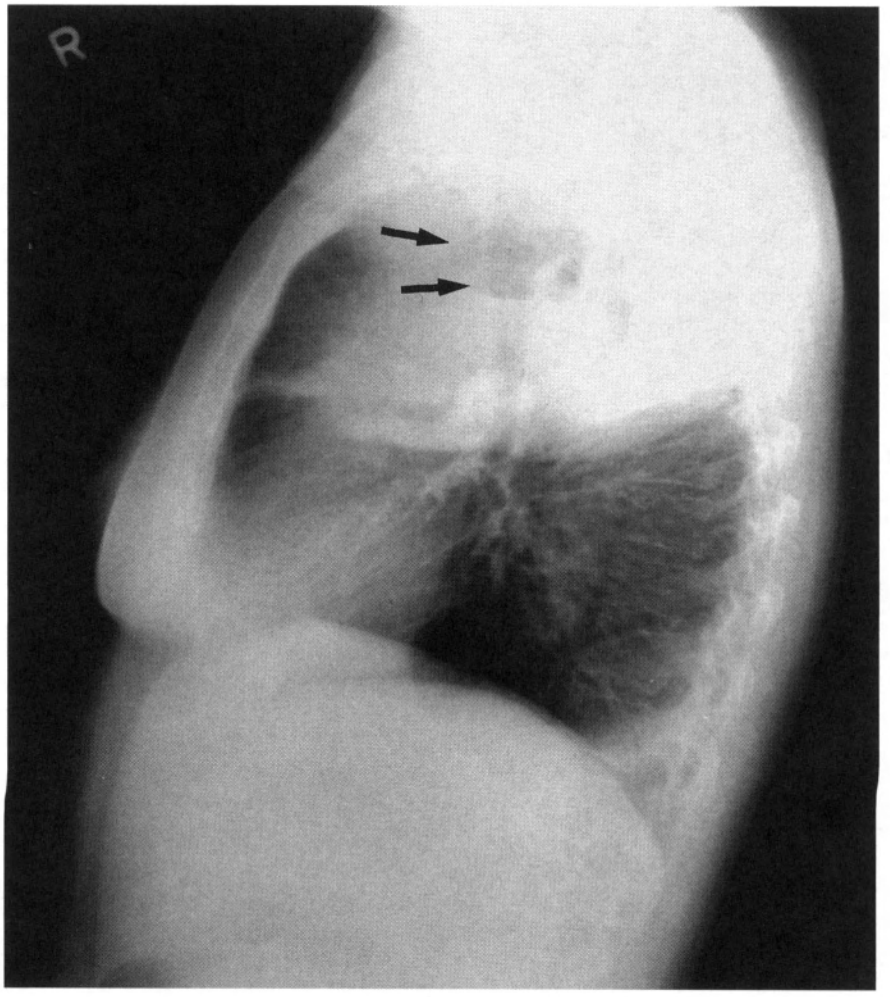


FIGURE 11. (*Continued*)

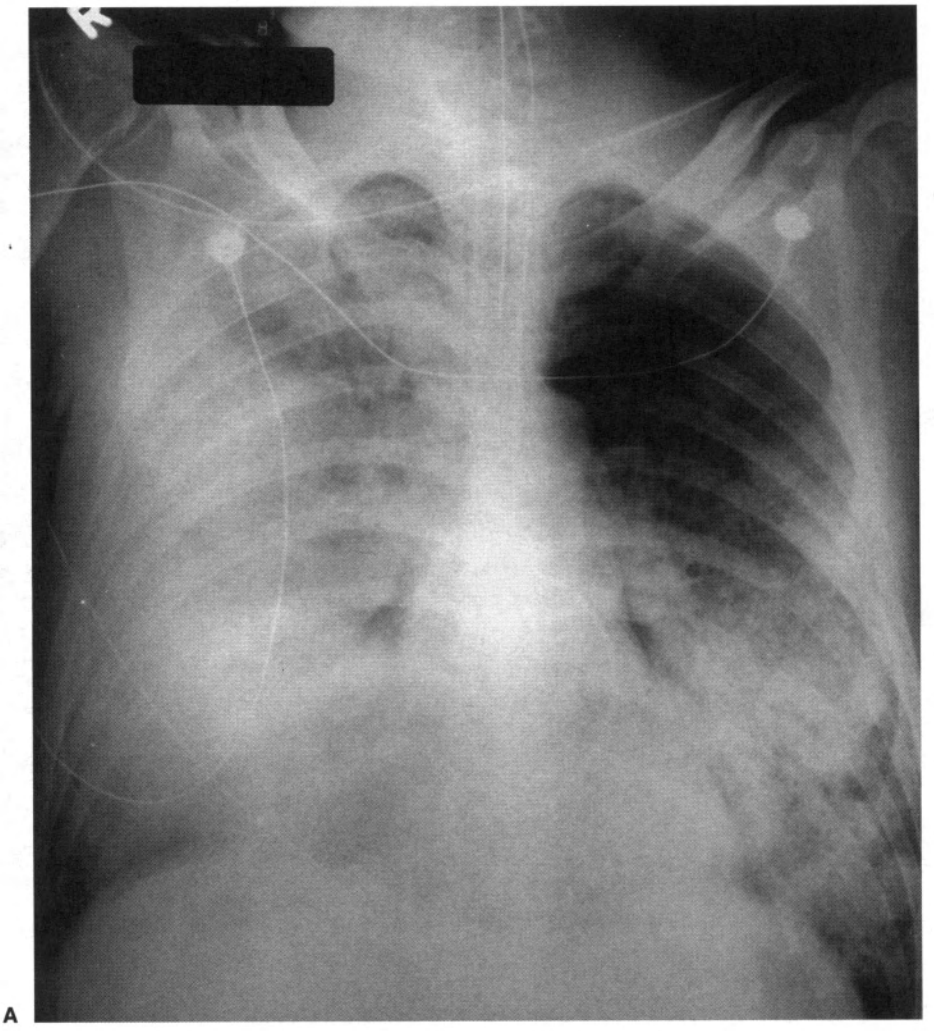
cavitate. The opacities may be pleural and wedge-shaped. In outpatients they occur most typically in intravenous drug abusers, patients with indwelling central venous catheters, and those with endocarditis and infected thrombophlebitis (Conces, 1994). The pathogens are most commonly *S. aureus,* gram-negative bacilli, anaerobes, and streptococci.

Also included in this category are the various causes of a miliary pattern of lung infection (Fig. 14). Hematogenously disseminated mycobacterial or fungal infection may cause numerous small nodules measuring less than 5 mm in diameter. The fungi most associated with this pattern are *H. capsulatum* and C. *immitis.*

Diffuse Pneumonia

A diffuse distribution in one or both lungs can be seen with lobar (primary air space) pneumonia, bronchopneumonia, and nodular pneumonia. Lobar pneumonia or bronchopneumonia with a diffuse distribution typically represents an advanced bacterial pneumonia and a seriously ill patient. Diffusely distributed acinar nodules or confluent acinar nodules may be seen in bronchopneumonia or disseminated fungal pneumonia (Conces, 1994).

M. pneumoniae, C. pneumonia, and viral pneumonias typically present as an interstitial pneumonia. The chest radiograph demonstrates ac-



A

FIGURE 12. (A) diffuse bilateral *Klebsiella* pneumonia with relatively homogeneous opacification of the involved lung regions. Four days later (B) there are numerous lucencies in both lungs consistent with pneumatoceles. (*Continued*)

centuated bronchovascular markings and reticular or reticulonodular opacities. The involved region usually does not extend beyond one lobe (Möller, 1992) but the interstitial pneumonia may be diffusely distributed and may progress to a bronchopneumonia pattern (Woodridge, 1992). An interstitial pattern can be seen in disseminated fungal and mycobacterial infections (Conces, 1993). Other bacterial infections may present as an interstitial pneumonia. This is especially true of *S. pneumoniae* in HIV-infected patients (Yu & Maurer, 1996). *Pneumocystis carinii* pneumonia (PCP) (Fig. 2) primarily involves the alveoli but is usually first seen on the chest radiograph as diffuse bilateral interstitial reticular or reticulonodular opacities. If unchecked the opacities typically progress to regions of air space consolidation that may contain air bronchograms (Conces, 1993). A similar but coarser pattern may be seen with *Toxoplasma gondii.*

Location of the Pneumonia

There are pneumonia etiologies that favor certain regions of the thorax. Reactivation or postprimary tuberculosis (Miller, 1992) (Fig. 13) in ambulatory patients characteristically involves the apical and posterior segments of the upper lobes and the

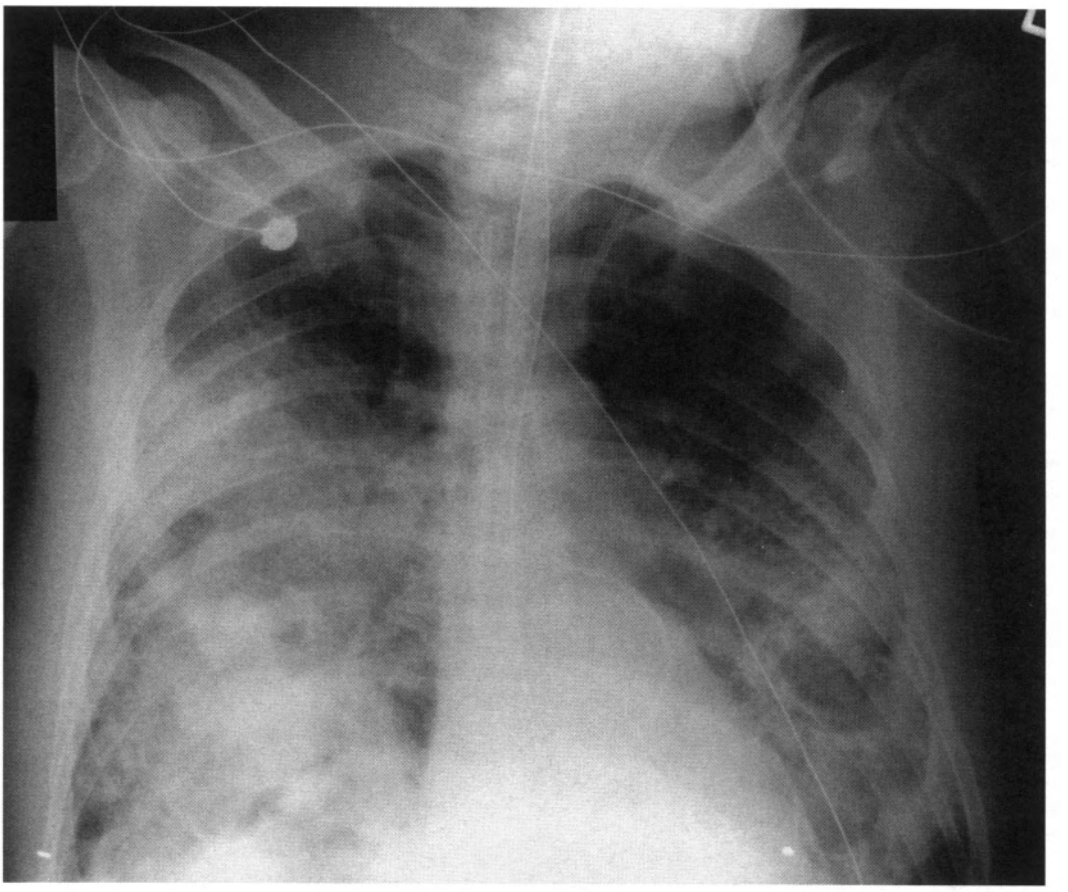


FIGURE 12. (*Continued*)

superior segments of the lower lobes. If fact, tuberculosis confined to another segment is likely to be primary infection. In patients with AIDS, primary tuberculosis usually presents as a mid- or lower-lung air space disease (Miller, 1992). PCP relapse in patients receiving pentamidine prophylaxis is seen typically in the apical regions of the lungs in ambulatory patients.

A lower-lung distribution with a peripheral bias is typical of hematogenous pulmonary infections (Woodridge, 1992). Acute miliary varieties of mycobacterial, fungal, and bacterial infections are included in this group. However, chronic miliary tuberculosis and blastomycosis will show an upper-lung preference (Gurney, 1992), likely reflecting different pathophysiology.

Aspirated infected oropharyngeal secretions and gastric contents will most heavily contaminate the dependent regions of the lung and the resulting aspiration pneumonia, typically gram-negative and anaerobic bacterial infections, will be most often found in the dependent regions predicted by the patient's position at the time of the aspiration episode. In the supine patient, the posterior aspect of both lower and upper lobes are the typical locations.

Pneumonia caused by viruses, *P. carinii,* and the atypical organisms may have a bilateral distribution and will (especially *M. pneumoniae)* radiate outward from the hila (Conces, 1993; Miller, 1994).

Lymphadenopathy

Lymphadenopathy is not a feature of the common acute bacterial pneumonias unless there is a

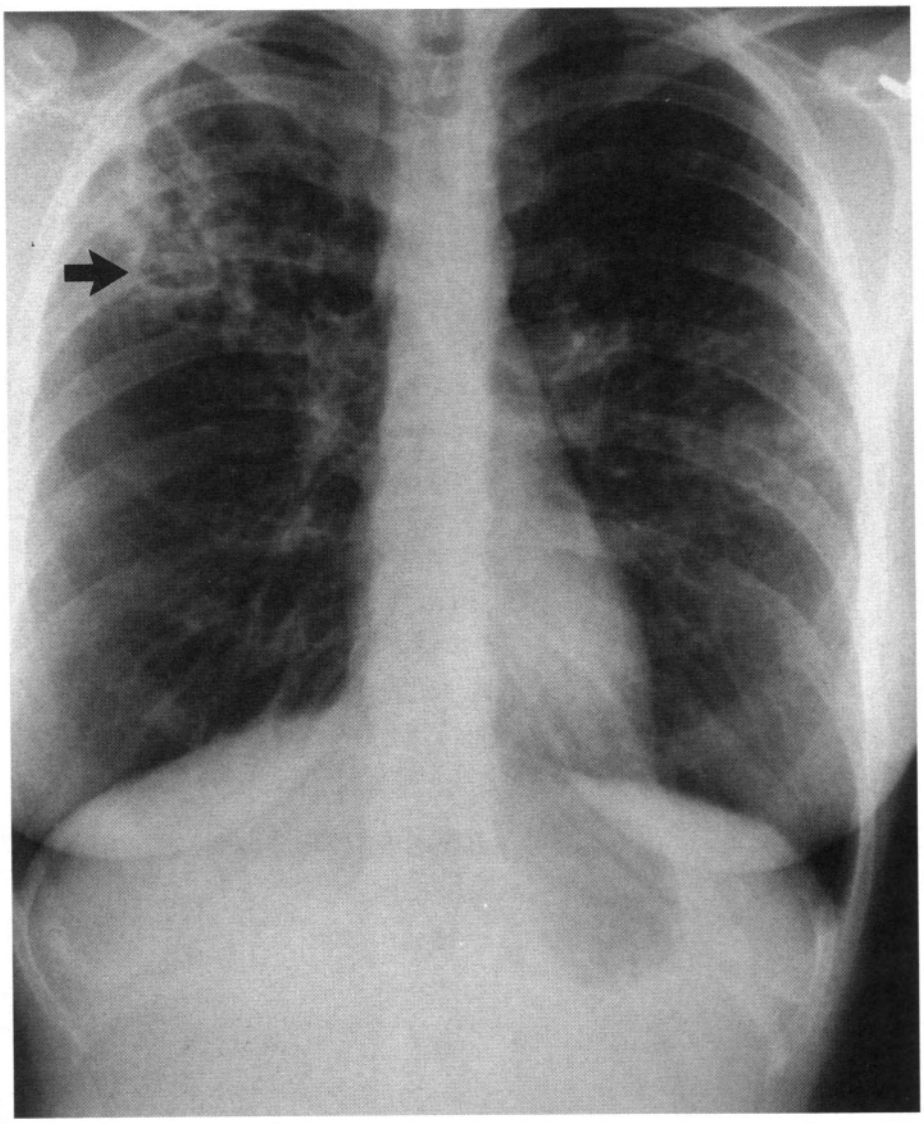


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FIGURE 13. Reactivation tuberculosis. There is coarse reticulonodular opacification with cavitation (arrows) in the right upper lobe with slightly less prominent predominantly nodular opacification in the left lung consistent with intrabronchial spread of the infection from the right upper lobe likely due to a ruptured cavity. (*Continued*)

complicating lung abscess or the pneumonia is secondary to an obstructing neoplasm. It is most typically associated with granulomatous infections caused by fungi and mycobacteria (Miller, 1994). Adenopathy accompanying pulmonary tuberculosis is strongly associated with primary infection (Miller, 1992). Adenopathy is not associated with reactivation tuberculosis or pulmonary infection with atypical mycobacteria (Woodridge, 1992; Conces, 1994). It is not a feature of pulmonary infection due to *L. pneumoniae* (Freundlich & Bragg, 1992) or *P. carinii* (Goldsmith, 1993; Goodman, 1992). Lymphadenopathy can occasionally be seen in pulmonary infection due to viruses and the atypical organisms *M. pneumoniae* and *C. psittaci* (Woodridge, 1992; Marrie, 1996). Tularemia is also a cause of hilar adenopathy (personal communication, Marrie, 1999).

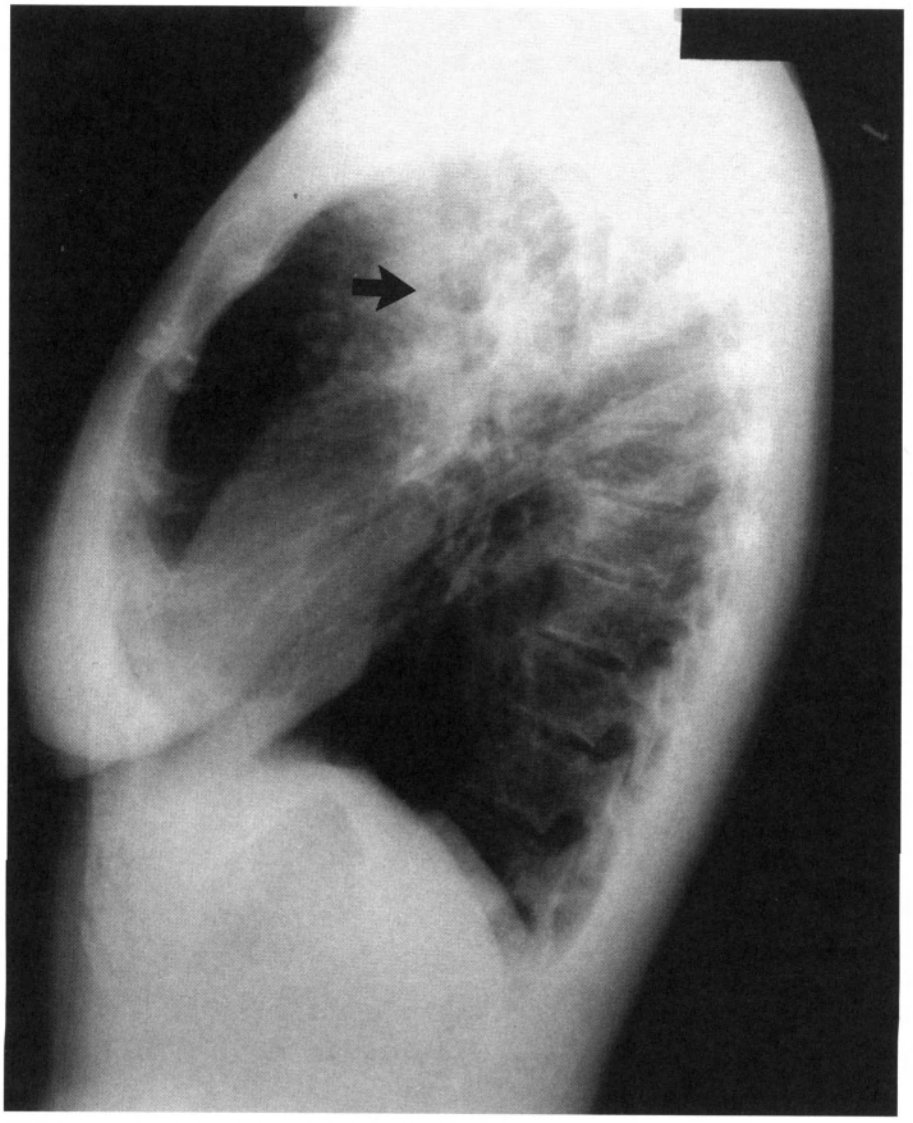


FIGURE 13. (*Continued*)

Specific Etiologies

Streptococcus pneumoniae is the most common cause of CAP (Woodridge, 1992) (Table 1). Classically, lobar pneumonia has been the most typical radiographic pneumonia pattern ascribed to this organism (Freundlich, 1992). However, in the experience of recent and current clinical practice, bronchopneumonia is becoming a more frequent presentation of *S. pneumoniae* pulmonary infection, and lobar pneumonia caused by this organism is becoming considerably less common (personal communication, Marrie, 1999). *S. pneumoniae* is the most common cause of round pneumonia (Fig. 4) and complete lobar consolidation (Fig. 5). *S. pneumoniae* may also cause lobar enlargement. *S. pneumoniae* pneumonia may be complicated by empyema or bronchopleural fistula. Pulmonary

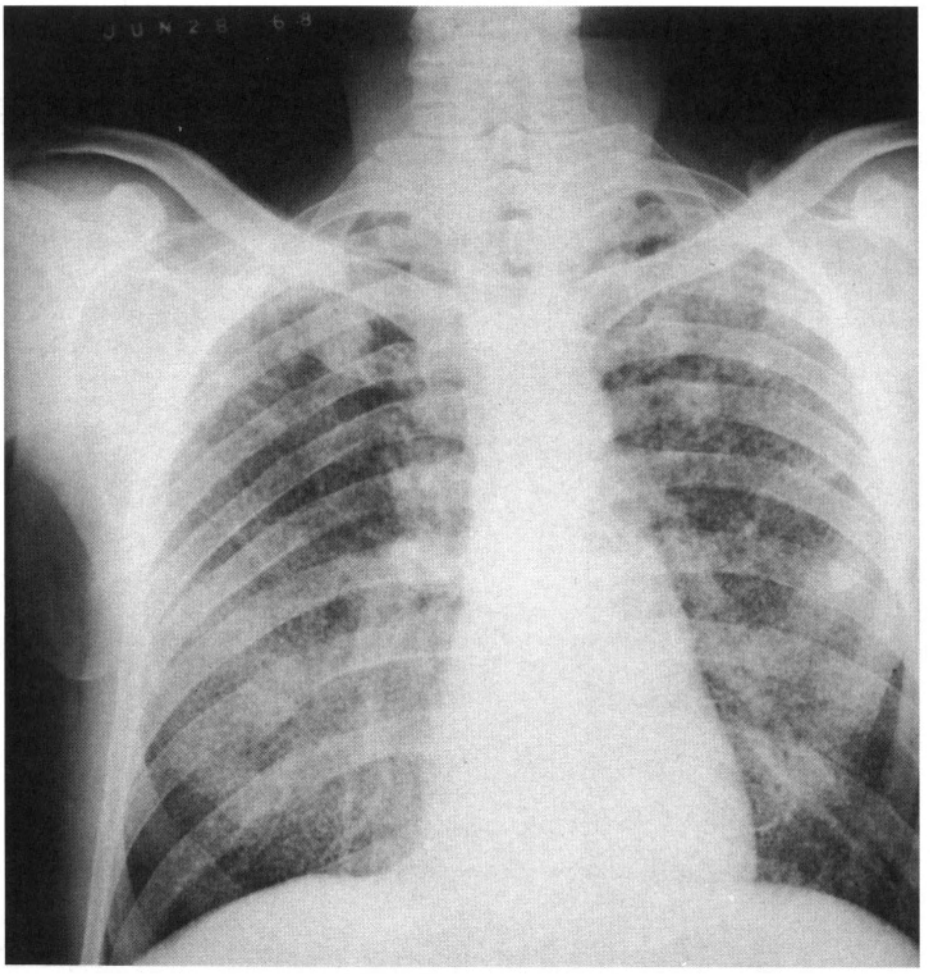


FIGURE 14. Miliary tuberculosis.

gangrene can be seen, especially when lobar enlargement has occurred. Cavitation is uncommon and pneumatoceles are rare.

H. influenzae pulmonary infection is associated with both lobar pneumonia and, occasionally, interstitial pneumonia patterns (Yu & Maurer, 1996). *H. influenzae* and *S. pneumoniae* cause the majority of air space CAP in children (Condon, 1991) and are the cause of most bacterial pneumonias in patients with AIDS and COPD (Yu & Maurer, 1996). It may occasionally cause lobar enlargement and pulmonary necrosis with pneumatoceles or gangrene. It is one of the most common causes of severe CAP (Marrie, 1996; Torres et al., 1996) and is one of the two organisms which cause the majority of abscesses and empyema in children (Wallenhaupt, 1991). The other is *S. aureus.*

Klebsiella is typically associated with lobar pneumonia and is the second most common cause of complete lobar consolidation. It is strongly associated with lobar enlargement and pulmonary gangrene.

S. aureus may cause lobar pneumonia, with or without lobar enlargement, or bronchopneumonia with a unilateral or bilateral distribution. *S. aureus* is the most common cause of septic emboli. Complications strongly associated with this infection include cavitation, pneumatoceles, and a fulminant course with adult respiratory distress syndrome (ARDS).

TABLE 1. Pneumonia Caused by Pyogenic Bacteria

Organism	Patterns	Complications	Comments
S. pneumoniae (Woodridge, 1992; Yu & Maurer, 1996)	Lobar[a] Bronchopneumonia Interstitial	Lobar enlargement Empyema Bronchopleural fistula Pulmonary gangrene	Most common cause of CAP, round pneumonia, and complete lobar consolidation; cavitation uncommon, pneumatoceles rare
H. influenzae (Condon, 1991; Ely & Haponik, 1991; Marrie, 1996; Wallenhaupt, 1991; Torres et al., 1996; Yu & Maurer, 1996)	Lobar[a] Interstitial	Lobar enlargement Pulmonary necrosis Pneumatoceles Pulmonary gangrene	*H. influenzae* and *S. pneumoniae* cause most air space CAP in children and most bacterial pneumonia in patients with AIDS and COPD *H. influenzae* causes up to 20% of CAP in adults and is one of the most common causes of severe CAP *H. influenzae* and *S. aureus* cause most abscesses and empyema in children.
Klebsiella (Woodridge, 1992)	Lobar[a]	Lobar enlargement Pulmonary gangrene	Second most common cause of complete lobar consolidation
S. aureus (Woodridge, 1992)	Lobar[a] Bronchopneumonia[a] Septic emboli	Lobar enlargement Cavitation Pneumatoceles Fulminant course ARDS	Most commmon cause of septic emboli
Gram-negative bacilli (Woodridge, 1992)	Lobar[a] Bronchopneumonia[a]	Empyema Cavitation Pneumatoceles Bronchopleural fistula Pulmonary gangrene	May cause complete lobar consolidation Septic emboli may contain gram-negative bacilli
Anaerobic bacteria (Woodridge, 1992)	Bronchopneumonia[a] Septic emboli	Empyema Cavitation Bronchopleural fistula Pulmonary gangrene	

CAP, community-acquire pneumonia; COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome.
[a]Most common pattern observed.

Gram-negative bacilli are associated with both lobar and bronchopneumonia patterns. In lobar pneumonia there may be complete lobar consolidation. Complications include empyema, cavitation, pneumatoceles, and bronchopleural fistula (Woodridge, 1992).

Anaerobic bacteria are associated with bronchopneumonia patterns. Complications include empyema, cavitation, pulmonary gangrene, and bronchopleural fistula (Woodridge, 1992).

Pulmonary infections due to *M. tuberculosis* (Table 2) can be classified as primary, reactivation, miliary, and progressive primary (Miller, 1992). Primary tuberculosis typically causes pulmonary air space consolidation. Occasionally there may be lobar enlargement which may be complicated by necrosis, pneumatoceles, cavitation, and pulmonary gangrene. These will be manifested by lucencies developing within the consolidated area. Hilar and mediastinal adenopathy is associated with primary tuberculosis. The incidence of hilar adenopathy in primary tuberculosis decreases with age. It ranges from virtually 100% in toddlers to about 40% in young adults to as low as 10% in the older population (Leung, 1999). Pleural effusions are also common; they may be loculated and indolent but nevertheless up to one third will harbor active *M. tuberculosis* organisms (Leung, 1999). Rarely the clinical course may be fulminant and complicated by ARDS. In the normal host, the adenopathy and pneumonia usually resolve over several months. The enlarged lymph nodes progressively shrink and frequently calcify. The parenchymal consolidation clears by contracting until it disappears or forms a nodule that may mimic a neoplasm. The nodule is known as a Ghon's focus. When it is accompanied by calcified central lymph nodes the combination is known as a Ranke's complex. The nodule typically

TABLE 2. Pneumonia Caused by Granulomatous Bacteria

Organism	Patterns	Complications	Comments
M. tuberculosis (Miller, 1992)	Primary air space consolidation	Effusion Atelectasis Lobar enlargement Necrosis pneumatoceles Pneumothorax Cavitation Pulmonary gangrene Bronchopleural fistula Fulminant course with ARDS	Hilar and mediastinal adenopathy common Pleural effusion common (may locutate, may contain MTB) Consolidation typically resolves in several months; may clear or shrink to form granuloma (Ghon's focus) Ghon's plus calcified central nodes is a Ranke's complex With time Ghon's disappears or shrinks and calcifies. Immunocompromised hosts may demonstrate progressive primary disease where the infection spreads from one lobe to the other
	Reactivation: consolidation (usually upper lung)	Cavitation Opacification may be pleural, with pleural thickening Usually causes fibrocalcific scarring and architectural distortion	To be considered radiographically stable there must be no change for at least 6 months (Miller, 1992)
	Miliary TB: Acute; numerous 1-mm nodules with diffuse basal predominance. Chronic; 3- to 5-mm nodules with upper predominance (Gurney, 1992; Miller, 1992)		Most commonly in patients with compromised immunity (Miller, 1992)
Atypical mycobacteria (Miller, 1992)	Solitary or multiple air space opacity[a] Nodules	May become chronic Cavitation	More mid- and lower-lung and less upper lung involvement than MTB Immunocompetent: lymphadenopathy uncommon and cavitation frequent Immunocompromised: cavitation rare and lymphadenopathy frequent Direct inhalation of contaminated soil or water (no human-to-human transmission) Virtually all primary infections, no reactivation form
Nocardia asteroides (Champter, 1993; Miller, 1992)	Localized[a] or extensive air space consolidation	Cavitation Effusion	May mimic a pulmonary mass Severely immunocompromised may have disseminated disease Ubiquitous in soil; inhalation of spores will cause disease only in immunocompromised or chronic lung disease, especially pulmonary alveolar proteinosis
Actinomyces israeli (Chambers, 1993; Miller, 1992)	Region of air space opacification	Cavitation Effusion	May mimic a pulmonary mass Adenopathy is rare Where infection abuts chest wall or mediastinum it may become locally invasive Organism is component of normal oropharyngeal flora and pulmonary disease is usually due to aspiration

MTB, *Mycobacterium tuberculosis*; ARDS, adult respiratory distress syndrome; TB, tuberculosis.
[a]Most common pattern observed.

continues to shrink over several more months until it disappears or becomes a 5- to 10-mm, usually calcified, chronic granuloma.

In cases of reactivation tuberculosis (Stauffer, J. L., 1993), the chest radiograph demonstrates consolidation, alone or with cavitation, usually in the apical and posterior segments of the upper lobe and superior segment of the lower lobes. Other regions may be involved at the same time but active tuberculosis not involving the apical, posterior, or superior segments is probably a primary infection. Reactivation tuberculosis usually leaves fibrocalcific opacification consisting of coarse reticular or reticulonodular opacities with or without associated calcification. The opacification may be pleural, with pleural thickening and architectural distortion due to fibrotic contraction. To be considered radiographically stable there must be no change for at least 6 months (National Tuberculosis and Respiratory Disease Association) (Miller, 1992). However, radiographically stable disease may continue to harbor and shed active *M. tuberculosis,* and clinical correlation is still necessary to rule out active disease (Leung, 1999).

Miliary tuberculosis (Fig. 14) is due to hematogenous dissemination of the organisms. It is seen most commonly in patients with compromised immunity (Miller, 1992). Miliary tuberculosis may be acute or chronic. The acute form has the typical vascular distribution and the chest radiograph demonstrates numerous tiny, approximately 1-mm nodules that are more predominant in the lower lungs. The chronic form consists of larger nodules, 3 to 5 mm, which may have an acinar appearance. They are more predominant in the upper lungs (Gurney, 1992; Miller, 1992).

The immunocompromised patient may also demonstrate progressive primary tuberculosis where disease appearing initially in one lobe spreads to involve multiple ipsilateral and contralateral lobes.

Tuberculosis may be complicated by pleural effusion, empyema, cavitation, bronchiectasis, aspergilloma, hemoptysis, bronchopleural fistula, pneumothorax, and atelectasis. A solitary tuberculous granuloma may mimic a carcinoma.

Mycobacterium kansasii and *Mycobacterium avium-intracellulare* are the atypical mycobacteria that most commonly cause pulmonary disease (Miller, 1992). Unlike *M. tuberculosis,* there is no human-to-human transmission of these pathogens. Pulmonary disease is usually caused by direct inhalation of contaminated soil or water. There is no reactivation form of atypical mycobacterial infection. Virtually all are primary infections. Atypical mycobacterial infections may become chronic.

Atypical mycobacterial pulmonary infection typically causes solitary or multiple regions of air space opacification or nodules. Unlike tuberculosis there is more mid- and lower-lung involvement and less upper lobe predominance. In the immunocompetent patient, lymphadenopathy is uncommon and cavitation in the affected regions or nodules is frequent. The cavities are often thin-walled and may simulate bronchiectasis on the chest radiograph. On the other hand, in the immunocompromised patient with AIDS the situation is reversed. Cavitation is rare while lymphadenopathy is common.

Nocardia asteroides has in the past been classified as a fungus but it is now classified as a member of the actinomycetes group and recognized to be a higher-level bacterium (Chambers, 1993). It is ubiquitous in the soil. Inhalation of its spores will typically cause infection only in patients who are immunocompromised or who have chronic lung disease, particularly pulmonary alveolar proteinosis. It most often causes a localized region of air space consolidation. The margins of this region may be quite well defined and mimic a pulmonary mass. Cavitation and effusion are common. The air space disease may be extensive. Disseminated disease may occur in the severely immunocompromised.

Actinomyces Israeli also used to be classified as a fungus but is now recognized to be a higher-level bacterium (Chambers, 1993). It is a component of the normal oropharyngeal flora. Pulmonary disease is usually due to aspiration of oropharyngeal secretions. On chest radiograph the infection manifests as a region of air space opacification that cannot be differentiated from other causes of pneumonia. The region of consolidation may resemble a pulmonary mass. Cavitation and effusion are common whereas adenopathy is rare. Where the infection abuts the chest wall or mediastinum it may become locally invasive, occasionally causing localized osteomyelitis or a draining sinus (Miller, 1992).

Atypical pneumonia is a term used to desig-

nate a pneumonia syndrome that is marked by a slow onset, an early prominence of systemic rather than respiratory symptoms, a nonproductive cough, and more marked findings on the chest radiograph than would be suggested by the clinical examination. The currently recognized causes of this syndrome include several bacteria and a number of viruses (Marrie, 1996). *M. pneumoniae, L. pneumophila, C. pneumoniae, C. psittaci,* and *Coxiella burnetii* are the bacterial agents (Table 3). The viral agents are Hantavirus and a number of others, including adenovirus, respiratory syncytial virus, papainfluenza virus, influenza A and B, rubeola, varicella, Epstein-Barr, and cytomegalovirus.

M. pneumoniae is spread by inhalation of droplets. The most typical initial chest radiographic pattern is interstitial pneumonia with reticular, micronodular, or reticulonodular opacification which may be diffuse but is usually confined to one lobe (Müller, 1992). *M. pneumoniae* is the most common bacterial cause of interstitial pneumonia (Woodridge, 1992). It may progress to segmental or lobar pneumonia or bronchopneumonia. With severe *M. pneumoniae* pulmonary infection, the most frequent complication is respiratory failure.

L. pneumophila is an aquatic organism found in natural and manmade water supplies. It is spread by inhalation of contaminated water droplets. Most patients with pulmonary infection caused by this organism have comorbidity due to cardiac or pulmonary disease. In the majority of patients the chest radiograph will demonstrate patchy air space disease with a segmental, lobar, or diffuse distribution. Another frequent radiographic presentation is multiple poorly defined nodular opacities. In some studies there has been a predilection for the lower lobes. There is typically rapid progression of inhomogeneous disease to produce bilateral bronchopneumonia or complete uniform consolidation in the affected lobe or lobes. *L. pneumophila* is the second most common cause of severe CAP and may have a fulminant course with ARDS. Pleural effusions are common complications. Adenopathy and cavitation are uncommon (Woodridge, 1992; Freundlich & Bragg, 1992). *Legionella* pneumonia clears slowly compared to other pneumonias, and delayed resolution should suggest the possibility of this disease (Freundlich & Bragg, 1992).

C. pneumoniae pulmonary infection accounts for 10% or more of CAP and up to 10% of severe CAP (Marrie, 1996). *C. psittaci,* a closely related bacterium carried by psitticine birds (e.g., parrots, parakeets, finches, and turkeys), can cause an atypical pneumonia known as psittacosis. Chest radiographic appearances are similar to those found in other cases of atypical pneumonia or atypical pneumonia syndromes.

Pulmonary infection due to inhalation of *C. burnetii* is known as Q fever. The chest radiographic features may be similar to the other causes of CAP. The most common findings (90%) are segmental, lobar, or patchy air space disease. Nodular or mass-like disease is found in about 7% and interstitial pneumonia in about 3% (Gikas et al., 1999). Gikas et al. reported pleural effusion in about 17% in the series of 85 patients, but they did not see any evidence of adenopathy. In their series, resolution was slow and took up to 6 weeks. When the radiographic features are nonspecific, multiple rounded pulmonary nodules following exposure to parturient cats should suggest Q fever (Gordon et al., 1984).

Viral pneumonias account for an estimated 25% of CAP cases. Infections typically result from inhalation of contaminated droplets and initially involve the walls of the airways and may be limited to them. Spread of the infection to the peribronchial interstitium, peribronchiolar interstitium, and interlobular septa causes acute interstitial pneumonia. Further spread to the intralobular interstitium (Webb et al., 1996) and peribronchiolar alveoli will cause either a bronchopneumonia pattern or, if the interstitial opacities are not prominent, nodular (typical of varicella) or patchy air space opacification. The disease may be diffuse and bilateral or confined to one region or lobe. If confined to one lobe it may simulate bacterial lobar pneumonia. Acute fulminant viral pneumonia causes a generalized hemorrhagic pulmonary edema that begins with a central distribution and spreads to involve the whole lung, causing ARDS. This is typical of influenza and Hantavirus infection but may be caused by other viruses especially varicella and cytomegalovirus. Complications of viral pneumonias include adenopathy, small effusions, and ARDS (Woodridge, 1992; Freundlich & Bragg, 1992).

Fungal pneumonias (Miller, 1992) due to *H. capsulatum, C. immitis, Blastomyces dermatitidis.*

TABLE 3. Organisms Causing an Atypical Pneumonia Syndrome[a]

Organism	Patterns	Complications	Comments
Mycoplasma pneumoniae (Müller, 1992; Woodridge, 1992)	Interstitial pneumonia[b] Segmental or lobal pneumonia Bronchopneumonia	Respiratory failure	May be diffuse but usually confied to one lobe Most common bacterial cause of interstitial penumonia
Chlamydia pneumoniae (Marrie, 1996)	Interstitial pneumonia[b] Segmental or lobal pneumonia Bronchopneumonia	Severe CAP	Accounts of 10% of CAP and 10% of severe CAP *Chlamydia psitacci* is closely related, carried by healthy birds and causes a similar atypical pneumonia syndrome known as psittacosis
Coxiella burnetii (Marrie, 1996; Gikas et al., 1989)	Segmental or lobar pneumonia Bronchopneumonia Multiple rounded opacities Interstitial pneumonia[b]	Respiratory failure	Q fever
Legionella pneumophila (Freundlich & Bragg, 1992; Woodridge, 1992)	Patchy air space disease with segmental, lobar or diffuse distribution[b] Poorly defined nodular opacities	Pleural effusions Rapid progression to complete lobar consolidation or bilateral bronchopneumonia Fulminant course with ARDS	Aquatic organism found in all water supplies Spread likely by inhalation of contaminated water droplets Second most common cause of severe CAP Predilection for lower lobes Clears slowly compared with other pneumonias Adenopathy and effusion are uncommon Patients with *Legionella* pneumonia usually have comorbid cardiac or pulmonary disease Adenopathy and cavitation are uncommon
Viruses (Freundlich & Bragg, 1992; Webb et al., 1995; Woodridge, 1992)	Interstitial pneumonia[b] Bronchopneumonia Nodular pneumonia Patchy air space Pneumonia	Adenopathy Small effusions Fulminant pneumonia with hemorrhagic edema and ARDS (especially influenza, Hantavirus, CMV, and varicella)	Accounts for about 25% of CAP Pulmonary infections caused by inhalation of contaminated droplets Disease may be diffuse and bilateral or confined to one region or lobe If confined to one lobe is may simulate bacterial lobar pneumonia

CAP, community-acquired pneumonia; ARDS, adult respiratory distress syndrome; CMV, cytomegalovirus.

[a]Atypical pneumonia is a term used to designate a pneumonia syndrome which is marked by a slow onset, an early prominence of systemic rather than respiratory symptoms, a nonproductive cough, a more marked findings on the chest radiograph than would be suggested by the clinical examination. The currently recognized causes of this syndrome include several bacteria (*M. pneumoniae*, *L. pneumophila*, *C. pneumoniae*, *C. psittaci*, *Coxiella burnetii*) and a number of viruses (Hantavirus, adenovirus, respiratory syncytial virus, parainfluenza virus, influenza A and B, rubeola, varicella, Epstein-Barr, and CMV) (Marrie, 1996).

[b]Most common pattern observed.

and *C. neoformans* are virtually always caused by inhalation of contaminated dust and are relatively common where these organisms are found naturally in the soil (Table 4).

On the chest radiograph an acute pneumonia due to histoplasmosis is typically seen as solitary or multiple focal air space opacities frequently accompanied by adenopathy. Multiple nodules throughout both lungs may be seen if there has been a more marked degree of exposure to this fungus. The nodules may be well or poorly defined. Their sizes range from 1 to 5 mm. Pulmonary infection with this fungus may cause a solitary granulomatous nodule measuring up to about 4 cm which may mimic a neoplasm. Chronic pulmonary histoplasmosis may occur in patients with bullous lung disease. Air space opacification with cavitation and architectural distortion due to fibrosis occur and may mimic tuberculosis or carcinoma. Disseminated disease may occur in the immunocompromised patient. Complications of pulmonary infection by *H. capsulatum* include mediastinal adenopathy and fibrosing mediastinitis.

Acute pulmonary infection with *C. immitis* in the immunocompetent patient usually presents as a region of patchy air space consolidation most often involving a lower lobe. Adenopathy occurs in an estimated 20% of cases. Persistent air space consolidation is most commonly due to persistent primary disease. Reactivation pulmonary coccidioidomycosis and chronic pulmonary coccidioidomycosis may cause persistent regions of air space opacification or nodules and may cavitate. An asymptomatic, solitary thin-walled cavity may be found. It is considered to be the classic lesion for this disease and is seen in 10% to 15% of patients with this disease. Disseminated disease, including miliary disease, may occur, especially in the immunocompromised patient (Miller, 1992).

Pulmonary blastomycosis is seen on chest radiograph most often as a region of focal or patchy pneumonia that may be found in any lobe. Solitary or multiple nodules may occur. Adenopathy and cavitation are unusual. Rarely there is diffuse nodular, micronodular, or miliary disease.

The most common chest radiographic finding in pulmonary cryptococcosis is a solitary pleural mass that may measure up to 10 cm in diameter and mimic carcinoma. It may also present as a region of air space opacification. These findings may be multifocal. Cavitation, adenopathy, and effusion are uncommon. Diffuse air space or miliary disease may occur in immunocompromised patients.

A. fumigatus and other species of this group are ubiquitous in nature and form part of the normal human oropharyngeal ecology. Aspiration or inhalation of oropharyngeal secretions containing these organisms normally does not cause pulmonary disease unless lung architecture or immunity has been altered or compromised. Pulmonary infections with this fungus are classified as noninvasive, semi-invasive, and invasive aspergillosis and allergic bronchopulmonary aspergillosis.

Noninvasive aspergillosis is a saprophytic colonization of a bronchiectatic airway, bulla or preexisting cavity, or other space by *Aspergillus* species. The colonization may occur in the host with normal immunity when there is a preexisting cavity to which the fungal spores can gain access. The fungus proliferates within the space and fills it with a mass of matted hyphae called a mycetoma (Fig. 15). The mass may be mobile within the space. *Aspergillus* species are not the exclusive causes of mycetomas. Saprophytic colonization may also occur with semi-invasive aspergillosis.

Semi-invasive aspergillosis occurs when there is mild immunosuppression, for example, due to age or debilitating illness. The pulmonary infection begins as a region of air space pneumonia, usually at an apex, that eventually cavitates due to internal necrosis. A mycetoma may form within the cavity, typically in association with apical pleural thickening. An "air crescent sign" can be seen during this process when either the necrotic tissue or the mycetoma separates from the wall of the developing space and forms a radiolucent arc along its margin.

Invasive aspergillosis occurs when there is severe immunocompromise. Most commonly there are multiple bilateral nodular foci of pulmonary infiltration or diffuse patchy air space opacification although in some cases there may be only a solitary region of air space opacification or a solitary nodule. Cavitation typically does not occur while the immune system is at its nadir but, rather, as the immune system is recovering. A crescent sign may be seen as central necrotic tissue separates from the margins of the cavity. Pleural effusion may occur and adenopathy is uncommon.

TABLE 4. Pneumonia Caused by Fungi

Fungus	Patterns	Complications	Comments
Histoplasma capsulatum[a] (Miller, 1992)	Solitary or multiple air space opacities[b] Solitary or multiple nodules	Mediastinal adenopathy Cavitation Focal pulmonary fibrosis Fibrosing mediastinitis	Nodules (1–5 mm) may be well or poorly defined Solitary nodule may be up to 4 cm and mimic neoplasm Chronic disease may be seen in bullous lung disease Immunocompromised may have disseminated disease
Coccodioides immitis[a] (Miller, 1992)	Region of air space opacification, usually lower lung[b]	Adenopathy Solitary thin-walled cavity (classic lesion)	Immunocompromised may have disseminated disease including miliary nodules Persistent air space disease most likely persistent primary Infection but reactivation and chronic forms do occur
Blastomyces dermatitidis[a] (Miller, 1992)	Focal or patchy air space disease in any lobe[b] Solitary or multiple nodules	Rarely, adenopathy and cavitation	Diffuse nodular or miliary disease may occur
Cryptococcus neoformans[a] (Miller, 1992)	Solitary pleural mass[b] Region of air space opacification; may be multifocal	Uncommonly, cavitation, adenopathy, effusion	Mass may mimic carcinoma
Candida albicans (Miller, 1992)	Bronchopneumonia[b] Multiple pulmonary nodules	Effusion Seldom, cavitation, adenopathy	Usually only in immunocompromised patients Infection caused by aspiration of oropharyngeal secretions comtaminated by *C. albicans*
Aspergillus fumigatus (Miller, 1992)			Ubiquitous in nature; normal human oropharyngeal flora Aspiration causes disease only if there is prior lung damage or if immunity is altered or compromised Infections classified as noninvasive, semi-invasive, invasive, and ABPA
Noninvasive	Mycetoma		Colonizes and proliferates within a cavity, bulla, or bronchiectactic airway Mycetoma may be mobile within the space
Semi-invasive (mildly immunocompromised)	Region of air space opacification usually at apex	Eventually cavitates due to necrosis May form mycetoma	Air cresent may be seen as necrotic tissue separates from margin of cavity
Invasive (severely immunocompromised)	Multiple bilateral nodular opacities or diffuse patchy air space opacification (may be solitary)	Cavitation not seen until immune system begins to recover May have pleural effusion	Air crescents may be seen as cavities form Adenopathy is uncommon
ABPA (seen in asthmatics)	Finger-in-glove mucous casts of opacified airways Segmental or lobar atelectasis Post-obstruction pneumonia	Rarely cavitates with mycetoma formation	Bronchial walls are hyperreactive to fungal spores and marked mucus production leads to masses of hyphae wihtin inspissated mucus within the affected airways

ABPA, allergic bronchopulmonary aspergillosis.
[a]Found in the soil; pulmonary infection usually caused by inhalation of contaminated dust.
[b]Most common pattern observed.

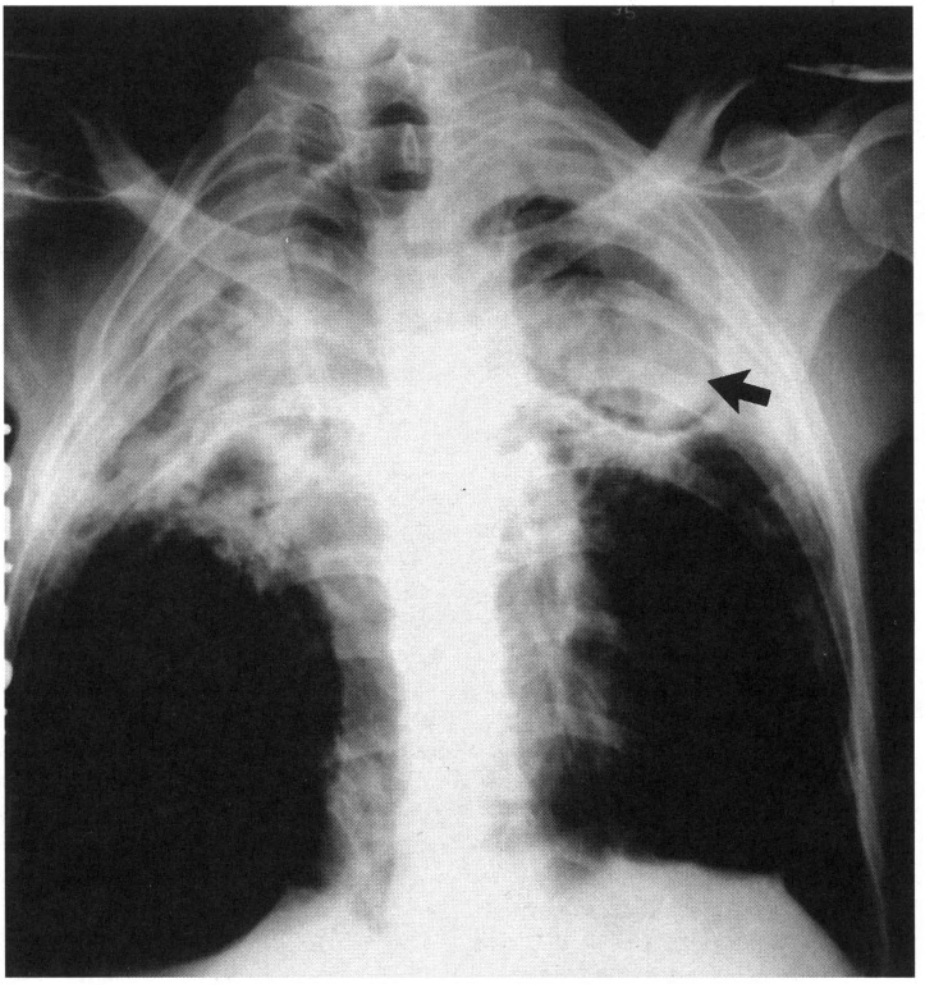


FIGURE 15. An aspergilloma (arrow) within a left upper lobe cavity.

Allergic bronchopulmonary aspergillosis (ABPA) occurs in asthmatics whose lungs have become hyperreactive to *Aspergillus* spores residing in the airways. The allergic reaction causes marked mucus production in the affected regions. *A. fumigatus* hyphae proliferate in the mucus and generate more spores which then provoke a more widespread and severe reaction, and the cycle repeats itself. Eventually large masses of hyphae suspended in inspissated mucus will fill the involved airways, usually central airways. These mucus plugs can be seen on chest radiograph as typical "finger in glove" opacities which are actually radio-opaque casts of the airways. The mucus plugs will obstruct the affected airways and cause segmental or lobar atelectasis or post-obstruction pneumonia. Rarely cavities may occur and mycetomas may develop within them.

P. carinii, an opportunistic pathogen formerly thought to be protozoal but recently recognized as likely to be fungal (Goldsmith, 1993), is the most frequent cause of pulmonary infection in patients with AIDS (Table 5). On chest radiograph PCP is most commonly seen as a diffuse mild to moderate interstitial pneumonia (Goodman, 1992) (Fig. 2). If treatment is delayed it may progress rapidly to cause diffuse bilateral pulmonary opacification and ARDS. In some patients it may present as a focal or

TABLE 5. *Pneumocystis carinii* Pneumonia

Organism	Patterns	Complications	Comments
Pneumocystis carinii (Goldsmith, 1993; Goodman, 1992)	Diffuse bilateral interstitial pneumonia (most common) Focal or regional interstitial pneumonia Focal or regional lobar pneumonia One or more noduules (uncommon)	Pneumatoceles Pneumothorax May progress rapidly to diffuse bilateral opacification and adult respiratory distress syndrome	Opportunistic pathogen classically classified as protozoal but recently recognized as probably fungal Most frequent cause of pulmonary infection in AIDS Adenopathy and pleural effusion are rare Patients on pentamidine may have upper-lung disease resembling reactivation tuberculosis

regional interstitial or lobar pneumonia. Rarely, it presents as one or more pulmonary nodules. An upper-lung pattern resembling reactivation tuberculosis may be seen, especially in patients receiving pentamidine prophylaxis. Complications of this infection include pneumatoceles and pneumothorax and, as mentioned above, ARDS. Adenopathy and pleural effusion are rarely caused by this organism.

Specific Complications of Pneumonia

A poor response to treatment may be due to treatment failure or to complications of the pneumonia (Fein, 1996). The former may be due to a resistant organism, to an unusual or unanticipated pathogen, or to a noninfectious pneumonia mimic. Complications of the pneumonia include parapneumonic pleural effusion, empyema, bronchopleural fistula, lung abscesses, pulmonary gangrene, pneumatoceles, and ARDS.

A parapneumonic pleural effusion (Hanna et al., 1991) is caused by the pleural response to a nearby pulmonary infection and is the most common complication of pneumonia. It is most commonly seen in bacterial pneumonias, especially those due to *S. aureus, H. influenzae, L. pneumophila, Nocardia,* anaerobic bacteria, gram-negative bacilli, and *S. pneumoniae.* A pleural effusion is usually evident on plain radiographs, especially if an erect film can be obtained. On a supine film, fluid accumulates in the dependent portion of the hemithorax and is best appreciated at the apex (as a crescent of soft tissue density), in the lateral costophrenic angle or as an increased subpulmonic density accompanied by a flattening of the diaphragm contour with a lateral shift of the dome apex.

Parapneumonic pleural effusion is most commonly unilateral and on the same side as the pneumonia (Hanna et al., 1991), with the pneumonia being the dominant feature. If the effusion is the dominant feature and adjacent lung opacities are less conspicuous it is likely that the effusion is a primary process with passive atelectasis causing the lung opacities (Webb et al., 1996). A bilateral parapneumonic effusion is usually larger on the side of the pneumonia. If it is symmetrical it is more likely due to something other than the pneumonia (Hanna et al., 1991).

An infected pleural effusion is known as an empyema. All empyemas begin as a sterile pleural effusion which becomes secondarily infected. The source is usually an adjacent pneumonia or lung abscess. Radiographic evidence of loculation developing within a previously mobile pleural effusion strongly suggests empyema. If loculation is suspected on the routine chest radiograph it may be confirmed or ruled out by right and left lateral decubitus views. More specific radiographic signs of empyema are tension hydrothorax and chest wall edema. Within a few weeks the inflammatory reaction will generate a thick pleural peel which will impair regional lung function. Rarely the infection may spontaneously drain through the chest wall (empyema necessitatis). To avoid these complications empyema must be detected and treated in its earliest stages (Woodridge, 1992; Conces, 1994; Hanna et al., 1991).

Pneumonia complicated by parenchymal necrosis may cause a bronchopleural fistula which is a fistulous communication between the pulmonary airways and the pleural space. A bronchopleural fistula may cause a secondary pneumothorax or, if there is associated parapneumonic effusion or empyema, a secondary hydropneumothorax or pyopneumothorax. The air fluid levels in the pleural fluid are best detected on horizontal beam chest radiographs. The organisms most commonly associated with bronchopleural fistula include *S. aureus,* gram-negative bacilli, anaerobic bacteria, and streptococci, occasionally *S. pneumoniae.*

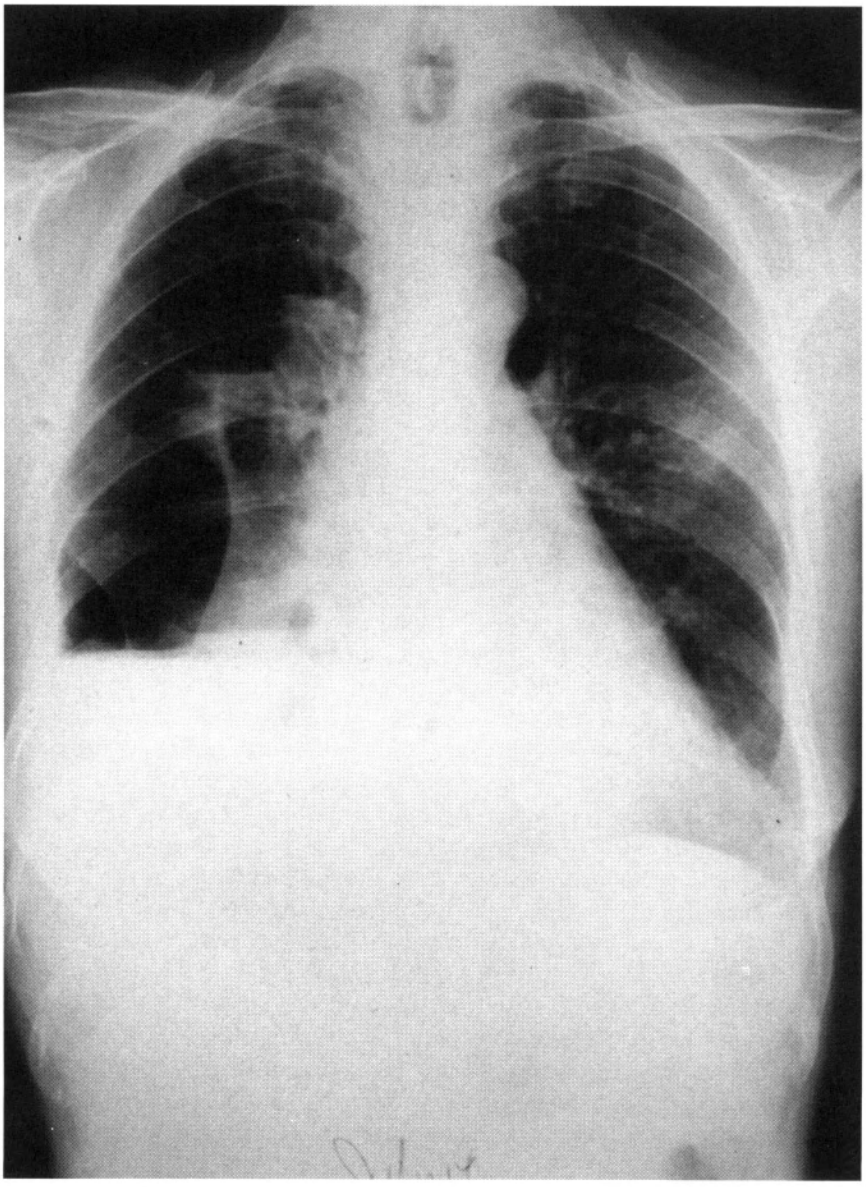
Radiographic differentiation between a bronchopleural fistula with a pleural air fluid level and an air fluid level within a lung abscess can on occasion be difficult. A pleural location for the air collection is suggested when it has relatively thin and uniform walls, when the fluid contour is oblong and conforms to the pleural space with obtuse angles between it and the lung, and when the air fluid levels on orthogonal horizontal beam projections are of unequal length (Fig. 16). A pleural fluid collection may be seen to cross the anatomical location of a pleural fissure. Multiple air fluid levels are more frequently associated with pleural fluid because abscesses typically, but not always, have a single air fluid level (Fig. 17) (Hanna et al., 1991; Woodridge, 1992; Conces, 1994).

Pulmonary infection by particularly virulent bacteria, such as *S. aureus,* streptococci, gram-negative bacilli, and anaerobic bacteria evokes an intense inflammatory response that causes varying degrees of pulmonary parenchymal necrosis that may become radiographically discernible by causing cavitation or pneumatoceles. Cavitation may occur within an abscess, microabscesses, or pulmonary gangrene.

A pyogenic lung abscess most commonly occurs as a complication of a focal pneumonia caused by aspiration of infected oropharyngeal or gastric secretions (Groskin et al., 1991; Hanna et al., 1991; Woodridge, 1992; Conces, 1994; Bragg & Freundlich, 1992). In one study (Groskin et al., 1991) fewer than 2% of cases occurred in the right middle lobe or lingula. A cavity filled with purulent fluid forms following central necrosis. Over a period of 7 to 14 days after the initiating event, the necrosis may spread and penetrate the wall of the abscess and establish free communication between the abscess cavity and adjacent airways. The purulent contents of the abscess may be coughed up as foul-smelling sputum and air can enter the abscess cavity. Chest radiographs obtained during the early phase of a lung abscess, before communication with the airways has become established, will demonstrate simply a nonspecific opacity with ill-defined margins for which the differential diagnosis will include pneumonia and neoplasm. After communication with the airways has become established the intracavitary air may be seen as an air fluid level on chest radiographs performed with a horizontal beam. It may be differentiated from bronchopleural fistula by obtaining orthogonal views. An abscess is roughly spherical and the air fluid levels will have equal lengths on orthogonal horizontal beam views as opposed to the unequal lengths typically seen with intrapleural air fluid levels (Fig. 17). Early radiographic diagnosis of a lung abscess therefore requires that a high index of suspicion be maintained and that horizontal beam views of the chest be obtained to detect an intracavitary air fluid level when a lung abscess is suspected. A vertical beam chest radiograph, such as the typical portable supine or semi-erect frontal examination obtained for very ill patients, will not show an air fluid level, and an abscess that contains air will continue to be imaged as a nonspecific opacity and may be missed. A visibly cavitated lung abscess with or without an air fluid level will have a chest radiographic appearance that overlaps with the radiographic appearance of other cavitated lesions such as nonpyogenic abscess, cavitated granuloma, and cavitated neoplasm. The differential diagnosis cannot be made on the basis of the radiographic features alone and the clinical setting and the clinical findings must be taken into consideration.

When there is a widespread intense inflammation, such as would be seen in lobar pneumonia with lobar enlargement, the entire region of involved lung may become necrotic and separate from the adjacent still viable lung. A large cavity may form, a phenomenon known as pulmonary gangrene (Fig. 18).

Multiple microabscesses may form in a region or regions of intense inflammation and be radiographically visible as multiple lucencies with or without air fluid levels. This is termed necrotizing

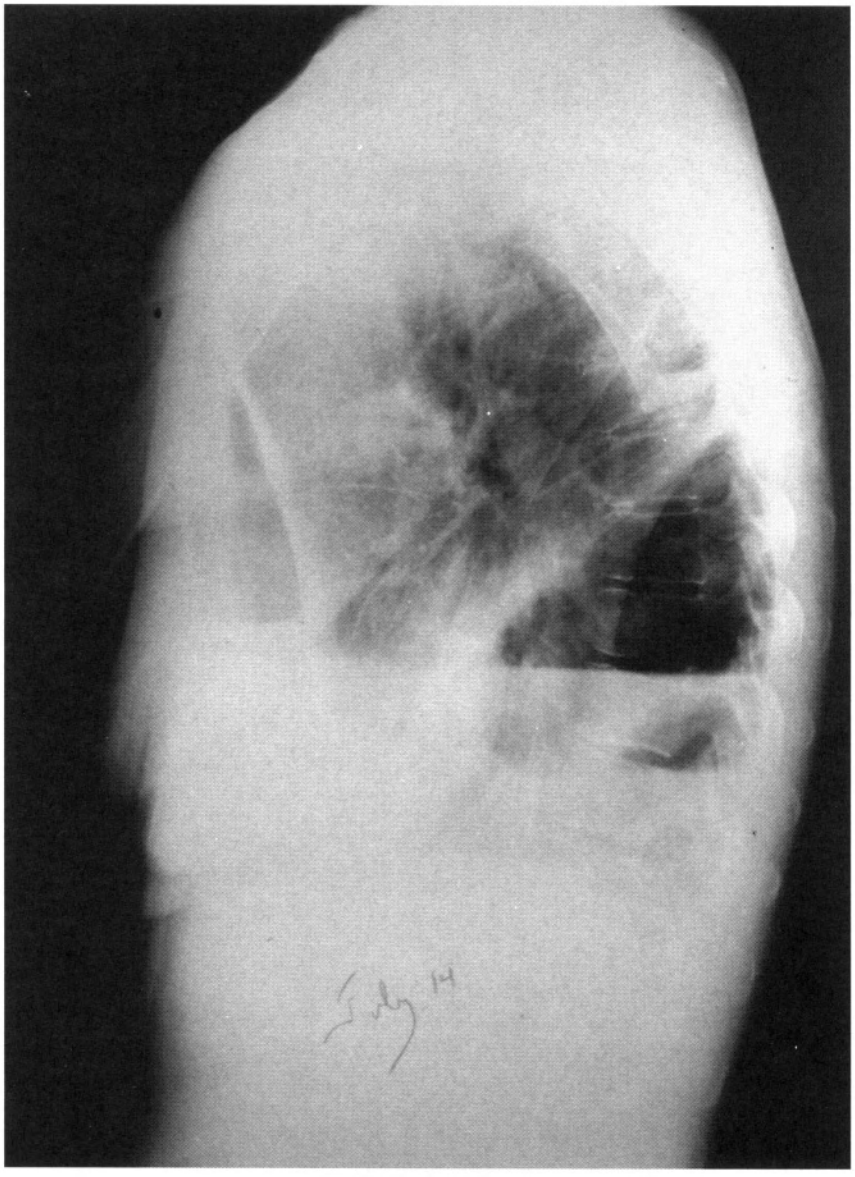


A

FIGURE 16. Air and fluid in the pleural space. Note that there are several asymmetric air-fluid levels on the patient's right side.

pneumonia. The microabscesses may become confluent to produce a focal abscess or a region of pulmonary gangrene.

A pneumatocele is thought to form when necrotizing pneumonia causes focal loss of alveolar wall integrity and air is allowed to enter the lung interstitium and form a subpleural collection (Fig. 12). If the point of rupture becomes a check valve the collection can become massive. Pneumatoceles may be multiple. Unlike abscesses, pneumatoceles have thin smooth walls, may form and change rapidly, and are not marked by the sudden production of foul-smelling sputum. Rupture of a pneumatocele may cause a pneumothorax.



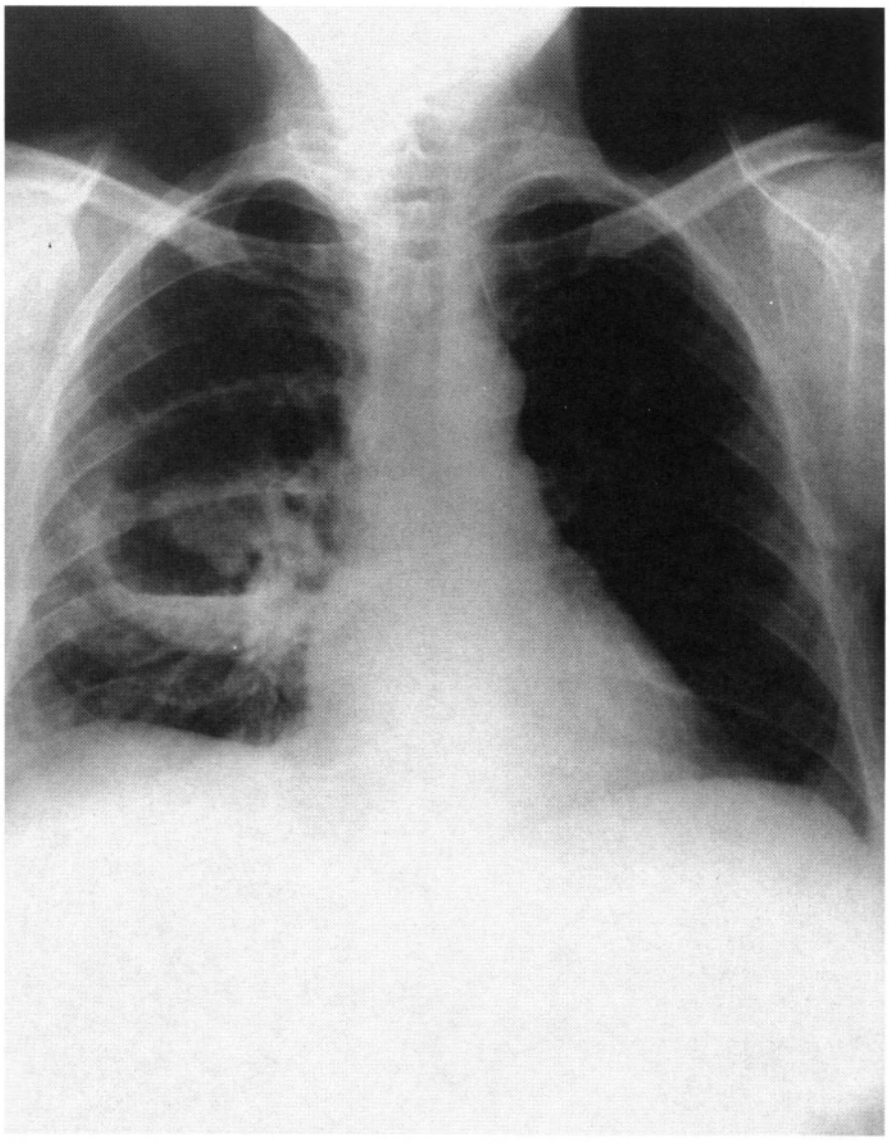
B

FIGURE 16. (*Continued*)

Pneumonia may have a fulminant course culminating in ARDS (Fig. 1). This complication can be secondary to pneumonia of any cause but is most particularly associated with viral, PCP, staphylococcal, streptococcal, and *Legionella* pneumonia and miliary tuberculosis (Woodridge, 1992; Goodman, 1992).

Additional Imaging—Chest Radiographs

Radiographic evidence of clinically suspected pneumonia will usually appear within 12 to 24 hours (Herold, 1997). If the chest radiograph is negative at presentation it should be repeated in 2 to



A

FIGURE 17. Symmetrical air-fluid levels within an abscess in the superior segment of the right lower lobe on posteroanterior (A) and lateral (B) views.

3 days. If it is still negative the need for additional diagnostic studies should be considered.

Early in the course of uncomplicated CAP frequent imaging is of little value to monitor response to treatment. With effective therapy clinical improvement should be noted within 48 to 72 hours with resolution of fever and leukocytosis by day 4 (Fein, 1996). Chest radiographic improvement, however, will typically lag behind the clinical improvement by several days and may even get worse immediately following the initiation of treatment (Fein, 1996). In otherwise uncomplicated CAP worsening of the chest radiographic findings in the first few days is of no concern if the clinical indicators are improving. On the other hand, it is associated with a poorer prognosis if the patient has severe CAP (Areno et al., 1996).

Radiographic findings are typically slow to

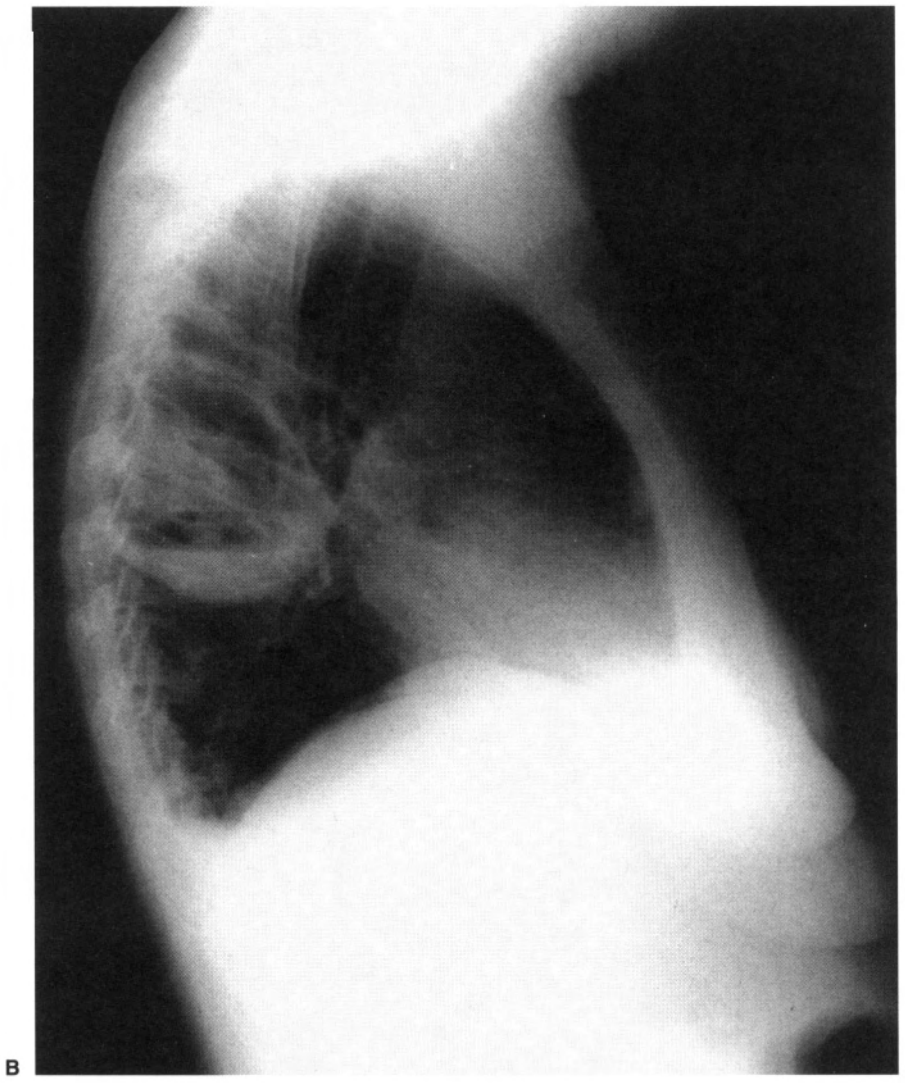
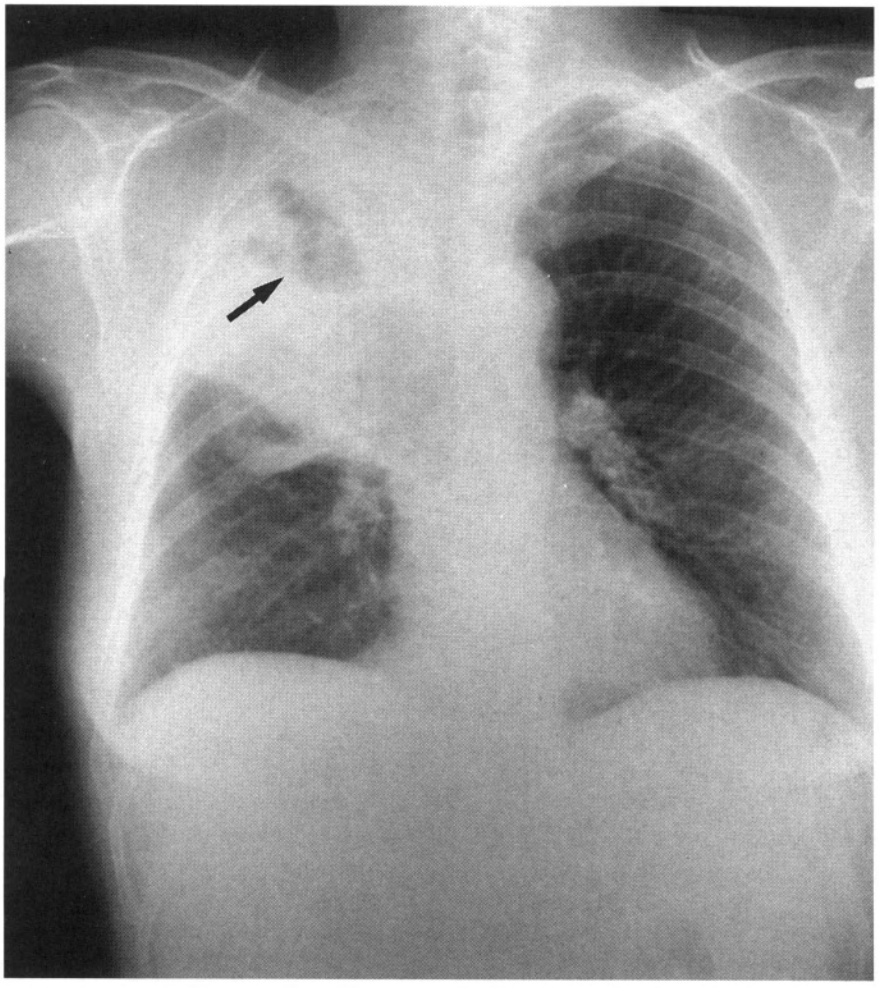


FIGURE 17. (*Continued*)

clear in patients with pneumonia. In young and middle-aged patients they usually clear in 2 to 4 weeks but may persist for up to 8 weeks. For the elderly, it will typically take longer, up to about 3 months. It may take even longer for immunocompromised patients and those with debilitating illness such as alcoholism and COPD (Webb et al., 1996; Freundlich & Bragg, 1992; Ely & Haponik, 1991; Herold, 1997). Beyond 2 to 3 days from the start of treatment the chest radiograph should not get worse, but rather show a steady improvement to resolution. It is particularly important to document complete resolution in middle-aged and elderly patients to exclude carcinoma or other structural abnormality, especially in refractory or recurrent pneumonia (Webb et al., 1996). Routinely obtaining frequent chest radiographs to follow these patients is of little benefit. Follow-up chest radiographs should only be obtained when indicated by the patient's clinical course, especially when the clinical response to treatment is not as expected.

Failure to resolve is only occasionally due to bronchogenic carcinoma and is more frequently due to the nature of the disease or to inappropriate



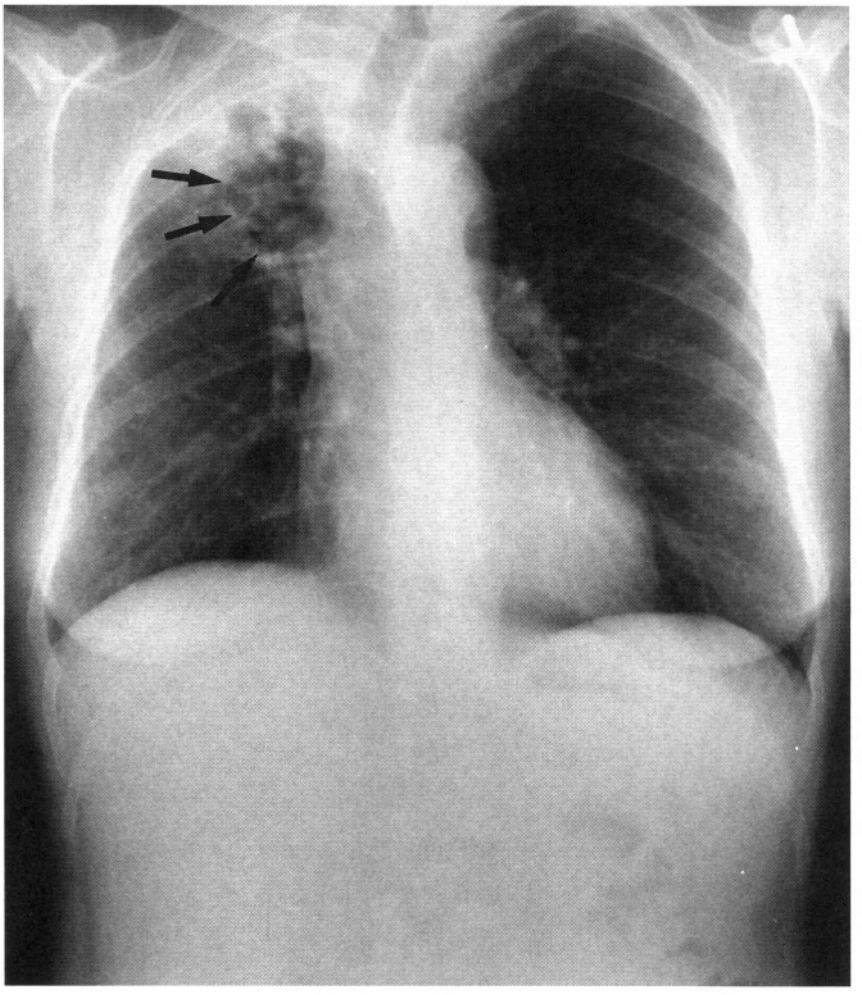
A

FIGURE 18. Follow-up examinations of the patient shown in Figures 10 and 11 with *Legionella pneumophila* pneumonia enlarging the right upper lobe. The examinations were obtained at 3 weeks (A) and 3 months (B). A large cavity has been revealed (arrows) indicating the extent of the pulmonary necrosis.

therapy (Woodridge, 1992). This has implications for additional imaging at the time of work-up and indicates that chest radiography is more appropriate for follow-up than other modalities. Over 90% of recurrent pneumonia is associated with predisposing factors (Woodridge, 1992). These include COPD, bronchiectasis, congestive heart failure, extrathoracic disease, or a combination of these. Recurrent pneumonia in one location is most frequently associated with a pulmonary abnormality in that location, most frequently bronchiectasis (Woodridge, 1992). Only about 1% of patients with recurrent pneumonia have bronchogenic carcinoma (Woodridge, 1992). It is therefore recommended that investigation for bronchogenic carcinoma be limited to patients with recurrent pneumonia in the same location (Woodridge, 1992).

Additional Imaging—Other Modalities

The overall sensitivity of chest radiography for detecting pulmonary disease is approximately 80%. Up to 16% of patients with interstitial lung disease and up to 10% of immunosuppressed patients with acute lung disease will have a normal



B

FIGURE 18. (*Continued*)

chest radiograph (Webb et al., 1996). The probability that a chest radiograph will miss clinically silent pneumonia is about 5% to 7% (Ely & Haponik, 1991).

Conventional computed tomography (CCT) and high-resolution computed tomography (HRCT) are more sensitive and specific than chest radiography for detecting and diagnosing both acute and chronic lung disease.

CCT is the modality of choice for evaluating the state of the lungs and to detect underlying pathology such as tumor, necrotizing pneumonia, abscess, fluid loculations, and empyema (Yu & Maurer, 1996). CCT gives a more precise demonstration of the extent of pulmonary parenchymal involvement than is possible with a chest x-ray. CCT is better able to define the proportion of pleural versus parenchymal disease when both are present and accurately differentiates between effusion and lung opacification (Fu & Maurer, 1996). CCT is better able to demonstrate the presence and location of a pleural fluid collection and to detect loculation of the fluid and the need for thoracenteses. CCT is especially useful where empyema is known but the presence and extent of a pleural peel is not. CCT may be used to guide thoracentesis and chest tube

placement and to later assess the position of the tubes and the adequacy of drainage. Bronchoscopy with BAL may be facilitated by CCT to direct the examination to the specific branch of the airway most likely to yield useful results.

HRCT is a technique designed to assess the lung parenchyma with anatomic detail similar to gross pathology specimens (Webb et al., 1996). HRCT is better than CCT and chest radiographs for the demonstration of localized and diffuse pulmonary parenchymal disease. In selected cases HRCT may detect abnormalities when chest radiographs are normal, confusing, or equivocal (Syrjala et al., 1998). In this regard it plays an especially important role in detecting diffuse pneumonia in immunocompromised patients (Webb et al., 1996). HRCT has a sensitivity of 99% and a specificity of 93% for detecting acute lung disease in patients with AIDS (Webb et al., 1996). HRCT is also indicated for patients presenting with hemoptysis and can be used to assess the need for and the optimal site for lung biopsy (Webb et al., 1996). CCT assessment of diffuse lung disease is better than HRCT only for the detection of small nodules (Webb et al., 1996).

HRCT may suggest a specific diagnosis when pneumonia due to the organism has a distinctive appearance, for example, selected cases of PCP or cytomegalovirus pneumonia (Webb et al., 1996). HRCT may help to avoid confusion with noninfectious causes of diffuse parenchymal lung disease which mimic pneumonia on chest radiograph. A number of them may have a distinctive appearance on HRCT (Webb et al., 1996).

Ultrasound is useful for assessing the amount

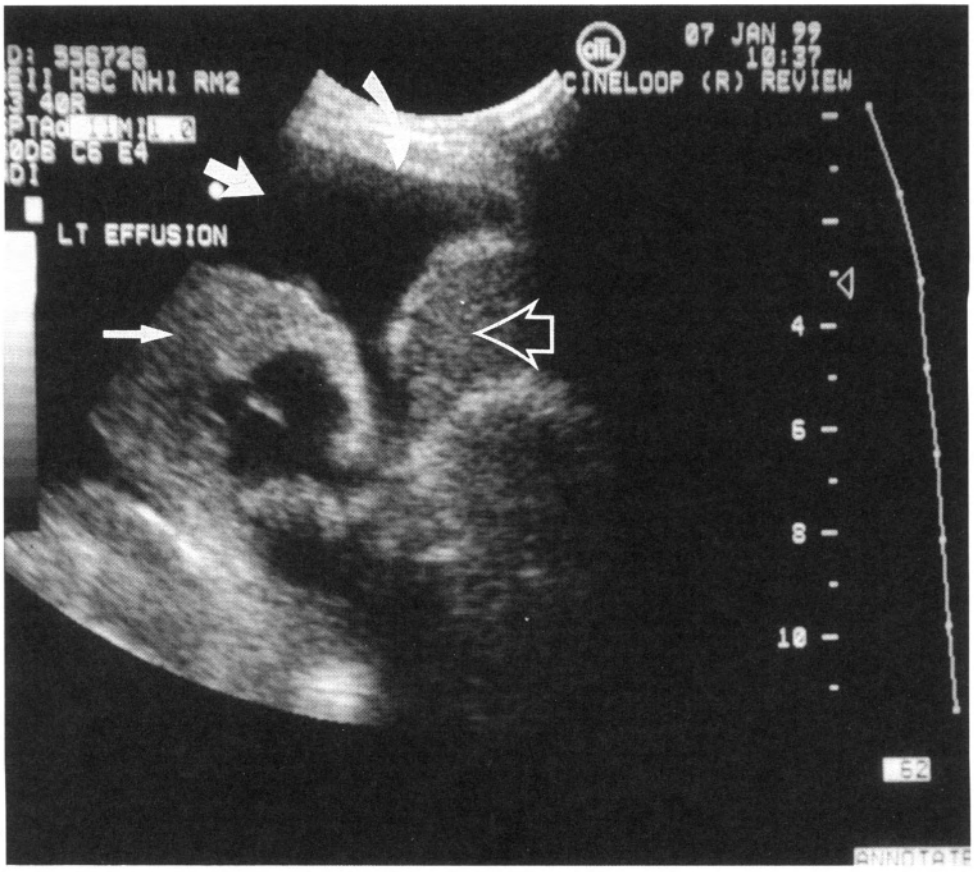


FIGURE 19. An ultrasound image of the left upper quadrant showing a pleural effusion (wide arrow) and the consolidated lung base (thin arrow). The open arrow indicates the spleen, the curved arrow marks the normal-thickness parietal pleura.

and location of pleural fluid (Fig. 19), detecting loculation, and for differentiating pleural fluid from pleural organization. It may also be used to guide thoracentesis and closed pleural drainage procedures (Hanna et al., 1991; Wallenhaupt, 1991). Its main advantage is that it can be brought to the bedside of a seriously ill patient when the need is urgent and movement of the patient is contraindicated.

The use of pulmonary scintigraphy in patients suspected of having acute pulmonary infection is likely to be restricted to those who are immunocompromised when chest radiography and CCT are negative or equivocal. Gallium-67 citrate scintigraphy is very sensitive for PCP and is typically positive before the chest radiograph. In PCP there is diffuse homogeneous or heterogeneous uptake of the radionuclide. Focal uptake will suggest bacterial infection and perihilar uptake will suggest cytomegalovirus infection (Conces, 1992). An indium 111-labeled autologous white blood cell scintigram may be able to detect focal purulent pulmonary infection such as an abscess when conventional imaging is unhelpful (Conces, 1992).

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7

The Pathology of Community-Acquired Pneumonia

CLAUDIA MOLINA AND DAVID H. WALKER

Introduction

The respiratory tract is constantly confronted with numerous noxious agents present in the environment, including a variety of microbial pathogens. Fortunately, it contains a complex host defense system that protects the lung against potentially injurious agents. This system consists of structural, mechanical, secretory, and cellular mechanisms that are designed to eliminate or contain the majority of these pathogenic agents (Canto et al., 1994). Indeed, the lower respiratory tract is normally sterile despite its continuous exchange of gases with the external environment.

Pulmonary infection can result whenever these defense mechanisms are impaired. For example, loss or suppression of the cough and gag reflexes may lead to aspiration of oropharyngeal secretions and gastric contents; smoke, viral infection, or chemical inhalation may alter the mucociliary clearance function of the airways' epithelial cells; exposure to increased oxygen tension, tobacco smoke, or alcohol may impair the phagocytic activity of the alveolar macrophages; accumulation of airways secretions and pulmonary edema may impair clearance and favor bacterial growth (Canto et al., 1994; Kobzik & Schoen, 1994).

Pulmonary defenses are also affected by the overall immunocompetence of the individual. Factors that impair the resistance of the host include immunosuppressive drug therapy, malnutrition, chronic debilitating diseases, and generalized immunodeficiency diseases including AIDS (Linder & Sisson, 1994). Most microorganisms that cause pneumonia are normal inhabitants of the oropharynx and nasopharynx and reach the alveoli by aspiration of secretions. Other routes of infection include inhalation of aerosols containing the microorganisms from the environment, hematogenous dissemination from an infectious focus elsewhere, and rarely, spread of bacteria from an adjacent site (Barnes, 1994).

Traditionally, the pathologic characterization of pneumonia has been by macroscopic distribution. It has been classified as either lobar pneumonia or bronchopneumonia, but these classic categorizations are often difficult to apply, because the patterns overlap.

Lobar Pneumonia

Lobar pneumonia is an infectious process that involves the greater part of a lobe of the lung and classically affects the entire lobe. The consolidation is delimited by the pleura or by a major fissure. Laennec (1781–1826) made a large number of contributions to medicine, but one of the most significant was his accurate description of the basic progression of the consolidative process in lobar pneumonia (Epifano & Brandstetter, 1993; Loosly, 1940). Four stages of the inflammatory response have been described. Two or more stages in the

CLAUDIA MOLINA AND DAVID H. WALKER • University of Texas Medical Branch, Galveston, Texas 77555-0609.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

process of consolidation may coexist in the same lung (Berry, 1920). The first stage, congestion, occurs in the first 24 hours of infection. The lung is heavy, and its parenchyma is red and doughy. Microscopically, there is vascular engorgement, and the alveolar spaces contain edema fluid, scattered neutrophils, desquamated epithelium, and numerous bacteria (Kobzik & Schoen, 1994; Winn & Chandler, 1994).

In the second stage, termed red hepatization, the lung parenchyma is distinctly red, firm, airless, noncrepitant, and heavy with a granular consistency. Microscopically, the alveolar spaces are filled with red blood cells, neutrophils, desquamated epithelial cells, and fibrin. The stage of gray hepatization is characterized by a dense, friable, gray-brown to yellow, and dry pulmonary parenchyma due to progressive disintegration of red cells and the persistence of a fibrinopurulent exudate. Microscopically, there is an extensive alveolar exudate composed of abundant neutrophils and macrophages, and bacteria are generally not identifiable. Cellular outlines are indistinct, and hemosiderin pigment may be evident (Kobzik & Schoen, 1994; Berry, 1920; Winn & Chandler, 1994).

In the final stage of resolution, the consolidated alveolar exudate undergoes progressive enzymatic digestion. The residual debris is resorbed, ingested by macrophages, or coughed up, and the normal pulmonary architecture is restored (Kobzik & Schoen, 1994). When the inflammation extends across the pleura, there is a pleural fibrinous reaction that may similarly resolve or undergo organization, producing a roughened pleural surface with fibrous thickening or permanent fibrous thickening (Kobzik & Schoen, 1994; Winn & Chandler, 1994). The time course for the inflammatory process is variable. The duration of the second and third phases has been estimated to be 2 to 3 days each. The time of maximal consolidation has been estimated to be 2 to 6 days (Winn & Chandler, 1994). Lobar pneumonia rarely progresses through all four stages because they are modified by antimicrobial therapy.

Community-acquired lobar pneumonia is classically associated with *Streptococcus pneumoniae,* but *Klebsiella pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila,* and streptococci may also produce a typical lobar configuration (Kobzik & Schoen, 1994; Winn & Chandler, 1994; Winn & Myerowitz, 1981). Individual cases have been ascribed to *Neisseria gonorrhoeae* (Enos et al., 1980), *Mycoplasma pneumoniae* (Macfarlane et al., 1979), adenovirus type 7 (Leers et al., 1981), *Aspergillus* spp. (Young et al., 1969), *Proteus* spp. (Seriff, 1969), *Pseudomonas aeruginosa* (Krafft, 1968), and in patients with HIV infection, *Pneumocystis carinii* (Miller et al., 1994).

Bronchopneumonia

Bronchopneumonia is a patchy consolidation of the lung that involves one or several lobes. It usually involves the dependent and posterior portions of the lung, because of the tendency of secretions to gravitate into the lower lobes. Grossly, the consolidated areas usually have poorly defined margins and appear dry, granular, and gray-red to yellow (Kobzik & Schoen, 1994). In some cases, consolidation affects entire lobules with normal parenchyma on the other side of the interlobular septum. Histologically, there is a suppurative neutrophilic exudate that fills bronchi, bronchioles, and adjacent alveoli. The common causative agents are streptococci, staphylococci, pneumococci, *H. influenzae, P. aeruginosa,* and coliforms (Kobzik & Schoen, 1994).

Lobar pneumonia and bronchopneumonia can undergo complete resolution, but abscess formation may follow with extensive necrosis of the pulmonary parenchyma, particularly with infections caused by type 3 pneumococci, *Klebsiella,* and *Staphylococcus.* Spread of the infection to the pleural cavity can lead to empyema. Some cases may be complicated with bacteremic dissemination and metastatic abscesses in many organs (Kobzik & Schoen, 1994; Winn & Chandler, 1994).

Interstitial Pneumonia

The pneumonic involvement in interstitial pneumonia may be patchy or diffuse. It may involve whole lobes bilaterally or unilaterally. Grossly, the lung parenchyma appears red and congested with no obvious consolidation. The pleura is smooth, and pleuritis or pleural effusions are infrequent (Barnes, 1994).

Microscopically, the inflammatory process is confined to the interstitium, which includes the alveolar walls and the connective tissue around the bronchovascular structures. The alveolar septa are infiltrated with a mononuclear infiltrate composed of lymphocytes, plasma cells, and histiocytes. In the earliest phase, neutrophils may also be present. There is a lack of significant alveolar exudate, but in many cases proteinaceous material is present in the alveolar spaces. Pink hyaline membranes lining the alveolar wall indicate nonspecific alveolar damage similar to that seen diffusely in adult respiratory distress syndrome (ARDS) (Kobzik & Schoen, 1994; Barnes, 1994). Some viruses may be associated with necrosis of bronchial and alveolar epithelium. In some viral pneumonias, the inflammatory exudate undergoes extensive karyorrhexis and karyolysis with abundant cell fragmentation and nuclear dust (Nash, 1972). In most cases, there is complete resolution with restoration of the pulmonary parenchyma. In severe necrotizing infections, fibrosis may occur.

Common etiologic agents include *Mycoplasma pneumoniae,* viruses such as influenza viruses A and B, parainfluenza viruses, respiratory syncytial virus, adenoviruses, rhinoviruses, varicella-zoster virus, *Chlamydia* spp., *Coxiella burnetii,* and *P. carinii* (Kobzik & Schoen, 1994; Winn & Chandler, 1994; Winn & Walker, 1994).

Mixed Patterns

Bacterial infection superimposed on viral pneumonia can modify the histologic picture and can produce a mixed pattern of interstitial and alveolar inflammation, leading to a fibrinopurulent air space inflammatory reaction with mononuclear interstitial inflammation and bronchiolar epithelial necrosis (Kobzik & Schoen, 1994; Barnes, 1994).

Miliary Pattern

Tuberculosis is a disease that goes hand in hand with factors such as poverty, crowding, and undernourishment (Grzybowski, 1982). In 90% of the cases, the primary tuberculous infection heals without progression of the disease. The pulmonary lesions from *Mycobacterium tuberculosis* infection may resolve completely or they can undergo fibrosis and form a fibrotic, scarred nodule, or they may calcify (Pratt, 1979).

In a minority of patients, the disease progresses and is characterized by enlargement of the primary complex or primary focus, with regional lymph node involvement. These lesions can erode into a blood vessel, and bacilli can then embolize in large numbers into the capillaries of the organs supplied by the eroded vessel. The embolization of numerous bacilli produces 2- to 3-mm discrete lesions that resemble millet seeds; thus the disorder is called miliary tuberculosis (Sahn & Neff, 1974). The same pattern of hematogenous dissemination can be seen in patients with overwhelming histoplasmosis (Goodwin et al., 1980) and coccidiodomycosis (Bayer, 1981). The tissue reaction can vary from caseous granulomas to foci of necrosis, fibrinous exudate, and a weak, poorly formed cellular reaction. Hematogenous spread of herpesviruses, varicella-zoster virus, and cytomegalovirus to the lung can occur in severely immunocompromised patients, leading to acute necrotizing hemorrhagic lesions (Winn & Walker, 1994; Ramsey et al., 1982; Beschorner et al., 1980).

The Pathology of Specific Agents

Pneumonia has been classified on the basis of the etiologic agent because the clinical and morphologic features, and the therapeutic implications often vary with the causative organism.

Bacterial Pneumonia

Streptococcus pneumoniae

Streptococcus pneumonia accounts for 30% to 70% of the cases of community acquired-pneumonia (CAP) in general and accounts for 15% to 46% of cases of severe CAP requiring intensive care unit (ICU) management (Coonrod, 1989; Hager et al., 1990; Leeper, 1996). This bacterium is often part of the usual microbial flora of the nasopharynx of healthy individuals but also seems to have a predilection for the airway mucosal surfaces of subjects with chronic lung diseases (Reynolds, 1996).

The pattern of pneumonia is lobar or lobular, and the main pathological features involve the classical evolution of stages of lung consolidation (Winn & Chandler, 1994). The purulent exudate consists of fibrin, polymorphonuclear leukocytes, and macrophages. Bacteria are easily identified in the infiltrate of early infections. Most uncomplicated cases show complete regeneration of the alveolar epithelium without residual scar formation, but massive necrosis of the lung tissue and pneumatocele formation has been reported in children (Anderson & Turner, 1991; Kerem et al., 1994; Asmar et al., 1978). Lung abscess has been reported as a complication of pneumococcal pneumonia with bacteremia (Isaacs, 1986). Alterations of the anatomic, physiologic, and immunologic pulmonary defense mechanisms prior to and during the infection as well as virulence factors of *S. pneumoniae* (i.e., rapid multiplication, presence of capsular polysaccharides, and inhibition of phagocytosis) in concert may result in decreased bacterial clearance from the lung, with consequent necrosis of lung parenchyma (Winn & Chandler, 1994; Yangco & Deresinski, 1980).

Klebsiella pneumoniae

Generally an acute disease of adults, *Klebsiella* pneumonia is most common in alcoholic men in their fifth to seventh decade of life and is strongly associated with poor oral hygiene (Barnes, 1994). It characteristically produces a lobar pattern, but lobular or diffuse patchy infiltrates have been described, having a predilection for dependent sites. Frequently, there is extension across the lobar fissure to involve adjacent parenchyma (Winn & Chandler, 1994). The expectorated sputum and the consolidated lung show a wet mucoid or gelatinous appearance, and gram-negative bacilli can be demonstrated in tissue or respiratory secretions. Extensive necrosis of the lung parenchyma and abscess formation have been reported (Belk, 1926; Majumdar, 1992). More than one half of the cases of pulmonary gangrene or sloughing of a large amount of lung tissue have been ascribed to *K. pneumoniae* in the cases reported by Penner (Penner et al., 1994). Chronic pneumonia has also been attributed to this organism (Winn & Chandler, 1994).

Legionella pneumophila and Other Legionella

There are currently 42 described species of *Legionella* representing 64 serogroups in the family Legionellaceae (Benson & Fields, 1998), but the most important human pathogen is *L. pneumophila,* which accounts for 75% or more of human infections (Winn & Chandler, 1994). *L. pneumophila* has been subdivided into six serogroups on the basis of antigenic structure, and serogroup 1 accounts for more than 70% of the infections, followed by serogroup 6 (Winn & Myerowitz, 1981; Benson & Fields, 1998). Two clinically and epidemiologically distinct respiratory syndromes are caused by *Legionella* spp. Pontiac fever is a self-limiting, influenza-like illness that occurs with extremely high attack rates (>90%) in outbreak settings with a short incubation period and no evidence of pneumonia (Winn & Myerowitz, 1981; Breiman & Butler, 1998). This syndrome has been caused by *L. pneumophila, Legionella feeleii, Legionella micdadei,* and *Legionella anisa* (Winn & Myerowitz, 1981).

The more commonly recognized illness is a systemic infection with acute pneumonia that begins with the abrupt onset of malaise, myalgias, headache, and fever. Cough productive of inflammatory sputum usually occurs later in the course of the infection. *L. pneumophila* occurs in the environment where the causative agent has the capacity to multiply within amoebae in warm water. Person-to-person transmission has not been demonstrated to occur. Outbreak investigations have shown that Legionnaires' disease can be transmitted via contaminated cooling towers and evaporative condensers, whirlpool spas, showers, humidifiers, supermarket vegetable sprayers, decorative fountains, and respiratory therapy equipment. Infection has also resulted from wounds being inoculated with contaminated tap water (Breiman & Butler, 1998; Friedman et al., 1998).

Legionnaires' disease consists of an acute bronchopneumonia that may progress to a lobar pattern. The disease is bilateral in as many as two thirds of the patients (Fig. 1) (Benson & Fields, 1998). *L. micdadei* pneumonia is similar clinically as it occurs in compromised hosts. Other cases have been ascribed to *L. bozemanii* and *L. dumoffii.* All

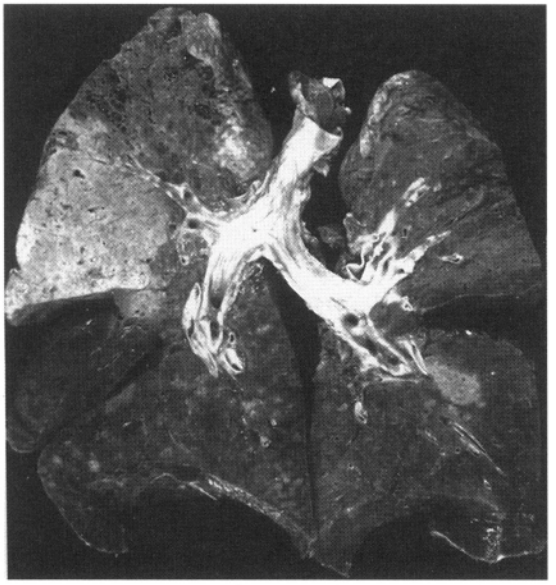

FIGURE 1. *Legionella micdadei* pneumonia. Large area of consolidation in the right upper lobe, primarily in stage of gray hepatization. The right lower lobe contains areas of bronchopneumonia and the left lower lobe a prominent round pneumonic infiltrate.

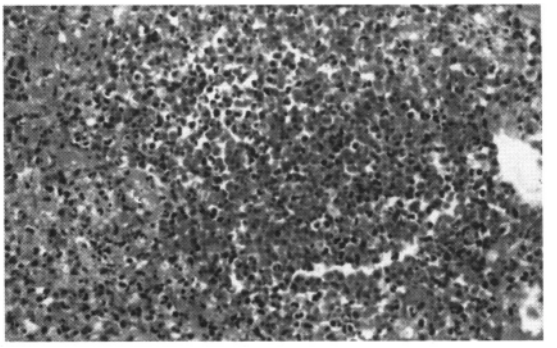

FIGURE 2. *Legionella micdadei* pneumonia. Air spaces are infiltrated with polymorphonuclear leukocytes; cellular exudate is undergoing extensive lysis. Hematoxylin and eosin, ×250.

Legionella species produce a severe confluent lobular or lobar pneumonia, and abscess formation and small pleural effusions are not uncommon. Poorly demarcated, rounded opacities, based in the pleura, may be initially mistaken radiographically for pulmonary embolism or neoplasms (Winn & Chandler, 1994; Muderet al., 1989). Microscopically, a leukocytoclastic inflammatory infiltrate of neutrophils and macrophages is seen, with many nuclear fragments and a dusty appearance, as well as vasculitis of small blood vessels, coagulation necrosis, and focal septal disruption of the parenchyma (Fig. 2). These are characteristic but not pathognomonic features (Winn & Myerowitz, 1981). Fibrin is a prominent part of the exudate, and hemorrhage in the air spaces is common. The periphery of active lesions contains edema and a sparse cellular infiltrate. The interstitium frequently contains a cellular infiltrate, but considerably less than in the adjacent air spaces (Winn & Chandler, 1994). Reaction to damage in the pneumonic areas can be manifested by prominent alveolar lining cells and occasionally hyaline membranes, especially with *L. pneumophila* and *L. micdadei* (Winn & Chandler, 1994; Winn & Myerowitz, 1981; Nusser & Tarkoff, 1978). The bacteria can be demonstrated in tissues by silver impregnation stains, using the Dieterle, Steiner, or Warthin= Starry method or with monoclonal or polyclonal fluorescent antibodies (Winn & Chandler, 1994; Winn & Myerowitz, 1981).

Few cases of chronic organizing pneumonia and pulmonary fibrosis have been attributed to *Legionella* (Winn & Chandler). Factors associated with delayed resolution include altered host defense mechanisms secondary to age or underlying medical conditions (Coletta & Fein, 1998). Other organisms associated with infection in immunosuppressed patients are *L. longbeachae, L. gormanii, L. maceachernii,* and *L. lansingensis* (Schlossberg & Bonoan, 1998).

Staphylococcus aureus

S. aureus is an uncommon cause of CAP but is important because cases are often severe. The incidence of *S. aureus* as a cause of bacterial pneumonia, in the absence of an influenza epidemic, is 1% to 5%; however, the incidence of CAP from *S. aureus* can increase as high as 25% during an influenza epidemic (Leeper, 1996). In the cases reported by Woodhead et al. (1987), 50% of the patients had some underlying disease. The infection occurs at the extremes of life and in patients with cystic fibrosis (Winn & Chandler, 1994; Leeper, 1996).

The lesions may take any pattern, including a lobar configuration. Multiple metastatic lesions may occur when the lungs are seeded hematogenously from distant foci of infection. Histologically, the exudate is rich in polymorphonuclear leukocytes and bacteria. Frequently, there are associated thick-walled abscesses (Winn & Chandler, 1994), pneumatoceles or thin-walled "abscesses," empyema, and spontaneous pneumothorax (MacFarlane & Rose, 1996); Olutola et al., 1984). Methicillin-resistant *S. aureus* (MRSA) strains are a recognized etiology with the majority of community-acquired MRSA infections occurring in intravenous drug users (Johnston, 1994).

Streptococcus pyogenes

S. pyogenes (group A beta-hemolytic *Streptococcus)* is an uncommon cause of pneumonia, and the majority of the pulmonary infections follow influenza. The distribution of the lesions ranges from focal, lobular infiltrates to lobar pneumonia (Winn & Chandler, 1994). Abscess and empyema formation have been described (Mclntyre et al., 1989; Kevy & Lowe, 1961). An important cause of neonatal pneumonia is *Streptococcus agalactiae* (group B beta-hemolytic *Streptococcus),* which can also produce pneumonia in the elderly (Winn & Chandler, 1994; Lerner et al., 1977). Other streptococci which rarely cause pneumonia include *S. anginosus* and enterococci (Winn & Chandler, 1994).

Haemophilus influenzae

H. influenzae, a common cause of lower respiratory tract infections such as purulent bronchitis, accounts for 2% to 8% of CAP. It occurs in the elderly and patients with chronic obstructive pulmonary disease, usually following a viral respiratory infection (MacFarlane, 1994). The viral infection damages the bronchial mucosa, facilitating the bacterial invasion (Wallace et al., 1978). Capsular polysaccharide, lipopolysaccharide, IgA1 proteases, and factors that inhibit ciliary activity are putative virulence determinants of *H. influenzae* (Moxon & Wilson, 1991). Bronchopneumonia and, less frequently, lobar pneumonia have been described. Histologically, there is a purulent exudate containing the gram-negative bacilli. Extensive necrosis can result in abscess, empyema, and pneumatocele formation (Winn & Chandler, 1994; Winn & Myerowitz, 1981; Wallace et al., 1978). Encapsulated strains of types B, C, D, E, and F are associated with pneumonia (Winn & Chandler, 1994). H. *influenzae* is frequently a copathogen with *S. pneumoniae* in severe CAP (Leroy et al., 1995).

Moraxella catarrhalis

Moraxella catarrhalis is a common cause of bronchial infections. It accounts for fewer than 2% of cases of CAP, usually in association with chronic lung disease and lung cancer (MacFarlane, 1994). Radiologically, the infiltrates are described as patchy with focal consolidation or having an interstitial appearance. Bacteremia is rare, and empyema or abscess formation has not been described (Winn & Chandler, 1994).

Rhodococcus equi

Rhodococcus equi, a ubiquitous gram-positive, pleomorphic bacillus, causes respiratory and other infections in domestic animals. Human disease occurs mainly in immunocompromised hosts as in the HIV-infected population (Verville et al., 1994; Prescott, 1991). Usually, a unilobar pulmonary infiltrate progresses to involve several lobes. Acute suppurative bronchopneumonia progresses to necrotizing pneumonia with formation of thick-walled cavities, as those seen in immunocompetent hosts with tuberculosis or nocardiosis. These cavities may contain air-fluid levels and can be associated with empyema (Drancourt et al., 1992; Johnson & Cunha, 1997). Hematogenous dissemination has been reported (Verville et al., 1994). The bacterium can be identified in tissues within macrophages and, less often, polymorphonuclear leukocytes by a modified gram stain such as Brown-Brenn and by Gomori's methenamine-silver stain. Most strains are weakly acid-fast and can be detected by Fite or Fite-Farraco stain (Winn & Chandler, 1994).

Bordetella pertussis

Until recently, whooping cough was considered to have been controlled by immunization. Failure of

vaccination programs, especially in underdeveloped countries, and waning immunity in previously vaccinated people contribute to the current rise in incidence of pertussis. The disease is being recognized increasingly in adolescents and adults. *Bordetella pertussis* has been isolated from patients with AIDS and respiratory infections (Ng et al., 1989). In general, the lesions are in the airways rather than in the alveoli. There is infiltration of the bronchial mucosa with mononuclear cells, and focal or extensive sloughing of the epithelial cells. These features are not pathognomonic of *B. pertussis* and can occur also in infections with respiratory syncytial virus, adenoviruses, and parainfluenza viruses (Winn & Chandler, 1994).

Gram-negative enteric bacilli (GNEB) other than *K. pneumoniae* that are described in some of the studies of CAP include *Escherichia coli, P. aeruginosa, Acinetobacter, Proteus, Serratia,* and other specific organisms. Alcoholics and the elderly, particularly when admitted from nursing homes, are at risk for GNEB infection (MacFarlane, 1994; Elbright & Rytel, 1980; Verghese & Beck, 1983). The reported proportion of GNEB pneumonias is as high as 20% (Lerner, 1983). *E. coli* has been described as causing a patchy and dense consolidation. Bacteremia and empyema have been reported (Winn & Chandler, 1994).

Pseudomonas aeruginosa

P. aeruginosa produces proteases, including elastases that are responsible for the characteristically extensive necrosis. Macroscopically, pneumonia occurs as a terminal bronchiolitis with firm, yellow-brown, elevated, necrotic nodules with sharp delimitation from the surrounding lung tissue in the shape of 2- to 5-mm shamrocks *or fleur de lis* that may progress to an extensive confluent bronchopneumonia with abscess formation (Tillotson & Lerner, 1968). Focal nodular and poorly delimited hemorrhagic lesions have also been reported, often in a subpleural location. Abscesses with liquefactive necrosis occur frequently. The lesions are hemorrhagic, with necrosis of the alveolar septa, scattered inflammation, and numerous gram-negative bacteria. These nodules may show an intense inflammatory infiltrate that consists of neutrophils, macrophages, and lymphocytes. Grossly, similar necrotic nodules or lesions resembling pulmonary infarcts reveal extensive coagulative necrosis and large numbers of gram-negative bacilli and leukocytes infiltrating the blood vessels and concentrated in the adventitia where they appear as a bluish haze in hematoxylin and eosin-stained sections (Fig. 3) (Fetzer et al., 1967).

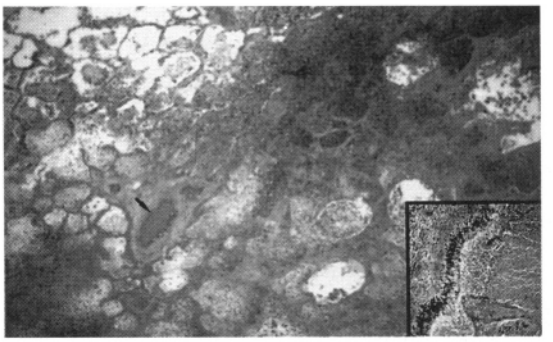

FIGURE 3. *Pseudomonas aeruginosa* pneumonia. An intense acute inflammatory exudate and fibrin fill the air spaces with areas of alveolar septal necrosis; small arteries show perivascular necrosis (*arrow*) and early infiltration by leukocytes. Hematoxylin and eosin, ×100. **Inset**: Note the large number of bacilli densely packed in the medial and adventitial layers of a pulmonary vessel. Steiner stain, ×250.

Burkholderia pseudomallei

Primary pulmonary infections follow the inhalation of aerosolized water droplets or dust contaminated with *Burkholderia* (formerly *Pseudomonas) pseudomallei,* a small, motile, gram-negative, aerobic bacillus that is found frequently in tropical regions such as Southeast Asia (Winn & Chandler, 1994). Grossly, the lungs reveal consolidation or small nodular densities in the upper lobes. The disease can mimic tuberculosis due to the frequent formation of cavities (Everett & Nelson, 1975). Microscopically, the acute infection is characterized by multiple discrete abscesses rich in neutrophils, macrophages, multinucleated giant cells, and fibrin. The stellate abscesses become surrounded by epithelioid histiocytes, lymphocytes, and Langhans and foreign-body-type multinucleated giant cells that may also be observed in lymph nodes. The granulomata may contain a central area of caseous necrosis later in the course. The bacteria can be

demonstrated within macrophages in the tissue sections of acute lesions using Steiner, Dieterle, Brown–Hopps, and Giemsa stains (Everett & Nelson, 1975; Piggott & Hochholzer, 1970).

Francisella tularensis

Approximately 10% to 20% of cases of tularemia either present with pneumonia as a primary event from inhalation of aerosolized droplets or develop pneumonia as a hematogeneous complication of ulceroglandular or typhoidal tularemia (Gill & Cunha, 1997). The bacterium is a small, pleomorphic, nonmotile, intracellular, gram-negative coccobacillus. The bacteria can enter the body by tick or deer-fly bite, skin cut, inoculation of the conjunctiva, ingestion, or inhalation (Gill & Cunha, 1997; Cunha, 1990; Spach et al., 1993). Six classic clinical forms correlate with the portal of entry: ulceroglandular (which accounts for 70% to 80% of cases), glandular, oculoglandular, oropharyngeal, typhoidal, and pleuropulmonary. The pleuropulmonary form, which more often results from hematogenous spread to the lungs, usually portends a poor prognosis (Stuart & Pullen, 1945). A case of tularemia presenting as CAP without classic epidemiological risks has been reported in the literature (Fredericks & Remington, 1996). The lungs show multifocal areas of pneumonia or lobar consolidation. Multiple abscesses can be present. Histologically, abundant fibrin and macrophages fill the alveoli and bronchioles (Fig. 4). Extensive thrombosis of small and medium-sized arteries and veins may lead to necrosis of pulmonary parenchyma resembling caseation or infarction. Giant cells are seldom observed in foci of granulomatous inflammation (Stuart & Pullen, 1945; Miller & Bates, 1969; Avery & Barnett, 1967). In tissue sections, the bacteria are generally difficult to detect.

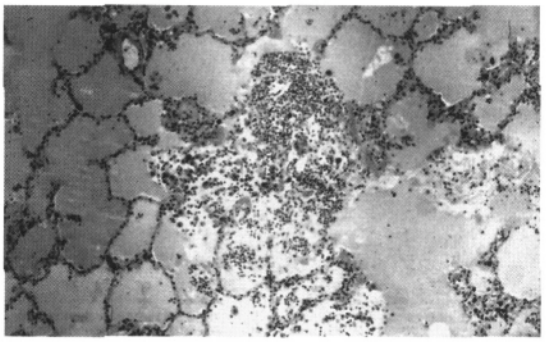

FIGURE 4. Tularemic pneumonia. Edema fluid fills alveolar spaces. Note focal acute inflammation, fibrin, and macrophages. Hematoxylin and eosin, ×250 (Contributed by L. W. Lamps, M.D., Little Rock, Arkansas).

Yersinia pestis

Yersinia pestis, a pleomorphic, gram-negative coccobacillus, is transmited to humans by flea bite or inhalation of contaminated aerosol (Butler, 1995). Clinical syndromes include bubonic, septicemic, and pneumonic plague. The bubonic form is most common, accounting for 75% of cases worldwide. After inoculation of the organism, the regional lymph nodes become infected and develop the typical fluctuating buboes. Septicemia occurs frequently (Butler, 1995; Cleri et al., 1997; Morris & McAllister, 1992). Plague pneumonia may occur after bacteremic spread during bubonic or septicemic plague, or after inhalation of bacteria from a person or animal (most often a domestic cat) with plague pneumonia (Doll et al., 1994; Werner et al., 1984). The gross appearance of the lungs includes hemorrhagic lesions in a lobular, lobar, or multilobar pattern. Peribronchial and mediastinal lymph nodes are enlarged and may be hemorrhagic (Burmeister et al., 1962). Microscopically, a mild inflammatory infiltrate consists of scant neutrophils and macrophages with hemorrhage, edema, and extensive parenchymal necrosis. Massive numbers of gram-negative coccobacilli are present in alveolar spaces, bronchi, and bronchioles. In impression smears, the bacteria display bipolar staining with methylene blue and gram stain. In tissue sections, the bacteria can be demonstrated with Brown–Hopps and silver impregnation stains, such as the Steiner, Warthin-Starry, or Dieterle procedures (Burmeister et al., 1962; Smith, 1976).

Bacillus anthracis

Inhalational anthrax is a highly lethal form of infection with toxemia. Humans are infected through exposure to animal products contaminated by spores of this nonmotile aerobic gram-positive rod, most often from animal hair and wool used in the textile

industry (Van Ness, 1971; Smith, 1973). Inhalational anthrax is rare in comparison with cutaneous disease, which accounts for over 90% of cases (Penn & Klotz, 1997). In the United States, the most recent fatal case of inhalation anthrax was documented in 1976 (LaForce, 1994). After inhalation of the spores, the alveolar macrophages transport them to the mediastinal lymph nodes where they germinate and multiply, followed by secretion of lethal toxin and edema toxin and hematogenous dissemination (Dalldorf et al., 1971). Radiologically, chest radiographs are characterized by a widened mediastinum (Vessal et al., 1975). In most cases, there is no pneumonia, but rather a severe hemorrhagic necrotizing mediastinal lymphadenitis and mediastinitis and death due to the effects of the toxins (Fig. 5). The lungs are heavy and may show extensive hemorrhagic pulmonary edema and a serofibrinous exudate. In a recently reported outbreak associated with release of aerosols from a military facility in Russia in 1979, there were a few cases that showed round areas of necrotizing pneumonia. In either situation, numerous large and elongated bacilli can be demonstrated in impression smears or tissue sections by Brown–Brenn stain or direct immunofluorescence (Ross, 1957; Cowdery, 1947; Cherry & Moody, 1965; Abramova et al., 1993). The majority of bacteria are observed within capillaries. The disease is often accompanied by hemorrhagic meningitis, and cerebrospinal fluid analysis yields evidence of hemorrhagic fluid with easily identified gram-positive bacilli (Abramova et al., 1993).

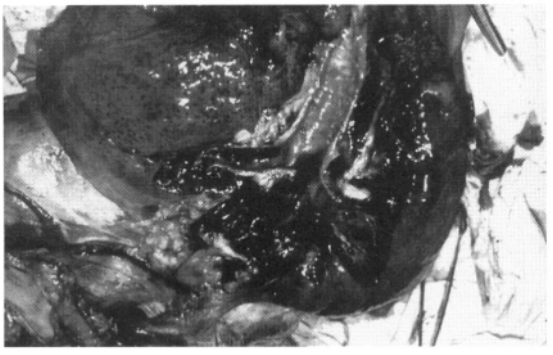

FIGURE 5. Inhalational anthrax. Note necrotizing and hemorrhagic mediastinitis and lymphadenitis (Provided by Lev Grinberg, M.D., and Faina Abramova, M.D.).

Brucella Species

In contrast with the Middle East and some Mediterranean countries where brucellosis remains a major health problem, only 95 cases were reported in the United States in 1994 (Sanford, 1997). The disease is acquired by ingestion, inoculation through abraded skin or the conjunctiva, or inhalation of infectious droplets from tissues or body fluids of chronically infected animals, particularly cattle with *Brucella abortus,* goats and sheep with *B. melitensis,* and swine with *B. suis* (Buchanan et al., 1974). Following entry into the body, the organisms spread to the regional lymph nodes, and subsequently through the blood to the liver, spleen, and lungs (Sanford, 1997). In the subacute stage of infection, patients may develop noncaseating epithelioid cell granulomata and lymphocytic infiltrates in the reticuloendothelial system, meninges, genitourinary tract, and lungs. The organisms can be demonstrated within macrophages in the acute and subacute lesions using Brown–Hopps tissue gram stain and the Steiner, Dieterle, or Warthin–Starry silver impregnation procedures (Hunt & Bothwell, 1967; Weed et al., 1956). In the chronic stage, there are caseous or suppurative granulomas that may resemble tuberculosis. Residual fibrocaseous granulomas or coin nodular lesions can resemble tuberculosis, histoplasmosis, or coccidioidomycosis (Weed et al., 1956).

Nocardia Species

Among the nine species of *Nocardia, N. asteroides* accounts for 80% to 90% of all infections; 3% to 9% are caused by *N. brasiliensis,* and 0.5% to 3% are caused by *N. ottidiscaviarum* (previously known as *N. caviae)* (Rolfe et al., 1992). This gram-positive, weakly acid-fast, filamentous, branching bacillus occurs in soil and decaying organic material worldwide (Filice, 1993). Approximately half of the patients with nocardiosis are immunocompetent, but immunosuppressive therapy, organ transplantation, diabetes mellitus, and pulmonary alveolar proteinosis increase the risk of contracting the infection (Palmer et al., 1974). *Nocardia* is a rare cause of CAP. In a prospective study of more than 1100 cases of CAP, no cases of nocardiosis were reported by Marrie (1994). The infection causes a lobular,

lobar, or diffuse consolidation, and in the acute stage suppurative and necrotizing inflammation leads to formation of sinus tracts and walled-off abscesses. In chronic infections, the latter are filled with thick exudate composed of neutrophils and macrophages. Epithelioid histiocytes and multinucleated giant cells are present at the periphery of the abscesses. The bacteria appear as beaded, branching filaments that can be demonstrated in tissue sections by Brown–Brenn, Brown–Hopps, modified Ziehl–Neelsen, or Gomori's methenamine-silver stain. Empyema and cavitation are frequent (Winn & Chandler, 1994; Marrie, 1994; Frazier et al., 1975).

Actinomyces Species

Pulmonary actinomycosis may occur as part of a mixed anaerobic infection in an immunocompetent host as a result of aspiration of infectious material or a direct extension of cervicofacial infection (Winn & Chandler, 1994). Pulmonary consolidation may be accompanied by numerous small abscesses and cavitation. Sinus tracts into soft tissues can be seen with the characteristic sulfur granules (Oddo & Gonzalez, 1986). Microscopically, these delicate, branched, gram-positive and often beaded filaments arranged in tangled aggregates or radially oriented at the periphery of the granule are frequently surrounded by eosinophilic material, an example of the Splendore–Hoeppli phenomenon. Fragmented coccobacillary forms may be present. Brown–Brenn and Gomori's methenamine-silver stain may be used to demonstrate actinomycetes in tissue sections (Oddo & Gonzalez, 1986; Hotchi & Schwarz, 1972).

Anaerobes

Anaerobic bacteria are rarely identified as a cause of CAP. Perhaps because the diagnosis of anaerobic pneumonia depends on obtaining pulmonary samples anaerobically, these infections may go unrecognized. Conditions that predispose to aspiration and poor oral hygiene increase the likelihood of anaerobic infections (Meeker & Longworth, 1996). Sixty percent to 90% of patients with anaerobic infections have conditions associated with stasis of secretions or necrosis of tissue such as pulmonary infarction, tumors causing endobronchial obstruction, or bronchiectasis (Bartlett, 1991). The two main overlapping patterns of pulmonary infection are lung abscess and necrotizing pneumonia. Histologically, there is extensive necrosis, and often foreign material including cell walls of plant substances with foreign body giant cells are present. Aspiration of gastric contents may induce a chemical pneumonitis with intense neutrophilic interstitial reaction and diffuse alveolar damage. In this context, extensive necrosis of the right middle and lower lobes is common. Pleural fibrosis, empyema, and bronchiectasis may develop (Barnes, 1994; Anderson & Turner, 1991). The etiologic anaerobic organisms include *Peptostreptococcus, Peptococcus, Fusobacterium,* and *Bacteroides* species (Bartlett, 1991). Superinfection in aspiration pneumonia often involves mixed anaerobic and/or aerobic microorganisms including Enterobacteriaceae, *P. aeruginosa,* and others (Anderson & Turner, 1991).

Mixed Infections

Mixed viral and bacterial pneumonia is more frequent than pneumonia due to virus alone. The incidence is approximately 9% (MacFarlane, 1994). Viral infections promote epithelial cell desquamation and destruction of mucociliary defenses, which decreases bacterial clearance. Superinfection with *S. pneumoniae, S. aureus, A. fumigatus,* or *H. influenzae* may follow influenza or measles. Infection with respiratory syncytial virus may be followed by *S. pneumoniae* or *H. influenzae* pneumonia (Anderson & Turner, 1991; Fischer & Walker, 1979). The histological features are those of bacterial and viral pneumonia.

Mycobacterial Pneumonia

Mycobacterium tuberculosis

From 6 to 8 million new cases of tuberculosis occur worldwide each year, with 2 to 3 million fatalities, making *M. tuberculosis* the most common identifiable cause of death of any infectious agent. In the developing world, tuberculosis accounts for 6.7% of all deaths (Wallis & Ellner, 1994). Although the incidence of *M. tuberculosis*

as a cause of CAP varies, it must be considered as a potential pathogen. It is transmitted by airborne droplet nuclei that usually implant in the middle or lower lung fields. The bacilli stimulate an acute inflammatory reaction which is replaced by alveolar macrophages. These macrophages enter the lymphatics and transport some of the bacilli to the regional lymph nodes, from which they may be carried lymphohematogenously throughout the body and lodge and multiply in the posterior half of the upper lobes of the lungs due to the high oxygen tension and relative lymphostasis (Hruban & Hutchins, 1994). In more than 90% of cases, the primary tuberculous lesions heal without progression of disease. These lesions undergo fibrosis and/or calcification (Pratt, 1979). In susceptible individuals, the primary infection progresses. The primary complex enlarges, eroding into a blood vessel embolizing large numbers of bacilli. This spread results in many 2- to 3-mm lesions that resemble millet seeds (Fig. 6). If the lesion erodes into a bronchus, the bacilli are spread to other areas of the lung resulting in tuberculous bronchopneumonia, fibronodular lesions (Pratt, 1979; Sahn & Neff, 1974), cavitation, and/or tuberculous empyema (Hruban & Hutchins, 1994). In tissue sections, stains used most commonly for detection of acid-fast bacilli (AFB) are

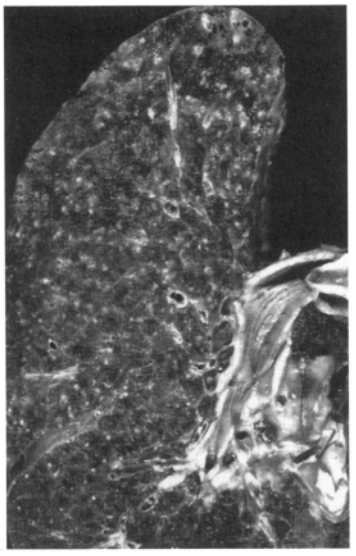

FIGURE 6. Miliary tuberculosis as a result of hematogenous dissemination of numerous bacilli.

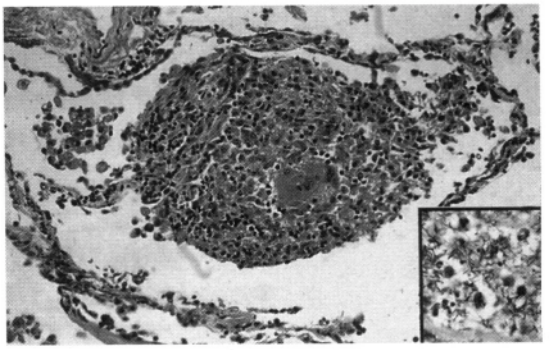

FIGURE 7. Miliary granuloma with abundant epithelioid histiocytes and occasional giant cells. Hematoxylin and eosin, ×250. **Inset**: Multiple acid-fast organisms. Ziehl-Neelsen stain, ×1000.

Ziehl–Neelsen (Fig. 7), Kinyoun, and auramine O (with or without rhodamine) (Woods & Walker, 1996).

Nontuberculous Mycobacteria

Infection with nontuberculous mycobacteria (NTM) is acquired directly from the environment, and patients with decreased immunity and underlying lung diseases are particularly susceptible (Hruban & Hutchins, 1994). Four clinical syndromes can be identified: pulmonary disease, lymphadenitis, skin or soft tissue lesions, and disseminated disease in AIDS (Horsburgh, 1996). Before AIDS, pulmonary disease was the most frequent clinical presentation of NTM infection, in the United States most commonly caused by *M. avium* complex (MAC). In immunocompetent individuals, the classic picture resembles chronic tuberculosis. Involvement of the upper lobes predominates, frequently with thin-walled cavities. Pleural thickening may be present, but pleural effusion is rare. Noncaseating granulomas are characteristic. Primary pulmonary MAC infection, analogous to primary tuberculosis, is difficult to identify (Rosenzweig, 1996). *M. kansasii* infections closely resemble pulmonary disease caused by MAC but are less frequent, accounting for 10% to 15% of NTM cases (O'Brien et al., 1987). These bacteria are slightly larger and more coarsely beaded than most of the other mycobacteria (Hruban & Hutchins, 1994). Thin-walled cavities also are characteristically present in the upper lobes (O'Brien et al.,

1987). Rapidly growing mycobacteria, including *M. abscessus, M. fortuitum,* and *M. chelonae,* account for fewer than 5% of cases. Cavity formation is uncommon, and nodular infiltrates are the rule (Ahn et al., 1982). Other NTM that cause lung disease in humans include *M. simiae, M. szulgai, M. xenopi,* and *M. malmonense* (Gangadharam, 1996). In addition to stains specific for the detection of AFB, MAC bacilli stain positively with periodic acid-Schiff (PAS), a unique feature among the mycobacteria and, therefore, a useful diagnostic criterion (Woods & Walker, 1996).

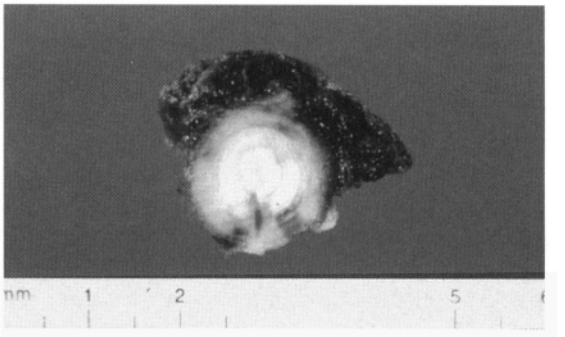

FIGURE 9. Residual pulmonary nodule (histoplasmoma) contains concentric layers of dense calcifications.

Fungal Pneumonia

Histoplasma capsulatum

Among the causes of acute fungal pneumonia acquired in communities in the United States, histoplasma is the most common. Infection occurs after inhalation of spores from aerosols of contaminated soil. Once infection is established, polymorphonuclear leucocytes infiltrate the tissues, followed by macrophages which engulf the yeasts. Lymphatic spread occurs with subsequent access to the circulation (Johnson & Sarosi, 1989). The majority of infections are asymptomatic, and the presence of calcified granulomata in the lung and spleen are usually incidental findings. In susceptible individuals, there is progressive disseminated histoplasmosis in the classical miliary pattern (Fig. 8) (Goodwin et al., 1980). Rarely, the infection leads to the development of thin-walled cavities with extensive destruction of the parenchyma. Chronic pulmonary infection is associated with extensive fibrosis, emphysema, bronchiectasis, and the residual solitary nodule or histoplasmoma (Fig. 9). The latter varies from 0.5 to several centimeters in diameter, is usually subpleural, and consists of a large central zone of caseous necrosis surrounded by lymphoid aggregates, epithelioid and multinucleated giant cells, and a thick fibrous capsule in the periphery. The necrotic zone may contain stippled or concentric calcifications (Goodwin et al., 1976; Goodwin et al., 1969; Baker, 1964). Pleural effusions are uncommon. In tissue sections, the intracellular yeast cells are spherical and oval, often in clusters, and are readily stained with Gomori's methenamine-silver method.

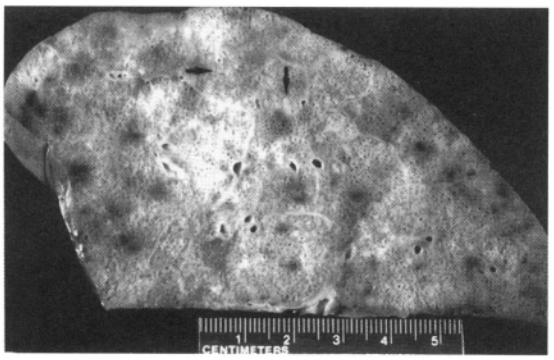

FIGURE 8. Disseminated histoplasmosis capsulati. Cut surface shows numerous miliary nodules (*arrows*) resembling "millet seeds."

Coccidioides immitis

Pulmonary infections with *C. immitis* are usually asymptomatic. Single or patchy infiltrates occur in a segmental or lobar distribution. Necrosis of lung tissue is accompanied by the development of both thick- and thin- walled cavitary lesions. Pleural effusions are observed, and pneumohydrothorax results when a peripheral cavity erodes into the pleural space (Rosenzweig, 1996; O'Brien et al., 1987). Single pulmonary nodules may cavitate or appear as coin lesions in chest radiographs. Miliary spread of *C. immitis* occurs in 4% of the patients, most commonly immunosuppressed individuals, with a suppurative reaction rather than a well-developed granulomatous response to the infection. Histologically, the spherules are generally abun-

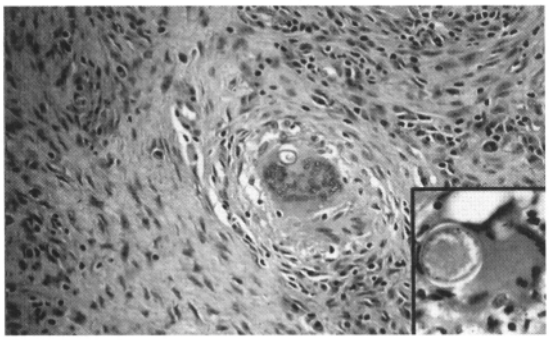

FIGURE 10. Coccidioidal pneumonia. Granuloma with multinucleated giant cell surrounded by epithelioid histiocytes and other mononuclear cells. Hematoxylin and eosin, ×250. **Inset**: Spherule within a multinucleated giant cell. Hematoxylin and eosin, ×400.

dant in active pulmonary and disseminated lesions (Fig. 10). They are visualized with hematoxylin and eosin stain and may be surrounded by a radiating corona of eosinophilic Splendore–Hoeppli material. Septate hyphae and arthroconidia are seldom produced in tissue (Bayer, 1981; Drutz & Catanzaro, 1978a,b; Chandler & Watts, 1994).

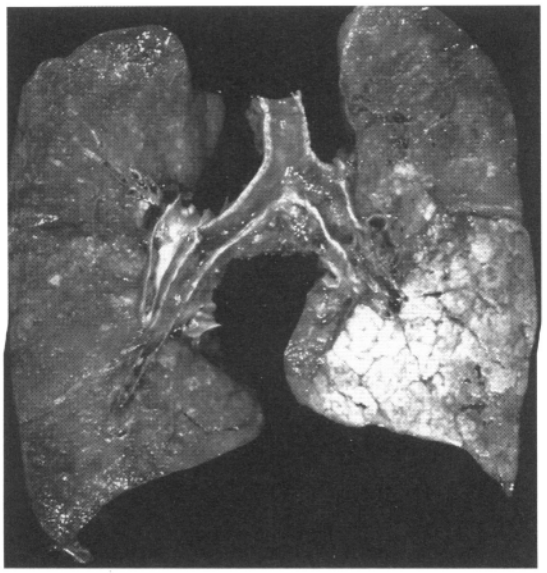

FIGURE 11. Acute pulmonary blastomycosis with dense area of consolidation in left lower lobe.

Blastomyces dermatitidis

Blastomyces, a soil-dwelling organism, can cause an asymptomatic infection similar to histoplasmosis and coccidioidomycosis. In overt disease, pleura-based infiltrates or lobar consolidation infrequently lead to cavitation or pleural involvement (Fig. 11) (Klein et al., 1986). Hematogenous dissemination is not frequent and occurs most commonly in immunocompromised individuals. Histologically, there is an intense neutrophilic infiltrate. *B. dermatitidis* is found in both suppurative and granulomatous foci as intracellular and extracellular, round to oval, multinucleated yeast cells with thick, refractile, doubly contoured walls and broad-based budding. Organisms are as readily identified in hematoxylin and eosin-stained sections as with the PAS method or Gomori's methenamine-silver technique (Sarosi & Davies, 1979).

Aspergillus Species

Ubiquitous within the environment, *A. fumigatus, A. flavus,* and *A. niger* are the most commonly isolated species in compromised patients, and less often acute pulmonary aspergillosis has been reported to cause CAP in immunocompetent hosts. The classic presentation is colonization of preexisting cavities, which waxes and wanes insidiously over months to years (Clancy & Nguyen, 1998). Underlying conditions include cavitary tuberculosis or sarcoidosis, chronic obstructive pulmonary disease, and neoplasia (Young et al., 1969; Clancy & Nguyen, 1998; Aslam et al., 1971). Microscopically, septate hyphae with uniform diameter and 45° angle dichotomous branching are seen on Gomori's methenamine-silver or PAS stain. The hyphae may be seen surrounded by eosinophilic Splendore–Hoeppli material or may appear with bizarre, globose, thick walls. Fungus ball consists of convoluted layers of radially arranged mycelia containing both typical viable and distorted, necrotic hyphae in a prominent inflammatory exudate and, particularly with *A. niger,* calcium oxalate crystal deposition in the surrounding tissue (Chandler & Watts, 1994; Clancy & Nguyen, 1998).

In patients with alcoholism or previous influenza A infection, invasive pulmonary aspergillosis can occur as a CAP. Hyphae invade through the

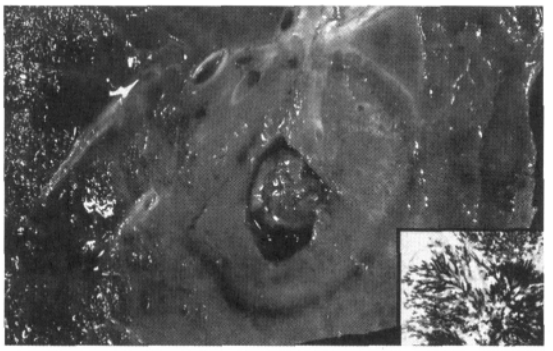

FIGURE 12. Cavitation in nodular infarct in a case of *Aspergillus fumigatus* pneumonia. Cavity contains necrotic lung with invasive hyphae. **Inset**: Hyphae are septate with dichotomous branching. Gomori's methenamine-silver stain, ×1000.

walls of the bronchi and into the adjacent pulmonary and bronchial arteries causing thrombosis, obstruction, and pale anemic infarction, owing to obstruction of both the pulmonary and bronchial arteries. The necrotic tissue frequently undergoes cavitation; in contrast to the preexisting cavities, these cavities contain necrotic lung tissue with invasive hyphae (Fig. 12) (Seriff, 1969; Fischer & Walker, 1979; Chandler & Watts, 1994).

Mycoplasmal, Chlamydial, and Rickettsial Pneumonias

Mycoplasma pneumoniae

Transmitted from person to person, *M. pneumoniae* is responsible for about one fifth of all cases of CAP, is more common in children and young adults, but is not uncommon in the elderly (Johnson & Cunha, 1993). The organism appears to contain adhesion proteins for attachment to host cells and damages the respiratory tract epithelium by liberating hydrogen peroxide and superoxide radicals (Murray & Tuazon, 1980). Tracheobronchitis occurs more often than pneumonia. The pattern of pneumonia ranges from unilateral lobar or lobular consolidation to a diffuse interstitial pneumonitis (Barnes, 1994; Johnston & Cunha, 1993). Microscopically, there is interstitial infiltration by macrophages, lymphocytes, and plasma cells. The lumens of bronchi and bronchioles contain polymorphonuclear leukocytes, mucus, fibrin, and desquamated epithelial cells (Maisel et al., 1967).

Chlamydiae

Chlamydial pneumonia may be caused by all three species that are pathogenic for humans. *C. trachomatis* can produce pneumonia in children aged 1 to 18 months, but infection has also been reported in adults as CAP (Andersen, 1998). Most of the pathologic features have been described in children, with a mixed picture of interstitial and alveolar pneumonitis and bronchiolitis with lymphocytes, plasma cells, eosinophils, neutrophils, and macrophages (Harrison et al., 1979). *C. psittaci* is transmitted to humans from infected birds, either by direct contact or by inhalation of aerosols of infectious excreta or dust (Leigh & Clyde, 1987). Tracheobronchitis and interstitial and alveolar pneumonitis with hilar lymphadenopathy are common pathological features. Pulmonary inflammation consists mainly of mononuclear cells. There is proliferation and desquamation of alveolar lining cells (Gregory & Schaffner, 1997). *C. pneumoniae* is the third or fourth most frequent cause of CAP (Reynolds, 1996). Ninety percent of the infections are mild or asymptomatic, but severe pneumonia has been reported in the elderly and persons with underlying disease, where small pleural effusions have been described (Johnson & Cunha, 1993; Grayston & Thom, 1991).

Rickettsia rickettsii, R. typhi, R. prowazekii

The etiologic agents of Rocky Mountain spotted fever, murine typhus, and epidemic typhus are transmitted by tick bite, infected flea feces, and louse feces, respectively, and reach the endothelial cells of blood vessels of many organs and the pulmonary microcirculation via the bloodstream (Donohue, 1980). As a consequence, the lungs show edema, congestion, focal hemorrhage, interstitial pneumonia, and diffuse alveolar damage. Microscopically, there is endothelial damage and interstitial and alveolar edema with diffuse interstitial mononuclear inflammatory infiltrate and perivascular lymphohistiocytic infiltration. Intra-alveolar hemorrhage and small-vessel vasculitis may be

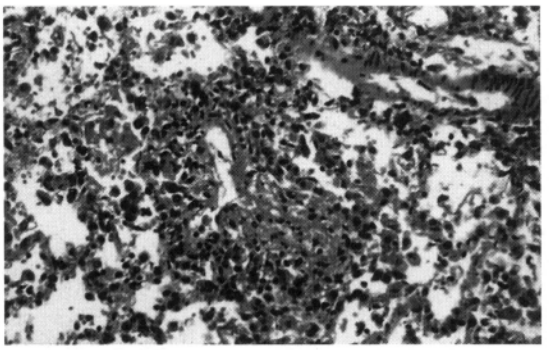

FIGURE 13. Interstitial pneumonia associated with Rocky Mountain spotted fever. Note the dramatic perivascular infiltration by lymphocytes and macrophages. Hematoxylin and eosin, ×250.

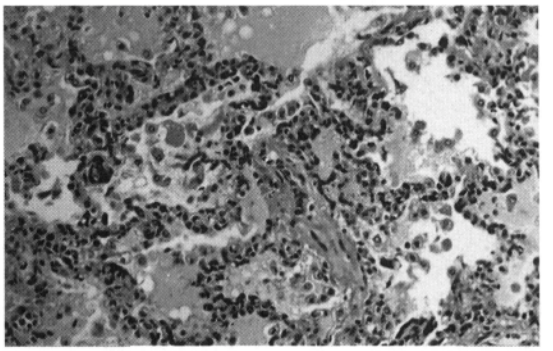

FIGURE 14. Scrub typhus interstitial pneumonia with edema filling the alveolar spaces. Hematoxylin and eosin, ×250.

present (Fig. 13). Intracellular organisms may be demonstrated within endothelial cells using immunohistochemistry (Walker et al., 1980; Roggli et al., 1985).

Orientia tsutsugamushi

Scrub typhus is a zoonosis transmitted to humans by the larval mite (chigger) of *Leptotrombidium* spp. (Traub & Wisseman, 1974). Infected patients can develop encephalitis and pneumonitis. Grossly, the lungs show hemorrhage and congestion. Histologically, there is intra-alveolar and interstitial infiltration by lymphocytes and plasma cells, alveolar and interlobular septal edema, and diffuse alveolar damage with hyaline membranes lining the alveolar spaces (Fig. 14) (Traub & Wisseman, 1974; Levine, 1946; Settle et al., 1945). Superinfection with bacterial bronchopneumonia may coexist in 30% of the cases (Chayakul et al. 1988).

Coxiella burnetii

This organism is a small obligately intracellular gram-negative pleomorphic coccobacillus that infects humans who inhale the aerosol of products of conception of sheep, cattle, goats, cats, rabbits, and dogs (Antony & Schaffner, 1997). Radiologically, lesions are patchy infiltrates or round opacities that tend to be more frequent in the lower lung fields. Pleural infiltrates may occur, some with small pleural effusions (Millar, 1978). Focal or lobar consolidation may be present. The organisms can be demonstrated within alveolar macrophages by immunohistochemistry. Granulomas, plasma cells, and lymphocytes characterize the inflammatory response; polymorphonuclear leukocytes are rarely present (Pierce et al., 1979).

Viral Pneumonia

Influenza Viruses

Influenza viruses are orthomyxoviruses that infect a wide range of avian and mammalian hosts, including humans. Influenza viruses, particularly type A, produce pandemic disease, are the leading viral etiology of pneumonia in adults, and account for 10,000 to 40,000 excess deaths each winter. Influenza virus B produces epidemic disease and is rarely associated with mortality (Ruben, 1993). Both viruses contain hemagglutinin and neuraminidase, which are important for the attachment of the virus to the cells and their subsequent entry. Viral infection impairs the function of the mucociliary escalator, allowing bacteria to invade the lower respiratory tree and predisposing to the development of secondary bacterial pneumonia, frequently caused by *S. aureus, H. influenzue,* or *S. pneumoniae.* Functional impairment of the phagocytes by the deterrent action of the virus has also been described (Spera & Shepp, 1994). There are many reports of

the pathology of fatal influenza pneumonia, and those from Hers et al. (1958) dealing with the Asian influenza epidemic in the 1950s are particularly noteworthy. They described focal lesions sometimes in a lobular distribution. Characteristically, there were cytopathic changes of the respiratory and alveolar epithelium; capillary thrombosis and necrosis with focal leukocytic exudate; capillary aneurysms and hemorrhage (Fig. 15); presence of a plasma–rich exudate after 3 to 4 days with hyaline membranes lining the alveolar spaces (Fig. 16); and metaplastic regeneration of the respiratory and alveolar epithelium after 5 to 7 days. Similar findings were observed by Winternitz et al. (1920) in 1918 (Fig. 17). Changes in the upper respiratory tract have been well described by Walsh et al. (1961) who performed tracheal and bronchial biopsies in patients with clinically uncomplicated influenza. Histologically, there was desquamation of the respiratory epithelium with loss of cilia, edema, hyperemia, areas of necrosis, ulceration of the mucosa, vacuolation of columnar epithelium with nuclear hyperchromasia, and a mononuclear cell infiltrate in the submucosa (Walsh et al., 1961). Viral antigen can be found in type 1 and 2 pneumocytes and in alveolar macrophages. No viral inclusions have been described (Walsh et al., 1961; Oseasohn et al., 1959). Interstitial fibrosis has been observed with residual inflammation. Obliterative bronchiolitis and metaplasia may persist for weeks or months after the infection (Winn & Walker, 1994).

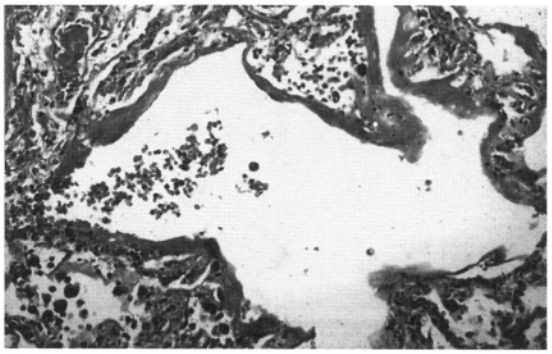

FIGURE 16. Influenza virus A pneumonia. Thick hyaline membranes line the alveolar spaces. The interstitium is congested, edematous, and contains mononuclear leukocytes. Hematoxylin and eosin, ×250.

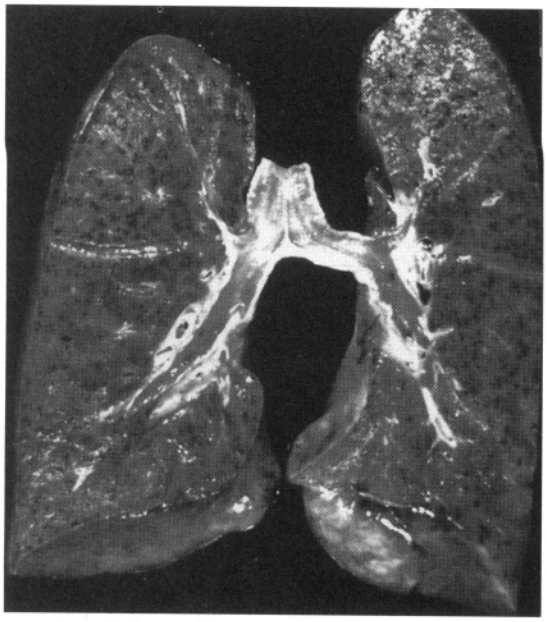

FIGURE 15. Influenza virus A pneumonia. The cut surface of the pulmonary parenchyma is markedly congested and hemorrhagic.

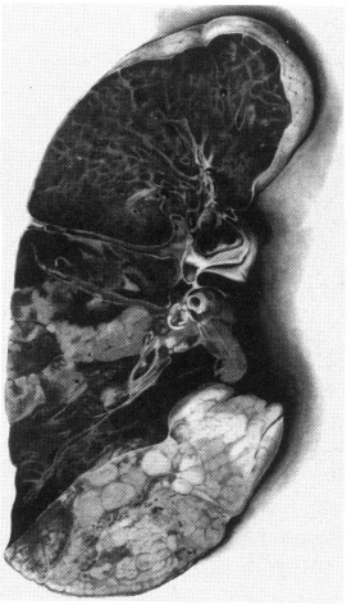

FIGURE 17. A case of influenza virus A pneumonia from the epidemic of influenza in New Haven, Connecticut, 1918. Watercolor representing a cross section of the lung with a diffuse hemorrhagic appearance. The lower lobe shows areas which may represent bacterial superinfection (From Winternitz et al., 1920).

Parainfluenza Viruses

These paramyxoviridae are an important cause of respiratory disease in infants and young children, ranging from croup and bronchiolitis to pneumonia. Human infection with types 1, 2, 3, 4A, and 4B rarely results in the patient's death (Clover, 1994). The lung pathology includes bronchitis with regenerative epithelial hyperplasia, hyperplasia of alveolar lining cells, and interstitial pneumonia. Immunocompromised patients may show an alveolar exudate, alveolar cell hyperplasia, interstitial fibrosis, and alveoli lined by multinucleated giant cells with large cytoplasmic inclusions (Little et al., 1981).

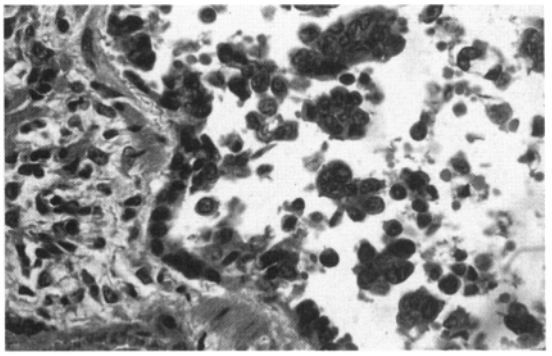

FIGURE 18. Respiratory syncytial virus bronchiolitis. Damage of the epithelium is evident with formation of small papillary projections and multinucleated giant cells. There is a mononuclear peribronchiolitis, and mononuclear cells are present in the lumen. Hematoxylin and eosin, ×250.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) pneumonia occurs in early childhood, particularly in children aged 1 to 3 years, and is most severe in children less than 1 year of age (Ruben, 1993). It has been reported to cause pneumonia in healthy adults and death in immunocompromised hosts (Vikerfors et al., 1987; Englund et al., 1988). Lung infections are characterized by the scanty fusion of RSV-infected cells and occasional multinucleated syncytial giant cells, hyperplasia of alveolar epithelial cells, epithelial necrosis of bronchioles and bronchi, papillary epithelial hyperplasia, and an inflammatory infiltrate composed of lymphocytes and macrophages in the peribronchial space and interstitium (Fig. 18). Alveolar edema and hyaline membranes have been reported. Bacterial superinfection by *H. influenzae* has been described (Winn & Walker, 1994).

Measles Virus

Among a small portion or unvaccinated children and young adults, cases of fatal measles pneumonitis have shown diffuse, patchy, or nodular lesions with areas of hemorrhage in a peribronchial and peribronchiolar distribution. Histologically, the classic giant-cell pneumonitis contains readily demonstrable intranuclear inclusions that may resemble those of herpes simplex virus, as well as eosinophilic cytoplasmic inclusions and mononuclear interstitial infiltration (Fig. 19) (Radoycich et al., 1991). Hyaline membranes and pulmonary thromboemboli have been described (Winn & Walker, 1994). Necrotizing bronchiolitis may be present (Radoycich et al., 1991).

Adenoviruses

Adenoviral respiratory infections affect young children, military recruits, and immunocompromised hosts. The types 1–7, 7a, 11, 21, 31, and 35 have been associated with pneumonia (Winn & Walker, 1994). Extensive necrotizing bronchiolitis

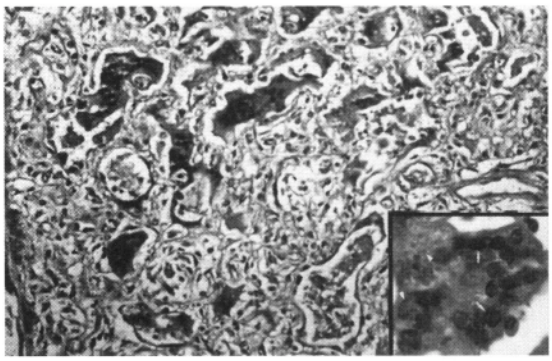

FIGURE 19. Measles pneumonia. The air spaces are obliterated by a mixed inflammatory infiltrate, proliferation of alveolar epithelial cells, and formation of multinucleated epithelial cells. Hematoxylin and eosin, ×250. **Inset**: Eosinophilic intranuclear (*arrows*) and cytoplasmic (*arrowheads*) inclusions are easily seen in multinucleated giant cells. The nuclear inclusions resemble those of herpes simplex virus. Hematoxylin and eosin, ×400.

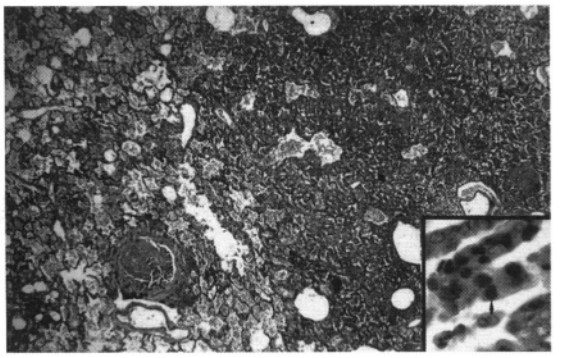

FIGURE 20. Adenovirus pneumonia. Alveolar spaces are lined with hyaline membranes. Interstitial pneumonia is present. Hematoxylin and eosin, ×100. **Inset**: Dense adenoviral (herpes-like) intranuclear inclusions (*arrow*) and smudge cells can be seen. Hematoxylin and eosin, ×1000.

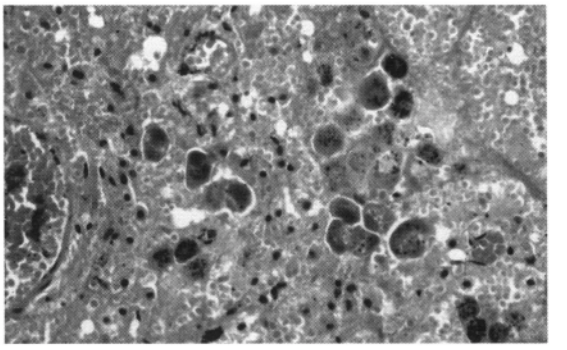

FIGURE 21. Cytomegalovirus pneumonia. Necrosis of the pulmonary parenchyma with sparse mononuclear cells. Numerous enlarged cells contain both intranuclear and cytoplasmic inclusions. Hematoxylin and eosin, ×250.

and alveolitis with basophilic to amphophilic nuclear change (smudge cells) or eosinophilic herpes-like nuclear inclusions, alveolar edema, and hyaline membranes have been reported (Fig. 20) (Pinto et al., 1992). Electron microscopy of lung tissue may show the characteristic intranuclear crystalline arrays of typical icosahedral virions (Green & Williams, 1989).

Cytomegalovirus

Human cytomegalovirus (CMV) pneumonitis is a major problem with a high mortality rate in bone marrow and organ transplant recipients, patients with malignant neoplasms receiving intensive chemotherapy, and patients with AIDS. In immunocompetent hosts, the infection is usually asymptomatic (Oda et al., 1994). Histologically, enlarged cells contain viral inclusions in both the nucleus and the cytoplasm (Fig. 21). The intracellular inclusions are larger and more rounded than the inclusions of herpes simplex and varicella-zoster viruses. The amphophilic inclusions are usually surrounded by an artefactual halo in formalin-fixed tissue. The basophilic cytoplasmic inclusions are round or granular and can be stained by PAS and Gomori's methenamine-silver methods (Winn & Walker, 1994). In the lungs, especially in immunocompromised hosts, the cytomegalic cells may be found in the alveolar epithelium with minimal evidence of inflammation. A second pattern of multifocal miliary lesions that contain cytomegalic inclusion cells has also been described. In these focal lesions the pulmonary architecture shows an exudative inflammatory response in the interstitium and air spaces, sometimes with central necrosis, hemorrhage, and accumulation of fibrin, mononuclear cells, and neutrophils (Winn & Walker, 1994; Norhfelt et al., 1993). A diffuse interstitial pneumonia with lymphocytes, macrophages, and plasma cells may also be seen. In this pattern, there is edema in the interstitium, serofibrinous exudates in the alveolar spaces, and hyperplasia of the alveolar lining cells, and hyaline membranes may be also present. The infection may resolve completely or undergo organization (Winn & Walker, 1994; Craighead, 1971).

Herpes Simplex Virus

Herpes simplex viruses (HSV) types I and II, are spread from person to person by contaminated secretions. Viral pneumonia occurs most often in immunocompromised hosts (Oda et al., 1994). Focal and diffuse interstitial pneumonia and miliary hemorrhagic, necrotic lesions have been described, but most often necrotizing pneumonia with ulcerations of trachea and bronchi and peribronchial alveolar spaces obliterated by nuclear debris, fibrin, necrotic cells, and inflammatory cells mimic bacterial bronchopneumonia. A careful search will di-

vulge multinucleated giant cells containing angulated, eosinophilic, intranuclear inclusions that are surrounded by a clear halo with margination of chromatin (Winn & Walker, 1994).

Varicella-Zoster Virus

Varicella-zoster virus (VZV) infection occurs primarily as chickenpox or herpes zoster. Viral pneumonia is the most serious manifestation of disseminated VZV infection, especially in newborns, pregnant women, and patients with compromised immunity. The incidence of varicella pneumonia in healthy adults with primary chickenpox has been estimated to range from 10% to 50% (Feldman, 1994) and, if untreated, is fatal in approximately 10% of pneumonia cases (Triebwaser et al., 1967). The lungs are firm, heavy, and plum-colored. Necrotic, hemorrhagic, miliary lesions are evident. Histologically, these lesions involve the alveolar walls, blood vessels, and small bronchioles. Eosinophilic intranuclear inclusions and multinucleated giant cells are identified, sometimes only after a prolonged search (Fig. 22). Other findings include interstitial pneumonia, mononuclear cell infiltrates with intra-alveolar fibrinous exudates, hemorrhage, and hyaline membranes. Occasionally there are necrotizing bronchitis and bronchiolitis. Secondary bacterial pneumonia and pulmonary fibrosis with diffuse nodular pulmonary calcifications are common complications (Winn & Walker, 1994; Feldman, 1994).

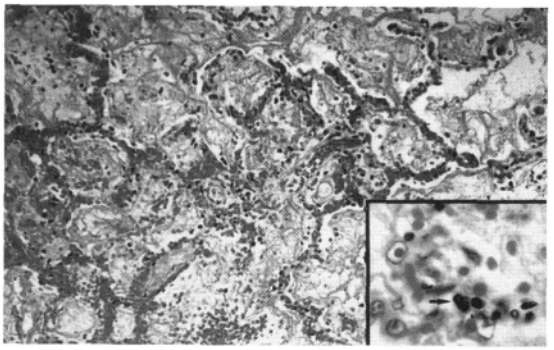

FIGURE 22. Varicella-zoster pneumonia. Extensive necrosis of the parenchyma with intra-alveolar edema and few mononuclear cells in the interstitium. Hematoxylin and eosin, ×100. **Inset**: Intranuclear inclusions (*arrow*) in a focus of necrosis. Hematoxylin and eosin, ×1000.

Hantavirus Pulmonary Syndrome (HPS)

The Hantavirus genus, within the *Bunyaviridae* family, includes a group of single-stranded RNA viruses responsible for Hantavirus pulmonary syndrome. The virus shed in saliva, urine, and feces of the deer mouse, *Peromyscus maniculatus,* infects humans through inhalation of aerosols (Kahl et al., 1997). The hallmark of HPS is respiratory insufficiency owing to noncardiogenic pulmonary edema. Most cases progress to severe disease. Radiographic findings include rapid progression to bilateral interstitial and alveolar edema, and pleural effusions (Moolenaar et al., 1997). Gross examination reveals heavy, edematous, airless lungs, usually with bilateral serous pleural effusions. Histologically, there is intra-alveolar and septal edema, patchy fibrinous alveolar exudate and hyaline membranes, interstitial infiltration with mononuclear cells, and an absence of neutrophils, cellular debris, and evidence of vasculitis or thrombosis. Although the disease resembles ARDS histologically, there are no neutrophilic infiltrates or type II pneumocyte hyperplasia unless there is a prolonged course or history of prolonged mechanical ventilation (Kahl et al., 1997; Moolenaar et al., 1997). Immunohistochemical analysis shows the widespread presence of hantaviral antigens in endothelial cells of the microvasculature. Hantaviral inclusions are usually present in endothelial cells of the lungs in association with pulmonary capillary leak (Zaki et al., 1995).

Human Herpesvirus 6

Human herpesvirus 6 (HHV-6) infects more than 90% of the U.S. population early in life, causing fever and rash in some children, a disease called roseola or exanthem subitum (Yamanishi et al., 1988). In immunocompetent adults, DNA of HHV-6 is commonly found in peripheral blood mononuclear cells and saliva, suggesting that the infection is lifelong (Cone et al., 1993). Over the past several years it has been demonstrated that HHV-6 is an important opportunistic pathogen in immunocompromised patients and causes fatal pneumonitis

in adult bone marrow transplant recipients and in adult patients with AIDS (Cone et al., 1993; Knox et al., 1995). Pathological findings include interstitial pneumonitis, diffuse alveolar damage, extensive atelectasis, diffuse mononuclear inflammatory infiltrates, and hyperplasia of type II pneumocytes (Knox et al., 1995).

Epstein-Barr Virus

Pulmonary involvement during acute infectious mononucleosis is rare (Dunnet, 1963). Epstein-Barr virus-infected lymphocytes can infiltrate the lung, especially in AIDS patients, and this condition is characterized pathologically by interstitial pneumonitis with marked mononuclear inflammatory infiltrate (Sriskandan et al., 1996).

Protozoal Infections

Toxoplasma gondii infection is a major cause of morbidity and mortality in HIV-infected patients (St. Georgiev, 1993). The overall prevalence of pulmonary toxoplasmosis in AIDS is approximately 0.5%. Reactivation of latent disease is the most common cause of pulmonary toxoplasmosis in the immunocompromised host. Rare cases have been reported in immunocompetent individuals. It usually accompanies cerebral or disseminated infection. Radiologically, diffuse bilateral pneumonia, multiple miliary nodules, and interstitial and lobar infiltrates have been described. Pleural effusion and pneumothorax have also been reported. Histologically, there may be necrotizing pneumonia, diffuse alveolar damage, and interstitial pneumonitis (Campagna, 1997). Organisms may be found in the alveolar spaces, alveolar macrophages, and capillary endothelial cells. Giemsa, hematoxylin-eosin, and eosin-methylene blue stains may show crescent-shaped tachyzoites (Campagna, 1997; Baird et al.. 1994).

Amebiasis is the third leading parasitic cause of death in the world. Pleuropulmonary complications of *Entamoeba hixtolytica* infection occur almost exclusively in individuals with liver abscess. Common pleuropulmonary complications of rupture of hepatic amebic abscess into the pleural space include right-sided pleural effusions, empyema, basilar atelectasis, and lung abscess (Lyche & Jensen, 1997). The core of an amebic abscess contains necrotic debris with occasional inflammatory cells and trophozoites. The latter are concentrated in the periphery of viable tissue around the abscess (Baird et al., 1994; Lyche & Jensen, 1997).

Protozoa such as *Plasmodium, Babesia,* and *Cryptosporidium* seldom cause pulmonary disease. Infection with *P. falciparum* produces acute pulmonary insufficiency in 7% of nonimmune hosts via the development of pulmonary edema (Kemper, 1997). Pleural effusions, interstitial edema, and lobar consolidations have also been reported (Baird et al., 1994). *Babesia microti* can also produce respiratory failure and ARDS similar to *P. falciparum.* Many cases of *Cryptosporidium parvum* infection have been complicated by the presence of concurrent pulmonary infections, but the contribution of the cryptosporidial infection to significant pulmonary disease in these cases is not clear. Virtually all the cases reported with evidence of the organism in respiratory specimens also had intestinal disease. The organism was found along the ciliated border of the bronchial and tracheal mucosa and in the bronchial submucosal glands (Baird et al., 1994; Kemper, 1997). Microsporidium has been reported in AIDS patients who developed pleuritis and a lobar infiltrate with edema, vascular congestion, and a mixed inflammatory infiltrate. Microsporidian spores of *Encephalitozoon helium* can be found within the cytoplasm of bronchiolar and alveolar duct epithelial cells (Kemper, 1997).

P. carinii pneumonia is caused by an organism more closely related to fungi than protozoa. This organism is a common cause of pneumonia in immunocompromised patients (Kroe et al., 1997). Grossly, the pulmonary parenchyma appears pale-gray and firm. The infiltrate may be patchy or progress to lobar or whole lung involvement. Atypical bronchopneumonic patterns are not uncommon (Miller et al., 1994; Sobonya, 1994). When associated with the histologic pattern of diffuse alveolar damage, the process involves a large portion of the pulmonary parenchyma, and the lungs are pink-gray (Sobonya, 1994). The most characteristic histologic feature is the presence of intra-alveolar foamy eosinophilic exudates on hematoxylin and eosin stain. Basophilic dots may be seen within the exudates. The alveolar septa are lined by hyperplastic type II pneumocytes. The interstitium in some

cases contains an infiltrate composed of plasma cells, lymphocytes, and histiocytes (Weber et al., 1977). Cavitary lesions, pneumothoraces, granulomas, and pleural effusions are less common (Sobonya, 1994; Travis et al., 1990).

Helminthic Infections

Unlike most pulmonary pathogens, many helminthic parasites migrate to the lung from distant portals of entry. Many respiratory syndromes are a direct result of parasite migration through the lung as part of its natural life cycle. Although the role of parasites as etiologic agents of CAP is unclear, some parasitic infections deserve consideration.

Strongyloides stercoralis is endemic in tropical and subtropical areas worldwide. The parasitic females live buried in the crypts of the duodenum and upper jejunum producing eggs that develop rapidly into larvae that pass in the feces (rhabditoid larvae) and continue maturation to the infective form in the fecal mass or soil. Infective (filariform) larvae penetrate the skin and travel via the bloodstream to the lungs, break into the alveoli, migrate to the epiglottis, are swallowed, and once in the duodenum, mature to adult females (Gutierrez, 1990). Migration of the larvae through the lungs is obligatory. In the pulmonary capillaries, the larval penetration of the alveoli causes petechial hemorrhages and infiltrates of polymorphonuclear leukocytes and monocytes. Sensitized patients may experience discomfort, but usually there are no symptoms (Baird et al., 1994; Haque et al., 1994). However, in patients with compromised immunity, autoinfection leads to life-threatening hyperinfection. Large numbers of larvae migrate to the lungs. Grossly, there is uniform consolidation of all lobes, hemorrhagic cut surfaces, and bronchi filled with inspissated mucus. Microscopically, there is hemorrhage, a variable inflammatory reaction, and presence of *S. stercoralis* infective larvae in alveolar spaces, in the bronchi, and within mucous plugs (Fig. 23) (Baird et al., 1994; Gutierrez, 1990). Chronic strongyloidiasis, especially in immunocompromised hosts, may cause cavities and abscesses in the lungs. ARDS may be present. The lung may also show changes secondary to superimposed bacterial infection (Baird et al., 1994; Haque et al., 1994; Wehner & Kirsh, 1997).

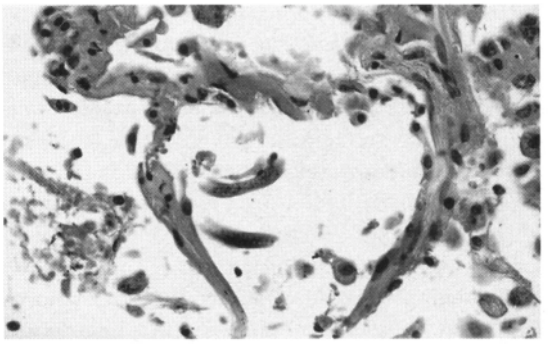

FIGURE 23. *Strongyloides stercoralis* in alveolar spaces (filariform larvae) in an immunosuppressed patient (Contributed by A. K. Haque, M.D., Galveston, Texas).

Pulmonary manifestations *of Ascaris lumbricoides* occur during the stage of larval migration through the lungs and are rarely a complication of the intestinal phase. This is the most common worldwide cause of transient eosinophilic pulmonary infiltrates (Löffler's syndrome) (Sarinas & Chitkara, 1997). Pathologically, the lungs show consolidated gray patches most often in the lower lobes. Bronchioles contain eosinophils and fibrin. Interstitial pneumonitis with thickened alveolar walls may be present. *A. lumbricoides* may be found within alveolar walls, bronchioles, and bronchi. Granulomata may develop and consist of larvae surrounded by clusters of eosinophils, histiocytes, and epithelioid cells (Baird et al., 1994; Sarinas & Chitkara, 1997). Lung pathology in hookworm infection *(Ancylostoma duodenale* and *Necator americanus)* may show intra-alveolar hemorrhage caused by the larval migration through capillary walls and interstitial pneumonitis (Sarinas & Chitkara, 1997).

Dirofilaria, Toxocara, and the filarial parasites, *Wuchereria* and *Brugia,* produce an array of pulmonary manifestations in humans. Infections are common in temperate, tropical, and subtropical regions of the world. Human pulmonary dirofilariasis is caused by a ubiquitous canine parasite, *Dirofilaria immitis,* the dog heartworm (Chitkara & Sarinas, 1997). Larvae are transmitted by mosquito bite to another dog or human being. Most larvae die in the subcutaneous tissue. Some develop further and reach the right ventricle before dying and em-

bolizing to the pulmonary arteries, producing thrombosis, infarction, and subsequently a granulomatous reaction. Most commonly, radiologic studies show a spherical, peripherally located solitary pulmonary nodule that ranges from 1 to 4.5 cm in diameter (Asimacopoulos et al., 1992). The nodule is a localized infarct that shows a narrow zone of granulomatous reaction surrounded by a well-formed fibrous wall and in some cases eosinophilic inflammation. *Dirofilaria* is identified as a smooth multilayered organism with a thick cuticle, transverse striations, broad lateral cords, and a thick band of somatic muscles projecting far into the body cavity (Fig. 24) (Baird et al., 1994; Chitkara & Sarinas, 1997). If the parasite has degenerated, it can easily be missed in hematoxylin and eosin-stained tissue. Nonspecific fluorescent whitening stain aids in distinguishing the organisms or its fragments within granulomas (Green et al., 1994). Visceral larva migrans (VLM) or systemic toxocariasis is a zoonotic disease with human viscera involved by the migrating larvae of *T. canis* or *T. cati.* Pulmonary involvement, both in children and adults, occurs in 20% to 85% of cases of VLM. Asthma, acute bronchiolitis, and acute pneumonia can develop (Taylor et al., 1988), frequently with bilateral segmental, or diffuse alveolar infiltrates. Eosinophils predominate in the early response. Histiocytes and granulomata are present (Baird et al., 1994; Chitkara & Sarinas, 1997).

Wuchereria bancrofti and *Brugia malayi* usually cause tropical pulmonary eosinophilia with functional alterations in the lungs characterized by wheezing, dyspnea, and pain or tightness in the chest. Extreme eosinophilia persists for weeks (Baird et al., 1994). Histologically, there are eosinophilic abscesses and granulomata with foreign-body giant cells and palisading epithelioid cells (Baird et al., 1994; Chitkara & Sarinas, 1997). Interstitial fibrosis may develop with a residual mixed inflammatory infiltrate. Cavitation, bronchiectasis, and pleural effusions are uncommon.

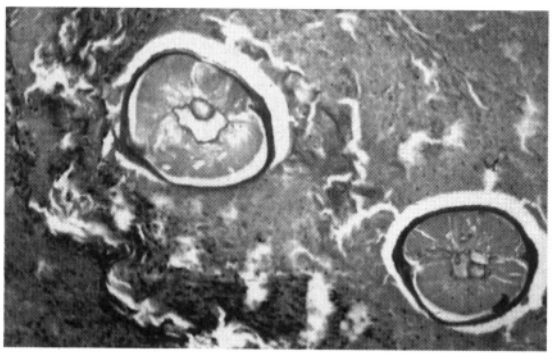

FIGURE 24. Transverse section of immature *Dirofilaria immitis* in a pulmonary vessel surrounded by necrotic tissue. Hematoxylin and eosin, ×250.

Paragonimiasis (caused by *Paragonimus westermani)* is a parasitic disease of carnivorous animals including humans. The clinical symptoms are often the cause for an erroneous diagnosis of tuberculosis (Kagawa, 1997). When the larvae penetrate the visceral pleura, they may cause a small to massive exudative effusion. They can also cause bronchiectasis, interstitial pneumonitis. or bronchopneumonia with transitory hemorrhage. An exudate of eosinophils and neutrophils surrounds the worms. A fibrous wall may rupture into a bronchiole, and the patient may expectorate blood-streaked sputum containing parasite eggs, inflammatory cells, Charcot–Leyden crystals, and necrotic tissue (Baird et al., 1994; Kagawa, 1997).

Echinococcosis (hydatid disease) is caused by the postlarval metacestode stage of the dog tapeworms *Echinococcus granulosus* and *E. multilocularis* (Bhatia, 1997). Pulmonary disease is a complication of liver involvement (Baird et al., 1994). Cysts in the lung are not life-threatening. Histologically, cysts of *E. granulosus* and *E. vogeli* are surrounded by a thick wall of the host fibrous tissue. Cysts of *E. multilocularis* are surrounded by necrotic debris and occasionally cavitate. Those that rupture into the bronchi may cause chronic suppuration and abscess. Necrotizing granulomas have been reported (Baird et al., 1994; Bhatia, 1997).

Chemical Pneumonia

There are noninfectious conditions that can produce a clinical syndrome similar to pneumonia which may result in lung injury and consequent impairment of pulmonary function following acute or chronic exposure. If the clinical picture does not fall in line with the more common causes of CAP, consideration of these "unusual" causes of pneumonia may be essential. Two mechanisms account for the lung toxicity encountered in most patients

with chemical pneumonia: (1) inhalation of the toxic agent, causing direct irritation and inflammation of the tracheobronchial tree resulting in pulmonary edema (e.g., ammonia, nitrogen dioxide) and (2) absorption of noxious substances that can affect the lung directly or through their metabolites (White & Templeton, 1992).

Organic Chemical Agents

Mineral Oils

The aspiration of mineral oils used as laxatives or nose drops by the elderly patients is well known. However, occupational exposure occurs in industries in which large amounts of lubricants are used. Pulmonary disease may be caused by acute or chronic inhalation of oil mists or aspiration (White & Templeton, 1992). Radiologically, there are multiple small opacities and more focal, often basal, consolidations (Weill, et al., 1964). The lungs are gray to yellow and solid. The air spaces are filled with vacuolated or foamy macrophages. There are foreign–body multinucleated giant cells, an inflammatory exudate, and fibrous obliteration and reduction of the lung parenchyma (Pinkerton, 1928).

Organophosphates

The organophosphates are a group of anticholinesterase-inhibiting compounds that have attained global usage as agricultural pesticides. Farmers and crop sprayers are at risk for occupational exposure, especially from parathion and malathion (Namba et al., 1971). They are absorbed through the gastrointestinal tract, the lungs, and the mucous membranes. The depletion of synaptic acetylcholinesterase results in a prolongation of the effects of acetylcholine and systemic parasympathetic symptoms. In the lungs, organophosphate toxicity is characterized by bronchial hypersecretion, bronchoconstriction, and depression of the respiratory center and musculature, leading to hypoxia and death. The lungs show diffuse pulmonary edema (Bledsoe & Seymour, 1972).

Paraquat

Paraquat is an herbicide that is used in agriculture in more than 130 countries. Poisonings may be occupational but are often intentional. Paraquat accumulates in the lungs and is thought to be responsible for the production of superoxide radicals, which indirectly damage the pulmonary alveoli (Bismuth et al., 1990). The lungs show diffuse pulmonary consolidation due to pulmonary edema followed by alveolar fibrosing alveolitis (Im et al., 1991; Davidson & MacPherson, 1972).

Polyvinyl Chloride

Polyvinyl chloride (PVC) is a polymer used in the plastics industry. Workers sustain ill effects from fumes or dust caused by PVC or vinyl chloride. Inhalation of PVC fumes has been associated with acute bronchospasm. Lengthy exposure leads to a pneumoconiosis characterized histologically by pulmonary fibrosis with a granulomatous reaction (Cordasco et al., 1980; Lilis, 1980).

Thesaurosis

The term thesaurosis has been applied to lung disease associated with the use of hair sprays. Hairdressers are at occupational risk, and significant accidental exposure may occur at home. The most important chemical in hair sprays, polyvinylpyrrolidone, is responsible for inciting a sarcoid-like illness. Interstitial pneumonitis, fibrosing alveolitis, and granulomata are the histological findings (Bergmann et al., 1958).

Other organic chemicals that produce pulmonary edema after exposure include tetrafluoroethylene (Teflon®) fumes and trimellitic anhydride (TMA). The latter is used in the manufacture of paint, epoxy resins, and plasticizers (White & Templeton, 1992). Inhalation of kerosene may produce pulmonary edema and interstitial pneumonitis (Nussinovitch et al., 1992). Similar findings may be seen after furniture polish and lighter fluid ingestion, frequently seen in small children. Pneumatoceles are a late complication of hydrocarbon ingestion after the consolidation has cleared. These are often large, septate, and irregular, and sometimes contain fluid (Akisu et al., 1996). Chronic intoxication due to abuse of solvents, including thinner, by workers who inhale the solvent vapor is frequently encountered, but acute intoxication may lead to severe complications such as rhabdomyolysis, polyneuropathy, and chemical pneumonia (Harris & Brown, 1975).

Inorganic Chemicals

Gases

Ammonia is a corrosive gas used in the production of explosives, petroleum, agricultural fertilizers, and plastics. The chemical is also used in refrigeration. Prolonged exposure produces pulmonary edema. Patients who survive may develop bronchiectasis or bronchiolitis obliterans (Caplin, 1941). Chlorine is an irritant gas used in the manufacture of plastics and bleaches and in water purification. Its irritant properties made it a desirable agent for chemical warfare in World War I (Jones et al., 1986). Toxicity results from its reaction with water, which produces unstable oxidizing agents. The reaction of the oxidizing agents to form hydrates of organic chloride causes tissue damage, with ulceration and swelling of mucosal surfaces. Chest radiographs usually demonstrate bilateral opacities typical of pulmonary edema. A complicating pneumonia may occur within several days (Beach et al., 1969). The toxic effects of nitrogen oxides are best described in workers exposed to forage silo gas (silo–filler's disease), but occupational hazard is well recognized in mining, acetylene welding, and in the manufacture of explosives. In forage silos, nitrogen oxides are produced by the fermentation of corn or hay. When inhaled, they combine with water to form nitric acid, which causes severe tissue damage (Morrissey et al., 1975). Histopathologic examination of the lungs during the acute phase demonstrates mucosal edema and inflammatory cell exudation. Alveolar capillaries are dilated and congested with edema fluid and blood filling the alveolar space. Bronchiolitis obliterans may also develop (Casey, 1991). Phosgene ($COCl_2$) is best known as a lethal chemical warfare agent used in World War I. It is also used as a chlorinator in the production of organic dyes and in the separation of metals (Everett & Overholt, 1968). The gas produces pulmonary edema, which may be fulminant. In animals, it can produce ulcerative bronchitis and obliterative bronchiolitis (Casey, 1991).

Metals

Occupational exposure to cadmium fumes occurs in ore smelting, alloying, and welding. After inhalation, it is absorbed into the bloodstream and produces tracheobronchitis and pulmonary edema. Long-term exposure has been implicated in the development of emphysema, both panacinar and centrilobular (White & Templeton, 1992). Exposure to mercury vapor occurs in the manufacture of thermometers and in the cleaning of boilers. Severe tracheobronchitis and pulmonary edema may develop. Interstitial fibrosis occurs in some patients (Seaton & Bishop, 1978; Hallee, 1969). Pneumonitis, bronchitis, and pulmonary edema have also been described in association with exposure to compounds of osmium, manganese, nickel, and vanadium (White & Templeton, 1992; Casey, 1991).

The variety of CAP cases that occur throughout the world are influenced by epidemiologic and host factors that require careful evaluation of the past medical history, travel, and occupation as well as microbiologic, histopathologic, and in some cases, toxicologic investigation.

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8

Etiology of Community-Acquired Pneumonia

THOMAS J. MARRIE

Introduction

There are many microbial causes of community-acquired pneumonia (CAP), including bacteria, viruses, fungi, and parasites. One of the major considerations in studies detailing the etiology of pneumonia is the certainty of the diagnosis. Marston and coworkers (1997) have categorized patients according to the certainty of the etiological diagnosis.

Definite Diagnosis

1. Isolation of *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* Enterobacteriaceae, or *Pseudomonas aeruginosa* from blood or pleural fluid cultures
2. Four-fold rise in antibody titer to *Legionella pneumophila* (to ≥1:128), *Mycoplasma pneumoniae* (to ≥1:64), or *Chlamydia pneumoniae,* respiratory syncytial virus, or influenza virus antigens (to ≥1:32)
3. Isolation of *Legionella* species or influenza virus from respiratory secretions
4. A ratio of ≥3 of sample-to-control *L. pneumophila* serogroup 1 urinary antigen

Probable Diagnosis

1. Isolation of *S. aureus, S. pneumoniae, H. influenzae, M. catarrhalis,* Enterobacteriaceae, or *P. aeruginosa* from purulent sputum (defined as sputum with moderate or large numbers of neutrophils seen on Gram's stain) in which a compatible organism was seen in moderate or large amounts in a sputum gram stain.

Possible Diagnosis

1. Isolation of pneumonia pathogens other than *Legionella* species from purulent sputum in the absence of a compatible gram stain or a gram stain of purulent sputum demonstrating a predominance of gram-positive diplococci (possible diagnosis of infection with *S. pneumoniae),* gram-positive cocci in clusters (possible diagnosis of infection with *S. aureus*), or gram-negative coccobacilli (possible diagnosis of infection with *H. influenzae*)
2. An antibody titer of ≥ 1:1024 to *L. pneumophilia* in either acute- or convalescent-phase serum specimen
3. An antibody titer of ≥ 1:64 to *M. pneumoniae* in either the acute- or convalescent-phase serum sample
4. An IgG antibody liter of ≥ 1:512 or an IgM titer of ≥ 1:16 to *C. pneumoniae.*

The above definition does not include a positive stain for *Pneumocystis carinii* as a definite

THOMAS J. MARRIE • Department of Medicine, WMC, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

cause of pneumonia. We would also add the following as a definite cause of the pneumonia: demonstration of a four-fold rise in antibody to *Coxiella burnetii;* a single titer of ≥ 1:128 to phase 11 *C. burnetii* antigen; demonstration of antibody to Hantavirus; detection of DNA of *Legionella* species, *M. pneumoniae, C. pneumoniae, Mycobacterium tuberculosis,* or Hantavirus in nasopharyngeal secretions; and isolation of *M. tuberculosis, Blastomyces dermatitidis, Histoplasma capsulatum,* or *Coccidioides immitis* from sputum or other respiratory specimen.

Marston and coworkers (1997) did not include serological testing for antibodies to *S. pneumoniae* or amplification of pneumolysin gene as part of the diagnostic criteria for streptococcal pneumonia (Kauppinen et al., 1995; Burman et al., 1993; Porath et al., 1997).

Aspiration should also be included as an etiological category. Silent aspiration was found in 71% of elderly patients with CAP (mean age, 77 years; range, 62–87 years) compared with 10% of age-matched control subjects (Kikuchi et al., 1994). However, in many patients macroaspiration is the sole cause of the pneumonia.

TABLE 1. Etiology of Community-Acquired Pneumonia[a]

Agent	Number	%	Number of study cohorts reporting data
Unknown etiology	11,229	33.8	27
Streptococcus pneumoniae	4,432	13.3	59
Haemophilus influenzae	833	2.5	27
Mycoplasma pneumoniae	507	1.5	22
Mixed bacterial species	301	0.9	10
Legionella species	272	0.8	20
Coxiella burnetii	182	0.5	7
Staphylococcus aureus	157	0.4	25
Influenza A virus	100	0.3	10
Klebsiella species	56	0.16	12
Chlamydia pneumoniae	41		2
Chlamydia psittaci	32		8
Parainfluenza virus	30		6
Influenza B virus	28		7
Respiratory syncytial virus	20		5
Adenovirus	19		4
Pseudomonas aeruginosa	18		6
Escherichia coli	17		6
Proteus spp.	12		3
Streptococcal species	6		3

[a]Fine and colleagues (1995).

Overview of the Etiology of Community-Acquired Pneumonia

Fine and colleagues (1995) reviewed all citations from a MEDLINE® search of articles dealing with CAP published from January 1966 through June 15, 1995. They found 4573 citations and using a number of criteria narrowed this number to 122 articles which reported on 33,148 patients (see Table 1). This is a useful list even though epidemiologically there are many flaws in the data. The authors' main objective in this study was to examine the outcomes of CAP and they did not apply selection criteria regarding assignment of etiology to these articles. Thus criteria for assignment of etiology differ from study to study. Furthermore, as with almost all the studies cited in this chapter, the diagnostic criteria varied considerably from cohort to cohort. Nevertheless, the category of unknown etiology accounted for 33.8% of the patients. *S. pneumoniae* was the most commonly identified etiological agent, accounting for 13.3% of the patients. Overall 20 etiological categories were identified for these 33,148 patients.

Bacteremic Community-Acquired Pneumonia

Tables 2 and 3 summarize data from nine studies of CAP in which 5521 patients were enrolled. Of these patients, 507 (9.2%) had positive blood cultures for a pathogen. The percentage of patients with positive blood cultures ranged from 6.6% to 23.6% in the various studies. The highest rate was from a study by Sullivan and colleagues (1972) carried out at Grady Memorial Hospital in Atlanta, Georgia, during 1967–1968. Only 14.3% of the patients in this study had received antibiotic therapy prior to collection of the blood for culture. Some 14 years later, only 6.6% of the patients with CAP at the same hospital had positive blood cultures. It is clear from the data in Table 2 that *S.*

TABLE 2. Bacteremic Community-Acquired Pneumonia (CAP)

Authors	Study site	Study period	Number	Number (%) of positive blood cultures	
Macfarlane et al., 1982	Nottingham, U.K.	Jul 1980–Aug 1981	127	18	(14)
Marston et al., 1997	Ohio, U.S.	1991	2776	208	(7.5)
Dorff et al., 1973	Milwaukee, U.S.	Oct 1969–Mar 1970	148	24	(16.2)
Sullivan et al., 1972	Atlanta, U.S.	Jul 1967–Jun 1968	292	69	(23.6)
Chalasani et al., 1995	Atlanta, U.S.	1991	517	34	(6.6)
Bates et al., 1992	Little Rock, U.S.	1985	198	19	(9.6)
Marrie et al., 1989	Halifax, Canada	Nov 1981–Mar 1987	588 CAP	40	48 (6.6)
			131 NHAP	8	
Fang et al., 1990	Pittsburgh, U.S.	Jul 1986–Jun 1987	359	28	
Mundy et al., 1995	Baltimore, U.S.	Nov 1990–Nov 1991	205 HIV-negative	31 (15.5)	59 (15.3)
			180 HIV-positive	28 (15.6)	
Total			5521	507	(9.2)

NHAP, nursing home-acquired pneumonia.

pneumoniae is the predominant cause of bacteremic CAP, accounting for 352 of the 507 cases (69%). *Escherichia coli* was the second most commonly isolated agent, accounting for 27 cases; *S. aureus* was third at 25 cases and *H. influenzae* fourth at 17. *Klebsiella* spp. (chiefly *K. pneumoniae)* was fifth, accounting for 12 cases. Group A streptococcus was causative in eight cases. *P. aeruginosa* accounted for five cases.

In 13 cases more than one microorganism was present. A large number of microorganisms were represented once or twice, including *Serratia* spp. (1); *L. pneumophilia* (1); *Acinetobacter* spp. (1); *Enterobacter* spp. (2); *Proteus* spp. (1); *Haemophilus parainfluenzae* (1); *Streptococcus sanguis* (3); *S. mitis* (2); *Enterococcus fecalis* (1); *Neisseria meningitidis* (1); Group G streptococcus (1); Group F streptococcus (1); Group B streptococcus (1); *Streptococcus uberis* (1); *Salmonella montevideo* (1); *Actinomyces israeli* (1); *Bacteroides fragilis* (1); *Eubacterium lentum* (1); *Bifidobacterium* spp. (1).

Two studies provided data for subgroups of their populations. Marrie and colleagues (1989) noted that 40 of 588 (6.8%) of patients with CAP were bacteremic whereas 8 of 131 (7.6%) nursing home residents who required admission to a hospital for treatment of pneumonia were bacteremic. Mundy and coworkers (1995) found that 31 of 205

TABLE 3. Microorganisms Isolated from Blood in Bacteremic Community-Acquired Pneumonia

Authors	*S. pneumoniae*	*E. coli*	*S. aureus*	*H. influenzae*	Group A streptococcus	*Klebsiella* spp.	*Pseudomonas* spp.
Macfarlane et al., 1982	18	—	—	—	—	—	—
Marston et al., 1997	154	18	12	10	7	4	2
Dorff et al., 1973	17	1	2	—	—	3	—
Sullivan et al., 1972	53	2	3	—	—	1	—
Chalasani et al., 1995	29	1	—	3	1	—	—
Bates et al., 1992	6	2	3	1	—	2	1
Marrie et al., 1989	28	3	1	2	—	2	1
Fang et al., 1990	16	—	4	1	—	—	1
Mundy et al., 1995	31	—[a]	—[a]	—[a]	—[a]	—[a]	—[a]
Total	352	27	25	17	8	12	5

[a]Unable to determine what other agents were isolated from blood.

(15.1%) nonimmunocompromised patients with CAP were bacteremic whereas 28 of 180 (15.6%) patients infected with human immunodeficiency virus who had CAP were bacteremic.

Etiology of Community-Acquired Pneumonia Treated on an Ambulatory Basis

Tables 4 and 5 summarize data from four studies that investigated the etiology of pneumonia in patients treated on an ambulatory basis. The data from these studies are incomplete and blood and sputum cultures were rarely performed. About half (48%) of the 439 patients studied had pneumonia of unknown etiology. *M. pneumoniae* was the most common agent identified in all four studies, accounting for 24% of the patients. Influenza A was the second most common agent at 7%. *S. pneumoniae* was next at 5%. It is likely that *S. pneumoniae* is underdiagnosed in this group of patients because of the lack of cultures. *Chlamydia psittaci* was found at three of the study sites. In the one study with complete *C. pneumoniae* serology this was the second most commonly identified agent (10.7%).

Etiology of Community-Acquired Pneumonia among Patients Requiring Admission to Hospital

The population comprising patients with CAP requiring hospital admission has been most extensively studied. Data from nine studies are summarized in Tables 6–8. *S. pneumoniae* was the most commonly identified agent, accounting for 17.7% of the 5225 patients studied. It is noteworthy that the three studies (Kauppinen et al., 1995; Burman et al., 1993; Porath et al., 1997) that used serological methods in addition to blood and sputum cultures in the diagnosis of pneumococcal pneumonia had the highest rates of infection due to this microorganism. In these studies 42.8% (Porath et al., 1997), 32% (Burman et al., 1993), and 55% (Kauppinen et al., 1995) of the cases of pneumonia were due to *S. pneumoniae* compared with 17.7% for the entire group. There was a wide range in the rate of pneumococcal pneumonia by study site, from a low of 9% at Halifax, Nova Scotia (Marrie et al., 1989) to 55% at Oulu, Finland (Kauppinen et al., 1995). There are several key observations that can be made from a review of Tables 6–8. These are that Legionellaceae account for 3.5% of all causes of CAP; *M. tuberculosis* continues to present as CAP; and *P. carinii* is now an important cause of CAP and always has to be considered in the differential diagnosis of interstitial pneumonia. Anaerobic bacteria were infrequently implicated; only nine cases were identified as the etiology of CAP, but this likely represents failure to obtain specimens that could be used to isolate anaerobic bacteria. Tables 6–8 also contain data on patients who had pneumonia distal to an obstructed bronchus (postobstructive pneumonia) and those who had aspiration pneumonia. Neither of these are etiological categories. There are four major clinical categories associated with aspiration: airway obstruction, chemical pneumonitis, drowning, and infection (Finegold, 1991). The bacteriology of postobstructive pneumonitis has been defined by Liaw and colleagues (1994). These workers performed needle aspiration under ultrasound guidance of the pneumonia area in 26 patients with postobstructive pneumonitis. Five cases had a monomicrobial etiology; the remainder were polymicrobial. Eight of the 26 had anaerobic bacteria isolated. Other isolates included *K. pneumoniae,* Viridans streptococci, *P. aeruginosa, Stenotrophomonas maltophilia, S. aureus,* and aerobic gram-positive bacilli.

There are also agents missing from Tables 6–8 that may be important in a specific geographic area at a specific point in time, for example, Hantavirus. It is also likely that there are causes of pneumonia that have not been yet identified. Legionellaceae, *C. pneumoniae,* and Hantavirus are all newly described causes of CAP. Halls coccus, a chlamydia-like obligate parasite of free-living amoebae, may also account for a few cases of CAP each year (Birtles et al., 1997).

Etiology of Nursing Home-Acquired Pneumonia

Table 9 summarizes data on the etiology of nursing home–acquired pneumonia (NHAP) requiring hospitalization. The studies cited in this table

TABLE 4. Etiology of Community-Acquired Pneumonia Treated on an Ambulatory Basis, Number (%)

Reference	Location	Study dates	Number studied	*S. pneumoniae*	*H. influenzae*	*M. pneumoniae*	*C. psittaci*	*C. pneumoniae*
Berntsson et al., 1986	Goteborg, Sweden	3 years[a]	54	5 (9)	6 (12).	20 (37)	2 (4)	ND
Marrie et al., 1996	Halifax, Nova Scotia, Canada	Nov 1991–Mar 1994	149	1	1	34 (22.8)	2 (1.3)	16 (10.7)
Erard et al., 1991[b]	Neuchatel, Switzerland	4 years[a]	161	17 (11)	3 (2)	28 (17.4)	9 (5.6)	ND
Langille et al., 1993[c]	Amherst, Nova Scotia, Canada	Jul 1989–Jun 1990	75	—	—	22 (28)		1 (5.3)
Total			439	23 (5)	10 (2.3)	104 (24)		

[a]Start and stop dates not given.
[b]8.7% required hospitalization.
[c]35% required hospitalization.

TABLE 5. Etiology of Community-Acquired Pneumonia Treated on an Ambulatory Basis, Number (%)

Reference	Influenza A	Influenza B	*Coxiella burnetii*	Parainfluenza viruses	*Legionella* spp.	RSV	*Moraxella catarrhalis*	Adenovirus	Unknown etiology	Comment
Berntsson et al., 1986	3 (6)	1 (2)	ND	1 (2)	—	1 (2)	—	1 (2)	41%	Serology only
Marrie et al., 1996	4 (2.7)	3 (2)	4 (2.7)	0	—	0	—	3 (2)	48%	Only 3 patients had cultures done for bacteria
Erard et al., 1991	19 (11.8)	—	2 (1.2)	—	3 (1.8)	—	2 (1.2)	—	47%	
Langille et al., 1993	5 (7)	—	2 (3)	—	2 (3)	—	—	2 (3)	55%	
Total	31 (7)	4 (0.9)	8 (1.8)		5 (1.1)			6 (1.4)	211 (48)	

RSV, respiratory syncytial virus.

TABLE 6. Etiology of Community-Acquired Pneumonia Requiring Hospitalization, Number (%)

Reference	Location	Study date	Number	*S. pneumoniae*	*H. influenzae*	*S. aureus*	*L. pneumophila*	*Legionella* spp.	AGNR
Marrie et al., 1989	Halifax, Nova Scotia, Canada	Nov 1981–Mar 1987	588	52 (9)	26 (4.5)	22 (3.7)	14 (2.3)	2 (0.3)	19 (3.2)
Fang et al., 1990	Pittsburgh, PA	Jul 1986–Jun 1987	359	55 (15.3)	39 (10.9)	12 (3.3)	22 (6)	2 (0.5)	21 (5.9)
Levy et al., 1988	Columbes, France	Feb 1983–Jan 1984	116	30 (26)	13 (12)	3 (2.5)	5 (4)	—	8 (7)
Kauppinen et al., 1995[a]	Oulu, Finland	May 1986–May 1987	125	69 (55)	14 (11)	—	—	1 (1)	1 (1)
Burman et al., 1993[a]	Umea, Sweden	Dec 1982–Nov 1984	196	63 (32)	8 (4)	3 (1.5)	3 (1.5)	—	1 (0.5)
Mundy et al., 1995	Baltimore, MD	Nov 1990–Nov 1991	385	69 (17.9)	28 (7.3)	14 (3.6)	13 (3.4)	—	26 (6.8)
Porath et al., 1997[a]	Southern Israel	Nov 1991–Nov 1992	346	148 (42.8)	19 (5.5)	—	—	56 (16.2)	—
Marston et al., 1997	Ohio	1991	2776	351 (12.6)	184 (6.6)	94 (3.4)	—	63[b] (3.0)	124 (4.5)
Bohte et al., 1995	Leiden, Netherlands	1991–1993	334	90 (27)	26 (8)	4 (1)	8 (2)	—	11 (3.2)
Total			5225	927 (17.7)	357 (6.8)	152 (2.9)	64 (1.2)	124 (2.3)	211 (3.9)

[a]Serological tests for *Streptococcus pneumoniae* (usually antibodies to pneumolysin immune complexes) used to diagnose pneumococcal pneumonia in addition to blood and in some cases sputum culture.
[b]Data are for Legionella spp only.
AGNR, aerobic gram-negative rod-like bacteria.

TABLE 7. Etiology of Community-Acquired Pneumonia Requiring Hospitalization, Number (%)

Reference	Influenza A	Influenza B	RSV	Parainfluenza viruses	Other viruses	*M. pneumoniae*	*C. pneumoniae*	*Chlamydia* spp.
Marrie et al., 1989	29 (4.9)	14 (2.3)	5 (0.8)	20 (3.4)	—	39 (6.6)	—	—
Fang et al., 1990	—	—	—	—	—	7 (2)	22 (6.1)	—
Levy et al., 1988	—	—	—	—	5 (4)	4 (3.5)	—	1 (0.8)
Kauppinen et al., 1995[a]	—	—	—	—	10 (8)	6 (5)	54 (43)	4 (3)
Burman et al., 1993[a]	2 (1)	15 (7.6)	8 (4)	2 (1)	7 (3.6)	13 (6.6)	—	5 (2.5) all *C. psittaci*
Mundy et al., 1995	1	5	—	—	26 (6.8)	3 (0.8)	14 (3.6)	1 *C. psittaci*
Porath et al., 1997[a]	—	—	—	—	35 (10.1)	101 (29.2)	62 (17.9)	—
Marston et al., 1997	58/782 (7.4)	17/782 (2.2)	14/454 (3.1)	ND	—	404/1938 (32.5)	172/1923 (8.9)	ND
Bohte et al., 1995	—	—	—	—	27 (7)	19 (6)	—	9 (3)
Total	90 (1.7)	51 (0.9)	27 (0.5)	24 (0.4)	110 (2.1)	595/4207 (14.1)	324 (6.2)	20 (0.3)

RSV, respiratory syncytial virus.
[a]Serological tests for *Streptococcus pneumoniae* (usually antibodies to pneumolysin immune complexes) used to diagnose pneumococcal pneumonia in addition to blood and in some cases sputum culture.

TABLE 8. Etiology of Community-Acquired Pneumonia Requiring Hospitalization, Number (%)

Reference	*C. burnetii*	Aspiration	*M. tuberculosis*	Postobstructive pneumonia	*M. catarrhalis*	Fungi	Anaerobes	*P. carinii*	Other	Unknown
Marrie et al., 1989	22 (3.7)	33 (5.6)	9 (1.5)	11 (1.9)	2	—	2	14 (2.3)	26 (4.4)	264 (45)
Fang et al., 1990	—	12 (3.3)	4	19 (5.3)	3	—	2	9 (2.5)	10 (2.7)	118 (33)
Levy et al., 1988	—	—	12 (10)	—	1	—	3	—	—	41 (35.3)
Kauppinen et al., 1995[a]	—	—	—	—	8 (6)	—	—	—	—	15 (12)
Burman et al., 1993[a]	—	—	—	—	3 (1.5)	—	—	1 (0.5)	—	70 (35.7)
Mundy et al., 1995	—	34 (8.8)	9 (2.3)	—	6 (1.6)	5 (1.3)	2	49 (12.7)	10 (2.6)	122 (31.7)
Porath et al., 1997[a]	20 (5.8)	—	—	—	—	—	—	—	21 (6.1)	67 (19)
Marston et al., 1997	ND	—	39 (1.4)	—	21 (0.76)	—	—	39 (1.4)	—	1545 (55.6)
Bohte et al., 1995	1	—	—	—	5 (1.5)	—	—	—	—	151 (45)
Total	44 (0.8)	79/1352 (5.9)	73 (1.4)	30 (0.5)	49 (0.9)	5	9	112/4304 (2.6)	67 (1.2)	2392 (45.7)

[a]Serological tests for *Streptococcus pneumoniae* (usually antibodies to pneumolysin immune complexes) used to diagnose pneumococcal pneumonia in addition to blood and in some cases sputum culture.

TABLE 9. Etiology of Nursing-Home Acquired Pneumonia, Number (%)

Reference	Number studied	*S. pneumoniae*	*C. pneumoniae*	*H. influenzae*	*S. aureus*	*M. catarrhalis*	*K. pneumoniae*	Other AGNR	Aspiration	Unknown
Garb et al., 1978	35	9 (26)	—	2 (6)	9 (26)	—	14 (40)	—	—	0
Marrie et al., 1989	131	9 (6.8)	—	1	7 (5.3)	—	—	7 (5.3)	19 (14.5)	77 (59)
Phillips & Branaman-Phillips, 1993	104	31 (29.8)	—	20 (19)	11 (10.5)	4 (3.8)	—	24 (23)	—	14 (13)
Drinka et al., 1994	56	5 (8.9)	—	4 (7.1)	1 (1.8)	3 (5.5)	—	—	—	43 (77)
Chow et al., 1994	115	7 (6)	—	3 (2.5)	2 (1.7)	—	7 (6)	20 (17)	—	83 (72.8)
Orr et al., 1996[a]	30	—	2 (6.6)[b]	—	—	—	—	—	—	23 (76.7)
Total	471	61 (12.7)	—	30 (6.4)	30 (6.4)	7 (1.5)	21 (4.4)	41 (8.7)	—	250 (51)

AGNR, aerobic gram-negative rod-like bacteria.
[a]Serological study.
[b]An additional three patients had *C. pneumoniae* and a viral infection (RSV—1; parainfluenza 3 virus—1; influenza virus A—1). One patient each had influenza A and parainfluenza virus type 3.

TABLE 10. Etiology of Community-Acquired Pneumonia among Patients Requiring Admission to an Intensive Care Unit, Number (%)

Reference	Location	Study date	Number	*S. pneumoniae*	*L. pneumophila*	AGNR	*M. tuberculosis*	*P. carinii*	*E. fecalis*	*H. influenzae*
Rello et al., 1993	Spain	1988–1990	58	13 (37)	8 (22.8)	4 (11.4)	4 (11.4)	3 (8.5)	1 (2.8)	—
BTS, 1992	U.K. (25 hospitals)	1987	60	11 (18)	7 (12)	—	—	—	—	7 (12)
Moine et al., 1995[a]	France	1987–1989	132	43 (32)	4 (3)	14 (11)	—	—	—	14 (11)
Olaechea et al., 1994	Spain (26 ICUs)	1991–1992	262	30 (11)	21 (8)	8 (3)	—	12 PCP + TB	—	10 (4)
Ortqvist et al., 1985	Sweden	1977–1981	53	15 (28)	—	—	—	—	—	—
Pachon et al., 1990	Seville, Spain	1985–1987	67	12 (37.5)	7 (21.8)	8 (25)	1	1	—	—
Torres et al., 1991[a]	Barcelona, Spain	1984–1987	92	13 (14)	13 (14)	5 (5)	—	—	—	—
Leroy et al., 1995	Lille, France	1987–1991	299	80 (26.7)	—	52 (17.3)	—	—	—	—
Total			1023	217 (21.2)	60 (5.8)	91 (8.9)	5	16 (1.6)	1	31 (3)

AGNR, aerobic gram-negative rod-like bacteria, BTS, British Thoracic Society Research Committee; PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.
[a]Immunosuppressed patients excluded.

TABLE 11. Etiology of Community-Acquired Pneumonia among Patients Requiring Admission to an Intensive Care Unit, Number (%)

Reference	Influenza A	Mixed aerobic/ anaerobic	Polymicrobial	*M. pneumoniae*	*C. burnetii*	*S. aureus*	Viral	Miscellaneous	Unknown	Ventilation	Mortality (%)
Rello et al., 1993	1 (2.8)	1 (2.8)	—	—	—	—	—	—	23 (39)	42 (72)	22.4
BTS, 1992	3 (5)	—	1	4 (6)	—	2	2	—	18 (30%)	53 (88)	48
Moine et al., 1995[a]	—	—	—	1	2	5 (4)	7 (5)	4	37 (28)	36 (27)	24
Olaechea et al., 1994	—	—	—	8 (3)	—	10 (4)	5 (2)	7	108 (41.2)	NS	NS
Ortqvist et al., 1985	1	—	—	—	—	2 (4)	5 (10)	—	13 (25)	31 (58)	25
Pachon et al., 1990	—	—	1	—	—	—	—	—	35 (52.3)	NS	20.8
Torres et al., 1991[a]	—	—	—	5 (5)	—	—	—	5	27 (30)	56 (61)	20
Leroy et al., 1995	—	—	52 (17.3)	2	—	57 (staph spp.) (19)	—	20 (6.6)	101 (34.1)	149 (50)	28.5
Total	5 (0.5)	1 (0.2)	54 (5)	2 (1.9)	2	76 (7.4)	19 (1.8)	36 (3.5)	362 (35.4)	367/694 (52.8)	203/761 (26.6)

BTS, British Thoracic Society Research Committee.
[a]Immunosuppressed patients excluded.

were based mostly on the results of sputum culture. Since the upper airways of elderly nursing home patients are frequently colonized by aerobic gram-negative bacilli (Valenti et al., 1978), distinguishing colonization from infection can be problematic in this group of patients. It is noteworthy that *S. pneumoniae* is the most common cause of NHAP, despite the recommendation that all nursing home residents receive the pneumococcal vaccine.

Etiology of Community-Acquired Pneumonia among Patients Who Require Admission to an Intensive Care Unit

An etiological diagnosis is made in about 70% of the patients admitted to an intensive care unit (ICU) (Tables 10, 11). *S. aureus* was more commonly isolated in this group of patients than in the overall CAP population requiring hospitalization (7.4% vs. 2.9%). Aerobic gram-negative rod bacteria were also more common (8.9% vs. 3.9%). The proportion of the causes of pneumonia due to *S. pneumoniae* was about the same in both groups, but *H. influenzae* was less common in the ICU population (3% vs 6.8%).

TABLE 12. Etiology of Community-Acquired Pneumonia among Military Personnel, Number (%)

	San Diego 1989–1989	Finland Mar 1983–Feb 1984
Number studied	75	106
Mycoplasma pneumoniae	16 (21)	23 (21.7)
Haemophilus influenzae	12 (16)	6 (5.6)
Influenza A	7 (9)	—
Adenovirus	5 (7)	23 (21.7)
Streptococcus pneumoniae	4 (5)	53 (50.0)
Rous sarcoma virus	1 (1.3)	—
Streptococcus pyogenes	1 (1.3)	—
Moraxella catarrhalis	—	1 (0.9)
Neisseria meningitidis	—	1 (0.9)
Bordetella pertussis	—	1 (0.9)
Chlamydia spp.	—	1 (0.9)
Parainfluenza virus	—	5 (4.7)
Mixed infections	—	28 (31)
Unknown	29 (38.6)	15 (14.1)

Etiology of Community-Acquired Pneumonia in Military Personnel

This population in general is young and is often housed in closed quarters increasing the potential for person-to-person spread of respiratory pathogens. Amundsen and Weiss (1994) studied 75 military recruits with pneumonia at the San Diego Naval Training Center from October 1987 through April 1989. Lehtomaki and colleagues (1988) studied 106 Finnish military conscripts with CAP from March 1983 through February 1984. Table 12 gives the results of these studies.

Etiology of Community-Acquired Pneumonia in Other Subgroups of Patients

University Students

In studies carried out at the University of North Carolina from 1965 to 1971 and 1984 to 1987, 104 cases of radiographically confirmed pneumonia were reported among university students (Fernald & Clyde, 1989). *M. pneumoniae* accounted for 51% of the pneumonia cases in the first time period and 13% in the second.

Patients with Chronic Obstructive Pulmonary Disease

Torres and colleagues (1996) studied 124 patients (115 males and 9 females) with chronic obstructive pulmonary disease (FEV_1 > 60% of predicted) and pneumonia. *S. pneumoniae* caused 43% of the cases and 26% were of unknown etiology. Other agents included *C. pneumoniae* (12%); *H. influenzae* (9%); *Legionella* spp. 9%; Viridans streptococci (4%); *Coxiella burnetii* (4%), *M. pneumoniae* (3%); *Nocardia asteroides* (3%); and one case each of pneumonia caused by *Aspergillus fumigatus, Proteus mirabilis, E. fecalis, Acinetobacter calcoaceticus, S. aureus, E. coli, Corynebacterium* sp., respiratory syncytial virus, and *Peptostreptococcus* sp.

Pneumonia in pregnant women, HIV-infected persons, and immunocompromised patients (not due to HIV), children, and adolescents are reviewed in separate chapters in this book. Since the etiology

of pneumonia is rarely known at the time that therapy must be instituted it is critical that clinicians be familiar with the rank order of the various pathogens that cause pneumonia in the different subgroups of patients discussed in this chapter.

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9

Nursing Home-Acquired Pneumonia

ANDREW E. SIMOR

Introduction

More than a century ago it was recognized that pneumonia was a disease that caused considerable morbidity and mortality, particularly in the elderly. In his classic textbook of internal medicine, Osier wrote, "Pneumonia is the special enemy of old age. In the aged, chances are against recovery. So fatal is it in this group that it has been called the natural enemy of the old man" (Osier, 1892). When he referred to pneumonia as the "friend of the aged" in a later edition of his textbook (Osier, 1898), he was commenting on the occurrence of pneumonia as a terminal illness among older persons with chronic, debilitating diseases. Even today lower respiratory tract infections (pneumonia and influenza) represent the fifth leading cause of death in the United States in those older than 65 years (Centers for Disease Control, 1990; National Center for Health Statistics, 1993). Aged individuals who are institutionalized in long-term care facilities are at particularly high risk for the development of pneumonia and represent a patient population with unique and challenging problems in the diagnosis, management, and prevention of these infections.

Approximately 5% of the population over the age of 65 years in the United States and Canada reside in a nursing home or other long-term care facility; more than one in five individuals over age 85 years live in a nursing home (Van Nostrand et al., 1979; Smith, 1985). This aged population is heterogeneous, and includes some relatively "healthy" and ambulatory individuals who require minimal nursing care, as well as those who are more severely impaired and totally dependent on their caregivers for assistance with the performance of activities of daily living. Infection accounts for approximately 27% of transfers from nursing homes to acute-care hospitals, and nearly half of these infections involve the respiratory tract (Irvine et al., 1984). Moreover, pneumonia has been the most frequent cause of death in nursing homes, occasionally unrecognized antemortem (Rossman et al., 1974; Nicolle et al., 1984; Gross et al., 1988a). Pneumonia, influenza, and other lower respiratory tract infections are also common causes of outbreaks in long-term care facilities, are associated with significant costs, and have an enormous impact on morbidity and mortality. This chapter reviews currently available data regarding the epidemiology, pathogenesis, etiology, diagnosis, treatment, and prevention of nursing home-acquired pneumonia. Although tuberculosis is also an important respiratory infection in long-term care facilities, a discussion of tuberculosis is beyond the scope of this review.

Epidemiology, Risk Factors, and Outcome

Lower respiratory tract infections are generally recognized to be the second or third most common infections occurring in nursing home residents, accounting for up to 46% of all infections in long-term care facilities for the elderly (Garibaldi et al., 1981; Finnegan et al., 1985; Setia et al., 1985; Price et al., 1985; Scheckler & Peterson, 1986; Vlahov et al., 1987; Alvarez et al., 1988; Jacobson

ANDREW E. SIMOR • Department of Microbiology, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, North York, Ontario M4N 3M5, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

& Strausbaugh, 1990; Darnowski et al., 1991; Jackson et al., 1992; Beck-Sague et al., 1994; Lee et al., 1996). These infections are also among the most common causes of outbreaks occurring in chronic-care institutions (Jackson & Fierer, 1985; Li et al., 1996; Smith & Rusnak, 1997). Studies that have examined the incidence and prevalence of nursing home-acquired pneumonia are summarized in Tables 1 and 2, and indicate that approximately 2% to 5% of nursing home residents can be expected to develop such an infection annually, with an incidence ranging from 0.5 to 1.9 infections per 1000 resident-days. Some of the variability in the results found in these studies may be a reflection of the different types of long-term care facilities, various definitions of infection used, and variable methods of infection surveillance (McGeer et al., 1991).

Pneumonia has been identified as one of the most common reasons for transfer to a hospital from a nursing home (Irvine et al., 1984; Gordon et al., 1985). Approximately 30% of patients with nursing home-acquired pneumonia are transferred to a hospital (Degelau et al., 1995; Muder et al., 1996; Loeb et al., 1999) and in one study, pneumonia accounted for 12% of all hospital admissions among nursing home residents (Farber et al., 1984). The incidence of pneumonia requiring hospitalization is much higher in elderly nursing home residents (rates: 33–114 per 1000 population) than it is among non-institutionalized elderly subjects (rates: 1-7 per 1000 population) (Niederman & Fein, 1986; Marrie, 1990; Morris & Munasinghe, 1994).

TABLE 2. Prevalence of Nursing Home-Acquired Pneumonia and Other Lower Respiratory Tract Infections

Reference	Prevalence (%)	% of infections
Garibaldi et al., 1981	2.1	20
Setia et al., 1985	2.3	18
Price et al., 1985	1.1	44
Scheckler & Peterson, 1986	2.5	21

Several studies examining risk factors for the development of pneumonia in nursing home residents have identified the presence of underlying conditions such as chronic obstructive pulmonary disease, a tracheostomy, and a bedbound state as important determinants (Magaziner et al., 1991; Beck-Sague et al., 1993). Deteriorating health (odds ratio [OR], 4.95) and difficulty with oropharyngeal secretions (OR, 12.6) have also been associated with the acquisition of pneumonia in nursing home residents, suggesting the importance of aspiration (Harkness et al., 1990). Surrogate markers for aspiration were also found to be risk factors for pneumonia in a 3-year prospective study of nursing home-acquired pneumonia conducted by Loeb and coworkers (1999) involving 475 residents of five nursing homes. In a multivariate logistic regression analysis, older age (OR, 1.7 per 10-year interval; $P = 0.01$), swallowing difficulty (OR, 1.9; $P = 0.03$),

TABLE 1. Incidence of Nursing Home-Acquired Pneumonia and Other Lower Respiratory Tract Infections

Reference	Incidence	% of infections
Freeman et al., 1982	0.56 infections/year	
Farber et al., 1984	0.19/100 resident-days	
Nicolle et al., 1984	59/100 resident-years	
Scheckler & Peterson, 1986	1.9/100 resident-months	21
Marrie et al., 1986	33/1000 population	
Vlahov et al., 1987	1.0–1.9/1000 resident days	30–32
Berman et al., 1987	21/100 resident-years	
Alvarez et al., 1988	1.87/1000 resident-days	46
Hoffman et al., 1990	1.0/1000 resident-days	21
Harkness et al., 1990	0.73/1000 resident-days	
McDonald et al., 1992	1.46/1000 resident-days	
Degelau et al., 1995	0.5/1000 resident-days	
Loeb et al., 1999	0.7/1000 resident-days	

and inability to take oral medications (OR, 8.3; $P = 0.02$) were found to be associated with the development of pneumonia. Receipt of influenza vaccine was protective (OR, 0.04; $P = 0.01$).

In a meta-analysis of 127 studies of community-acquired pneumonia (CAP), among the highest mortality rates were found in the subgroup of 556 nursing home patients (Fine et al., 1996). Reported mortality rates for nursing home-acquired pneumonia have ranged from 6% to 40% (Nicolle et al., 1984; Finnegan et al., 1985; Marrie et al., 1986; Mehr et al., 1992; Beck-Sague et al., 1993; Drinka et al., 1994; Degelau et al., 1995; Muder et al., 1996; Marrie & Blanchard, 1997; Medina-Walpole & McCormick, 1998), and nursing home residence has been found to be an independent risk factor associated with increased mortality (Marrie et al., 1989; Marrie, 1990; Fine et al., 1997). Marrie and Blanchard (1997) found that the in-hospital mortality rate of 32% for nursing home-acquired pneumonia was significantly higher than the 14% mortality rate for age-matched controls with CAP. Mortality at 1 year following an episode of pneumonia was 58% in nursing home residents, similar to the 50% mortality in age-matched controls who were nursing home residents hospitalized without pneumonia, but significantly higher than the 30% 1-year mortality rate in age-matched individuals admitted to hospital with CAP ($P < 0.01$). The major determinants of survival for the nursing home residents with pneumonia were a lack of complications during the hospital admission and the ability to perform activities of daily living independently. Impaired cognitive and/or functional status have been consistently identified as risk factors for both short-term and long-term mortality in elderly nursing home residents with pneumonia (Mehr et al., 1992; Salive et al., 1993; Fried et al., 1995; Muder et al., 1996; Medina-Walpole & McCormick, 1998). One study found that the use of oral broad-spectrum antibiotics (e.g., trimethoprim-sulfamethoxazole, ciprofloxacin, cefaclor, amoxicillin-clavulanate) as initial therapy was associated with an improved outcome (Fried et al., 1995).

Host Defenses and Pathogenesis

With increasing age, several structural, physiological, and immunological changes occur that may affect host defenses and responses to infection (Table 3).

Age-related immunological changes that have been described include a decreased ability to generate a cell-mediated immune response and a dysregulation of humoral immunity. Specific examples of altered immune responses in the elderly have included diminished lymphocyte responses to mitogens, decreased serum IgG and IgM antibody levels, diminished antibody responses to vaccines, and depressed in vitro phagocytic cell function (Phair et al., 1978; Amman et al., 1980; Goodwin et al., 1982; Simons & Reynolds, 1990; Scordamaglia et al., 1991). An altered systemic immune response may also be mirrored by changes in the lower respiratory tract of aged individuals. In a mouse model of bacterial pneumonia, normal aging of the animals was associated with changes in bronchoalveolar cellular responses to infectious agents such as *Staphylococcus aureus* and *Klebsiella pneumoniae,* although there was no apparent increase in susceptibility to pulmonary infection (Esposito & Pennington, 1983). Older mice had recruitment of larger numbers of neutrophils to the alveoli and bronchoalveolar spaces, and this was associated with more rapid pulmonary clearance of bacteria. In humans, changes in lymphocyte subsets in peripheral blood and alveolar secretions have been observed in older versus younger adults (Meyer et al., 1996). Other studies have found increased numbers of inflammatory cells and changes in surface immunoglobulins in lower respiratory tract secretions in aged individuals (Thompson et al., 1992). The role of immune senescence in predisposing individuals to the development of infection remains uncertain, although impaired cell-mediated immunity, as measured by defects in delayed hypersensitivity in the elderly, has been associated with an increased risk of tuberculosis and varicella-zoster.

Structural and physiologic pulmonary changes that occur with aging have been reviewed by Morris (1994) and will only briefly be summarized here. It is recognized that with age there is a loss of elastic recoil of the lung associated with changes in alveolar elastin and the development of panlobular emphysema (Knudson et al., 1977; Morris, 1994). There may also be increased bronchial wall compliance due to connective tissue degeneration, and the older individual may experience weakness of the diaphragmatic, chest wall, and abdominal muscles.

TABLE 3. Factors Predisposing Elderly Nursing Home Residents to the Development of Pneumonia

Factor	Effects
Immunosenescence	Impaired cell-mediated immunity
	Impaired humoral immune responses
Altered pulmonary defense mechanisms	Increased pulmonary compliance
	Decreased functional residual capacity
	Impaired mucociliary function and clearance of respiratory secretions
	Respiratory muscle weakness
Presence of underlying disease	
Chronic obstructive pulmonary disease	Reduced cough
	Impaired mucociliary clearance
Neurologic disease (cerebrovascular accident, dementia, Parkinson's disease)	Increased risk of aspiration
	Decreased clearance of respiratory secretions
Cardiac disease (congestive heart failure, pulmonary edema)	Impaired pulmonary alveolar macrophage function
Esophageal disease	Increased risk of aspiration
Diabetes mellitus	Impaired phagocytic cell function
Renal failure	Impaired humoral immunity and phagocytic cell function
Other factors	
Immobility	Impaired clearance of respiratory secretions
Malnutrition	Impaired immune function
Medications (e.g., sedatives, immunosuppressive agents)	Reduced cough or gag reflexes
	Increased risk of aspiration
	Impaired immune function

The net result of these changes is premature air trapping, larger residual volumes, and decreased functional residual capacity. Pulmonary function tests typically reveal mild airflow obstruction and reduced diffusing capacity (Crapo & Morris, 1981; Morris, 1994). With increasing age, there is also decreased efficiency in the clearance of respiratory secretions due to diminished gag and cough reflexes, decreased mucociliary function, and reduced tracheal mucus velocity (Fein et al., 1991).

Although alterations in pulmonary defenses and changes in systemic immune mechanisms with aging contribute to decreased physiologic reserve and thereby may increase the risk of respiratory infections, it is likely that the principal risk factor for pneumonia in the elderly is the presence of concomitant underlying disease. Conditions or diseases that occur with increased frequency in aged individuals that may alter host defenses and thereby increase the risk for development of pneumonia are summarized in Table 3. Many of these underlying conditions are associated with an impaired ability to clear respiratory secretions and/or an increased risk of aspiration.

The initial description of the pathogenesis of pneumonia in elderly nursing home residents by Verghese and Berk (1983) is still believed to be an accurate reflection of the sequence of events in most patients. The elderly, debilitated resident of a long-term care facility is more likely to have oropharyngeal colonization with virulent organisms (e.g., aerobic gram-negative bacilli). Silent or inapparent aspiration of oropharyngeal secretions occurs frequently in the elderly, especially in the presence of underlying neurologic or esophageal diseases. Following aspiration, there may be an impaired ability for the host defenses to clear the inoculum of aspirated bacteria (due to diminished mucociliary clearance, decreased ability to generate an effective cough, or impaired pulmonary alveolar macrophage function). An antecedent viral respiratory tract infection may further compromise host defenses. The end result is the development of bacterial pneumonia.

It has been assumed that there is an association between swallowing dysfunction in the elderly and respiratory infection because of an increased risk of aspiration. The important role of aspiration in the development of nursing home-acquired pneumonia (Pick et al., 1996) is supported by the observation

that older patients with pneumonia are more likely to experience silent aspiration than are age-matched controls (Kikuchi et al., 1994) and by multivariate logistic regression analyses that have identified surrogate markers for aspiration (presence of swallowing disorders, difficulty with oral medications, and difficulty with oropharyngeal secretions) associated with the development of pneumonia in nursing home residents (Harkness et al., 1990; Loeb et al., 1999). In addition, Nakagawa and coworkers (1997) reported that the incidence of pneumonia was significantly higher in elderly nursing home residents with basal ganglia infarction and silent aspiration during sleep than in control residents in the facility.

Oropharyngeal colonization with aerobic gram-negative bacilli occurs frequently in the institutionalized elderly and is associated with requirements for greater assistance with the performance of activities of daily living (Valenti et al., 1978; Nicolle et al., 1986). Approximately one third of nursing home residents will be found to have oropharyngeal colonization with gram-negative bacilli, compared with less than 20% of those in the community (Valenti et al., 1978). Although such colonization may be transient (Irwin et al., 1982; Sveinbjörnsdóttir et al., 1991), the presence of gram-negative bacilli in the pharynx suggests either impaired bacterial clearance mechanisms or changes in mucosal receptors that allow altered bacterial adherence. Pharyngeal colonization with gram-negative bacilli among elderly nursing home residents has been associated with decreased functional status and increased mortality after 1 year of follow-up, but it is not clear that colonization leads to respiratory infection (Irwin et al., 1982; Nicolle et al., 1986). In addition, excess mortality in those who were colonized could be explained by the observation that colonization occurred more frequently in the more debilitated group (Nicolle et al., 1986). Therefore, the significance of oropharyngeal colonization with gram-negative bacilli in nursing home residents in predisposing them to the development of pneumonia or in influencing the microbial etiology of infection is uncertain.

Microbial Etiology

There have been relatively few studies of nursing home-acquired pneumonia that include comprehensive investigations to determine the microbial etiology. It is difficult to obtain sputum or other respiratory tract specimens for culture in elderly nursing home residents, and diagnostic tests, especially for viral pathogens, are typically not ordered or available in long-term care facilities. Therefore, it is often impossible to identify the specific etiologic agent (Marrie et al., 1989; Venkatesan et al., 1990; Drinka et al., 1994; Janssens et al., 1996). Table 4 summarizes the results of selected studies that used extensive laboratory investigations and stringent diagnostic criteria in an attempt to establish the microbial etiology of nursing home-acquired pneumonia.

The most common sputum isolates in the institutionalized elderly with pneumonia have been *Streptococcus pneumoniae* and *Haemophilus influenzae,* although in several studies *S. aureus,* and a variety of Enterobacteriaceae have also been frequently identified. *S. pneumoniae* has been the most common blood culture isolate in patients with nursing home-acquired pneumonia (Marrie et al., 1989; Hirata-Dulas et al., 1991; Muder et al., 1992; Marrie & Blanchard, 1997). *S. aureus, H. influenzae,* and other aerobic gram-negative bacilli have also been associated with bacteremic pneumonia in these patients, but less frequently (Marrie et al., 1989; Muder et al., 1992; Marrie & Blanchard, 1997). Mixed bacterial infections, possibly related to aspiration, have been documented by some investigators (Bentley, 1984). Anaerobic pulmonary infection may occur in nursing home residents, although this generally occurs in patients with dental caries and poor oral hygiene, and is rarely found in those who are edentulous.

Some studies have suggested an increased incidence of pneumonia due to gram-negative bacilli in the elderly, particularly in those who reside in long-term care facilities (Garb et al., 1978; Ebright & Rytel, 1980; Bentley, 1984; Alvarez et al., 1988; Crossley & Thurn, 1989; Fein et al., 1991). Garb and colleagues (1978) found that patients with nursing home-acquired pneumonia were more likely to have gram-negative bacilli (especially *K. pneumoniae)* and *S. aureus* identified as etiologic agents than were elderly patients with CAP. However, sputum specimens in this study were often obtained after the start of antimicrobial therapy and were not assessed for adequacy prior to culture, making interpretation of culture results difficult. Although

TABLE 4. Microbial Etiology of Nursing Home-Acquired Pneumonia[a]

Pathogen identified	Study			
	Marrie et al., 1986 (74 episodes)	Marrie et al., 1989 (131 episodes)	Drinka et al., 1994 (56 episodes)	Loeb et al., 1999 (113 episodes)
Streptococcus pneumoniae	4%	7%	9%	2%
Other streptococci	3%	5%	2%	0
Staphylococcus aureus	4%	5%	2%	2%
Haemophilus influenzae	0	1%	7%	2%
Moraxella catarrhalis	0	0	5%	0
Other aerobic gram-negative bacilli	1%	8%	0	3%
Legionella pneumophila	1%	0	0	1%
Chlamydia pneumoniae	1%	0	0	2%
Mycoplasma pneumoniae	1%	1%	0	1%
Influenza virus	8%	11%	N/A	5%
Parainfluenza virus	1%	2%	N/A	5%
Cytomegalovirus	5%	4%	N/A	1%
Respiratory syncytial virus	0	0	N/A	1%
Other viruses	0	0	N/A	0
Aspiration	18%	15%	N/A	N/A
No etiology identified	64%	59%	75%	75%

[a]In prospective studies using stringent diagnostic criteria and extensive bacteriologic, virologic, and/or serologic evaluations.
N/A, test not done

aerobic gram-negative bacilli may be recovered relatively frequently from sputum cultures of nursing home residents, these organisms are also more likely to colonize the oropharynx of the institutionalized elderly. In studies using more stringent diagnostic criteria, there has been no increased incidence of gram-negative bacilli causing pneumonia (Marrie et al., 1989; Hirata-Dulas et al., 1991; Phillips & Branaman-Phillips, 1993; Drinka et al., 1994; Marrie, 1994).

Viral lower respiratory tract infections are common in long-term care facilities, and many elderly nursing home residents with viral upper respiratory tract infection develop pneumonia (Nicholson et al., 1990; Wald et al., 1995b; Nicholson et al., 1997; Fiore et al., 1998). In the absence of an outbreak, laboratory investigations to identify a viral pathogen are rarely done in long-term care facilities. However, the viruses that have been identified most often in nursing home residents with lower respiratory tract infection are influenza A and B, parainfluenza viruses, and respiratory syncytial virus (RSV) (Morales et al., 1983; Falsey et al., 1990, 1992; Nicholson et al.. 1990; Falsey, 1991; Loeb et al., 1999). Adenovirus and cytomegalovirus have been detected less frequently. Although rhinoviruses and coronaviruses are typically associated with upper respiratory tract symptoms, these infections may also be complicated by lower respiratory tract involvement in the elderly (Wald et al., 1995b; Nicholson et al., 1997; Falsey et al., 1997).

Legionella pneumophila, Chlamydia pneumoniae, and *Mycoplasma pneumoniae* have only occasionally been identified as causes of pneumonia in long-term care facilities (Drinka et al., 1994; Janssens et al., 1996; Loeb et al., 1998). There have been a few reported outbreaks of infection due to *Legionella* species in nursing homes (Brennen et al., 1987; Mafsaki et al., 1992), but sporadic infection appears to occur infrequently. In a serosurvey of nursing home residents, only 2% had *Legionella* antibody titers > 1:64 (Storch et al., 1979), and studies that have attempted to detect *Legionella* in nursing home residents with pneumonia have rarely identified the organism (Marrie et al., 1989; Drinka et al., 1994; Janssens et al., 1996). Nursing home outbreaks of infection due to *C. pneumoniae* have been described (Troy et al., 1997), and a serological survey of nursing home residents has also detected evidence of occasional infection due to this organ-

ism (Orr et al., 1996). Studies that have looked for serologic evidence of *M. pneumoniae* respiratory infection in long-term care facilities for the elderly have rarely identified this organism, or have found evidence of mixed infection (Andrews et al., 1984; Arroyo et al., 1988; Orr et al., 1996; Loeb et al., 1999).

Outbreaks of respiratory tract infection in nursing homes occur commonly, and are most often due to viruses, especially influenza A and influenza B (Table 5). RSV is probably the most common non-influenza virus causing lower respiratory tract infection with serious morbidity in the elderly (Falsey et al., 1992). Similar to influenza, RSV infection in the elderly may also be associated with excess mortality (Fleming & Cross, 1993; Falsey et al., 1995). Numerous nursing home RSV outbreaks have been reported, associated with rates of pneumonia in up to 67% of patients and mortality rates as high as 50% (Garvie & Gray, 1980; Hart, 1984; Sorvillo et al., 1984; Mandal et al., 1985; Mai & Tamblyn, 1987; Agius et al., 1990; Osterweil & Norman, 1990). Nursing home outbreaks due to parainfluenza viruses have been described with rates of pneumonia ranging from 17% to 29% (Centers for Diseases Control, 1978; Public Health Laboratory Service, 1983; Glasgow et al., 1995), and pneumococcal pneumonia complicating antecedent parainfluenza virus infection has been reported (Fiore et al., 1998). Other pathogens associated with nursing home outbreaks of pneumonia have included *S. pneumoniae* (Quick et al., 1993; Kludt et al., 1997; Nuorti et al., 1998; Musher, 1998), *H. influenzae* (Patterson et al., 1988; Smith et al., 1988; Goetz et al., 1994), *C. pneumoniae* (Troy et al., 1997), and *Legionella* species (Brennen et al., 1987; Mafsaki et al., 1992). Rhinoviruses and *Bordetella pertussis* have also been associated with outbreaks of lower respiratory tract infection in long-term care facilities (Addiss et al., 1991; Wald et al., 1995b). It is worth noting that outbreaks of respiratory infection in long-term care facilities are often mixed, with more than one pathogen circulating (Mathur et al., 1980; Gross et al., 1988b; Falsey, 1991; Fiore et al., 1998; Loeb et al., 2000).

TABLE 5. Microorganisms Associated with Outbreaks of Lower Respiratory Tract Infections in Nursing Homes

Common	Uncommon
Influenza A	*Streptococcus pneumoniae*
Influenza B	*Haemophilus influenzae*
Parainfluenza virus	*Legionella pneumophila*
Respiratory syncytial virus	*Chlamydia pneumoniae*
Rhinovirus	*Mycobacterium tuberculosis*
	Bordetella pertussis

Specific Pathogens

Streptococcus pneumoniae

S. pneumoniae is the most common identified cause of bacterial nursing home-acquired pneumonia. The rate of sporadic pneumococcal disease among nursing home residents (~ 352 per 100,000 population) is nearly 14 times higher than that among the noninstitutionalized elderly (~ 26 per 100,000) (Haglund et al., 1993). Mortality associated with bacteremic pneumococcal pneumonia is also higher in the elderly, with reported case-fatality rates as high as 35% to 44% (Finkelstein et al., 1983; Plouffe et al., 1996). In a retrospective review of adults with pneumococcal bacteremia, those over 65 years of age were more likely to be afebrile on admission to hospital, to have a delay in diagnosis, and to have a higher mortality rate (Finkelstein et al., 1983). It is likely that pneumococcal pneumonia is frequently unrecognized in nursing homes. The clinical features of pneumococcal pneumonia are indistinguishable from those associated with other respiratory pathogens (Marrie, 1992). Moreover, cultures are often not obtained in nursing homes, or they may fail to grow the organism due to delays in specimen processing. As a result, both sporadic cases and clusters of *S. pneumoniae* infection may be missed.

Several nursing home outbreaks of pneumococcal pneumonia in nursing homes have been reported (Quick et al., 1993; Yao et al., 1994; Kludt et al., 1997; Nuorti et al., 1998; Musher, 1998). In these long-term care facilities, attack rates of infection ranged from 7% to 15%, with significant rates of bacteremia and mortality (20%–71%). One of the outbreaks involved a multidrug-resistant strain of *S. pneumoniae,* serotype 23F (Nuorti et al., 1998). The

mode of transmission of *S. pneumoniae* in nursing homes is uncertain, but is possibly related to direct spread among colonized or infected residents in a closed environment and living close to one another. It is also possible that transmission originates from colonized staff. Of great significance is the observation that these outbreaks occurred in facilities with a highly susceptible and unvaccinated resident population; less than 12% of the nursing home residents had received the pneumococcal vaccine prior to the outbreak (Quick et al., 1993; Yao et al., 1994; Kludt et al., 1997; Nuorti et al., 1998; Musher, 1998). Further transmission of *S. pneumoniae* in the outbreaks was interrupted with the administration of prophylactic antibiotics and pneumococcal vaccine.

Although the overall antibody response to the currently available polyvalent polysaccharide pneumococcal vaccine in aged individuals is adequate, there may be a substantial number of more debilitated elderly with a suboptimal antibody response (Sankilampi et al., 1996; Rubins et al., 1998). In addition, some investigations have failed to demonstrate efficacy of the pneumococcal vaccine in the elderly (Fine et al., 1994; Örtqvist et al., 1998). However, most studies have confirmed that the vaccine is efficacious and cost-effective in reducing the incidence of invasive (bacteremic) pneumococcal disease in the aged (Sims et al., 1988; Shapiro et al., 1991; Butler et al., 1993; Sisk et al., 1997; Koivula et al., 1997). As *S. pneumoniae* is the most common cause of nursing home-acquired pneumonia and the potential for serious outbreaks of infection among unvaccinated nursing home residents has been demonstrated, it is recommended that long-term care facilities for the elderly offer pneumococcal vaccine to all eligible residents and to new residents on admission to the facility (Centers for Diseases Control and Prevention, 1997). Unfortunately, despite these vaccine recommendations by the Advisory Committee on Immunization Practices, only a minority (~ 36%) of those over age 65 years in the United States have received the pneumococcal vaccine (Behavioral Risk Factor Surveillance System, 1997).

Influenza Virus

Excess rates of mortality and hospitalization associated with influenza epidemics have been recognized for decades (Monto, 1987). The most severe impact has been reported among the institutionalized elderly or in those with various underlying medical conditions (Barker & Mullooly, 1980; Goodman et al., 1982; Arden et al., 1988; McBean et al., 1993; Morens & Rash, 1995), and both influenza A virus and influenza B virus have been implicated (Van Voris et al., 1982; Simor et al., 1988). More recently, it has also become evident that influenza virus infection occurring in nursing home residents may be associated with functional decline following recovery from infection (Barker et al., 1998). Influenza virus is known to interact with a variety of host defense mechanisms, increasing susceptibility to secondary bacterial superinfection and other complications (Couch, 1981; Scheiblauer et al., 1992). However, the elderly may be more susceptible to serious complications associated with influenza because of an age-related decrease in influenza A virus-specific cytotoxic T-lymphocyte activity (Powers, 1993).

Influenza is transmitted from person to person either by aerosol inhalation or by direct mucosal inoculation of the virus. Therefore, transmission may be facilitated in the closed environment of a long-term care facility, and sources of infection may include infected residents, staff, or visitors. Numerous nursing home outbreaks due to influenza are reported annually, with high attack rates and case-fatality rates (Patriarca et al., 1986; Brammer et al., 1997). Variables that have been identified as significant risk factors for the occurrence of influenza outbreaks in long-term care facilities include a larger facility size, a larger proportion of unvaccinated residents, and a larger proportion of residents susceptible to influenza virus infection (Patriarca et al., 1986). These three variables are interrelated and in a multivariate logistic regression analysis, the number of susceptible residents was found to be the most important factor predicting occurrence of an outbreak. These results suggest that high rates of immunization with the influenza vaccine would be protective.

There has been controversy regarding the efficacy of influenza vaccination in elderly nursing home residents, with reports of disappointingly low efficacy in long-term care facilities (Cartter et al., 1990). However, in a study of nursing homes experiencing outbreaks of infection due to influenza A, unvaccinated residents were more likely than those

vaccinated to become ill with a respiratory infection (risk ratio [RR], 2.6; 95% confidence interval [CI], 1.8–2.6), to be hospitalized (RR, 2.4; CI, 1.6–5.3), or to die (RR, 5.6; CI, 1.2–9.1) (Patriarca et al., 1985). In a meta-analysis of 20 studies assessing influenza vaccine efficacy in the elderly, pooled estimates of vaccine efficacy were 56% (CI, 35%–68%) for preventing respiratory illness, 53% (CI, 35%–66%) for preventing pneumonia, 50% (CI, 28%–65%) for preventing hospitalization, and 68% (CI, 56%–76%) for preventing death (Gross et al., 1995). In a randomized controlled study in long-term care facilities for the elderly in Scotland, there was a lower incidence of respiratory tract infections in facilities with vaccination programs for residents and staff, and decreased mortality in facilities with staff vaccination campaigns (Potter et al., 1997; Carman et al., 2000).

Recommended measures for the prevention and control of influenza in nursing homes include (1) annual influenza vaccination programs for residents and staff; (2) active surveillance for influenza-like illness with availability of rapid diagnostic tests to confirm the diagnosis of influenza virus infection; and (3) prompt implementation of infection control measures and chemoprophylaxis with amantadine hydrochloride or rimantadine hydrochloride in the setting of an outbreak (Gravenstein et al., 1992; Gomolin et al., 1995; Centers for Disease Control and Prevention, 1996). The value of using amantadine hydrochloride in controlling nursing home outbreaks due to influenza A virus has been demonstrated (Arden et al., 1988; Peters et al., 1989; Staynor et al., 1994; Monto et al., 1995), although there is an increased risk of neurologic adverse effects with this drug in the elderly (Stange et al., 1991; Guay, 1994). Newer neuraminidase inhibitors, such as zanamivir and oseltamivir, may also have an important role in the management of influence in long-term care facilities.

Clinical Features

It has long been recognized that the clinical manifestations of pneumonia in the elderly may be atypical or nonspecific compared with the features commonly seen in younger adults. Osier (1892) wrote more than a century ago that "in old age pneumonia may be latent, coming on without chill; the cough and expectoration are slight, the physical signs ill-defined and changeable ..." These observations have since been confirmed by numerous investigators, although only a few studies have included control groups for comparison (Marrie et al., 1985, 1986; Marrie & Blanchard, 1997; Metlay et al., 1997).

A minority of elderly nursing home patients with pneumonia are able to cough or produce a purulent sputum sample, and physical signs of consolidation are infrequently found on examination (Bentley, 1984; Marrie et al., 1985). However, confusion, lethargy, or an altered mental state are often prominent features of pneumonia in the aged (Freeman et al., 1982; Bentley, 1984; Marrie et al., 1985; Starczewski et al., 1988; Venkatesan et al., 1990). Nursing home residents with pneumonia often present with "failure-to-thrive," deterioration in functional status, or exacerbation of an underlying disease, such as congestive heart failure. Several studies have also emphasized the presence of tachypnea (respiratory rate > 25 breaths per minute) as an important clue to the diagnosis of pneumonia in the elderly, often preceding the appearance of other clinical findings (McFadden et al., 1982; Starczewski et al., 1988; Venkatesan et al., 1990).

A blunted or absent febrile response to infection has been noted in many older adults (Darowski et al., 1991; Castle et al., 1991, Norman & Yoshikawa, 1996). This may be related to a defect in thermoregulation with aging, lower basal temperature in the elderly, or technical difficulties in temperature measurement in older individuals. Pneumonia in the elderly, including bacteremic infection, may also present without fever (Finkelstein et al., 1983; Bentley, 1984; Starczewski et al., 1988; Venkatesan et al., 1990; Riquelme et al., 1997). A temperature less than 37.5°C on admission has been found to be associated with an increased risk of mortality (McAlpine et al., 1986; Ahkee et al., 1997).

Comparing older versus younger adults with CAP, Metlay and colleagues (1997) found that the elderly had a significantly lower prevalence of respiratory and constitutional symptoms such as fever, chills, cough, dyspnea, pleuritic chest pain, headache, and myalgias. In a linear regression analysis controlling for patient comorbidity and illness severity, older age remained associated with lower symptom scores. In a study of 74 elderly patients with nursing home-acquired pneumonia, Marrie

and coworkers (1986) found that only 68% were febrile, chills were present in 16%, cough in 62%, productive cough in 38%, and signs of pulmonary consolidation in 27%; 53% of patients presented with confusion. Although not statistically significant, the nursing home residents with pneumonia were less likely to have these respiratory symptoms or signs and more likely to be confused than were age-matched controls with CAP.

It is not possible to determine the etiologic agent responsible for respiratory tract infection based on the clinical presentation. The clinical features of pneumococcal pneumonia are indistinguishable from those of lower respiratory tract infection caused by other agents (Marrie, 1992), and it is not possible to reliably distinguish influenza virus infection from that due to RSV or other respiratory viruses by clinical criteria (Mathur et al., 1980; Falsey et al., 1992; Wald et al., 1995a; Nicholson et al., 1997).

The lack of classic signs or symptoms of pneumonia in the aged may either be due to altered physiological responses to infection, or because the older individual is unable to adequately express the presence of symptoms. Moreover, manifestations of pneumonia may be masked by the coexistence of other underlying diseases, such as chronic obstructive pulmonary disease or congestive heart failure. As a result, the diagnosis of pneumonia in the elderly nursing home resident is often delayed, and in one study was initially misdiagnosed in approximately 30% of patients (Riquelme et al., 1997).

Diagnosis

The diagnosis of pneumonia in the elderly is challenging because of the atypical and nonspecific clinical manifestations. Patient assessment is further hampered because nursing home residents often have an ineffective cough and are unable to produce a purulent sputum sample. Laboratory testing and radiology facilities may not be readily available, and it may be difficult to obtain x-rays of good quality in confused or bedridden institutionalized patients. Nevertheless, recommended investigations for the evaluation of nursing home residents with suspected pneumonia include obtaining a chest x-ray and attempting to obtain sputum and blood cultures. Although other laboratory tests, such as a complete blood count, serum electrolytes, measurements of renal and hepatic function, and determination of arterial oxygen saturation, are not useful for establishing the diagnosis of respiratory infection, they may provide information useful for subsequent management of the patient.

Chest radiography should be done to confirm the presence of a pulmonary infiltrate and to determine whether there are other complications or underlying diseases. The chest x-ray usually reveals an infiltrate at the time of presentation, although interpretation may be complicated by the presence of underlying conditions (e.g., chronic bullous or fibrotic changes, congestive heart failure, or malignancy). "Classic" changes of lobar consolidation may or may not be present, and it is hazardous to make an etiologic diagnosis based on the radiographic appearance (Andrews et al., 1984; Fein, 1994). It has been found that radiographic progression of disease is more likely to occur in older adults hospitalized with pneumonia (in 48% of those over age 65 years), than in younger adults (11% in those less than 65 years of age; $P < 0.001$) (Marrie et al., 1985). Slower resolution of radiographic changes in the elderly recovering from pneumonia has also been documented (British Thoracic Society, 1987; Woodhead, 1994).

Cultures of lower respiratory tract secretions are generally used to determine the microbial etiology of pulmonary infection. However, only a minority of acutely ill nursing home residents are able to provide an adequate sputum sample for Gram stain examination and culture (Marrie et al., 1986; Fein, 1994; Drinka et al., 1994). Interpretation of sputum culture results is further complicated by the possibility of contamination of the specimen with oropharyngeal bacterial flora. Fastidious organisms such as *S. pneumoniae* may fail to grow because of delays in transporting the specimen to the laboratory for processing.

Blood cultures should be obtained in any patient with nursing home-acquired pneumonia who is sick enough to require hospital admission. Infections of the lower respiratory tract are among the most common sources of bacteremia in long-term care facility residents (Windsor, 1983; Setia et al., 1984; Muder et al., 1992), although blood cultures are positive in only about 4% to 8% of patients with

nursing home-acquired pneumonia (Marrie et al., 1986; Peterson et al., 1988; Hirata-Dulas et al., 1991; Phillips & Branaman-Phillips, 1993; Marrie & Blanchard, 1997).

Respiratory viral infection may be confirmed by virus isolation, detection of viral antigens, or serological tests. Such testing may be particularly important for the early recognition of outbreaks of respiratory infection in long-term care facilities. In these circumstances, viral antigens in nasopharyngeal swabs may be detected by immunofluorescence (DFA) or enzyme immunoassay (EIA) using one of several commercially available test kits. These tests can be done in a few hours, thereby providing same-day results. Both DFA and EIA for the rapid detection of influenza viral antigens have been found to have sensitivities of 87% to 100% and specificities greater than 92% (Waner et al., 1991; Leonardi et al., 1994). Leonardi and colleagues (1994) found that the rapid diagnosis of influenza using direct antigen detection tests and subsequent implementation of appropriate interventions could prevent significant morbidity.

Acute and convalescent serology or other diagnostic tests may be required for the identification of other potential respiratory pathogens, such as *L. pneumophila, C. pneumoniae,* or respiratory viruses. Serologic testing is of greater value for subsequently confirming a diagnosis than it is for the clinical management of individual patients.

Treatment

The vast majority of patients with nursing home-acquired pneumonia are treated empirically without knowledge of the specific etiologic agent. The treating physician must initially consider at least two questions: (1) Should the nursing home resident be hospitalized, or can he or she be safely treated in the long-term care facility? (2) What empiric antimicrobial agent(s) should be used, and should the drug(s) be administered orally or parenterally?

Advantages of treating the patient with pneumonia in the nursing home include decreased costs of care and avoidance of nosocomial complications such as precipitation of acute confusion or delirium, immobilization, and development of decubitus ulcers. Several retrospective studies have suggested that many nursing home residents with pneumonia can be safely and effectively treated in the facility using oral antimicrobial agents and without being transferred to a hospital (Degelau et al., 1995; Fried et al., 1995; Thompson et al., 1997; Fried et al., 1997). These studies found that there was no increased mortality in residents with pneumonia who were initially treated in the nursing home, compared with residents transferred to an acute-care hospital for their treatment. In the one study that assessed short-term functional outcomes, no significant differences were detected in residents with pneumonia treated with and without hospital transfer (Fried et al., 1997). Treatment failure for those managed in the nursing homes was associated with tachypnea (Degelau et al., 1995; Fried et al., 1995; Thompson et al., 1997), the presence of abnormal vital signs, and the requirement for feeding assistance or a mechanically altered diet (Degelau et al., 1995).

These studies suggest that the majority of patients with nursing home-acquired pneumonia can be treated safely in the facility with oral antibiotics. How to select patients for hospital transfer remains uncertain. In general, it would appear that those who are clinically stable (i.e., stable vital signs and adequate oxygenation) and who are able to tolerate oral medications would be suitable candidates for therapy within the nursing home. However, other factors to consider include the availability of any required supportive therapy or monitoring and appropriate goals of therapy for the individual.

There have been only a few prospective, randomized, controlled trials comparing the efficacy of different antimicrobial therapies for the treatment of nursing home-acquired pneumonia (Table 6; Peterson et al., 1988; Hirata-Dulas et al., 1991; Phillips & Branaman-Phillips, 1993; Nicolle et al., 1996b). These studies generally involved small numbers of subjects and primarily included those who were transferred to an acute-care hospital for the treatment of their infection. Therefore, only scanty data are available for the development of evidence-based treatment guidelines. In fact, the recently published guidelines from the Infectious Diseases Society of America (Bartlett et al., 2000) for the management of community-acquired pneumonia in adults did not address the issue of nursing

TABLE 6. Randomized, Controlled Trials of Antimicrobial Therapy for Nursing Home-Acquired Pneumonia

Study	Most common bacterial isolates (no.)	Antimicrobial therapy	Number treated	% efficacy (*P* value)
Peterson et al., 1988	*S. pneumoniae* (7)	Cefamandole (IM)	30	70
	H. influenzae (7)	Ciprofloxacin (PO)	30	77 ($P > 0.05$)
	E. coli (4)			
Hirata-Dulas et al., 1991	*S. pneumoniae* (7)	Ceftriaxone (IV/IM)	26	54
	H. influenzae (5)	Ciprofloxacin (IV/PO)	24	50 ($P > 0.05$)
	S. aureus (2)			
Phillips & Branaman-Phillips, 1993	*S. pneumoniae* (31)		54	94
	H. influenzae (20)	Ceftriaxone (IM)	50	90 ($P > 0.05$)
	S. aureus (11)	Cefoperazone (IM)		
Nicolle et al., 1996b	*S. pneumoniae* (4)	Ampicillin (IV)	20	70
		Ceftriaxone (IV)	17	93 ($P = 0.07$)

IM, intramuscular; IV, intravenous; PO, orally.

home-acquired pneumonia at all. Treatment guidelines adopted by the American Thoracic Society (1993) acknowledged that older age was an important prognostic factor, but did not categorize nursing home-acquired pneumonias separately because of a consensus that the place of residence was less important than the presence of coexisting disease and advanced age. Only the Canadian consensus guidelines for the treatment of community-acquired pneumonia considered specific therapy for nursing home residents (Mandell et al., 1993).

Recommended empiric therapy for pneumonia in long-term care facilities has generally included broad-spectrum coverage of *S. pneumoniae, H. influenzae,* and aerobic gram-negative bacilli (Yoshikawa, 1991; Saltiel & Weingarten, 1993; Mandell et al., 1993; Mylotte et al., 1994; Marrie & Slayter, 1996). Published consensus treatment guidelines that address nursing home-acquired pneumonia are summarized in Table 7. The Canadian treatment guidelines (Mandell et al., 1993) recommend the use of broad-spectrum agents that possess activity against aerobic gram-negative bacilli. In contrast, the Position Paper of the Long-Term-Care Committee of the Society for Healthcare Epidemiology of America (Nicolle et al., 1996a) indicates that "quinolones, broad-spectrum cephalosporins or penicillins, and aminoglycosides should not be prescribed as agents of first choice" for the empiric treatment of nursing home-acquired pneumonia.

Since the publication of these recommendations, newer fluoroquinolones such as levofloxacin have become available. These agents are available as oral formulations and have enhanced in vitro activity against *S. pneumoniae* and other respiratory pathogens. Several features of these drugs would appear to make them suitable for the treatment of lower respiratory tract infections in long-term care facilities, but the role of the newer quinolones in the management of nursing home-acquired pneumonia will need to be defined.

Infection Control and Prevention

Unfortunately, there are currently few strategies for the prevention of nursing home-acquired pneumonia that are of proven benefit. Pneumococcal infection and influenza are each able to cause considerable morbidity and mortality in long-term care facilities. Even though currently available pneumococcal and influenza vaccines may have suboptimal efficacies in the elderly, the impact of these infections may be substantially reduced by immunization. Therefore, nursing homes should offer the pneumococcal vaccine to all eligible residents and to new residents on admission to the facility (Centers for Disease Control and Prevention, 1997). In addition, each resident should receive the influenza vaccine annually unless medically contraindicated (Centers for Disease Control and Prevention, 1996). Staff should also be offered

TABLE 7. Published Consensus Guidelines for the Treatment of Nursing Home-Acquired Pneumonia

Canadian Community-Acquired Pneumonia Consensus Conference Group (Mandell et al., 1993)	Society for Healthcare Epidemiology of America Long-Term-Care Committee Position Paper (Nicolle et al., 1996a)
Treatment options in the nursing home	Oral therapy
Second-generation cephalosporin ± macrolide	Trimethoprim-sulfamethoxazole
Trimethoprim-sulfamethoxazole ± macrolide	Amoxicillin
Ceftriaxone ± macrolide	Cefuroxime-axetil
Amoxicillin-clavulanate	Macrolide
Penicillin + ciprofloxacin	Amoxicillin-clavulanate
Clindamycin + ciprofloxacin	Parenteral therapy
Treatment options for hospitalized patients	Ceftriaxone
Second/third-generation cephalosporin ± macrolide	
Trimethoprim-sulfamethoxazole ± macrolide	

and encouraged to receive annual influenza vaccination. Despite recommendations for vaccination of high-risk and institutionalized elderly subjects, there is considerable room for improvement in the implementation of institutional policies for influenza and pneumococcal immunization programs in long-term care facilities (McArthur et al., 1995; Behavioral Risk Factor Surveillance System, 1997).

Every long-term care facility should have an effective infection control program in order to identify potentially preventable sporadic infections and for early detection of outbreaks of infection (Nicolle & Garibaldi, 1995; Smith & Rusnak, 1997). Staff should be familiar with the basic principles of infection transmission and infection control; the importance of basic hygiene and handwashing should be emphasized. There should be policies for tracheostomy care and for the appropriate care and cleaning of respiratory therapy equipment. Residents should be screened for tuberculosis on admission and staff should be periodically monitored with tuberculin skin tests. Policies regarding visitors should be developed to reduce the risk of introducing community-acquired respiratory infections (e.g., influenza) into the facility. Infection surveillance should be conducted for early detection of outbreaks, and there should be policies for rapid response to outbreaks when they occur. Provisions for rapid influenza diagnostic testing should be in place before the onset of influenza season each year, including prior arrangements with the local laboratory and ensuring the on-site availability of appropriate specimen swabs and supplies. Specific recommendations in the presence of an influenza A outbreak include the following: symptomatic residents should be isolated or grouped together; symptomatic staff should be removed from patient care activities; ill visitors should refrain from visiting the facility; and chemoprophylaxis with amantadine hydrochloride or rimantadine hydrochloride (or possibly a neuraminidase inhibitor) should be provided (Gomolin et al., 1995).

Summary and Future Studies

Elderly residents of long-term care facilities who develop pneumonia experience significant morbidity and mortality. These infections are also associated with substantial costs, especially those related to hospitalization. Much of the currently available data regarding these infections is based on relatively small, retrospective studies or on investigations that involved a subset of patients who were transferred to an acute-care hospital. There is clearly a need to develop improved strategies for the diagnosis, management, and prevention of nursing home-acquired pneumonia. Examples of specific research questions regarding respiratory tract infections in long-term care facilities that need to be addressed are listed in Table 8.

Clinicians caring for the elderly are challenged by difficulties in establishing the diagnosis and determining the microbial etiology of pneumonia in nursing homes. Problems arise because these patients tend to present with nonspecific clinical fea-

TABLE 8. Questions to Be Addressed in Order to Improve the Management and Prevention of Nursing Home-Acquired Pneumonia

What modifiable risk factors can identity nursing home residents at high risk for the development of pneumonia?
Are there specific interventions aimed at reducing these risks that are effective in preventing the development of pneumonia (e.g., feeding practices; patient positioning; use of oral anti-infective mouthwashes)?
What is the role of oropharyngeal colonization with aerobic gram-negative bacilli on the microbial etiology of nursing-home acquired pneumonia?
Is empiric therapy using antimicrobial agents with broad-spectrum activity against gram-negative aerobes (e.g., ceftriaxone, fluoroquinolones) more efficacious than treatment with antibiotics having a narrower spectrum of activity (e.g., amoxicillin; cephalexin; trimethoprim-sulfamethoxazole; macrolides)?
Is it possible to identify which residents with pneumonia can be safely and effectively treated in the nursing home, and which ones should be more appropriately hospitalized?
What are the most appropriate infection surveillance methods for lower respiratory tract infections in long-term care facilities?
How can immunization rates with pneumococcal and influenza vaccines be improved in nursing homes?
What is the best way to improve staff influenza vaccination rates in long-term care facilities?
What infection control interventions are most effective during nursing home outbreaks due to influenza or other respiratory viruses?

tures, often have coexistent underlying diseases, and are typically unable to provide appropriate diagnostic specimens. Moreover, on-site laboratory and x-ray facilities are infrequently available, and there may be difficulties in the interpretation of culture results. Therefore, carefully designed prospective studies are needed for improved identification of patients at risk and to better define the microbial etiology of nursing home-acquired pneumonia. Such information is critical in order to determine the most effective empiric treatment. It is also important to be able to identify which residents with pneumonia may be safely treated in the nursing home and which ones should be transferred to a hospital for management. In order to design effective preventive measures, modifiable risk factors for nursing home-acquired pneumonia must be defined. The effectiveness of interventions, such as those aimed at preventing aspiration, should be determined. Similarly, the effectiveness of infection control measures recommended for the management of outbreaks of respiratory infections needs to be evaluated.

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10

Treatment of Community-Acquired Pneumonia

MARK WOODHEAD

Introduction

Interest in the treatment of community-acquired pneumonia (CAP) is probably more intense now than at any time since the introduction of penicillin. The combined stimuli of the rising costs of healthcare, evidence-based medicine, guidelines, and managed care on the one hand and two decades of the delineation of the common causative pathogens, the evolution of acquired bacterial resistance, and the development of new antibiotics on the other, are now focusing our thoughts in this area like never before. The recognized range of possible causative pathogens has never been so extensive and the choice of possible antibiotics has never been so wide. Care for the CAP patient can be delivered in the home (or nursing home), in hospital, in the intensive care unit (ICU), or in a combination of these sites.

The Aims of Treatment

In the preantibiotic era the mortality from CAP was as high as 75% (Heffron, 1939). Mortality from CAP is still significant, ranging from 1 to 2% of those who are ambulatory to 37% of those reaching the ICU (Fine et al, 1996). Therefore, the first aim of treatment is to prevent death. The second aim is to reduce morbidity. The symptoms of CAP are unpleasant for the patient and often the patient is unable to continue his or her normal daily activities, including work. Reducing the severity of symptoms and/or reducing the duration of the illness will improve morbidity. These aims must be achieved at acceptable cost to both the patient and society, which means that treatment must be stratified according to the patient's needs, allowing appropriate use of different modalities of care. Not all patients need the facilities of the ICU and not all can be managed at home.

The Components of Treatment

Certain key questions must be addressed when the patient first reaches medical contact (Table 1). The severity of the patient's illness at presentation is a central issue that should guide the answer to most of these questions. Treatment is directed at both the cause and the consequences of the pneumonia. In the majority of patients microorganisms, principally bacteria, will have a role in the pathogenesis of the condition, so antimicrobial agents, principally antibiotics, are a central part of treatment and will be the main subject of this section. The responsible microbe in an individual patient is usually not known when the decision about initial antibiotic prescription is made so the patient is usually started on empirical or "best-guess" therapy. If a specific microbe is found, antibiotic therapy can be modified later.

When death occurs it is due to uncontrolled infection, isolated respiratory failure, or multiorgan failure (British Thoracic Society Research

MARK WOODHEAD • Department of Respiratory Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Key Questions in the Management of Community-Acquired Pneumonia

Does the patient have pneumonia?
Is it community-acquired?
Is the patient severely ill?
Should the patient be managed at home or in hospital?
Should the patient be managed in hospital general ward or intensive care unit?
Which antibiotic(s) should be given?
Should the oral or intravenous route be used?
How long should antibiotics (oral and intravenous) be given?

Committee, 1992). Central to the management and prevention of respiratory and multi-organ failure are gas exchange and fluid balance monitoring and manipulation. These topics are covered elsewhere in this volume.

Is It Community-Acquired Pneumonia?

Is It Pneumonia?

In hospitalized patients with features suggestive of lower respiratory tract infection (LRTI), the presence of new shadowing in the lung fields on the chest radiograph is the key to the diagnosis. Although inter-observer variability in chest radiograph interpretation of pneumonia occurs (Albaum et al., 1996; Young & Marrie, 1994; Melbye & Dale 1992), and may be more common among inexperienced staff (Melbye & Dale, 1992), this is probably of little importance when a radiologist's interpretation is available (Albaum et al., 1996). Diagnostic problems may occur when a patient presents without lower respiratory tract symptoms or signs—this is more common in the elderly (Metlay et al., 1997a; Venkatesan et al., 1990; Marrie et al., 1985).

It is in the community where the diagnosis of CAP may be much more difficult. The degree of difficulty will depend on whether chest radiographs are easily available at the point of first patient contact with healthcare facilities. If the patient presents to a facility where chest radiographs can be performed, a diagnostic problem is unlikely and the diagnosis of CAP is as for hospitalized patients. In many countries however, where the patient is first seen in the community by a general or family practitioner it may be impractical or difficult to obtain a chest radiograph, unless the patient's illness severity dictates the need for hospital referral. This means that a clinical diagnosis of CAP, without radiographic confirmation, is often used. If a chest radiograph is performed in such patients, it is often because the clinical findings suggest that a chest radiograph will show an abnormality. However, the relationship between clinical symptoms/physical signs and chest radiographic abnormality in this group of patients, who by definition are not severely ill, is weak. Inter-observer variability in symptom and sign assessment is great and these features are not specific to underlying pulmonary pathology (Metlay et al., 1997b).

Studies that have sought to quantify the relationship between clinical features and radiographic abnormalities in CAP have found both high false-positive and false-negative rates and as in hospitalized patients this may be especially true in the elderly (Houston et al., 1995). These studies are very difficult to compare since they are based in different countries with different healthcare structures and the population base for each study may be very different. For example, it may not be appropriate to correlate the findings in a group of patients presenting to an army medical center with cough (Diehr et al., 1984; Bushyhead et al., 1983) with those of emergency room attendees with fever and respiratory illness (Melbye et al., 1992a,b) or with those who present to a general practitioner in the community and who have a clinical diagnosis of pneumonia (Woodhead et al., 1987) since the probability of radiographic pneumonia in each group is likely to be very different. Clinical findings that have a higher specificity for pneumonia (e.g., asymmetrical respiration, dullness to percussion, "strong lateral chest pain," and "very annoying dyspnoea" [Melbye et al., 1992b]) all have a low sensitivity, and findings with a higher sensitivity (e.g., crackles on auscultation) are not specific (Diehr et al., 1984). Attempts to produce formulae or algorithms for use in radiographic pneumonia prediction may be useful in research studies, but are probably not helpful for routine clinical practice (Heckerling, 1986; Diehr et al., 1984).

Against this background it is interesting to note that there is some evidence that patients with clinical pneumonia in the absence of radiographic change, and those with radiographic changes, but

who lack clinical features of pneumonia, have other features in common with patients who have both clinical and radiographic features of pneumonia. Elevated erythrocyte sedimentation rate (ESR) or C–reactive protein levels may be equally common and similar pathogens are identified (Melbye et al., 1992a). It may therefore be that the gold standard of chest radiograph opacity is no more than a marker of more extensive alveolar involvement in a group of patients who all have parenchymal lung pathology due to infection. In support of this is the finding that patients with chest radiograph shadowing were more likely to be admitted to hospital than those without (Everett, 1983), and in another study those with such shadowing had higher mortality (12%) than those without (2%) (Woodhead, 1988). In the community, categorization of such patients according to illness severity might be more clinically useful than distinction between those with and without radiographic change. Further studies are needed in this area, especially of that group of patients who lack clinical features of pneumonia but nevertheless have radiographic shadowing. For the moment it must be considered that patients with pneumonia in the community may be different from those in hospital, and may need different treatment.

Is the Pneumonia Community–Acquired?

The answer to this question is usually fairly obvious, however it should not be forgotten that patients presenting from the community may have been in hospital in the preceding 2 weeks and may thus have nosocomial pathogens that require different therapy. In some centers, a high proportion of patients presenting from the community with pneumonia are immunocompromised (many with HIV infection) (Mundy et al., 1995), and in some patients this is the first presentation of that illness. The spectrum of pathogens and hence the management of this group may be different from that of patients with CAP, emphasizing the need for their early identification.

Assessment of Illness Severity

It has not been shown that systematic adoption of a process of initial severity assessment alters outcome. However, this is probably the key step in the management of a patient with CAP since it can influence decisions about where the patient should be managed and what treatment is to be given. Most patients requiring intensive care management do so within 24 hours of admission (Hirani & Macfarlane, 1997) and of those patients who die from CAP, as many as 25% do so within 24 hours of hospital admission, suggesting that these patients are severely ill at presentation (Woodhead, 1992). There is some data to suggest that current management practices are inadequate. In a study of the management of young adults dying of CAP, severity assessment was inadequate in many cases (Tang & Macfarlane, 1993). In another study, routine clinical assessment underestimated the need for intensive care compared with a structured severity assessment (Neill et al., 1996). In three other studies, between 7% and 25% of patients only reached the ICU following cardiorespiratory arrest in the general medical ward, suggesting that illness severity had been underestimated (Hirani & Macfarlane, 1997; British Thoracic Society Research Committee and the Public Health Laboratory Service, 1992; Woodhead et al., 1985). Severity assessment must therefore begin at the first point of healthcare contact and be based on data that is available at presentation or shortly thereafter.

Features that are more frequent in patients who die from CAP than in those who survive have been documented in a number of studies of CAP (Table 2). A meta-analysis of 127 studies of 33,148 patients identified 11 of these features to be of prognostic significance: male sex, absence of pleuritic chest pain, hypothermia, systolic hypotension, tachypnea, diabetes mellitus, neoplastic disease, neurologic disease, bacteremia, leukopenia, and multilobar radiographic infiltrates (Fine et al., 1996). However, a list of features is of little use to the physician. How many features are needed to label the illness as severe and are some features of greater significance than others? In an attempt to answer these questions a number of studies have now tried to incorporate these features into predictive rules. Studies centered on the ICU have used scoring systems developed for the critically ill, such as the APACHE system (van Eeden et al., 1988), the acute physiology scoring system (APS), and simplified APS (Feldman et al., 1989; Durocher et al., 1988).

TABLE 2. Presenting Features Associated with Death in Community-Acquired Pneumonia[a]

Demographic characteristics
Age
Male sex
Underlying disease (ultimately fatal disease, multiple underlying diseases, steroid therapy, digoxin therapy, alcoholism, malignant disease, stroke, diabetes mellitus, immunosuppression)
Nursing home residence
Employment status
Clinical history
Short duration
Symptoms suggesting aspiration
Absence of chest pain
Absence of vomiting
Clinical signs
Raised respiratory rate
Hemodynamic instability (including shock, hypotension, reduced peripheral perfusion, jugular venous pulse not visible, raised heart rate, atrial fibrillation)
Cerebral dysfunction (including impairment of alertness, confusion, reduced mental score quotient)
Lack of fever
Laboratory tests
Peripheral blood count (including low or high white cell count, low neutrophil count, low lymphocyte count, low platelet count, and low hematocrit)
Low protein or albumin
Abnormal renal function (acute renal failure, high urea nitrogen or creatinine)
Abnormal blood gases (low PaO_2, high $PaCO_2$, low pH)
Abnormal liver enzymes
Raised lactic dehydrogenase
Low phosphate
Negative antigen skin tests
Radiology
Bilateral shadowing
Bronchopneumonia
Rapid spread of shadowing
Microbiology
Bacteremia
No pathogen identified
Pathogen identified
Individual pathogens

[a]Compiled from Leroy et al., 1995; Olaechea et al., 1996; Ortqvist et al., 195; Rello et al., 1993; Torres et al., 1991; Pachon et al., 1990; Moine et al., 1994; Feldman et al., 1995; Farr et al., 1991; Macfarlane et al., 1982; Gomez et al., 1996; Ausina et al., 1988; Berntsson et al., 195; Steinhoff et al., 1996; Ortqvist et al., 1990; Kurashi et al., 1992; British Thoracic Society, 1987; Woodhead et al., 1985; Fang et al., 1990; Neill et al., 1996.

These studies were generally small and retrospective and were probably not applicable to the average emergency room attendee. There is some evidence that a disease-specific severity scoring system for CAP is more accurate than generic systems such as those mentioned previously (Fine et al., 1995). A prognostic rule that allows an individual patient's risk of death to be predicted was developed in a large study of adults admitted to hospital with CAP (British Thoracic Society, 1987). In this study, patients with two or more specific risk factors (i.e., respiratory rate $\geq$ 30/min, diastolic blood pressure $\leq$ 60 mmHg, blood urea > 7 mmol/L had a death rate of 19% and those with one or less had a death rate of 1.6%. This rule has been applied prospectively in three additional studies in different populations and found to be reproducible. It has the additional advantage of simplicity; however, it has low positive predictive value and has not been validated in the elderly.

A two-step prediction rule to identify low-risk patients has been developed in a North American study. The rule was derived from a large population of 14,199 adults admitted to hospital with CAP and has been validated in another sample of 38,039 adults with CAP (Fine et al., 1997a). In a subsample of 2287 patients who were in a community-based study, mortality was 0.1% in the 772 patients in risk class I, 0.6% in the 477 patients in risk class II, 0.9% in the 326 patients in risk class III, 9.3% in the 486 patients in risk class IV, and 27% in the 226 patients in risk class V. A similar stratification by class in relation to ICU admission and length of hospital stay was found. The first step—separating class I from classes II through V—is based on clinical information available in the community. Data available only in the hospital setting is needed for separation of risk classes II through V, which may be a limiting factor in the clinical use of this rule as may the need to score 19 different characteristics to separate these groups.

The American Thoracic Society CAP guidelines suggested that the presence of one or more of ten features justified the definition of severe pneumonia (American Thoracic Society, 1993). One study attempting to validate this suggestion (Ewig et al., 1998) found that this definition was sensitive (98%), but lacked specificity (32%) and positive predictive value (24%); a modification to this defi-

nition was later suggested. This study demonstrates that guidelines must be validated before widespread application can be justified.

No single severity assessment method can yet be recommended. It may well be that a number of methods may be equally valuable or that some are superior to others. Further studies in different populations, especially in different healthcare systems are required to further validate the above suggestions and to tailor severity assessment rules to the appropriate clinical management settings.

Where Should the Patient be Managed?

The choice of where to treat the patient is usually between home and hospital and within the hospital, between the general ward and the ICU. In different healthcare systems other care stages, such as high dependency areas, may be available. Current hospital admission rates vary widely and ranged from 5% to 51% of cases in 11 community-based studies in different countries (Woodhead, 1998). The definition for pneumonia varied in these studies and undoubtedly contributed to the proportion admitted, as did the healthcare system within which the study was conducted. However, even within the same healthcare system, admission rates for patients with CAP at low risk of death have been found to range from <5% to >20%, suggesting that uniform standards are not being applied (Rosenthal et al., 1997) and that patients are being inappropriately admitted. Using the Appropriateness Evaluation Protocol, a tool that was not specific to pneumonia, two studies found that 61% of pneumonia admissions may have been inappropriate. However, these studies also found that 38% (Fine et al., 1990) and 39% (Porath et al., 1996) of these patients went on to have a complicated hospital course, evidence that a better tool for assessing appropriateness of hospital admission for CAP is required.

A requirement for facilities or interventions not available in the community should be the deciding factor in hospital admission. Inability to maintain gas exchange or fluid intake and absence of nursing or social support mechanisms are factors that may determine hospital admission (Fine et al., 1997b). Illness severity, and therefore the need for intravenous antibiotics or fluids, or complex gas exchange manipulation, is the most important parameter for minimizing mortality and morbidity. Patients, not surprisingly, generally prefer to be managed at home (Coley et al., 1996). This may be feasible if intravenous therapy and nursing support were available in the home (Fine et al., 1997b). It follows from this that use of a CAP–specific severity assessment tool would be the best way to determine the need for hospital admission. The scoring system outlined at the end of the previous section is so far, perhaps, the best way to do this (Fine et al., 1997b), but it needs further prospective testing. Patients in risk class I to III have a low mortality and could therefore be considered for management at home. Risk class I can be determined in the community, but hospital-based facilities would, in most countries, be required to distinguish classes II and III. In the future, this may mean that hospitals will have a greater role as assessment centers as well as admission centers.

Admission to intensive care will depend on the patient's need for facilities not available in the general ward and the admission policy of the ICU. Facilities available in the general ward will vary in different healthcare settings; however, intubation and assisted ventilation are usually absolute requirements for ICU admission. Ideally, patients likely to need such treatment should be identified early so that treatment can begin in a controlled environment. Identifying those at risk by severity assessment and careful monitoring of gas exchange in these patients is important, but the best way to assess such severity is yet to be determined. Ideally each hospital should have a local consensus policy, based on the above data, for the management of such patients.

Principles of Antimicrobial Therapy

Microbiological Factors

Antibiotics must fulfill a number of criteria before they can be considered in the management of CAP (Table 3). First, they must kill the causative pathogen in vitro. This is usually assessed by the minimum inhibitory concentration that kills 90% of isolates (MIC_{90}), which is not difficult to determine for most organisms (Table 4). The relatively recent

TABLE 3. Factors in Antibiotic Choice

Activity against the common causative agents in vitro
Ability to reach the sites where the pathogens grow at concentrations that kill the pathogen
Activity at those sites
Clinically acceptable side effects
Low cost

appearance of acquired antibiotic resistance has complicated this issue since local patterns of antibiotic susceptibility for an individual organism can vary widely (Figure 1) and can change rapidly with time. Second, an antibiotic must reach the tissues where the pathogens grow. This usually means the lung, and for conventional bacteria, blood or serum, in view of the propensity for bacteremia in severe infections with these organisms. Pharmacokinetic studies of antibiotic concentrations in serum/blood after single or multiple antibiotic doses, given orally or parenterally, are again not difficult to perform. In the lung, however, this is much more complicated (Baldwin et al., 1992a,b). Organisms may occur in a number of different compartments within the lung—bronchial secretions, epithelial lining fluid, the interstitium, and within cells, especially macrophages. For conventional bacteria the site or sites of importance are less well understood, and indeed they may be present at more than one site simultaneously. Measuring antibiotic concentrations at these different individual sites is difficult since any lung sample may contain a number of such sites. Recently such problems have been largely overcome, and measurement of antibiotic concentrations at these sites is part of the development program of all new antibiotics likely to be used in respiratory infection.

The relationship between bacterial killing and antibiotic levels at a site is complex and it is therefore not sufficient just to show that an antibiotic reaches a particular site (Hand & King-Thompson, 1986). Factors at the active site (e.g., local pH, protein binding) may alter the activity of the antibiotic. For predominantly intracellular bacteria (e.g., *Mycoplasma, Chlamydia,* and *Legionella)* a direct relationship to response is almost impossible to show in man; thus animal models (e.g., guinea pig model of *Legionella* infection) have been used to study these relationships. For other organisms, the dynamic interaction between bacteria and different antibiotics is beginning to be understood

TABLE 4. Antibiotic Sensitivity of Common Respiratory Bacteria[a]

	Penicillins	Cephalosporins	β-Lactam + β-lactamase inhibitor	Tetracycline	Macrolide	Ciprofloxacin/ Ofloxacin	New Quinolone
Streptococcus pneumoniae	***	***	***	***	***	*	***
Haemophilus influenzae	**	***	***	***	**	***	***
Staphylococcus aureus	**	**	*	*	*	***	***
Gram-negative bacteria	*	***	*	*	*	***	***
Legionella species	*	*	?	***	***	***	***
Chlamydia pneumoniae and *psittaci*	*	*	*	***	***	***	***
Mycoplasma pneumoniae	*	*	*	***	***	***	***
Coxiella burnetii	*	*	*	***	***	***	***

[a]These generalizations may not apply to all molecules in a given antibiotic class.
[b]*, Unlikely to be active against this organism; **, only some molecules in the group will be active against this organism; *** organism usually sensitive to these agents unless acquired resistance has developed.

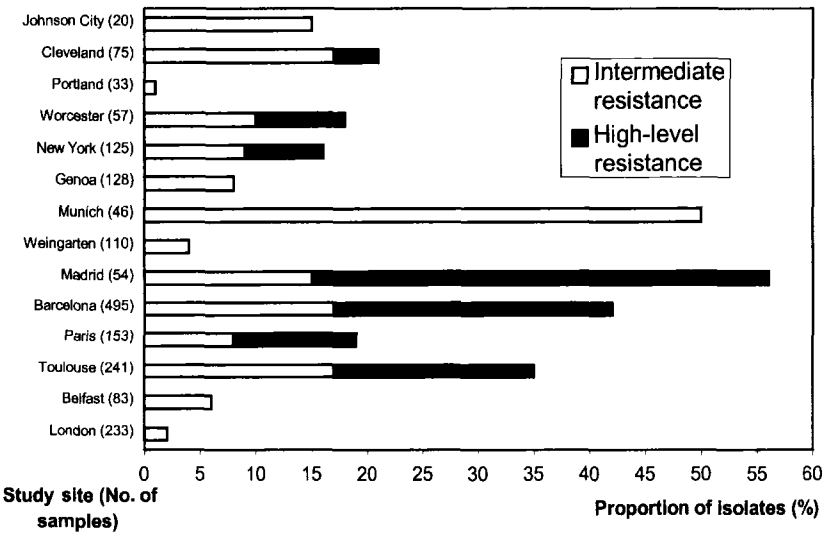

FIGURE 1. Frequency of penicillin resistance in *Streptococcus pneumoniae* isolates from respiratory samples. Reproduced, with permission, from Goldstein & Acar, 1996.

(Drusano & Craig, 1997). Two broad groups of antibiotics have been identified: agents whose killing activity is determined by the time that the local antibiotic concentration is above the MIC, and agents whose killing ability is directly a function of the antibiotic concentration. The β-lactams (e.g., penicillins and cephalosporins) and most macrolides (e.g., erythromycin and clarithromycin) show time-dependent bacterial killing. For azithromycin, which achieves high and prolonged tissue concentrations, the ratio of the time under the plasma concentration-time curve (AUC) to the MIC_{90} best predicts bacterial killing. Quinolones show concentration-dependent bacterial killing, and the maximum concentration (C_{max}) at a site or the $AUC:MIC_{90}$ ratio is the best guide to outcome.

Finally, the side-effect profile of each antibiotic needs to be considered. By considering these complex factors an informed antibiotic choice can be made (see Table 5).

Clinical Factors

Antibiotic therapy should be started as soon as the diagnosis of CAP is made or even suspected. The occurrence of deaths soon after hospital admission (Woodhead, 1992) and data linking late initiation of antibiotic therapy with poor outcome (Meehan et al., 1997) supports this recommendation. Most authors now agree that clinical, laboratory, and radiographic features, although statistically different with different causative pathogens, cannot be used (other than in occasional extreme cases such as chickenpox pneumonia) to predict the causative pathogen in an individual patient (Fang et al., 1990; Woodhead & Macfarlane, 1987). This, coupled with the low frequency of microbial identification in routine practice (Woodhead et al., 1991), and the delay before microbial results are available in the minority where investigation is helpful, means that empirical therapy is nearly always blind. Antibiotic therapy remains blind in up to three quarters of patients throughout their illness (Woodhead et al., 1991).

For these reasons initial antibiotic therapy for CAP nearly always includes one or more broad-spectrum antibiotics. If a pathogen is subsequently identified, a narrow-spectrum agent active against that organism can be substituted. The initial empirical antibiotic(s) and route of administration chosen must be directed by illness severity and gastrointestinal integrity and be based on knowledge of likely causative pathogens, local antibiotic resistance patterns, pharmacokinetics, side effects, cost acceptability, and the "cost" of making the wrong choice. For the severely ill CAP patient, the cost of

TABLE 5. Other Factors Related to Antibiotic Choice[a]

	Oral absorption	Tissue penetration	Acquired antibiotic resistance	Common side effects	Other limiting factors
Penicillins	Good	Poor	Common	Rash Gastrointestinal	No oral form of benzylpenicillin
Cephalosporins	Poor	Poor	Common	Rash Gastrointestinal *C. difficile*	No oral form for some molecules
β-Lactam and β-lactamase inhibitor	Good	Poor	Less common	Rash Gastrointestinal	
Tetracycline	Good	Good	Common	Gastrointestinal	Discolors growing teeth; contraindicated in children
Macrolide	Variable	Good	Common	Gastrointestinal Thrombophlebitis	
Ciprofloxacin/ofloxacin	Good	Good	Rare	Nausea	Affects developing cartilage; contraindicated in children
New quinolones	Good	Good	Very rare	Variable depending on molecule	Affects developing cartilage; contraindicated in children

[a]These generalizations may not apply to all molecules in a given antibiotic class.

administering the wrong antibiotic is death and it is therefore logical to use antibiotics active against all the common causes of severe CAP. This usually means using a combination of two or more antibiotics, usually intravenously to ensure antibiotic access in adequate amounts to the systemic circulation and lung. For the CAP patient who is not severely ill, the decision may be more difficult. Such patients are unlikely to die and have a much lower risk for complications or deterioration. It may therefore be unnecessary to use antibiotics active against all causative pathogens, but instead target the organism(s) most frequently encountered.

Guidelines for Empirical Oral, Intravenous, and Switch Therapy

Ideally the antibiotic prescription decision should be guided not only by an understanding of an antibiotic's in vitro activity, pharmacokinetics, and side effects, but also by the results of prospective, double-blind randomized controlled trials comparing different antibiotics in patients with CAP. Although many such trials have been performed, they are of limited value in guiding this decision (Table 6). Such trials are usually sponsored by the pharmaceutical industry for licensing purposes and do not have the statistical power to prove that one antibiotic is better than another. These studies also often contain methodological flaws such as small sample sizes, multiple sites, inappropriate exclusion criteria (e.g., prior antibiotics, severe illness), and questionable endpoints. Our knowledge of how antibiotics are currently used in the management of CAP is poor. The available data suggest a wide variation in prescribing practices both between and within countries (Gilbert et al., 1998; Huchon et al., 1996; Ortqvist, 1995). One of these studies suggested that these prescribing differences did not affect outcome but did affect costs (Gilbert et al., 1998).

This information, together with the spectrum of causative pathogens, the inability to identify the causative agent in most patients, and wide geo-

TABLE 6. Potential Flaws in Antibiotic Trials in Community-Acquired Pneumonia

Designed to suit licensing authorities rather than clinical need
Powered to show equivalence rather than superiority
Small number of patients from many centers; poor data standardization
Patients highly selected; results may not be relevant to clinical practice
Soft endpoints

graphic variability in the frequency of resistance and the extensive choice of potential antibiotic types emphasize the need for treatment guidelines for this condition.

Guidelines

The purpose of CAP management guidelines is to provide systematically developed recommendations to assist clinicians in the optimal treatment of patients with CAP. These should be based on critical assessment of the available published evidence. Where such evidence is not available a consensus view of a panel of experts is the norm. For many of the issues in the management of CAP, little grade I evidence (evidence from at least one randomized controlled trial or equivalent) is available, which means that recommendations are seldom category A (good evidence to support the recommendation). CAP guidelines must therefore be interpreted with common sense and within the context of the healthcare setting in which the reader is working. The heterogeneity of the disease and the human population means that guidelines cannot capture every clinical situation so the management of some patients will always fall outside their remit. Guidelines are usually developed at a national level. Care must be taken when applying them outside such national boundaries since differences in the population, the causative organisms and their resistance patterns, the structure of the healthcare system, and the available antibiotics may all invalidate such guidelines. Even at a local level within the healthcare system in which the guidelines were developed, operational or medical differences may mean that local adaptation of the guidelines is necessary. This is often useful as it engenders "ownership" of the guidelines at a local level, which is perceived to be an important factor in their utilization.

Despite the enthusiasm for guidelines there is little or no evidence to confirm that they improve outcomes of CAP (Gleason et al., 1997; Hirani & Macfarlane, 1997). In view of the limited evidence on which many of the guidelines are based, validation studies are essential. One of the few published studies assessed the antibiotic recommendations for outpatients with CAP in the American Thoracic Society (ATS) guidelines (American Thoracic Society, 1993). The authors found that for those aged $\leq$60 years, adherence to the guidelines had no effect on outcome, but did reduce cost. For those aged $>$60 years, adherence to the guidelines was associated with higher costs and a trend toward worse outcomes (Gleason et al., 1997). Another study assessed the validity of the severity criteria in the ATS guidelines (Ewig et al., 1998). Both of these studies corroborated some aspects of the guidelines, but suggested that modification of other aspects might be necessary.

The published guidelines (European Study on Community-Acquired Pneumonia Committee, 1998; Bartlett et al., 1998; Dorca et al., 1997; Gialdroni Grassi & Bianchi 1995; British Thoracic Society, 1993; American Thoracic Society, 1993; Mandell et al., 1993; Société de Pathologie Infectieuse de Langue Française, 1991) cover many aspects of the management of the patient with CAP, such as severity assessment, investigation, and antimicrobial chemotherapy, but only this last area will be covered further in this section. Patients with CAP are managed in three main healthcare settings: the community, in the general ward, and in the ICU. The type and route of antibiotic administration may differ in each setting.

It is probably naive to consider that only a single antibiotic, or combination of antibiotics, is appropriate in one clinical setting. The reality is probably that a number of different options are equally appropriate. Some guidelines give a single recommendation, some a choice depending on the setting. Some of the differences between guidelines are evolutional since many developments have occurred in the years between the publication of the French and the Infectious Disease Society of America (IDSA) guidelines. For example, our knowledge of antibiotic resistance has grown dramatically and the new fluoroquinolones, which appear in the European Respiratory Society (ERS) and IDSA guidelines, were not available in 1991.

The Ambulatory Patient

Ambulatory patients with CAP are generally not severely ill and do not have features that suggest that gastrointestinal absorption will be significantly impaired (Table 7). Oral therapy is therefore appropriate and a single antibiotic is recommended in all of the guidelines. A macrolide or an aminopeni-

TABLE 7. Antibiotic Recommendations for Ambulatory Patients

Country	Reference	Recommendation
France	Société de Pathologie Infectieuse de Langue Française	Amoxicillin or macrolide Young adult: macrolide Risk of unusual pathogens: amoxicillin/clavulanate
United Kingdom	British Thoracic Society, 1993	—
United States	American Thoracic Society, 1993	Previously fit ± age <60 years: macrolide or tetracycline Comorbid illness ± age >60 years: second-generation cephalosporin or cotrimoxazole or β-lactam/β-lactamase inhibitor ± macrolide
Canada	Mandell et al., 1993	Previously fit ± age <65 years: macrolide or tetracycline Comorbid illness ± age >65 years: second-generation cephalosporin or cotrimoxazole or β-lactam/β-lactamase inhibitor ± macrolide
Italy	Gialdroni Grassi & Bianchi, 1995	Amoxicillin/clavulanate or ampicillin/sulbactam
Spain	Dorca et al., 1997	No risk for unusual pathogens Typical: amoxicillin or cefuroxime or procaine penicillin Atypical: macrolide or tetracycline Risk of unusual pathogens: (amoxicillin/clavulanate or cefuroxime or ceftriaxone) ± macrolide
Europe	European Study on Community-Acquired Pneumonia Committee, 1998	Aminopenicillin or tetracycline or oral cephalosporin or fluoroquinolone[a] or oral streptogramin or macrolide Young adults at time of *Mycoplasma* epidemic: macrolide β-lactamase producing *Haemophilus influenzae*, common or chronic lung disease, or recent treatment or failure of aminopenicillin: aminopenicillin ± β-lactamase inhibitor
United States	Infectious Disease Society of America; Bartlett et al., 1998	Macrolide, fluoroquinolone,[a] or doxycycline Penicillin-resistant *Streptococcus* suspected: fluoroquinolone[a] Aspiration suspected: amoxicillin/clavulanate Young adult (17–40 years): doxycycline

[a]With enhanced activity against *S. pneumoniae*

cillin are the choices in most documents. Differing frequencies of penicillin resistance in *Streptococcus pneumoniae,* and differing perceptions about the presence of intracellular organisms such as *M. pneumoniae* and *C. pneumoniae* and the need to direct antibiotic therapy against these organisms probably underlies the different recommendations. The guidelines do not agree about the need for different recommendations for subgroups of the population, such as the elderly or those with comorbid illness. Other β-lactams; (alone or in combination with β-lactamase inhibitors), tetracyclines, or the new fluoroquinolones with enhanced activity against *S. pneumoniae* are alternatives.

The Hospitalized Patient

The treatment guidelines for hospitalized patients with CAP vary widely (Table 8). There is no agreement as to whether a single antibiotic or a combination of antibiotics is necessary, and most guidelines give the option of a combination. Combination therapy was, until the advent of the new fluoroquinolones, the only way to cover the entire spectrum of causative pathogens of CAP, but whether this is necessary is not known. Benzylpenicillin features only in the British guidelines, presumably because of fears about its narrow spectrum, especially in areas with a high prevalence of penicillin-resistant pneumococci. The most frequently recommended combination is a β-lactam plus a macrolide. The need for a macrolide in all patients has been questioned in a recent study (Mundy et al., 1998). In this study, intracellular pathogens, for which the first choice antibiotic would be a macrolide, were only found in 7.5% of cases and in 55% of these, a copathogen was also found. Only 14% of these patients received macrolide or tetracycline therapy, and none of them died.

The new fluoroquinolones now give the option

TABLE 8. Antibiotic Recommendations for Hospitalized Patients

Country	Reference	Recommendation
France	Société de Pathologie Infectieuse de Langue Française	(Amoxicillin/clavulanate or third-generation cephalosporin) + (macrolide or fluoroquinolone[a])
United Kingdom	British Thoracic Society, 1993	Aminopenicillin or benzylpenicillin (or macrolide or second- or third-generation cepahlosporin)
United States	American Thoracic Society, 1993	(Second- or third-generation cephalosporin or β-lactam/β-lactamase inhibitor) ± macrolide
Canada	Mandell et al., 1993	Second- or third-generation cephalosporin ± macrolide ± rifampicin Penicillin allergy: trimethoprim/sulfamethoxazole ± macrolide
Italy	Gialdroni Grassi & Bianchi, 1995	(Ampicillin + sulbactam or amoxicillin/clavulanate) ± macrolide
Spain	Dorca et al., 1997	(Third-generation cephalosporin or amoxicillin/clavulanate) ± macrolide
Europe	European Study on Community-Acquired Pneumonia Committee, 1998	Second- or third-generation cephalosporin or β-lactam/β-lactamase inhibitor or aminopenicillin or benzylpenicillin) ± macrolide
United States	Infectious Disease Society of America; Bartlett et al., 1998	[(Third-generation cephalosporin or β-lactam/β-lactamase inhibior) ± (macrolide or fluoroquinolone[a])] or (cefuroxime ± macrolide) or azithromycin

[a]With enhanced activity against *Streptococcus pneumoniae*.

of monotherapy with activity against all common pathogens, but the role of these antibiotics compared to β-lactams and macrolides is not yet clear.

The Severely Ill Patient

There is general agreement that in severely ill patients (i.e., those admitted to an ICU) a combination of two or more antibiotics is the optimal therapy (Table 9). The combination is usually a β-lactam with a macrolide or fluoroquinolone, sometimes with rifampicin to combat concomitant *Legionella* infection in those with severe CAP. Parenteral therapy is recommended until recovery is under way.

Intravenous, Oral, and Switch Therapy

Until recently the route of antibiotic administration was a subject about which there had been little research. In addition to antibiotic pharmacokinetics, illness severity, and gastrointestinal integrity, tradition was one of its most important determinants. The assumption that hospital admission meant severe illness, together with medicolegal concerns about the consequences of failure of oral therapy and lack of confidence in the pharmacokinetics of the oral form of some antibiotics (e.g., penicillin), had led to the use of intravenous therapy for most if not all patients. For most patients, intravenous therapy continued for 7 to 10 days or longer. This paradigm is now being questioned, especially with the arrival of newer oral antibiotics (e.g., fluoroquinolones). A small Swedish study suggested that oral phenoxymethylpenicillin was as effective as intravenous benzylpenicillin in the treatment of selected hospitalized patients with pneumococcal pneumonia (Fredlund et al., 1987). A randomized controlled trial in patients admitted to hospital with lower respiratory tract infection (of whom 37% to 45% had radiographic shadowing) found no difference in outcome between those treated with oral versus intravenous antibiotics (Chan et al., 1995). It is likely that some of these hospitalized patients could have been managed at home, and some may not have benefitted from antibiotics at all, but some could have been managed in hospital with oral therapy alone. It is not clear how such patients should be identified. Although oral therapy is recommended mainly for those with nonsevere illness, the advent of the fluoroquinolones may extend the recommendation to include some patients who are more severely ill.

The observation that patients who were switched to oral antibiotics early in their hospital stay came to no harm and the recognition of the cost of prolonged intravenous antibiotic therapy and its asso-

TABLE 9. Antibiotic Recommendations for Severely Ill Patients

Country	Reference	Recommendation
France	Société de Pathologie Infectieuse de Langue Française	(Amoxicillin/clavulanate or third-generation cephalosporin) + (macrolide or fluoroquinolone)
United Kingdom	British Thoracic Society, 1993	(Macrolide + second- or third-generation cephalosporin) or (ampicillin + flucloxacillin + macrolide)
United States	American Thoracic Society, 1993	Macrolide + (third-generation cephalosporin or imipenem/cilastatin or ciprofloxacin)
Canada	Mandell et al., 1993	(Macrolide + rifampicin) + (third-generation cephalosporin or imipenim/cilastatin or ciprofloxacin)
Italy	Gialdroni Grassi & Bianchi, 1995	Second- or third-generation cephalosporin ± macrolide ± fluoroquinolone
Spain	Dorca et al., 1997	Third-generation cephalosporin + macrolide + rifampicin
Europe	European Study on Community-Acquired Pneumonia Committee, 1998	Second- or third-generation cephalosporin (+ fluoroquinolone[a] or macrolide) ± rifampicin
United States	Infectious Disease Society of America; Bartlett et al., 1998	(Macrolide or fluoroquinolone[a]) + (third-generation cephalosporin or β-lactam/β-lactamase inhibitor)

[a]With enhanced activity against *Streptococcus pneumoniae*.

ciated hospitalization led to a formalized approach to evaluate the practice of early switch from intravenous to oral antibiotics of the same or different type (Table 10). It was found that patients identified at admission to be at low risk for a complicated hospital course could be switched to oral antibiotics after 3 days of admission with no detriment (Weingarten et al., 1994). These results have been confirmed (Weingarten et al., 1996), and this approach has been used successfully after 2 days (Siegel et al., 1996) and as soon as fever has resolved; cough, respiratory distress, and leukocytosis has improved; and gastrointestinal tract absorption has returned to normal (Ramirez et al., 1995). This approach has led to a significant reduction in the duration of hospital stay (Omidvari et al., 1998; Laing et al., 1998) and costs (Omidvari et al., 1998). Questions remain as to how many of these patients could have been managed with oral antibiotics throughout their hospital stay and whether it is safe to switch to a single oral antibiotic if two antibiotics were used intravenously.

TABLE 10. Terms Used for Changes in Antibiotic Therapy

Term	Definition
Switch	Replacing IV antibiotic with oral antibiotic
Step-down	Replacing IV antibiotic with the same antibiotic in oral form
Sequential	Replacing IV antibiotic with a different oral antibiotic

Duration of Antibiotic Therapy

The optimum duration of antibiotic therapy has been studied even less than the route of administration. The ATS guidelines (American Thoracic Society, 1993) suggest that bacterial infections should be treated for 7 to 10 days. The duration is 10 to 14 days for *M. pneumoniae, Legionella,* and *C. pneumoniae* infections. The British Thoracic Society guidelines (British Thoracic Society, 1993) suggest "at least 5 days therapy" for uncomplicated pneumonia and "2 weeks or longer" for staphylococcal and *Legionella* pneumonias. The IDSA guidelines (Bartlett et al., 1998) suggest treating the patient until he or she has been afebrile for 72 hours with at least 2 weeks treatment for *M. pneumoniae, Legionella,* or *C. pneumoniae* infections. In one study from North America (Grasela et al., 1990), the mean duration of antibiotic therapy in those with satisfactory progress was 10.3 (culture-negative) days and 12.0 (culture-positive) days, reducing to 7.2 and 7.9 days, respectively, in those switched to

oral therapy. A median duration of 6 days (intravenous) and 14 days (total) was found in another study (Gilbert et al., 1998). In the latter study those managed as outpatients had a median duration of therapy of 12 days. This compares with mean durations of 6.4 to 9.8 days for outpatients in Europe (Huchon et al., 1996). The duration of therapy may depend on the pharmacokinetics of the individual antibiotic. For example, since azithromycin penetrates lung tissue well and persists in high concentrations, 3 days' treatment with this antibiotic may be sufficient for patients with nonsevere CAP (Schoenwald et al., 1991). Further studies are required to clarify the optimum duration of antibiotic therapy.

Conclusions

Selection of the appropriate treatment path for the patient with CAP is a complex issue. Important factors that can guide the decision-making process are beginning to be understood. Nevertheless, in vitro evidence of the ability of an antibiotic to kill a bacterium is still the main determinant of antibiotic choice. More research is necessary, especially in the area of clinical comparisons of antibiotic efficacy.

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11

Pathophysiology of Pneumonia and the Clinical Consequences

WARD PATRICK

Introduction

Pneumonia is a common infection affecting both ambulatory and inpatient populations. The overall attack rate for community-acquired pneumonia is 12 per 1000 population per year and 20% to 50% of all adults with pneumonia will require hospitalization (Marrie, 1994). This reported range for the incidence of pneumonia is due, in part, to the fact that hospitalization rates increase with age. In Halifax County, for example, the hospitalization rate rose from 0.54/1000/year in people aged 35 to 44 years up to 11.6/1000/year for those ⩾75 years of age (Marrie, 1994). The need to hospitalize a patient carries with it important economic and prognostic implications.

Although the number of people hospitalized with pneumonia is a small percentage of the total patient population, the bulk of the healthcare dollars are spent on this aspect of disease management. Also, mortality is rare in outpatients with this disease. However, the literature suggests it can be as high as 21% (Marrie et al., 1989) in those patients requiring hospitalization.

Thus, despite advances in antimicrobial therapy and diagnostic techniques, pneumonia remains a challenge to all physicians in clinical practice. Treatment options are limited to antibiotics and, when necessary, cardiorespiratory support. However, as the pathophysiology of this condition is better understood, treatment options will expand. Eventually preventive measures may be offered to high-risk patients in addition to the influenza and pneumococcal vaccine.

An important question is why the disease has a high prevalence. The lung offers a huge epithelial surface that is exposed to the environment. It has been estimated that the surface area of the epithelial lining of the lung is 70 m^2 (Nelson et al., 1995; Murray, 1986; Baggiolini et al., 1989). This surface is constantly exposed to a multitude of potential pathogens. Pathogens can reach the lung through hematogenous spread from distant foci, by inhalation of airborne pathogens, or most commonly by microaspiration. The respiratory tract has a multilayered defense mechanism to contain and eliminate these bacteria. A breach of these defenses at any level will make an individual more prone to infection of the respiratory tract. Thus, the real question becomes why pneumonia is not more prevalent. In this chapter, the current understanding of the pulmonary pathophysiology at both the organ and cellular level will be explored.

Routes of Bacterial Exposure

As previously noted there are three principal mechanisms by which microorganisms can gain access to the lower respiratory tract: hematogenous spread, inhalation of airborne pathogens, and microaspiration.

Hematogenous spread is most commonly en-

WARD PATRICK • Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia B3H 2Y9, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

countered in the setting of nosocomial pneumonia. In these conditions, *Staphylococcus aureus* is allowed to breach the skin, tor example, following the common use of intravenous catheters. The risk of infection from these catheters tends to increase the longer they are in place and with increasing frequency of breaking into them to deliver medications. Although numerically the number of infections caused in this manner is low, these are important clinical consequences, as the mortality rate for nosocomial pneumonia is high. Once the pathogen reaches the lung, it encounters the cellular defense mechanisms in the lower airways, principally the alveolar macrophages.

Airborne pathogens can also gain entrance into the lower respiratory system. The defense mechanisms combating these pathogens depend on the site of deposition in the respiratory tract. The site of deposition depends largely on the particle size and the physics of gas flow through the respiratory system. Large particles in excess of 10 μm are impacted in the nasal passages. The nasal passages are an effective filtering system due to the curvature of the nasal turbinates and the initial linear acceleration as air passes through the nasal ostia (Nelson et al., 1995). Particles between 2 and 10 μm reach the conducting airways of the respiratory system. Here the frequent branching of the bronchial tree leads to increasing inertia and thus their deposition (Nelson et al., 1995). Bacteria impacted in these areas are subject to the natural defenses of these airways such as the cough reflex and the barriers imposed by the epiglottis and glottis. Small particles of 0.5 to 2 μm are deposited in the terminal respiratory units and the alveoli by a process of sedimentation (Nelson et al., 1995). This is the size range of the most common respiratory pathogens and thus the physics of gas flow offers these organisms direct access to the terminal respiratory units. Particles smaller than 0.5 μm will gain access to the alveoli through diffusion. However, these organisms may also be exhaled in the expired gas flow before they can. Inhalation is an important method for viruses, fungi, and atypical bacteria such as *Legionella* to breach the defenses of the respiratory system.

Although most respiratory pathogens are the appropriate size to gain access to the respiratory tract in the aerosolized form, the process of microaspiration of oropharyngeal secretions is thought to cause most cases of pneumonia (Berk et al., 1981; Marrie, 1992). Aspiration of these secretions is common and has been demonstrated to occur even in normal individuals during sleep (Huxley et al., 1978).

The upper airway is densely colonized by a variety of commensal organisms (Mackowiak, 1982). However, gram-negative, aerobic enteric organisms are infrequent colonizers, isolated in less than 2% of normal individuals (Nelson et al., 1995; Johanson et al., 1969). Indeed the pharynx in normal individuals appears to be resistant to colonization with these organisms (LaForce et al., 1976). Hospitalized patients on the other hand seem to lose this natural resistance and these gram-negative organisms colonize up to 60% of these patients (Nelson et al., 1995, Johanson et al., 1972). It is due to colonization with the gram-negative organisms and subsequent microaspiration that nosocomial pneumonia develops by gram-negatives (Johanson et al., 1972).

Interestingly the rate of oropharyngeal colonization with aerobic gram-negative bacilli also increases with increasing age (Berk et al., 1981; Valenti et al., 1978). Colonization occurs in up to 25% of those ≥75 years of age living at home and in 12% to 42% of those living in a nursing home (Berk et al., 1981). The pathogenesis of most pneumonia cases in the aging population is related to the aspiration of oropharyngeal secretions (Yoshikawa, 1991; Verghese & Beck, 1983).

Once bacteria have gained entrance to the lower respiratory system, by any of these three mechanisms, pneumonia results depending on the number of bacteria present, the virulence of the organisms, and the integrity of the respiratory defense mechanisms.

Host Defenses of the Upper Airway

Aside from the mechanical filter function of the nasopharynx resulting from its anatomical structure, this region has a mucociliary clearance system. The nasal mucosa is composed of ciliated epithelial cells and mucus (Nelson et al., 1995) that together form a barrier to microbes. Any microbe deposited in this area is either cleared through the nasopharynx or moved back to the pharynx where it can be swallowed. In addition to this mechanical

clearance, there are humoral mechanisms at play. Approximately 10% of the protein found in nasal secretions is IgA, which has both antibacterial and antiviral functions (Nelson et al, 1995). The importance of this immunoglobulin is demonstrated by the fact that patients with a selective IgA deficiency are prone to recurrent upper respiratory tract infection (Green et al., 1977). Lack of IgA has also been correlated with increased bacterial adherence to the mucosa, which may be the initial step in the development of bacterial pneumonia (Neiderman et al., 1986).

The squamous epithelium of the oropharynx does not have a ciliary function to clear organisms. This area has a rich microbial flora that appears to interfere with colonization by pathogenic aerobic gram-negative bacteria. In addition, there are a variety of mechanisms to control bacterial growth, such as the flow of saliva over mucosal squamous cells, constant turnover of the epithelial surface itself, local production of IgA and IgG, and alterations in mucosal pH (Nelson et al., 1995; Mackowiak, 1982).

Host Defenses of the Lower Airway

The glottis forms an anatomic barrier to the passage of infected fluid boluses into the lower airways. However, when this fails to keep unwanted substances out, a strong cough reflex is triggered.

The mucosa of the lower conducting airways is composed of ciliated epithelium. The cilia move in a fluid layer that is called the periciliary layer. The tips of the cilia move a more viscous mucous layer. The movement of the cilia acts to propel this mucous layer toward the more central airways. The mucus is eventually removed by the cough reflex or moved up to the hypopharynx where it can be swallowed. Congenital defects of either the cilia (e.g., the immotile cilia syndrome) or the mucus (e.g., cystic fibrosis) predispose an individual to recurrent respiratory tract infections (Nelson et al., 1995; Camner, 1980).

A number of bactericidal mechanisms are operative at the epithelial surface of the lower airways. IgA antibodies present on these surfaces have both antibacterial and antiviral properties (Zeiher & Hornick, 1996; Coonrod, 1986). Lysozyme degrades peptidoglycan linkages in the cell wall of gram-positive organisms (Zeiher & Hornick, 1996). Lastly, secretions contain lactoferrin, which chelates iron, depriving bacteria of this important nutrient (Coonrod, 1986; Finkelstein et al., 1983). In vitro lactoferrin is bacteriostatic (Masson, 1966) and can irreversibly damage the outer membrane of gram-negative bacteria (Ellison et al., 1988; Ellison & Giehl, 1991).

The respiratory epithelial cells of most mammals are capable of producing a group of peptides called defensins. These arginine-rich peptides are capable of killing bacteria, fungi, and encapsulated viruses (Zasloff, 1992). Although these compounds have not yet been found in humans it is believed that they may well exist (Zeiher & Hornick, 1996).

If a microorganism is able to survive its journey through the airways and arrive in the alveolus of the lung, it will meet yet another defense mechanism, the alveolar macrophage (AM). This is the final sentinel of the respiratory system. It is a potent phagocytic cell that has been found under experimental conditions to eliminate a challenge of up to 10^5 colony-forming units of *S. aureus.* When faced with a bacterial load it can not handle, the AM activates the recruitment of polymorphonuclear leukocytes into the alveolus from reserves in the pulmonary vasculature (Lipscomb et al. 1983; MacNee & Selby, 1990) by producing cytokines. These cytokines include tumor necrosis factor, interleukin-1, and interleukin-8 (Nelson et al., 1995). These cytokines also activate the recruited cells for enhanced respiratory burst and phagocytosis, allowing them to destroy the invading microorganisms (Nelson et al., 1995; Baggiolini et al., 1989; Klebanoff et al., 1986; Shalaby et al., 1995).

If a microorganism is able to evade or overcome all of these defenses, it can flourish in the alveolus and cause pneumonia.

Effect of Pneumonia on Lung Mechanics and Pulmonary Function Testing

Although bacterial pneumonia is a very common clinical entity, the derangements in lung mechanics and pulmonary function testing associated with the condition are still incompletely understood.

Colp et al. (1962) measured vital capacity (VC) in patients with pneumonia but no other lung disease. These investigators attempted to correlate the change in VC with the volume of infiltrate on chest radiograph. They found that the loss in VC was larger than predicted from the degree of consolidation on the radiograph. It was postulated that either the mechanics of the uninvolved lung were abnormal or extrapulmonary factors such as splinting could account for some of this loss in VC. However, part of this discrepancy may have been due to an underestimation of the volume of lung involved due to the limitation inherent in using a two-dimensional view in a chest radiograph to estimate a three-dimensional space.

Other investigators (Marshall & Christie, 1954) followed the changes in the elastance (elastance = 1/compliance) of the lung during the acute and convalescent phases of bacterial pneumonia. Again, the chest radiograph was used to estimate the degree of lung involvement. They found that elastance was increased (i.e., compliance was decreased) more than predicted by the degree of involvement on the radiograph. Thus, they also postulated that this difference was due to a change in the elastance of the uninvolved lung. However, as was later pointed out by Mink et al. (1981), functional residual capacity (FRC) was not measured in this study and may have affected the interpretation of their results. Indeed, when other investigators examined the effect of pneumonia on FRC (Binger & Brow, 1924), there were large reductions in FRC that returned toward normal during convalescence from the disease.

In a canine model of pneumococcal pneumonia, Mink et al. (1981) were able to demonstrate a 15% reduction in total lung capacity (TLC) and a similar reduction in other subdivisions of lung volume. The loss in TLC was entirely explained by the decrease in volume of the infected lung. These investigators confirmed there was an increase in elastance for the entire lung. Furthermore, there was no change in the deflation elastic properties of the uninvolved lung. This indicated that the decrease in compliance was due to the loss of lung volume.

The same animal model was again used to investigate the effect of pneumonia on pulmonary mechanics, this time using *Pseudomonas aeruginosa* as the infecting agent (Hanley & Light, 1987). This study gave similar results to the previous study in that there was a significant and proportional fall in FRC and TLC in these animals. This was believed to be related to lung units not inflating at FRC due to inflammatory exudate. These units also failed to inflate as lung volumes increased to TLC. Likewise, the significant fall in lung compliance was explained by the loss of lung volume caused by pneumonia. As with the previous study, there was no evidence of any change in the elastic properties of the uninvolved lung.

These observations are relevant to patients encountered in clinical practice in a number of ways. The increase in elastance (decreased compliance) seen in this disease will increase as the pneumonic process in the lung advances. This increased elastance will require an increase in negative intrapleural pressure for a given tidal volume. The increased negative pressure translates into increased work performed by the inspiratory muscles for any given tidal volume. That increased work may lead to respiratory muscle fatigue and may be expected to disproportionately affect patients with either a preexisting respiratory disease already associated with increased work of breathing (e.g., chronic obstructive pulmonary disease) or patients with disease affecting the respiratory muscles (e.g., neuromuscular diseases). These patient populations are at the highest risk for ventilatory failure in the setting of pneumonia.

Experimental evidence supports the concept of the potential for respiratory muscle fatigue in the setting of pneumonia (Desmecht et al., 1996). Although increased work of breathing would be correlated with the degree of lung involvement, there is no simple, useful test that allows the estimation of the amount of excess work imposed on patients.

The change in FRC and TLC could be used to estimate the amount of lung parenchyma involved in the pneumonic process. It might be possible to look at progression or improvement in a patient using serial pulmonary function testing. This has not been advocated in adults, but there is a suggestion that in children serial determinations of FRC might aid in their management (Gea et al., 1991).

In children aged to 4 months, it has been difficult to measure the degree of physiological disorder or the response to therapy in respiratory diseases.

Technology is now available to allow pulmonary function testing in these young, uncooperative children, opening the possibility of using these measurements in clinical management. Shannon (1989) suggested that measures of FRC are part of the minimum physiologic information necessary for successful use of a mechanical ventilator.

Pathophysiology of Abnormal Gas Exchange in Pneumonia

Patients with pneumonia often present with dyspnea, and on arterial blood gas analysis are found to have an abnormal alveolar to arterial gradient (A—a gradient) for oxygen and some degree of arterial hypoxemia.

There are five pulmonary pathophysiological mechanisms responsible for the development of hypoxemia: (1) a low fraction of inspired oxygen (F_{IO_2}), (2) ventilation perfusion ($\dot{V}_A/\dot{Q}$) mismatch, (3) increased shunt (Qs/Qr), (4) alveolar hypoventilation, and (5) diffusion defect.

A low F_{IO_2} is an uncommon cause for hypoxemia in most circumstances but this does present a problem at high altitudes. The Mexico City Olympic Summer Games substantiated the profound effect of a low F_{IO_2} on the performance of even world-class athletes.

Ventilation-perfusion mismatch occurs whenever there is an imbalance between ventilation and perfusion of a lung unit. At one extreme of mismatch, shunt occurs when there is perfusion to a lung unit without ventilation. This is the most common clinical cause of hypoxemia in patients presenting with pneumonia.

Alveolar hypoventilation is an interesting cause of hypoxemia. Oxygenation is a "passive" process and does not require the "bellows function" of the lung for gas exchange to occur. Therefore, the question raised is why a loss of this "bellows function" leads to hypoxemia. The answer lies in the alveolar gas equation. This equation states that the total pressure in the alveolus is equal to the sum of the partial pressures of the constituent gases. The total pressure in the alveolus of a spontaneously breathing individual is barometric pressure, which is a constant. Alveolar hypoventilation causes an increase in alveolar carbon dioxide (P_{ACO_2}). The P_{AO_2} decreases to maintain constant barometric pressure in the alveolus. This leads to a decreased pressure gradient for oxygen transport across the alveolar-capillary membrane.

The least common mechanism for hypoxemia is a diffusion defect. In this circumstance, there is a thickening of the tissue barrier for gas exchange in the alveolus. This mechanism may contribute to hypoxemia in some types of pneumonia, such as the interstitial pneumonia due to *Pneumocystis carinii.*

A number of articles in the literature have addressed the cause of arterial hypoxemia in the setting of pneumonia (Hanley & Light, 1987; Gea et al., 1991; Rodriguez-Roisin & Roca, 1996; Lampron et al., 1985; Walmrath et al., 1995). The predominant causes of hypoxemia appear to be a combination of intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ mismatch (Hanley & Light, 1987; Gea et al., 1991; Lampron et al., 1985; Walmrath et al., 1995). These studies demonstrated a high level of shunt, in the range of 8% to 32% of the cardiac output, with moderate to severe amounts of blood flow distributed to alveolar units with low $\dot{V}_A/\dot{Q}$ ratios (range, 4% to 21% of cardiac output) (Rodriguez-Roisin & Roca, 1996). The greater the severity of the pneumonia, the greater the amount of intrapulmonary shunt and the more severe the abnormality of the $\dot{V}_A/\dot{Q}$ distributions (Rodriguez-Roisin & Roca, 1996).

Humans and other mammals have developed an adaptive mechanism in the pulmonary vasculature to minimize $\dot{V}_A/\dot{Q}$ mismatch and the resulting hypoxemia. This adaptation is termed hypoxic pulmonary vasoconstriction. As the name suggests, there is vasoconstriction in the pulmonary vasculature in response to alveolar hypoxia. The anatomical site of this vasoconstriction has not been conclusively determined. However, evidence suggests that small pulmonary arteries at the precapillary level are the most likely site (Kato & Staub, 1966). The consequence of hypoxic pulmonary vasoconstriction is a reduction in perfusion and a shift in blood flow away from nonventilated regions or very low $\dot{V}_A/\dot{Q}$ units. This in turn decreases $\dot{V}_A/\dot{Q}$ mismatch, preventing dramatic reductions in P_{AO_2}.

There have been several experimental studies examining hypoxic pulmonary vasoconstriction in the setting of pneumonia. In a canine model of acute bacterial pneumonia, evidence suggests a failure of hypoxic pulmonary vasoconstriction (Light, 1986;

Goldzimmer et al., 1974; Voelkel, 1986). These investigators showed that pulmonary blood flow could not be diverted away from the consolidated, poorly ventilated lung units.

At present, the reason for the loss of hypoxic pulmonary vasoconstriction in pneumonia is not known. However, there is some evidence that it may be due to production of nitric oxide (NO) (Archer et al., 1989; Persson et al., 1990). However, there are also conflicting data that suggest that NO is not involved in this process (McCormack & Paterson, 1993). There may be multiple mechanisms to account for the attenuation of hypoxic pulmonary vasoconstriction in patients with pneumonia.

Patients sick enough to require hospitalization for pneumonia usually require treatment with supplemental oxygen. Oxygen must be considered a drug, and like all other pharmacologic therapy it carries with it potential risks and benefits to the individual patient. The different methods of delivery of oxygen therapy are beyond the scope of this chapter but can range from simple nasal prongs to mechanical ventilatory support.

Oxygen therapy requires monitoring the patient so that therapy can be withdrawn as soon as possible. This is accomplished in the ward setting with the use of pulse oximetry and/or the measurement of arterial blood gases. Pulse oximetry is a reliable and noninvasive method to measure arterial hemoglobin oxygen saturation (Spo_2) (Chapman et al., 1983; Saunders et al., 1976; Yelderman, 1983; Flick & Block, 1977).

The pulse oximeter measures the absorption of two wavelengths of light passing through a body part perfused with arterial blood. Saturated and reduced hemoglobin each absorbs particular wavelengths of light. Oxyhemoglobin absorbs much less red (±660 nm) and slightly more infared (±910–940 nm) light than reduced (deoxygenated) hemoglobin (Curley & Smyrnios, 1991). A probe is placed on the finger or earlobe. On one side of the probe are two light-emitting diodes and on the other is a light-sensitive photodetector. A modulated or pulsating electronic signal is then emitted. Other fluids and tissues also absorb the light, however, only the pulsatile arterial flow will modulate the light and thus be sensed. In this way, the monitor is able to isolate the arterial blood flow for the Spo_2 determination.

As with any technique, pulse oximetry has limitations. The dyes that are sometimes used for cardiac output determination (e.g., indocyanine) will interfere with the measurement. These agents will cause a falsely lowered Spo_2 reading (Curley & Smyrnios, 1991). Clinically, this is rarely a limitation as most critical care environments use the thermodilution technique for cardiac output determinations. Other factors that may lower the Spo_2 measurement include dark skin, nail polish, or elevation of serum lipids (Curley & Smyrnios, 1991).

Elevated levels of dyshemoglobins (e.g., methemoglobin, carboxyhemoglobin) may also interfere with the accuracy of pulse oximetry. The presence of these dyshemoglobins tends to cause an overestimation of the Spo_2 (Shippy et al., 1984; Ries et al., 1985). Dyshemoglobinemias are not rare in clinical medicine. For example, patients who are receiving dapsone for *Pneumocystis* prophylaxis may have elevated levels of methemoglobin in their blood.

Lastly, there is the potential for a problem with signal failure in patients with low cardiac output, poor tissue perfusion, incorrect position of the probe, or hypothermia.

It must be remembered that although pulse oximetry can offer the clinician a convenient noninvasive method to monitor arterial oxygenation it can do no more than that. However, as a bare minimum, patients presenting to the hospital with pneumonia should have pulse oximetry performed to screen for evidence of hypoxemia.

Hypoxemia is vitally important since nearly all the oxygen carrying capacity of the blood ($Cao_2 = (1.39 \times Hb \times Sao_2) + (0.0031 \times Pao_2)$) and thus oxygen transport ($Vo_2 = CO \times Cao_2$) comes from hemoglobin (Hall et al., 1992). Most patients should be maintained with a $Sao_2 \geqslant 90\%$ at all times to optimize oxygen delivery and minimize the risk of tissue hypoxia (Curley & Smyrnios, 1991; Hall et al., 1992; Wheeler & Bernard 1999).

A Sao_2 of $\geqslant 90\%$ is chosen due to the nonlinear shape of the oxygen-hemoglobin dissociation curve. A patient with an oxygen saturation below 90% is on the steep portion of this S-shaped curve. A minor deterioration in gas exchange may cause large reductions in Sao_2 and oxygen delivery, which may lead to tissue hypoxia.

If information is required about the ventilatory function of the patient ($Paco_2$) or about their acid-base status, pulse oximetry is not sufficient and

arterial blood gas sampling should be performed. Patients at high risk for ventilatory failure with pneumonia are those who have preexisting lung disease that requires increased work of breathing. The most common clinical example is the patient presenting in ventilatory failure with pneumonia and underlying chronic obstructive pulmonary disease.

Septic Shock Associated with Pneumonia

A number of patients presenting with pneumonia will progress to the stage of septic shock. Sepsis is the leading cause of shock in most intensive care units (ICUs) and is the leading cause of death in the ICU (Light, 1992; Piper, 1998; Parker, 1998; Astiz & Rackow, 1998). Death from this syndrome usually results from the development of multiple organ dysfunction and failure (Murphy et al., 1998). Sepsis is the 13th leading cause of death in the United States, with approximately 100,000 patients developing septic shock annually (Shapiro & Gelfand, 1993). The mortality rate quoted in the literature varies between 20% and 60% for this condition (Astiz & Rackow, 1998; Smith, 1998).

A great deal of research has focused on the underlying pathophysiology of septic shock. However, before discussing the pathophysiology, it is important to understand certain definitions.

Definitions

The American College of Chest Physicians and the Society of Critical Care Medicine convened a consensus conference in August 1991. Until that point it had been difficult to interpret the literature because there were varying definitions used for such terms as "sepsis" and "septic syndrome." The goal of this conference was to provide a conceptual and practical framework to define the systemic inflammatory response syndrome (SIRS) and the processes that fall under the term "sepsis" (Bone et al., 1992; American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992).

Infection was defined as a "microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms" (Bone et al., 1992).

Bacteremia was denned as the presence of viable bacteria in the blood (Bone et al., 1992). The presence of viruses, fungi, and parasites were similarly termed "viremia, fungemia, and parasitemia" (Bone et al., 1992).

Sepsis was defined as the systemic inflammatory response to infection. This systemic response is manifested by the presence of two or more of the following:

- Temperature $> 38°C$ or $< 36°C$
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or $Paco_2 < 32$ mm Hg
- WBC $> 12{,}000$ cells/mm^3, < 4000 cells/mm^3, or $> 10\%$ immature forms

These physiologic measurements must represent an alteration from baseline with no other cause(s) known (Bone et al., 1992).

These individuals also recognized that the inflammatory response seen with infection was not exclusive to that clinical condition. They coined the phrase "systemic inflammatory response syndrome" to describe the inflammatory response independent of its cause (Bone et al., 1992). The SIRS occurs due to a large number of very different insults, sepsis being only one. This response is manifested by two or more of the following conditions:

- Temperature $> 38°C$ or $< 36°C$
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or $Paco_2 < 32$ mm Hg
- WBC $> 12{,}000$ cells/mm^3, < 4000 cells/mm^3, or $> 10\%$ immature forms (Bone et al., 1992)

This group defined severe sepsis as sepsis associated with organ dysfunction, hypoperfusion, or hypotension (Bone et al., 1992). Septic shock was defined as sepsis with hypotension despite adequate fluid resuscitation (Bone et al., 1992). In addition, septic shock requires the presence of perfusion abnormalities such as lactic acidosis, oligurea, or a decreased level of consciousness (Bone et al., 1992).

These definitions are not simply a research tool to ensure recruitment of patients with the same disease process. They are also of clinical importance to the physician and the patient. Mortality, for

example, differs if a patient has sepsis (16%) or septic shock (40%–60%) (Astiz and Rackow, 1998). With these definitions, we can now discuss the pathophysiology of these conditions.

Pathophysiology of Septic Shock at a Cellular Level

Advances in molecular and cell biology have given new insight into the cellular pathophysiology of septic shock.

The cellular mechanisms of sepsis have been extensively worked out for gram-negative organisms with endotoxin as the inciting event. However, other bacterial products such as formyl peptides, exotoxins, and proteases from gram-negative organisms are now recognized to initiate the same inflammatory process (Astiz and Rackow, 1998). Septic shock is not the sole domain of gram-negative organisms. Gram-positive organisms have long been recognized as being able to initiate the inflammatory pathway leading to sepsis and septic shock. Indeed, there is now some information suggesting that the mortality in gram-positive septic shock may be higher than for the gram-negative equivalent (Geerdes et al., 1992; Horn, 1998). Components of the gram-positive organism, such as exotoxins, enterotoxins, hemolysins, peptidoglycans and lipoteichoic acid, can all initiate this process (Astiz & Rackow, 1998). The gram-negative, endotoxin-induced model will be examined in more detail, as it is the most studied and best understood to date.

It is now recognized that patients with septic shock have a biphasic immunological response (Bone, 1996). The first phase of this immunological response is characterized by overwhelming inflammation and activation of pro-inflammatory mediators. The second part of this process has been largely neglected until recently. It was only after negative results in multiple, large, clinical trials targeting pro-inflammatory mediators that the model of SIRS as a persistent uncontrolled inflammation came into question. There is increasing evidence that an opposite and compensatory response, termed the compensatory anti-inflammatory response syndrome (CARS) by Bone (1996), plays a crucial role in the pathogenesis of septic shock (Klosterhalfen & Bhardwaj, 1998). The literature suggests that CARS is the main immunological mechanism during the chronic stages of septic shock in humans. The anti-inflammatory mediators involved have been shown to affect humoral and cellular immunological properties (Klosterhalfen & Bhardwaj, 1998), causing immunosuppression.

Phase I: Pro-inflammatory Phase

The endotoxin model will be used to illustrate the process. Endotoxin is a lipopolysaccharide (LPS) found in the outer membrane of gram-negative organisms. Bacterial endotoxin may be shed with membrane fragments into the circulation. Once liberated by these organisms the LPS can enter the bloodstream where it can bind to an LPS-binding protein (LBP). This LPS-LBP combination can bind to CD-14, a cell receptor found on monocytes and macrophages.

CD-14 lacks an intracellular signal transduction domain and thus it is hypothesized that it associates with another protein or proteins. The intracellular signal from CD-14 and its associated protein(s) occurs through the activity of tyrosine kinase (Murphy et al., 1998). The mitogen-activated protein (MAP) kinase pathway induces transcription of multiple LPS-inducible genes by causing nuclear localization of the nuclear transcription factor nuclear factor-κB (NF-κB) (Murphy et al., 1998). Additionally, MAP kinase causes translation of the tumor necrosis factor (TNF)-α messenger ribonucleic acid (mRNA) (Murphy et al., 1998).

The human TNF-α gene is located on the short arm of chromosome 6 close to the major histocompatibility complex (Spies et al., 1986). The association of monocytes with LPS causes an increase in TNF-α mRNA transcription and translation (Beutler et al., 1986; Sariban et al., 1988). There is growing support for the concept that the amount of TNF-α formed depends on the genetic constitution of an individual. Thus, TNF-α production may affect the clinical outcome of septic shock (Murphy et al., 1998).

The result of these signals is the liberation of the pro-inflammatory mediators TNF-α and interleukin-1 (IL-1). Both of these cytokines potentiate the septic state by affecting the temperature set point, decreasing vascular resistance, depressing cardiac function, and stimulating neutrophil mobilization from the bone marrow (Smith, 1998). They also mobilize IL-6, IL-8, and arachidonic acid to

form leukotrienes, thromboxane A_2, and prostaglandins, which have a role in the pathophysiology of acute respiratory distress syndrome (ARDS). IL-1 also activates T cells to produce interferon-γ, IL-2, IL-4, and granulocyte-monocyte colony-stimulating factor (GM-CSF) (Bone, 1992). TNF-α is thought to be responsible for activation of complement and coagulation cascades, leading to a series of inflammatory events including vasodilation, increased vascular permeability, and induction of polymorphonuclear cells, mast cells, macrophages, and platelets to produce more cytokines (Smith, 1998). TNF-α is also known to activate the extrinsic clotting pathway and blood coagulation associated with disseminated intravascular coagulation (Smith, 1998).

In addition, adhesion molecules are expressed on endothelial cells and neutrophils in response to inflammatory mediators (Adams and Shaw, 1994). The endothelial adherence of activated neutrophils and their transmigration into the extravascular space leads to subsequent tissue damage (Smith, 1998).

Nitric oxide is postulated to be a major mediator of the vasodilation seen in septic shock. The pro-inflammatory mediators stimulate the inducible form of NO synthetase. The result is the release of increased amounts of NO from endothelial cells, vascular smooth muscle cells, and macrophages. It has also been postulated that the formation of peroxynitrite may cause direct cellular injury (Astiz & Rackow, 1998). Peroxynitrite is formed by the combination of NO with superoxide radicals from activated white blood cells. Nitric oxide has also been postulated to mediate cytokine-induced myocardial depression and increased intestinal permeability during septic shock (Astiz & Rackow, 1998).

Anti-inflammatory substances are also released in response to this pro-inflammatory phase. The role of these substances is to act as a negative feedback loop for the inflammatory process and possibly to aid in tissue repair.

Phase 2: The Compensatory Anti-inflammatory Response Syndrome

The CARS was ignored for years but there is increasing evidence that it plays a critical role in the pathophysiology of septic shock. Factors that are thought to play a role in this arm of the process include endogenous corticosteroids and catecholamines, transforming growth factor-β, soluble TNF receptors, IL-1 receptor antagonist (IL-lra), IL-10, IL-4, IL-11, and IL-13 (Astiz & Rackow, 1998, Smith, 1998). The best studied of these factors thus far is IL-10. IL-10 has been shown to inhibit cytokine synthesis by human monocytes and affect monocyte function including antigen-presenting activity in vivo (Klosterhalfen & Bhardwaj, 1998; de Waal-Malefyt et al., 1991).

The potential significance of the anti-inflammatory factors was shown by invariably high levels of IL-10 in nonsurviving patients with septic shock, whereas IL-10 levels were significantly lower in the survivors (Van der Poll, 1997). Parsons et al. (1997), who studied a group of patients at risk of developing ARDS, reported similar results. They found that the levels of IL-10 and IL-lra were significantly higher in the nonsurvivor group than in the survivor group (Parsons et al., 1997).

Much more needs to be learned about the balance between the pro-inflammatory and anti-inflammatory parts of this process to allow specific targeting of the pathways by immunotherapy. At this time, there is no effective immunotherapy for sepsis and septic shock.

Clinical Presentation of Pneumonia with Septic Shock: Case Study

A 75-year-old male living in a nursing home presents to the emergency department complaining of increasing shortness of breath for the past 3 days. On closer questioning, he relates a history of fever and chills and has had a nonproductive cough for 3 days. There is no significant past medical history and of note is the absence of neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or preexisting renal disease.

On physical examination, this patient looks his stated age and appears to be in mild to moderate respiratory distress. His Sao_2 on room air was 90% on arrival in the emergency department and improved to 98%–100% on a fraction of inspired oxygen (Fio_2) of 0.40 delivered via Venturi face mask. His respiratory rate is 32 breaths/minute, heart rate is 110 beats/minute, temperature is 38.6°C (oral), and blood pressure is 140/80 mm Hg with no postural drop. The examination is also remarkable for

the findings consistent with bilateral lower lobe consolidation with crackles heard in these same lung fields.

Laboratory investigations include a chest radiograph that confirms the physical examination findings of bilateral lower lobar consolidation with a small pleural effusion noted on the right. Electrolytes are normal, however, the blood urea nitrogen is 16.0 mmol/L and creatinine is 140 mmol/L. A complete blood cell count (CBC) is done which shows a white blood cell count of 18.6×10^9/L with a prominent left shift of 92% neutrophils. The hemoglobin concentration is 156 g/L with a hematocrit of 0.490 and a platelet count of 256×10^9/L.

The immediate clinical question is whether this patient requires hospital admission or can be treated as an outpatient. Until recently, there was little to guide the clinician in making this decision other than clinical experience. Fine et al. (1997) published a prediction rule to help make this decision based on evidence rather than opinion. This is vitally important to the healthcare system, as most of the cost of treating this illness is associated with hospitalization. The full details of this prediction rule can be found elsewhere in this book. However, this patient scores 125 points, placing him in risk class IV. The mortality rate for this group is approximately 8.5% and it is recommended that patients in this category receive conventional inpatient care. Thus, this patient is admitted to hospital. Blood cultures are drawn and urine *Legionella* antigen is sent.

The next question is which antibiotic(s) should be used in this patient. At first glance, this is a simple question with ample literature devoted to the question. Both the American Thoracic Society and the Canadian Thoracic Society put forward guidelines to address this question in 1993 (Neiderman et al., 1993; Mandell & Neiderman, 1993). According to both of these guidelines, the patient should be treated with a second- or third-generation cephalosporin with or without the addition of a macrolide depending on the clinical suspicion of the presence of *Legionella* species. More recently, the Infectious Disease Society of America has developed guidelines (Bernstein, 1999) suggesting that *Legionella* should be covered by the antibiotic(s) chosen in all hospitalized patients. Newer antibiotic choices such as the extended-spectrum fluoroquinolones must be considered as the initial empiric antibiotic for these patients.

This patient is given an intravenous dose of cefuroxime and erythromycin in the emergency department and these medications are to be continued on a regular basis. The patient is also prescribed intravenous fluids for rehydration and oxygen therapy as required to keep oxyhemoglobin saturation above 90% by pulse oximetry.

Three hours after arriving on the hospital floor the patient deteriorates with a temperature of 40.9°C, blood pressure of 70 mm Hg palpable with a pulse rate of 140 beats/minute, decreasing level of consciousness, decreased urine output, and increasing respiratory distress. Examination of the patient at that point reveals that the extremities are warm to touch.

The patient is clearly in distributive shock. The hemodynamic alterations present would include low cardiac filling pressures and low cardiac output. Hypovolemia is the cardinal reason for this hemodynamic picture. As noted in the previous section, there is increased vascular permeability with loss of albumin and fluid in the tissues. This is further aggravated by the widespread vasodilatation possibly due to the action of NO. The net result is a greatly reduced preload coming back to the heart and low cardiac output.

The patient is given 2 L normal saline over the next 20 minutes. The blood pressure increases to 90/40 mm Hg. However, he remains oligo-anuric and arrangements are made to transfer him to the ICU.

In the ICU, a Swan-Ganz catheter documents a cardiac output of 15 L/min (normal, 4-6 L/min), a systemic vascular resistance (SVR) of 400 dyne-(sec)/cm^5 (normal, 800–1200 dyne(sec)/cm^5), and a pulmonary capillary wedge pressure (PCWP), which is an estimate of left atrial pressure, of 7 mm Hg (normal, 5-12 mm Hg). These are the diagnostic hemodynamics of distributive shock with a high cardiac output and low SVR. The patient is given more crystalloid to raise the PCWP up to 12 mm Hg; however, he remains hypotensive and anuric and is started on intravenous norepinephrine to support his blood pressure.

This patient is showing all the signs of the pro-inflammatory phase of septic shock. The massive vasodilation seen with the SVR of 400 dyne(sec)/

cm^5 is thought to be due to the effects of NO. Despite a cardiac output of 15 L/min the patient is unable to maintain an adequate mean arterial pressure and perfusion to his vital organs. This is due, at least in part, to the presence of the myocardial depressant factors of sepsis (TNF, IL-1, and NO).

There is a range of medications available to support the blood pressure in this setting, however, the dose used should always be the lowest necessary to restore circulation. Norepinephrine, phenylephrine, and dopamine could all be used in this setting.

The antibiotic therapy is changed at this point to include erythromycin plus a third-generation cephalosporin with anti-pseudomonal activity. This is in accordance with the American Thoracic Society (Neiderman et al., 1993) and Canadian Thoracic Society (Mandell & Neiderman, 1993) guidelines for the treatment of patients with severe community-acquired pneumonia. These guidelines need to be re-evaluated in light of the newer extended-spectrum ftuoroquinolones.

Within 2 hours of arrival in the ICU, the patient develops a respiratory acidosis noted on arterial blood gas analysis. Also, the patient's oxygen requirements increase, and F_{IO_2} is increased to 0.90. The decision is made to intubate and mechanically ventilate the patient.

The large A–a gradient for oxygen in pneumonia patients, as discussed, is due to the loss of pulmonary hypoxic vasoconstriction, which may or may not be mediated through NO. The result is an increase in intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ mismatch.

As previously noted, the cause of the hypercapnic ventilatory failure is thought to be multifactorial. First, there is a change in the static respiratory mechanics of the lung with an increase in elastance. This increase in elastance results in an increased work of breathing. Secondly, pyrexia causes a hypermetabolic state, with increased CO_2 production. The resultant compensatory increase in minute ventilation places an increased workload on the respiratory muscles. Finally, there is now increasing evidence that ventilatory muscle contractile performance is significantly impaired during the course of septic shock (Hussain, 1998). This is similar to the myocardial depression seen with this syndrome and like the myocardial depression, it is thought to be secondary to cytokines (TNF and IL-1) and NO.

The patient stabilizes on this cardiorespiratory support. In 12 hours, the blood cultures are reported to be growing *S. pneumoniae* sensitive to penicillin. Antibiotics are again changed, this time to intravenous penicillin.

Over the next 48 hours, the patient becomes afebrile and the norepinephrine is weaned off. He is able to be extubated after a 30-minute T-piece trial on the second day in the ICU. He is transferred to the floor the next day (hospital day 4) on oral antibiotics and is transferred back to the nursing home by day 8 of the hospitalization.

This case is an excellent example of the pro-inflammatory phase of septic shock. The cardiorespiratory disorders resulting from this phase are well illustrated. Fortunately, the second phase or CARS was not prominent. This may have been due to the early initiation of appropriate antibiotic therapy. Not all patients are as fortunate. Patients who do develop the second stage of septic shock become immunosuppressed, with the potential for developing superinfection or multiple organ dysfunction syndrome.

Much work is currently under way to enhance our understanding of the cellular processes involved in septic shock. The hope is that this knowledge of the pathophysiology of sepsis will allow the clinician to have more effective treatments than are presently available for this condition.

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12

Intensive Care Unit Management of Pneumonia

THOMAS J. NOLAN AND DAVID G. McCORMACK

Severe Community-Acquired Pneumonia

Definition

A small subset of patients with community-acquired pneumonia (CAP) require intensive care unit (ICU) admission for mechanical ventilation, hemodynamic support, or monitoring. The term severe CAP evolved after a number of prospective studies reported a series of reasonably consistent characteristics seen in this particular population of patients. This classification is worthwhile since the bacteriology, management, and prognosis of CAP patients requiring ICU admission are distinct from those of other CAP syndromes. A practical definition of severe CAP based on clinical and radiographic criteria was formulated by an American Thoracic Society consensus conference (Niederman et al., 1993). In general, severe CAP requires ICU admission and is characterized by at least one of the criteria listed in Table 1. Although this definition is helpful, it may describe a sizeable proportion of hospitalized patients *not* requiring ICU management. Ewig et al. (1998) have proposed a more stringent definition for severe CAP in which two of three minor criteria (systolic blood pressure < 90 mm Hg, multilobar involvement, $Pao_2/Fio_2 < 250$) and one of two major criteria (mechanical ventilation, septic shock) must be present. The sensitivity and specificity of this revised definition for predicting pneumonia requiring ICU admission are 78% and 94%, respectively.

Pathogens of Severe Community-Acquired Pneumonia

Diagnostic Yield

Discussion of etiologic microorganisms in severe CAP is tempered by the fact that, despite rigorous investigations, diagnosis remains elusive in as many as half of all cases. Rello et al. (1993) studied 58 consecutive patients admitted to an ICU for CAP and established the cause in 60%. Diagnosis was confirmed by either positive blood or pleural fluid cultures, serology, or protected brush specimens obtained at the time of bronchoscopy. Torres et al. (1991) evaluated 92 patients in a Spanish ICU and determined exact etiology in 52% of cases. In an earlier series, Pachon et al. (1990) were able to diagnose the cause of severe CAP in 42% of 67 patients. Both Pachon and Torres used transthoracic needle aspiration in addition to more conventional techniques to establish a bacteriological diagnosis.

Despite the availability of invasive diagnostic-tests in most ICUs, several factors conspire against a specific diagnosis in this setting. Thus, many patients receive antibiotic therapy prior to admission to the ICU. This not only reduces the likelihood of a positive culture result but also predisposes individ-

THOMAS J. NOLAN AND DAVID G. Mc CORMACK
London Health Sciences Centre, Victoria Campus, London, Ontario NGA 4G5, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Criteria for Severe Pneumonia[a]

	Sensitivity (%)	Specificity (%)[b]
Respiratory failure		
Respiratory rate >30/min	64	57
Pao_2/Fio_2 <250	64	65
Mechanical ventilation required	58	100
Shock		
Systolic BP <90 or diastolic <60 mm Hg	12	99
Vasopressors required for >4 hours	38	100
Acute renal failure requiring hemodialysis	30	96
Radiographic		
Bilateral infiltrates	41	86
Multilobar infiltrates	52	89
Increase in infiltrate by 50% at 48 hours	28	92

[a]Niederman et al., 1993.
[b]Ewig et al., 1998.

uals to upper airway colonization from potentially pathogenic bacteria. Furthermore, certain groups of patients are more likely to require ICU management of their pneumonia, such as the elderly, and those with concomitant illness are also more likely to have misleading upper airway colonization with potentially pathogenic bacteria (Valenti et al., 1978). Despite this uncertainty, knowledge of common pathogens of severe CAP is crucial as initial and appropriate empiric therapy is likely to be associated with improved outcome (Pachon et al., 1990; Moine et al., 1994).

Pathogens

Common pathogens responsible for severe CAP are shown in Figure 1. As in other CAP syndromes, *Streptococcus pneumoniae* remains the most frequently identified etiologic pathogen. *Legionella* spp. and aerobic gram-negative bacteria are identified more frequently in these patients than in other less critically ill subjects with CAP.

Streptococcus pneumoniae

A common feature of virtually all studies examining etiologic diagnoses in severe CAP is the

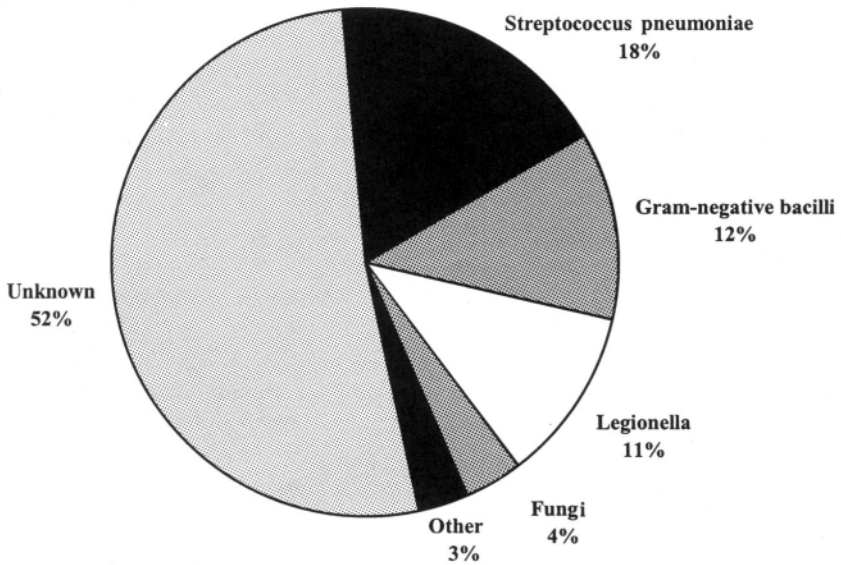


FIGURE 1. Pathogens in severe community-acquired pneumonia. Other includes viruses, *Mycobacterium tuberculosis*, and *Pneumocystis carinii*. Adapted from Pachon et al., 1990.

prevalence of *Pneumococcus.* The most common organism in six recent prospective studies involving 435 patients from four different countries was *S. pneumoniae,* isolated in 15% to 46% of patients requiring ICU management. *Pneumococcus* remains the most frequently identified pathogen in all age groups requiring ICU admission for CAP.

Legionella pneumophila

Legionella has been found to be a particularly common cause for admission to the ICU, second only to *S. pneumoniae* (Table 2). The frequency of *Legionella* in severe CAP is conspicuous relative to its incidence in the community, suggesting that *Legionella* infection results in a more severe form of pneumonia than do other pathogens. Despite this apparent virulence, *Legionella* does not appear to be an independent risk factor for death following admission to an ICU, with mortality rates of 25% to 30%, similar to the overall rates for severe CAP.

Pseudomonas aeruginosa

While pseudomonal species are common pathogens in nosocomial pneumonia, their role in severe CAP is not clear. In 1993, consensus guidelines for the treatment of severe CAP advocated the use of antibiotics with anti-pseudomonal activity—a third-generation cephalosporin such as ceftazidime, ciprofloxacin, or imipenem. However, three prospective trials involving 235 patients failed to identify *P. aeruginosa* as a potential pathogen in patients admitted to the ICU with severe CAP. When it *has* been reported, its prevalence is generally very low (3%–5%), and its presence is typically associated with underlying structural lung disease such as bronchiectasis or neoplasia (Rello et al., 1996; Leroy et al., 1995; Torres et al., 1991) or recent discharge from hospital (Hirani & Macfarlane, 1997).

Mycoplasma pneumoniae

Mycoplasma is a common causative agent in CAP in young adults but progression to respiratory failure is rare. In patients requiring hospitalization, Marrie (1993) found that approximately 10% went on to require assisted ventilation but none of these patients died from their infection. Indeed, Torres et al. (1991) found that while *M. pneumoniae* was the third most commonly identified pathogen in their series of severe CAP, no mortality was associated with this infection.

Enterobacteriaceae

While these pathogens are unusual in patients with CAP outside the ICU, they collectively represent an important cause of severe CAP. Together *Klebsiella pneumoniae, Escherichia coli,* and *Enterobacter* spp. are generally reported as the third most common cause of CAP identified in the ICU. Upper airway colonization with gram-negative rods is an important step in the pathogenesis of this disease and therefore the elderly, debilitated, and chronically ill are at particular risk.

Viruses

Despite the frequency of acute respiratory infections due to viruses, there is a paucity of information on the role of these pathogens in severe CAP. Retrospective studies rarely obtain comprehensive serological data and few prospective studies

TABLE 2. *Legionella* and Severe Community-Acquired Pneumonia

Author	Country	Number of patients	% *Legionella*	*Legionella* mortality (%)	Study mortality (%)
Rello et al., 1996	Spain	95	3	66	40
Moine et al., 1994	France	132	3	25	24
Rello et al., 1993	Spain	58	23	25	22
Pachon et al., 1990	Spain	67	22	0	21
Sorenson et al., 1989	Sweden	36	8	33	24
Woodhead et al., 1985	United Kingdom	50	30	33	54

are able to examine all relevant viruses. Moine et al. (1994) identified seven patients with either varicella-zoster, influenza, or parainfluenza pneumonia, representing 5% of their patients with severe CAP. Cytomegalovirus was identified by Sorensen et al. (1989) in two patients out of 36 with CAP requiring 1CU admission. Diagnosis usually requires paired serology with convalescent liters; consequently most patients who die with viral pneumonia do not have a confirmed diagnosis.

Viral infections, particularly those due to influenza A and B, play a unique role in severe CAP due to their propensity to result in a secondary infection, often from *Staphylococcus aureus.* Hirani and Macfarlane (1997) found that the majority of severe CAP pneumonias due to *S. aureus* were associated with recent infection with influenza A or B virus.

Hantavirus has been characterized only recently but has a significant propensity to cause acute respiratory failure. Endemic to the southwestern United States, hantavirus pulmonary syndrome has also been described in additional geographic areas in North and South America. Although Hantavirus is a relatively rare cause of CAP, it appears that virtually all individuals with this infection require ICU management, and the case fatality rate is close to 50% (Levy & Simpson, 1994).

Mycobacterium tuberculosis

Tuberculosis infection should always be considered in a differential diagnosis of severe CAP. Although it is relatively uncommon in most Western cohorts (Torres et al.,1991; Sorensen et al.,1989; Woodhead et al., 1985), the importance of *M. tuberculosis* as an infectious disease worldwide should not be underestimated. In a Singapore ICU, the incidence of tuberculosis as a cause of severe CAP was 16% (Tan et al., 1998) and in Saudi Arabia 8% (Dahmash & Chowdury, 1994).

Diagnosis

An array of diagnostic procedures exist for the elucidation of specific etiologic pathogens in severe CAP. However, the cost, potential complications, and questionable clinical utility of these procedures have resulted in considerable controversy in this subject.

In trials in which pathogenic etiology was exhaustively sought, the proportion of undefined pathogens remained frustratingly high. Hirani and Macfarlane (1997), for example, failed to identify a causative agent in about one third of all patients studied despite a combination of cultures, convalescent serology, and antigen testing. Moreover, the inability to diagnose etiology has not yet been found to be an independent predictor for mortality in multivariate analysis (Leroy et al., 1996). Nevertheless, there are compelling arguments in favor of establishing an etiologic diagnosis. For example, fewer patients would require prolonged courses of broad-spectrum antibiotic therapy, thereby decreasing the development of resistant organisms. Furthermore, current empiric antibiotic treatment strategies are based on previous regional experience which can come only from prior etiologic investigations.

Invasive diagnostic techniques are warranted in patients with severe CAP who fail to respond to empiric therapy. This may be defined as the absence of a clinical response (persistence of fever, leukocytosis, increasing infiltrates) 48 to 72 hours after initiation of treatment. In these instances, the possibility of antimicrobial resistance, superinfection, or *M. tuberculosis,* fungal, or viral pneumonia should be considered, and fiberoptic bronchoscopy with bronchoalveolar lavage and protected specimen brushing is warranted. Open lung biopsy is rarely, if ever, used to diagnose CAP but may be indicated when diagnoses other than pneumonia are being considered.

Treatment

The treatment of severe CAP requires management of acute respiratory failure, initiation of empiric antimicrobial therapy, and identification of complications frequently seen in the ICU.

Management of Acute Respiratory Failure

Respiratory failure may be defined as a significant impairment of the respiratory system's capacity to perform gas exchange. This is manifest clinically by arterial hypoxemia and/or hypercapnia.

Respiratory failure is defined as a Pa_{O_2} less than 60 mm Hg while breathing room air and/or a Pa_{CO_2} greater than 45 mm Hg. Patients with severe CAP will present with type 1 or oxygenation failure due to ventilation-perfusion ($\dot{V}_A/\dot{Q}$) imbalance and shunting. Lampron et al. (1985) demonstrated that the most common pattern of $\dot{V}_A/\dot{Q}$ mismatch in patients with bacterial pneumonia severe enough to require mechanical ventilation was a combination of intrapulmonary shunt and increased perfusion to lung units with low $\dot{V}_A/\dot{Q}$ ratios. This impairment of gas exchange represents a potential threat to life and must be rapidly identified and aggressively treated.

There are three components in the initial management of acute respiratory failure secondary to pneumonia: airway management, ventilation, and oxygenation.

Airway Management

Although upper airway obstruction is generally not the primary cause of acute respiratory failure in pneumonia, all patients should initially be evaluated for upper airway patency. Secondary obstruction can occur due to loss of oropharyngeal tone or poor clearance of secretions in moribund patients and necessitates immediate endotracheal intubation. Additional indications for intubation are listed in Table 3.

Ventilation

Alveolar Ventilation. The typical blood gases of a patient with severe CAP demonstrate hypoxemia associated with a normal or slightly reduced Pa_{CO_2}. In fact, significant disorders of ventilation are unusual unless concomitant illness is present or respiratory arrest is incipient. Alveolar ventilation ($\dot{V}_A$) is the volume of gas entering the lungs each minute that is available for gas exchange. The relationship between $\dot{V}_A$ and Pa_{CO_2} can be expressed by the following equation:

$$P_{CO_2} \propto \frac{\dot{V}_{CO_2}}{\dot{V}_A}$$

where $\dot{V}_{CO_2}$ is the rate of carbon dioxide production. This is of particular relevance to patients with depression of central respiratory drive, abnormal neuromuscular function, or airflow obstruction who develop pneumonia and a consequent increase in metabolic activity and V_{CO_2}, and are then unable to increase $\dot{V}_A$.

TABLE 3. Indications for Endotracheal Intubation and Assisted Ventilation

Refractory hypoxemia
Ventilatory failure—severe respiratory acidosis (pH <7.25)[a]
Impending respiratory failure—rising Pa_{CO_2}, respiratory muscle fatigue[a]
Airway control—impaired secretion clearance, loss of protective reflexes

[a]May be improved with noninvasive ventilation, thereby obviating the need for endotracheal intubation.

Mechanical Ventilation. Acute ventilatory failure has traditionally been treated with intubation and mechanical ventilation. The primary goal of mechanical ventilation in this setting is to provide assistance when the work of breathing is excessive and unsustainable or when insufficient VA results in unacceptable acidosis.

Noninvasive Ventilation. The usefulness of noninvasive mechanical ventilation (NIV) has been established for patients with acute respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Keenan et al., 1997). More recently, NIV has been shown to be as effective as conventional ventilation in improving gas exchange in patients with hypoxemic respiratory failure (Antonelli et al., 1998). NIV is an attractive alternative to conventional forms of ventilation; it eliminates the need for endotracheal intubation, reduces the length of stay in the ICU, and improves outcome. A trial of NIV in acute respiratory failure secondary to pneumonia should be considered in centers with experience in this technique and where continuous monitoring is available.

Oxygenation

Hypoxemia is the hallmark of acute respiratory failure due to pneumonia and must be corrected. The goal of therapy is to ensure adequate delivery of oxygen to tissues (Do_2). The determinants of Do_2 include concentration of hemoglobin (Hb) and car-

diac output (CO) as well as oxygen saturation (Sao_2):

$$Do_2 = 13.4 \times Hb \times \frac{Sao_2}{100} \times CO$$

Therefore, in addition to increasing Sao_2, Do_2 can also be improved by increasing cardiac output and correcting anemia. If necessary, patients should be placed on 100% oxygen administered by a nonrebreather face mask and the unaffected lung should be positioned dependently to improve $\dot{V}/Q$ matching. An inspired concentration of oxygen of only about 60% is attainable by face mask and often patients with high degrees of $\dot{V}/Q$ mismatch (or shunts) are refractory to this therapy. In these instances, endotracheal intubation and mechanical ventilation is required. Intubation permits the delivery of a greater concentration of oxygen, and mechanical ventilation reduces the work of breathing, thereby diminishing oxygen consumption.

Antibiotics

Empiric Therapy

The emergence of multidrug-resistant strains of bacteria, regional variation in common pathogens (and patterns of resistance), newer antibiotics, and the difficulty in establishing an etiologic diagnosis makes the subject of empiric therapy somewhat contentious. Nevertheless, early empiric antimicrobial therapy is important in the treatment of severe CAP. In fact, failure to provide effective initial antibiotic treatment has been identified as an independent prognostic factor for poor outcome in severe CAP (Torres et al., 1991; Leroy et al., 1996).

Several guidelines for the empiric treatment of severe CAP have been published in the last decade and are summarized in Table 4. There is common agreement on the need to provide effective coverage of *S. pneumoniae,* aerobic gram-negative rods, and *Legionella* with appropriate rationalization of treatment when pathogenic organisms are identified.

In 1993, the British Thoracic Society suggested the use of erythromycin combined with a second- or third-generation cephalosporin or, alternatively, ampicillin with flucloxacillin and erythromycin (Finch et al., 1993). In the same year the American Thoracic Society recommended a regimen consisting of a macrolide combined with a third-generation cephalosporin with anti-pseudomonal activity such as ceftazidime (Neiderman et al., 1993). Imipenem/cilastatin or ciprofloxacin may be used in lieu of the cephalosporin.

TABLE 4. Treatment Guidelines

	Treatment
Infectious Disease Society of America (Bartlett et al., 1998)	Erythromycin, azithromycin, or a fluoroquinolone[a] *plus* cefotaxime, ceftriaxone, or a β-lactam–β-lactam inhibitor[b]
American Thoracic Society (Niederman et al., 1993)	Macrolide *plus* third-generation cephalosporin with anti-*Pseudomonas* activity[c]
British Thoracic Society (Finch et al., 1993)	Erythromycin *plus* second- or third-generation cephalosporin or ampicillin plus flucloxacillin

[a]Levofloxacin, sparlfoxacin, trovafloxacin, or grepafloxacin.
[b]Ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam.
[c]Ciprofloxacin or imipenem/cilastatin.

More recently, the Infectious Disease Society of America advocated the use of erythromycin, azithromycin, or a fluoroquinolone combined with a third-generation cephalosporin or a β-lactam–β-lactamase inhibitor (Bartlett et al., 1998). These guidelines are the first to incorporate the newer fluoroquinolones such as levofloxacin, sparfloxacin, or moxifloxacin, all of which have enhanced activity against *S. pneumoniae* (compared to first-generation fluoroquinolones) and appear to be effective against atypical pathogens as well (File et al., 1997).

Specific Pathogens

Streptococcus pneumoniae. The most commonly identified pathogen in severe CAP, *S. pneumoniae* has historically been sensitive to penicillins and cephalosporins. The emergence of drug-resistant *S. pneumoniae* (DRSP) calls into question the adequacy of current guidelines advocating the use of second or third generation cephalosporins. Although in vitro resistance has been associated with poor outcome in patients with DRSP meningitis treated with penicillin, the same does not

appear to apply to patients with pneumonia. Observational studies show no difference in outcome if pneumonia due to DRSP is treated with penicillins or third-generation cephalosporins (Pallares et al., 1995; Plouffe et al., 1996). Therefore, current guidelines for empiric treatment of severe CAP are adequate unless high levels of resistance (MIC >4 μmg/mL) are suspected on the basis of regional prevalence. In such cases, vancomycin, imipenem, or a newer fluoroquinolone should be considered.

Legionella pneumophila. There is little debate regarding the need to provide empiric coverage for *Legionella* in cases of severe CAP requiring ICU admission. Distinguishing *Legionella* pneumonia from other pneumonias can be difficult if not impossible on clinical grounds. Furthermore, *Legionella's* propensity for causing severe disease and the knowledge that delay in appropriate therapy significantly increases mortality (Stout & Yu, 1997) argue strongly in favor of empiric coverage. Erythromycin (1 g IV every 6 hours) is the drug of choice and the addition of rifampin is warranted for confirmed cases. Both azithromycin and the newer fluoroquinolones have significant in vitro and in vivo activity against *Legionella* and may become acceptable therapy in the future.

Nutrition

Critical illness of any kind precipitates a metabolic environment of increased energy expenditure and catabolism. Therefore, patients with severe CAP who may require mechanical ventilation for more than 24 hours should be provided with adequate nutrition. Enteral nutrition has several advantages over total parenteral nutrition (TPN). In patients with critical illness, it appears to support gut barrier function, reduce septic complications, and improve outcome compared with TPN (Minard & Kudsk, 1998). It is also less costly and obviates the potential for TPN-related catheter sepsis or liver disease. For these reasons, whenever possible, enteral feedings should be initiated within 24 hours of admission to the ICU. Parenteral nutritional support should be considered for patients with a nonfunctioning gut or those intolerant of enteral feeding such that the period of fasting does not exceed 5 days.

Complications of Severe Community-Acquired Pneumonia

Acute Respiratory Distress Syndrome

Definition

A relatively common complication of severe CAP is progression to acute respiratory distress syndrome (ARDS). This is a process of nonhydrostatic pulmonary edema and hypoxemia and is associated with an overall mortality rate of about 50% (Krafft et al., 1996).

Acute Respiratory Distress Syndrome versus Acute Lung Injury

ARDS is a severe form of acute lung injury (ALI). ALI is defined as a syndrome of inflammation and increased pulmonary capillary permeability associated with a constellation of clinical, radiographic, and physiologic abnormalities not explained by, but possibly coexistent with, left atrial hypertension (Bernard et al., 1994). The distinction between ARDS and ALI is made based on the degree of hypoxemia. In ALI, the Pao_2/Fio_2 ratio is 200 to 300 mm Hg, whereas in ARDS the ratio is less than 200 mm Hg.

Patients with severe CAP are at risk for ARDS, with a reported incidence of about 12%. Patients with CAP are at further risk for the development of ARDS if the course of their illness is complicated by sepsis, multiple transfusions, aspiration, or prolonged administration of high inspired concentrations of oxygen (Garberetal.,1996). The distinction between overwhelming pneumonia and ARDS can be difficult, particularly when diffuse radiographic infiltrates are present.

Treatment

Mechanical Ventilation. The goal of treatment for pneumonia complicated by ARDS is the provision of adequate gas exchange and a reversal of the underlying infection. This typically requires intubation and mechanical ventilation. Guidelines for mechanical ventilation of patients with ARDS are summarized in Table 5. Oxygen toxicity and ventilator-induced barotrauma or volutrauma are the main concerns in this patient population.

TABLE 5. Mechanical Ventilation and Acute Respiratory Distress Syndrome

Maintain Sao_2 at 90%
Attempt to minimize Fio_2 and limit plateau pressure to <35 cm H_2O
Permit hypercapnia if lower tidal volume required to limit plateau pressure
Titate PEEP empirically for best oxygen delivery at lowest PAWP and Fio_2
Tidal volume between 7 and 10 mL/kg
If oxygenation and ventilation continue to be a problem consider paralysis and/or prone positioning

PEEP, postive end-expiratory pressure; PAWP, positive arterial wedge pressure

Fluid Management. The role of fluid management in ARDS is somewhat controversial. Pulmonary edema develops at a lower pulmonary capillary hydrostatic pressure as the permeability of the alveolar capillary membrane increases. Therefore, intravascular volume overload should be avoided and careful diuresis may be undertaken to lower pulmonary artery wedge pressure without compromising cardiac output.

Corticosteroids. A pharmacologic means to attenuate the course of ARDS has been the subject of considerable research. The use of high-dose corticosteroids within the first 48 hours of ARDS has produced disappointing results in randomized trials (Bone et al., 1987). However, it appears that selecting patients during the fibroproliferative phase of ARDS (5 to 10 days after onset) for steroid therapy may be an effective strategy. Recent evidence suggests that methylprednisolone, 2 mg/kg daily followed by a slow taper, may reduce lung injury and improve survival in patients with late ARDS (Meduri et al., 1998).

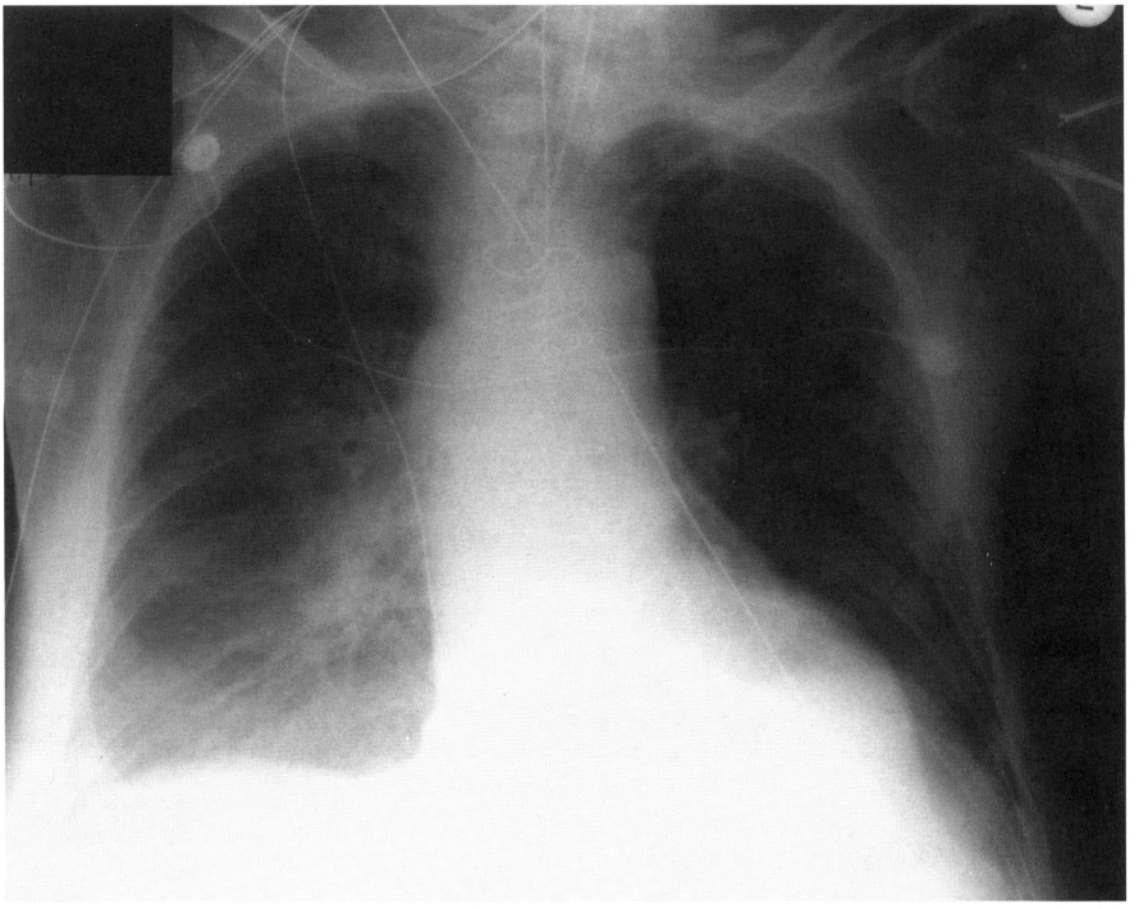
Prone Positioning. Some patients with refractory hypoxemia from CAP may benefit from prone positioning. The fact that prone positioning can improve Pao_2 has been known for many years (Piehl & Brown, 1976) but only recently has the mechanism of this improvement been determined. $\dot{V}/Q$ distribution in the lung improves mainly as a result of a shift of blood flow away from dependent shunt regions (Pappert et al., 1994). In patients with acute respiratory failure in whom mechanical ventilation has been optimized, prone positioning may represent a temporizing measure while the underlying infection is treated. However, whether this maneuver confers an overall survival benefit has not yet been studied.

Nitric Oxide. Nitric oxide (NO) is a highly reactive, endogenously produced molecule with many biological effects. In the lung, NO is a potent vasodilator that helps to maintain low resting pulmonary vascular tone. The administration of inhaled NO to patients with ARDS can result in a significant improvement in oxygenation without apparent adverse hemodynamic or systemic effects (Dellinger et al., 1998; Rossaint et al., 1993). Despite these acute physiologic improvements in patients the usefulness of inhaled NO in altering outcome in patients with ARDS appears doubtful, with two randomized trials showing no survival benefit from the administration of NO (Michael et al., 1998; Troncy et al., 1998).

Exogenous Surfactant. Administration of aerosolized surfactant is the mainstay of treatment for neonatal respiratory distress syndrome. There is evidence that ARDS is a state of both functional and quantitative surfactant deficiency. For these reasons, there is considerable interest in surfactant replacement as a means to improve lung compliance and attenuate alveolar collapse in the ICU. Despite these theoretical benefits, clinical studies examining exogenous surfactant administration have shown mixed results. One large randomized controlled trial by Anzueto et al. (1996) found that aerosolized surfactant failed to confer any significant short- or long-term benefit in patients with ARDS.

Line Sepsis

Patients in the ICU frequently have central venous and intra-arterial catheters to permit continuous hemodynamic monitoring. Despite the wealth of information these catheters provide, they are not without complications. Bacteremia, often from *Staphylococcus* spp., (coagulase positive and negative), is a common consequence of invasive monitoring and should be considered whenever unexplained fever, leukocytosis, or persistent systemic inflammatory response syndrome occurs. Routine replacement of indwelling catheters is not war-



A

FIGURE 2. (A) Supine portable chest x-ray in a patient admitted to hospital with pneumonia in the apical segment of the right lower lobe. A general increase in density of the right hemithorax was noted as the patient continued to spike fevers despite appropriate antibiotic therapy. (B) A CT scan confirmed the presence of a right-sided parapneumonic effusion. The fluid was cultured and grew *Pneumococcus*. After chest tube drainage, the patient's fever cleared and he made a full recovery. (*Continued*)

ranted in the absence of these signs. Nevertheless, the need for such invasive lines should be reviewed daily.

Empyema

Parapneumonic effusions are frequent complications of severe CAP. Pleural effusions may be difficult to appreciate radiographically, particularly in ICUs where daily chest radiographs are obtained in the supine position. When the patient is supine, the pleural fluid is spread over a greater area and therefore a greater amount of fluid must accumulate before it can be seen. The earliest sign is blunting of the costophrenic angle followed by an increased homogeneous density superimposed over the lung (Ruskin et al., 1987) (Figure 2).

These parapneumonic effusions should be managed in the same way as in patients outside the ICU, with the decision to initiate chest tube drainage based on information obtained from diagnostic thoracentesis. This procedure can be performed safely on patients who are mechanically ventilated. The use of ultrasound to locate the collection of fluid minimizes the likelihood of pneumothorax and is recommended. In a series by McCartney et al. (1993) the incidence of pneumothorax following thoracentesis in mechanically ventilated patients

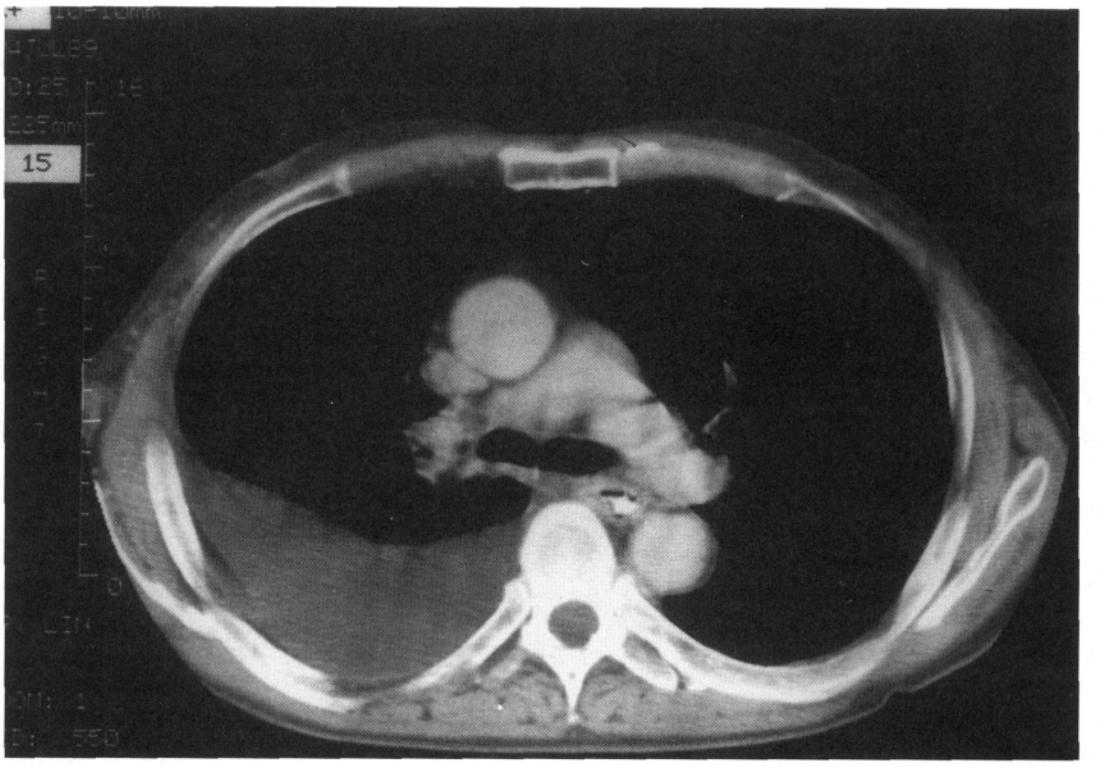


FIGURE 2. (*Continued*)

was 10% and these patients were successfully managed with a chest tube.

Prognosis

The mortality rate for severe CAP is about 25% (Torres et al., 1991; Leroy et al., 1995). This is similar to death rates seen in patients hospitalized with CAP but not requiring ICU management (Marrie et al., 1989).

Several studies have now examined independent predictors of mortality in severe CAP using multivariate analysis and recursive partitioning (Table 6). Several of these predictors, including a high simplified acute physiologic score and septic shock, simply reflect the severity of the underlying infection and may not be amenable to intervention. Interestingly, Leroy et al. (1996) demonstrated that failure to provide effective initial empiric therapy was an independent predictor of mortality, with a risk ratio of 4.94.

Summary

CAP is a common cause of ICU admission and continues to be associated with a significant mortality rate. Several large epidemiologic studies have established the importance of *S. pneumoniae, L. pneumophila,* and gram-negative bacilli as major pathogens in severe CAP. The provision of adequate tissue oxygenation with noninvasive or invasive mechanical ventilation, hemodynamic support, aggressive empiric antibiotic therapy, and vigilance for common complications represents the foundation of ICU management of severe pneumonia.

TABLE 6. Prognosis and Severe CAP

Author	Number of patients	Design	Predictors of mortality
Leroy et al., 1996	335	Retrospective	SAPS $\geq$ 12 Neutrophils $\leq$ 3500/mm^3 Delayed mechanical ventilation Immunosuppression OSF score $\geq$ 2 Ineffective initial antimicrobial therapy
Moine et al., 1994	132	Prospective	Septic shock SAPS > 13 *Streptococcus pneumonia* Enterobacteriaceae
Torres et al., 1991	92	Prospective	Radiographic spread of pneumonia Septic shock

SAPS, Simplified acute physiologic score; OSF, organ system failure.

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End-of-life Decision-making in Community-Acquired Pneumonia

KENNETH ROCKWOOD AND COLIN POWELL

Introduction

All people die, and many, especially the elderly, die of pneumonia. In some cases of death from pneumonia, the result is regarded as a tragedy; in others, it is regarded as a blessing. In this chapter, we discuss pneumonia in the context of end-of-life decision-making.

Difficulties in end-of-life decision-making arise broadly from two sources: complexity of patients' problems and uncertainty about patients' wishes. The problems of patients are often complex, resulting in uncertainty about their diagnoses, treatment needs, and, most importantly, their prognoses. The wishes of patients can be difficult to determine. This is due to their own uncertainty about what they want, cognitive impairment, personal and/or cultural barriers to articulation of their preferences, and competing preferences of patients and relatives.

An Approach to End-of-life Decision-making

Often, the most difficult aspect of end-of-life decision-making is to know when an event such as pneumonia actually represents the end of life. For the most part, terminal pneumonia arises in a setting that demands intentionally curative care. Here, however, we are concerned with those cases in which the merit of initiation or continuation of treatment is in doubt. Recognizing that the ethical principles of autonomy, nonmaleficence, and beneficence require specific knowledge if they are to be implemented, we propose a series of factors to consider in end-of-life decision-making.

Physician Attitude

Physicians' attitudes toward their roles in death and dying are informed by many considerations of principle and practice, and by life circumstance. One need only compare Osier's view over the course of his life and practice to witness a change from considering pneumonia as the "handmaiden" or "captain of the ship of death" (tuberculosis) to a view of pneumonia as "the old man's friend" (Berk, 1984). For our part, we both hold the conventionally religious view that a moral sense precedes reason, the conventional trinitarian approach to ethical decision-making (autonomy, beneficence, nonmaleficence), and a Canadian sensibility of tolerance and compromise. We reject both physician-assisted suicide and the routine institution of maximally aggressive treatment at all costs. Our point in this disclosure is threefold: to reassure the reader that nothing that we are proposing appears to us to fall outside conventional medical practice; to acknowledge that readers who do not share these precepts are unlikely to be persuaded by what we say; and to suggest that there is merit both in unhurried reflection on such matters by ourselves

KENNETH ROCKWOOD AND COLIN POWELL • Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

as physicians, and in the encouragement of such reflections in those whom we are privileged to teach.

We press the point of disclosure of our precepts a little further, however, in recognizing that we are likely to stray into areas that fall outside of other cultural norms, especially for some readers in the United States. We practice in areas where long-term tube feeding of nursing home patients is exceptionally rare (and outside our experience in the case of those with dementia) and where we have admitted patients to hospital to die under our care without antibiotic treatment of an underlying pneumonia of which we and they have been aware.

Assessing the Patient's Medical and Functional Problems

In assessing a patient with pneumonia, both predisposing and precipitating factors are important. The virulence of the organism and the medical state of the patient have been discussed elsewhere. We draw attention, however, to two important prognostic factors that might be overlooked: the patient's current and recent (2 weeks prior to admission) functional capacity and the presence of an "atypical" disease presentation, such as delirium or falls (Jarrett et al., 1995). Both are common among frail elderly people, and each increases the risk of death, institutionalization, and prolonged hospital stays. Nevertheless, precise prognosis of community-acquired pneumonia (CAP) in community-dwelling elderly patients remains difficult to determine, with variable evidence for the roles of age, comorbidity, and functional status (Lieberman et al., 1997; Marrie et al., 1985).

To extend prognostication beyond traditional medical diagnostic factors, it is necessary to take into account the functional state of the patient. For the elderly, this is accomplished through a technique known as comprehensive geriatric assessment (CGA) (Rockwood et al., 1998). Briefly, CGA is a standardized assessment of key assets and deficits as outlined in the frailty balance model, but in principle is applicable in other settings, such as cancer and AIDS, in which pneumonia is common and can be terminal.

Although a full CGA commonly takes 30 or more minutes in addition to the standard history and physical examination, useful prognostic information can be gained in just 1 or 2 minutes, by systematic inquiry around a few points. The most important of these is whether the patient currently is impaired in his/her ability for self-care at home. If that is the case, two questions must be asked. The first is what level of self-care impairment is present. Three broad categories are recognizable and form a hierarchy: complex self-care activities (such as handling money, taking medications, or using the telephone), intermediate self-care (e.g., bathing, walking outside, housework, meal preparation, shopping), and basic self-care (e.g., toileting, grooming, feeding) (Thomas et al., 1998).

Second, it is important to determine how long this degree of dependence has been present. As a rule of thumb, the information for these questions can be interpreted as follows: the greater the acute change in function, the worse the prognosis; and the worse the level of function, the worse the prognosis. Thus, a patient who was previously well who is now dependent in basic self-care has a worse prognosis than the patient with dependence in intermediate self-care, and both have a worse prognosis than a comparably ill patient without functional impairment. Both factors (dependence and worsening of function) are additive, and also add to medical prognostic factors and to the presence of so-called atypical disease presentations, such as delirium, falls, or immobility.

The principles and practice of CGA can be adapted to a number of circumstances and provide important insights that may become lost when focusing on, for example, organisms, organ systems, and medications and their metabolism. In this chapter, CGA will be illustrated by considering some prototypical cases. CGA has three functions. First, it seeks to translate pathology (physical, mental, or social) into function (e.g., self-care, domestic care, communication, mobility). Second, the process of CGA also identifies gaps in information required to undertake this translation accurately and reliably. Third, the result of CGA enables patients and their caregivers to implement the recommendations arising from the assessment (e.g., deciding to obtain more diagnostic information, establishing drug regimens, negotiating with providers of community services). By relating all this information to the frailty balance model, it is possible to identify why the balance has changed and how the perturbation

might be restored to a balanced, if somewhat still precarious, state.

Case 1: Frailty and Pneumonia

A 73-year-old former school teacher with established Parkinson's disease (controlled with an L-dopa preparation four times daily) lives alone in a two-story house. He has suffered two myocardial infarctions in the past 6 years and experiences angina when climbing the stairs. He has walked with a cane since he suffered a left hip fracture 2 years previously. He is independent in self-care although he takes 25 minutes to dress because of his Parkinsonism. For the past 2 years a private homemaker has done his housework and prepared a main meal 3 days weekly. On the other days he enjoys attending an adult day care program.

He develops a cough, nasal congestion, rhinorrhea, sore throat, hoarseness, and a fever. The cough produces greenish sputum and he complains of chest tightness that is distinct from his angina. Next he notices breathlessness on exertion and can no longer dress himself. This information is obtained from his homemaker who that morning finds him rather muddled and not his usual coherent self. She calls an ambulance and telephones his next-of-kin, a niece in New Jersey.

This patients' assets and deficits are summarized in Table 1 based on the frailty balance model. From the previous analysis we might deduce that adult day care could be the origin of the respiratory infection. We can predict that his hospital stay will be prolonged because of comorbidity, particularly one that affects mobility (Parkinson's disease, ischemic heart disease). Delirium is another adverse feature, and given the lack of detailed information about his premorbid cognitive function, some persistent cognitive impairment is possible (Rockwood, 1993). Because of all these factors, the pneumonia may be enough to result in permanent institutional (i.e., nursing home) care. Hence, his inpatient management must vigorously address his nonrespiratory problems if he is to return home.

TABLE 1. Case 1: Frailty and Pneumonia[a]

Assets	Deficits
Health	Illness
Hitherto controlled Parkinson's disease	Parkinson's disease
Previously intact cognition	Ischemic heart disease
	Past hip fracture
	Acute pneumonia with delirium
	Unknown predelirium mood
Attitudes and practices	Disability
No information regarding smoking/exercise or self-rated health	Walks with cane
	Angina when climbing stairs
Resources	Dependency
Presumed financial adequacy	Slow dressing, otherwise independent in self-care
No geographically close family	Help wtih housework and meal preparation (*shopping, banking?*)
Unknown social contacts (adult day care)	
Caregiver	Caregiver burden
Privately funded homemaker thrice weekly	*Unlikely*
	Lives alone

[a]Italics indicate inadequate information.

Case 2: End-stage Dementia and Pneumonia

An 83-year-old widow has been living with her supportive daughter and son-in-law and their children for the past 4 years because of increasing memory loss and inability to care for herself. Currently she is unaware of her urinary incontinence and resents attempts to bathe her or change soiled clothing. She exhibits day-night reversal, which is exhausting for the family. She is increasingly reluctant to eat in spite of her daughter's encouragement. Alzheimer's dementia was diagnosed 3 years earlier, and the family is well aware of its prognosis and likely terminal inanition and bronchial pneumonia. They have resources to keep her at home until the end. Following a winter cold, her daughter reports that she is chesty and wonders if she has bronchitis or even pneumonia. A visit from the family doctor confirms likely pneumonia (febrile, respiratory rate 30/minute, mild but definite flaring of *alae nasi,* apex rate 105 regular, blood pressure 130/90 mm Hg lying down, right basal crackles).

The patients' assets and deficits are summarized in Table 2. Appropriate care (including treatment of infections) of demented subjects generally improves their quality of life (and possibly its duration). However, at some point in the progression of

TABLE 2. Case 2: End-Stage Dementia and Pneumonia[a,b]

Assets	Deficits
Health	Illness
Physically well until recently	Acute pneumonia
	Severe dementia
	Possible superadded delirium
Attitudes and practices	Disability
Unknown	Urinary incontinence
Resources	Dependency
Supportive immediate family	Virtually total
	Needs help with feeding
Presumed financial resources	
Other social contacts/ relief for principal caregiver?	
Caregiver	Caregiver burden
Supportive daughter and son-in-law	Caregivers at risk?
	Are there other children?
	What is the grandchildren–patient relationship?

[a]Italics indicate inadequate information.
[b]From Reisberg et al., 1982.

the dementia such a course becomes inappropriate. Palliative terminal care is needed. Pulling patients back "from the brink" only for them to return within a few weeks should be avoided.

The diagnostic and management dilemma of end-stage dementia with supervening bronchial pneumonia is as follows: Is this *the* terminal bronchial pneumonia? It is reasonable to conclude from the history and examination that this is end-stage dementia (Reisburg et al., 1982), although this must always be verified. Commonly, patients present with delirium and their premorbid cognitive function is unknown. In such a situation urgent treatment of the pneumonia is required, with the expectation that the delirium will clear as the pneumonia resolves (Rockwood, 1993). Often, the history of chronic cognitive impairment is recognized later, which if available at the outset might have tempered the initial therapeutic vigor.

The diagnosis and prognosis of the patients' end-stage dementia overshadows all other investigations and treatment. For example, it would be inappropriate to try to glean her health attitudes and practices and further investigation (e.g., white cell count, chest x-ray) may not be helpful in her management; indeed they could disturb her further. The immediate issue is to decide whether to treat her pneumonia with antibiotics. Distressing productive purulent sputum can be diminished with antibiotics which are therefore administered for a palliative rather than a curative effect. The particular issues in palliation for this patient are pain (e.g., pleuritic), exhaustion, immobility (pressure sores, constipation), incontinence, and oral care (dehydration).

Given that one is unable to establish coherent communication with the patient, what options can be offered to the family? Is the family capable of providing terminal care for this patient? Do they desire this? Is this solely the daughter's wish? What is the role of the son-in-law?

In considering how terminal palliative care might be offered at home, in addition to the family's (i.e., largely the daughter's) role, it is likely that daily home care nursing and thrice-weekly visits from the family doctor will be required in the first instance. Usually the family's appreciation of such attention will greatly outweigh the apparent inconvenience of the house calls; often less than 10 minutes is needed to review control of symptoms, encourage patient and family (and nurse), and continue preparation for the patient's death. The availability of a physician willing to provide supportive palliative care in the patient's home is a major determinant of whether a patient receiving community-based home care dies at home or in hospital (Fried et al., 1999).

Case 3: A Fit Elderly Man with Pneumonia

A golfer aged 76 years cares for his wife who is 73 years old and bedridden following a stroke 2 years before. A daughter living nearby visits twice weekly to help him bathe her mother. He is independent in his self-care and domestic care. He says his only vice is an evening postprandial cigar and Laphroiag, which is a brand of Scotch. He proudly avoids the healthcare system himself although he values his family doctor's attendance upon his wife. This year he again refused a flu vaccination although he insisted on this for his wife.

When a flu epidemic sweeps his locality, he is an early victim. His sudden incapacity increases the need for domestic help that the community home

care program is unable to supply. The flu rapidly goes to his chest and his sudden inability to help his wife as he has done makes him depressed, guilty, and hopeless. He insists on staying at home but clearly is deteriorating daily (i.e., looks ill, raised temperature, respiratory rate 25/minute, tachycardia 110 regular, exhaustion after minimal effort, difficulty getting around the house, new nonproductive cough, new crackles on auscultation).

This case is included, but without CGA analysis, as an example of an apparently medically straightforward situation, although one hopes the patient's wife's predicament is recognized and managed. This factor is likely to be the key to his effective treatment.

The functional assessment of elderly patients who have chronic multi-organ system failure can be complex, and when doubt exists, a consultation with a specialist geriatric service can be helpful (Stuck et al., 1993). However, a study from Pittsburgh provides a cautionary tale about not getting too involved in the process of assessment. In this study, no treatment or other intervention beyond the assessment was carried out in one third to one half of cases prompting referral (Silverman et al., 1997).

Assessing a Patient's Capacity to Consent to Treatment. There are no universally held standards for the assessment of a patient's capacity to consent to the initiation of specific medical treatments. Not surprisingly, therefore, a recent review notes considerable divergence of practice (Fellows, 1998). Nevertheless, several principles appear to be widely endorsed, as illustrated in Table 3.

Competence is not an "all or none" phenomenon, so the capacity to consent to treatment is recognized as one sphere of competence among many (e.g., testamentary capacity, competence to drive). The context of decision-making can vary, and different contexts can influence competence. For example, a delirious patient can be competent in the morning, and not in the afternoon. Patients with mild cognitive impairment or mood/anxiety disorders may be competent to make decisions that have been presented in calm environments in their own language by people that they trust, but quite unable to do so if any of these conditions are absent. Similarly, patients must be able to make an informed choice between the specific options which are available. In every circumstance, consent must be given voluntarily.

Given the varying practices with respect to the assessment of competence (Fellows, 1998) a "sliding scale" of inferences about competence may be appropriate (Drane, 1985). This argument proposes that the demonstration of a patient's capacity to judge must be more rigorous as the risk of harm becomes greater. The highest standard of evidence about capacity is the patient's ability to give a reasoned account of his or her decision. A reasoned account means a logical argument, or one that is at least self-sustained and consistent with the cultural norms of the patient or with the patient's stated or inferred set of values. "Reasoned" does not necessarily mean "reasonable" to another. The patient who refuses amputation to avert life-threatening toxemia because of an unacceptable distortion of body image and consequent loss of self-esteem is demonstrating a reasoned argument. The patient in a similar predicament who refuses an operation on the grounds that being one-legged will preclude effective escape should the Martians land is not demonstrating a reasoned argument. Both may appear unreasonable to the interrogating physician. The first patient is competent, the second is not. There is no ethical requirement that the patient's values be shared by the physician, although it is widely accepted that no physician need be party to a course of treatment which he or she believes to be medically and morally wrong.

Sometimes the request of a patient's family that active treatment be withheld is a form of neglect. An elderly person is defined as being neglected when he or she is left alone when not able to

TABLE 3. Guidelines for Assessment of Competence[a]

Competence is not "all or none."
The context of decision-making can variously influence competence.
Patients must be able to make and communicate an informed choice.
The choice must reflect the specific options that are available.
The patient need not remember the decision.
Reproduceability of the decision, if forgotten, lends credence to its validity.
Consent must always be given voluntarily.

[a]Modified from Fellow, 1998.

provide himself/herself the services necessary to maintain physical and mental health, or when he or she "is not receiving those services from a responsible caretaker" (Lachs et al., 1998). Such a judgment therefore rests both on a determination of competence and an understanding of the patient's circumstances of care prior to hospitalization. As with other information required for the proper execution of the ethical obligation to the patient, it is apparent that a multidisciplinary approach is necessary to obtain, evaluate, and act upon comprehensive intelligence.

Advance Directives

The use of advance directives has been the subject of considerable study, and of advocacy (Singer et al., 1999). In many countries, there appears to be a substantial risk that, without adequate consultation, patients will receive care at levels that are not consistent with what they or their families otherwise would have wished (Molloy et al., 1991).

Epidemiology of Resuscitation in Healthcare Institutions

Much information about the epidemiology of resuscitation orders in health care institutions comes from U.S. sources and this arises largely from federal and state legislation designed to force institutions and professional caregivers to take into account patients' wishes and preferences for their future, particularly end-of-life care (Fader et al., 1989; Stewart & Rai, 1990).

Such legislative enthusiasm has probably increased the prevalence of "do not resuscitate" (DNR) orders and related discussions. Using this legislation as the experimental intervention and relying on before-and-after methodology, Holtzman et al. (1994) found an increase from 12% to 37% of documented DNR orders between 1984 and 1988 among nursing home Medicaid patients in a Minnesota county; Miller and Cugliari (1990) described an increase in policies concerning withdrawing or withholding treatment from 19% to 26% between 1986 and 1988 in New York state nursing homes. They also described an increase in advanced directives from 25% to 35%. Bradley et al. (1988) found that documented discussions about future treatment wishes (principally concerning life-support issues) increased from 20% to 37% in Cincinnati nursing homes. Teno et al. (1997a) surveyed nursing homes in ten states in 1990 and 1993 and found an increase in DNR orders from 31% to 52% and in living wills from 4% to 13%, but found no change in "do not transfer to hospital" orders or in orders to forego artificial hydration and nutrition. These studies often report considerable and unexplained geographical variation. Levin et al. (1999) found that 74% of nursing home patients (413 residents of 20 homes) had DNR orders and 32% had advance directives, but only 29% reported discussions with their doctor about life-sustaining treatment (i.e., almost half of the residents with "no cardiopulmonary resuscitation" (CPR) orders who did not have cognitive impairment and could be interviewed reported having no such discussions).

By allowing DNR orders this legislation established the provision that CPR would be attempted unless there was an order to the contrary. Much of this reflects the American thinking of the 1980s (e.g., Miles & Ryden, 1985). Currently there is a trend toward policies whereby CPR is considered a treatment option only for selected subjects for whom it is likely to be advantageous (Johnson 1998; Bruce-Jones, 1996; Fisher, 1989; Gordon & Cheung, 1991). The poor success of CPR, particularly in nursing home patients, is hardly surprising when one recalls that it was introduced to control arrhythmia, especially ventricular fibrillation, in a relatively undamaged myocardium. This is not the case in most older patients, especially institutionalized ones, among whom significant ischemic heart disease with accompanying cardiorespiratory comorbidity is common. Applebaum et al. (1990) studied 115 nursing home patients subjected to attempted CPR and found that 102 were dead on arrival at the hospital and 13 died within 5 days. They concluded that "the benefits of cardiopulmonary resuscitation in nursing homes are extremely limited."

Unfortunately, a recent paper shows no change in the expectations of CPR. Kaufman's careful ethnographic study of ICU deaths in elderly patients in one midsize U.S. urban hospital records some disastrous horrors based apparently on the assumption that "hospital policy across the United States dictates CPR use for cardiac arrest on all patients unless the patient or surrogate strongly advocates

otherwise ..." (Kaufman, 1998). There was acknowledgment but no application of the doctrine of medical futility, which may have precluded these horrific (and expensive) sagas. Kaufman (1998) recognized the "technological imperative" that medicine imposes upon diagnosis and management of acute illness and hence so often "the option of stopping" only emerges after "an obviously downward course" which could and should have been avoided.

In less litigious societies it has not been found necessary to "allow" doctors not to assault patients with treatment known to be useless, and indeed harmful—"a process most of the world's people would consider a barbaric and futile assault on a dying human" (Solomon, 1990).

The Use of Advance Directives to Help Guide End-of-Life Decision-making

In the United States, a large controlled trial to improve care for seriously ill hospitalized patients was carried out under the acronym SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) (Teno et al., 1997c). The intervention was coupled with legislation, in the form of the Patient Self-Determination Act. The results must have been disappointing to the investigators, who found that, following implementation of the intervention, there was no difference in the rates of documentation of patient preferences, discussions about resuscitation, DNR orders, and attempts at resuscitation. Few patients discussed their treatment preferences with their physicians, most physicians were unaware of whether their patients had completed advance directives, and there was no impact on healthcare utilization in the intervention group (Teno et al., 1997b,c). There appears to have been no effective way to prevent dying patients from being caught in the medical machinery of treatment, even when the treatment was not likely to have been effective, or, indeed, had been rejected. An accompanying editorial well summarized some of the frustration felt by the investigators, who largely faulted poor physician–patient communication for the negative outcome. The editorialist's sense, in quoting from a book titled *What This Patient Needs is a Doctor,* appears to have been that it is not just a matter of communication, but also a lack of physician advocacy in helping to allow better dying (Fins, 1997). Quoting from the same book, the editorialist cautions against confusing the research surrounding advance directives with their potential effectiveness in the right hands. Subsequent analysis of the SUPPORT data has suggested that local health system practices have much more influence on the place of death than do patient preferences (Alemayehu et al. 1991; Pritchard et al., 1998).

In this context, it is interesting to note that a parallel effort, with a somewhat different result, took place in Oregon. There, a considerable investment was made in the development and use of a standardized statement of patient preference, constructed as a physician order form (Tolle, 1998; Dunn et al., 1996). This form, known as the Physician Orders for Life-Sustaining Treatment (POLST), records patient wishes and is used throughout Oregon. It is credited, in part, in that state having the lowest rates of in-hospital deaths (about 31% dying in hospital, compared with more than half elsewhere) (Tolle, 1998). Remarkably, in a study of POLST regarding CPR in 180 nursing home residents, treatment preferences were found to have been respected in each case (Tolle et al., 1998). In a commentary on the latter study, it was noted that these results may be peculiar to the circumstances in Oregon at the time: "when the threat of legalization of physician-assisted suicide ... was spurring a number of other efforts to improve and enhance the quality of medical care for dying patients and their families" (Teno, 1998). Clinical experience suggests that compliance by acute care hospitals with advance directives originating in the community is usually not as high, and there is some evidence, apart from the SUPPORT experience, to suggest that carryover of directives between institutions remains less than adequate (Ghusn et al., 1997b).

The Canadian experience, as reported thus far, parallels the SUPPORT results. Despite wide variation in the practices of long-term care institutions, and an appreciation that many policies were ineffective (Gordon & Schwartz, 1996), the introduction of a comprehensive healthcare directive had no impact on healthcare utilization (Molloy et al., 1997). Although an earlier study by Molloy and colleagues found no impact on healthcare utilization (Molloy et al., 1997) a more recent randomized

controlled trial of the implementation of an advanced health care directive in nursing homes using Molloy's *Let Me Decide* with trained health care facilitators (Molloy & Mepham, 1996) reported fewer hospital admissions and less use of health care resources and hence was cheaper (Molloy et al., 2000).

The Oregon experience and the background to SUPPORT nevertheless constitute a cautionary tale. There is societal apprehension about a medically driven imperative for unwanted and inappropriate intervention that is so great that physician-assisted suicide is seen by many as a necessary remedy. Physicians seeking some middle ground between "life at all costs" and physician-assisted suicide would do well to learn and practice the principles of palliative care (Twycross, 1990).

There is evidence that, in the setting of a nursing home, where diseases have expressed themselves in significant disability, where patients are surrounded by others with similar disabilities, and where death is not uncommon, there is a tendency for advance directives to favor less treatment, and even to move toward less intervention (Molloy et al., 1997; Berger & Majerovitz, 1998). Nevertheless, a preference for intravenous antibiotics remained, as they were seen as life-sustaining, and likely neither to be permanent nor to induce disability (Molloy et al., 1997; Berger & Majerovitz, 1998). When carers of long term institutionalized demented subjects were asked their wishes for the patients in the event of life-threatening situations, 46% wanted cardiac resuscitation, 60% wanted intravenous fluids, 52% wanted intravenous antibiotics and 60% wanted oral antibiotics! The authors hoped that "improved discussion ... may be helpful" (Potkins et al., 2000).

Stability of preferences about end-of-life decision-making has also been described in community-dwelling, but functionally impaired, elderly Dutch people, where practices that would hasten death are an option (Sullivan et al., 1998). A New Zealand study of community-dwelling elderly people admitted to hospital offers further insight into the translation of patient preferences concerning end-of-life decisions into documentation on the medical record: While 84% of patients wanted to make decisions regarding cardiopulmonary resuscitation, only 57% wanted these decisions recorded in the medical record, and only 43% wanted their primary care physician to be aware of the decision. The themes of patients not wanting to give up too soon, and of physicians attempting to accommodate these wishes, is also reflected in a Texas study of Veterans Administration patients, in whom a high prevalence (82%) of discussion about CPR orders was documented. Most patients focused on limiting, rather than completely foregoing, resuscitation attempts (Ghusn et al., 1997a).

A widespread criticism of the discussions between physicians and patients/families has been the failure to communicate—or sometimes to cope with—clinical uncertainty about treatment (Tulsky et al., 1998). In one study of nursing home residents (again following passage of the Patient Self-Determination Act) no discussion about end-of-life care occurred in most cases, and, where discussion was initiated, it did not go beyond consideration of CPR (Bradley et al., 1998). In another study, physicians were observed to engage in these discussions for an average of 5.6 minutes, during which they spoke about two thirds of the time, with options for the treatment or nontreatment of intercurrent illness, such as pneumonia, usually not mentioned (Tulsky et al., 1998).

There is a fear among patients that "no resuscitation" too readily translates into "no treatment." It is possible nevertheless to distinguish, in practice, between full care, including intensive care, to the point of death, with and without attempting CPR. An American national survey of end-of-life care for critically ill patients reported that the majority who died did not have CPR initiated (Prendergast et al., 1998).

Patients in Whom Potentially Life-sustaining Treatment Seems Futile

Many physicians will be familiar with cases in which their assessment obliges them to conclude that no curative treatment can be effective, so that any such attempt would be futile. Where the patient and family concur, there is not likely to be controversy or the need for further discussion about cure, and everyone's attention can be turned to palliation. When disputes arise, decisions can be agonizingly difficult, especially if refracted or distorted through the prisms of the courts or the media.

Although some commentators have concluded that because futility cannot be precisely defined, it does not exist in any meaningful or knowable sense (Truog et al., 1992), others recognize both grades of futility and the inherent uncertainty in reasoning from the general to the particular (White, 1994). In Canada, there appears to be strong support for the view that demands for futile therapy are better construed as demands for inappropriate therapy, with which a physician is not obliged ethically to comply. This formulation attempts to sidestep the "two morally distinct cases" that together comprise what has been described as futility: demand for ineffective treatment and demand for treatment that supports a controversial end (e.g., permanent unconsciousness) (Weijer et al., 1998). However, that clinical uncertainty often invalidates such neat distinctions, so that gradations again become important: for example, in the second "morally distinct case," how certain is the permanence of the unconsciousness?

Physicians appear to have an operational sense of when requests for medical treatment are unreasonable. In a postal survey of VA physicians in the United States, approximately 9 in 10 said that they would attempt to change a patient's mind if a request for treatment was felt to be uninformed or not medically reasonable (Markson et al., 1997). Moreover, it has been demonstrated that physician counseling can help resolve patients' apparently conflicting demands between not wanting CPR withheld (interpreted as a form of "giving up") and not wanting aggressive therapy when there is little chance of a favorable outcome (Murphy et al., 1994).

A physician who believes that a proposed course of –treatment is futile should seek the opinion of an independent colleague. If the colleague concurs, or if the attending physician remains unpersuaded of the merit of treatment, it is best to withdraw from the case, providing that suitable alternative arrangements for the care of the patient can be made.

Manos and Marrie (1999) studied 712 consecutive patients with community-acquired pneumonia at low risk for mortality. They found that a third needed help during the 90 days following diagnosis and that two thirds of the caregivers who were employed experienced "at least moderate interference" with their work during the caring period. Families and friends are the principal resources for caring for frail or disabled elderly people. Families may not reliably indicate patients' preferences concerning resuscitation (Uhlmann et al., 1988) or high-risk procedures (Ouslander et al., 1989). It is important to distinguish between a patient's wishes and a family's wishes. No doctor is obliged to undertake harmful or futile treatment at the insistence of a family member. Families may be divided at this point. Those who have had less contact with the patient in the recent past may be determined to restore the situation to what it was when they last saw the patient (Molloy et al., 1991). Professional caregivers often have little time to help such family members traverse the clinical and emotional ground to bring them to the present situation and dilemma.

The situation can be particularly difficult when physicians must make decisions for incompetent patients who do not have advance directives, even when the family is united in its view. The physician must distinguish between the wishes of the patient, the family, and the staff, and the obligation is to try and understand what the patient, when competent, may have wanted. Family members in these circumstances can be distressed by the claim (implicit or otherwise) that the professional caregivers have a better understanding of what the patient, in his or her current state, actually wants (Watson et al., 1997). In such a case, the physician should also elicit, in addition to the family's preference, evidence about the patient's anticipation of such an event. Was a similar circumstance witnessed with a close relative or friend? What comments were made at that time? In a Danish study, relatives generally wanted more aggressive intervention than did staff members (Moe & Scholl, 1997). Ironically, in cases where patients were competent (and thus any differences moot) there was little disagreement between patients, families, and staff members with regard to the most appropriate level of treatment.

Providing Palliative Care

Palliative care has historically followed the cancer paradigm of three stages: curative (where the objective is the removal or reversal of pathology); palliative (where symptom control is obtained with return to usual function at least for some time);

and terminal (where symptom control and preparation for death are the aims). In the past decade palliative care has come to mean these latter two stages with "terminal" thought, perhaps too intimidating a label for terminally ill patients. Replacing "symptom" with "problem and need" may provide a more pertinent view of the patient's predicament (Corner, 1997).

The cancer paradigm also assumes a relatively short trajectory, with the terminal phase taking weeks or months in contrast to other life-threatening chronic illnesses (e.g., congestive heart failure, Alzheimer's disease) which might take months to years. In practice, palliative care services have focused on cancer and more recently AIDS. Sometimes, other dying patients have not been viewed as appropriate for admission. For many years it has been known that "discomfort was not the greatest in patients dying from cancer. Patients dying from heart failure, renal failure or both had most physical distress" (Hinton, 1963). The care of dying patients must take into account what is already known to be effective. For example, the SUPPORT study found that 50% of those dying in hospital experienced pain rated as moderate to severe at least half the time in their last 3 days of life. A recent review concluded that "comprehensive, inter-disciplinary palliative care is the standard of care for persons with progressive, advanced disease for whom prognosis is limited and the focus of medical management is quality of life" (Quill et al., 1998). Although palliative care units provide exemplary care for the dying, the move toward professional palliative care can be a double-edged sword. This is not to speak against the tremendous advances in care and knowledge that have been developed by specialists in palliative care, but simply to acknowledge that care of the dying cannot be narrowly circumscribed.

Techniques of Palliative Care

In a recent comprehensive review of pneumonia in long-term care facilities no mention is made of which patients are best managed palliatively nor of the content of such palliative care (Muder, 1998). Practical methods of quality assurance performance monitoring have been proposed for terminal care in U.S. nursing homes, and would appear to have broad application (Table 4). The widespread promulgation of such guidelines may provide a balance between the appropriate treatment of dying patients in a familiar environment and the development of hospice care.

TABLE 4. Guidelines for the Provision of Palliative Care[a]

Ascertainment and documentation of patient wishes or advance directives
Relief of pain
Relief of dyspnea
Relief of other uncomfortable symptoms
Provision of psychological and social support
Avoidance of interventions or procedures not wanted by the patient
Maintenance of the patients' standards of hygiene
Counseling of patient, family, and friends
Follow-up bereavement counseling, including recognition of hidden losses (e.g., the lover of an AIDS patient)

[a]Modified from Kay et al., 1994; Parkes, 1998.

In patients dying from pneumonia, common symptoms are dyspnea and cough (Lane, 1997) and the "death rattle." Dyspnea is reported differently by different observers, with relatives reporting more dyspnea than professional caregivers. The general population commonly reports respiratory symptoms of chronic obstructive pulmonary disease, such as wheezing, cough, and shortness of breath (Littlejohns et al., 1989). Superimposed on these symptoms may be the patient's anxious response to breathlessness—hyperventilation, or "behavioural breathlessness" (Howell, 1990). This may develop into a vicious circle of shortness of breath and subsequent fear of suffocation leading to increased anxiety with exacerbation of dyspnea.

Some of the mechanisms giving rise to dyspnea may be reversed (e.g., correctable hypoxia; lung compression by fluid relieved by controlled thoracentesis; nasal intermittent positive pressure to aid weak respiratory muscles). Intense anxiety can be reduced with instruction in relaxation techniques, massage, and other complementary approaches. Sitting up in a supported position with a nearby humidified fan directed across the patient's face can ease a patient's distress regardless of the arterial biochemistry (Schwartzstein et al., 1987). Persistent smoking may alienate the family's (and

professionals') continued support. Explanation of the pattern and prognosis of Cheynes–Stokes respiration will help relatives understand and accept the episodic apnea.

Cough can arise from different mechanisms that need to be identified and managed. Airways inflammation may require steroids and antibiotics; a postnasal drip may need topical attention; an obstructive mass may need palliative radiotherapy; acid gastroesophageal reflux may need histamine-2-receptor blockers or proton pump inhibitors; excessive respiratory secretions may need hyoscine; angiotensin-converting enzyme inhibitors may need to be discontinued; and cough of presumed central origin may need to be suppressed with opioids. Disturbing excessive purulent sputum may respond to antibiotics given for symptom relief rather than cure. Conversely, a cough with sticky viscous phlegm that is difficult to expectorate may be relieved by humidification, expectorants, or physiotherapy (Selsby, 1989).

Three particularly distressing terminal phenomena affect patients with CAP and their caregivers: "death rattle," respiratory panic, and agonal breathing.

Death rattle evocatively describes the harsh gurgling sounds resulting from air passing through oropharyngeal secretions, which the dying person is unable to clear unaided. It occurs in the patient's last hours or sometimes days. This is a distressing symptom, the appropriate management of which is still under investigation (Hughes et al., 1996). If the patient is conscious, upper airway suction may bring relief, although it may itself cause momentary distress. If the patient is unconscious, which is more common, a change of position, gentle oropharyngeal suction with a soft catheter, and administration of anticholinergic agents (e.g., atropine 0.3 mg subcutaneously, hyoscine 0.4 mg, scopolamine 0.6 mg by subcutaneous injection or transdermally [Dawson, 1989] may relieve the rattle). The classic anticholinergic side effects (e.g., glaucoma, ileus, overflow incontinence) are no longer a concern. The conscious patient may be aware of an intense dry mouth and this can be assuaged with appropriate oral hygiene.

Respiratory panic describes paroxysmal respiratory distress of rapid onset. This may result from airways obstruction, cardiac or bronchial asthma, or pulmonary embolism. It is best managed by parenteral opiates and benzodiazepines (Ahmedzai, 1993).

Agonal breathing, distinct from Cheyne–Stokes respiration, is the labored gasping respiration that may occur in the conscious or unconscious patient. In the latter situation, there may be a sudden gasp after a prolonged apneic spell. Families can be reassured that the patient is totally unaware of his or her predicament and the phenomenon is essentially the last effort of the patient's respiratory center to sustain life. Patients' families need not be frightened by these last breaths, especially if they are appropriately counseled. Families can often understand the final breaths as an act of cessation.

Involving informal caregivers in helping the patient encourages a calm environment, puts patients and caregivers at greater ease, relieves patient's symptoms, and increases the caregivers' contribution to the patient's welfare, which can be a powerful aid in the subsequent grieving.

Drugs may be indicated to relieve symptoms of reversible airways obstruction, heart failure, pulmonary embolism, or pleurisy. Palliation of dyspnea may require respiratory sedation, which suppresses *awareness* of breathing and breathlessness rather than the actual ventilatory drive. Anxiolytic agents may be helpful although they can aggravate or cause delirium and may mask underlying pain and hence avert necessary analgesia. Oxygen therapy is often given for symptomatic relief and has been advocated as a way to show that "something is being seen to be done" (Bruera et al., 1993). However, in patients who chronically retain carbon dioxide, the loss of hypoxemic ventilatory drive upon uncontrolled oxygen therapy can produce dangerous apnea.

Opiates produce both cerebral and respiratory sedation as well as pulmonary vasculature dilation and redistribution. All these effects can help relieve the patient's perception of breathlessness caused by lung and heart disease. Although opiates are usually given as analgesics, they may be given intermittently to relieve exercise-induced dyspnea. The benefit of nebulized opiates in patients with severe obstructive lung disease has not been confirmed. Young and colleagues (1989) studied 11 patients in a double-blind, placebo-controlled, randomized crossover trial and found that inhaled morphine significantly increased endurance time. Beauford et al.

(1993) in a similar study concluded that nebulized opiates have no beneficial effect on exercise tolerance of patients with chronic obstructive lung disease. The bioavailability of nebulized opiates is 5% compared with 20% to 40% for orally administered opiates. In general, the palliative care literature, largely reporting uncontrolled cases, supports the use of nebulized opiates, whereas the respirology literature is negative.

Special Considerations in the Nursing Home Patient

Commonly, patients are transferred from nursing homes to hospital when pneumonia develops. If nursing homes were able to provide access to domiciliary radiography, intravenous antibiotic administration, and regular visits from family doctors (or nurse practitioners), a majority of transfers could be avoided and the patients could be managed appropriately in the nursing home (Turrell & Castleden, 1999). Fried et al. (1997) compared nursing home patients with pneumonia who were transferred to hospital with those who stayed in the nursing home. The nursing home was able to provide radiography, intravenous therapy, and on-site doctors. Patients were more likely to be transferred if their respiratory rate was over 40 per minute or if they were seen in the evening. The mortality rate was the same in both groups (12%), but in those who returned from hospital, activities of daily living had deteriorated 2 months later and more had died at 2 months compared with those who had remained in the nursing home. In an earlier paper Fried et al. (1995) advised that decisions about transfer to hospital should be discussed with patients and families *before* acute illness supervened, to encourage DNH (do not hospitalize) order.

Mylotte et al. (1998) found that patients with the same degree of severity of pneumonia can be successfully treated with intravenous therapy in a nursing home with a mortality rate comparable to those treated in hospital (30-day mortality: 21% in hospital, 24% in nursing home). One should remember that the U.S. nursing home, in contrast to the Canadian nursing home, admits patients for subacute care, where recovery, rehabilitation, and return home are expected (Zimmer & Hall, 1997). The availability of a physician willing to provide supportive palliative care in the patient's home is a major determinant of whether a patient receiving community-based home care dies at home or in hospital (Fried et al., 1999).

Decisions about the management of pneumonia reflect such programmatic considerations as we have outlined. The greatest challenge can be to ensure that policies allow management decisions to include or to forego antibiotic therapy, as deemed appropriate in each case. Attempts at curative care and attempts at palliation require skills that must be in place if the benefits of on-site management are to be realized.

Special Considerations for a Patient Dying at Home

In Western industrialized societies, many people die in hospital, despite their preferences to the contrary (SUPPORT Principal Investigators, 1995). Careful planning and judicious advocacy can help ensure that patient preferences can be effected. Two prerequisites allow dying at home to be a realistic option for a terminally ill patient (Blyth, 1990; Thorpe, 1993): assurance of prompt competent anticipatory clinical palliation and assurance that family and friends will not be unduly stressed physically, emotionally, or financially.

Skilled palliation is expected of the professional caregiver. In the case of community-acquired pneumonia, palliation demands the ability to detect and assuage breathlessness, chest pain, excessive sputum production, nonproductive cough, fever, possible rigors, and associated comorbidity (e.g., heart failure). Pervasive exhaustion is common and little needs to be done for this other than emphasizing to the patient and informal caregivers that unrealistic physical effort is not being demanded. For example, the exhausted patient should be allowed to sleep without being disturbed for exercise, beds can be moved downstairs to avoid stair-climbing, and visitors can be warned that the patient cannot be expected to entertain them. The professional caregivers also must intervene to prevent complications of immobility (e.g., pressure sores), poor oral hygiene and dehydration (e.g., parotitis), and incontinence (e.g., excoriated skin).

Many terminally ill patients opt for hospital admission in an attempt to relieve their informal

caregivers of the additional stresses of terminal care superimposed on chronic care at home. Similarly, informal caregivers seek hospital care at the end because of the need for respite from their own physical or emotional exhaustion, or because they believe that only in hospital can the patient obtain expert advice, attention, and medications. Families may be convinced that dehydration, if not relieved with intravenous therapy, always produces intense discomfort (Parkash & Burge, 1997) whereas frequent oral hygiene will relieve thirst—the only distressing symptom of dehydration—at this stage (McCann et al., 1994). The prospect of what to do at the actual moment of death may cause fear and anxiety in hitherto stoic caregivers and hospital admission relieves this distress. Without coercing these caregivers into continuing care in the home, it is possible to relieve their fears with information, preparation, the professional's presence or assured availability, and provision of necessary aids and equipment. Jurisdictions providing modern comprehensive community palliative care services have a great advantage in that care is not directly dependent on the patient's financial resources and the patient's family doctor and primary healthcare team have ready access to palliative care expertise (McWhinney & Stewart, 1994).

In situations where those at home have been properly prepared to expect and accept terminal bronchopneumonia (e.g., related to end-stage chronic obstructive airways disease, congestive heart failure, late-stage dementia, or advanced cancer), there is time to plan the terminal care without the urgency of a crisis and its consequential demand for instant resolution. Families and friends can be prepared to understand when delirium supervenes with failure to recognize family, when paranoia over trivial matters threatens to disrupt relationships, and when other apparent changes of personality can leave distressing last memories of the patient.

If dying at home is planned, then what to do after the death needs to be discussed (e.g., legal notification, removal of the body) so that well-meaning paramedics do not insist on resuscitation. The family member who is unprepared for a death at home may demand hospital admission and curative attempts (Molloy et al., 1991). Preparation can moderate well-intentioned but inappropriate requests. Care of relatives and friends before and during the death will reduce the likelihood of pathological grieving after bereavement. It will help forestall persistent recriminations about the right or wrong of hospital or home as the location for the death, having earlier discussed with them, and the patient where feasible, that there is no absolute right or wrong in this matter.

Summary

The care of patients who are dying is a special purview of physicians, but it requires an assessment both of medical needs and the psychological, spiritual, and social needs of the dying patients and their families. Most situations yield to a comprehensive assessment of the patient as a person with many needs and expectations, informed by principles that can result in demonstrably ethical decision-making, and accompanied by techniques that can provide for a peaceful death. The *Lancet* has published excerpts of interviews with leading physicians and scientists. One question asked of all is how they would like to die, and invariably the answer accentuates brevity, and an expectation of having led a full life. Where both conditions cannot be met, skilled physicians can provide important leadership in providing the type of care for others that they would want for themselves.

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14

Prevention of Community-Acquired Pneumonia:

Influenza and Pneumococcal Vaccines

JAY C. BUTLER, KEIJI FUKUDA, AND ROBERT F. BREIMAN

Introduction

Influenza and pneumonia are major causes of suffering and death throughout the world. Despite the substantial impact of antimicrobial agents and modern medical care on mortality, pneumonia and influenza were the sixth leading cause of death in the United States at the end of the 20th century and the leading cause of infectious disease deaths (National Center for Health Statistics, 1998). From 1972 through 1992, influenza caused up to 11,800 excess pneumonia and influenza deaths (i.e., number of deaths above the expected baseline number of deaths) and up to 47,200 excess all-cause deaths during each influenza season in the United States alone (Simonsen et al., 1997). *Streptococcus pneumoniae* (the pneumococcus) is the most common cause of community-acquired pneumonia (Marrie, 1994; Marston et al., 1997). Roughly one in five older adults with pneumococcal bacteremia will die from the infection, and case fatality approaches 40% among persons aged ≥85 years (Plouffe et al., 1996). Moreover, the global emergence of drug-resistant strains of *S. pneumoniae* emphasizes the need for prevention of pneumococcal infections through immunization. Vaccination against influenza and pneumococcal infection are among only a small number of preventive health interventions for the elderly that have been shown to be cost-saving (Office of Technology Assessment, 1981; Sisk et al., 1997; Nichol et al., 1994,1998). Thus, influenza and pneumococcal vaccination may be the most effective methods for preventing community-acquired pneumonia from both a clinical and economic standpoint.

Vaccines are under investigation to prevent community-acquired lower respiratory tract infection caused by other agents including respiratory syncytial virus (RSV), parainfluenza virus, and *Mycobacterium tuberculosis* (Murphy et al., 1994; Jacobs et al., 1997; Dudas & Karron, 1998; Breiman et al., 1999). The focus of this chapter is the prevention of community-acquired pneumonia through the use of two currently available vaccines—inactivated influenza virus vaccines and pneumococcal polysaccharide vaccines—with an update on developmental vaccines against influenza and pneumococcal infections. Other chapters in this volume provide reviews of the epidemiology, clinical features, diagnosis, and treatment of influenza and pneumococcal pneumonia.

JAY C. BUTLER • Arctic Investigations Program, Centers for Disease Control and Prevention, 4055 Tudor Centre Drive, Anchorage, Alaska 99508. **KEIJI FUKUDA** • Influenza Branch, Division of Viral and Ricksettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop A-32, Atlanta, Georgia 30333. **ROBERT F. BREIMAN** • National Vaccine Program Office, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop A-11, Atlanta, Georgia 30333.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Influenza Vaccines

Development of Inactivated Vaccines

Early influenza vaccines, based on live viruses grown in mice lung suspension, were tested in the 1930s (Chenoweth et al., 1936). The discovery that influenza viruses could be propagated in large quantities in chicken embryos led to the development and testing of inactivated whole-cell vaccines in the 1940s (Francis et al., 1945). Early preparations often caused systemic and local reactions, due in part to contamination with bacterial endotoxins. The introduction of additional purification steps to remove nonviral contaminants substantially reduced side effects (Couch et al., 1997). Vaccines prepared by disruption of viral components with ethyl ether or detergents (split-virus vaccines) and vaccines composed of partially purified viral surface proteins (surface antigen vaccines) further reduced the incidence of localized and systemic reactions after influenza vaccination.

Trivalent whole-virus, split-virus, and surface antigen inactivated influenza vaccines are currently available in North America. These vaccines generally contain viral hemagglutinin (HA) and neuraminidase (NA) antigens to two strains of influenza A and one strain of influenza B and are standardized to contain 15 μg of each HA per 0.5-mL dose. Formulation of influenza vaccines needs to be reconsidered annually, and one or two vaccine strains are usually replaced each year because of *antigenic drift.* In this process, minor antigenic changes resulting from mutations in genes encoding for the HA and NA lead to the emergence of antigenic variants. Immunity afforded by vaccination or previous influenza infection is reduced depending on the degree of HA or NA antigenic change among circulating influenza virus strains. Vaccine effectiveness can be markedly reduced when antigens in the vaccine and in circulating influenza strains differ greatly. Episodic major changes in the antigens also occur due to *antigenic shift;* that is, the appearance in human populations of a new subtype of influenza A virus bearing a novel HA or HA and NA combination. Only influenza A viruses undergo antigenic shift, which can occur by the reassortment of genes between human and animal influenza A viruses. Such reassortment is facilitated by the segmented influenza virus genome. Alternatively, newly reassorted strains my be transmitted to humans directly from animals. Most of the human population will have little or no immunity to the new strains that result from an antigenic shift. A novel influenza virus strain that can infect humans and be transmitted from person to person will have the potential to spread rapidly, resulting in a global pandemic of influenza illness. Vaccine composition is reviewed annually on the basis of intensive global surveillance designed to assess the prevalence of viral subtypes in circulation and to detect the appearance of new strains (Cox et al., 1994).

Effects of Vaccination

Immune Responses

Prevention of influenza infection following vaccination requires production of antibodies to homologous HA in both serum and respiratory secretions (Couch et al., 1997). In addition, antibodies to HA and NA can ameliorate the clinical severity of influenza infection. Vaccine-induced T-cell cytotoxicity may also reduce the severity of illness and play a major role in recovery from infection. Healthy children and young adults develop high levels of antibody to HA after vaccination, but the elderly and persons with certain chronic medical conditions may develop lower postvaccination liters (Centers for Disease Control and Prevention [CDC], 1999; de Bruijn et al., 1999). Peak antibody concentrations occur within 1 to 2 weeks after vaccination (Gross et al., 1997). Antibody response is less brisk and results in lower peak antibody levels among immunologically naive persons, such as young children, who have never previously experienced influenza infection or vaccination (Kilbourne, 1994). Duration of protection appears to be related to antibody concentrations 1 month after vaccination (Clark et al., 1983), but it is assumed that immunity rarely persists for more than 1 year (Kilbourne, 1994).

Clinical Impact

Randomized Trials The elderly, the very young, pregnant women, and persons with certain chronic medical conditions are at greatest risk for

severe illness and death due to influenza. Only one prospective, randomized double-blind trial of inactivated influenza vaccine has been conducted among the elderly (Govaert et al., 1994). Prior to recommendations for routine influenza vaccination for all elderly residents of the Netherlands, 1838 patients in family practices were randomized to receive a quadrivalent split-virus vaccine or placebo. Compared to patients who received placebo, vaccine recipients had a 50% reduction in serologically confirmed influenza and a 53% reduction in clinical influenza during a 5-month follow-up period.

In healthy subjects aged <65 years, influenza vaccines have been shown to prevent 70% to 90% of clinical influenza illness when there is a good antigenic match between the vaccine and circulating virus (Kilbourne, 1994; Davenport, 1961; Dowdle, 1981; Meiklejohn, 1983; CDC, 1999). Among healthy 30- to 60-year-old volunteers, the proportion of persons who shed virus during influenza season was 39% lower, on average, for those vaccinated with an inactivated, whole-cell influenza vaccine over a 5-year period compared with enrollees receiving placebo (Keitel et al., 1997). In a double-blind, randomized trial, working adults aged 18 to 64 years were assigned to influenza vaccination or placebo injection; those who received vaccine had 25% fewer episodes of upper respiratory illness, 43% fewer days of sick leave from work due to upper respiratory illness, and 44% fewer physician visits for upper respiratory illness compared with those receiving placebo (Nichol et al., 1995).

In a trial among healthcare workers, a group for whom vaccination is recommended primarily to reduce the risk of transmission of influenza virus to susceptible persons at high risk of severe disease, vaccine efficacy against serologically defined infection was 88% for influenza A and 89% for influenza B (Wilde et al., 1999). Vaccine recipients had 29% fewer days of febrile respiratory illness and 53% fewer days of work absence than did workers receiving placebo, although these differences were not statistically significant.

Epidemiological Studies. Estimates of influenza vaccine effectiveness depend on several factors, including the age and health of the study population, the prevalence of influenza infections, the interval between administration of vaccine and exposure to circulating viruses, the antigenic match between vaccine and circulating viruses, and study design, including the outcome being measured. Among persons aged 65 years and older, influenza vaccination reduces pneumonia and influenza hospitalization by 45% to 57% (Foster et al., 1992; Nichol et al., 1994). Furthermore, all-cause mortality among the middle-aged and elderly is reduced by 27% to 50% by influenza vaccination (Fedson et al., 1993; Nichol et al., 1998). In a meta-analysis of 20 observational cohort studies among the elderly, pooled estimates of influenza vaccine effectiveness were 56% for preventing respiratory illness, 53% for preventing pneumonia, 50% for preventing hospitalization for any reasons, and 68% for preventing death (Gross et al., 1995.) In nursing home elderly, influenza vaccination can be more effective in preventing serious complications (hospitalizations, pneumonia, and death) than in reducing primary illness (Arden et al., 1986).

Among younger adults, a retrospective assessment of a workplace influenza immunization program at the 3M Company's corporate, research, and manufacturing facilities showed that vaccinated employees took significantly less hours of sick leave than did unvaccinated employees (Olsen et al., 1998). The reduction in sick leave hours was greatest for younger women with two or more children at home, suggesting that the employees most likely to be exposed to respiratory viruses circulating in the community benefitted most from vaccination.

Cost-Effectiveness The cost-effectiveness of influenza vaccine can be expected to vary from year to year depending in part on the group under consideration and their risk for complications from influenza, the prevalence and type of circulating influenza viruses, and the antigenic match between vaccine and circulating influenza viruses. A large study conducted by the Office of Technology Assessment of the United States Congress found that influenza vaccination was cost-saving for people 65 years and older (Office of Technology Assessment, 1981). An analysis of an administrative database for persons aged 65 and older and enrolled in a Minnesota health maintenance organization during three influenza seasons in the early 1990s found that influenza vaccination resulted in a savings of $117 in

medical costs annually for each person vaccinated (Nichol et al., 1994). Further analysis over six influenza seasons showed that savings were greatest for elderly persons with chronic heart and lung disease but lower for healthy persons aged 65 years and older because of lower risk of complications requiring hospitalization in the healthier group (Nichol et al., 1998). Although younger adults are at lower risk for incurring hospital-related expenses during influenza illness, vaccination may also be cost-saving in this group. In a controlled trial of influenza vaccination among working adults aged 18 to 64 years, direct savings in medical costs were estimated to be $5.99 per person vaccinated, and indirect cost savings, primarily attributable to less work loss due to illness, were $40.86 per person vaccinated (Nichol et al., 1995). While it is generally accepted that influenza vaccine is cost-saving and cost-effective in the elderly, it should be noted that the cost-effectiveness of annually vaccinating all young and healthy adults has yet to be demonstrated.

Safety

Side Effects and Adverse Reactions

The most common side effect of influenza vaccination is soreness at the injection site, reported by up to 64% of vaccine recipients (Margolis et al., 1990; Govaert et al., 1993; Nichol et al., 1996). These local reactions generally are mild, last 2 days or less, and rarely interfere with the activities of daily life (CDC, 1999). Influenza vaccine has not been demonstrated to cause systemic symptoms (fever, malaise, and myalgia) among the elderly (Margolis et al., 1990; Govaert et al., 1993), but such reactions may occur in persons who have had no previous exposure to the influenza antigens in the vaccine (e.g., young children). When they occur, systemic reactions most often develop beginning 6 to 12 hours after vaccination and last for 1 to 2 days. Split-virus vaccine is less likely to cause febrile reactions in children; therefore, only split-virus vaccines are recommended for children aged 12 years and younger (CDC, 1999). Immediate hypersensitivity reactions, including systemic anaphylaxis, rarely occur after influenza vaccination. Most of these reactions likely are caused by residual egg protein from vaccine preparation.

In 1976-1977, a mass campaign to vaccinate the population of the United States against influenza A/New Jersey ("swine flu") was halted because of cases of Guillain-Barré syndrome reported among vaccine recipients. Estimates of the relative risk for Guillain-Barré syndrome during the 6 weeks following vaccination range from 3.96 to 7.75, representing approximately five to six cases of Guillain-Barré syndrome attributable to vaccination per million vaccinees (Langmuir et al., 1984). The number of cases relative to the interval between vaccination and onset occurred in a log-normal curve, suggesting a causal relationship between Guillain-Barré syndrome and the vaccine. During the years immediately following the 1976–1977 season, no association between influenza vaccination and Guillain-Barré syndrome was found (Kaplan et al., 1982). To date, only one study has indicated increased risk of Guillain-Barré syndrome after vaccination against influenza strains other than swine flu. In a review of 180 patients diagnosed with Guillain-Barré syndrome during the 1992-1993 and 1993-1994 influenza vaccination seasons, influenza vaccine had been administered during the 6 weeks before onset of neurologic symptoms in 19 cases; onset was 9 to 12 days after vaccination in 9 cases (Lasky et al., 1998). The overall relative risk of Guillain-Barré syndrome adjusted for age, sex, and season during the 6 weeks after influenza vaccination was 1.7 (95% confidence interval [CI], 1.0 to 2.8). This risk translates into approximately one additional case of Guillain-Barré syndrome per 1 million doses of influenza vaccine administered. The relative risk for persons aged ≥65 years was 1.5 (95% CI, 0.7 to 3.3), and no cases of vaccine-associated Guillain-Barré syndrome were observed among persons less than 45 years of age. Given that approximately 20,000 to >300,000 influenza-associated hospitalizations occur each year in the United States with up to 40,000 deaths (CDC, 1999), these data suggest that the risk of Guillain-Barré syndrome associated with influenza vaccination is substantially less than the risk of severe influenza, particularly for the elderly and other persons at high risk for serious complications from influenza.

In some studies, but not in others, influenza vaccination of persons with HIV infection has been associated with a transient increase in replication of

HIV in plasma or peripheral blood mononuclear cells for 2 to 4 weeks after influenza vaccinations (O'Brien et al., 1995; Fuller et al., 1999). However, the clinical significance of these transient increases in plasma "viral load" is unknown and similar increases in viremia have been observed after immunization with other vaccines (Stanly et al., 1996; Brichacek et al., 1996; Katzenstein et al., 1996). The effect of vaccines on HIV replication in persons on highly active antiretroviral therapies is also unknown. Case reports indicate that influenza can lead to severe complications in HIV-infected individuals (Safrin et al., 1990). A retrospective analysis of women enrolled in Tennessee's Medicaid program found that women with HIV infection had an elevated risk for cardiopulmonary hospitalizations during the influenza season, at least comparable to women with other conditions that placed them at high risk for influenza-related complications (Neuzil et al., 1999). Because influenza illness may be prolonged and complications may be more common among HIV-infected persons, available data suggest that benefits of vaccination likely outweigh potential risk among persons with HIV infection (CDC, 1999; U.S. Public Health Service/Infectious Diseases Society of America [USPHS/IDSA] Prevention of Opportunistic Infections Working Group, 1997).

Precautions and Contraindications

Persons with acute febrile illnesses generally should not be vaccinated until symptoms have abated (CDC, 2000). Inactivated influenza viruses used in vaccines are grown in egg cell culture; therefore, these vaccines should not be administered to persons known to have anaphylactic hypersensitivity reactions to eggs. For patients at risk for severe influenza illness and a history of anaphylaxis to eggs or to influenza vaccine components, options for prevention of infection include desensitization or use of chemoprophylaxis. One recent report describes safe vaccination of 83 children with clinical history of egg allergy confirmed by skin testing using a two-dose protocol (James et al., 1998). However, it should be noted that the vaccines used in this investigation contained no more than 1.2 μg/mL egg protein. Other commercially available vaccines may contain up to 2 log higher concentrations of egg protein and may not be tolerated as well. Other protocols for desensitizing patients have been published (Murphy & Strunk, 1985).

Recommendations for Use

The U.S. Public Health Service's Advisory Committee on Immunization Practices (ACIP) and HealthCanada's National Advisory Committee on Immunizations recommend annual influenza immunization for persons at increased risk for influenza-related complications and for persons who could transmit infection to persons at increased risk through occupational or household exposure (Table 1) (CDC, 2000; Laboratory Centre for Disease Control [LCDC], 1998). In the northern hemisphere, influenza transmission most commonly occurs during December through March; therefore, influenza vaccine is usually administered during the autumn (October through November). However, it is important to note that influenza vaccine should continue to be offered to unvaccinated persons at high risk for influenza-related complications even after this

TABLE 1. Groups for Whom Annual Influenza Vaccination is Recommended[a]

Persons at high risk for influenza-related complications
Persons aged ≥50 years
Residents in nursing home or other chronic care facilities
Adults and children who have chronic cardiopulmonary diseases
Adults and children with diabetes mellitus, renal dysfunction, hemoglobinopathies, immunosuppressive illnesses, or conditions requiring immunosuppressive medication
Children aged 6 months to 18 years who are receiving long-term aspiration therapy
Women who will be in the second or third trimester of pregnancy during influenza season
Persons who can transmit influenza to persons at high risk of serious influenza
Physicians, nurses, and other personnel at high risk of serious influenza
Employees of nursing homes and chronic care facilities who have contact with patients or residents
Providers of home care (e.g., visiting nurses and volunteer workers) to person at high risk
Household members (including children) of persons in high-risk groups

[a]From CDC, 2000.

period. In the tropics, influenza can occur throughout the year and in the southern hemisphere, most influenza transmission occurs during April through September. Therefore, persons traveling to regions where influenza transmission is likely should review their influenza vaccination histories, and if the vaccine is available, persons in high-risk groups should receive the most current vaccine prior to departure (CDC, 1999). Influenza virus isolates in the initial phases of an epidemic are often obtained first from school children, and families with children in day care or school have higher illness attack rates during influenza epidemics than do families without such children (Glezen & Couch, 1978; Couch et al., 1986). However, routine vaccination of healthy children using currently available vaccines is not recommended at this time because of questions about the logistical feasibility, long-term immunologic implications, and cost-effectiveness of routinely vaccinating this population against influenza each year. Nonetheless, the possibility of recommending routine vaccination of young children is under consideration because this group may be at elevated risk for complications of influenza.

Influenza Pandemic Preparedness

During the 20th century, the appearance of new influenza viruses in 1918 ("Spanish flu"), 1957 ("Asian flu"), and 1968 ("Hong Kong flu") led to influenza pandemics—global epidemics of influenza. In each pandemic, there were substantial worldwide increases in influenza-associated illness and mortality (Glezen, 1996; Noble, 1982). Pandemics occur when influenza A viruses undergo antigenic shift. Because eight single-stranded RNA segments make up the genome of influenza viruses, new strains of influenza A virus that can replicate in humans and that contain novel surface glycoproteins occasionally appear through reassortment of gene segments during chance co-infections of a single host with both human and avian or possible swine viruses (Webster et al., 1992; Scholtissek, 1994). Not all novel strains are pathogenic in humans or easily transmitted from person to person. However, when such new strains are virulent and transmittable in humans, they can spread rapidly among nonimmune persons. It is estimated that there have been 10 to 20 global influenza pandemics during the past 250 years (Webster, 1998). The most devastating influenza pandemic known, the Spanish flu of 1918 to 1919, affected more than 200 million people globally and killed more than 20 million, including more than 500,000 people in the United States (Glezen, 1996; Noble, 1982). During annual influenza epidemics, excess mortality occurs primarily among the elderly; in contrast, a large proportion of influenza deaths during the 1918-1919 pandemic and, to a lesser degree, during subsequent pandemics in 1957-1958 and 1968-1969, were among young, otherwise healthy persons (Simonsen et al., 1998). Transmission of nonhuman influenza strains to humans without reassortment but with mutational changes causing infectivity and virulence in humans may also be a mechanism for the emergence of pandemic strains (Scholtissek, 1994).

In the United States and other countries, comprehensive plans to prepare for future influenza pandemics are under development. Improved global surveillance and mass immunization with effective and safe vaccines will be the key for decreasing influenza-associated morbidity and mortality during future pandemics (Patriarca & Cox, 1997). Additionally, more rapid methods of vaccine development, production, and distribution will be needed for timely administration of a vaccine against a new pandemic strain. Even under optimal conditions, at least 4 to 8 months will be required given current technology from the time that a new pandemic strain is identified until tens of millions of doses of vaccine would be available for use. Assuming the vaccine will become available gradually (i.e., 1 to 10 million doses per week), initial use should be directed at persons providing critically essential community services and patients at greatest risk for severe illness or death. Chemoprophylaxis against influenza will have an important role during a pandemic in selective situations, but it will not be a feasible intervention using currently licensed antiviral agents for the population at large because of cost, limited availability, and risk of drug-related adverse events. Nonetheless, antiviral drugs will have a therapeutic role for persons with severe illness and could be used prophylactically for persons who provide essential community services.

Production of hundreds of millions of doses of inactivated influenza vaccines will require that

huge numbers of fertilized eggs be readily available during response to a pandemic. The potential that a pandemic strain could also be lethal in chickens, reducing flock size and egg production, highlight the importance of developing tissue culture methods for influenza vaccine production. Finally, given the importance of *S. pneumoniae* infection as a secondary complication of influenza, raising pneumococcal vaccine coverage rates among those at greatest risk of serious pneumococcal disease constitutes an immediately achievable goal for influenza pandemic preparedness.

Influenza Vaccines Under Development

Live, Cold-Adapted Influenza Vaccines

Live attenuated influenza vaccines contain influenza viruses that replicate in the upper respiratory tract. These vaccines provide a number of potential advantages over inactivated vaccines, including the ability to induce a broad mucosal and systemic immune response using an intranasally administered preparation, obviating the need for injections. The observation that influenza A and B viruses passaged at 25°C in primary chick kidney cell culture were attenuated in humans led to the creation of vaccine strains through recombination of these cold-adapted strains with HA and NA genes from circulating pathogenic influenza viruses (Maassab et al., 1972). Such vaccines generally are considered genetically stable and safe and are immunogenic in infants and children (Edwards et al., 1994; Gruber et al., 1996). Live attenuated influenza vaccines have been under development since the 1960s and have been studied as monovalent, bivalent, and trivalent formulations (Murphy, 1993; Clements & Stephens, 1997).

A randomized, double-blind, placebo-controlled trial among children aged 15 to 71 months showed that a trivalent, live, cold-adapted influenza vaccine administered as an intranasal spray was 89% efficacious for preventing culture-confirmed influenza after a single dose and 94% efficacious after two doses (Belshe et al., 1998). Moreover, vaccinated children had a 35% reduction in febrile otitis media episodes with concomitant reduction in antibiotic use. There has been no published trial directly comparing the efficacy of trivalent inactivated influenza vaccine and trivalent live, cold-adapted influenza vaccine.

Recombinant Subunit Vaccines

Cloning of genes for antigens from circulating influenza viruses and expression of these genes in eukaryotic cells could produce vaccines with the exact match of HA or NA without dependence on reassorted viruses or eggs for production (Lakey et al., 1996; Deroo et al., 1996). HA expressed in insect cells by a recombinant baculovirus was well tolerated and was immunogenic in healthy young and elderly volunteers (Treanor et al., 1996). Such an approach, if effective, could be particularly useful when rapidly responding to a global influenza pandemic.

DNA Influenza Vaccines

An innovative approach to immunization involves introduction of a DNA plasmid carrying a protein-coding gene into the vaccine recipient's own cells, leading to expression of an antigen which elicits an immune response directed against influenza viruses (so-called DNA vaccines). Such immunizing agents could be manufactured more easily and may be more stable during storage and distribution than vaccines composed of inactivated or attenuated microorganism, subcellular fractions, or recombinant proteins (Whalen, 1996). Studies in mice have shown that immunization with DNA-expressed HA protected against lethal viral challenge (Robinson et al., 1997). However, a great deal of research remains to be done to clearly demonstrate safety, immunogenicity, and efficacy of DNA vaccines in humans.

Pneumococcal Vaccines

Development of Polysaccharide Vaccines

In 1911, Wright and his coworkers developed a crude whole-cell pneumococcal vaccine which was used to immunize South African gold miners (Wright et al., 1914), a group with an extremely high incidence of serious pneumococcal infections, and observed some decrease in the number of pneu-

monia cases and deaths from pneumonia among inoculated miners compared with those who were not inoculated. In the 1940s, controlled trials of vaccines containing the capsular polysaccharides of two to four serotypes were conducted and provided strong evidence that these vaccines were efficacious (MacLeod et al., 1945; Kaufman, 1947). Two hexavalent vaccines subsequently were commercially produced and marketed. At about the same time, antimicrobial drugs that were effective against pneumococci became available and the outcomes of patients with pneumococcal infections improved substantially. The seemingly miraculous efficacy of penicillin led to the widespread belief that pneumococcal infections were entirely curable and clinicians, researchers, and public health officials lost interest in prevention of this previously feared pathogen. The pneumococcal vaccines were withdrawn from the market by the early 1950s.

A decade later, the complacency about pneumococcal disease was broken by Austrian and Gold (1964) and their clinical description of some 2000 cases of pneumococcal pneumonia diagnosed at Kings County Hospital in Brooklyn from 1952 to 1962. Although penicillin therapy had made a substantial impact in reducing the number of deaths caused by pneumococcal infection, mortality was still nearly 25% among patients admitted with pneumococcal bacteremia, and mortality was greatest among the elderly and persons with certain chronic medical conditions. As a direct result of these findings, polyvalent pneumococcal polysaccharide vaccines were redeveloped. These vaccines were evaluated in double-blind, randomized trials, and as in earlier decades, young gold miners in South Africa were recruited into these studies (Austrian etal., 1976; Smit et al., 1977). Results of these trials documented the efficacy of polysaccharide vaccine for prevention of pneumococcal pneumonia and led to licensure of a vaccine containing 50 μg of capsular polysaccharide for each of 14 serotypes in 1977. In 1983, the 14-valent vaccine was replaced by a 23-valent vaccine containing 25 u.g of purified pneumococcal capsular polysaccharide antigens for serotypes 1,2,3,4,5,6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 serotypes cause >85% to 90% of clinically significant pneumococcal infections.

Effects of Vaccination

Immune Responses

Pneumococcal capsular polysaccharide antigens induce serotype-specific antibodies that enhance opsonization, complement-dependent phagocytosis, and killing of pneumococci by leukocytes and other phagocytic cells. Concentrations of antibodies to pneumococcal polysaccharides, as measured by radioimmunoassay or by enzyme-linked immunosorbent assay, begin to increase within 1 week after vaccination and, for most vaccine antigens, remain elevated above prevaccination levels for >5 years in healthy adults (Mufson et al., 1987; Musher et al., 1993). Antibody concentrations decline more rapidly in some groups, such as the elderly and persons with certain underlying illnesses (Minor et al., 1979; Vella et al., 1980; Hilleman et al., 1981; Schmid et al., 1981; Kraus et al., 1985; Davidson et al., 1993; Sankilampi et al., 1997). Immune responses may not be consistent among all 23 serotypes in the vaccine and the magnitude of responses among vaccinees varies widely (Go & Ballas, 1996). Although substantial antibody responses may occur even among persons ⩾85 years old, reduced effectiveness may be due to functional differences in antibodies produced by persons in this age group compared with younger vaccinees (Romero-Steiner et al., 1999). Genetic factors may play an important role in the response to polysaccharide antigens. In one family, impaired responsiveness to pneumococcal capsular polysaccharides was inherited in a mixed, codominant fashion (Musher et al., 1997).

The clinical relevance of antibody concentrations measured after vaccination is difficult to determine because levels of antibodies that correlate with protection against pneumococcal disease have not been clearly defined. Moreover, measurements of antibody concentration do not take into consideration the functional activity of the antibody produced. Laboratory methods assessing functional immune responses to vaccination, such as opsonophagocytic activity and antibody avidity for pneumococcal antigens, may prove to be a better way to predict protection and be more clinically relevant than quantitative antibody measurements (Romero-Steiner et al., 1997).

Clinical Impact

Randomized Trials Pre-licensure randomized controlled trials of pneumococcal vaccine efficacy were conducted in the 1970s among young, healthy South African gold miners. The estimates of protective efficacy against pneumococcal pneumonia in these trials ranged from 76% to 92% (Austrian et al., 1976; Smit et al., 1977). In nonepidemic situations in industrialized countries, most pneumococcal disease in adults occurs in the elderly or in persons with chronic medical conditions. Vaccine efficacy for pneumonia without bacteremia has not been consistently proven for these populations. Results of one randomized clinical trial suggested that the vaccine provided some protection against pneumococcal pneumonia among high-risk elderly persons (Koivula et al., 1997), whereas two other trials did not demonstrate efficacy against pneumonia or bronchitis without bacteremia (Simberkoff et al., 1986; Örtqvist et al., 1998). However, the inability of these studies to document vaccine efficacy is partly due to a lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. An inaccurate case definition of pneumococcal pneumonia would bias the findings of a trial to the null. Additionally, these studies lacked statistical power to assess efficacy against bacteremia or meningitis. Two open trials have indicated efficacy for prevention of pneumococcal pneumonia among elderly long-term care facility residents (Kaufmann, 1947; Gaillat et al., 1985).

Epidemiological Studies Epidemiological studies assessing pneumococcal vaccine effectiveness provide several advantages over randomized clinical trials. They permit rapid gathering of data with better statistical power to adequately evaluate vaccine effectiveness (Clemens & Shapiro, 1984). Moreover, ethical concerns about withholding a vaccine from controls make post-licensure randomized trials among persons at highest risk of disease impractical. Finally, randomized trials evaluate vaccine performance under optimal conditions, whereas epidemiological studies provide a more pragmatic perspective by assessing the impact of a vaccine under ordinary conditions of clinical practice (Clemens et al., 1996).

Post-licensure epidemiologic studies have documented effectiveness of pneumococcal polysaccharide vaccines for prevention of invasive infection (bacteremia and meningitis) among the elderly and persons ≥ 2 years old with certain chronic medical conditions (Sims et al., 1988; Shapiro et al., 1991; Butler et al., 1993; Farr et al., 1995; Fiore et al., 1997). Only one case-control study failed to demonstrate effectiveness against bacteremic disease (Forrester et al., 1987), possibly because of study limitations, such as small sample size and incomplete ascertainment of vaccination status of patients. The overall effectiveness against invasive pneumococcal disease among immunocompetent persons aged ≥ 65 years is 75% (Butler et al., 1993); however, efficacy may decrease with advancing age (Shapiro et al., 1991). Polysaccharide vaccine is 65% to 84% effective for preventing bacteremia and meningitis among persons at increased risk for serious pneumococcal illness due to certain medical conditions including diabetes mellitus, chronic heart and lung diseases, and anatomic asplenia (Butler et al., 1993).

Cost-Effectiveness Based on surveillance data collected in the late 1980s and early 1990s and vaccine effectiveness estimates from epidemiologic studies, an analysis of cost-effectiveness of pneumococcal vaccination among persons aged ≥ 65 years for prevention of bacteremia and meningitis indicated that vaccination saved $8.27 per person vaccinated (Sisk et al., 1997). Thus, vaccination of the 23 million unvaccinated elderly Americans in 1993 would have saved $194 million.

Safety

Side Effects and Adverse Reactions

On the basis of 25 years of clinical experience, pneumococcal polysaccharide vaccines are considered safe (CDC, 1997a). Severe adverse effects (e.g., anaphylactic reactions) rarely have been reported, and neurologic disorders (e.g., Guillain-Barré syndrome) have not been associated with administration of pneumococcal vaccine (Fedson et al., 1999). In a recent meta-analysis of nine randomized controlled trials of pneumococcal vaccine efficacy, mild local reactions (e.g., pain at the injec-

tion site, erythema, and swelling) were observed among approximately one third or fewer of patients receiving the vaccine, and there were no reports of severe febrile or anaphylactic reactions (Fine et al., 1994). Local reactions generally occur within 48 hours of vaccination and are more common after revaccination than after primary vaccination. Among persons aged 50 to 74 years, redness or swelling extending 4 or more inches around the injection site was reported by 11% of persons who had been vaccinated 5 or more years previously and by 3% of those vaccinated for the first time (Jackson et al., 1999). These reactions generally did not interfere with the activities of daily life and were self-limited, with a mean of 3.6 days from vaccination to complete resolution of symptoms. Swelling, pain, and redness at the injection site have been associated with the higher prevaccination concentrations of anticapuslar antibodies, consistent with the occurrence of a localized Arthus-type reaction (type III hypersensitivity reaction), caused by formation of antibody-antigen complexes at the injection site (Sankilampi et al., 1997; Jackson et al., 1999).

Although preliminary data have suggested that the pneumococcal vaccine may cause transient increases in HIV replication (Brichacek et al., 1996; Katzenstein et al., 1996), the clinical significance of this occurrence is unknown. This phenomenon has also been observed after immunization with other vaccines (O'Brien et al., 1995; Stanly et al., 1996) and during episodes of acute bacterial pneumonia (Bush et al., 1996).

Precautions and Contraindications

The safety of pneumococcal polysaccharide vaccination during early pregnancy has not been evaluated, although no adverse consequences have been reported regarding newborns whose mothers were inadvertently vaccinated during pregnancy. In fact, vaccination of pregnant women during the third trimester has been studied as a means of inducing transplacental passage of anticapsular antibodies to protect infants living in developing countries with high rates of death caused by pneumococcal infection during the first months of life (O'Dempsey et al., 1996). Nonetheless, women at increased risk for acquiring pneumococcal disease should be vaccinated before pregnancy, if possible. Intradermal administration may cause severe local reactions and is inappropriate (CDC, 1997a). The only contraindication to pneumococcal polysaccharide vaccine is severe reaction to a previous dose of the vaccine (Fedson et al., 1999).

Recommendations for Use

The ACIP and HealthCanada's National Advisory Committee on Immunization recommend pneumococcal vaccination of persons at increased risk for serious pneumococcal disease, including all persons aged 65 years and older and persons aged 2 to 64 years with certain chronic medical conditions as well as persons living in certain social settings, such as Alaskan Natives and certain Native American populations (Table 2) (CDC, 1997a; LCDC, 1998). Recent outbreaks of pneumococcal pneumonia in nursing homes where less than 5% of residents had been vaccinated underscore the great importance of providing pneumococcal vaccine to elderly residents of long-term care facilities (CDC, 1997b; Nuorti et al., 1998; Fiore et al., 1998).

Persons $\geq$65 years of age should receive a second dose of vaccine if the initial dose was at least 5 years earlier and was received before age 65. For persons with functional or anatomic asplenia and immunocompromised persons $>$10 years of age, a single revaccination should be provided $\geq$5 years after the first dose. Revaccination should be considered after 3 years for children $\leq$10 years of age and at highest risk of infection. Routine revaccination is not recommended for persons with other chronic medical conditions or for those in special environments and social settings. At present, the need for subsequent doses of pneumococcal vaccine after the second dose is unclear and few data are available to evaluate the safety of three or more doses; therefore, revaccination following a second dose is not routinely recommended at this time.

Because invasive pneumococcal infection can be an early manifestation of HIV infection and antibody responses to pneumococcal vaccine may be greater early in the course of illness, persons with HIV and a CD4+ lymphocyte count $\geq$200 cells/μL should be vaccinated as soon as possible after HIV is diagnosed (USPHS/IDSA, 1997). For persons who have CD4+ lymphocyte counts of $<$200 cells/μL, pneumococcal vaccine may be of-

TABLE 2. Recommendations of the Advisory Committee on Immunization Practices for Use of Pneumococcal Polysaccharide Vaccine[a]

Groups for which vaccination is recommended	Strength of recommendation[b]	Revaccination[c]
Immunocompetent persons	A	Second dose of vaccine if vaccine received more than 5 years previously and were <65 years of age at the time of vaccination
Persons ≥65 years of age[d]		Not recommended
Persons ≥2 and <65 years of age with chronic illness		
chronic cardiovascular disease (e.g., congestive heart failure, cardiomyopathies)	A	
chronic pulmonary disease (e.g., chronic obstructive pulmonary disease, emphysema)	A	
diabetes mellitus	A	
alcoholism	B	
chronic liver disease (cirrhosis)	B	
cerebrospinal fluid leaks	B	
Persons ≥2 and <65 years of age with functional or anatomic asplenia (e.g., sickle cell disease, splenectomy)	A	If >10 years of age, single revaccination 5 years after previous dose If ≤10 years of age, consider revaccination 3 years after previous dose
Persons ≥2 and <65 years of age living in special environments or social settings (e.g., Alaska Natives, certain American Indian populations)	C	Not recommended
Immunocompromised persons ≥2 years of age, including persons with:	C	Single revaccination if at least 5 years have passed since receipt of first dose
HIV infection		
leukemia		
lymphoma		
Hodgkin's disease		
multiple myeloma		
generalized malignancy		
immunosuppressive chemotherapy, including chemotherapy		
chronic renal failure		If ≤10 years of age, consider revaccination 3 years after previous dose
nephrotic syndrome		
organ failure or bone marrow transplant		

[a]From CDC, 1997a.
[b]Categories reflect the strength of evidence supporting vaccination recommendations. A, Both strong epidemiological evidence and substantial clinical benefit support the recommendation for vaccine use; B, Moderate evidence supports the recommendation for vaccine use; C, Effectiveness of vaccination not proven, but high risk of disease, potential benefits, and safety of vaccine justify vaccination.
[c]Strength of evidence for all revaccination recommendations: C.
[d]If earlier vaccination status is unknown, patients in these groups should be given pneumococcal vaccine.

fered, although the humoral response is likely to be diminished (Rodriquez-Barradas et al., 1992).

Vaccine should be administered to patients with an indication for pneumococcal vaccination but who are uncertain about their vaccination history. To avoid unnecessary doses, every patient should be given a vaccination record. However, in the absence of such records, healthcare providers should rely on patients' verbal history and not withhold pneumococcal vaccine for those patients with uncertain vaccination status.

Indications for pneumococcal and influenza vaccination are similar. Pneumococcal and influenza vaccines may be administered at the same time by separate injection in each arm without an increase in side effects or decreased antibody response to either vaccine (Hilleman et al., 1981; DeStefano et al., 1982).

New and Future Pneumococcal Vaccines

Pnenmococcal Conjugate Vaccine

Rates of invasive *S. pneumoniae* infection are highest during the first 2 years of life. Unfortunately, pneumococcal capsular polysaccharides are T-cell-independent antigens that induce limited antibody responses in children <2 years of age. Clinical trials of pneumococcal capsular polysaccharide vaccines among young children have demonstrated limited or no evidence of efficacy, and for many of the serotypes that most commonly cause disease in young children (6A, 14, 19F, and 23F), immune responses are poor in children <5 years old (Douglas et al., 1983; Koskela et al., 1986; Leinonen et al., 1986). By conjugating polysaccharide antigens to a carrier protein, the immunologic responses elicited become T-cell-dependent and induce higher antibody concentrations in infants. In addition, memory B cells are produced and primed for booster responses—rapid and dramatic increases in antibody concentrations to subsequent immunizations with pneumococcal polysaccharide (O'Brien et al., 1996). This strategy has led to the development of *Haemophilus influenza* type b (Hib) conjugate vaccines that are safe and efficacious in children younger than 2 years of age. The use of conjugate Hib vaccines has been accompanied by a dramatic reduction in the incidence of invasive Hib infections in the United States (Adams et al., 1993; Schoendorf et al., 1994), suggesting that regional elimination of Hib disease may be feasible (CDC, 1998). Vaccination with Hib conjugate vaccines, but not unconjugated Hib polysaccharides, generally reduces oropharyngeal carriage of the organism, thus reducing transmission of Hib in vaccinated populations (Takala et al., 1991; Barbour et al., 1995; Adegbola et al., 1998).

Phase I and II studies demonstrate that pneumococcal conjugate vaccines are safe and induce primary and booster antibody responses in infants and young children (Steinhoff et al., 1994; Käyhty et al., 1995; Anderson et al., 1996; O'Brien et al., 1996; Rennels et al., 1998). Preliminary data from a large randomized trial of a heptavalent pneumococcal conjugate vaccine among infants and children enrolled in a California health maintenance plan show a high degree of efficacy for prevention of invasive pneumococcal disease (Black et al., 1998). Several other large randomized trials assessing the efficacy of conjugate vaccines to prevent invasive infection and acute otitis media in infants are ongoing.

A limitation to conjugate pneumococcal vaccines is that it does not appear possible to include more than a limited number of antigens in a conjugated formulation (Siber, 1994). Thus, vaccinated persons would remain susceptible to serotypes not included in the vaccine. Most conjugate pneumococcal vaccines under evaluation contain capsular polysaccharides of 7 to 11 serotypes. Among infants and young children, the seven most common serotypes (14, 6B, 19F, 18C, 23F, 4, and 9V) account for 80% of blood and cerebrospinal fluid isolates in the United States, but only 50% of isolates among older children and adults (Butler et al., 1995). Additionally, there are substantial differences in the serotypes of pneumococci that commonly cause invasive infections in other areas of the world (Sniadack et al., 1995). Consequently, a heptavalent vaccine that is based on the most prevalent serotypes among children in one country may not be optimal for children in a different region of the world.

The role of conjugate vaccines for older children and adults remains to be determined. Preliminary data indicate that in healthy persons ≥50 years old and in patients vaccinated after treatment for Hodgkin's disease, antibody responses to pneumococcal conjugate vaccines have not been substantially better than responses to the polysaccharide vaccine (Powers et al., 1996; Molrine et al., 1995). In one study, localized reactions (pain, stiffness, and induration at the injection site) were more common among persons who received the conjugate vaccine, although these symptoms were generally mild (Powers et al., 1996). One potential approach to the use of conjugate vaccines in adults is to administer conjugate vaccine to prime the immune system and to subsequently give a dose of 23-valent polysaccharide vaccine to induce a booster response to the serotypes present in both vaccines as well as primary T-cell-independent responses to the serotypes in the 23-valent vaccine only (Chan et al., 1996; Vernacchio et al., 1998).

Pneumococcal Protein Vaccines

A promising complementary or alternative approach for prevention of pneumococcal infections is to develop vaccines directed against noncapsular antigens common to all pneumococcal serotypes.

Candidate antigens include a number of pneumococcal proteins: NA, autolysin, pneumolysin, pneumococcal surface proteins A and C (PspA and PspC), and pneumococcal surface adhesin A (PsaA or 37-kDa protein) (Lock et al, 1988; McDaniel et al., 1991; Sampson et al., 1997; Briles et al., 1997). These proteins could not only provide protection against all pneumococcal serotypes, but would also induce a T-cell-dependent response with immunologic memory. To date, only pneumolysin, PspA, and PsaA have been extensively examined for suitability as vaccine candidates. Intranasal immunization of mice with PspA-induced mucosal and systemic antibody responses, prevented pneumococcal colonization, and provided protection against systemic infection after intravenous, intratracheal, and intraperitoneal challenge (Wu et al., 1997). A vaccine consisting of a live recombinant *Salmonella typhimurium* vaccine strain expressing pneumococcal PspA colonized gut-associated lymphoid tissues, spleens, and livers of orally immunized mice, induced serum and mucosal anti-PspA antibodies, and provided protection against challenge by a mouse-virulent *S. pneumoniae* (Nayak et al., 1998).

DNA Vaccines

The potential advantages of DNA vaccines are particularly attractive for prevention of pneumococcal disease in developing countries where low-cost vaccines that do not require refrigeration during shipping and storage are needed. Results of preliminary work on a pneumococcal DNA vaccine are promising. Immunization of mice with a plasmid expressing PspA has been shown to induce a significant immune response and provided some protection against a challenge with intravenously administered serotype 3 *S. pneumoniae* (McDaniel et al., 1997).

ACKNOWLEDGMENT

The authors thank Dr. Nancy Cox for thoughtful review of the manuscript and Ms. Terri Brandon for secretarial assistance.

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15

Aspiration Pneumonia

MARCIO SA-BORGES AND JORDI RELLO

Introduction

In community-acquired pneumonia (CAP), the pathogens enter the lung via aspiration of oropharyngeal secretions or gastric contents (the usual source of *Streptococcus pneumoniae, Haemophilus influenzae,* anaerobic bacteria, gram-negative bacilli), inhalation of contaminated aerosols *(Mycobacterium tuberculosis, Legionella pneumophila),* hematogenous dissemination *(Staphylococcus aureus),* or by contiguity. The most frequent pathway is by aspiration of oropharyngeal secretions or gastric contents.

Aspiration pneumonia is a pulmonary consequence of the abnormal entrance of fluids, exogenous particulates, or endogenous secretions in the lower airways. Generally, aspiration pneumonia is associated with an underlying illness or with a functional defect of the natural defenses. It usually involves a compromise of the mechanical defenses of the tracheobronchial tree and upper gastrointestinal tract, such as impaired cough reflex, discoordinated closure of the glottis, or presence of gastroesophageal reflux. A decisive factor in the development of pulmonary complications is the frequency, volume, and characteristics of the material aspirated which begins the inflammatory process or causes the obstruction.

Although the prevalence of aspiration pneumonia is high, the prognosis and risk factors remain only partially understood; indeed, they vary according to series. Overall, aspiration is suspected in approximately 10% of patients hospitalized for pneumonia, and this proportion is significantly higher in institutionalized patients. The spectrum of aspiration extends from an asymptomatic group of healthy people to acute life-threatening events. In any case, aspiration pneumonia is uniformly reported as a poor prognosis factor (Fine, 1990; Leroy, 1995). The case fatality rate varies from one study to another, ranging from 7.5% to 80% (Lewis et al., 1970; Cameron et al., 1973; Kicking & Howard, 1988), depending on the study population.

Classification

Aspiration pneumonia is a syndrome that involves several types of aspiration, which differ in terms of the inoculum, the pathogenesis of the pulmonary complications, their clinical presentation, and their treatment. A traditional classification based on the type of inoculum differentiates three groups: (1) aspiration of fluid, (2) aspiration of solid particles, and (3) aspiration of pathogenic bacteria (Table 1). This classification identifies different pathogenic processes, outcomes, and preventive measures and helps to guide specific therapeutic approaches (Bartlett & Gorbach, 1975a). According to clinical presentation and management, patients should be differentiated depending on the importance of the toxic injury (Mendelson's syndrome), obstruction (either by massive aspiration of inert fluids or of solid particles), or infection, which may ultimately complicate the other two presentations. Chronic recurrent chemical injury due to small-

MARCIO SA-BORGES • Intensive Care Department, Hospital Doce de Octubre, Madrid, Spain. **JORDI RELLO** • Critical Care Department, Hospital University Joan XXIII, University Rovira & Virgili, Carrer Dr. Mallafre Guasch, 43007 Tarragona, Spain.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Classification of Aspiration Pneumonia According to Inoculum

Toxic fluids	Inert substances	Pulmonary infection
Acid	Fluids	Oropharyngeal flora
Bile	Particulate matter	Gastric flora
Alcohol		
Hydrocarbons		
Animal fats		
Mineral oil		
Others		

volume or microaspiration involves major diagnostic challenges, but is out of the scope of this review. Although antimicrobial agents are usually prescribed in patients with suspected aspiration pneumonia, infection can be difficult to diagnose but probably occurs in 50% or fewer of patients who suffer acute aspiration.

Risk Factors and Prevention

Many series have indicated that some degree of microaspiration occurs during sleep in up to 50% of healthy people, but generally without any apparent clinical consequence (Bartlett, 1992). Amberson (1937) reports that after placing iodized oil in the mouth of sleeping patients, the material was aspirated into the lungs, but no clinical manifestations appeared. Huxley et al. (1978), using indium chloride, reported that 45% of control subjects and 70% of patients with reduced consciousness aspirated pharyngeal secretions during sleep. During REM sleep, the normal cough reflex may be totally absent, which explains the fact that normal people may silently aspirate oropharyngeal contents (Phillipson, 1979). An interesting study by Kikuchi et al. (1994) investigated episodes of silent aspiration during sleep in 14 elderly patients with acute episodes of pneumonia and 10 age-matched control subjects by a technique using indium chloride; aspiration was observed in 71% of patients with pneumonia, but in only 10% of controls. No patients in either group had preexisting illness or specific risk factors for aspiration. This study suggests that elderly people frequently aspirate during sleep and the development of pneumonia may occur even in patients with normal defenses.

The main risk factors associated with aspiration pneumonia are closely related to significant failures in the different physiologic defense mechanisms, above all in the upper gastrointestinal and respiratory tract. The muscles of the pharynx and upper gastrointestinal tract work in a coordinated and synchronized fashion and are the most important defensive mechanism against the aspiration of fluids or food. In the presence of diseases associated with neuromuscular disorders, such as myasthenia gravis, Parkinson's disease, polymyositis, alcoholism, malnutrition, achalasia, and congenital or degenerative disorders, the risk of aspiration is high. Other important factors in the pathogenesis of the condition in the elderly (Palmer, 1976; Huxley et al., 1978; Phillipson, 1979; Bartlett, 1992) are deficient mastication, poor or absent dentition, inappropriate closure of vocal cords, sedation, unconsciousness, tracheostomy, and frequent presence of gastroesophageal reflux during sleep (Table 2).

The respiratory defenses can be divided into immunologic and nonimmunologic defenses (Table 3) (Irwin, 1996). The material aspirated can cause pulmonary disease if it is not immediately expelled or eliminated. The size of the particles is an important pathogenic factor, because particles between 2 and 10 μm in diameter can reach the airways, and those between 0.5 and 2μm in diameter can reach the alveoli. Generally, mucociliary clearance removes the larger particles, and alveolar macrophages and neutrophils eliminate the smaller particles. The infectious particles are detoxified by lysozymes and proteases in the mucus and by the alveolar macrophage and neutrophil enzymes, and alveolar macrophages also opsonize bacteria (Toews et al., 1979; Rehm et al., 1980). Cough is a secondary defense mechanism; it only has a clearing function if mucociliary function is inefficient or has been overwhelmed.

To study the association of potential factors with development of aspiration pneumonia, two approaches can be used: evaluation of the incidence of the complication among all patients with specific diseases, or focusing on patients in whom aspiration pneumonia has been diagnosed (Bartlett & Gorbach, 1975a). In the first case, the aspiration event is often associated with anesthetic procedures, head injuries, cerebrovascular accidents, or chronic debilitating diseases; for example, about 10% to 20% of patients with gastrointestinal reflux

TABLE 2. Underlying Risk Factors and Diseases/Conditions that Predispose to Aspiration

Risk factors	Disease/condition
Witnessed large aspiration	Post-cardiac arrest
	Drug overdose
	Upper gastrointestinal endoscopy
	Anesthetic procedures
Altered mental status	Drug overdose
	Alcohol intoxication
	Seizures
	Cerebrovascular accident
	Head trauma
	General anesthesia
	Encephalopathy
Neuromuscular disorders	Multiple sclerosis
	Myasthenia gravis
	Parkinson's disease
	Tetraplegia
	Charcot-Marie-Tooth disease
Dysphagia and gastroesophageal reflux	Esophageal and gastric disorders
Mechanical disruption	Nasogastric tube
	Endotracheal intubation
	Tracheostomy
	Bronchoscopy
	Upper gastrointestinal endoscopy
Recumbent position	
Disability/chronic diseases	Diabetes
	Alcoholism
	Chronic bronchitis
	Malnutrition
	Periodontal disease
	Rheumatic disease

TABLE 3. Alterations in the Mechanisms of the Pulmonary Defenses and Factors that Favor Development of Aspiration Pneumonia

- Decreased clearance or increase in inoculum
  - Depression of cough reflex: alcoholism, malnutrition, altered consciousness, neuromuscular or thoracic disease
  - Decrease of mucociliary transport: smoking, chronic obstructive pulmonary disease, alcoholism, upper respiratory infection, ciliary disease, bronchiectasis, malnutrition, diabetes
  - Altered glottis closure: altered consciousness, tracheostomy, orotracheal intubation, altered deglutition
  - Increase in concentration of bacteria in the secretions: periodontal diseases, malnutrition, bronchiectasis
  - Altered humidification of inspired air: tracheostomy, respiratory infections, oxygen by masks
- Change in oropharyngeal colonization
  - Alteration of bacterial adherence: tracheostomy, orotracheal intubation, malnutrition, viral infections
  - Decrease in fibronectin: alcoholism, diabetes, older persons, debilitating and chronic disease
  - Miscellaneous: antibiotic treatment, isolated community (nursing home residences, military)
- Factors that favor pulmonary infection
  - Deficit of immunoglobulins (IgA, IgG): malnutrition, alcoholism, hypogammaglobulinemia, myeloma, nephrotic syndrome, splenectomy, diabetes
  - Deficit of complement: sepsis, alcoholism, lupus
  - Alteration of phagocytosis by polymorphonuclear and macrophages: diabetes, corticoids, uremia, acidosis, alcoholism, HIV infection
  - Alteration of oxide-reduction potential or the surfactant: pulmonary infarct, bronchial obstruction, alveolar edema

or achalasia have recurrent or chronic aspiration pneumonitis. In the second situation, the main predisposing conditions to aspiration pneumonia are alcoholism, seizures, cerebrovascular accidents, drug dependence, general anesthesia, esophageal disease, and enteral feeding by nasogastric tube (Bartlett & Gorbach, 1975a; Irwin, 1996).

Other populations at risk are those who have undergone surgery affecting the upper airways or upper gastrointestinal tract; mechanical disruption due to large-bore nasogastric feeding tubes, tracheostomy, endotracheal tube, bronchoscopy, digestive endoscopy, and recumbent position (Table 3). These procedures expose patients to a decrease in natural defenses, increasing the risk of aspiration and their pulmonary complications. In a study of community-acquired aspiration pneumonia patients requiring admission in the intensive care units, Leroy et al. (1997) evaluated the risk factors for aspiration pneumonia, reporting that drug overdose is the most frequent cause. The specific relevant factors in the pathogenesis of anaerobic pleuropulmonary infection (Finegold, 1995) are described in Table 4.

The pharmacologic methods recommended for preventing aspiration are based on altering residual gastric volume and pH. The principal drugs include histamine H_2 blockers, antacids, proton pump inhibitors, and cholinergic receptor agonists. Histamine H_2 blockers both reduce gastric volume and alkalinize the pH (Boysen & Modell, 1995). Proton pump inhibitors (e.g., omeprazole) reduce gastric acid and raise pH because they prevent secretion of hydrogen ions. The cholinergic receptor

TABLE 4. Factors Involved in the Pathogenesis of Anaerobic Pleuropulmonary Infections

Breakdown of anatomical barrier
Alteration of host defense mechanisms
Antibody
Polymorphonuclear leukocytes
Cell-mediated immune responses
Altered oxide-reduction potential
Size of bacterial inoculum
Synergy with other organisms
Characteristics of virulence
Invasion
Production of toxins and enzymes
Altered adherence
Altered surface constituents

agonists (e.g., metoclopramide) facilitate gastric emptying and have a key antiemetic effect (Bartlett, 1992; Boysen & Modell, 1995). Another effective nonpharmacological method is the reduction of gastric volume by direct gastric suction. This technique is particularly useful in emergency events if trained staff are available to perform it. In states of altered consciousness (Glasgow Coma Scale score <8), elective orotracheal intubation is recommended to prevent aspiration (Bartlett, 1992; Boysen & Modell, 1995). In patients with altered deglutition mechanisms, restricting feeding through small-bore nasogastric tubes, jejunostomy, or percutaneous endoscopic gastroscopy or gastrostomy decreases the risk of aspiration (Irwin, 1996). In general, body position modification, using semirecumbent or upright position in intubated patients, or with the head down in nonintubated unconscious patients, is a useful preventive measure (Bartlett, 1992; Vallés et al., 1995).

Aspiration of Fluid

Many types of fluid (gastric, biliary secretions, hydrocarbons) can initiate a pulmonary inflammatory process, causing an acute chemical injury (Table 1). Gastric acid aspiration is the most frequently observed cause. Other nontoxic fluids may also cause mechanical obstruction or reflux airway closure.

Chemical Pneumonitis

Chemical pneumonitis was described for the first time in humans by Mendelson in 1946, who described 66 obstetric patients who aspirated gastric contents during anesthesia. Five patients aspirated food particulates and showed acute obstructive symptoms, but 61 others aspirated liquid gastric contents alone. These patients suddenly developed an acute respiratory distress syndrome, clinically characterized by wheezing, cough, cyanosis, dyspnea, tachypnea, tachycardia, and hypoxemia; all patients had bronchospasm. Mendelson concluded: "this type of reaction may be likened to an acute asthmatic attack." Indeed, this type of presentation is probably less common than the finding of fever, tachypnea, and crackles after a latent period of 1 to 2 hours. The radiologic changes were characterized by irregular, patchy pulmonary infiltrates, predominant in the right lower lobe or both lower lobes. Although most patients were in a critical condition, they improved rapidly and stabilized within the first 24 to 36 hours, while the roentgenographic infiltrates cleared within 4 to 7 days. In this presentation, infection was a relatively uncommon complication, appearing in eight out of 66 patients, only 19 of whom were treated with antibiotics. Only two patients died, both from the group that aspirated solid particles (Mendelson, 1946).

Many series have been described since Mendelson's original study and present substantial differences. Most authors report a higher incidence of fever, but a lower frequency of bronchospasm. An interesting finding is the increase in mortality, ranging from 30% to 62% (Lewis et al., 1971; Cameron et al., 1973). These differences may be explained by the fact that Mendelson's patients were younger, previously asymptomatic females, while in the later series most patients were older and had debilitating underlying diseases with more severe forms of presentation.

The pathophysiology of aspiration of stomach fluids is due either to chemical damage or to obstruction (Fisk et al., 1970). In the first case, two essential aspects are required: gastric pH must be 2.5 or below, and large-volume aspiration generally between 1 and 4 mL/kg. Fluid aspiration events with lower volumes or pH higher than 2.5 usually produce a less severe lung injury. This is suggested

by the fact that many cases of recurrent pneumonitis or pulmonary fibrosis are observed in patients with esophageal or gastric reflux (Dines et al., 1970; Mays et al., 1976). Direct injury from acid aspiration is limited because the acid itself is rapidly neutralized (Matthay & Rosen, 1996). Thus, aspiration of acid from the contents of the stomach into pulmonary spaces induces a release of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-8 (Goldman et al., 1990; Folkesson et al., 1995; Matthay & Rosen, 1996). These and other cytokines induce recruitment and activation of neutrophils (Bartlett, 1992; Matthay & Rosen, 1996). Other experimental and clinical observations have demonstrated that the presence of neutrophils alone in the alveolar spaces is not sufficient in itself to initiate lung injury, because neutrophil activation can occur without alteration of pulmonary endothelium (Martin et al., 1989; Wiener-Kronish et al., 1991). Neutrophil activation is a fundamental step, but other conditions are required for acid-induced lung injury to occur. Indeed, neutrophil sequestration and activation in the development of lung injury depends also on the interaction of other adhesive molecules on the neutrophils with their pulmonary counterreceptors located on the lung endothelial and epithelial cells (Goldman et al., 1990; Wiener-Kronish et al., 1991; Folkesson et al., 1995; Goldmann et al., 1995). In many experimental studies, acid-induced lung injury has been reduced either by blocking neutrophil activation or by neutrophil depletion (Matthay & Rosen, 1996).

Clinical events after acid aspiration initially include dyspnea, bronchospasm, tachycardia, and severe hypoxia, which may be secondary to a reflex airway closure. Further symptomatology is associated with the degree of alteration of normal surfactant activity, migration of protein and fluids into the damaged tissues (pulmonary edema), or additional airway obstruction by food particles. If bronchoscopy is performed, the finding of erythema localized to subsegmental bronchi is highly suggestive of aspiration of gastric contents.

Acid-induced lung injury is characterized by an epithelial degeneration of the bronchi, pulmonary edema and hemorrhage, atelectasis, decrease in pulmonary compliance, increase in lung weight and intrapulmonary shunt, necrosis of type I alveolar cells and, after a few hours, degeneration of type II alveolar cells (Lewis et al, 1971; Bartlett & Gorbach, 1975a; Boysen & Modell, 1995; Irwin, 1996). Hypotension may result from the loss of fluid of the circulation, and volume administration is often required to fill the reduced intravascular compartment. As the situation progresses, the alveolar capillary membrane is injured, followed by an exudation of proteins and fluids that causes polymorphonuclear infiltration. This infiltration initiates an inflammatory process within 24 and 36 hours and can cause pulmonary consolidation. After 48 hours it may be manifested as an adult respiratory distress syndrome (ARDS). Later, the pulmonary vasculature may be affected, manifesting as pulmonary hypertension with increased pulmonary vascular resistance (PVR) and constriction of pulmonary arterioles. The increase in PVR may be attributed to many causes: hypoxia, which is a strong inducer of pulmonary vasoconstriction; hypercapnia and acidosis, which can induce vasospasm; loss of pulmonary volume; alveolar overdistention with transmission of microvasculature pressures; and PVR increases. The PVR increase has hemodynamic consequences in the right ventricle which may cause its dilation, with a decrease in the right ejection fraction, and manifesting as severe right ventricular failure (Fisk et al., 1970; Toussaint et al., 1974; Boysen & Modell, 1996). The mortality of patients with chemical pneumonitis who develop acute lung injury ranges from 40% to 50% and has not improved in recent years (Fowler et al., 1983; Doyle et al., 1995). In epidemiological studies of ARDS the role of gastric content aspiration is very important, and usually represents the second or third cause of illness; it is even more prevalent in the postoperative setting (Fowler et al., 1983; Bartlett, 1992; Doyle et al., 1995; Boysen & Modell, 1995).

Aspiration of Inert Fluids

Some fluids, not inherently toxic, that may be aspirated with relative frequency include barium, water, saline, or gastric contents with a pH exceeding 2.5. In these cases, lung injury is usually limited, with development of transient and moderate hypoxia, and only occasionally is severe hypoxia reported in association with reduced pulmonary

compliance (Fisk et al., 1970; Bartlett & Gorbach, 1975b). Experimentally, these effects can be recovered with administration of atropine, isoproterenol, or by vagotomy, suggesting the involvement of intrinsic pulmonary reflex closure (Toussaint et al., 1974; Bartlett, 1992). The most important consequence of the aspiration of large volumes of nontoxic fluids is mechanical obstruction. Many healthy patients tolerate aspiration of relatively large volumes without major consequences. In contrast, severe clinical manifestations (Fig. 1) are usually found in those unable to clear the airway due to ineffective cough reflex or presence of coma (Donowitz & Mandell, 1995; Irwin, 1996).

Aspiration of Solid Particles

The aspiration of particles can induce varying degrees of respiratory obstruction depending on the diameter of the material and the airways involved. The patients who most frequently present with respiratory obstruction caused by solid materials are children between the ages of 1 and 3 years. Additional groups at risk include the elderly, patients with periodontal disease, alcoholics, those who have had drug overdose, and patients in coma. The materials most commonly associated with aspiration are peanuts, inorganic materials, teeth, and other vegetable particles (Fig. 2). In previous studies, aspiration of foreign bodies could be established in 38% of cases; 22% only presented with a history of acute airway obstruction and the remaining 40% only reported cough, dyspnea, and wheezing (Halmagyi et al., 1962; Kim et al., 1973; Aabdulmajid et al., 1976; Bartlett, 1992).

Radiographic studies are essential to identify a foreign body (Fig. 3), although the presence of a foreign body should be suspected in cases of atelectasis or obstructive emphysema. Nevertheless, in 80% of cases, thoracic radiographs are normal. This is a particularly frequent problem in the presence of materials such as vegetables, which do not show on a radiograph due to their hydroscopic properties; in many cases this technical deficiency delays correct diagnosis (Halmagyi et al., 1962; Kim et al., 1973; Aabdulmajid et al., 1976; Bartlett & Gorbach, 1975a).

The clinical manifestations of the aspiration of solid materials depend on the size of particle and the diameter of the airway obstructed. Large objects that wedge in the larynx or trachea can induce

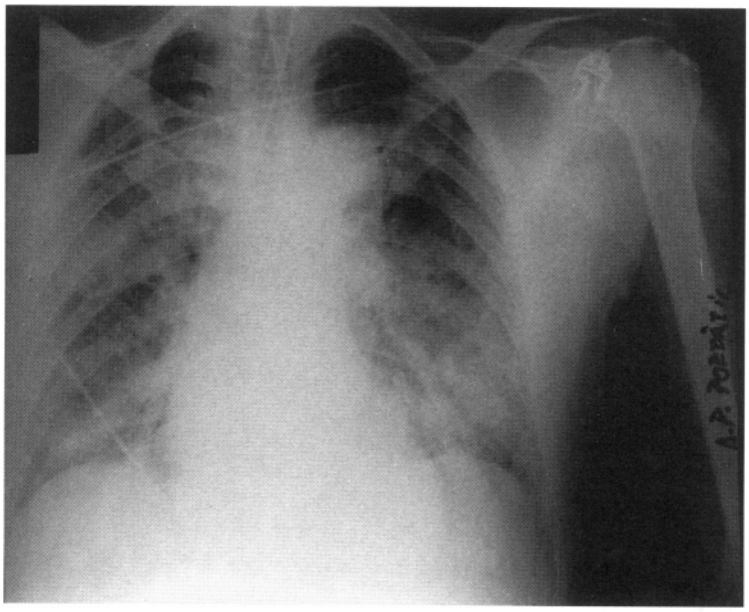

FIGURE 1. Pulmonary infiltrates in a patient with pneumonia associated with near-drowning.

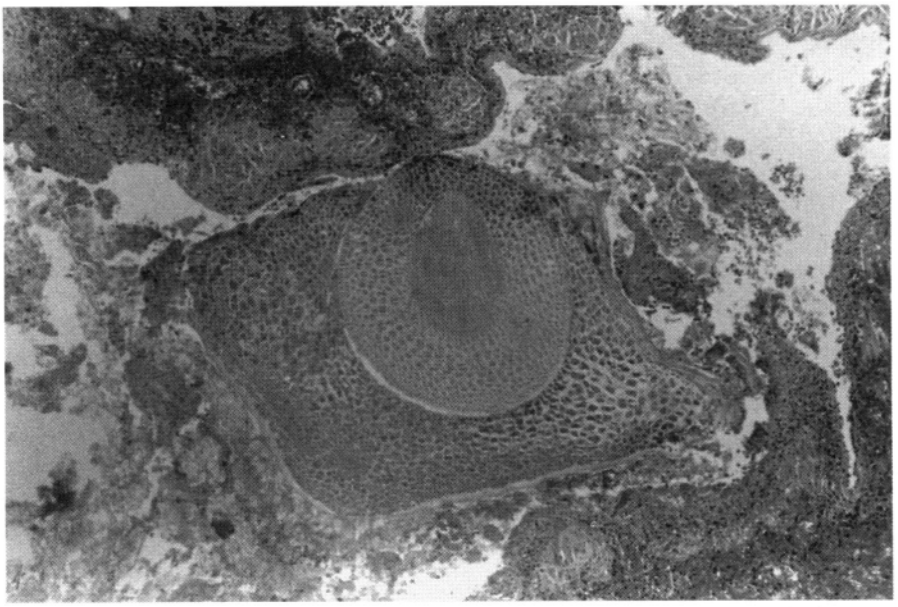

FIGURE 2. Microphotography of the lung of a patient who died from aspiration pneumonia. The photograph shows vegetable fibers in the alveoli.

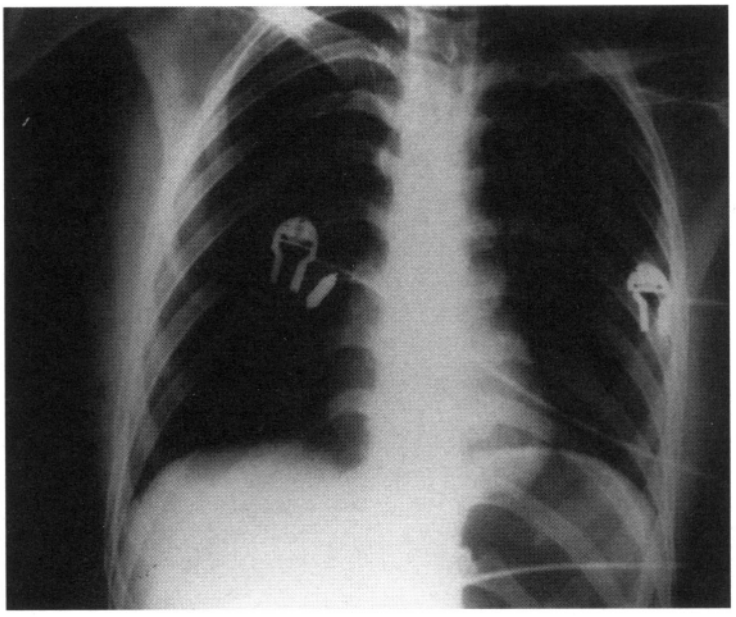

FIGURE 3. Light-bulb aspiration following instrumentalization for endotracheal intubation (Courtesy of Miguel Leon, Hospital de Lleida).

severe cyanosis, sudden dyspnea, inability to talk (this is the principal sign that suggests diagnosis), and sudden acute respiratory distress. In this case, the obstructing material must be removed to avoid immediate death. When the aspirated material is a piece of food, often meat, ingested during a meal the situation may appear to be an acute myocardial infarction; this is known as the "cafe coronary syndrome." In these cases, a rapid Heimlich maneuver should be performed to dislodge the particle. This involves the application of rapid, firm pressure on the upper abdomen in an effort to force the diaphragm upward, increasing abdominal pressure and secondarily intrathoracic pressure (Halmagyi et al., 1962; Lansing & Jamieson, 1963; Kim et al., 1973; Aabdulmajid et al., 1976; Bartlett & Gorbach, 1975a; Bartlett, 1987; Finegold, 1991; Irwin, 1996).

Aspiration of smaller particles causes less severe clinical manifestations of obstruction or simply partial obstruction, but involves peripheral and smaller-diameter airways. In this case, the principal symptom is a cough, followed by bronchial irritation. In contrast, when the obstruction affects a major bronchus it is characterized by cyanosis, dyspnea, wheezing, chest pain, nausea, and vomiting. Chest radiographs can show atelectasis or obstructive emphysema. When the obstruction is partial or incomplete, unilateral wheezing with chest pain may develop, whereas in some cases an expiration radiograph will suggest the diagnosis, showing a shift in the mediastinum (Lansing & Jamieson, 1963; Kim et al., 1973; Aabdulmajid et al., 1976; Bartlett & Gorbach, 1975a).

These patients require medical attention in two stages that present different clinical aspects: (1) the early obstructive or irritative phase; and (2) a later stage characterized by bacterial complications. Bacterial infection is a common complication when the complete or partial obstruction persists for more than 7 days, and includes pneumonitis, bronchiectasis, empyema, and lung abscess. An important clue is that infections involve the same anatomic site as the obstruction. The most commonly involved pathogens are anaerobic bacteria, usually present in the upper airways. Unfortunately, few reports have used appropriate diagnostic methods to analyze the bacteriologic pattern of infection secondary to obstruction by solid particles. In experimental studies, cotton plugs have been used to obstruct the lower airway, and the pneumonia that develops distal to the obstruction usually involves a mixture of aerobic and anaerobic bacteria—predominantly the latter—from the oropharyngeal flora (Toews et al., 1979; Bartlett, 1993a,b; Irwin, 1996).

Aspiration of Pathogenic Bacteria

The most common form of aspiration pneumonia results from aspiration of bacteria that reside in the upper airways and stomach. Aspirative pleuropulmonary infections are frequently produced as a consequence of repetitive microaspiration of anaerobic and microaerophilic bacteria from the oropharyngeal cavity or the stomach (Bartlett & Gorbach, 1975a; Finegold, 1991; Donowitz & Mandell, 1995). This syndrome can have three different forms of presentation: aspirative pneumonitis, necrotizing pneumonia, and lung abscess (Gudiol & Carratala, 1999). The differences between them are only formal, as they are expressions of the same process at different stages of development. Aspirative pneumonitis is the first manifestation, and chest radiographs are characterized by the presence of infiltrates without cavitation. Necrotizing pneumonia is also characterized by small, multiple cavitations. Finally, lung abscess presents one or many cavitations 2 cm or more in diameter, very often with a hydroaereal level (Bartlett, 1993a,b; Irwin, 1996). All three presentations can be associated with an empyema. Many authors propose the term anaerobic pleuropulmonary infections (API) to cover the different clinical forms in which anaerobic bacteria have a predominant role (Bartlett, 1993a; Gudiol et al., 1990). The concept of API helps to differentiate the entity from other pneumonic processes such as nosocomial gram-negative pneumonia or tuberculous abscess.

The most common CAP is due to bacterial aspiration of *S. pneumoniae* and anaerobes (Lorber & Swenson, 1974; Pick & Reynolds, 1983). Today, an important problem is differentiating API from typical bacterial pneumonia caused by *S. pneumoniae, H. inftuenzae,* gram-negative bacilli, or *S. aureus,* because in most cases bacterial pneumonia is also secondary to upper airway aspiration (Donowitz & Mandell, 1995; Leroy et al., 1997; Gudiol

& Carratala, 1999). For example, pneumococcal pneumonia probably occurs because an aspirated inoculum of *S. pneumoniae* cannot be cleared and detoxified by pulmonary defenses (mucociliary clearance and alveolar phagocytosis). One difference with regard to classical aspiration pneumonia is the volume of inoculum, because a typical bacterial pneumonia is usually caused by more virulent organisms and a smaller quantity of aspiration is required. In an API, larger volumes of aspiration are necessary, and generally these patients have altered mechanisms of defense, such as unconsciousness, dysphagia, or alteration of the pulmonary mechanisms of clearance (Lorber & Swenson, 1974; Bartlett et al., 1974; Bartlett, 1992; Finegold, 1995; Gudiol & Carratala, 1999).

The incidence of API is decreasing as a result of improvements in the social and economic conditions in industrialized countries in the last 40 years. But there is still little information about its real incidence. The majority of cases published in the literature are described as lung abscesses, and their incidence has been estimated to be 3 to 5 cases per 100,000 persons/year (Fick & Reynolds, 1983; Gudiol & Carratala, 1999). In studies of CAP with appropriate diagnostic methods, anaerobes are detected in 22% to 33% of cases (Pollack et al., 1983; Gudiol et al., 1990). In fact, many studies suggest that the incidence of API may be even higher in either community-acquired or nosocomial pneumonia episodes (Leroy et al., 1997; Donowitz & Mandell, 1995; Rello et al., 1997).

The three major virulence factors in API are the ability to adhere to or invade mucosal surfaces; the production of enzymes, toxins, or other factors that play a pathogenic role; and the presence of surface components such as polysaccharides or lipopolysaccharides (Bartlett, 1987, 1993a; Finegold, 1991, 1995). The risk factors for API are similar to the other forms of the aspiration syndrome, but poor oral hygiene is particularly prevalent. Normal hosts are transient carriers of primary endogenous flora involving *S. pneumoniae, Streptococcus pyogenes, H. influenzae,* and *Moraxella catarrhalis.* The presence of periodontal disease is very important because it increases the levels of oral bacteria in the saliva and changes the composition of the salivary flora. Aspiration of oropharyngeal secretions, mainly saliva, explain many of the anaerobic bacteria that have been cultured from aspiration pneumonia (Bartlett & Gorbach, 1975a; Bartlett, 1987, 1992; Finegold, 1991). Although the bacterial flora of the oropharynx can be altered by a range of processes such as severe underlying diseases, malnutrition, antibiotic therapy, or chronic gastroesophageal reflux, the role of periodontal disease is crucial (Bartlett & Gorbach, 1975a; Loesche et al., 1995a,b; Langmore et al., 1998). Indeed, about 1011 colony-forming units of bacteria are shed from buccal mucosa, gingival sulcus, and teeth per day (Bartlett, 1992; Finegold, 1995). The bacteria that originate specifically in the oropharyngeal flora are extremely complex. Rosebury lists 21 different genera of bacteria considered normal cohabitants of the upper airway (Johanson et al., 1969). The development of periodontal disease (gingivitis, plaque erosion, and tooth decay) contributes to the change in normal flora. Langmore et al. (1998) found the presence of periodontal disease and aspiration pneumonia to be associated in bivariate analysis. Another important problem that alters the normal flora of the mouth is a reduction of the salivary flow (e.g., after drug administration), which increases the concentration of bacteria in saliva; if aspirated, up to 108 bacteria per milliliter of fluid could enter the lungs (Loesche et al., 1995a). An increase in the proteolytic activity of the saliva can damage the fibronectin (a glucoprotein that covers the surface of the oral mucosa). The fibronectin interacts with the receptor of the normal gram-positive flora in the oropharynx. A lack of fibronectin results in the exposure of receptors of the epithelial cellular surface to aerobic gram-negative flora (Finegold, 1991, 1995; Langmore et al., 1998).

The clinical features of API in a susceptible host include fever, cough, purulent sputum, dyspnea, and pulmonary infiltrates in dependent segments of the lung. Specific clinical features depend on the virulence of bacteria, volume of aspiration, and the host's defensive status. The process of pneumonia is generally indolent in the initial phase and is manifested by anorexia, tiredness, sweating, weight loss, and low fever for several days, or even weeks. Later, in the majority of cases, fever rises and an intense cough appears, producing purulent, usually putrid sputum. Presentation may be severe in patients who do not receive rapid medical atten-

tion and treatment. The initial lesion is pneumonitis, but it can progress to necrotizing pneumonia or lung abscess with empyema (or a bronchopleural fistula). Patients with aspirative pneumonitis usually have a history of acute episodes, frequently diagnosed as a "classical bacterial pneumonia," followed by development of necrotizing pneumonia or lung abscess. The most frequent signs and symptoms of lung abscess are cough, fever (initially subacute), putrid sputum, pleuritic pain, weight loss, and hemoptysis (Bartlett, 1987, 1991; Finegold, 1991, 1995; Gudiol & Carratala, 1999). The typical case of API in characterized by pulmonary infiltrates in dependent pulmonary zones accompanied by an indolent clinical course in the presence of classical risk factors (impaired mental status, dysphagia, advanced age) plus poor oral hygiene or periodontal disease (Bartlett & Finegold, 1974; Bartlett & Gorbach, 1975a; Bartlett, 1987, 1993b; Finegold, 1991, 1995). The pulmonary infiltrates, with or without cavitation, are frequently localized in dependent pulmonary zones, either in the posterior segments of the upper lobes or apical segments of the lower lobes, which are the lowest zones in the recumbent position. Basilar pulmonary segments of the lower lobes are favored in patients who aspirate in the sitting or upright position. Computed tomography is useful when cavitation is suspected, in the presence of pleural injury, if an underlying tumoral mass is suspected, or in selected cases with delayed resolution, but it should never be a routine screening test (Bartlett, 1992, 1993a,b).

Large-volume aspiration of oropharyngeal or gastric contents usually results in an infection caused by polymicrobial flora. Specimens to establish a microbiologic diagnosis in pulmonary infections include blood, pleural fluid, transthoracic aspirates, tracheal aspirates, and bronchoscopic samples (Bartlett, 1977,1993a,b; Gudiol & Carratala, 1999). In the first three cases information is limited because blood cultures are positive in less than 2% of cases, empyema occurs in a minority of patients, and transthoracic aspiration is indicated in only selected cases (Bartlett, 1987; Gudiol et al., 1990). The use of samples of expectorated sputum is even less effective, because they are usually contaminated with organisms from the upper airways many of which are causes of API (Bartlett, 1993b; Finegold, 1991,1995; Langmore et al., 1998). The classical studies of Bartlett and Finegold (1974) of patients with necrotizing pneumonia or lung abscess, using transtracheal aspiration, obtained approximately five pathogens per sample, for the most part anaerobic bacteria and less frequently aerobic or microaerobic bacteria. This finding was confirmed by other procedures (e.g., bronchoscopy) to obtain samples for microbiologic investigation, but these studies showed a lower percentage of cases of *Bacteroides fragilis* and Enterobacteriaceae (Gudiol et al., 1990; Henriquez et al., 1991; Bartlett, 1992; Barreiro et al., 1994; Donowitz & Mandell, 1995; Gudiol & Carratala, 1999).

The three most important pathogenic groups in API are gram-positive anaerobic cocci *(Peptostreptococcus),* gram-negative bacilli *(Prevotella, Porphyromonas,* and *Bacteroides* species, including *Bacteroides fragilis)* and *Fusobacterium* (especially *Fusobacterium nucleatum).* Gram-negative bacilli are particularly frequent in nosocomial episodes of aspiration pneumonia, because these bacteria are not usually resident in the normal oropharyngeal flora of healthy people (Bartlett, 1992; Finegold, 1991,1995; Langmore et al., 1998; Gudiol & Carratala, 1999). Therefore, many studies indicate that the rate of colonization of the upper airway is directly correlated with the severity of associated conditions (Bartlett, 1992). This observation reflects the differences in microbiological patterns between CAP and hospital-acquired aspiration pneumonia. Hospitalized patients can present oropharyngeal colonization with enteric gram-negative bacilli (e.g., *Escherichia coli* or *Klebsiella pneumoniae), Pseudomonas* sp., or *S. aureus.* These bacteria can be considered potential pathogens in hospital-acquired aspiration pneumonia (Bartlett & Gorbach, 1975a; Bartlett, 1987, 1993a,b; Finegold, 1995). This finding was confirmed by Bartlett & Gorbach (1975a,b), who evaluated the bacteriologic pattern of aspiration pneumonia in the community versus the hospital setting. The API presents particularly useful clues, which are described in Table 5. The most frequently isolated aerobic and facultative bacteria are *H. influenzae* and some enterobacteria *(E. coli* and *K. pneumoniae),* which are isolated in 5% to 10% of cases, and, increasingly often, *Viridans* group streptococci (Stewardson & Nyhus, 1977). *Streptococcus anginosus* is isolated in more than 20% of specimens from patients with lung abscess and in more than 50% of patients with pleural empyema, in many cases as the only respon-

TABLE 5. Characteristics of Anaerobic Pleuropulmonary Infections

Unique morphology on Gram's stain
Growth in anaerobic zone of fluid media or of agar deeps
Characteristic colonies on agar plates (anaerobic)
No growth on routine cultures ("sterile pus")
Gas in tissues
Tissue necrosis, gangrene, abscess
Septic thrombophlebitis
Cancer as underlying disease
Previous antimicrobial treatment with an aminoglycoside, trimethoprim/sulfamethoxazole, quinolones, or cephalosporins with poor activity against anaerobes

sible pathogen (Stewardson & Nyhus, 1977; Jerng, 1977).

Treatment

The best therapeutic approach, as in other medical complications, is prevention strategies targeted at specific risk populations. Prophylaxis is the best strategy for reducing mortality from aspiration pneumonia, but it is very difficult to perform in the community setting. In intubated patients, preventing microaspiration of secretions by using continuous subglottic secretions drainage significantly reduces episodes of pneumonia over the first week of intubation, particularly in patients without antibiotic exposure (Vallés et al., 1995). Specific details regarding prevention of aspiration pneumonia have been discussed above. Approaches to the treatment of aspiration pneumonia vary depending on the specific characteristics of each type of aspiration: toxic action, obstruction, or infection.

Aspiration of Toxic Fluids (Mendelson's Syndrome)

Aspiration of acid fluids (gastric juice) is compared with a chemical burn in which most of the injury has occurred by the time the patient is initially treated. Similar considerations are also valid for aspiration of biliary contents. The most important procedure is an early correction of hypoxia by vigorous, immediate oxygenation (Boysen & Modell, 1995). The aim of mechanical ventilation with positive end-expiratory pressure is to improve oxygenation, reduce pulmonary shunt, increase the residual functional capacity, and increase alveolar pressure so as to reduce the transduction of fluids. In a patient at high risk of developing this complication, prophylactic intubation should be considered for airway protection until the patient is awake. Elevation of the head of the bed also decreases gastroesophageal reflux and the risk of aspiration. Repeated tracheal suction is often necessary to keep the airway clear of fluids and particulate matter which may cause an inflammatory process or obstruction (Bartlett & Gorbach, 1975a; Toews et al., 1979; Bartlett, 1992; Irwin, 1996).

Intravenous fluid support is very important for expanding intravascular space in patients with severe hypotension. The detection of infiltrates by x-ray should suggest noncardiogenic pulmonary edema; these patients often have intravascular volume depletion, and central venous pressure is low. Colloids should be given to restore intravascular volume and osmotic pressure, although their actual value, compared with administration of saline solution or other nonosmotic fluids, remains controversial (Bartlett & Gorbach, 1975a,b; Bynum & Pierce, 1976; Boysen & Modell, 1995).

Tracheal inoculation of buffering solutions to neutralize the corrosive action of the toxin is futile, because fluids are neutralized within a few minutes by normal lung defenses. The same can be said of pulmonary lavage, as pulmonary injury has already occurred by the time of diagnosis. The local instillation of diluents are specifically contraindicated, because they would add mechanical obstruction to an already compromised airway (Bartlett & Gorbach, 1975b; Boysen & Modell, 1995). One controversial area for many years was the use of corticosteroids in the therapy of acid aspiration (Wolfe, 1997). Some (though not all) studies in animals have produced promising results, but in humans this approach has been uniformly unsuccessful, so this therapy is not indicated today. These drugs should not be administered in patients with acute lung injury—a relatively common complication in these cases—and ongoing studies are evaluating their usefulness in the late proliferative phase (Johanson et al., 1974; Bynum & Pierce, 1976; Bartlett, 1992; Irwin, 1996).

The role of antibiotics in acid pneumonitis is controversial. Most studies in animals and in humans concluded that the bacterial burden is not an

important factor in the initial acute process. Indeed, the pH of the inoculum required to initiate an acid pneumonitis is incompatible with bacterial survival. On the other hand, some studies in animals have shown that lung injury by acid aspiration is particularly susceptible to bacterial challenge (Dines et al., 1970). The use of antimicrobial therapy is common in many cases of acid pneumonitis because it is very difficult to rule out the coexistence of respiratory infection as a contributing factor. Superinfections occur in 13% to 26% of patients during the course of chemical pneumonitis (Bynum & Pierce, 1976; Finegold et al., 1985; Irwin, 1996), but there is no evidence today in favor of the use of prophylactic antibiotics in this setting (Bartlett, 1992). Antibiotics should be used only when the chemical pneumonitis is complicated by pulmonary infection. Infectious complications of aspiration should be suspected if worsening occurs, such as fever, leukocytosis, or radiographic infiltrates after initial stabilization or improvement.

Recent studies in animals suggest a possible role for intratracheal instillation of antibodies to adhesion molecules including selectins and integrins (Matthay & Rosen, 1996). Many studies suggest that antibodies to selectins, β2 integrins, and intercellular adhesion molecules may be involved in a range of types of lung injury such as allograft rejection, ischemia reperfusion, or immune complex-mediated lung injury (Mulligan et al., 1995; Albelda et al., 1995). A primary objective is to inhibit neutrophil activity and to decrease and avoid inflammatory responses. Other investigators have reported that intravenous administration of anti-tumor necrosis factor-α antibody therapy can reduce influx of neutrophils into the alveolar space, and their deformability and activation as well. In summary, the objective of new therapies is to inhibit neutrophil adhesion, chemotaxis, and activation after aspiration-induced lung injury (Doerschuk et al., 1990; Albelda et al., 1995; Goldmann et al., 1995; Mulligan et al., 1995; Matthay & Rosen, 1996; Gallego et al., 1997).

Aspiration of Inert Fluids

Obstruction is the major problem for large-volume aspiration of water or other inert fluids. The most effective treatment is immediate tracheal suction. If a chest radiograph does not show pulmonary infiltrates, further treatment is not required, and efforts should focus on preventing a new episode of aspiration. Ventilatory support with positive pressure and high oxygen concentrations combined with vasoactive drugs may be necessary in selected cases with poor recovery. Once again, antibiotic prescription is recommended only when there is evidence of pulmonary infection; prophylactic use of broad-spectrum antibiotics only contributes to the selection of resistant pathogens (Bartlett & Gorbach, 1975a,b; Boysen & Modell, 1995).

Aspiration of Solid Particles

The most important procedure is the removal of the foreign body from the lower airways in order to resolve mechanical obstruction. Fiber-optic bronchoscopy is the therapy of choice in the case of an obstruction of the lower airways that does not totally block the trachea. Solid particles that do totally obstruct the trachea must be removed immediately by subdiaphragmatic abdominal thrusts and finger sweeps in the unconscious patient, or by chest thrusts in highly obese patients or those in advanced stages of pregnancy. Potentially infectious complications should be treated accordingly. As in the conditions mentioned above, systematic prophylactic therapy with antibiotics should be discouraged (Bartlett & Gorbach, 1975a,b; Bartlett, 1992; Irwin, 1996), but aspiration of solid particles with obstruction predisposes individuals to anaerobic bacterial superinfections.

Aspiration of Pathogenic Bacteria

In contrast to the conditions discussed above, a key point here is the systematic use of antibiotic therapy, because large-inoculum aspiration of pathogenic bacteria is uniformly associated with development of API. Clearly, if the pathogens responsible are identified by appropriate bacteriologic studies, specific antimicrobial agents should be selected. In clinical practice, however, it is impossible to obtain samples in a large proportion of patients, and microbiologic tests are frequently negative in others. In the presence of clinical signs of sepsis, empirical therapy should not be delayed until the microbiologic results are available. The choice of

initial empirical antibiotic treatment requires knowledge of the most frequently involved potential pathogens, as well as the percentage of resistance in each geographic area. Establishing this last point is difficult, because most epidemiologic and microbiologic studies of aspiration pneumonia are based on diagnostic methods with poor specificity; in addition, most of these studies were performed in the 1970s or 1980s. Invasive testing is usually performed only when the specimen can be obtained easily (e.g., thoracentesis in the presence of empyema), when diagnosis is doubtful, in the presence of poor clinical resolution, or to rule out associated illness, such as a tracheoesophageal fistula or a lung neoplasm (Bartlett & Gorbach, 1975a,b; Mays et al., 1976; Bartlett, 1987, 1993b; Fine et al., 1990; Gudiol et al., 1990; Leroy et al., 1995). Adjunctive therapies include respiratory physiotherapy, postural drainage, requirement of mechanical ventilation, thoracentesis, pleural drainage, or fibrinolytic agents for selected empyemas. Surgery should be restricted to selected cases associated with poor resolution.

Bartlett and Gorbach (1975a) reported the preponderant role of anaerobic flora in aspiration pneumonia and the concept of synergy in mixed aerobic/anaerobic infections. They recommended that therapy for aspiration pneumonia be directed at anaerobic bacterial flora and sporadically at specific aerobic bacteria (Bartlett et al., 1974; Bartlett & Finegold, 1974; Bartlett & Gorbach, 1975a,b; Finegold et al., 1985; Finegold, 1991). Other authors have demonstrated that lung abscesses usually have a satisfactory outcome with long-term antibiotic therapy alone, whereas a surgical approach should be discouraged as it is associated with higher morbidity and mortality rates(Weiss & Chermiack, 1974). In a retrospective series, Bartlett & Gorbach (1975b) observed that penicillin at high doses and clindamycin had similar efficacy, reaching about 90% of clinical and radiologic resolution. In the same study, the authors reported a great individual variation in clinical and radiologic response, regardless of choice of antimicrobial treatment. Differences in either underlying conditions of patients, infiltrate extension, or the size of cavities may explain the variability in clinical response, manifested in different periods of resolution or it the percentages of therapeutic failure (Bartlett & Gorbach, 1975b). As a result of these studies, the use of penicillin G at high doses over 6 to 8 weeks became widespread as the treatment of choice. Administration of clindamycin was used as an alternative option, due to its higher cost and its greater risk of side effects, but a similar clinical response was obtained (Bartlett et al., 1974; Bartlett & Gorbach, 1975b; Levinson et al., 1983; Gudiol et al., 1990; Finegold, 1991, 1995; Gudiol & Carratala, 1999). Metronidazole, another first-line antianaerobic agent, should not be used as a single agent because approximately 50% of patients do not respond, probably due to the presence of aerobic and microaerophilic streptococci (Sanders et al., 1979; Perlino, 1981; Irwin, 1996). As a result of these findings, most patients have been treated with penicillin, with excellent results due to the low rates of resistance to penicillin among the flora involved.

Unfortunately, penicillin resistance became a problem in the mid-1980s, when up to 40% *of Fusobacterium* spp. and 60% of *Bacteroides nonfragilis* were reported to produce penicillinases (Bartlett, 1993; Finegold et al., 1985; Finegold, 1991). In 1983, Levinson et al. reported a randomized study in which clindamycin showed better efficacy than penicillin in patients with API. In 1990, a study by Gudiol et al. confirmed these findings, showing a clinical failure rate of approximately 40% in patients treated with penicillin. These authors obtained highly specific bronchoscopic samples in all patients at the beginning of the process, with additional sampling in cases with poor resolution (Gudiol et al., 1990). They found most episodes of penicillin failure to be secondary to the presence of *Prevotella melaninogenica,* which produces β-lactamases. The mechanisms by which these anaerobic bacteria become resistant to β-lactams are similar to those described in aerobes; one of them is the production of β-lactams. Changes in penicillin-binding proteins were associated with subsequent changes in membrane permeability to β-lactams (Table 6) (Finegold, 1995). Therefore, clindamycin alone or in combination with a β-lactam was recommended as the treatment of choice for API in a wide range of publications on the subject between 1985 and 1995.

Once again, an increase in the incidence of anaerobic bacteria resistant to clindamycin has recently been reported, raising concern about the

TABLE 6. Anaerobes Responsible for Aspiration Pneumonia that Produce β-lactamases[a]

Bacteroides fragilis group	*Porphyromonas* spp.
Bacteroides coagulans	*Fusobacterium* spp.
Prevotella spp.	*Bilophila wadsworthia*
P. oralis	

[a]Some strains of the anaerobes produce β-lactamase.

widespread use of this agent as a first-line therapy. One excellent alternative for API therapy is the combination of a β-lactam and a β-lactamase inhibitor, such as amoxicillin–clavulanate, because these agents are active against almost all anaerobic bacteria involved in aspiration pneumonia, along with streptococci of the *Viridans* group, as well as other potentially involved pathogens such as *S. aureus, S. pneumoniae,* or *H. influenzae.* Recent results obtained by Barreiro et al. (1994) with amoxicillin-clavulanate showed a clinical efficacy rate above 90%, with no therapeutic failures due to resistant bacteria. The route of administration should be intravenous during the first 2 weeks, and then oral, followed by early discharge. Patients with cavitation should prolong oral therapy for at least 4 more weeks (Finegold, 1991, 1995; Barreiro et al., 1994; Donowitz & Mandell, 1995).

Therapy with broader-spectrum antimicrobials, such as carbapenems or fourth-generation quinolones, should be considered only in cases with poor response to the first-line options or in specific patients with a high suspicion of previous colonization by multidrug-resistant pathogens, such as *Pseudomonas aeruginosa.* In addition, fourth-generation quinolones are the drugs of choice for patients with known hypersensitivity to β-lactams.

A range of studies of API have shown that therapy failure is frequently associated with resistant pathogens, more frequently anaerobic bacteria than facultative or aerobic bacteria, whereas an insufficient period of therapy is the most important factor in relapses. Treatment should therefore be long-term. Table 7 displays the sensitivity of the most frequent pathogenic flora in patients with aspiration pneumonia. Interestingly, aspiration of fluids in certain conditions predisposes patients to developing infection by specific pathogens. As proposed in a comprehensive review by Ender and Dolan (1997), individualized choices are required.

Conclusions

In summary, aspiration pneumonia is the result of large-volume aspiration into the lower airways of material from the upper respiratory or digestive tracts. Aspiration is suspected in approximately 10% of patients hospitalized due to CAP. The syndrome is subdivided into three different forms, depending on the nature of the inoculum, and each form has specific clinical presentations and therapies. These presentations include toxic injury of the

TABLE 7. Pattern of Microbiological Resistance in Anaerobic Pleuropulmonary Infections

Pathogen	Penicillin	Clindamycin	Amoxicillin + clavulanate	Metronidazole	Third-generation cephalosporin[a]	Imipenem/ Meropenem	Piperacillin ± tazobactam
Bacteroides fragilis	80–90[b]	30–40	<5	<5	50	<5	<5
B. nonfragilis	50	10	<5	<5	>50	<5	<5
B. gracilis	>50	20–30	5–10	5–15	40	<5	10
Prevotella sp.	60	<5	<5	10–15	10	<5	<5
Porphyromonas sp.	25	<5	<5	20	15	<5	<5
Fusobacterium sp.	10	0	0	<5	10	<5	<5
Bilophila wadsworthi	60	15	<5	<5	10	<5	<5
Peptostreptococcus sp.	<5	10	<5	15	<5	<5	<5
Streptococcus milleri	<5	10	<5	15	<5	<5	<5

[a]Includes ceftazidime, ceftriaxone, and cefotaxime.
[b]Values are expressed as percentages of strains that are resistant.

lung (Mendelson's syndrome), obstruction by foreign bodies or fluids, and infection. Aspiration pneumonia should be suspected in those patients with pulmonary infiltrates and a predisposing cause of aspiration (e.g., dysphagia or fall in consciousness). Anaerobes should be suspected in the presence of periodontitis, putrid discharge, infection complicating obstruction, and necrosis of tissue with cavitation or abscess formation. Empiric antibiotic coverage for suspected pathogens (anaerobic predominance) is generally appropriate. Penicillin and clindamycin, until recently the drugs of choice, should now be considered second-line therapies due to the progressive emergence of resistance; these agents should therefore be used with caution when selected empirically. Currently, β-lactam/β-lactamase inhibitor combination is the therapy of choice. Carbapenems are equally effective, but more expensive. Fourth-generation quinolones are excellent alternatives in patients with β-lactam hypersensitivity.

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16

Complicated Pleural Effusion in Community-Acquired Pneumonia

RICHARD W. LIGHT

Definitions and Introduction

Any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis is a *parapneumonic* effusion (Light et al., 1973). A complicated parapneumonic effusion is a parapneumonic effusion for which tube thoracostomy is necessary for its resolution. A loculated parapneumonic effusion is a parapneumonic effusion that is not free-flowing. A multiloculated parapneumonic effusion is a loculated parapneumonic effusion with more than one compartment. An empyema is, by definition, pus in the pleural space. Pus is thick, purulent-appearing fluid. Most empyemas are complicated parapneumonic effusions, but some empyemas have no associated pneumonia.

The annual incidence of bacterial pneumonia in the United States is approximately 4 million, and nearly 1 million of these patients are hospitalized (Neiderman et al., 1993). The incidence of parapneumonic effusion in patients hospitalized with pneumonia is about 40% (Light et al., 1980). The morbidity and mortality rate in patients with pneumonia and pleural effusions are higher than in patients with pneumonia alone. In a study by Hasley et al. (1996), the relative risk of mortality in patients with community-acquired pneumonia and bilateral effusions was 7.0 and was 3.4 for patients with unilateral pleural effusion of moderate or greater size. The mortality rate was 26% for patients with bilateral pleural effusions and 14.7% for patients with moderate or larger pleural effusion. Delay in instituting proper therapy for these effusions is responsible for much of the increased morbidity and mortality.

RICHARD W. LIGHT • Saint Thomas Hospital and Vanderbilt University, Nashville, Tennessee 37205.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

History

The first writing on empyema dates back to the time of Hippocrates in ancient Greece about 500 BC. At this early time, he treated empyemas with open drainage (Adams, 1948). Hippocrates recognized that the prognosis of a patient with an empyema depended on the characteristics of the pleural fluid when he wrote the following: "Those cases of empyema which are treated by incision or the cautery, if the water flows rapidly all at once certainly prove fatal. When empyema is treated, either by the incision or the cautery, if pure and white pus flows slowly from the wound, the patients recover" (Adams, 1948). If the fluid was clear the patient probably did not have an empyema, the lung collapsed when open drainage was initiated, and the patient died. Alternatively, if pus was obtained when open drainage was initiated, the pleural infection was drained and the patient benefitted.

Open drainage was the primary treatment of empyema from the time of Hippocrates until the middle of the 19th century. At this time, thoracentesis became a more frequently used procedure. Trousseau (1987) in France, and Bowditch (1853) in the United States demonstrated that open drainage

was not necessary in many cases. The next advance was provided by Hewitt (1876), who described a method of closed drainage of the chest in which a rubber tube was placed into the empyema cavity through a cannula. He was the first to use the water seal for chest tubes.

By the end of the 19th century it was well recognized that a significant problem when dealing with empyema was the management of the empyema cavity. As long as a cavity persisted, it was very difficult to eradicate the pleural infection. The cavity persists because the thick coating of fibrous tissue on the visceral pleura prevents the underlying lung from expanding. Thoracoplasty was proposed as a solution to the cavity problem in the 1890s by Estlander (1897) and Schede (1890). Thoracoplasty involves resection of the ribs, intercostal muscles, and parietal pleural peel which lie over the cavity. The remaining defect is covered by the few remaining muscles, the scapula, and the subcutaneous tissue and skin. Thoracoplasty does eliminate the cavity, but it involves major surgery which is disfiguring. At about the same time that thoracoplasty was described, Fowler (1893) and Beck (1897) proposed decortication as a solution to the cavity problem. With decortication, all the fibrous tissue is removed from the visceral pleura, which allows the underlying lung to expand. In addition, all fibrous tissue is removed from the parietal pleura and all pus is removed from the pleural space.

The treatment of parapneumonic effusions and empyema received a thorough review after catastrophic results were obtained with the treatment of parapneumonic effusions during World War I. Despite the fact that Hippocrates realized 2400 years previously, and Paget (1896) had again emphasized that open drainage should not be instituted for empyema before at least the 15th day of the illness, by World War I open drainage had become the accepted treatment for *all* cases of parapneumonic effusions. During World War I there was a high incidence of parapneumonic effusions among American soldiers, and the treatment of all such patients with open drainage had disastrous results. The United States Surgeon General in 1919 found that the average mortality of individuals with pleural infections was 30.2%, and in some hospitals the mortality rate was as high as 70% (Graham & Bell, 1918). The explanation for the high mortality was that the open drainage procedures were performed too early, resulting in collapse of the underlying lung. *Streptococcus hemolyticus* was responsible for many of these cases and this organism characteristically produces a large nonloculated pleural effusion (Olch & Evarts, 1989).

An empyema commission headed by Evarts Graham was formed at this time to address the high mortality. Graham (1925) demonstrated that when dogs with experimental empyema were treated early with open drainage, the mortality rate was higher and deaths occurred earlier than in dogs who were not treated with open drainage. The Empyema Commission (1918) made the following recommendations: (1) The pleural fluid should be drained, but one must avoid an open pneumothorax in the acute pneumonic phase; (2) care should be taken to avoid a chronic empyema by rapid sterilization and obliteration of the infected cavity; and (3) careful attention should be paid to the nutrition of the patient. When these guidelines were followed, the mortality from streptococcal empyema secondary to influenza fell to 4.3% (Stone, 1919). In general, these guidelines are still useful. However, some surgeons use these guidelines to justify a delay of several weeks before decortication is performed in patients with complicated parapneumonic effusions. There is no need to delay decortication as long as open drainage procedures are not used (Morinetal, 1972; Hoover et al., 1986).

Natural History of Parapneumonic Effusions

The evolution of a parapneumonic pleural effusion can be divided into three stages which are not sharply defined, but rather form a continuous spectrum. The first stage is the *exudative stage* in which there is the initial accumulation of fluid in the pleural space. Most of the pleural fluid probably originates in the interstitial spaces of the lung (Wiener-Kronish et al., 1993), but it may also come from the capillaries in the visceral or parietal pleura. In the exudative stage, the pleural fluid is characterized by a low white blood cell (WBC) count and lactic acid dehydrogenase (LDH) level, and a normal glucose level and pH (Light, 1995). The pleural fluid is not loculated and the underlying

lung freely expands if the pleural fluid is removed. If appropriate antibiotic therapy is instituted at this time, the pleural effusion does not progress to the fibropurulent stage and tube thoracostomy is not required (Light, 1995).

The second stage is the *fibropurulent stage,* which is characterized by the accumulation of large amounts of pleural fluid with many polymorphonuclear leukocytes, bacteria, and cellular debris. As this stage progresses, the pleural fluid pH and glucose level become progressively lower and the LDH level progressively higher. The pleural fluid WBC count is frequently lower than one would anticipate from looking at the thickness of the fluid; fibrin and cellular debris rather than intact white cells account for the thickness and opacity of the fluid. Fibrin is deposited in a continuous sheet covering both the visceral and parietal pleura. As this stage progresses, there is a tendency toward loculation and the formation of limiting membranes. These loculations contain the infected pleural fluid within compartments, but make drainage of the pleural space increasingly difficult. As the layer of fibrous tissue becomes thicker, the cavity in the pleural space becomes more difficult to eradicate.

The third stage is the *organization stage,* which is characterized by the growth of fibroblasts into the thick exudate from both the visceral and parietal pleural surfaces to produce an inelastic membrane called the pleural peel. The peel prevents the underlying lung from expanding; a decortication is required to cure the patient at this stage. In this stage, the fluid is usually multiloculated and thick. If the patient is not treated, the fluid may drain spontaneously through the chest wall *(empyema necessitatis)* or into the lung, producing a bronchopleural fistula. If a bronchopleural fistula develops in this situation, immediate drainage of the pus from the pleural space is imperative. Otherwise the pus from the pleural space will enter the tracheobronchial tree and produce an overwhelming pneumonia (Light, 1995).

Classification of Parapneumonic Effusions

It is important to realize that not all parapneumonic effusions are the same. A patient with a very small effusion will do well regardless of treatment as long as appropriate antibiotics are given. In contrast, a patient with multiloculated pus in the pleural space will probably require a decortication. The classification outlined in Table I was developed to assist the practicing physician in the initial care of patients with parapneumonic effusions. However, this classification is probably most useful for stratifying patients with parapneumonic effusions who are research subjects. Much of the literature on parapneumonic effusions and empyema is confusing because there was no adequate description of the patients being studied. This classification is based on the amount of fluid, the gross characteristics of the pleural fluid, the biochemical characteristics of the pleural fluid, and whether or not the pleural fluid is loculated. Table 1 lists the classifications of pleural effusions in order of their severity. As severity increases, the treatment of the parapneumonic effusion becomes more difficult and increasingly invasive procedures are required (Light, 1995).

Class 1: Nonsignificant Parapneumonic Effusion

Patients with Class 1 parapneumonic effusions have free-flowing fluid which is less than 10 mm

TABLE 1. Classification of Parapneumonic Effusions and Empyema[a]

Class 1	Small
	Less than 10 mm thick of decubitus x-ray
	No thoracentesis indicated
Class 2	More than 10 mm thick
	Glucose >40 mg/dL, pH > 7.20
	Gram's stain and culture negative
Class 3	7.00 < pH <7.20 and/or LHD >1000 and/or loculation
	Glucose >40 mg/dL
	Gram's stain and culture negative
Class 4	pH <7.00 and/or glucose <40 mg/dL and/or positive
	Gram's stain culture
	Not loculated, no frank pus
Class 5	pH <7.00 and/or glucose <40 mg/dL and/or positive
	Gram's stain or culture
	Multiloculated
Class 6	Frank pus present
	Single locule or free flowing
Class 7	Frank pus present
	Multiple locules

[a]Adapted, with permission, from Light, 1995.

thick on the decubitus chest radiograph. Individuals with Class 1 effusions should not be subjected to thoracentesis because the effusion almost always resolves if they are treated with appropriate antibiotics (Light et al., 1980). In addition, a thoracentesis is more difficult in patients with a small amount of pleural fluid. If a patient with a Class 1 effusion subsequently develops a larger pleural effusion, a diagnostic thoracentesis should be performed.

Class 2: Typical Parapneumonic Effusion

Patients with a typical parapneumonic effusion have pleural fluid which is free-flowing with a thickness of greater than 10 mm on the decubitus radiograph. In addition the pleural fluid glucose is above 40 mg/dL, the pleural fluid pH is above 7.20, the pleural fluid LDH level is below three times the upper limit of normal for serum, and the bacterial smears and cultures are negative. Patients with Class 2 parapneumonic effusions require no invasive procedure other than the initial thoracentesis to delineate the characteristics of the pleural effusion (Light et al., 1980). If a Class 2 effusion rapidly enlarges or if the patient remains toxic with significant pleural fluid, then a repeat thoracentesis should be performed.

Class 3: Borderline Complicated Parapneumonic Effusion

Patients with Class 3 parapneumonic effusions have negative bacterial smears and cultures and a glucose above 40 mg/dL, but the pH is between 7.00 and 7.20, the LDH is above 1000 IU/L, or the pleural fluid is loculated. The relatively low pH, the relatively high LDH level, and the loculation all indicate a high level of inflammation in the pleural space. Some Class 3 pleural effusions will resolve with no invasive procedure, whereas others will not.

Class 4: Simple Complicated Parapneumonic Effusion

Patients with Class 4 parapneumonic effusions have a pleural fluid pH less than 7.00, a pleural fluid glucose level less than 40 mg/dL, and/or a positive gram stain or culture. The pleural fluid does not look like pus and it is not loculated. Patients with Class 4 parapneumonic effusions should be treated with some form of invasive therapy since many will not resolve solely with antibiotics.

Class 5: Complex Complicated Parapneumonic Effusion

Patients with Class 5 parapneumonic effusion meet all the criteria for Class 4 parapneumonic effusions, but in addition the fluid is loculated. These patients require thrombolytics or thoracoscopy to break down the adhesions, and some patients require thoracotomy with decortication.

Class 6: Simple Empyema

Patients with Class 6 parapneumonic effusions have pleural fluid which is frank pus that is either free-flowing or confined to a single loculus. These patients should be treated with a relatively large (~28–36 F) chest tube because the thick pus is likely to obstruct a smaller tube. Patients who have Class 6 parapneumonic effusions frequently have a thick peel over the visceral pleura which prevents the underlying lung from expanding. If a sizeable empyema cavity remains after several days of chest tube drainage, consideration should be given to performing a decortication in order to eradicate the empyema cavity.

Class 7: Complex Empyema

Patients with Class 7 parapneumonic effusions have frank pus in their pleural space which is multiloculated. Although these patients should initially be treated with large chest tubes and intrapleural thrombolytics, more invasive measures such as thoracoscopy with the breakdown of adhesions or thoracotomy with decortication are necessary in the majority of patients (Smith et al., 1991). If the drainage of the pleural space is unsatisfactory or a large empyema cavity remains after several days, either thoracoscopy or thoracotomy should be considered.

Animal Studies of Empyema

There are very few good clinical studies on therapy for parapneumonic effusions and empy-

ema. There are a few explanations for the lack of studies. As mentioned previously, there is tremendous diversity in patients who have parapneumonic effusions and for studies to be good, the patients must be stratified. However, once patients are stratified, a given medical center sees relatively few patients in a given category over a 1- or 2-year period. Since a given medical center sees relatively few patients, multicenter studies are required, but these are very expensive.

Since it is difficult to perform studies in humans, is it possible to answer some questions regarding the treatment of parapneumonic effusions and empyema using animal studies? Questions that could be addressed include: (1) What is the role of therapeutic thoracentesis in the management of these patients? (2) What is the role of thrombolytics in the management of these patients? (3) Is there a difference in the penetration of various antibiotics into empyema fluid? (4) Is there a role for intrapleural antibiotics in the treatment of these patients?

To answer these questions there needs to be a good model for parapneumonic effusions and empyema. There has been surprisingly little work done with experimental empyema. It is difficult to produce empyemas in animals. If *Staphylococcus aureus, Escherichia coli,* or *Bacteroides fragilis* are injected into the pleural space of guinea pigs, the animals either survive without developing empyema or die of overwhelming sepsis (Mavroudis et al., 1985).

Three different models of experimental empyema have been described. The first model was developed to assess the factors that influence the development of an empyema when bacteria are injected into the pleural space (Mavroudis et al., 1985). In this model, umbilical tape is placed in the pleural space of guinea pigs to facilitate the development of the empyema. Using this model, Mavroudis and coworkers (1985) demonstrated that the development of an empyema is dependent on the organism. None of the animals injected with *Bacteroides fragilis* developed empyema, whereas 37% of those injected with *E. coli* and 58% of those injected with *S. aureus* developed empyema. However, with the combination of *B. fragilis* and *S. aureus,* the incidence of empyema is significantly greater than with the injection of *S. aureus* alone (Mavroudis et al., 1987). The development of empyema was also dependent on the concentration of organisms injected into the pleural space. If blood is injected with the bacteria in the presence of the umbilical tape, the incidence of empyema was not increased (Mavroudis et al., 1987). The guinea pigs that developed empyema were more likely to have underlying pneumonia (Mavroudis et al., 1985, 1987). The results of different treatment regimens in this experimental model have not been evaluated.

In a second model, sterile pleural effusions are induced in rabbits by the intrapleural injection of turpentine. Several days later, bacteria are injected into the pleural effusion resulting in an empyema with a low pH and a low glucose level (Sahn et al., 1979). Interestingly, if the rabbits are not treated with antibiotics or chest tubes after *S. pneumoniae* is injected, the animals do not die, and 7 days after the bacterial injection the pleural fluid is no longer purulent (Sahn et al., 1979). If *Klebsiella pneumoniae* is injected (Shohet et al., 1987), the pleural fluid pH will fall below 7.00 and the pleural fluid glucose level will fall below 10 mg/dL, but with the administration of gentamicin there will be complete resolution of the empyema with nonsignificant findings in the pleural cavities and lungs at autopsy. Therefore, one must question the relevance of this model to the human situation, where drainage is necessary for the resolution of the infected pleural fluid.

Clearly, neither of the above two experimental models accurately reflect the empyema that occurs naturally. The first model requires that a foreign body be placed in the pleural space. The second model produces gross injury to the pleura before the bacteria are injected and accordingly must markedly alter the defenses of the lung and pleural space. A third experimental model of empyema has been developed. In this rabbit model, *Pasteurella multocida* cultured in agar (rather than broth) is injected into the pleural space of the rabbits. The bacteria are placed in agar rather than in broth so they will remain in the pleural space longer (Sasse et al., 1996a). Starting 24 hours after the initial injection, procaine penicillin G is administered once per day to prevent death from sepsis. The rabbits do develop an empyema; 24 hours post-injection the mean pleural fluid pH is 7.01, the mean glucose is 10 mg/dL, the mean LDH level is 21,000 IU/L and the Gram's stain and culture of the pleural fluid are positive. By 96 hours, the Gram's stain and

culture of the pleural fluid are usually negative, but gross pus remains in the pleural space (Sasse et al., 1996a). Ten days post-injection, approximately 50% of the animals will have gross pus in their pleural spaces (Sasse et al., 1997). In this model, which closely mimics the clinical situation, about 60% of the rabbits survive for 14 days. At autopsy most animals have pus in their pleural spaces.

Sasse et al. (1997) have attempted to answer several questions concerning the management of empyema with this model. The first question addressed was whether the timing of the chest tube placement was important in the treatment of empyema. After the induction of empyema, rabbits were randomized to receive no chest tube or a chest tube after 24, 48, or 72 hours. The rabbits that received the chest tube at 24 or 48 hours had significantly better results than did the rabbits that received late chest tube placement (72 hours) or no chest tube placement (Fig. 1). This study documents that a relatively short delay in initiating tube thoracostomy adversely affects the outcome.

The next question was whether therapeutic thoracentesis was a reasonable alternative to tube thoracostomy in the management of rabbits with empyema. The rabbits were divided into three groups: 16 underwent daily therapeutic thoracentesis starting at 48 hours, 14 underwent chest tube placement at 48 hours, and 19 served as controls. The animals in the chest tube group had their chest tubes attached to a Heimlich valve and had their chest tubes aspirated at 12-hour intervals. Sasse et al. (1997) found that the mortality rate in the therapeutic thoracentesis group (0/16) was significantly less ($P = 0.02$) than the mortality rate in the other two groups combined (9/33). At autopsy at 10 days, the gross empyema score in the therapeutic thoracentesis group (2.1 ± 0.3) was significantly lower ($P < 0.05$) than that in the chest tube group (2.8 ± 0.3) or the control group (3.5 ± 0.2). From this study it was concluded that therapeutic thoracentesis is at least as effective as early chest tube placement for the treatment of early empyema using the rabbit model of empyema and should be evaluated as a treatment alternative in patients with early empyema (Sasse et al., 1996b).

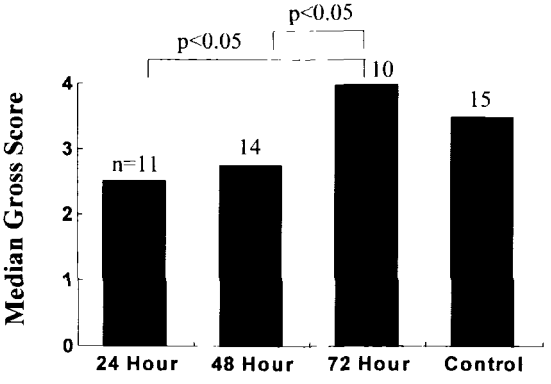

FIGURE 1. Relationship between gross anatomical score and time of placement of chest tube. A score of 4 = pus in the pleural space; 3 = moderate pleural peel without gross pus; 2 = minimal pleural peel; 1 = adhesions between the visceral and parietal pleura; and 0 = normal pleural space. Reprinted, with permission, from Sasse et al., 1997.

Texeira et al. (1999) evaluated the ease of penetration of various antibiotics into the pleural space using the rabbit model of empyema. After the induction of an empyema was verified, penicillin 24,000 units/kg, clindamycin 9 mg/kg, gentamicin 1 mg/kg, metronidazole 37 mg/kg, vancomycin 15 mg/kg, or ceftriaxone 30 mg/kg was administered intravenously. Antibiotic levels in samples of pleural fluid and serum, collected serially for up to 480 minutes, were determined using a bioassay. They found that the degree to which the different antibiotics penetrated the infected pleural space was highly variable. Metronidazole penetrated most easily, followed by penicillin, clindamycin, vancomycin, ceftriaxone, and gentamicin (Fig. 2). This variance in the penetration of antibiotics into pleural fluid should be considered when an antibiotic is selected for the treatment of patients with complicated parapneumonic effusions.

Light et al. (2000) also compared the efficacy of streptokinase (15,000 IU), urokinase (10,000 IU), Varidase (4000–15000 IU streptodornase + 15,000 IU streptokinase), or saline in liquefying purulent material obtained from the rabbit model 5 days after empyema induction. In this in vitro experiment these agents were added to five sets of four test tubes each. The amount of nonliquefied material which remained after incubation with the thrombolytic agents was quantitated. Over the 6-hour incubation period, the amount of nonliquefied material decreased from 0.5 g to 0.02 g in the Varidase group

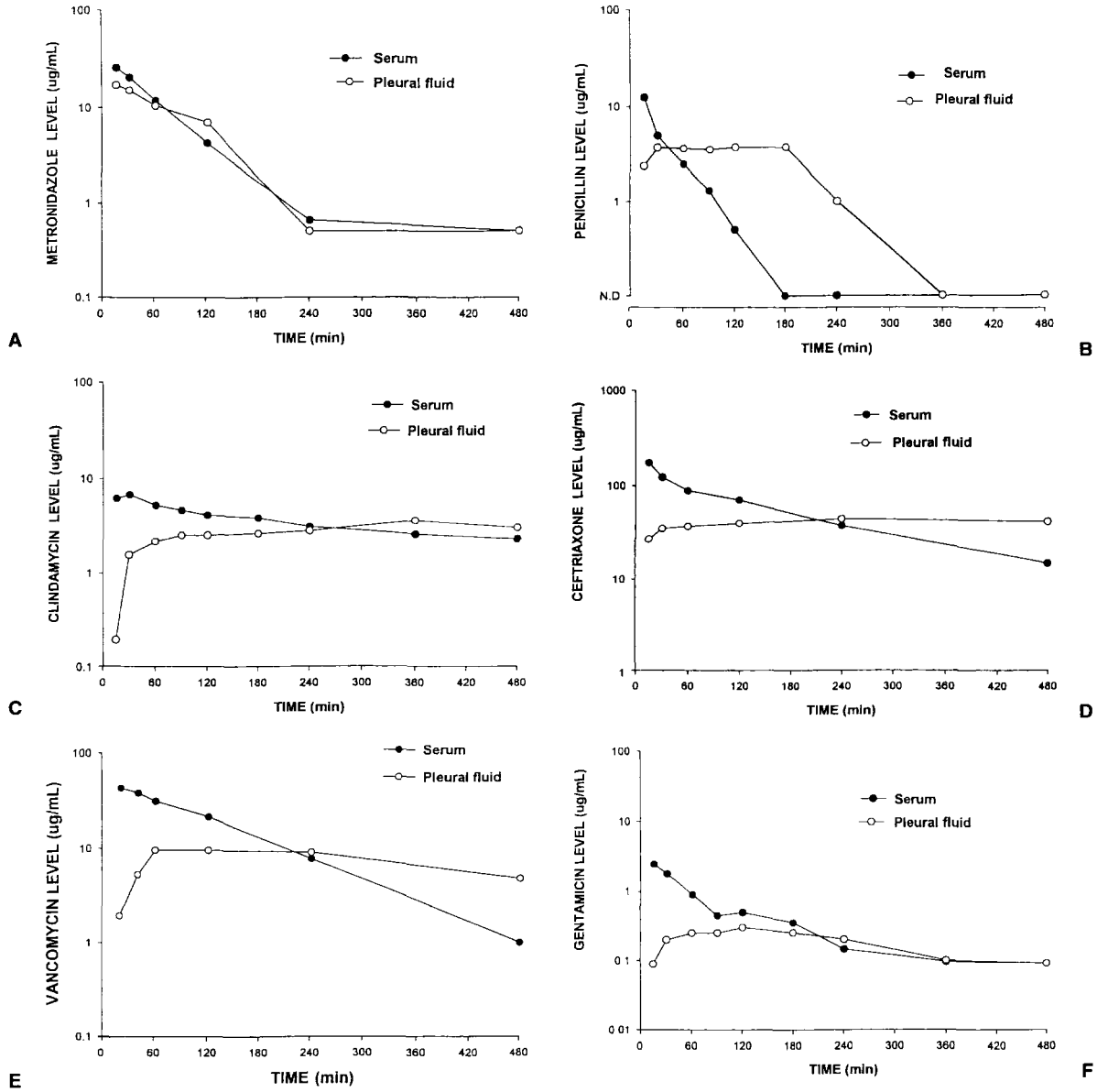

FIGURE 2. Levels of antibiotics in the serum and pleural fluid after administration of (A) metronidazole, (B) penicillin, (C) clindamycin, (D) ceftriaxone, (E) vancomycin, and (F) gentamicin. ND, nondetectable. Reprinted, with permission, from Teixeira et al., 1999.

but never decreased below 0.4 g in any of the other three treatment groups (Fig. 3). Streptodornase is streptococcal DNAase. The results from this experiment suggest that the utility of DNAase in the treatment of patients with loculated parapneumonic effusions should be assessed (Light et al., 2000).

Clinical Manifestations

The clinical manifestations of patients with parapneumonic effusions and empyema depend to a large part on whether the patient has an aerobic or an anaerobic infection. The clinical presentation of

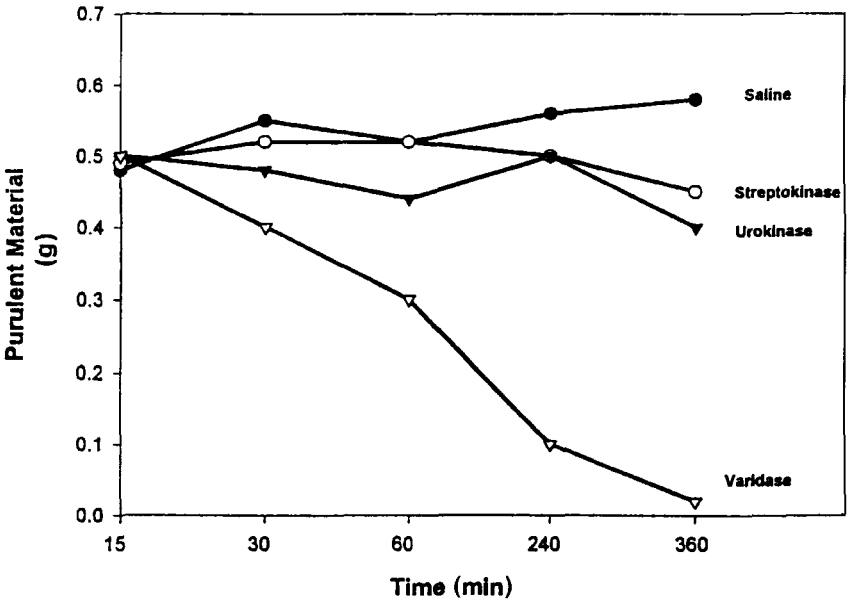

FIGURE 3. Amount of nonliquefied purulent material remaining on screen after incubation with saline, streptokinase, urokinase, and Varidase over a 6-hour period. Note that liquefaction occurs only with the Varidase. Reprinted, with permission, from Light et al., 2000.

patients with aerobic bacterial pneumonia and pleural effusion is no different from that of patients with bacteria] pneumonia without effusion (Light et al., 1980; Taryle et al., 1978; Van De Water, 1970). Patients present with an acute febrile illness with chest pain, sputum production, and leukocytosis. The prevalence of chest pain and the degree of leukocytosis are comparable whether or not the patient has a pleural effusion (Light et al., 1980). Patients who delay seeking medical attention are more likely to have a pleural effusion (Taryle et al., 1978). Some patients with aerobic pneumonias and pleural effusions do not have acute illnesses. In one report (Sahn et al., 1973), three patients who were receiving corticosteroid therapy developed an aerobic empyema, and all were afebrile with minimal symptoms referable to the chest. Therefore, the absence of fever or chest symptoms should not deter one from considering the diagnosis of complicated parapneumonic effusions.

The presentation of patients with anaerobic bacterial pneumonia tends to be less acute than that in patients with aerobic bacterial pneumonias. In one series of 47 such patients (Bartlett & Finegold, 1974), the median duration of symptoms before presentation was 10 days, and 60% had a substantial weight loss (mean 29 lbs.). Many patients have a history of alcoholism, an episode of unconsciousness, or another factor that predisposes to aspiration. The majority of patients also have poor dentition. Laboratory evaluation usually reveals leukocytosis (median WBC 23,500/mm^3) and mild anemia (median hematocrit 36%) (Bartlett & Finegold, 1974).

Diagnosis

The possibility of a parapneumonic effusion should be considered during the initial evaluation of every patient with a bacterial pneumonia. When a pleural effusion is present, it is important to determine at the time it is first discovered whether the effusion is complicated because a delay of even a day in instituting proper pleural drainage in such patients substantially increases morbidity.

In most instances the presence of a significant amount of pleural fluid is suggested on the lateral chest radiograph. If a posterior costophrenic angle is blunted or if a diaphragm is obscured by an infiltrate, bilateral decubitus chest radiographs should be obtained. Free pleural fluid is evidenced as an increased density between the outside of the

lung and the inside of the chest wall. The amount of free pleural fluid can be semiquantitated by measuring the distance between the inside of the chest wall and the bottom of the lung. If this distance measures less than 10 mm, one can assume that the effusion is not clinically significant, and therefore a thoracentesis is not indicated (Light et al., 1980). The view with the affected side up is also valuable because, in this position, the free fluid gravitates toward the mediastinum and allows one to assess how much of the increased radiodensity is due to the fluid and how much is due to the parenchymal infiltrate.

In many instances, after the posteroanterior, lateral, and decubitus chest radiographs are obtained, it is still difficult to determine how much of the increased density in a hemithorax of a patient with pneumonia is due to parenchymal infiltrates and how much is due to pleural fluid or pleural thickening. In such cases a computed tomography (CT) scan of the chest is invaluable. Chest CT scans should be obtained whenever doubt exists concerning the degree of pleural involvement in patients with pneumonia and pleural effusion.

Differential Diagnosis

It should be emphasized that not all patients with an acute illness, parenchymal infiltrates, and pleural effusion have an acute bacterial pneumonia. Other diseases that produce this constellation of symptoms include pulmonary embolization, acute pancreatitis, tuberculosis, Dressler's syndrome, and systemic lupus erythematosus. The possibility of pulmonary embolization should always be considered, and a spiral CT of the chest or a perfusion lung scan should be obtained if the patient does not have purulent sputum or a peripheral leukocytosis above 15,000/mm^3. A normal pleural fluid amylase level rules out pancreatitis, and most patients with acute tuberculous pleuritis have no infiltrate on the decubitus film with the involved side superior.

Hydrothorax versus Lung Abscess

On occasion, an air-fluid level will be present on the chest radiograph of a patient with community-acquired pneumonia. The two primary diagnoses to consider when an air-fluid level is present are loculated hydropneumothorax with a bronchopleural fistula and lung abscess. It is important to make this differentiation because the loculated hydropneumothorax with the bronchopleural fistula needs to be treated with chest tubes immediately in order to prevent discharge of the infected pleural fluid throughout the remainder of the lung. In contrast, only antibiotic therapy is necessary for the peripheral lung abscess.

It is frequently difficult to distinguish a loculated pyopneumothorax with a bronchopleural fistula from a peripheral lung abscess with the standard chest radiographs. An important differentiating point is the length of the air-fluid level on the posteroanterior compared to the lateral chest radiograph. If the length of the air-fluid level is comparable on both views, the patient probably has a lung abscess. Alternatively, if the length of the air-fluid level is considerably different, the patient probably has a pyopneumothorax.

Both ultrasound and CT are useful in distinguishing these two conditions. With ultrasonic examination during hyperventilation, asymmetric motion of the proximal (chest wall-parietal pleura) and the distal (visceral pleura-lung) interface occurs when the process is in the pleural space. If the process is within the lung parenchyma, the proximal and distal interfaces (anterior and posterior walls of the cavity) move symmetrically (Adams & Kolodny, 1979).

The chest CT scan is probably the best means of making the differentiation. With CT scanning, the air-fluid levels of a hydropneumothorax closely approximate the chest wall. The space characteristically has a smooth, regular margin that is sharply defined without side pockets. The appearance of the cavity often changes with variations in the patient's position. In contrast, a lung abscess is typically round with an irregular, thick wall and has an air-fluid level of equal length in all positions. When the patient's position is changed, the shapes of the cavity and of the mass do not change. Frequently, multiple side pockets are adjacent to the main cavity. An additional distinguishing feature is that the larger empyemas displace the adjacent lung, while lung abscesses do not (Pugatch & Spirn, 1985). With a contrast enhanced CT scan, the demonstration of vessels within a lesion unequivocally identifies the lesion as parenchymal rather than pleural. Moreover, after administration of contrast material, pulmonary parenchyma is enhanced, whereas most pleural lesions show minimal or no enhancement (Bressler et al., 1987).

Pleural Fluid Analysis

When a patient with a parapneumonic effusion is first evaluated, a thoracentesis should be performed. A Gram's stain and culture of the pleural fluid should be obtained as well as a WBC and differential, LDH level, glucose level, and the pH of the pleural fluid.

The pleural fluid with parapneumonic effusions varies from a clear, yellow exudate to thick, foul-smelling pus. If the odor of the pleural fluid is feculent, the patient probably has an anaerobic pleural infection (Bartlett & Finegold, 1974; Sullivan et al., 1973). The differential WBC on the pleural fluid almost always reveals predominantly polymorphonuclear leukocytes. If other cells predominate on the differential cell count, an alternate diagnosis should be sought. The pleural fluid WBC count is of surprisingly little use in the management of patients with parapneumonic effusions. Some patients will do well without pleural drainage despite having pleural fluid WBC above 100,000 mm^3, whereas many patients with pleural fluid WBC below 10,000 mm^3 will require pleural fluid drainage (Light et al., 1980). Many pleural fluids that are very cloudy have low pleural fluid WBC. The explanation for this observation is that the cloudiness is due to dead cells and debris rather than to viable cells.

The pleural fluid pH and glucose and LDH levels are indicators of the intensity of the inflammatory process in the pleural space. The lower the pleural fluid glucose level and pH and the higher the pleural fluid LDH level, the greater the inflammation. If one uses the pleural fluid pH in the assessment of a patient with a parapneumonic effusion, the pH must be measured with a blood gas machine; pH meters and indicator strip paper are not sufficiently accurate for this measurement (Cheng et al., 1998).

Options for Treatment of Complicated Parapneumonic Effusions

Antibiotics

The antibiotic therapy of patients with community-acquired pneumonia is discussed elsewhere in this volume. The initial antibiotic selection and the dose are not influenced by the presence or absence of a pleural effusion. Most antibiotics are present in pleural fluid at levels that are comparable with those in serum (Light, 1995). However, as depicted in Figure 2 there is substantial variation in the penetration of various antibiotics into an infected pleural space. In particular, aminoglycosides appear to penetrate poorly into purulent pleural fluid (Teixeira et al., 1999).

Therapeutic Thoracentesis

Therapeutic thoracentesis is the least invasive of the invasive treatment modalities for parapneumonic effusion. In 1962, the American Thoracic Society recommended repeated thoracenteses for nontuberculous empyemas that were in the early exudative phase (Andrews et al., 1962). Recently, however, therapeutic thoracentesis as a treatment for parapneumonic effusions has received relatively little attention.

In addition to the study in rabbits discussed previously, there have been a few studies that have suggested that there is a role for therapeutic thoracentesis in the management of patients with parapneumonic effusions. In one study, Storm and coworkers (1992) reported that 48 of 51 patients (94%) with empyema (purulent pleural fluid or positive microbiological studies on the pleural fluid) were successfully treated with daily thoracentesis. In a second study, Mandal and Thadepalli (1987) reported that 28 of 111 patients (25%) with bacterial empyema (purulent exudate or positive culture) were successfully treated with serial therapeutic thoracentesis and antibiotics. Ferguson et al. (1996) reported that 19 of 46 patients (41%) with empyema (opaque fluid in the pleural space with the cloudiness due to neutrophils and/or organisms) were treated successfully with repeated thoracentesis. There have been no controlled studies comparing therapeutic thoracentesis with small-tube thoracostomy in the treatment of patients with complicated nonloculated parapneumonic effusions.

Tube Thoracostomy

For the past several decades the initial treatment modality for most patients with complicated parapneumonic effusions has been tube thoracostomy. Failure of tube thoracostomy in the treatment of parapneumonic effusions is frequently due to the

improper placement of the tube, but it can also be due to loculations of the pleural fluid which prevent complete pleural drainage or to fibrinous tissue coating the visceral pleura which prevents the underlying lung from expanding. When drainage with tube thoracostomy is inadequate, a chest CT scan should be obtained to delineate which of the above factors is responsible for the inadequate drainage.

What size chest tubes should be used for the treatment of parapneumonic effusions? The standard practice for many years was to use relatively large (26–36 F) chest tubes. The basis for this recommendation was the belief that the debris in the fluid would obstruct the smaller tubes. However, it appears that many parapneumonic effusions can be managed successfully with smaller tubes. When two series (Kerr et al., 1991; Silverman et al., 1988) with a total of 53 patients are combined, 41 (77%) of the patients were managed successfully with smaller chest tubes (8.3–16 F). These results are at least as good as those reported in recent series in which larger tubes were used (All & Unruh, 1990; Ashbaugh, 1991). It is likely that the excellent results with the small chest tubes are due to accurate placement of the tubes by interventional radiologists. The obvious advantage of the smaller tubes is that they are more comfortable for the patient. If the pleural fluid is frank pus, a large chest tube is preferred (Light & Rodriguez, 1998).

How long should the chest tube be left in place if the drainage is successful? Although there has been surprisingly little written on this subject, the chest tubes should probably be left in place until the volume of the pleural drainage is under 50 mL/24 hours and until the draining fluid becomes clear yellow (Light, 1995). A chest tube that ceases to function (no fluctuation with respiratory efforts) should be removed because it serves no useful purpose and can be a conduit for pleural suprainfection. On occasion, purulent drainage continues from the chest tube despite clinical and radiologic improvement. In this situation, one must decide whether a more aggressive approach (e.g., decortication) is indicated. This decision can be aided by radiographs obtained after the injection of contrast material into the pleural space through the chest tube (Sherman et al., 1977). If only a tube tract is demonstrated, the chest tube can be gradually withdrawn over several days while the tract is allowed to fill in with granulation tissue. If a larger (>100 mL) cavity is demonstrated, one should consider decortication to eliminate the cavity. If one elects to continue with the chest tube drainage, progression of the empyema cavity can be assessed by repeated contrast studies through the tube at weekly intervals. Chest CT scans also provide much information about the status of complicated parapneumonic effusions.

Intrapleural Thrombolytics

The role of thrombolytics in the management of loculated parapneumonic effusions remains to be determined. The theory behind their use is that loculations in the pleural space are produced by fibrin membranes; if these membranes can be dissolved when thrombolytics are injected into the pleural space, then drainage of the pleural space is facilitated.

In the last 4 years there have been at least five uncontrolled studies (Bouros et al., 1997; Jerjes-Sanchez et al., 1996; Laisaar et al., 1996; Temes et al., 1996; Moulton et al., 1989), each with more than 20 patients, that have concluded that thrombolytics are useful in the management of patients with loculated parapneumonic pleural effusions. Success has been reported with both streptokinase (Bouros et al., 1997; Jerjes-Sanchez et al., 1996; Laisaar et al., 1996; Temes et al., 1996) and urokinase (Bouros et al., 1997; Temes et al., 1996; Moulton et al., 1989). Each agent can be given daily in a total volume of 50 to 100 mL as long as it appears to be facilitating pleural drainage. The usual dose of urokinase is 100,000 IU and for streptokinase it is 250,000 IU.

There have recently been three controlled studies on the use of thrombolytics for loculated parapneumonic effusions (Chin & Lim, 1997; Davies et al., 1997; Bouros et al., 1999). In the first study, streptokinase 250,000 U daily (the number of days determined by the clinical response) was compared with no thrombolytic agent in the management of 52 patients with loculated parapneumonic effusion. This study was not randomized or blinded in that the patients received no thrombolytics for the first half of the study and streptokinase for the latter half of the study. In this study there was no significant difference in the need for more invasive surgery or the mortality rate in the two groups (Chin & Lim, 1997). In the second study, 24 patients were randomized to receive streptokinase 250,000 IU daily

or control saline flushes for up to 3 days. The streptokinase group had a significantly greater reduction in the size of the pleural fluid collection and greater improvement in the chest radiograph (Davies et al., 1997). In the third study, 31 patients were randomly assigned to receive either intrapleural urokinase or normal saline for 3 days. The group that received urokinase had significantly greater improvement in the chest radiographs and a significantly reduced need for surgery (Bouros et al., 1999).

A trial of intrapleural thrombolytic therapy can be considered for patients with complicated parapneumonic effusions who have a loculated pleural effusion or inadequate drainage after 24 hours of treatment with tube thoracostomy. Alternatively, one can proceed directly to thoracoscopy. A successful response to the thrombolytic therapy will be indicated by an improvement in the chest radiograph, not just increased drainage from the chest tube. If improvement is not noted after the first one or two doses, more invasive procedures such as thoracoscopy or thoracotomy should be considered. Fibrinolytic agents are less likely to be effective if the process has been ongoing for more than 7 days or if the pleural fluid is very purulent. It appears that streptokinase and urokinase are probably equally effective. Animal studies described previously suggest that chemical debridement might be better if a DNAase is included in the regimen.

Thoracoscopy

Thoracoscopy, which involves the breakdown of adhesions and complete drainage of the pleural space, is the procedure of choice when tube thoracostomy (with or without thrombolytics) fails. One study has demonstrated that proceeding directly to thoracoscopy is more cost-effective than using an intermediate step with thrombolytics (Wait et al., 1997). A chest CT scan should be obtained prior to thoracoscopy to provide anatomic information about the size and extent of the empyema cavity (Silen & Naunheim, 1996). If the visceral pleura is markedly thickened and there are no septations in the pleural fluid, the empyema is probably chronic and will not be amenable to thoracoscopic debridement alone (Silen & Naunheim, 1996). With the advent of video-assisted thoracic surgery (VATS), video thoracoscopy is being used more for the management of loculated parapneumonic effusions. There have been several studies (again uncontrolled) in the last few years demonstrating the utility of thoracoscopy in the management of complicated parapneumonic effusions (Hornick et al., 1996; Mackinlay et al., 1996; Sendt et al., 1995). One advantage of this procedure is that the chest tube can be positioned in the most dependent part of the empyema cavity.

Thoracoscopy is the definitive procedure for the majority of patients with loculated complicated parapneumonic effusions. In one series, 30 of 44 (68%) patients who underwent thoracoscopy for their complicated parapneumonic effusion needed no additional therapy (Lawrence et al., 1997). Thoracoscopy can be effective in patients who have had symptoms for more than 30 days (Lawrence et al., 1997). An alternative to thoracoscopy is a mini-thoracotomy with the manual breakdown of adhesions and placement of one or more chest tubes.

Decortication

Decortications should be considered in those patients who require additional drainage following tube thoracostomy or thoracoscopy (Thurer, 1996). Decortication is also an alternative when thoracoscopy is unavailable. With decortication, a full thoracotomy is performed and all the fibrinous material and pus are removed from the pleural space. Accordingly, decortication eliminates the pleural sepsis and allows the underlying lung to expand. Decortication is major thoracic surgery and should not be performed on patients who are markedly debilitated. In the period immediately following a thoracic infection, decortication should not be performed just to remove thickened pleura because such thickening usually resolves spontaneously over several months. If, however, the pleural thickening persists and the patient's pulmonary function is sufficiently reduced to limit his or her activities, decortication should be considered.

Open Drainage (Eloesser Flap)

With this relatively minor surgical procedure, segments of one to three ribs overlying the lower part of the empyema cavity are resected, and one or more short large-bore tubes are inserted into the

cavity. The open drainage procedure allows more complete drainage and frees the patient from his attachment to chest-tube bottles. After the procedure, the cavity should be irrigated daily with a mild antiseptic solution, and the drainage from the tubes can be collected in a colostomy bag placed over the tubes. It is preferred to decortication only in those patients who are thought to be too ill to tolerate decortication. Patients treated by open drainage can expect to have an open chest wound for a prolonged period. In one series of 33 patients treated by an open drainage procedure, the median time for healing the drainage site was 142 days (Bartlett & Finegold, 1974).

Recommended Management of Parapneumonic Effusions

When a patient with a community-acquired pneumonia is initially evaluated, one should ask if the patient has a parapneumonic effusion. If the diaphragms are not visible throughout their entire length on the lateral radiographs, decubitus radiographs should be obtained to determine whether free pleural fluid is present.

If free pleural fluid is present and the distance between the inside of the chest wall and the outside of the chest lung is more than 10 mm, the pleural fluid needs to be sampled. If there is doubt as to how much of the density in a hemithorax is parenchymal and how much is pleural, a CT scan of the chest should be obtained. If more than minimal fluid is demonstrated on the CT, the pleural fluid should be sampled. The pleural fluid needs to be sampled in these situations to determine whether any poor prognostic factors are present (Table 2).

The options for the invasive treatment of complicated parapneumonic effusions are listed in Table 3. In general, one moves from the less invasive treatments to the more invasive treatments. It is important to abandon a treatment within 1 or 2 days if it is ineffective. Not every treatment need be used. If a patient is going to need a decortication, it should be performed within 10 days of the initial identification of the parapneumonic effusion.

If a patient has sufficient pleural fluid to justify a thoracentesis, a therapeutic rather than a diagnostic thoracentesis should be performed initially. If there is no reaccumulation of fluid after a therapeutic thoracentesis, one need not worry about the parapneumonic effusion. If the pleural fluid reaccumulates and there were no bad prognostic factors at the time of the initial thoracentesis, no additional therapy is indicated as long as the patient is doing well. If the fluid reaccumulates and there were poor prognostic factors present at the time of the initial thoracentesis, a second therapeutic thoracentesis should be performed. If the fluid reaccumulates a second time, a tube thoracostomy should be performed if any of the poor prognostic factors were present at the time of the second therapeutic thoracentesis.

Performance of the therapeutic thoracentesis will also delineate whether the pleural fluid is loculated. If the pleural fluid is loculated, and if any of the other poor prognostic factors listed in Table 2 are present, then more aggressive therapy should be initiated. The two options at this time are tube thoracostomy with the instillation of thrombolytics or thoracoscopy with the breakdown of adhesions. The choice between these two is dictated somewhat by local circumstances. If thoracoscopy is unavail-

TABLE 2. Poor Prognostic Factors for Parapneumonic Effusions and Empyema[a]

Pus in pleural space
Gram's stain positive for bacteria
Pleural fluid glucose below <40 mg/dL
Positive pleural fluid culture
Pleural fluid pH <7.00
Pleural fluid LDH more than three times upper normal limit for serum
Pleural fluid loculated

LDH, lactic dehydrogenase
[a]Listed in order of decreasing importance.

TABLE 3. Treatment Options for Complicated Parapneumonic Effusions[a]

Therapeutic thoracentesis
Tube thoracostomy
Tube thoracostomy with intrapleural administration of thrombolytics
Thoracoscopy with breakdown of adhesions
Thoractomy with decortication

[a]Listed in order of increassing invasiveness.

able, the obvious choice is thrombolytics. If both are available, one many want to try tube thoracostomy with thrombolytics initially. However, if complete drainage is not obtained with one or two administrations of the thrombolytics, one should move to thoracoscopy or thoracotomy with decortication without delay. Similarly, if thoracoscopy is not successful, thoracotomy should be performed without delay.

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17

A Critical Pathway for the Treatment of Community-Acquired Pneumonia

THOMAS J. MARRIE

Introduction

Many aspects of the treatment of community-acquired pneumonia (CAP) are subject to great variation. This chapter reviews the areas in which there is variation, attempts to explain the reasons for such variation, and proposes a critical pathway for the treatment of CAP based on data from the literature.

CAP is a serious and common infection. The overall attack rate is 12 per 1000 population per year, and 20% to 50% of all adults with pneumonia are admitted to the hospital. The hospitalization rate for CAP increases with age, thus in the 35-44-year age group in Halifax County, the hospitalization rate was 0.54 per 1000 population per year and was 11.6 per 1000 population per year among those ⩾75 yearsof age (Marrie, 1994a). The mortality rate from pneumonia requiring hospitalization can be as high as 21% (Marrie et al., 1989). Fortunately mortality is rare among those who are not hospitalized (Mandell et al., 1993). The major reason for the high mortality among hospitalized patients is that these individuals frequently have severe comorbidities (e.g., chronic obstructive lung disease, ischemic heart disease, cerebrovascular disease, dementia) that predispose these individuals to infection or that are made worse by the pneumonia. However, the mortality rate from pneumonia for hospitalized patients is low, and ⩽4% in some centers where less seriously ill patients predominate. Thus in order to compare such data among different institutions adjustment for severity of illness is necessary.

Many microbiological agents can cause pneumonia and there may be considerable difficulty in arriving at an etiological diagnosis (Marrie, 1994a). Antimicrobial treatment of pneumonia of unknown etiology has to be empiric. Guidelines for the empiric treatment of CAP have been issued by Canadian (Mandell et al., 1993), British (British Thoracic Society, 1993), and American (Niederman et al., 1993) expert committees. The most recent set of guidelines for the management of CAP were developed under the auspices of the Infectious Disease Society of America (Bartlett et al., 1998). There is considerable variation in the recommendations in each set of guidelines. This is not surprising since all of these guidelines are for the most part not based on data from randomized clinical trials. These guidelines only deal with the initial therapy, and no recommendations are made regarding the duration of therapy.

Other aspects of the management of CAP are also subject to variation. Fine et al. (1993), in a study of the length of stay for pneumonia at one Boston and three Pittsburgh facilities, found the unadjusted mean lengths of stay were 9.3,12.1, 9.1, 6.6 days, respectively. There were no differences in outcome, as measured by mortality rates at 6 weeks. Severity of illness accounted for only 7% of the variation in length of stay; ten independent variables (pneumonia risk class [three classes], age, nursing home residence, >1 comorbid illness, bac-

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

teremia, hyponatremia, anemia, and renal impairment) accounted for another 14% of the variation. Thus, most of the variation was unexplained by disease-specific factors (Fine et al., 1993). Halm et al. (1998) found that when patients who were hospitalized for the treatment of CAP reached stability (various definitions of stability were examined) clinical deterioration requiring intensive care, coronary care, or telemetry monitoring occurred in $\leq 1\%$ of the cases. They also noted, however, that 65% to 86% of the patients stayed in the hospital more than 1 day after reaching stability. In this study the median time to achieve a heart rate of 100 beats/min or less was 2 days, and it took 3 days to achieve a respiratory rate of ≤ 24 breaths/min, an oxygen saturation of $\geq 90\%$, and a temperature of $<37.2°C$ (Halm et al., 1998).

Weingarten et al. (1994) carried out a retrospective study of 503 patients hospitalized with CAP and found 166 (33%) who fit their low-risk category. They noted that if these patients had been discharged on the fourth day, 619 bed-days would have been saved. The average length of hospital stay for low-risk patients was 7.73 ± 6.12 days.

Another major source of variation is the admission rate for pneumonia. This rate can vary several fold from one country to another or within the same province or state (Cleary et al., 1991; Wennberg et al., 1987). An accurate assessment of severity of the pneumonia is necessary in order to eliminate some of the variability in the admission rate from area to area. Fine and colleagues have developed a pneumonia-specific severity-of-illness scoring system (Fine et al., 1997) (Table 1). Using this scoring system patients with CAP could be classified into five strata according to severity of illness. Table 2 gives the number of points used per stratum and mortality rates for each.

Why do such variations in the treatment of pneumonia occur? Such variations are not unique to pneumonia; indeed in studies of many other conditions, variations in hospital admission rates (Chaissin et al., 1986; McMahon et al., 1989), surgical procedure rates (Lewi, 1961; Wennberg, 1977) and length of hospital stay (Cleary et al., 1991; Wennberg et al., 1987) have been documented. The reasons for these variations are complex and as previously indicated are only partially accounted for by severity of illness. Instead it is likely that local (small area) practice patterns and physician factors account for most of this variation. In order to reduce this variation, utilization management—a set of techniques to manage healthcare costs by influencing patient care decision-making through case-by-case assessments—(Institute of Medicine, 1989) has been a growing trend in the United States (Herzlinger & Schwartz, 1985). Utilization management is used to some extent in Canada but because of a single-payer system there has been little incentive for private insurance companies to become involved in this aspect of healthcare in Canada. Instead most utilization management programs represent initiatives by individual hospitals, often targeting conditions that have been identified as outliers by national or local quality-of-care reviews.

Another method to reduce variations in medi-

TABLE 1. Pneumonia-Specific Severity of Illness Scoring System[a]

Patient characteristics	Points assigned
Demographic factors	
Age	
Males	Age (in years)
Females	Age (in years) minus 10
Nursing home resident	+10
Comorbid illness	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate >30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse >125/min	+10
Laboratory findings	
pH <7.35	+30
Blood urea nitrogen >10.7 mmol/L	+20
Sodium <130 mmol/L	+20
Glucose >13.9 mmol/L	+10
Hematocrit <30%	+10
Po_2 <60 mm Hg or Sao_2 <90%	+10
Pleural effusion	+10

[a]From Fine et al., 1997.

TABLE 2. Mortality Rate for Patients Treated on an Ambulatory Basis (Outpatients) and for Those Who Require Admission to a Hospital for Treatment of Community-Acquired Pneumonia (Inpatients)[a]

		Outpatients		Inpatients	
Class	Points	No.	% Dying	No.	% Dying
I	(<50 years old, no comorbidity)	587	0	185	0.5
II	≤70	243	0.4	233	0.9
III	71–90	72	0	256	1.2
IV	91–130	40	12.5	445	9.2
V	≥131	1	0	224	26.8
		944	0.6	1343	8

[a]Patients are grouped into five strate depending on the severity of illness score (Fine et al., 1997).

cal practice has been the development of practice guidelines (Weingarten et al., 1992, 1993; Evidence-based Care Resource Group, 1994). Tunis et al. (1994) found that the source of the guidelines was important in physician compliance. In the United States, physicians tended to distrust guidelines issued by Blue Cross and Blue Shield, whereas they had confidence in guidelines issued by their specialty or subspecialty society. Moreover, they felt that colleagues and review articles had a greater effect on their clinical practice than did guidelines, original research, or texts. This is supported by the observation that physician opinion leaders (those who adopt and disseminate new medical technologies or clinical management strategies more readily than their colleagues) effect practice change on a local level (Wenrich et al., 1971; Epstein, 1990; Stross & Bole, 1990).

Antibiotic Therapy

The choice of antibiotic therapy for patients with pneumonia is discussed elsewhere in this volume. Other aspects of antibiotic therapy, such as the duration of intravenous therapy, are discussed here.

Recently, in an effort to conserve scarce resources there has been emphasis on so-called step-down antibiotic therapy, that is, an early switch from an intravenous antibiotic to an oral antibiotic of the same class (Quintilani et al., 1987; Saltiel & Weingarten, 1993). In a series of studies Ramirez and colleagues defined criteria for the switch from intravenous to oral antibiotics and showed that this could be done safely with a variety of antibiotics (Ramirez, 1995; Ramirez et al., 1995). The criteria used to switch from intravenous to oral antibiotics included two normal temperature readings over 16 hours, white blood cell count returning toward normal, subjective improvement in cough, and subjective improvement in shortness of breath. Ramirez et al. randomized patients to receive 1 g ceftizoxime intravenously every 12 hours or 1 g ceftriaxone intravenously every 24 hours. As soon as the above criteria were met the patients were switched to oral cefixime 400 mg once daily. When they were stable for 1 day on oral therapy the patients were discharged. Of the 120 patients enrolled, 75 were evaluable. Thirty-three patients treated with ceftizoxime met switch criteria in a mean 2.76 days versus 3.17 days for 42 cetriaxone-treated patients.

The mean length of hospital stay was 4 days compared with a historical value of 6 days. Using a similar study design, Ramirez and Ahkee (1997) used ceftriaxone and erythromycin as initial intravenous therapy and then switched to oral clarithromycin. Of the 59 evaluable patients, all were cured. The average time to switch from intravenous to oral treatment was 3 days. The average length of stay was 4.8 days. Ehrenkranz et al. (1992) found that if physicians were provided with the recommendations of a nurse-interventionist on a patient-specific basis, the average length of stay was reduced by 2.4 days and average costs were reduced by $884 per patient among the 79% of patients whose physicians agreed to follow the nurse-interventionist recommendation.

Discharge Decision

Delays in discharge can occur because of delays in scheduling of tests, physician decision-making, discharge planning, and scheduling of procedures (Selker et al., 1989; Barrett et al., 1994). In a study by Selkar et al. (1989), delays could be placed in one of nine major categories or in one of 166 subcategories. For patients who require hospitalization for the treatment of pneumonia, it is usually evident by the third hospital day who is doing well and who is not, and a decision as to the timing of discharge can be made at this time.

Prevention

The prevention of pneumonia by immunization is discussed thoroughly elsewhere in this volume. Influenza vaccination has been shown to reduce the rate of hospitalization for pneumonia and influenza by 48% to 57% (Foster et al., 1992; Nichol et al., 1994). In addition, in a vaccinated cohort the rate of hospitalization for congestive heart failure was reduced during a season when influenza A was epidemic. The pneumococcal vaccine has not been demonstrated to prevent pneumococcal pneumonia in randomized controlled studies, but four case control studies have now demonstrated significant efficacy of pneumococcal vaccine in preventing pneumococcal bacteremia (Farr et al., 1995). The effectiveness of pneumococcal vaccine in the nursing home population remains to be proven (Fox, 1993). It is noteworthy that the pneumococcal immunization rate in pneumonia patients in Halifax is much lower than in Boston or Pittsburgh (T. J. Marrie, unpublished observations). A practical strategy is to immunize all those $\geq$65 years of age at time of discharge from the hospital.

Critical Pathways

Critical pathways were first developed in industry as a tool to identify and manage the rate-limiting steps in a production process (Pearson et al., 1995). This concept has now been applied in the healthcare setting. Critical pathways differ from clinical guidelines, protocols, and algorithms in that they focus on care after decisions to admit the patient have been made and they are designed along specific timelines (Pearson et al., 1995).

Despite our knowledge of pneumonia and its causes, as well as the pharmacokinetics and pharmacodynamics of the antibiotics used to treat it, the application of this knowledge is not optimal. The development of a care map (critical pathway) for pneumonia has been shown to reduce length of stay (Sperry & Birdsall, 1994), reduce resource utilization (Esler et al., 1994), and reduce the time from emergency room admission to initiation of antibiotic therapy from 6.8 hours to 3.6 hours (Rollins et al., 1994). Once a critical pathway is operating it is important to audit its performance periodically (May et al., 1994; Jolley et al., 1992) to determine compliance and effectiveness. From a scientific viewpoint the study of effectiveness of critical pathways is in its infancy. A recent review notes that no controlled study has shown that a critical pathway has reduced the duration of hospital stay or decreased resource use (Pearson et al., 1995). There are three commonly voiced concerns about critical pathways: (1) they represent cookbook medicine; (2) if physicians do not comply with a critical pathway they may be more vulnerable to malpractice suits; and (3) lack of evaluation. Physicians always have the option to change the pathway at any time in the best interests of patient care. There is no evidence that malpractice suits have increased in this setting—indeed, improved documentation should benefit the physician.

Some aspects of our knowledge of pneumonia are still incomplete and hence portions of any pathway may be subject to debate. Standard textbooks do not give guidance as to the duration of antibiotic therapy, probably because data from controlled clinical trials are not available. Sanford (Gilbert et al., 1998) states that pneumococcal pneumonia should be treated until the patient is afebrile for 3 days. For *Staphylococcus aureus* and *Legionella pneumophila* pneumonia a duration of 21 days of antibiotic therapy is recommended. Awunor-Renner (1979) treated 78 Nigerian patients with lobar pneumonia with penicillin for a mean of 2.4 days. His hypothesis was that antibiotics could be discontinued when the patient had been afebrile for 24

hours. Nineteen percent of the patients required > 3 days treatment—12 of these 15 patients had hepatosplenomegaly, suggesting that there might be another reason for fever in this group. Unfortunately there are no studies to suggest the correct duration of treatment in patients with pneumonia of unknown etiology. This subset accounts for at least 50% of all cases of CAP requiring hospitalization (Marrie et al., 1989). For patients who can be discharged from the hospital within the first 3 days, an additional 7 days of antibiotic therapy should be adequate. This conclusion is based partly on the observation that these patients have an uncomplicated course and partly upon recommendations of others (Gilbert et al., 1998). For patients whose hospital stay is longer than 3 days, the duration of antibiotic therapy is left to the discretion of the attending physician.

Follow-up Chest Radiographs

For patients who respond promptly to treatment there is no need for additional chest radiographs during the hospital stay. The question then is who should have a follow-up radiograph to determine that the pneumonia has cleared. The major concern is that one will miss carcinoma of the lung presenting as a postobstructive pneumonia. In a prospective study of 1269 patients with CAP, 25 (1.97%) had carcinoma of the lung. For 9 of the 23 histologically confirmed cases this episode of pneumonia was the initial manifestation of cancer of the lung (Marrie, 1994b). The youngest patient in this group was 47 years old and seven of the nine patients were ≥ 62 years old. Thus it was concluded that follow-up chest radiographs are not necessary in nonsmokers who are < 55 years old and in smokers who are <45 years old as long as they are asymptomatic at follow-up.

Pneumonia Complications

In a study carried out at Boston, Pittsburgh, and Halifax 39% of the inpatients with CAP had one or more complications. The most common were respiratory failure (13.2%), renal insufficiency (8.8%), shock (7.5%), rash (2.8%), cardiac-respiratory arrest (2.6%), myocardial infarction (2%), congestive heart failure (1.8%), and *Clostridium difficile*-associated diarrhea (0.6%).

Laboratory Investigation

A large number of hemograms (4.31 to 11.09 per episode) depending on the age group of the patient), serum chemistry analyses (2.47 to 6.15 per episode), and blood gas determinations (0.5 to 19.6 per episode) are carried out on patients with pneumonia who are hospitalized at a teaching hospital (Marrie, 1990). In the same study the number of chest radiographs ranged from 3.66 to 5.83 per episode. For patients with an uncomplicated course only one hemogram, one chemistry panel, and one blood gas analysis is necessary. Conversely, appropriate tests such as blood cultures and sputum cultures are not conducted as often as they should be. For example, in a multicenter pneumonia study, 16% of patients with CAP had a sputum specimen processed for culture within 24 hours of admission in Halifax, whereas 49% of the patients in Boston had such a specimen processed (Taylor et al., 1999).

The number of laboratory tests to be done after the initial work-up is best determined by the severity of the pneumonia and by the presence of comorbidities. For patients who are improving and have normal or mildly abnormal initial laboratory studies, no follow-up studies are necessary.

Physician Behavioral Change as a Result of Continuing Medical Education

In order to successfully implement a pneumonia critical pathway one must understand the factors that influence change in physician behavior. Davis et al. (1995) reviewed 100 randomized controlled trials of continuing medical education and concluded that physician education is least effective when only information is conveyed, as in a lecture. The most successful interventions are those that address not only knowledge but also enabling factors, in the practice context, and reinforcing fac-

tors that serve to ensure that new behaviors or ways of acting persist. Academic detailing (Auorn & Soumerai, 1983; Auorn et al., 1992) applies the same principles (one-to-one encounter) as pharmaceutical detailing but with an educational intent. Continuing medical education delivered through community-based educationally influential physicians (opinion leaders) is an effective way of changing physician behavior in small communities (Piterman, 1991). Good communication skills, humanism, and knowledge characterize these individuals, who must be identified by their peers rather than by educators.

Research on the characteristics of clinical decision-making skills suggests that these skills are specific to the case or problem encountered and are contingent on the effective manipulation of a few elements of the problem—the key features (Page & Bordage, 1995). The Medical Council of Canada now uses the key feature concept in its examinations. A clinical case scenario is presented followed by questions that focus on the critical steps (key features) in the resolution of the problem (Page et al., 1995). If the examiner does not recognize the key feature he or she won't be able to answer the questions posed.

Exclusion Criteria

Not all patients with CAP are suitable for inclusion in a critical pathway. Patients with HIV infection, cystic fibrosis, tuberculosis, or hematologic malignancy; patients hospitalized within the previous 10 days (many of these patients will have nosocomial pneumonia); organ transplant recipients; and those who require admission to an intensive care unit should generally not be included in a critical pathway.

Implementation of the Pneumonia Critical Pathway

The successful introduction of a care pathway requires the cooperation of medical, nursing and other staff who have a role in the management of patients with CAP.

TABLE 3. Pneumonia Care Pathway for Patients with Community-Acquired Pneumonia and None of the Exclusion Criteria

1. Calculate pneumonia-specific severity of illness score and group patient into low risk (classes I–III) or high risk (classes IV and V) for mortality.
   A. Classes I–III: In general treat on an ambulatory basis. There may be reasons for admission other than severity of illness, including psychosocial issues. Patients should be telephoned within 48 hours of discharge from the emergency room. Those who have positive blood cultures for a pathogen and those who are symptomatically worse should be reassessed.
   B. Classes IV and V: Admit. Diagnostic work-up includes blood and sputum cultures. Antibiotic therapy should be started within 4 hours of arrival at the emergency room. Do not delay antibiotics waiting for a sputum specimen.
2. Assess for suitability on day 2 and each day thereafter for the switch to oral antibiotics. Switch to oral antibiotics can occur when the following parameters suggesting clinical improvement or stable comorbidity are met:
   Temperature $<38°C$ over past 16–24 hours
   Respiratory rate ≤ 24/min for 16–24 hours (count for a full minute)
   Ability to maintain oral intake
   Negative blood cultures for pathogens, if done. (Only 10% of pneumonia patients have positive blood cultures.)
3. Criteria for discharge: First four criteria above plus
   Absence of serious complications (in the opinion of the attending physician) identified during the first few days of hospital stay such as acute myocardial infarct, pulmonary embolism, cardiac dysrhythmia (ventricular fibrillation, ventricular tachycardia, asystole, complete heart block, new or unstable atrial fibrillation, supraventricular tachycardia), new or unstable angina, pneumothorax, or congestive heart failure.
   $Sao_2 > 92\%$ while breathing room air or return to baseline for those with severe chronic obstructive pulmonary disease
   White blood cell count (if available) $\leq 12 \times 10^9$/L
4. Follow-up chest radiographs
   Patients with clinical improvement during hospitalization—none required
   Patients aged ≥ 45 years with history of smoking—At 6 weeks
   Patients aged ≥ 55 years—at 6 weeks
5. Vaccination
   Pneumococcal vaccine if not pneumococcal vaccine received within previous 6 years and patient is ≥ 65 years of age or has chronic obstructive lung disease or chronic heart disease, or meets the other criteria for pneumococcal vaccination
   Influenza vaccine for those who are hospitalized during October to December in the northern hemisphere and who meet the guidelines for the vaccine.
6. Patient information
   A brief overview of symptoms, signs, and natural history of pneumonia.

A pneumonia critical pathway that has been evaluated by Marrie et al. (1998) in a randomized clinical trial is shown in Table 3. In this trial, 20 Canadian teaching and community hospitals were randomized to the intervention arm (critical pathway) or to conventional management. Hospitals were matched for teaching or community hospital status and for historic length of stay for patients with CAP. One community hospital in the intervention arm withdrew after randomization and was not replaced. Levofloxacin was the antibiotic used in the intervention arm, whereas the choice of antimicrobial therapy for patients in the conventional arm was at the discretion of the attending physician. An intent-to-treat analysis was performed on data from 1753 patients enrolled in the study. At the intervention hospitals, the admission rate was lower for low-risk patients (classes I-III)—31% versus 49% for conventional management ($P = 0.013$), and there was a 1.7-day reduction in the average number of bed-days required per patient managed. Although the inpatients at the intervention sites had more severe disease (severity of illness score, 103.5 vs. 93.7, $P = 0.036$), they required fewer days of intravenous antibiotic therapy (4.6 vs. 6.3 days, $P = 0.013$) and were more likely to receive antibiotic monotherapy (64% vs. 27%, $P < 0.0001$), than patients in the conventional management arm. There were no negative effects on the patients' quality of life as measured by the 36-Item Short Form Health Survey; mortality rates were similar at 6.1% and 6.6% as were the readmission rates (9.3% vs. 8.8%) (Marrie et al., 2000). This study suggests that a critical pathway for the treatment of pneumonia can result in fewer admissions and shorter length of stay, without any adverse health outcomes.

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Pneumonia in Pregnancy

JOANNE M. LANGLEY

The 9-month period of human gestation is one of great changes for the pregnant woman. During this time there are ongoing endocrinologic, immunologic, cardiopulmonary, and psychologic adaptations to the development within the mother, and imminent arrival into the family, of a new baby. An acute illness such as pneumonia is an additional stress on this system. The population of childbearing women has changed in this century from predominantly healthy young women to include women now surviving chronic illness into their reproductive years and older women. Many of the clinical manifestations of pneumonia in pregnancy are similar in the pregnant and nonpregnant states. There are additional concerns when an acute lower respiratory tract illness occurs in pregnancy, including the effect of illness and treatment on the fetus. In this chapter we review the cardiorespiratory and immunologic changes of pregnancy that must be considered in the pregnant woman with pneumonia, what is known about the incidence of pneumonia and its consequences for the pregnancy, the clinical features of some specific pathogens reported as causing lower respiratory tract infection in pregnancy, and treatment considerations.

JOANNE M. LANGLEY • Department of Pediatrics, Community Health and Epidemiology, Dalhousie University, and Infection Control Services, Izaak Walton Killam Grace Health Centre for Children, Women and Families, Halifax, Nova Scotia, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

The Pregnant Woman as a Host: Respiratory and Immunologic Changes

Changes in respiratory ventilation occur as early as the first few weeks of pregnancy. In the first trimester, secretion of progesterone results in a state of maternal hyperventilation, with increased tidal volume and no change in respiratory rate, resulting in an increased resting minute ventilation. These effects may be seen in nonpregnant women in the luteal phase or in those administered progesterone (Branch, 1992). The arterial carbon dioxide tension is generally less than 30 mm Hg, resulting in a chronic respiratory alkalosis that is partially compensated by increased renal bicarbonate excretion.

As the uterus enlarges and maternal body weight increases, the shape of the chest is altered. The costal angle widens by about 50%, and the circumference of the lower chest wall increases 5 to 7 cm. Functional residual capacity decreases by 17% to 20% (300-500 mL) in the upright position and by 25% in the supine position (Crapo, 1996). Although the diaphragm is elevated, diaphragmatic excursion is unaffected.

Cardiac output increases beginning early in pregnancy, with increases in stroke volume and heart rate resulting in an output 30% to 50% greater than that of the nonpregnant woman by term. Plasma volume, red blood cell mass and white blood cell counts also increase (Branch, 1992). Because the red cell mass does not increase as much as plasma volume, a physiological anemia of pregnancy is observed.

The respiratory mucosa becomes more edematous during pregnancy, with 30% of women reporting rhinitis symptoms and others reporting a sensation of ear fullness (Crapo, 1996).

The mother's host defense system must adapt to the arrival of the semiallogeneic fetus, antigenically distinct from the mother. Investigation of this unique immunoregulatory process has yielded variable results, with some authors suggesting that maternal-infectious agent interactions are no different than in nonpregnant women (Nahmias & Kourtis, 1997) and others accepting that host susceptibility is altered (Brabin, 1985).

Although a consensus of understanding about maternal immunity does not yet exist, alterations in many components of host defense have been documented, including change in function and efficiency of T helper (TH) lymphocytes, reduction in receptor-mediated respiratory burst activity, and microbial killing of polymorphonuclear leukocytes (Crouch et al., 1995), predominance of TH-2 cytokines with downregulation of TH-1 associated responses and interferon-γ, decreased lymphocyte transformation and populations, and increased immune complex production (Brabin, 1985). Humoral immunity in pregnant and nonpregnant women appears to be similar.

Epidemiology of Pneumonia in Pregnancy

Observations of increased severity and frequency of pneumonia during pregnancy date to the time of Hippocrates, who believed that acute diseases occurring during pregnancy were dangerous and could result in death (Oxorn, 1955). Published reports of excess morbidity associated with pneumonia in pregnancy followed epidemics of influenza in the early 20th century. Following an epidemic in August and September of 1918, in which 11,599 people died of influenza and pneumonia in Philadelphia, a local obstetrician reported 337 cases of pregnant women with pneumonia (Bland, 1919). Of these 337 women 46% (155/337) died, a rate 15% higher than that for nonpregnant women. Most of the women were 20 to 30 years of age and clinical manifestations of pneumonia were not noted to be remarkably different than in the rest of the affected population. A review of national vital statistics data for the 1957–1960 influenza epidemic using United States mortality data showed that among the 86,000 deaths in excess of normally expected numbers, pregnant women were one of the three groups at highest risk of death from this infection (Eickhoff & Sherman, 1961).

Maternal death certificates from 1974–1978 in the United States show that pneumonia was the most frequent cause of nonobstetric infection, and the most common nonobstetric infection to cause peripartum mortality. Pneumonia accounted for 24 of 41 nonobstetric infectious deaths of the 2475 deaths reported during that period (Kaunitz et al., 1985). A MEDLINE® search from 1966–1999 using the terms "pneumonia" and "pregnancy," and perusal of references from these titles identified 13 studies on the incidence of pneumonia that used a denominator of a population of pregnant women (Table 1). The settings for these studies are not always described but most appear to be from large urban hospitals. One might expect that complica-

TABLE 1. Incidence of Pneumonia during Pregnancy Reported in Hospital-Based Studies

Author (year)	Cases	No. of pregnancies	Incidence (%)	Mortality rate, % (no.)
Jurgenson (1875)	?	1843	2.3	NA
Wessinger (1906)	47	2475	1.9	NA
Norris (1913)	120	13,611	0.8	NS
Oppel (1939)	15	15,000	0.10	NA
Finland (1939)	212	25,891	0.63	30 (65)
Nukkels (1938)	23	20,364	0.12	NA
Oxorn (1955)	64	60,000	0.11	12.5 (8)
Schaefer (1959)	21	16,619	0.13	NA
Hopwood (1965)	23	2720	0.84	8.6 (2)
Benedetti (1982)	39	89,219	0.04	0
Madinger (1989)	25	32,179	0.08	4 (1)
Berkowitz (1990)	26	9560	0.27	0
Richey (1994)	71	59,656	0.12	2.8 (2)

NA, not available.

tions might be higher in such women since they could have been referred for specialist care and therefore be at higher risk for a number of adverse pregnancy outcomes, or that such centers serve indigent populations whose health status was compromised before the pregnancy. In the 20th century the incidence of pneumonia in pregnancy is less than 1% in all studies. Death rates are given in five studies and range from 12.5% in Montreal in 1955 (Oxorn, 1955) and 8.6% in 1965 in Illinois, to no deaths in two studies. In the most recent study, from a large inner city hospital in Texas, 44% of women with pneumonia had chronic underlying disease including asthma, diabetes, and HIV infection (Richey et al., 1994), reflecting the increasing numbers of women with chronic diseases or of older age who are attempting pregnancy.

Obstetric outcomes are reported in five of the studies of the incidence of pneumonia in pregnancy. Preterm delivery occurred in a variable number of pregnancies ranging from none (Berkowitz & LaSala, 1990) or less than two cases of preterm delivery (Benedetti et al., 1982; Richey et al., 1994) to 30% to 50% of pregnancies (Madinger et al., 1989; Hopwood, 1965). In total, seven fetal deaths were reported from these studies. Pooling the outcomes from these five, albeit variable, populations, the maternal case fatality rate for pneumonia is 17% (78/460; 95% confidence interval [CI] 13.6–20.7), the incidence of preterm delivery is 11.4% (21/184; 95% CI 7.2–16), and the fetal case–fatality rate for women with pneumonia in pregnancy is 3.8% (7/184; 95% CI 1.5–7.7).

Clinical Features

The clinical presentation of pneumonia in the pregnant patient is similar to that in the nonpregnant patient. Established guidelines or critical pathways for nonpregnant patients with similar risk factors or preexisting morbidities should be followed, with special attention to fetal well-being, and to altered physiology and pharmocokinetics in pregnancy. Pregnant women with a febrile illness and signs suggestive of lower respiratory tract involvement (tachypnea, cough, dyspnea, extra work of breathing) should have a careful history to determine if risk factors for severe or unusual disease are present (e.g., cigarette smoking; cystic fibrosis; cardiac disease; reactive airway disease; poor nutritional status; immunocompromise including use of steroids and HIV; illegal drug use; tuberculosis exposure; travel).

Physical examination should determine the degree of respiratory distress, vital signs, level of consciousness, signs of consolidation, and associated bronchospasm, and any indication of extrapulmonary infection. The physical examination should include an assessment of fetal well-being, as hypoxemia may affect fetal oxygenation (Maccato, 1991).

Pneumococcal infection in pregnancy is similar to that in the nonpregnant state. Patients are usually febrile and may have chills or severe chest pain. Pleural effusions or empyema may occur and a third of patients may have a concomitant bacteremia. Although Legionnaires' disease is in many areas the second most common cause of community-acquired pneumonia after *Streptococcus pneumoniae,* only a few case reports of this illness in pregnancy have been reported (Eisenberg et al., 1997; Tewari et al., 1997; Soper et al., 1986). Clinical presentation has included septic shock and severe progressive consolidative pneumonia. In one case a term healthy infant was delivered (Eisenberg et al., 1997) and in another a low-birthweight baby was delivered prematurely and ultimately died (Soper et al., 1986).

The first presentation of HIV infection in pregnancy may be *Pneumocystis* carinii-associated pneumonia (PCP); this is the most common cause of pregnancy-associated AIDS-related death in the United States (Stratton et al., 1992). Characterized by fever, tachypnea, dyspnea, and nonproductive cough, the onset of PCP may be insidious, with weight loss, fatigue, and minimal or no respiratory findings. An increased alveolar-arterial oxygen gradient is found with bilateral alveolar disease on chest radiograph. Although initial case reports of pregnancy-associated PCP suggested that mortality was very high (Minkoff et al., 1986), more recent treatment successes have been published (Hicks et al., 1990; Albino & Shapiro, 1994).

Tuberculosis is another disorder that may herald the onset of AIDS during pregnancy, or may occur in the immunocompetent woman exposed in an endemic area. Pregnancy does not alter clinical manifestations of tuberculosis, and management is

similar to that for the nonpregnant patient (Saade, 1997). Appropriate early care is associated with good maternal and obstetric outcomes (Riley, 1997).

Pregnant women were among the population subgroups that were thought to suffer excess mortality and morbidity during the major influenza epidemics of the 20th century. Clinical features of respiratory illness do not differ from those of nonpregnant women with influenza, but an increased risk for hospitalization attributed to influenza was identified in the third trimester in women without other risk factors for influenza morbidity (Neuzil et al., 1998). This nested case–control study in a population of more than 25,000 women served by Medicaid in Tennessee found that of 10,000 women in their third trimester without other identified risk factors, severe respiratory compromise impaired fetal oxygenation.

Varicella infection in adults has a 25-fold increased risk of subsequent complications compared to that in children (Centers for Disease Control [CDC], 1984). Mortality rates of up to 35% have been reported in pregnant women with varicella pneumonia. Most women of childbearing age have natural immunity to varicella-zoster virus infection from childhood infection (Advisory Committee on Immunization Practices, 1996). The illness usually begins with a nonspecific prodrome of fever, myalgia, and malaise followed by maculopapular rash that evolves to vesicles on an erythematous base. Respiratory symptoms begin 2 to 5 days after rash onset and include cough, dyspnea, chest pain, and hemoptysis. Pulmonary involvement ranges from mild to severe, with diffuse bilateral fluffy nodular infiltrates and adult respiratory distress syndrome requiring mechanical ventilation (Smego & Asperilla, 1991). Maternal infection in the first trimester is associated with a 2% risk of congenital varicella syndrome (Pastuszak et al., 1994), and newborns delivered 5 days before to 2 days after the onset of maternal rash have a 17% to 30% risk of severe varicella infection (CDC, 1984).

Measles is an acute respiratory illness characterized by conjunctivitis, coryza, cough, fever, a generalized erythematous maculopapular rash, and an enanthem. Pneumonitis and laryngotracheobronchitis are complications that are thought to occur more commonly in young children with measles; these have also been reported in pregnant women (Ali & Albar, 1997; Eberhardt-Phillips et al., 1993; Atmar et al., 1992; Stein & Greenspoon, 1991). In one case-control study premature delivery was more frequent in 40 pregnant women with measles pneumonia than in nonpregnant women with measles or otherwise healthy pregnant women (Ali & Albar, 1997). In two other case series of a total of 70 pregnant women with measles, 31% (22/70) had pneumonia (Eberhardt-Phillips et al., 1993; Atmar et al., 1992), 31% (22/70) delivered prematurely, and 1.4% (1/70) died. Mild hepatitis is a frequent finding accompanying measles pneumonia in pregnancy.

Acute severe febrile illness with pneumonitis that may progress to adult respiratory distress syndrome has been reported in pregnant women with Hantavirus infection from Argentina and the United States (Pini et al., 1998; Gilson et al., 1994). Clinical features include a febrile prodrome with myalgia and progression to severe respiratory distress, hypotension, thrombocytopenia, acidosis, and hypoxic fetal damage in some cases. Hantavirus pulmonary syndrome has a mortality of up to 50% in the general population; the spectrum of outcomes in pregnant women has not yet been described.

Coccidioides immitis is a dimorphic fungus found in the soil of the southwestern United States, California, northern Mexico, and parts of Central and South America. Inhalation of dust-borne *Coccidioides* arthroconidia leads to primary pulmonary infection which is usually asymptomatic but may resemble an influenza-like illness or take on a progressive clinical course similar to pulmonary tuberculosis in immunocompromised individuals or pregnant women (Barbee et al., 1991). Women who have traveled to or live in endemic areas and who present with pleuritic pain and productive cough should undergo evaluation for coccidioidomycosis. Extrapulmonary manifestations include cutaneous lesions and erythema nodosum as well as dissemination to the bones, joints, central nervous system, and abdominal organs. Infection may be primary or may reactivate during pregnancy (Peterson et al., 1993). Although clinically apparent infection in pregnancy is not common, even in endemic areas (Wack et al., 1988), pregnant women do appear to be at increased risk for severe disseminated disease, including meningitis (Drutz & Huppert, 1983; Wack et al., 1988).

Blastomycosis with pulmonary involvement and dissemination occurs in pregnancy and may present with shortness of breath, nonproductive cough, and chest pain or cutaneous lesions with incidental lung findings on chest radiograph. A spectrum of outcomes has been reported including successful treatment with term delivery of an uninfected infant (Hager et al., 1988; Catanzaro, 1984), adult respiratory distress syndrome and premature delivery (MacDonald & Alguire, 1990), and perinatal transmission (Maxson et al., 1992).

Pulmonary cryptococcosis in pregnancy is a rare event but has been reported in women presenting with chest pain. This may be associated with low-grade fever, dyspnea, or cough (Ely et al., 1998; LaGatta et al., 1998; Catanzaro, 1984). The chest radiograph may reveal a nonspecific infiltrate or, less commonly, a focal density with nodular satellite lesions. Both maternal and fetal outcomes appear to be good.

The cystic fibrosis patient with longstanding progressive obstructive lung disease may develop acute lower respiratory tract infection during pregnancy. When antepartum lung dysfunction was limited and the disease was stable, pregnancy was not associated with irreversible clinical deterioration in a controlled study where pregnant cases were matched with their nonpregnant counterparts for age and severity of airflow obstruction (Frangolias et al., 1997). Acute pulmonary deterioration in the pregnant patient with advanced disease is associated with poorer outcomes for mother and child (Olson, 1997), including respiratory failure and death (Bose et al., 1997). Acute respiratory illness is managed similarly in the pregnant and nonpregnant patient, with consideration of community-acquired pathogens as well as colonizing flora such as *Pseudomonas aeruginosa, Burkholderia cepacia,* or *Staphylococcus aureus.*

Aspiration of stomach contents during labor and delivery, first described by Mendelson (1946), may lead to acute onset of bronchospasm and cough or more insidious onset of tachypnea, pulmonary edema, and hypotension. The timing and severity of clinical manifestions vary depending on whether the aspiration is of solid or liquid stomach contents or bacteria from the oropharynx, with the former having more rapid consequences. Although aspiration pneumonia during labor and delivery caused about 2% of maternal deaths in the past (Baggish & Hooper, 1974), prevention strategies (e.g., reduced oral intake, regional rather than general anesthesia, and antacids) before obstetric surgery have reduced the incidence of this pregnancy complication (Rowe, 1997).

Coxiella burnetii infection in pregnancy may be asymptomatic or present as a nonspecific febrile illness or as pneumonia (Langley, 1990; Marrie, 1993; Stein & Raoult, 1998). Patients may give a history of exposure to parturient cattle or domestic cats or dogs. The risk of premature birth or intrauterine death is not well described in Q fever pneumonia. Both normal and adverse pregnancy outcomes have been reported.

Diagnosis

As in the nonpregnant patient, diagnosis of pneumonia is made by a careful history and clinical examination and investigation, including a chest radiograph. The abdominal area is shielded from irradiation during a chest radiograph and a routine lateral and posteroanterior film exposes the patient to 6 millirads or less. The benefit of accurate diagnosis and treatment of maternal pulmonary disease is generally thought to outweigh the small risk of fetal radiation exposure (Murphy et al., 1996). An etiologic agent is identified in about half of cases of community-acquired pneumonia in pregnancy.

The most frequent agent causing pneumonia in pregnancy in all studies, other than during influenza epidemics, is *S. pneumoniae.* The exact incidence of pneumonia due to other causes is not known. Laboratory studies to determine an etiology include sputum gram stain and culture for *S. pneumoniae, Legionella pneumophila, Haemophilus influenzae, S. aureus,* or *Klebsiella pneumoniae;* nasal swabs for viral culture or direct fluorescent antibody for *Legionella;* acute and convalescent serology for *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* spp.; and a blood culture in the febrile or immunocompromised patient. If a skin rash suggestive of varicella is present a vesicular lesion may be sampled for electron microscopy, Tzanck smear, or viral culture and serology obtained for varicella-zoster antibody. In the immunocompromised host a search should be made for

opportunistic pathogens including *P. carinii,* cytomegalovirus, herpes simplex virus, or mycoses. In geographic areas where Hantavirus infection, coccidioidomycosis, or tuberculosis occur in the general population these pathogens should be sought using routine diagnostic methods. In cases where respiratory distress is present, initial stabilization of the patient should include maintenance of peripheral oxygen saturation at >90% to ensure adequate fetal saturation.

Treatment

S. pneumoniae accounts for more than 50% of community-acquired pneumonia in pregnancy, and in the previously well patient, therapy will be directed toward this agent and other common causes such as *M. pneumoniae.* Empiric treatment or treatment directed toward a known pathogen is generally the same for the pregnant and nonpregnant patient; however, the gravid state changes drug absorption, and the potential for fetal toxicity must be considered.

Changes in total body water and cardiac output alter the clearance of drugs in the mother, and essentially all drugs and many metabolites can be assumed to cross the placenta and reach the fetus (Koren, 1988). By the eighth month of gestation, body water has increased by 50% and consequently there is a larger volume of distribution; thus serum drug levels may be lower than in the nonpregnant state. Antimicrobial agents that are bound to albumin will have lower serum concentrations because of the decline in this serum protein early in pregnancy. Gastric emptying and intestinal motility are also slower in the pregnant woman, which may lead to suboptimal or variable absorption of agents administered orally (Parry et al., 1970). Aminoglycosides, β-lactams, erythromycin, and other drugs metabolized by the kidneys have lower serum levels in pregnancy because of the increased glomerular filtration rate resulting from increased renal blood flow (Godd & Johnson, 1971; Weinstein et al., 1976; Philipson, 1977; Giamerellou et al., 1983; Kafetzis et al., 1983; Landers et al., 1983). Although hepatic blood flow does not appear to be altered in pregnancy (Koren, 1988), progesterone may enhance drug metabolism and excretion by the liver (Krauer & Krauer, 1977; Fever, 1979).

The degree to which drugs delivered to the mother penetrate the placenta and their concentration in the fetal blood is determined by differences in protein binding, pH, and fetoplacental drug elimination; more detailed reviews of these issues may be found elsewhere (Koren, 1988).

Certain antimicrobial agents have been associated with teratogenicity. Tetracyclines given to the mother after calcification of fetal deciduous teeth (5–6 months' gestation) form a complex with fetal calcium orthophosphate, which causes a permanent yellow-brown discoloration (Cohlan, 1977). Streptomycin and kanamycin, two aminoglycosides used less commonly now than previously, achieve high concentrations in the fetal circulation and may result in ototoxicity. Numerous case reports of this complication have been published, and a survey of 391 pregnant women exposed to kanamycin for prolonged periods identified 9 cases (2.3%) with fetal hearing loss (Briggs et al., 1986). These consequences have not been reported for the more frequently used aminoglycosides gentamicin, tobramycin, and amikacin. A theoretical concern exists regarding the use of sulfonamides, which compete with unconjugated bilirubin for protein binding. Hyperbilirubinemia in the neonatal period may cause central nervous system damage or kernicterus. However, reports of antenatal sulfonamide administration resulting in kernicterus are not seen in the literature, and the Collaborative Perinatal Project, which followed 50,282 mother–child pairs and identified 1455 sulfonamide exposures, did not report malformations or other adverse consequences (Heinonen et al., 1977). Although concerns about potential arthopathogenicity of quinolones in pregnancy have limited their use in children and pregnant patients, the only studies in humans indicate that these agents do not increase the incidence of malformations, musculoskeletal problems, spontaneous abortions, fetal distress, prematurity, or low birthweight (Loebstein et al., 1998; Berkovitch et al., 1994).

The antifungal agent fluconazole has been associated with a malformation syndrome in a number of case reports (Aleck & Bartley, 1997; Pursley et al., 1996; Lee et al., 1992) and therefore ampho-

tericin preparations are preferred as systemic antifungal agents during pregnancy. The antiviral agents ganciclovir, ribavirin, amantadine, and foscarnet are not recommended for use in pregnancy (Watts, 1992), although clinical experience in pregnancy is limited or nonexistent. Amantadine has been associated in one case report with hemimelia and Fallot's tetralogy (Pandit et al., 1994) and in others with normal obstetric and fetal outcomes (Levy et al., 1991; Kirshon et al., 1988).

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Pneumonia in Children and Adolescents

ELAINE E. LING WANG AND HERBERT DELE DAVIES

Epidemiology

Lower respiratory infections, including pneumonia, are the leading infectious cause of death worldwide, accounting for 4.3 million deaths annually (Murray & Lopez, 1997). As a cause of death, such infections are overrepresented in children and in those in developing countries. In developing countries, the incidence of pneumonia varies from 21 to 296 episodes per 100 child-years (Selwyn & Board on Science and Technology for International Development of the National Research Council [BOSTID], 1990). The rates are at least an order of magnitude less in industrialized countries. For example, in North America, the incidence ranges from 30 to 35 episodes per 1000 children less than 5 years of age to 6 to 12 episodes per 1000 in older children and adolescents (Alexander et al., 1966; Foy et al., 1973; Murphy et al., 1981: Wright et al., 1989).

Studies of pneumonia have been hampered by the lack of an accepted standard for its diagnosis and the inability to obtain direct specimens for etiologic diagnosis. Furthermore, most studies have been conducted in hospitalized children. Thus, the literature on etiology, appropriate management, and prognosis relating to this syndrome must be interpreted with caution.

ELAINE E. WANG • Department of Pediatrics, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada M5S 1A8. **HERBERT DELE DAVIES** • Child Health Research Unit, Alberta Children's Hospital, and University of Calgary, Calgary, Alberta, Canada T6G 2B7.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Risk factors that increase the incidence or severity of pediatric pneumonia include prematurity, malnutrition, low socioeconomic status, passive exposure to cigarette smoke, and attendance at day care centers (Wang & Law, 1998). Underlying diseases, especially those affecting the cardiopulmonary, immune, or nervous systems, also increase the risk for developing severe pneumonia (Adler-Shohet & Lieberman, 1998; Wang & Law, 1998).

Etiologic Agents

Aside from one U.S. study (Rapkin, 1975), all studies that have obtained direct lung specimens for etiologic diagnosis have been conducted in developing countries (Vuori & Peltola, 1998). The dearth of these investigations in industrialized countries is presumably because obtaining such specimens is considered inordinately invasive for a condition that usually responds to empiric therapy. Thus, most etiologic diagnoses have been based on indirect methods of diagnosis. These methods can be grouped into two categories: (1) recovery of organisms from the upper respiratory tract, inferring that they are responsible for the lower tract symptomatology, and (2) recovery of organisms from another site, such as blood, in a patient with pneumonia, with serologic assays demonstrating either antigens or an increase in antibodies. As these methodologies have been developed in different centers, the spectrum of infectious agents has changed accordingly (Isaacs, 1989). These methods have been used without direct comparison with pulmonary speci-

mens and, in many investigations, without adequate controls. Even in such research settings, etiologies are identified in only 40% to 60% of cases (Claesson et al., 1989; Davies et al., 1996a; Heiskanen-Kosma et al., 1998; Hietala et al., 1989; Isaacs, 1989; Korppi et al., 1993a; Nohynek et al., 1991; Paisley et al., 1984; Ruuskanen et al., 1992; Turner et al., 1987).

The recovery of pyogenic bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* from the upper respiratory tract is not sufficient evidence to identify the causative pneumonia pathogen because these bacteria are frequent colonizers of the upper respiratory tract. However, because the majority of lower respiratory infections occur after aspiration of upper tract organisms, recovery of an organism that is not an upper tract colonizer may be more predictive of the lower tract pathogen.

Recognizing these pitfalls in determining etiologies, a number of generalities can be made because they have been found consistently across different studies. The greatest indicator of the causative pathogen is the age of the child (Table 1). Vertical transmission of organisms from the maternal genital tract is the main route of entry of pathogens in the neonatal and early infancy period. Infection with group B streptococci, *Listeria monocytogenes,* and gram-negative bacilli produces a septic picture that includes pneumonitis presenting soon after birth and associated with risk factors such as preterm labor, prolonged rupture of membranes, and maternal fever (Adler-Shohet & Lieberman, 1998). This presentation usually occurs within hours or days of birth. Afebrile pneumonitis syndrome with an insidious presentation in the first 3 months of life is seen with *Chlamydia trachomatis* pneumonia (Beem & Saxon, 1977; Harrison et al., 1978; Tipple et al., 1979). Although one early case series also found *Ureaplasma urealyticum,* cytomegalovirus, and *Pneumocystis carinii* to be responsible for this syndrome (Stagno et al., 1981), a more recent controlled study found *C. trachomatis* to be the only pathogen associated with this syndrome (Davies et al., 1996a).

TABLE 1. Age-Specific Causes of Pneumonia in Otherwise Healthy Children[a]

Age group	Pathogen (in order of frequency)
Neonate	Sepsis presentation. Group B streptococci, *Escherichia coli, Listeria monocytogenes*
1–3 months	Pneumonitis syndrome usually afebrile. *Chlamydia trachomatis*, respiratory syncytial virus, other respiratory viruses
4 months–5 years	Respiratory viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*
6–18 years	*M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, nontypeable *H. influenzae*, influenza viruses A and B, adenovirus, other respiratory viruses.

During the first 2 years of life, viruses are the most frequently implicated pathogens accounting for as much as 90% of pneumonias (Alexander et al., 1966; Denny & Clyde, 1986; Foy et al., 1973; Murphy et al., 1981; Wright et al., 1989). These include respiratory syncytial virus, parainfluenza virus types 1 to 3, influenza virus types A and B, adenovirus, herpes simplex virus, rhinoviruses, and enteroviruses (Henrickson, 1998). With increasing age and as the incidence of pneumonia decreases, bacterial pathogens including *S. pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* are more frequently implicated. By school age, only half of pneumonia cases are viral in origin (Denny & Clyde, 1986). A recent Finnish population-based serologic study found that *M. pneumoniae* was the second most common agent after *S. pneumoniae* in pneumonia infections in a school-age group and the most common pathogen in young adolescents, associated with half the cases (Heiskanen-Kosma et al., 1998). *C. pneumoniae* was the second most common agent after *M. pneumoniae* in young adolescents and was associated with one third of all pneumonia cases in that age group (Heiskanen-Kosma et al., 1998).

Clinical Findings

In the neonatal period, symptoms of pneumonia are usually secondary to the general manifestations of sepsis characterized by hypotonia, lethargy, apnea, floppiness, inability to maintain a normal body temperature, and hypotension (Adler-Shohet & Lieberman, 1998). The chest infection may be manifested by tachypnea and hypoxia, progressing

to apnea and a need for ventilatory support. Radiographic findings include discrete infiltrates or a diffuse reticulonodular pattern indistinguishable from the findings seen with hyaline membrane disease. This presentation is common to infection with all neonatal pyogenic pathogens.

A specific syndrome, the infant pneumonitis syndrome, has been well described with C. *trachomatis.* It typically occurs during the first to the third month of life with a repetitive staccato cough, tachypnea, progressive respiratory distress, and radiologic evidence of bilateral pulmonary infiltrates and air trapping (Beem & Saxon, 1977; Harrison et al., 1978; Tipple et al., 1979). The infant is usually afebrile. Chest examination may indicate diffuse crackles, but no wheezing. The patient is typically not as sick as the diffuse auscultatory and radiographic findings would suggest. Conjunctivitis is seen in half the cases. Other features include an elevated total IgM and eosinophilia.

The classic presentation of bacterial pneumonia has been described as a patient with a productive cough accompanied by abrupt onset of chills and rigors. Clinical assessment reveals decreased breath sounds and crackles, typically confined to one lobe. Lobar involvement can be confirmed on radiographic examination. The presentation of atypical pneumonia has been described as a nonproductive cough and low-grade fever, without the degree of toxicity that is seen with bacterial pneumonia. The radiograph seen with this syndrome typically shows more diffuse involvement. Although the classic presentation was thought to be indicative of infection by pathogens such as *S. pneumoniae* and *H. influenzae,* and the second presentation suggestive of infection by atypical agents such as *M. pneumoniae* and *C. pneumoniae,* it is now established that all pathogens may present in either way or along the spectrum between these two extremes (Fang et al., 1990). *Legionella pneumophila,* an important cause of community-acquired pneumonia in adults (Fang et al., 1990) is rarely seen in children who are not immunocompromised (Brady, 1989). Furthermore, in children, productive cough is distinctly uncommon and its sudden onset should suggest tuberculosis or cystic fibrosis.

In the adolescent presenting with cough and fever, reactivation tuberculosis should be considered as a possible diagnosis. Clues to this diagnosis include residence in a tuberculosis-endemic area or contact with individuals at high risk for tuberculosis such as aboriginal people, the urban homeless, incarcerated individuals, and those with HIV infection. A high prevalence of tuberculosis is found around the world including Asia, Africa, Latin America, and Eastern Europe. The illness may be subacute, lasting days to weeks, and may be associated with anorexia, weight loss, and night sweats (Starke & Correa, 1995). Sputum production and hemoptysis also differentiate tuberculosis from *C. pneumoniae* or *M. pneumoniae* infections.

Other aspects of a patient's epidemiologic history may be helpful in the diagnosis. For example, exposure to parrots or other psittacine birds is a clue to *C. psittaci* infection. Exposure to parturient farm animals such as sheep, goats, cattle, and cats raises the possibility of infection with *Coxiella burnetii.* Travel to or residence in certain areas may also be suggestive of fungal pulmonary infections. For example, *Coccidioides immitis* is endemic to southwestern United States, northern Mexico, and parts of Central and South America. *Histoplasma capsulatum* infection occurs in eastern and central United States and Canada. The presence of certain extrapulmonary findings such as erythema multiforme or joint manifestations is indicative *of M. pneumoniae* infection (Denny et al., 1971).

The accuracy of clinical criteria developed by the World Health Organization (WHO) for the diagnosis of pneumonia (WHO, 1984) in children presenting with fever and cough has been studied in industrialized countries (Table 2) (Berman et al., 1991; Grossman & Caplan, 1988; Leventhal, 1982; Taylor et al., 1995; Zukin et al., 1986). Using the presence of radiographically confirmed pneumonia as the gold standard, tachypnea—defined as >40 breaths per minute in children and >50 breaths per minute in infants—was found to be the most sensitive single indicator, with a sensitivity that ranged from 50% to 81% (Leventhal, 1982; Zukin et al., 1986). Respiratory rate may vary by the measurement method and the child's emotional state. Thus, the optimal assessment method is to count the rate by observation for a full 60 seconds with the child awake and not crying (Berman et al., 1991).

Although the presence of crackles was highly specific, it was not present in up to 57% percent of cases. Overall, no single sign was adequately sensi-

TABLE 2. Sensitivity and Specificity of Clinical Findings in Pediatric Patients with Radiographic Pneumonia[a]

	Berman et al., 1991	Leventhal, 1982	Zukin et al., 1986	Grossman & Caplan, 1988	Taylor et al., 1995
Number of patients	90	133	125	155	576
Number of pneumonia patients	63	26	18	51	42
Age range	<4 months	3 months–15 years	<17 years	<19 years	<2 years
Appearance					
Sensitivity (%)		92		67	
Specificity (%)		15		40	
Tachypnea					
Sensitivity (%)	62	81	50	64	75
Specificity (%)	63	60	68	54	70
Retractions					
Sensitivity (%)		35	17		
Specificity (%)		82	84		
Crackles					
Sensitivity (%)		44	57	43	
Specificity (%)		80	75	77	

[a]Adapted from Jadavji et al., 1997.

tive and specific to be used alone in diagnosing the presence or absence of pneumonia. One study found that all pneumonia cases had at least one of the following: respiratory distress, tachypnea, crackles, and decreased breath sounds (Leventhal, 1982). Thus, the *absence of all* four findings could be used to rule out pneumonia without need for a chest film. Measurement of tachypnea has good reproducibility compared with other findings such as detection of retractions, crackles, or wheezes (Godfrey et al., 1969; Wang et al., 1992, 1996). The accurate measurement of respiratory rate should be an integral part of the assessment of any child with suspected pneumonia.

Oxygenation status is a good predictor of disease severity associated with lower respiratory infection as measured by hospitalization duration (Hall et al., 1979; Shann et al., 1989; Simpson & Flenley, 1967). Cyanosis indicates severe hypoxia, but is usually absent in children with hypoxia (Simpson & Flenley, 1967). A normal general appearance and ability for the child to be consoled is a good indication of normal oxygenation (Margolis et al., 1994), but oximetry should be performed when hypoxia is a possibility, especially in a hospitalized child.

Diagnosis

Radiographs

Radiographic confirmation of the clinical diagnosis of pneumonia is necessary given the lack of agreement between clinical and radiologically confirmed pneumonia (Davies et al., 1996b; Redd et al., 1994). The entity of bronchitis, a viral infection, may present with similar findings but without demonstration of pulmonary infiltrates. Antibiotics are not indicated for this syndrome (O'Brien et al., 1998). The concern about overuse of antibiotics where they are not indicated is particularly cogent during this era of rising antibiotic resistance among the common community-acquired bacterial pathogens (Speert, 1996).

Radiographs provide an estimate of the extent of lung involvement and provide some clues to etiology. However, as with the clinical assessment, there is overlap of etiology with different radiographic findings (Bettenay et al., 1988; Isaacs, 1989; McCarthy et al., 1981), and radiographs can only provide guidelines as to etiology. Peribronchial thickening and diffuse interstitial infiltrates, particularly with hyperinflation, are associated with viral

infections, whereas lobar infiltrates and pneumatoceles are more suggestive of bacterial pneumonias (Korppi et al., 1993b; Redd et al., 1994). The finding of pleural effusions is more suggestive of pyogenic pneumonia (Asmar et al., 1978; Bartlett & Finegold, 1974; Chartrand & McCracken, 1982; Light et al., 1980) than of pneumonias due to *M. pneumoniae* or viruses (Fine et al., 1970). When effusions are seen with the latter infections, the amounts are much smaller (Fine et al., 1970).

The presence of hilar adenopathy on the chest radiograph suggests tuberculosis or pulmonary fungal infection, such as histoplasmosis or blastomycosis.

Routine follow-up films are not indicated unless the child has had recurrent pneumonias. In such situations, the follow-up films are helpful in determining whether there has been resolution between episodes (Wald, 1990).

Other Diagnostic Tests

The extent of investigation is tailored to the setting, the host, and the severity of illness. Thus, patients with mild to moderate illness can be managed expectantly without specific tests since empiric management is generally successful. A more aggressive investigative approach is indicated in those who have persistent or worsening symptoms, those who have underlying illness, or those who have severe disease. Infections for which treatment is different from empiric regimens should have priority. Studies that provide results in a timely manner relative to management decisions are helpful. Thus, only a few serologic assays are generally helpful, because many require the observation of a 4-fold rise in the convalescent titer taken 2 to 4 weeks after an acute serum sample is obtained.

Antigen detection of respiratory viruses allows rapid diagnosis, which may help provide specific treatment, including limiting unnecessary antibiotics, cohorting (Isaacs et al., 1991; Krasinski et al., 1990), and reducing unnecessary investigations. Such methods are available for detection of respiratory syncytial virus, parainfluenza viruses, influenza viruses, and adenoviruses (Hierholzer et al., 1989; Johnston & Bloy, 1993; Salomon et al., 1989; Thiele et al., 1989), but the sensitivity of these assays is limited by the availability and quality of the antisera used in either the enzyme immunoassay (EIA) or fluorescent assay. Compared with viral isolation, sensitivity of antigen detection for adenovirus is lowest, at about 20% compared with an average of 75% for other viruses (Henrickson, 1998).

Assays based on the polymerase chain reaction (PCR) have been combined into multiplex assays to detect different respiratory viruses (Henrickson, 1998). These methods are more sensitive than antigen detection assays, but the specificity of these assays needs improvement. These assays have also been developed for coronaviruses and rhinoviruses, which are difficult to grow on tissue culture (Pitkaranta et al., 1998). Their role in diagnosing the cause of pediatric pneumonia remains to be determined. The role of PCR in detecting *M. pneumoniae, C. pneumoniae,* and other organisms that do not normally colonize the upper respiratory tract is also being actively investigated.

Blood cultures should be performed in febrile patients with pneumonia since isolation of an organism provides proof of etiology. However, organisms are isolated in 10% to 30% of cases at most. When there is a pleural effusion, this fluid should be obtained for diagnostic as well as therapeutic reasons. In addition to cell count and biochemical tests, bacteriologic examination should be performed on the fluid. Gram's stain and aerobic and anaerobic culture for pyogenic organisms should be performed on all specimens, as this may be the only source of such an isolate. Etiologic agents are identified in up to 60% of empyemas (Cham et al., 1993; de la Rocha, 1982; Fajardo & Chang, 1987; Hoff et al., 1991). Where indicated, *M. tuberculosis* and fungal pathogens should also be sought, but pleural biopsy may have a better diagnostic yield (Boutin et al., 1990).

Serodiagnosis is the mainstay of diagnosis of *C. trachomatis* since infection by vertical transmission usually has occurred several weeks prior to onset of symptoms. Because of placental transmission of antibody to *C. trachomatis,* IgM-specific assays are confirmatory (Schachter, 1980). Serology may also be helpful in the diagnosis of *C. burnetii* (Sawyer et al., 1987) and *C. psittaci* infection. The role of *C. pneumoniae* serodiagnosis using microimmunofluorescence is controversial since the organism may be isolated in those who do

not demonstrate seropositivity (Hammerschlag, 1995). Neither method is widely available. Most serologic assays for respiratory viral diagnosis are of limited value because they are based on complement fixation (CF) methods, which are relatively insensitive particularly in young children with such infections. Serologic assays for *M. pneumoniae* using either CF or EIA methods may be helpful, but only retrospectively, because increases in antibody may only occur weeks after onset of illness (Kenny et al., 1990). The organism may be recovered from throat cultures, but this is performed only in research laboratories and may also take weeks to complete (Kenny et al., 1990). Serologic assays for antibody responses to pneumococcal antigens and pneumococcal immune complex assays have been used mainly in Finland (Heiskanen-Kosma et al., 1998).

When tuberculosis is suspected, skin testing with 5 Tuberculin units and culture of sputum or other respiratory specimen and gastric aspirates is indicated. The latter appears to be superior to a respiratory specimen in the pediatric patient with primary disease (Vallejo et al., 1994).

Management

General Management

Decisions about hospitalization of pneumonia patients must be individualized. Factors to consider include hydration status, oxygenation status, toxic appearance, lack of response to oral therapy, recurrence, or underlying disease. Parenteral hydration and antibiotics should be administered if oral intake is inadequate. Oxygen supplementation should be provided if patients are hypoxic. This should be specifically ruled out in patients who are hospitalized, and oxygenation status should be monitored until the patients are no longer hypoxic. Work of breathing should also be monitored and consideration given to positive airway pressure or ventilation in children who are "tiring out."

Three trials of vitamin A for the treatment of non-measles pneumonia have not found this intervention to be of benefit (Dowell et al., 1996; Kjolhede et al., 1995; Nacul et al., 1998). Thus, the addition of vitamin A is not indicated in the usual management of pneumonia.

Antimicrobial Treatment

Recommendations about the appropriate use of antimicrobials are limited by the dearth of randomized trials comparing drug efficacy. Thus, the antibiotic recommendations summarized in Table 3 are based on distribution of agents and their susceptibility most likely observed in different age groups.

Randomized trials conducted in adults with pulmonary tuberculosis have demonstrated the efficacy of 6-month regimens of combination isoniazid, rifampin, and pyrazinamide for 2 months followed by 4 additional months of treatment with the first 2 agents for susceptible tuberculosis (Combs et al., 1990; Snider et al., 1984). Twice-weekly therapy has been shown to reduce relapse rates from 21% to 6% and drug resistance from 14% to 2% through increased patient compliance (Weis et al., 1994).

Although randomized trials of ribavirin treatment of respiratory syncytial virus disease have been conducted, they have not been optimally designed, and a meta-analysis of their results concluded that further studies were needed to demonstrate efficacy (Randolph & Wang, 1996).

The choice of antibiotics in the early neonatal period reflects recommendations for the treatment of neonatal sepsis. Because of the high frequency of *C. trachomatis* in the afebrile pneumonia syndrome of infancy, a macrolide remains the treatment of choice (Beem et al., 1979). In those with more severe disease who are admitted to the intensive care unit, coverage is expanded to ensure efficacy against *S. aureus* and *H. influenzae* (Asmar et al., 1978; Chartrand & McCracken, 1982).

In those less than 5 years of age, *S. pneumoniae* is the most frequent bacterial organism. Unlike the case with pneumococcal meningitis, pneumonias due to penicillin-resistant *S. pneumoniae* continue to respond to penicillins and first- and second-generation cephalosporins (Bradley et al., 1995; Pallares et al., 1995). In a multicenter, retrospective study involving 254 children with pneumonia, Tan and colleagues (1998) compared the clinical characteristics of those with penicillin-susceptible and

TABLE 3. Empiric Antimicrobial Therapy for Pediatric Pneumonia, by Age Group

Age group	Outpatients	Patients in hospital	Patients in intensive care unit
1–3 months (afebrile pneumonitis)	Initial outpatient management not recommended	Erythromycin 40 mg/kg/d in four doses or other macrolide for 10–14 days	Erythrymycin 40 mg/kg/d in four doses or other macrolide for 10–14 days
1–3 months	Initial outpatient management not recommended	Cefuroxime 150 mg/kg/d in three doses for 10–14 days	Cefuroxime 150 mg/kg/d in three doses *or* cefotaxime 200 mg/kg/d in three doses *plus* cloxacillin 100–200 mg/kg/d in four doses for 10–14 days
3 months–5 years	Amoxicillin 40 mg/kg/d in three doses *or* erythromycin 40 mg/kg/d four doses *or* other macrolide for 7–10 days	Ampicillin 150 mg/kg/d in four doses *or* cefuroxime 150 mg/kg/d in three doses for 7–10 days	Cefuroxime 150 mg/kg/d in three doses *plus* erythromycin 40 mg/kg/d in four doses or other macrolide for 7–10 days
5–18 years	Erythromycin 40 mg/kg/d in four doses or other macrolide for 7 days	Erythromycin 40 mg/kg/d in four doses or other macrolide with or without cefuroxime 150 mg/kg/d in three doses or ampicillin 150 mg/kg/d in four doses for 7–10 days	Cefuroxime 150 mg/kg/d in three doses for 7–10 days, *plus* erythromycin 40 mg/kg/d in four doses or other macrolide for 7 days

[a]Adapted from Jadavji et al., 1997.

penicillin-nonsusceptible *S. pneumoniae.* Of the 257 pneumonia episodes occurring in these 254 children, 9% were of intermediate resistance and 6% were fully resistant to penicillin. No differences could be found in the clinical presentation of the children with susceptible and nonsusceptible disease. Although there was high variability in the choice of antibiotics, including parenteral and oral β-lactam antibiotics and second- and third-generation cephalosporins, the majority (97.6%) of patients had a good outcome. Six patients died, with only one death attributed to *S. pneumoniae* infection. Of these, five received vancomycin and a cephalosporin, and only one had a penicillin-resistant isolate (MIC = 2.0 μg/mL). The authors concluded that standard β-lactam therapy remains effective for pneumonias. A similar study involving 922 cases of pneumococcal bacteremia, 56 of which were nonsusceptible, came to identical conclusions. For non-meningitic disease, reduced antibiotic susceptibility did not alter clinical presentation and had little impact on clinical outcome (Silverman et al., 1999). β-lactam antibiotic therapy was associated with good outcome, and there was no need for vancomycin therapy. In a third study in Pakistan, 595 children with pneumonia diagnosed using the WHO criteria (WHO, 1984) were randomized in a 2:1 ratio to receive cotrimoxazole or amoxicillin (Straus et al., 1998). Children with a cough or difficulty breathing and lower chest indrawing were considered to have severe pneumonia. There were more therapy failures in the cotrimoxazole group than in the amoxicillin group (23% vs. 15%, P = 0.03), with most of the difference accounted for by infants with severe pneumonia (33% vs. 18%, P= 0.01). However, the groups were unbalanced with respect to isolation of resistant *S. pneumoniae* from blood, with more of these patients receiving cotrimoxazole. None of the patients treated with amoxicillin had a clinical isolate of resistant *S. pneumoniae,* but the three that had intermediate susceptibility responded to therapy. In contrast, 4/15 (27%) patients in the cotrimoxazole group with resistant *S. pneumoniae* failed therapy and two of eight with intermediate susceptibility failed therapy. In spite of the imbalance, the use of cotrimoxazole was an independent risk factor for therapy failure. Thus, β-lactam agents should be included in the empiric

management of infections in this age group, but ongoing monitoring for susceptibility patterns is warranted. The addition of macrolides in this age group, particularly in outpatients, is suggested for coverage of *M. pneumoniae* and *C. pneumoniae*. Two multicenter randomized clinical trials comparing erythromycin with either clarithromycin (Block et al., 1995) or azithromycin (Harris et al., 1998) found the newer agents to be equally efficacious, but with much fewer side effects. In the control group in the latter study, those less than 5 years of age received amoxicillin–clavulanate and those between 5 and 16 years of age received erythromycin (Harris et al., 1998). A randomized study with a similar study design of 168 children with community-acquired pneumonia also did not find any differences between amoxicillin–clavulanate recipients and macrolide recipients (Wubbel et al., 1999). The authors of that study concluded that antibiotic choice should be based on clinical judgment. However, this study had limited power to detect differences because of its small overall sample size. Interestingly, this study also detected relatively fewer cases of *C. pneumoniae* and *M. pneumoniae* than did the multicenter randomized trials.

Conclusions and Research Priorities

One of the major dilemmas in the management of pneumonias is the inability to diagnose an etiologic agent. In the past, the conservative route of management was to initiate antibiotics in all who had radiographically confirmed pneumonia. This still appears to be the most prudent course, at this time, given the high frequency of double infections, in which bacterial and viral agents may both be diagnosed in a patient (Heiskanen-Kosma et al., 1998). However, more controlled studies are needed to understand the significance of serodiagnostic methods. Whether some of the pneumococcal seropositive cases, for example, are false positives needs to be determined.

Few clinical trials have been conducted to determine the efficacy of macrolides compared with penicillins. Macrolides have been included as first-line agents in most treatment guidelines on the basis of their coverage of atypical organisms (Bartlett et al., 1998). Given the high success rate of current treatment of pneumonia and the increasing resistance rates to macrolides among group A streptococci (Seppala et al., 1997) and *S. pneumoniae* (Kellner et al., 1996) due to overuse of these agents, however, randomized trials that show an incremental benefit of these agents are needed to justify their inclusion in empiric therapy.

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Pneumonia in HIV-Infected Patients

WALTER F. SCHLECH III

Introduction

In 1982, a cluster of community-acquired pneumonia cases occurred in five homosexual men, resulting in three deaths (Centers for Disease Control [CDC], 1981a). The etiologic agent was identified as *Pneumocystis carinii,* at that time considered to be a protozoan pathogen, which caused nosocomial pneumonia in immunocompromised patients with malignancy or organ transplant. Other cases of *P. carinii* pneumonia (PCP) in homosexual men were reported in Los Angeles and New York along with an unusual malignancy of the skin, Kaposi´s sarcoma (CDC, 1981b). The infected individuals were found to have a profound defect in cell-mediated immune function, characterized by lymphopenia, primarily depletion of T helper (CD4) lymphocytes, and a reversal of T helper-suppressor cell ratios.

In 1983, a human retrovirus, HIV-1, was identified as the cause of this acquired immunodeficiency syndrome (AIDS) (Barre-Sinoussi et al., 1983). New groups at risk for this syndrome were soon discovered, including patients with hemophilia, Haitian immigrants, and injection drug users. The spectrum of disease suffered by these patients was also expanded to include other pathogens traditionally associated with cell-mediated immune dysfunction such as *Toxoplasma gondii* brain abscess, *Cryptococcus neoformans* meningitis, and cytomegalovirus retinitis. In addition, cases of severe community-acquired bacterial pneumonia, often recurrent and accompanied by bacteremia, were reported (Polsky et al., 1986; Simberkoff et al., 1984). These cases suggested that the immune defect associated with HIV-1 infection was not limited to abnormal cell-mediated immune responses but included heightened susceptibility to pathogens more commonly seen in immunoglobulin deficiency. These reports were sufficiently convincing that recurrent bacterial pneumonia became an AIDS-defining opportunistic illness in 1993 along with *Mycobacterium tuberculosis* infection and cervical carcinoma in the setting of H1V infection (CDC, 1993).

Subsequent studies of patients with AIDS have demonstrated that the etiology, diagnosis, and management of community-acquired pneumonia in this particular population has become increasingly complex. Effective prophylaxis for PCP and improvements in immune function associated with highly active antiretroviral therapy (HAART) have altered the natural history of AIDS and contributed to the recognition that pneumonia in patients with AIDS is not always caused by *P. carinii.*

Immunologic Defects in HIV Infection

The central feature in the pathogenesis of HIV infection is the destruction of CD4 lymphocyte populations essential to immune regulation. A complete review of HIV pathogenesis is beyond the scope of this chapter and can be found elsewhere (Stanley & Fauci, 1995), but understanding the increased risk for developing community-acquired pneumonia in these patients is important. The envelope proteins of HIV-1 and HIV-2 bind to the CD4

WALTER F. SCHLECH III • Division of Infectious Diseases, Department of Medicine, Dalhousie University Faculty of Medicine, Halifax, Nova Scotia.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

receptor and other coreceptors, primarily β-chemokines, on the surface of T lymphocytes or other cells such as macrophages expressing the CD4 phenotype. After entry into the cell and uncoating, reverse transcription and integration of proviral DNA into the host genome occur. Subsequent events that are poorly understood "trigger" the emergence of provirus, viral reproduction and destruction of the infected cell as progeny virus is formed. Enhanced programmed cell death (apoptosis) is also thought to be a component of this process. Recent work by Ho et al. (1995) has underscored the dynamic nature of this process and the tremendous immunologic redundancy that allows production of 10^9 new lymphocytes per day, followed by their rapid destruction, during a time when the total peripheral lymphocyte count may remain stable.

These events are accompanied by varying levels of plasma viremia and alterations in the lymphoid tissue infected during the initial viremia. The loss of HIV-specific cytolytic T-cell responses ultimately leads to a loss of control of productive HIV infection and further deterioration and collapse of the immune system.

For bacterial and some fungal infections, macrophage-monocyte responses are important for the early control of infection. Because HIV can infect these cells, functional impairment can occur. Phagocytosis is not as severely affected in advanced HIV infection but Interleukin (IL)-12 production and chemotaxis may be impaired as well as intracellular killing. Because macrophages are also important in processing antigens for presentation to B cells, impairment of this function may be reflected in faulty B-cell responses to infection or to immunization.

Impaired B-cell responses also lead to increased production of immunoglobulins IgG, IgA, and IgD that are not directed against specific antigens, and polyclonal gammopathies are almost universal in patients with mid- to late-stage HIV infection. These antibody responses may impair more appropriate antigen-specific responses when infection does develop. In vitro tests of B-cell function show poor responses to protein A, mitogens, and keyhole limpet hemocyanin. This abnormal and diminished response to antigen stimulation also has implications for immunization of patients with HIV infection. Antibody responses to polysaccharide vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b are impaired, and pneumococcal vaccine failure has been documented in HIV infected patients (Simberkoff et al., 1984; Frankel et al., 1996).

Polymorphonuclear leukocyte activity in patients with HIV infection is also impaired. Both qualitative and quantitative abnormalities can be seen. Intracellular killing and decreased opsonic activity can be found in vitro and may be important for control of such pathogens as *Staphylococcus aureus* and *Candida albicans.* In addition, neutropenia is frequently found in HIV-infected patients as a consequence of bone marrow suppression by HIV itself, or by antiretroviral drugs such as azidothymidine, antiviral agents such as ganciclovir that are used to treat cytomegalovirus (CMV) infection, or other drugs used to prevent opportunistic infections, such as trimethoprim-sulfamethoxazole. Quantitative defects can be managed with administration of cytokines, such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor but qualitative effects in leukocyte function may persist.

Finally, mucosal integrity is often damaged in patients with HIV infection. In the upper respiratory tract, cytomegalovirus, herpes simplex virus, and *C. albicans* are infections that lead to local or diffuse ulceration and may promote microaspiration of respiratory pathogens or direct invasion of the bloodstream. Malignancies, including Kaposi's sarcoma and lymphoma, may exist within the upper and lower respiratory tract and cause mucosal breaches. CMV co-infection of the lungs is common in patients with PCP and can be found frequently with other pathogens, suggesting a possible direct role of CMV in impairment of local as well as systemic immune responses. Thus, mucosal damage, accompanied by qualitative impairment of pulmonary macrophage and neutrophil function, leads to impaired clearance of inhaled microorganisms and establishment of active community-acquired pneumonitis.

The Changing Epidemiology of Community-Acquired Pneumonia in Patients with HIV Infection

Anecdotal case reports and reviews in the first decade of the HIV epidemic in North America em-

phasized the importance of opportunistic pulmonary infections in patients with AIDS. A workshop on Pulmonary Complications of HIV infection in 1983 sponsored by the National Heart, Lung and Blood Institute at the National Institutes of Health reviewed 441 patients with AIDS (Murray et al., 1984). Eighty-five percent of the infections identified were due to *P. carinii* This organism was followed in frequency by *Mycobacterium avium-intracellulare,* CMV, and *M. tuberculosis* as causes of pulmonary infection. *Legionella pneumophila* pneumonia and pneumonia caused by pyogenic bacteria, such as *S. pneumoniae,* represented only 4% and 2%, respectively, of all pneumonias. An update by the same group 3 years later reported an increased incidence of bacterial pneumonia as well as *M. tuberculosis* infection and a decreased incidence of *P. carinii* infections (Murray et al., 1987). Lymphoid interstitial pneumonitis, primarily a disease of childhood AIDS, was reported more frequently in adults, in addition to increased numbers of cases of nonspecific interstitial pneumonitis.

Eighteen episodes of community-acquired bacterial pneumonia among patients with AIDS were seen at the Memorial-Sloan Kettering Cancer Institute from 1979 to mid-1985 (Polsky et al., 1986). Community-acquired bacterial pneumonia represented 10.2% of all cases of pneumonia seen at this institute in patients with AIDS. Half of the infections were attributed to *S. pneumoniae* of which two cases were bacteremic. *H. influenzae* type b was the most common nonpneumococcal bacterial isolate, and one episode of *H. influenzae* bacteremia was noted.

The x-ray findings in these infections were often atypical. Two thirds of the *H. influenzae* infections presented as acute diffuse pulmonary infiltrates. Only one third of patients had lobar consolidation on chest x-ray and these all were due to *S. pneumoniae* infection.

The attack rate for pneumococcal pneumonia in this study was 17.9/1000, almost a 6-fold increase over expected rates in this age group in the general population. The authors also noted that recurrent pneumonia developed in 25% of patients. All patients had hypergammaglobulinemia. It was theorized that abnormal B-cell function was the cause of the increased incidence of pneumonia and the subsequent recurrences in this patient group.

In a study by Hirschtick et al. (1995), HIV-infected patients were followed at six centers from November 1988 to February 1990. Patients with previous AIDS-defining clinical diagnoses were excluded. Control groups were homosexual men or injection drug users who were seronegative for HIV infection. A standard definition for bacterial pneumonia combining radiologic findings, clinical diagnosis, and sputum blood or bronchial alveolar lavage cultures was used. Approximately 20% of the case group met a 1993 definition of AIDS by virtue of CD4 counts $<200/mm^3$. HIV-positive patients included bisexual men, intravenous drug users, and female sexual partners of HIV-positive men. A total of 237 cases of bacterial pneumonia developed in the follow-up period in 181 HIV-positive patients. Interestingly, the incidence of bacterial pneumonia (5.5/100 person-years) exceeded the incidence of PCP (5.1/100 person-years), and bacterial pneumonia was more common among HIV-positive than among HIV-negative individuals in the study population. The incidence of pneumonia was inversely proportional to the CD4 counts as expected, but pneumonia occurred in all risk groups. Bacterial pneumonia was more common among injection drug users than among homosexual or bisexual men, suggesting that pulmonary host defense mechanisms might be affected by injection drug use with a subsequent increased risk of bacterial pneumonia, regardless of HIV status. Bacterial pneumonia was also more common among blacks than among other races, but this finding may have been confounded by injection drug use as a risk factor. Finally, smoking appeared to be a significant risk factor for the development of pneumonia in HIV-positive patients although alcohol consumption was not.

Specific etiological diagnoses were established for bacterial pneumonia in 38% of the patients. *S. pneumoniae, S. aureus,* and *H. influenzae* were the most common infecting pathogens. One third of the pneumococcal infections were associated with positive blood cultures; the blood culture positivity rate was less frequent for other organisms. Surprisingly, the community-acquired infections also included *Pseudomonas aeruginosa, Escherichia coli* and *Serratia marcescens,* organisms usually associated with hospital-acquired pneumonia. Community-acquired *P. aeruginosa* pneumonia appears to be more frequent in HIV-positive patients than among other individuals in the community. In addition, cases of *Legionella pneumophila,*

Nocardia, and *Pasteurella multocida* pneumonia were identified. Prophylatic use of trimethoprim-sulfamethoxazole in patients with CD4 count <20/mm^3 appeared to reduce the risk of bacterial pneumonia (odds ratio [OR], 0.33, confidence interval [CI], 0.14–0.73). No assessment of the role of pneumococcal immunization was carried out.

With the availability of protease inhibitors for the treatment of HIV infection in combination with other antiretroviral drugs (HAART), the incidence of bacterial pneumonia among AIDS patients appears to have decreased. In a study of 1898 patients with CD4-defined AIDS followed between January 1993 and June 1998, incidence of bacterial pneumonia decreased from 19.3/100 patient-years to 12.2/100 patient-years. Patients with CD4 cell counts <50/mm^3 had a higher risk of developing bacterial pneumonia, as did injection drug users. However, protease inhibitor-containing treatments were associated with a decreased rate of bacterial pneumonia, although interestingly the use of trimethoprim-sulfamethoxazole or azithromycin for prevention of PCP and *Mycobaterium avium-intracellulare* infection was not associated with a decreased risk of bacterial pneumonia (Sullivan et al., 1999). A similar reduction from 12.5 cases of bacterial pneumonia in 1994 to 7.1 cases per 100 patient-years in 1998 has been reported in a cohort of 2224 HIV-positive patients in France (Baril et al., 1998). *S. pneumoniae* remained the most common isolate in HIV-positive patients with community-acquired pneumonia.

Pneumococcal Pneumonia in HIV-Positive Patients

The subset of patients with bacterial pneumonia in HIV infection caused by *S. pneumoniae* has been most extensively studied. A 10-year review at Denver General Hospital of patients with pneumococcal bacteremia identified 254 patients, of whom 18.9% were HIV-positive (Hibbs et al., 1997). Three quarters of these patients had AIDS by CD4 criteria. The overall mortality from pneumococcal bacteremia was 6.2%, and was highest in patients with HIV infection (9%). Analysis of serogroups of *S. pneumoniae* causing infection demonstrated that 96% of patients dying of pneumococcal bacteremia had serogroups represented in the 23-valent vaccine. The increased incidence of pneumococcal bacteremia noted in patients between the ages of 15 and 59 years suggested to the authors that HIV testing should be carried out in all patients in this age group who are diagnosed with community-acquired pneumococcal bacteremia or bacteremic pneumococcal pneumonia.

An analysis of penicillin susceptibility of isolates of *S. pneumoniae* from this 10-year experience showed increasing intermediate-level and some high-level resistance to penicillin in later years. These anecdotal observations have since been confirmed in a larger study from South Africa by Crewe-Brown et al. (1997). In a cohort of adults and children with pneumococcal pneumonia penicillin resistance was more common among HIV-positive than among HIV-negative patients and more common in HIV-positive children than adults.

Because injection drug use appears to be a specific risk factor for bacterial pneumonia and HIV infection, this group of patients has also been analyzed separately (Boschini et al., 1996). In a 3-year study of 4000 former injection drug users in Italy, of whom 25% were HIV-positive, the rate of pneumonia was 90.5/1000 person-years in HIV-positive patients and only 14.2/1000 person-years in the HIV-negative group. Once again, a decreased CD4 cell count was associated with an increased risk for developing pneumonia. Age, sex, and immunoglobulin levels were not correlated with pneumonia, but male sex and HIV-positive status was associated with recurrence of pneumonia. There was a 13-fold increase in recurrent pneumonia in the HIV-positive group in comparison to HIV-negative former injection drug users. In patients in whom an etiology was established (54% of the total) *Chlamydia pneumoniae* was almost as common as *S. pneumoniae* but the investigators noted two outbreaks of this infection during the study period. *H. influenzae* was the third most common cause of pneumonia. *Coxiella burnetii* was found in three patients, although Q fever has not been seen more frequently in HIV-positive patients in other studies. Once again, one third of the patients with pneumococcal pneumonia had bacteremia, a rate much greater than that expected in an HIV-negative community-based cohort.

Recurrent pneumococcal disease appears to be a significant marker for HIV infection. In a study of

153 episodes of invasive pneumococcal disease between 1992 and 1993 at Yale-New Haven Hospital 6 of 38 episodes were recurrences involving four adults and two children (Frankel et al., 1996). Only one of 114 patients without HIV infection had recurrent disease. Almost two thirds of the recurrent episodes were with the same serotype that caused the initial invasive infection. Six of the 150 isolates had high-level penicillin resistance (>2 μg/mL), but no differences in serotype distribution was found between HIV-positive and HIV-negative patients although serotype 9B was more common in HIV-positive patients. Overall, 92% of the bacteremic episodes were secondary to pneumococcal pneumonia, a higher proportion than seen in HIV-negative patients.

A review of pneumococcal disease in the developing world gave similar findings (Gilks et al., 1996). In this group of prostitutes in Nairobi, 99 episodes of invasive pneumococcal disease were identified in a cohort of 587 HIV-positive women, an incidence of 42.5/1000 person-years. Only one episode was demonstrated in 132 HIV-negative women (Relative risk [RR], 17.8; 95% CI, 2.5–126.5). More importantly, recurrent invasive pneumococcal disease was found at a rate of 264/1000 person-years, and was seen in >20% of the cohort. Serotyping results in this study suggested that reinfection rather than relapse was most common. Fifty-six percent of the cases of pneumococcal bacteremia were attributable to pneumococcal pneumonia , a percentage that is lower than in other studies. The study also demonstrated that neutrophil counts in response to infection were blunted and that CD4 cell counts were inversely associated with disease. Recurrent disease was more common at lower CD4 cell counts. In contrast to other studies of pneumococcal disease in HIV-infected patients, none of the 80 episodes in this study were associated with death.

The role of pneumococcal immunization in prevention of serious pneumococcal disease in HIV-positive patients is still undetermined although immunization is recommended (CDC, 1989; Rose et al., 1993). However, bacteremic pneumococcal pneumonia does occur in patients who have been appropriately immunized (Afessa et al., 1997), emphasizing the difficulty of mounting an immune response to vaccines in advanced HIV infection, particularly to polysaccharide vaccines. Prior to the use of HAART, one study suggested that antiretroviral therapy favorably affected the immune response to immunization and that immunization might appropriately be delayed until immune reconstitution was achieved with HAART (Glaser et al., 1991).

Other Bacterial Pneumonias Associated with HIV Infection

Haemophilus influenzae

Invasive *H. influenzae* infection appears to be the second most common cause of bacterial pneumonia in HIV-infected patients, accounting for 20% to 50% of bacterial pneumonias. However, some studies have noted rates less than 2.5%. Later reviews have reported a lower incidence, perhaps related to the use of trimethoprim-sulfamethoxazole for PCP prophylaxis. *H. influenzae* pneumonia appears to occur at a lower CD4 cell count than do *S. pneumoniae, C. pneumoniae,* or *M. pneumoniae.*

Schlamm and Yancovitz (1989) reviewed all cases of adult *H. influenzae* pneumonia during a 32-month experience early in the HIV epidemic in New York City (February 19884–November 1986). Fifty-one cases were identified, 34 of which were in patients with HIV risk factors, although serologic testing was not available at that time. Twelve percent of the patients had bacteremia and all had fever and productive cough. Almost half the patients had bilateral infiltrates on chest x-ray, and 25% had diffuse interstitial disease, as opposed to segmental or lobar pneumonia. Coexisting PCP was found in four patients. All bacteremic isolates were nontypable. A similar review of *H. influenzae* type b bacteremias from January 1983 to June 1991, also from New York (Casadevall et al., 1992), documented 15 cases of bacteremia, 10 of which were in patients with HIV risk factors or AIDS. Nine of 10 cases were inactive or former injection drug users, and all bacteremias were secondary to respiratory tract disease. In this case review, chest radiographs showed mostly focal infiltrates rather than diffuse disease. In another review of homosexual patients with bacteremia, no cases due to *H. influenzae* were seen, suggesting that injection drug use may be a specific

risk factor for this form of bacterial pneumonia (Krumholtz et al., 1989).

In another large series from Spain of 116 patients with *Haemophilus* bacteremia, HIV infection was the most common underlying predisposing factor (29%) (Munoz et al., 1997), with a prevalence of 5/1000 admissions compared with 0.2/1000 admissions in HIV-negative patients. Pneumonia was a more common predisposing factor for bacteremia in the HIV-positive group, and the incidence of infection increased through the study period from 1986 to 1994. Pulmonary disease was usually unilobar in nature and the clinical presentation was similar to that of patients with other risk factors such as malignancy or chronic obstructive pulmonary disease. The mortality rate for invasive *H. influenzae* infection was 22%. Trimethoprim-sulfamethoxazole resistance was high in both groups, and the rate of 71% in HIV-positive patients suggests that PCP prophylaxis, while protective against *S. pneumoniae,* may not be as effective against invasive *H. influenzae* disease. This resistance pattern, however, may be a reflection of the Spanish experience alone, since rates of resistance are much lower in the rest of Europe.

Because of the high rate of neutralizing antibody to *H. influenzae* type b in naturally immunized adults in the general population, immunization with the *H. influenzae* type b vaccine in HIV-positive patients has not been widely applied. However, a protective level of antibody has been found in only 40% of nonimmunized HIV-positive patients (Steinhoff et al., 1991), and immunization of this group, particularly at higher levels of CD4 lymphocyte counts, might prevent invasive pulmonary disease due to *H. influenzae* type b if not other serotypes or nontypable *H. influenzae.*

Pseudomonas aeruginosa

Retrospective reviews of bacterial pneumonia in HIV infection provide anecdotal evidence of an increased risk of both nosocomial and community-acquired pneumonia caused by *P. aeruginosa.* In a review of bacterial pneumonia early in the HIV epidemic, Wit et al. (1987) identified four nosocomial cases of *Pseudomonas* pneumonia among 18 pneumonia patients with AIDS or AIDS-related complex. Subsequent, larger series have reviewed a variety of *P. aeruginosa* infections in HIV-positive patients, many of which have represented pneumonia and often, bacteremic pneumonia (Shepp et al., 1994). Kielhofner et al. (1992) reviewed seven cases of serious *P. aeruginosa* infection in HIV-positive patients; three of the seven patients suffered from pneumonia. Lozano et al. (1992) identified 15 cases in patients with HIV infection, the majority with intravenous drug use as a risk factor. Thirty-three percent of the patients had bacteremic pneumonia. In another cohort of 1800 HIV-positive adults studied between 1988 and 1992, 16 developed *Pseudomonas* bronchopulmonary infection (Baron & Hollander, 1993). All patients had CD4 cell counts $<60/mm^3$ at the time of presentation. A particular syndrome noted in 75% of the patients was an indolent bronchopulmonary infection characterized by cough and fever rather than acute pneumonitis, reminiscent of exacerbations of cystic fibrosis. Almost all infections were community-acquired and the mortality was low. However, 12 of 16 patients had a relapse of their *Pseudomonas* pulmonary infection following initial recovery. Similar results were obtained in a series from New York City during a similar period, when Mendelson et al. (1994) described 27 cases of *P. aeruginosa* bacteremia, 50% of which originated in the respiratory tract. In contrast to the findings of Baron and Hollander (1993), the mortality rate in this series was 40%, but this may reflect the fact that bacteremia was used as a criterion for inclusion in the review. This review also found that treatment with combinations of antibiotics active against the organism led to more successful outcomes than did treatment with a single antimicrobial agent.

Fichtenbaum et al. (1994) studied risk factors for *P. aeruginosa* infection in patients with HIV, using a community control group with HIV infection but no documented *Pseudomonas* infection. Both inpatients and outpatients were studied. The annual incidence of *Pseudomonas* infection increased during the period of study from 3.5% in 1990 to 8.7% in 1992. Most infections were community-acquired and involved the respiratory tract (73%). HIV-positive patients with *Pseudomonas* infection were more likely to have AIDS as a diagnosis and a previous AIDS-defining opportunistic illness. The overall mortality rate was 36% and relapses were common. No significant differences were found be-

tween *P. aeruginosa*-infected patients and the control group for sex, race, or HIV risk factors. Prior hospitalizations were more common in both community- and hospital-acquired infections, suggesting that the microorganism may have been acquired in the hospital although the presentation of illness was in the community.

In a similar review, Dropulic et al. (1995) reviewed 58 patients with *P. aeruginosa* infections. Pneumonia represented the majority of both bacteremic and nonbacteremic infections. Twenty-five percent of cases presented as cavitary pneumonia, with an average time from symptoms to diagnosis of 32 days. However, patients with cavitary disease had a higher survival than patients with noncavitary pneumonia. Five patients who had postmortem examinations were found to have necrotizing pneumonia. Risk factors for *P. aeruginosa* infection included a decreased neutrophil count, presence of a central venous catheter, presence of a urinary catheter, steroid therapy, and recent prior antibiotic use. A multivariant analysis established central venous and urinary catheters and steroid therapy as significant risk factors. Risk factors for pneumonia were not studied separately.

In summary, relapsing pulmonary infection due to *P. aeruginosa* that follows an indolent course and is associated with cavitary change on chest x-ray is a new clinical syndrome in advanced HIV infection.

Legionella pneumophila

Series of patients with respiratory disease complicating HIV infection have demonstrated an incidence of *L. pneumophila* infection of up to 5% (Hirschtick et al., 1995; Murray et al., 1984). However, studies of *Legionella* infection in these patients are complicated by differing diagnostic criteria. A review of 180 HIV-infected patients who had bronchoalveolar lavage fluid or autopsy material for analysis demonstrated *Legionella* by direct fluorescent antibody testing in six patients (Bangsborg et al., 1990). Four were presumptive *L. pneumophila* infection and two were *L. micdadei.* Coinfection with *P. carinii* was seen in two patients and the course of pneumonia was not consistent with typical *Legionella* pneumonia. An autopsy series from Brazil of 100 patients dying of AIDS identified *L. pneumophila* as the cause of death in only one patient (Rodrigues et al., 1996). *L. pneumophila* serogroup 1 is most commonly reported although there are isolated cases of other *Legionella* infections caused by *Legionella bozemanii* (Harris et al., 1998), *Legionella feeleii* (Lo Presti et al., 1998), and other serogroups of *L. pneumophila* (Martin et al., 1995).

Despite infrequent reports of *Legionella* in AIDS, a review of all cases of Legionnaires' disease reported to the Centers for Disease Control between 1980 and 1989 identified the usual risk factors for *L. pneumophila* infection, such as a smoking history, but also noted a remarkably increased risk associated with AIDS (RR, 41.9; 95% CI, 12.9-71.0) (Marston et al., 1994). In Paris, Nauciel et al. (1996) found seven culture-proven *L. pneumophila* infections in patients with HIV infection in a series of 81 cases.

The clinical course of *L. pneumophila* or Legionnaires' disease in HIV-infected patients has been reviewed by Blatt et al. (1994) in a series of seven patients, one with recurrent infection. Five of seven cases were acquired in the hospital, and all patients had advanced HIV infection. The presentation was typical of pneumonia, with fever, cough, and dyspnea. *P. carinii* existed as a co-pathogen in four patients and *Rhodococcus equi* in two, and only one patient had a diagnosis established by a positive culture. Cavitary *L. pneumophila* was reported but both cases were in patients with coexisting *R. equi* infections and negative *Legionella* cultures. At the time of publication all patients had died but no deaths were caused by *Legionella.* Recurrent *L. pneumophila* infection has been identified in two cases in HIV-positive patients (Blatt et al., 1994; Morley et al., 1994).

Rhodococcus equi

Retrospective and prospective reviews of bacterial pneumonia in HIV-positive patients do not list *R. equi* as a cause of pneumonia in this risk group. However, Sarnies et al. (1986) reported the first case of lung abscess due to *Corynebacterium equi* in a patient with AIDS. Since that time anecdotal case reports (Kunke, 1987) and reviews (Emmons et al., 1991; Gallant & Ko, 1996; Arlotti et al., 1996) have emphasized the importance of this pathogen as a

cause of cavitary pneumonia in HIV-positive patients. The onset of pneumonia due to *R. equi* is usually indolent, with symptoms developing over several weeks. Exposure to farm animals, particularly horses, as well as person-to-person transmission have been suggested as methods of transmission (Arlotti et al., 1996). Cases of *R. equi* infection almost always occur at CD4 counts $<200/mm^3$ in HIV patients; pleural effusion occurs in approximately 20% of cases.

Approximately 50% of reported *R. equi* infections in humans have occurred in patients with HIV infection, although the infection is occasionally seen in immunocompetent hosts (Verville et al., 1994). In AIDS, the pulmonary disease is often accompanied by infection in the blood stream and in other organs. A comparison of *R. equi* infections in patients with and without HIV infection (Harvey & Sunstrum, 1991) demonstrated that HIV was a risk factor for both mortality and for the presence of positive sputum and blood cultures. In the few reported cases in immunocompetent hosts, infection appears limited to the lung in most instances.

The largest series of *R. equi* infections with HIV infection has been reported in Spain by Arriz-Abalaga et al. (1998). In this series, 96% of the cases had pulmonary infiltrates and two thirds had cavitary disease. Pleural effusion occurs in approximately 20% of cases but extrapulmonary involvement develops in less than 10%. The mean time from diagnosis to death, in this series, was 8 months with a mortality rate of 60% and a relapse rate, even on maintenance therapy, of 42%.

Treatment is difficult, although the organism is usually sensitive to antibiotics active against gram-positive organisms, with the exception of the β-lactams. Vancomycin or macrolides are often used in treatment, and surgical resection of cavitary lesions may improve resolution. The mortality rate can be as high as 50%, and relapses are common.

Community-Acquired Viral Pneumonia in HIV Infection

Viral pathogens are commonly isolated from the respiratory tract of HIV-infected patients. The human herpes virus group, primarily CMV and herpes simplex virus, are most frequently isolated and represent recodescent infections brought on by severe immunosuppression. HIV-positive patients, however, can also acquire de novo infections from typical respiratory pathogens such as influenza A, respiratory syncytial virus, and adenovirus. The clinical course of these infections may be more severe in HIV-positive patients, although prospective data are not available.

Connolly et al. (1994) examined bronchial alveolar lavage specimens from all immunocompromised patients at a university hospital over a 6-year period. They identified herpes simplex virus, influenza, parainfluenza, rhinoviruses, adenovirus, enteroviruses, and respiratory syncytial virus in decreasing order of frequency in this group. Most infections were self-limited. No increased morbidity or mortality was noted in patients with HIV infection. In a review by Khoo et al. (1998), 63 HIV-positive patients had 1125 patient-months of follow-up; urine, feces, and throat swabs were examined for atypical pathogens, including *Chlamydia* spp. and *M. pneumoniae,* as well as for respiratory viruses. In patients who had an influenza-like illness, 50% had a viral pathogen isolated. Paradoxically, influenza-like symptoms were common in patients with CD4 counts $>300/mm^3$, suggesting that the immunologic response to the viral infection may be more closely associated with symptoms than the infection itself. In contrast, Miller et al. (1996) followed 44 patients with 47 bronchoscopic examinations during a 6-month period over a winter season. They found no evidence of influenza A or B, respiratory syncytial virus, parainfluenza, adenovirus, or enterovirus in these patients who had symptoms and signs of lower respiratory tract infection. This was despite an increase in respiratory syncytial virus and influenza B infection in the general population at the same time.

Cytomegalovirus Pneumonia

Earliest reports of pulmonary diseases associated with AIDS highlight the role of CMV pneumonia in these patients (Murray et al., 1984). However, the specific pathologic role of CMV is uncertain, since co-infection with other opportunistic pathogens such as *P. carinii* and *M. avium-intracellulare* is common. Only two viral infections, CMV pneumonia and herpes simplex virus pneumonia, are commonly reported in larger series of pulmonary complications (Murray et al., 1987; Wallace et al.,

1993). CMV pneumonia appears much less common in prospective cohorts of patients with HIV infection, occurring in only 0.3% of 1000 such patients studied by Wallace et al. (1993). Perhaps because of its frequency as a co-pathogen with other organisms, there does not appear to be any specific clinical syndrome associated with CMV pneumonitis. Patients may respond to treatments for these other pathogens with a complete clinical resolution despite the isolation of CMV from bronchoalveolar fluid (Jacobsen & Mills, 1988). Small case series of patients with CMV pneumonia alone suggest that clinical symptoms including fever, cough, and hypoxia are associated with an increased viral load (Rodriguez-Barradas et al., 1996) and evidence of widespread CMV infection in other organs including the retina and gastrointestinal tract. Specific treatment for CMV with ganciclovir may be helpful in this setting when co-pathogens are demonstrated not to be present. Retrospective reviews, however, have suggested that the presence of CMV does not predict overall mortality in patients who present with atypical pneumonia and advanced HIV infection (Bozzette et al., 1992).

CMV may have a role to play in depressing local immune responses in the lung. CMV is commonly isolated by culture from bronchial alveolar lavage but this may not have the same sensitivity for pneumonia as biopsy-proven cytopathic change in the lung with intranuclear or intracytoplasmic inclusions. More sensitive techniques for the identification of CMV in the lungs such as polymerase chain reaction may unfortunately be associated with a decreased specificity for CMV pneumonia

Herpes Simplex Virus

Herpes simplex virus is a common opportunistic pathogen in HIV infection. It has been a difficult entity to treat since the beginning of the AIDS epidemic (Siegal et al., 1981). Involvement of the respiratory tree is less common and, as is the case for CMV infection, the diagnosis of herpes simplex virus pneumonitis may be difficult due to the common isolation of this organism from oral and pulmonary secretions. Herpes simplex virus is the most commonly isolated pathogen in prospective studies of bronchoalveolar lavage fluid (Kielhofner et al., 1992; Connolly et al., 1994). Diffuse interstitial pneumonitis has been described, but acute necrotizing tracheobronchitis may be a more common syndrome as is seen in other patients in intensive care units (Baras et al., 1994). The incidence of herpes simplex virus pneumonitis in case series appears to be less than one third the incidence of CMV infection (Wallace et al., 1993).

The management of herpes simplex virus infection in the upper and lower respiratory tree is straightforward, and for severely ill patients intravenous acyclovir remains the drug of choice for severe ulcerative disease. Resistance to acyclovir by thymidine kinase-deficient herpes simplex virus has been described in patients with chronic mucocutaneous disease but not in respiratory tract infection.

Other Viral Infections

Common community-acquired viral infections such as influenza A and B, adenovirus, and respiratory syncytial virus infection have all been reported in patients with HIV infection. However, there is little evidence that any of these agents causes a more severe clinical syndrome in patients with AIDS than in those with intact immune systems.

Adenovirus may be an exception to this rule. Primary adenovirus pneumonia with a fatal outcome has been described in AIDS patients. Vinti et al. (1993) reported a fatal case of adenovirus type 3 pneumonia in a patient who developed severe atypical pneumonia with a rapid course to death in the setting of posttransfusion HIV infection. More importantly, Gathe et al. (1996) described 15 patients in 1 year who underwent bronchoscopy for pneumonia. Twelve patients had only adenovirus isolated by culture, and progressive pneumonitis occurred in 15 patients, eight of whom died after a course ranging from 5 to 41 days. A variety of adenovirus serotypes were noted. A number of therapeutic interventions in this patient group were unsuccessful, including the use of ganciclovir, foscarnet, and ribavirin.

Respiratory syncytial virus infection is more common in children than in adults. In children, RSV is more likely to cause pneumonia in HIV-infected children than in those who are uninfected. RSV has also been described as a cause of severe pneumonia in adult patients with HIV infection (van der Ven et al., 1996). The role of ribavirin in the treatment of severe RSV infection in children or

adults has not been determined for those co-infected with HIV who have severe immunosuppression.

Community-Acquired Fungal Infection in HIV-Infected Patients

The geographically defined systemic mycoses are important causes of morbidity and mortality in HIV-infected patients. When outbreaks of histoplasmosis, blastomycosis, and coccidioidomycosis have occurred, HIV-infected patients have been reported to have more severe disease and may in fact be "sentinels" for the presence of a fungal epidemic in the community. While infection with these pathogens often presents with a nonspecific febrile syndrome and associated multi-organ involvement, the respiratory route of transmission may lead to primary and relapsing pneumonitis in patients with AIDS.

Two opportunistic fungal pathogens, *Aspergillus* and *Penicillium marneffei* have specific epidemiologic and clinical presentations in patients with HIV infection but these are discussed elsewhere in this book.

Histoplasmosis

In the pre-AIDS era most cases of histoplasmosis were identified as either primary pulmonary infection with an acute but ultimately benign course or relapsing cavitary disease mimicking tuberculosis. Disseminated histoplasmosis was relatively rare. In the AIDS era, progressive disseminated histoplasmosis has become the most important clinical syndrome.

HIV-positive individuals traveling to areas of the world where *H. capsulatum* is endemic may develop primary *Histoplasma* pneumonia but most cases of histoplasmosis represent relapsing infection from remote exposure associated with the severe immunosuppresion of AIDS. In parts of North America histoplasmosis may be more common than PCP as a presenting illness in patients with HIV infection.

Although disseminated infection is most common, pulmonary involvement occurs in 50% of patients (Wheat et al., 1990). Chest radiographs demonstrate a large variety of patterns and can include hilar adenopathy and pleural effusions. (Conces et al., 1993) The radiologic findings, however, are nonspecific and could represent other opportunistic infections. Development of hypoxia during the course of histoplasmosis suggests severe disease and the need for urgent treatment. Urinary antigen detection or the presence of antigen in bronchoalveolar lavage fluid can be important diagnostic tools, and both have a high specificity and sensitivity (Wheat et al., 1992). Since most nonprimary pulmonary infections are part of a disseminated infection syndrome, biopsies of other tissues such as bone marrow, skin, ulcers, or nodules, or lymph nodes may yield a diagnosis. Serologic tests are less helpful in reflecting abnormal B-cell function in patients with AIDS. Amphotericin B and itraconazole appear to be effective therapies for acute and maintenance treatment of histoplasmosis, and itraconazole may be preferred because of its lower toxicity.

Blastomycosis

The environmental range of *Blastomyces dermatitidis* almost completely overlaps that of *H. capsulatum* although it is a much rarer entity. Although cases of blastomycosis have been reported in patients with AIDS (Chiu et al., 1988), it is far less common than histoplasmosis. When the disease does occur in patients with AIDS, pulmonary disease predominates with symptoms of fever, cough, and dyspnea (Pappas et al., 1992). Chest radiographs are similar to those in patients with histoplasmosis although more focal pulmonary infiltrates have been described in some patients. The diagnosis depends on the isolation of the organism from sputum, as no antigen test is available. Therapy with amphotericin B followed by itraconazole for lifelong maintenance has been suggested. The mortality rate, less than 10% in normal hosts, is >50% in patients with HIV disease (Witzig et al., 1994).

Coccidioidomycosis

Coccidioides immitis has a discrete ecological niche in the desert of southwestern North America. A cohort of 170 patients with HIV infection followed in Arizona was reported by Ampel et al.

(1993). One quarter of these patients developed coccidioidomycosis within 3.5 years of diagnosis of HIV infection, and these cases were thought to represent new infections acquired by the respiratory route as opposed to endogenous reactivation. The severity of disease appears to correlate with the degree of immunosuppression associated with HIV infection; individuals with high CD4 counts have relatively mild respiratory infection. Patients with advanced HIV infection, however, develop progressive respiratory disease with typical macronodular infiltrates on chest x-ray and hilar and mediastinal adenopathy. This may be accompanied by skin involvement (pustules or nodules) and one third of patients also have meningeal involvement. Serologic diagnosis by immunodiffusion assay may be helpful, but the diagnosis is established by isolation of the organism from respiratory secretions or direct staining of bronchoalveolar lavage fluid. Treatment may have to be empiric in severely ill patients, based on the clinical and radiologic picture and an appropriate history of travel or residence in the southwestern United States or Mexico. Amphotericin B or fluconazole are the drugs of choice but responses to treatment are low in comparison to histoplasmosis and blastomycosis. Fluconazole may be helpful even in patients who fail amphotericin B therapy (Gaghani et al., 1993).

Cryptococcal Pneumonia

Cryptococcal meningitis was a commonly reported early opportunistic infection in patients with AIDS (Kovacs et al., 1985). Central nervous system disease was found in 90% of reported cases of Cryptococcal disease in patients with AIDS in early reviews (Zuger et al., 1986) However, Wasser and Tolavera (1987) reported five cases of pulmonary cryptococcosis in patients with AIDS; three cases had associated tuberculosis, and disseminated infection was common. Respiratory failure developed rapidly in two of the patients. The clinical syndrome associated with pulmonary disease was nonspecific and included fever, cough, and dyspnea. One patient had a pulmonary cryptococcoma at autopsy but infection has been more extensive in most postmortem examinations of patients dying with Cryptococcal disease and AIDS.

Clark et al. (1990) provided a subsequent review of 18 patients with Cryptococcal pulmonary infection. Two thirds of their patients had evidence of central nervous system involvement with their pulmonary disease. The most common chest x-ray finding was bilateral diffuse interstitial disease, but nodules and cavitary lesions were found in a few patients. Solitary pulmonary nodule is a common manifestation of pulmonary cryptococcosis in patients who are noncompromised hosts, but this radiologic finding is rare in patients with cryptococcal pulmonary disease in AIDS. In this study, which was carried out between 1985 and 1989, the mortality was 50% and relapsing infection appeared to be responsible for the increased mortality.

Pulmonary disease may be diagnosed *pari passu* when central nervous system disease is the predominant feature and the cerebrospinal fluid is positive for cryptococcal antigen. The presence of the organism in cerebrospinal fluid or blood may be the link to diagnosis of cryptococcal pneumonia. The organism can be isolated from sputum or bronchial washings as well, and coinfection with *P. carinii* has been described (Chechani & Kamholz, 1990).

As with other fungal infections that affect both normal and immunocompromised hosts, maintenance therapy after primary treatment of the acute infection appears to be mandatory in cryptococcal pneumonitis in AIDS.

Approach to Pneumonia in HIV-Infected Patients

Diagnostic Work-up

Pulmonary infection in HIV-positive patients remains a common problem despite advances in antiretroviral therapy and improvement in prevention of opportunistic infections. A careful history and physical examination is still a cornerstone of the diagnostic approach to respiratory disease. This should be followed by a good anterior–posterior chest x-ray. Patients with high fever, purulent sputum, and segmental or lobar infiltrates are likely to have pneumococcal pneumonia even if pneumococcal immunization has been provided in the past. On the other hand, patients with a near normal chest x-ray and significant hypoxia, particularly with an

indolent onset of symptoms, would be more likely to have PCP. This would be particularly true if there was a history of inadequate prophylaxis with trimethoprim-sulfamethoxazole or dapsone. Specific radiologic patterns of interest that may contribute to the differential diagnosis of respiratory disease include cavitary changes seen with *M. tuberculosis* and *R. equi* infections. Cystic lesions, especially when accompanied by pneumothorax, are commonly seen in PCP infection especially when aerosolized pentamidine has been used as a previous prophylactic intervention.

Blood cultures are important to obtain in patients with pulmonary infiltrates and HIV infection. Because of the high rates of bacteremia in patients with pneumococcal pneumonia all patients should have bacterial blood cultures. Special media to support the growth of fungal pathogens may be helpful if the clinical picture suggests cryptococcal disease or one of the endemic mycoses. Mycobacterial blood cultures may grow *M. tuberculosis* or *M. avium-intracellulare* in patients with profound immunodeficiency. Bacterial blood cultures may also yield *H. influenzae, P. aeruginosa,* or *L. pneumophila* in patients with respiratory illness attributable to these pathogens. Patients with rapidly progressive lobar pneumonia should have urinary antigen determinations for *Legionella* antigen.

In patients with a productive cough, sputum Gram´s stain and culture may contribute to the diagnosis, but the sensitivity and specificity of sputum examination in patients with AIDS has not been adequately evaluated except in the setting of induced sputum for PCP (Polsky et al., 1986). In an early study of bacterial pneumonia in patients with AIDS, the etiologic organism was found by culture Gram's stain in 11 of 16 patients. Hirschtick et al. (1995) identified *S. pneumoniae* pneumonia in 21 of 36 patients from sputum examination. One third of these patients had blood cultures that were positive as well.

Chave et al. (1989) used a combination of symptom duration, fever, and chest x-ray pattern to differentiate between nonopportunistic and opportunistic pneumonias in patients with AIDS. All patients with typical pneumonia had onset of symptoms of less than 7 days' duration, had a fever greater than 39.5°C, and were more likely to have focal pulmonary infiltrates. Patients with opportunistic infection had less fever of longer duration and had diffuse pulmonary infiltrates on chest x-ray.

Bronchoalveolar lavage has a high likelihood of identifying *P. carinii* infection (Golden et al., 1986) and can identify the pathogen in greater than 90% of the cases. The combination of bronchoalveolar lavage and transbronchial biopsy may also identify other pathogens with high specificity (Broaddus et al., 1985).

Percutaneous needle lung aspiration may also be used to diagnose *P. carinii* or other pathogens in patients with HIV infection, but pneumothorax is a common complication (44%) and a procedure is not commonly used (Wallace et al., 1985). A more aggressive approach using open lung biopsy has also been retrospectively reviewed (Fitzgerald et al., 1987). It is usually used when patients show rapid respiratory deterioration and bronchoscopy has not revealed the diagnosis. Unfortunately the likelihood of identifying a treatable pathogen in this setting is less than 10%. It may be most useful when lymphoproliferative disorder is a diagnostic consideration in a patient with advanced AIDS. Bronchoscopy with bronchoalveolar lavage is usually superior to transbronchial biopsy for PCP (Griffiths et al., 1989).

In summary, in cases where the combination of chest x-ray, induced sputum, and blood cultures do not establish a specific diagnosis and there has been no response to empiric therapy for likely pathogens, bronchoscopy with bronchoalveolar lavage should be carried out. It should be cautioned that this technique may indicate more than one microorganism because of its high sensitivity, and the identification of the causative pathogen may be a problem when interpreting the results. This is particularly true for isolation of herpes simplex virus or CMV from bronchoalveolar washings.

Empiric Treatment of HIV-Associated Pneumonia

Treatment decisions in HIV-related respiratory illness can be made immediately or deferred. In patients with rapidly progressive pulmonary symptoms empiric treatment should be instituted in concert with a diagnostic evaluation. For patients who have had adequate primary or secondary prophy-

laxis for PCP, rapidly progressive pulmonary infiltrates are more likely to represent bacterial pneumonia. Because of the development of penicillin resistance in *S. pneumoniae* infections, careful attention to the local susceptibility pattern of *S. pneumoniae* is important. Empiric therapy with a third-generation cephalosporin, which would also provide adequate treatment for *H. influenzae* infection, should be instituted. Where high levels of penicillin resistance exist, treatment with a respiratory fluoroquinolone may be preferable. No comparative data exist in this patient population to direct decisions. An extended-spectrum macrolide antibiotic such as clarithromycin or azithromycin may also be used empirically. Patients with features of bacterial pneumonia who do not respond to empiric therapy should undergo bronchoscopy for identification of opportunistic or more unusual bacterial pathogens such as *R. equi* or *Legionella.* Patients with rapidly progressive lobar pneumonia should have urine submitted for *Legionella* antigen.

Some physicians may elect to treat patients for presumed PCP using high-dose trimethoprim-sulfamethoxazole assuming that this agent would also be effective against *S. pneumoniae* or *H. influenzae* infection. However, resistance to this agent is common in both microorganisms and it may be safer to combine empiric therapy against bacterial pneumonia and PCP when this is a consideration. Because PCP usually follows a more indolent course, treatment can often be delayed until a specific diagnostic study has identified this pathogen.

Infection Control Issues in Pulmonary Infection in HIV-Positive Patients

The identification of multidrug-resistant M. *tuberculosis* infections in patients infected with HIV that are subsequently transmitted to healthcare workers has highlighted the importance of respiratory isolation in patients with unidentified pulmonary infiltrates. Hospitalized patients in areas where sensitive or resistant tuberculosis is endemic should be placed in respiratory isolation until the specific etiology of pneumonia is identified. This may be impractical in many jurisdictions, and careful attention to history and physical and initial laboratory data, including the chest x-ray, should temper the approach in geographic areas where tuberculosis is not highly prevalent. Patients who have typical features of reactivation tuberculosis on chest x-ray or who have acid-fast bacilli identified in initial sputum examinations should immediately be placed in respiratory isolation. Healthcare workers attending all patients with pneumonitis of unknown etiology should protect themselves with high-efficiency surgical masks. Personal respirators should be used in situations where multidrug-resistant tuberculosis is likely.

Specific guidelines for managing patients with unknown respiratory infections and HIV have been published and federal or local regulations may mandate aggressive infection control practices when managing these patients.

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Community-Acquired Pneumonia in the Immunocompromised Host

ROBERT H. RUBIN AND JAY A. FISHMAN

The past two decades have witnessed a remarkable change in the care and prognosis of individuals who are immunocompromised as a consequence of an underlying disease and/or its therapy. Prolonged patient survival has resulted from important advances in organ and bone marrow transplantation, in the therapy of a variety of autoimmune disturbances, in the management of an increasing number of malignancies, and in the treatment of AIDS. This has resulted in the return of these individuals to their families, the workplace, and the community at large. At the same time, care patterns have also changed. Whereas in the past, care of these individuals had been largely the province of academic subspecialists, increasingly these patients are being cared for by practitioners in the community. The most common problems encountered in these patients are the infectious disease problems that result from the interaction of the patient's state of immunocompromise and community-acquired pathogens. Of these infectious disease problems, the most common serious infection is pneumonia.

Pneumonia in the immunocompromised patient represents a particular challenge to the clinician for several reasons. On the one hand, a diverse array of microbial invaders must be considered, ranging from common viral and bacterial pathogens that can cause infection in anyone, to opportunistic fungi, bacteria, and even protozoans that rarely affect the normal host. On the other hand, noninfectious causes of pulmonary inflammation—radiation lung injury, drug reactions, thromboembolic disease, leukoagglutinin transfusion reactions, pulmonary hemorrhage, atypical pulmonary edema, alveolar proteinosis, and recurrent malignancy—may present a clinical picture similar to that produced by infection (Rubin & Greene, 1994; Williams et al., 1976; Rosenow et al., 1985; Murray & Mills, 1990; Ettinger & Trulock, 1991; Cisneros et al., 1998; Bartlett, 1998; Collin & Ramphal, 1998).

Clearly, a broad differential diagnosis must be considered. In addition, because many immunocompromised patients have an altered inflammatory response to the responsible agent, clinical and radiologic manifestations can be greatly attenuated until relatively late in the disease process. For example, in one series of cancer patients with pneumonia, only 8% of neutropenic patients produced purulent sputum, whereas 84% of patients without neutropenia had purulent sputum (Sickles et al., 1975). Since prognosis is related to the speed with which an etiologic diagnosis is made and specific therapy is instituted, even subtle clinical and radiologic findings in immunocompromised patients must be carefully assessed (Rubin & Greene, 1994). The purpose of this chapter is to provide a logical framework for the evaluation of the immunocompromised patient who presents from the community with fever and pulmonary infiltrates.

ROBERT H. RUBIN • Center for Experimental Pharmacology and Therapeutics, Harvard–Massachusetts Institute of Technology Division of Health Sciences and Technology, Massachusetts General Hospital, and Harvard Medical School, Boston. Massachusetts 02114. **JAY A. FISHMAN** • Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02114.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Risk of Pneumonia in the Immunocompromised Host

The risk of infection, in general, and pneumonia in particular in the immunosuppressed patient is largely determined by the interaction among three factors: the *epidemiologic exposures* the patient experiences, the patient's *net state of immunosuppression,* and the nature of the *preventative antimicrobial program* the patient has received (Rubin & Greene, 1994). Many epidemiologic exposures within the community affect the occurrence of pneumonia.

Respiratory virus infection, with person-to-person spread of such pathogens as influenza, parainfluenza, respiratory syncytial virus, adenovirus, and rhinoviruses, is the most important cause of pulmonary infection in immunocompromised patients who have returned to the community. The attack rate for both viral pneumonia and opportunistic superinfection due to bacteria and fungi is far higher among immunocompromised patients with respiratory virus infection than in the general population with similar infections (Rubin & Greene, 1994; Markovic et al., 1998; Whimbey et al., 1995; Ohori et al., 1995; Simsir et al., 1998; McGrath et al., 1998).

Causes of community-acquired pneumonia such as *Mycoplasma, Chlamydia,* and *Streptococcus pneumoniae* can have an increased impact on immunocompromised individuals (Khoo et al., 1998). Particularly in the case of *S. pneumoniae,* the presence of a significant rate of antibiotic resistance, especially to penicillin, can be of special importance in this patient population. As is the case for the respiratory viruses, these common causes of community-acquired pneumonia tend to cause disease of greater persistence and severity in the immunocompromised patient.

Mycobacterium tuberculosis and the endemic, geographically restricted systemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis) are important community-acquired infections in the immunosuppressed patent. All share several characteristics: a pulmonary portal of entry, with pneumonia as a frequent clinical presentation; systemic dissemination with a potential for metastatic seeding; and cell-mediated immunity as the key host defense. In immunocompromised patients with significant deficits in cell-mediated immunity (e.g., AIDS patients, transplant patients, patients receiving sustained corticosteroid therapy) three patterns of disease are observed: progressive primary infection, reactivation infection, and superinfection. Superinfection occurs in individuals whose previously acquired immunity has been attenuated by their immunosuppressed state, and who are, on reexposure, susceptible to new infection. In all three cases the emphasis is on pulmonary infection with systemic dissemination, the extent of which needs careful definition to guide therapy (Rubin & Greene, 1994; Holt et al., 1997; Wheat et al., 1983; Rubin, 1994).

Opportunistic infection with such pathogens as *Nocardia asteroides, Cryptococcus neoformans, Aspergillus* species, Mucoraceae, and *Pneumocystis carinii* will occur in individuals whose net state of immunosuppression is particularly high. In addition, intense environmental exposure to *Aspergillus* species, and, perhaps, to cryptococcal and nocardial organisms, can play a role in the occurrence of opportunistic pulmonary infection. Person-to-person spread of *Pneumocystis* between immunocompromised individuals can occur, but appears to be unusual (Helweg-Larsen et al., 1998).

Strongyloides stercoralis is the helminth infection of primary importance for the immunocompromised host. Because of its unique autoinfection cycle, this organism can persist asymptomatically in the gastrointestinal tracts of individuals for decades after exposure in an endemic area of the world. With the onset of immunosuppression, particularly that involving cell-mediated immunity, three types of clinical syndromes can develop: postobstructive pneumonia due to the natural migration of the larvae through the lungs; hemorrhagic pneumonia, often in association with hemorrhagic enterocolitis; and a disseminated strongyloidiasis syndrome in which the organism leaves the gut and invades multiple bodily tissues, often with complicating bacterial infection due to Enterobacteriaceae from the gut. Because of this potential for catastrophic illness, it is recommended that individuals with histories of residence in endemic areas be screened for the presence of antibody to *Strongyloides,* prior to immune suppression, with seropositive individuals being treated preemptively with thiobendazole or ivermectin (Rubin, 1994).

TABLE 1. Pulmonary Infections to Which Patients with Specific Host Defense Defects Are Predisposed[a]

Host defense defect	Pulmonary infections to which patient is predisposed
Oral and tracheobronchial ulceration and/or obstruction	Oral bacterial flora Enterobacteriaceae
Decrease in the number of fully functional granulocytes	Oral bacterial flora Enterobacteriaceae *Pseudomonas aeruginosa* *Aspergillus* species
Hypogammaglobulinemia	*Streptococcus pneumoniae* *Haemophilus influenzae* type b *Pneumocystis carinii*[b]
Depressed cell-mediated immunity	Typical and atypical mycobacteria Fungi Herpesviruses *Pneumocystis carinii* *Strongyloides stercoralis* *Toxoplasma gondii*[a]
Complement defects	*Streptococcus pneumoniae* *Haemophilus influenzae* type b

[a]Modified from Rubin & Greene, 1994.
[b]Uncommon cause.

Table 1 outlines the pulmonary infections associated with particular host defense defects. Although such a listing can be useful, most patients who are immunocompromised have multiple factors operating that affect their ability to fight infection–hence the concept of the "net state of immunosuppression," a complex function determined by the interaction of several factors. These include host defense deficits created by the underlying disease process; the dose, duration, and temporal sequence of immunosuppressive therapy; the presence or absence of damage to mucocutaneous surfaces or an indwelling foreign body that traverses these surfaces; the presence of neutropenia; metabolic abnormalities such as protein-calorie malnutrition, uremia, and, perhaps, hyperglycemia; and infection with one or more of the immunomodulating viruses—cytomegalovirus, Epstein-Barr virus, hepatitis B and C, and human immunodeficiency virus. Although the nature of the immunosuppressive therapy that the patient has received (and continues to receive) is the prime determinant of the net state of immunosuppression, the potential importance of the other factors is illustrated by the following observations. Among organ transplant patients treated at the Massachusetts General Hospital during the past 20 years, the incidence of life-threatening infection, including pulmonary infection, was ten times greater in those with a serum albumin less than 2.5 g/dL; 90% of opportunistic infections occurred in the setting of immunomodulating viral infection. The majority of the remaining 10% of cases led to the discovery of a previously unrecognized environmental hazard (Rubin, 1994).

Preventative antimicrobial therapy can be administered as prophylaxis or as preemptive therapy. Prophylaxis is defined as administering an antimicrobial agent before an event to an entire population without regard to individual risk for infection. For this to be justifiable, the infection to be prevented has to be common enough and/or important enough to justify the intervention, and the prophylactic therapy must be nontoxic. Perhaps the most effective prophylactic strategy in immunocompromised patients is the use of trimethoprim-sulfamethoxazole, which is quite effective in preventing pulmonary infection due to *P. carinii* and *N. asteroides* (Rubin & Tolkoff-Rubin, 1993).

Preemptive therapy is defined as the administration of an antimicrobial agent before the onset of clinical disease to a subgroup of patients defined as being at high risk for a particular infection on the basis of a laboratory test or a clinical epidemiologic characteristic. For example, it has been shown in both bone marrow and organ transplant recipients, as well as in those with hematologic malignancies, that once colonization of the respiratory tract with *Aspergillus fumigatus* occurs, there is a subsequent 50% to 75% risk of developing invasive pulmonary aspergillosis. Hence, systemic antifungal therapy is indicated to preempt this process (Rubin & Tolkoff-Rubin, 1993; Fishman & Rubin, 1998; Wald et al., 1997).

Clinical Clues to the Diagnosis of Pulmonary Infection in the Immunocompromised Host

The most useful clue to the correct diagnosis in patients who present with fever and pulmonary infiltrates may come from an assessment of the

mode of onset and rate of progression of the pulmonary process. Thus, an acute onset with less than 24 hours of symptoms severe enough to bring the patient to medical attention suggests conventional bacterial infection (and, of the noninfectious causes, pulmonary embolic disease, pulmonary edema, a leukoagglutinin reaction, or pulmonary hemorrhage). A subacute onset over a few days to a week suggests viral or *Mycoplasma* infection, *Pneumocystis,* or, in some instances, *Aspergillus* or *Nocardia.* A more chronic course over one or more weeks suggests fungal, nocardial, or tuberculous infection (as well as tumor or radiation- or drug-induced pneumonitis). When the mode of clinical presentation is combined with radiologic findings, the spectrum of etiologic possibilities becomes considerably smaller and the differential diagnosis more manageable for the clinician (Table 2) (Rubin & Greene, 1994).

Thus, focal or multifocal consolidation of acute onset is likely to be caused by bacterial infection; similar lesions with subacute-chronic histories are most likely secondary to fungal, tuberculous, or nocardial infections. Macronodules are usually a sign of fungal or nocardial disease, particularly if they are subacute in onset. Subacute disease with diffuse abnormalities, either peribronchovascular types or miliary micronodules, are usually caused by viruses or *Pneumocystis* (although in the highly immunosuppressed, disseminated tuberculosis and systemic fungal infection are also considerations). Noninfectious causes are added to the differential diagnosis when the history is appropriate, the radiologic findings are consistent, and certain ancillary radiologic findings are present (e.g., hilar adenopathy in patients with pulmonary invasion by Hodgkin's disease; or nonanatomic perimediastinal lung opacification that corresponds to the shape of radiation portals) (Rubin & Greene, 1994).

Radiologic Evaluation

The depressed inflammatory response of the immunocompromised host may greatly modify or delay the appearance of pulmonary infection on x-ray. This depression is most frequently observed in patients with severe neutropenia, but is also seen with steroid treatment. When such severe neutropenia is present, atelectasis may be the only radiologic clue on conventional chest x-rays of clinically important infection. This is particularly true when the pathogen in question is a fungal organism, which characteristically induces a less exuberant

TABLE 2. Differential Diagnosis of Fever and Pulmonary Infiltrates in the Immunocompromised Host According to Radiographic Abnormality and the Rate of Progression of the Symptoms[a]

Radiographic abnormality	Acute	Subacute–chronic
Consolidation	Bacterial	Fungal
	Thromboembolic	Nocardial
	Hemorrhage	Tuberculous
	Pulmonary edema[b]	Tumor
		Viral, drug-induced, radiation, *Pneumocystis carinii*[b]
Peribronchovascular or interstitial	Pulmonary edema	Viral
	Leukoagglutinin reaction	*Pneumocystis carinii*
	Bacterial[b]	Radiation
		Drug-induced
		Fungal, nocardial, tuberculous, tumor[b]
Nodular infiltrate	Bacterial, pulmonary edema[b]	Tumor
		Fungal
		Nocardial
		Tuberculous
		Pneumocystis carinii, viral[b]

[a]Modified from Rubin & Greene, 1994.
[b]Uncommon cause.

inflammatory response than does bacterial infection. In contrast, in patients recovering from neutropenia, there may be a paradoxical increase in the radiologic findings (and sputum production) as the granulocyte count recovers, despite a good clinical response to antimicrobial therapy (Rubin & Greene, 1994).

Computed tomographic (CT) scanning of the chest has revolutionized the care of immunocompromised patients with possible pneumonia, providing vital information in many circumstances (Rubin & Greene, 1994).

In the evaluation of febrile, severely neutropenic patients with negative or subtle findings by conventional radiography, CT is far more sensitive in the detection of potentially treatable opportunistic infection, particularly that due to fungal pathogens. In the AIDS patient, CT is of value in evaluating patients for possible *P. carinii* pneumonia in the face of normal chest radiographs (10%–20% of AIDS patients with *Pneumocystis* infection) (Golden & Sollitto, 1988).

Although an abnormal chest radiograph may lead to the diagnosis of infection, it may greatly underestimate the extent of the disease process. A general rule of thumb in the treatment of opportunistic infection is that the best clinical results will be obtained if the clinician continues therapy until all evidence of clinical disease has resolved. This can be best accomplished with CT guidance.

The morphology of the lesions found on CT scan can be very useful in defining the diagnostic possibilities. Cavitary lesions are particularly suggestive of fungal or nocardial infection, with rapidly expanding pulmonary lesions with cavitation and/or hemorrhage being particularly associated with the Mucoraceae. Opacified secondary lobules in the lung periphery are consistent with bland pulmonary infarcts or, particularly if cavitation is present, *Aspergillus* infection. Peribonchial or interstitial distribution of CT opacities is suggestive of pulmonary edema, viral or *Pneumocystis* infection, as well as allograft rejection in the lung transplant patient and in radiation- or chemotherapy-induced lung injuries. In contrast, dense regional or lobar consolidation on CT is most suggestive of bacterial pneumonia. Finally, although hilar and mediastinal lymphadenopathy due to pulmonary infection is uncommon in immunocompromised patients, on occasion, mycobacterial, cytomegalovirus, *Legionella*, and cryptococcal infections of the lung, as well as Epstein-Barr virus associated posttransplant lymphoproliferative disease can produce adenopathy that is demonstrable on CT scan.

Since dual or sequential pulmonary infection is not uncommon in the immunocompromised host, more than one etiologic agent may be responsible for the clinical symptoms. In patients who have responded slowly or poorly to what should be appropriate therapy, CT can provide clues that additional diagnostic possibilities should be considered. For example, in AIDS patients with *Pneumocystis* pneumonia, the characteristic CT and radiographic findings reflect the diffuse interstitial and alveolar abnormalities. Since acinar and macronodular opacities, as well as thick-walled cavities, are unusual manifestations of *P. carinii* pneumonia, their demonstration on CT should suggest the possibility of concomitant infection (or Kaposi's sarcoma) requiring additional therapy (Murray & Mills, 1990).

CT can be very useful in defining which invasive diagnostic procedure is most likely to yield a diagnosis and the anatomic site that should be sampled for highest diagnostic yield. CT is also the best means of predicting whether bronchoscopy is likely to be the most appropriate diagnostic modality for a particular patient. Thus, in patients with pulmonary nodules, CT demonstration of the feeding bronchus correlates with a 60% diagnostic yield with bronchoscopy, as opposed to a 30% yield if this finding is not present. If CT demonstrates centrally located diffuse opacifications, a bronchoscopic approach is the modality of choice for diagnosis. Conversely, a thoracoscopic approach may be useful for peripheral lesions (Naidich et al, 1988; Janzen et al., 1993).

Timetable of Infection

A useful tool for the clinician in constructing a differential diagnosis in the individual patient with pneumonia is the timetable of infection; that is, although pneumonia can occur at any point in the patient´s clinical course, the etiologies are very different at different time points. For example, in the organ transplant patient, pneumonia in the first month after transplant is almost invariably due to

aspiration; in the period 1 to 6 months after transplant, cytomegalovirus and opportunistic infection, particularly that due to *P. carinii,* are the major considerations; finally, in the late period, more than 6 months after transplant, the patients can be divided into two major categories: those with a good result from transplant, for whom the major risk is from community-acquired respiratory viruses and those with a poor result (impaired allograft function, exposure to excessive amounts of immunosuppression, and, often, chronic immunomodulating viral infection) who are at highest risk from such opportunistic pathogens as *P. carinii, N. asteroides, C. neoformans,* and *Aspergillus* species (Rubin, 1994; Fishman & Rubin, 1998).

Such timetables can be developed for each category of immunosuppressed patients and used as a guide to the differential diagnosis of an episode of pneumonia in the individual patient; as an epidemiologic tool (i.e., exceptions to the timetable should be regarded as prima facie evidence of an excessive environmental exposure that merits identification and correction); and as a guide for the deployment of cost-effective preventative strategies (Fishman & Rubin, 1998).

Noninfectious Causes of Pneumonia in Immunocompromised Patients

The noninfectious causes of fever and pneumonitis in the immunocompromised host are determined by the underlying disease and its therapy. For the patient with malignant disease, the major causes are radiation pneumonitis, drug-induced pulmonary injury, parenchymal tumor invasion, and, rarely, an unusual form of alveolar proteinosis. In the organ transplant patient and patients receiving immunosuppressive therapy for autoimmune and inflammatory disorders, the major concerns are pulmonary emboli and pulmonary edema. In the patient with HIV infection, the most important noninfectious causes of pulmonary infiltrates include Kaposi's sarcoma, non-Hodgkin's lymphoma, and nonspecific interstitial pneumonitis. Although a rare occurrence, any patient with a coagulopathy can develop pulmonary hemorrhage, and any transfused patient is at risk for the development of a leukoagglutinin reaction (Rubin & Greene, 1994).

In addition to the direct consequences of these forms of lung injury to the immunocompromised patient, the risk of bacterial and fungal superinfection is far greater than that observed in the nonimmunosuppressed population; that is, any form of lung injury increases the risk of superinfection. For example, in one series of renal transplant patients with fever and pulmonary infiltrates, 8 of 9 patients who had pulmonary emboli developed life-threatening superinfection. This risk is greatly compounded if prolonged intubation is required because of the extent of the primary injury (Ramsey et al., 1980).

Radiation and Drug-Induced Pneumonitis

Both radiation injury and the radiomimetic effects of alkylating agents (Table 3) can produce comparable pulmonary syndromes: a febrile interstitial pneumonia that closely resembles that produced by *P. carinii* and a variety of viruses, and is characterized by subacute presentation, fever without rigors, nonproductive cough, and responsiveness to corticosteroids; and chronic fibrosis, which can follow symptomatic pneumonia or develop insidiously, presenting eventually with dyspnea, orthopnea, cyanosis, clubbing, and cor pulmonale. It has been suggested that both radiation therapy and

TABLE 3. Cytotoxic and Noncytotoxic Chemotherapeutic Agents Known to Induce Pulmonary Disese[a]

Cytotoxic	Noncytotoxic
Azathioprine	Bleomycin sulfate
Bleomycin sulfate[b]	Cytosine arabinoside
Busulfan	Methotrexate sodium
Chlorambucil	Procarbazine hydrochloride
Cyclophosphamide	
Hydroxyurea	
Melphalan	
Mitomycin	
Nitrosoureas (carmustine, lomustine, methyl-lomustine)	
Procarbazine hydrochloride[b]	

[a]Modified from Rosenow et al., 1985.
[b]Although both bleomycin and procarbazine are associated mainly with cytotoxic reactions, noncytotoxic reactions have also been observed, albeit uncommonly.

alkylating agents induce lung injury through the production of oxygen free radicals, which are the proximate cause of the subsequent tissue injury (Gross, 1977; Rubin & Greene, 1994).

Radiation lung injury typically begins within 6 months after the completion of a course of radiation therapy. The incidence and severity of radiation lung injury are determined by the characteristics of the radiation administered—the greater the volume of lung exposed, the higher the dose, and the shorter the period of time over which the therapy is administered, the higher the incidence of radiation lung disease. Typically, but not universally, the areas of lung injury correspond to the fields used to deliver the radiation therapy. In the uncommon cases when unirradiated tissue is involved (e.g., bilateral disease in the face of unilateral radiation), a hypersensitivity reaction initiated by the radiation has been proposed as the pathogenetic mechanism (Arbetter et al., 1999; Gibson et al., 1988). At present, radiation pneumonitis is rarely seen at doses below 30 Gy, may develop at doses between 30 and 40 Gy, and is almost always evident with doses above 40 Gy. Because of the nature of the radiation therapy administered, symptomatic radiation injury of the lung is most common in patients receiving radiotherapy for breast cancer, lung cancer, and lym–phoma, with clinical manifestations developing in 3% to 15% of these individuals. Certain modifying factors greatly enhance the risk of such injury: previous radiotherapy to the lung, abrupt withdrawal of corticosteroid treatment, the concomitant administration of cytotoxic cancer chemotherapy, as well as some component of individual susceptibility (Rubin & Greene, 1994; Libshitz et al., 1973; Phillips et al., 1975; Castellino et al., 1974).

Drug-induced pulmonary disease usually becomes symptomatic weeks to months after significant amounts of the drug have been administered, with dose (and the time course over which it is administered) and individual susceptibility playing key roles in its occurrence. Of all the drugs listed in Table 3, the single most common cause of drug-induced pulmonary injury is bleomycin, in large part due to its efficacy in the treatment of a wide variety of tumors. Clinically overt pulmonary disease occurs in 2.5% to 13% of patients receiving this drug, with a mortality rate as high as 50%. The occurrence of bleomycin lung disease is dose-dependent, with the majority of individuals receiving >500 mg as a cumulative dose developing clinically manifest pulmonary disease. However, individual susceptibility also plays a role, as several reports of life-threatening pulmonary disease have appeared when as little as 50 to 180 mg has been administered. In addition, as with all radiomimetic compounds, the combination of bleomycin with radiation therapy greatly potentiates the occurrence of lung injury. Finally, the observation that the concomitant administration of oxygen during bleomycin therapy increases the risk of lung injury supports the oxygen free-radical hypothesis for the causation of this entity. Diagnostically, a decrease in diffusing capacity, a positive gallium scan, and characteristic findings on CT scan, even in the absence of findings on a conventional chest x-ray, should suggest the diagnosis and the need for drug cessation and a trial of corticosteroids (Rubin & Greene, 1994; Rosenow, 1990; Rosenow et al., 1985; Ginsberg & Comis, 1982; Samuels et al., 1976; Horowitz et al., 1973; lacovino et al., 1976).

Methotrexate, a folic acid antagonist widely used in the treatment of leukemia, lymphoma, and other neoplasms, can also produce acute and chronic lung injury clinically similar to that produced by radiation and alkylating drugs. However, methotrexate usually produces an allergic, granulomatous reaction and, not surprisingly, has a different time course and relationship to dose from the other forms of drug-induced lung injury. The duration of methotrexate therapy before the onset of symptoms can range from less than 1 month to more than 5 years, and total dose before onset can range from as little as 12.5 mg to 6 to 10 g. Again, corticosteroid therapy can be useful early in the course of the disease (Rubin & Greene, 1994; Sostman et al., 1976; Ridley et al., 1988; Hargreaves, 1992; Kremer & Phelps, 1992).

There are other drugs that immunocompromised patients can receive as part of their overall care that may be associated with the production of a febrile pneumonia and/or chronic interstitial fibrosis: azathioprine, diphenylhydantoin, amitriptyline, parenteral gold therapy, D-penicillamine, nitrofurantoin, and amiodarone. Amiodarone, a potent antiarrhythmic agent, has been a particular problem in heart transplantation, when patients who were receiving amiodarone at the time of transplant have

developed acute respiratory failure, with fever and pulmonary infiltrates (Rubin & Greene, 1994).

Neoplastic Pulmonary Invasion

Patients can present with fever and pulmonary infiltrates due to neoplastic invasion of the lung under special circumstances. In patients with Hodgkin's disease pulmonary invasion in association with mediastinal lymphadenopathy, past or present, is not uncommon; in patients with non-Hodgkin's lymphoma, primary pulmonary disease can occur in the absence of mediastinal nodal disease. In both cases, the infiltrates are usually focal and nodular in character. Patients with leukemia, especially those with acute monocytic and chronic lymphatic leukemia, may develop leukemic infiltrates of the lung, particularly when the disease is out of control. The most common association between neoplastic pulmonary invasion and the febrile pneumonitis syndrome is related to endobronchial lesions from primary or metastatic cancer that may cause bronchial obstruction, distal atelectasis, and bacterial infection. Bronchoscopic demonstration of such lesions can be quite useful and lead to effective surgical or radiation therapy (Rubin & Greene, 1994).

Other Noninfectious Causes of the Febrile Pneumonitis Syndrome

Even in immunosuppressed patients without neoplastic disease, noninfectious causes of the febrile pneumonitis syndrome account for as many as 25% of such cases. Here, pulmonary emboli and atypical pulmonary edema are the major causes. In transplant patients, the administration of such antilymphocyte antibody therapies as OKT3 can lead to a febrile pulmonary edema picture due to cytokine release (Rubin & Greene, 1994; Ettinger & Trulock, 1991).

An unusual cause of fever and pulmonary infiltrates in the immunocompromised host is a leukoagglutinin reaction, which results in a syndrome of febrile pulmonary edema of noncardiac origin. Typically, there is an abrupt onset of fever, chills, tachypnea, nonproductive cough, and respiratory distress in the first 24 hours following blood transfusion (and most commonly during the transfusion or in the first few hours following it). Such reactions are initiated by the interaction of preformed agglutinating antibodies with antigens on leukocyte surfaces, probably of both human lymphocyte antigen (HLA) and non-HLA type. The antibodies are usually present in the patient´s serum because of sensitization by past transfusions or pregnancies and are directed against leukocytes transfused with the unit of blood; rarely, the antibodies may be present in the plasma of the blood being transfused, and they then act against the patient´s leukocytes. Similar reactions may be observed during the infusion of antilymphocyte antibody preparations and following the administration of such cytokines as interferon (as in the treatment of hepatitis C) (Ward, 1971; Thompson et al., 1971; Rubin & Greene, 1994).

Infectious Causes of Pneumonia in the Immunocompromised Host

Bacterial Infections

Bacterial infections of the lung in immuno--compromised patients presenting from the community can be divided into three general categories: conventional, mycobacterial, and opportunistic infection. Conventional bacterial infection usually occurs as a consequence of aspiration (vomiting is often the trigger for a significant episode of aspiration in the immunocompromised patient); following a viral respiratory infection; or as superinfection in patients with respiratory failure (particularly those requiring prolonged intubation) or other forms of lung injury (e.g., bland pulmonary infarction). Thus, these infections resemble those seen in nonimmunosuppressed individuals, but some differences do exist. Although pneumococcal infection is the most common single cause of bacterial pneumonia in these patients, because of the increased rate of nasopharyngeal carriage with gram-negative bacilli in these patients, the incidence of gram-negative pneumonia is far higher. In those with superinfection, gram-negative bacteria, particularly *Pseudomonas, Klebsiella,* and *Enterobacter* species, as well as *Staphylococcus aureus,* are particularly common, with antibiotic resistance among these organisms constituting a particular problem. In communities where infection due to *Legionella* species is an ongoing issue, the attack rate will be particularly

high in patients who are immunocompromised. *M. pneumoniae* and *Chlamydia pneumoniae* affect non-immunocompromised and immunocompromised patients in a similar manner (Fishman & Rubin, 1998; Baril et al., 1998).

Tuberculosis occurs more commonly among immunocompromised individuals than in the general community. In addition, the extent of tuberculosis in the individual patient tends to be greater; that is, the incidence of extrapulmonary disease, and of miliary or disseminated infection, is greater among immunosuppressed individuals. Particular risk factors for tuberculosis other than recent intense exposure and known positive tuberculin reaction include the following: non-Caucasian racial background, history of active tuberculosis in the past (particularly if not optimally treated), presence of significant abnormalities on chest radiograph attributable to tuberculosis, recent development of a positive tuberculin reaction, and the presence of protein-calorie malnutrition or a second immunosuppressing condition. Isoniazid prophylaxis is usually recommended for immunosuppressed patients with positive tuberculin tests, but is particularly indicated for those individuals with one or more of these additional risk factors. It is worth noting, however, that false-negative tuberculin skin testing is often misleading in highly immunosuppressed patients, such as those with AIDS or those receiving high-dose corticosteroid therapy. In addition to disease due to *M. tuberculosis,* atypical mycobacterial infection is more common among immunosuppressed individuals, particularly that caused by *M. avium-intracellulare.* This is true not only for individuals with AIDS, but also other populations, such as organ transplant recipients with significant impairment of cell-mediated immunity (Rubin, 1994; Fishman & Rubin, 1998; Barber & Sugar, 1994).

The three major causes of opportunistic bacterial infection of the lung are *Nocardia* species, particularly *N. asteroides, Rhodococcus equi,* and *Legionella* species. The first two of these infections occur in patients whose net state of immunosuppression is relatively high, presenting subacutely with fever, nonproductive cough, and chest discomfort, with focal abnormalities (often with cavitation) on chest x-ray, and the common presence of a pleural effusion. Nocardial infection is characterized by a high rate of metastatic spread, typically to the skin (with subcutaneous nodules being a common presentation of disseminated nocardial infection), brain, and bone. Indeed, once the diagnosis of nocardiosis is made, a metastatic work-up is required to guide therapy. Nocardial infection may be resistant to sulfa drugs and has been described in small numbers of patients receiving trimethoprim-sulfamethoxazole prophylaxis. Typically, at least 4 to 6 months of therapy with trimethoprim-sulfamethoxazole, imipenem, or meropenem is required to cure this infection (Barber & Sugar, 1994). *Rhodococcus* infection tends to be more desultory than nocardial infection, with metastatic disease to brain and bone being far less common. Optimal therapy for *Rhodococcus* infection remains unclear, although some cases have been successfully treated with prolonged courses of vancomycin or a macrolide, sometimes in combination with rifampin (Muñoz et al., 1998; Segovia et al., 1994; Capdevila et al., 1997).

Pulmonary infection due to *Legionella* species can be acquired nosocomially or in the community. Typically, immunocompromised patients are more susceptible to infection with these organisms, with a higher attack rate and more severe disease than the general population. Although *L. pneumophila* accounts for the majority of these infections, immunocompromised patients are particularly susceptible to such species as *L. micdadei, L. cincinnatiensis,* and others. *Legionella* infection typically has a nonspecific prodrome of diarrhea, encephalopathy, and malaise that is followed by a rapidly progressive pneumonia. Lung cavitation, pleural effusion, and the development of respiratory failure requiring intubation are indications of a poor prognosis. High-dose macrolide therapy, particularly with azithromycin (although erythromycin and clarithromycin are reasonable alternatives), with or without rifampin is the treatment of choice (Prodinger et al., 1994; Jernigan et al., 1994; Tkatch et al., 1998; Ernst et al., 1998; Ampel & Wing, 1994).

Bacteremic spread of infection to the lungs is increased in some immunocompromised patients. Unique susceptibility may be observed following plasmapheresis (*S. pneumoniae, H. influenze* type b), or with primary immunodeficiencies (e.g., *S. aureus* in patients with chronic granulomatous disease).

Fungal Infections

Fungal infections in the immunocompromised individual can be divided into two general categories: those due to the geographically restricted systemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis) and those due to opportunistic fungi, such as *P. carinii, C. neoformans, Aspergillus* species, and Mucoraceae. Extensive studies of immunocompromised individuals with systemic mycotic infections, particularly those with defects in cell-mediated immunity, have revealed that the pattern of disease observed is similar to that observed with tuberculosis: progressive primary disease, reactivation disease, and a high incidence of systemic dissemination. The use of fluconazole prophylaxis for coccidioidomycosis and itraconazole prophylaxis for blastomycosis and histoplasmosis in individuals deemed to be at high risk of these diseases has greatly decreased the incidence of clinical disease among immunocompromised individuals. Amphotericin, however, remains the treatment of choice for active disease in immunocompromised individuals at least until clinical control has been achieved, at which time therapy can be completed with a less toxic agent (e.g., azoles) (Rubin, 1994).

P. carinii is the single most important cause of opportunistic pulmonary infection due to fungi, affecting a wide variety of immunocompromised patients, but most commonly AIDS patients, organ and bone marrow transplant recipients, lymphoma patients, other individuals receiving immunosuppressive therapy (especially corticosteroids) that impairs cell-mediated immunity, those with severe protein-calorie malnutrition, and children with hypogammaglobulinemia. The natural reservoir of *Pneumocystis* infection is unknown. Person-to-person spread between immunosuppressed individuals can occur, but it is thought that most cases represent reactivation of latent infection due to impairment of host immune function. The illness produced by *Pneumocystis* is characterized by fever, nonproductive cough, progressive hypoxemia, and diffuse interstitial infiltrates on chest radiograph. Prophylaxis with trimethoprim-sulfamethoxazole is remarkably effective; atavoquone, pentamidine, and dapsone offer useful but not as complete protection in individuals unable to tolerate trimethoprim–sulfamethoxazole. Therapy for active *Pneumocystis* infection is high-dose trimethoprim–sulfamethoxazole or pentamidine (corticosteroids for patients with hypoxemia), which is effective, but associated with a high degree of toxicity (Rubin & Greene, 1994; Fishman, 1998a; Fishman, 1998b; Gallant et al., 1998; El-Sadr et al., 1998).

The portal of entry for cryptococcal infection is the lungs. A subacute pneumonia characterized by fever, nonproductive cough, and a focal infiltrate on chest radiograph may result from such infection, particularly in AIDS patients and those who have received high-dose steroid therapy for a prolonged period. More commonly, cryptococcal infection of the lung is discovered when a chest radiograph uncovers an asymptomatic pulmonary nodule. Hematogenous spread of cryptococci to the central nervous system, skin, urinary tract, and skeletal system is common and often dominates the clinical presentation, particularly in individuals with a profound deficit in cell-mediated immunity. The diagnosis of cryptococcal infection by biopsy or demonstration of cryptococcal antigen in blood or cerebrospinal fluid should stimulate a metastatic work-up, as therapy needs to be continued until all sites of infection are eradicated. Therapy is with amphotericin or fluconazole, with oral fluconazole therapy playing a major role in preventing relapse, particularly in AIDS patients (Rubin & Greene, 1994; Hibberd & Rubin, 1994; Hadley & Karchmer, 1995; Hadley et al., 1995).

Invasive pulmonary aspergillosis is the most important hospital-acquired fungal pulmonary infection, but is an uncommon cause of community-acquired infection. Exposure to construction sites or garden work can result in the inhalation of *Aspergillus* spores, and initiate this infection, particularly in individuals with neutropenia or major deficits in cell-mediated immunity. *Aspergillus* invasion of the lung is characterized by vascular invasion, producing the clinical hallmarks of the disease—infarction, hemorrhage, and metastatic spread. Management of invasive aspergillosis includes an assessment for metastatic disease, high-dose amphotericin (1–1.5 mg/kg/day of conventional amphotericin or 3–5 mg/kg/day of lipid formulations), and a consideration of surgical resection if a single lesion is present (Hadley et al., 1995 Hibberd & Rubin, 1994; Hadley & Karchmer, 1995).

Mucoraceae produce a rapidly progressive,

necrotizing pulmonary process in immunosuppressed individuals, particularly those who are diabetic and/or acidotic or who are receiving deferoxamine therapy. Early diagnosis is essential, as therapy requires surgical resection plus adjuvant high-dose amphotericin therapy (Rubin & Greene, 1994).

Notable for their absence from this discussion is pulmonary infection due to *Candida* species. Although candidal isolation from sputum cultures is common, cases of pulmonary invasion, even in highly imunosuppressed individuals, are vanishingly rare, and such cultural results should not, by themselves, lead to antifungal therapy or an aggressive diagnostic program. Fungemia, as from a contaminated vascular access catheter, can lead to hematogenous spread to the lung, producing nodular lesions in the setting of disseminated infection (Rubin & Greene, 1994).

Viral Infections

Most viral pulmonary infections begin insidiously with constitutional symptoms including fever and malaise; a dry, nonproductive cough; and varying degrees of tachypnea, dyspnea, and hypoxemia. Unlike acute bacterial pneumonias which typically present over several hours, viral pneumonias, even in the immunocompromised individual, typically develop over several days before coming to medical attention. The viruses of importance for the immunocompromised patient can be divided into three general categories: cytomegalovirus (CMV), a betaherpesvirus that rarely causes pulmonary disease in the immunocompetent host but is an important pathogen in bone marrow and organ transplant patients as well as AIDS patients; the previously discussed community-acquired respiratory viruses (e.g., influenza, parainfluenza, respiratory syncytial virus, etc.); and varicella-zoster virus (VZV) and herpes simplex virus (HSV).

The critical first step in the pathogenesis of CMV pneumonia is the reactivation of latent virus that is endogenous, that is present in the allograft, or is transfused with blood products from CMV-seropositive individuals. Person-to-person spread does not play a significant role in the direct pathogenesis of CMV pneumonia in immunocompromised patients (although intimate contact in the past is usually responsible for the acquisition of the infection that is reactivated after the initiation of immunosuppression). Both therapeutic and prophylactic strategies are available that have significantly decreased the morbidity and mortality due to CMV. In contrast, the respiratory viruses are acquired through person-to-person spread, and are poorly prevented or treated with currently available antiviral therapies. Although annual influenza immunization is advocated for immunocompromised patients, its efficacy is less than in the general population, and avoidance of exposure is the most important strategy currently available. With both of these categories of viral pneumonia, attention has to be paid both to the viral invasion of the lungs and the possibility of superinfection with such organisms as *S. aureus,* gram-negative bacteria, and *Aspergillus* species (Rubin & Greene, 1994; Rubin, 1994).

Primary varicella-zoster infection is a major cause of morbidity and mortality in a wide variety of immunocompromised patients, most notably leukemic patients, transplant recipients, AIDS patients, and lymphoma patients. Progressive pneumonia is an important part of the visceral spread of VZV in these patients. In contrast, dermatomal zoster, which is due to reactivation infection, uncommonly causes visceral involvement, with the notable exception of AIDS and Hodgkin's disease patients. The VZV serologic status should be determined in all immunocompromised individuals. Seronegative individuals should receive the varicella vaccine, although its efficacy in many immunocompromised patients has yet to be demonstrated. Seronegative individuals (even those who have previously received the vaccine) should promptly receive zoster immune globulin following any significant exposure to the virus and then observed for early signs of chickenpox or of a febrile illness. Prompt intervention with intravenous acyclovir, or oral valacyclovir or fanciclovir can be life-saving (Rubin, 1994).

In bone marrow transplant recipients, HSV can spread hematogenously to the lungs. Otherwise, HSV should be considered a secondary invader of the lung, occurring in individuals with replicating virus in the oropharynx (usually with associated herpetic lesions) who are intubated. The endotracheal tube provides a conduit for infection

to the tracheobronchial tree and the lungs. Intravenous acyclovir or oral valacyclovir are again very useful in the management of these infections (Rubin & Greene, 1994).

Diagnostic Approach to Pneumonia in the Immunocompromised Host

The cornerstone of clinical management of pneumonia in the immunocompromised host is specific diagnosis. The techniques available include immunologic techniques (serologic assays and skin testing), antigen detection systems, polymerase chain reaction (PCR) assays, expectorated sputum examination, and invasive techniques that include bronchoscopy, aspirational needle biopsy, thoracoscopic biopsy, and open lung biopsy. The skill with which the clinician deploys the diagnostic techniques available will determine in large part the success of therapy.

The use of serologic assays and skin tests for the diagnosis of infectious processes is a time-honored approach to invasive infection. However, in the immunocompromised patient with pneumonia such approaches are of limited use for several reasons: (1) There is too great a lag time between the onset of invasive infection and the development of a meaningful immunologic response in this group of patients; (2) many of the opportunistic infections are ubiquitous, and positive tests to such organisms as *Aspergillus* or *Candida* species are commonly seen in the general population, so specificity as well as sensitivity can be a problem; and (3) for many of the diagnostic considerations, no suitable immunologic assays are available. Thus, the major utility of immunologic assays is to stratify risk so that appropriate prophylactic or preemptive strategies can be initiated; they have little role in the diagnosis of a clinical syndrome (Rubin & Greene, 1997).

In contrast, specific tests for microbial antigen in the blood (e.g., cryptococcal antigen and CMV antigenemia testing) and PCR assays for microbial DNA (e.g., CMV and other herpesviruses, as well as HIV) are becoming increasingly useful in the diagnosis of invasive infection in the immunocompromised host. The advantages of these assays are that they do not depend on a host response for their diagnostic value and they can, in many instances, provide a quantitative assessment of microbial load, a major prognostic determinant.

The usual clinical approach to the diagnosis of pneumonia is based on the gram stain and cultural examination of expectorated sputum specimens. It should be emphasized that strict criteria should be employed in evaluating the gram stain: few squamous epithelial cells (<10 per low power field) and many polymorphonuclear leukocytes (>24 per low power field). If such criteria are not met, the validity of the specimen is in question. For a number of reasons, the expectorated (and even the induced) sputum specimen examined under the microscope and by culture have an unacceptably low sensitivity and specificity in immunocompromised patients with pneumonia. First, many of these patients, particularly those with significant leukopenia, fail to produce sputum. Second, the upper respiratory tract of many of these patients is frequently colonized with a large number of potential pathogens, particularly gram-negative bacilli and fungi, even in the absence of pneumonia. Third, certain organisms that commonly cause pneumonia in this population, particularly the fungi, rarely shed sufficient organisms into the sputum to permit diagnosis by cultural or microscopic examination. Finally, the noninfectious causes of pulmonary infiltrates will not be diagnosed by examination of sputum specimens (Sickles et al., 1975; Murray & Washington, 1975; Masur et al., 1985).

Thus, invasive techniques are essential in the evaluation of the immunocompromised patient with pneumonia. In approaching the issue of which invasive technique is indicated, the answers to two stratification questions can be very useful. The first question is the characterization of the patient´s clinical status: Is he/she a "therapeutic emergency" or a "diagnostic dilemma?" If the patient is a therapeutic emergency then the definitive procedure, an open-lung biopsy, should be immediately performed (Kramer et al., 1998). If the patient is a diagnostic dilemma, then one of the less invasive procedures should be chosen. If these fail to yield the diagnosis, the more definitive procedure can be performed subsequently. Which procedure should be used is determined in large part by the answer to the second stratification question: What is the appearence of the chest radiograph and/or CT? If

there is diffuse lung disease present, then fiber-optic bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy is the procedure of choice (Chan et al., 1996; von Eiff et al., 1995; Mares & Wilkes, 1998); if disease is focal and peripheral, then needle aspiration (if there is a cavity present) or thoracoscopic biopsy is indicated. The key point is to avoid delay in the deployment of this armamentarium of diagnostic procedures (Rubin & Greene, 1994).

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22

Chronic Bacterial Pneumonia

STEVEN H. KIRTLAND AND RICHARD H. WINTERBAUER

Introduction

Most community-acquired lower respiratory tract infections have an acute onset, and medical attention is sought within the first 1 to 2 weeks of symptoms. Some patients, however, have an indolent course with protracted symptoms lasting weeks to months. Many of these patients receive multiple courses of antibiotics with transient or no improvement. These chronic pneumonias can be confusing and frustrating because of their atypical presentations and varied etiologies. They often require invasive testing for diagnosis and prolonged therapy for cure.

Various infectious and noninfectious agents may cause chronic symptoms and x-ray abnormalities and therefore be included in the class of chronic pneumonias. Many of the specific organisms included are extensively discussed elsewhere in this book. An in-depth review of all of the etiologies is beyond the scope of this chapter; rather, we will focus on chronic *bacterial* pneumonia.

History

First recognized and described by Laennec in the early 1800s, chronic pneumonia was a common pulmonary diagnosis (Laennec, 1962). Mycobacterial tuberculosis (phthisis) was rampant and became the prototypical chronic pulmonary infection. In this pre-antibiotic era, patients with bacterial infection frequently succumbed quickly but a minority progressed to a chronic illness. Often the correct diagnosis was not recognized until necropsy.

From 1911 through 1967, there were only 15 reports describing chronic bacterial pneumonia (Ackerman et al, 1954; Collins & Kornblum, 1929; Floyd, 1922; Friedländer & Wolpaw, 1940; Kerschner & Adams, 1948; Larmi & Dammert, 1967; Milne, 1911; Robbins & Sniffen, 1949; Scadding, 1936, 1938; Sellors et al., 1946; Silver et al., 1965; Solomon, 1940; Sullivan et al., 1961; Waddell et al., 1948). The number of patients in these series varied from 3 to 17 and often included individuals with lung abscess and bronchiectasis with surgery or autopsy as the common means of diagnosis. These studies defined the histology of the infection, but most suffered from a lack of precise microbiology. *Klebsiella pneumoniae* (Friedländer's bacillus) was described as a common pathogen in chronic bacterial pneumonia (Solomon, 1940). Since 1967, original reports concerning chronic pneumonia have been limited to individual case descriptions (Essig et al., 1994; Henry, 1983; Linares et al., 1997; Ribas et al., 1997; Rose, 1968; Rubin et al., 1992). Reviews have focused on predisposing host diseases or nonbacterial pathogens (Carrizosa & McNamee, 1984; Dismukes, 1990). A MEDLINE® search of chronic pneumonia did not reveal any new series since the original study of 115 patients published in 1994 (Kirtland et al.). This experience will serve as the foundation for this chapter.

Definition

Initially a pathologic term, the definition of chronic pneumonia has been modified to designate

STEVEN H. KIRTLAND AND RICHARD H. WINTERBAUER • Section of Pulmonary and Critical Care Medicine, Virginia Mason Medical Center, Seattle, Washington 98111.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

a clinical syndrome of prolonged respiratory symptoms and persistently abnormal chest roentgenogram due to an infectious organism. More recent reviews define it by a duration of symptoms of at least 4 weeks (Carrizosa & McNamee, 1984; Dismukes, 1990; Kirtland & Winterbauer, 1991). Distinction from recurrent and slowly resolving lower respiratory tract infections is necessary. Recurrent pneumonias require an asymptomatic period of time between infections along with intermittent clearing of the chest radiograph (Winterbauer et al., 1969; Geppert, 1992). Slowly resolving infections refer to the prolonged persistence of a roentgenographic abnormality in a clinically improved host (Corley & Winterbauer, 1993; Fein et al., 1993; Kirtland & Winterbauer, 1991). In contrast, chronic pneumonia represents an infection that persists both symptomatically and radiographically for more than 1 month.

Epidemiology

The current frequency of this syndrome is not known. Geppert estimated that a busy pulmonologist can expect to encounter patients with chronic, nontuberculous pneumonia once or twice a year. Fein found that in 1 year, approximately 15% of consultations and 8% of bronchoscopies were performed to evaluate unresolved roentgenographic infiltrates. In a review of 1263 patients with respiratory tract infection documented by brush quantitative culture, Kirtland and colleagues (1994) found that 115 patients (9.1%) suffered from chronic bacterial pneumonia as defined by symptoms and roentgenographic abnormalities of greater than 1 month's duration in association with a quantitative culture of a brush specimen obtained at bronchoscopy showing 4000 or more colony-forming units of a single bacterial species. Although prior studies of chronic bacterial pneumonia had suggested a male predominance, females outnumbered males (72 vs 43) in this patient population.

Clinical Presentation

Chronic bacterial pneumonia occurs in patients with and without predisposing disease. In the study by Kirtland et al. (1994), 75 of 115 patients (68%) had some underlying predisposing illness, whereas 40 (35%) had no recognizable predisposing disease to explain their infection (Table 1). Obstructive lung disease was the most common underlying illness. Only 10 of these patients were receiving prednisone for their obstructive disease at the time of onset of chronic pneumonia. Intrathoracic malignancy, found in 22 patients, was the next most common predisposing disease. Bronchogenic carcinoma was discovered at the time of diagnosis of the chronic pneumonia in 16 of the 22 cases. Other predisposing conditions included interstitial lung disease, nonneoplastic endobronchial obstruction, bronchiectasis, and assorted systemic illnesses. Nineteen of the 20 patients with systemic disease had a previously recognized illness with chronic bacterial

TABLE 1. Predisposing Diseases in 115 Patients with Chronic Bacterial Pneumonia[a]

	Number of patients	
Pulmonary anatomic abnormalities		
Chronic obstructive pulmonary disease/ asthma	34	
Intrathoracic malignancy	22	
Obstructing		15
Nonobstructing		7
Interstitial lung disease	4	
Idiopathic pulmonary fibrosis		2
Sarcoidosis		1
Histiocytosis X		1
Non-neoplastic bronchial obstruction	3	
Foreign body		2
Fibrotic stenosis		1
Post-thoracotomy changes	2	
Postoperative fibrotic stenosis		1
Infected bronchial stump		1
Bronchiectasis	2	
Lung cavity from previous invasive aspergillosis	1	
Systemic diseases predisposing to infection	20	
HIV		3
Lymphoma/leukemia		6
Neurologic disease		3
Diabetes mellitus		8
Corticosteroid therapy	16	
Chemotherapy	6	
Alcohol abuse	2	
No associated disease	40	

[a]From Kirtland et al., 1994.

pneumonia occurring as a late complication (Kirtland et al., 1994).

Foreign-body (FB) obstruction leading to chronic pneumonia warrants some additional attention. Four patients in this series had non-neoplastic bronchial obstruction and distal pneumonia (Kirtland et al., 1994). One patient had aspirated a vitamin tablet, two had aspirated vegetable matter, and one patient had an airway cicatrix after surgical bronchoplasty for bronchogenic carcinoma without evidence of recurrent lung cancer. Foreign-body aspiration remains a common problem worldwide. Although 60% to 80% of cases occur in children less than 3 years of age, a significant number can be found in older children and adults, generally with a normal sensorium (Banerjee et al., 1988; Elhassani, 1988; Al-Majed et al., 1997; Weissberg & Schwartz, 1987). The average age in one large series of 60 adults with FB aspiration presenting to the Mayo Clinic between 1956 and 1989 was 60 years, with a predominance of cases in the seventh decade (Limper & Prakash, 1990). A careful history will elicit the diagnosis in less than 50% of cases (Abdulmajid et al., 1976; Steen & Zimmerman, 1990; Wiseman, 1984). Although the classic triad of coughing, choking, and wheezing is present in only a small percentage of patients, 80% or more will have at least one feature (Banerjee et al., 1988; Black et al., 1984; Wiseman, 1984). Many patients present after a significant delay despite having a witnessed choking event; 20% to 50% may present after delays of weeks to months and most series include patients with delays of years (Banerjee et al., 1988; Daniilidis et al., 1977; Weissberg & Schwartz, 1987). Single cases of foreign-body aspiration up to 25 years prior to diagnosis have been observed (Al-Majed et al., 1997). Organic material may swell as it absorbs moisture, but it does not dissolve, leading to late complications such as postobstructive pneumonia and bronchiectasis. The chest radiograph is of only limited help in the diagnosis of FB aspiration. Subtle signs such as air trapping may be present in addition to atelectasis and pulmonary infiltrates. The lower lobes are involved almost exclusively, with the left lower lobe involved only slightly less often than the right.

The majority of aspirated FBs consist of vegetable material (Limper & Prakash, 1990). Cultural differences account for the diversity in the most commonly aspirated materials. Peanuts predominate in series within the United States and northern Europe, while pumpkin and watermelon seeds are the most common FBs in Greece and the Middle East, respectively (Abdulmajid et al., 1976; Banerjee et al., 1988; Steen & Zimmerman, 1990; Wiseman, 1984). Dental equipment or prostheses are also common FBs aspirated (Limper & Prakash, 1990). The literature contains a fascinating variety of other foreign bodies, including hypodermic needles in drug addicts, and small animal bones in areas where small game is cooked in the form of soup or stew (Casson & Guy, 1987; Nussbaum et al., 1987).

Due to its confusion with chronic pneumonia, lipid pneumonia requires mention. Lipid can accumulate in the lungs from either endogenous or exogenous sources. Accumulation of endogenous lipid is seen in chronic obstructive pneumonitis as well as in pulmonary alveolar proteinosis and lipid storage disease (Antico et al., 1996; Bartlett, 1989). These conditions are entirely different in nature from exogenous forms, which involve aspiration into the lungs of mineral oil or vegetable or animal oils in food or radiographic contrast material (Annobil et al., 1991; Antico et al., 1996). In general, the patient with this second form is asymptomatic and the abnormality is discovered on screening chest x-ray (Antico et al., 1996; Salm & Hughes, 1970). Some patients may complain of chronic cough or pleuritic pain (Annobil et al., 1991). Although the roentgenographic pattern varies, its most common form is persistent, relatively homogeneous consolidation of one or more segments, often in precise segmental distribution. Occasionally, nodular lesions suggestive of primary or metastatic cancer are present (Antico et al., 1996). In most cases, the lower lobes are predominantly affected. Endoscopic examination and bronchoalveolar lavage (BAL) can typically make the diagnosis (Corwin & Irwin, 1985; Laugue et al., 1990; Silverman et al., 1989).

The clinical presentation of chronic bacterial pneumonia is similar in patients with and without predisposing disease (Table 2). Onset of illness is typically insidious without a defining acute event; duration of symptoms before diagnosis averages more than 5 months (Kerschner & Adams, 1948; Kirtland et al., 1994; Scadding, 1938; Silver et al.,

TABLE 2. Symptoms at Presentation in 115 Patients with Chronic Bacterial Pneumonia[a]

Symptom	Number (%) of patients with predisposing disease (n = 75)	Number of patients without predisposing disease (n = 40)
Respiratory		
Cough	64 (85)	39 (98)
Productive (≥30 mL/day)	30 (40)	18 (45)
Dyspnea	43 (57)	17 (43)
Chest pain	20 (27)	26 (40)
Hemoptysis	14 (19)	5 (13)
Constitutional		
Fatigue/malaise	55 (88)	28 (70)
Weight loss	36 (48)	15 (38)
Fever (≥100.5° for ≥5 days)	13 (17)	12 (30)

[a]From Kirtland et al., 1994.

1965; Solomon, 1940; Waddell et al., 1948). Cough is present in 90% of cases, but it is productive of sputum in less than half (Kirtland et al., 1994). Dyspnea is noted in approximately 50%. Constitutional symptoms are common and include malaise and weight loss. Fever is found in a minority (22%) (Kirtland et al., 1994). Most patients have taken at least one course of antibiotics, often with some transient improvement. In one series, 86 of 115 patients had received at least one course of antibiotics, and 15 had taken four or more courses (Kirtland et al., 1994). In most, the antibiotic was found to be effective against the organism eventually isolated at bronchoscopy.

Roentgenography

There is no chest roentgenographic pattern unique to chronic bacterial pneumonia. The appearance may vary from unifocal parenchymal disease mimicking tumor to a diffuse parenchymal pattern suggesting interstitial lung disease. All lobes are at risk. In contrast to earlier reviews which may have included patients with mycobacterial disease, Kirtland et al. (1994) found the lower lobes a common site of involvement. The chest roentgenogram cannot distinguish between those with and without underlying predisposing diseases. Sixty percent of patients with predisposing disease had parenchymal disease limited to a single lobe or segment, compared with 53% of those patients without predisposing disease (Kirtland et al., 1994). Bilateral infiltrates were seen in 28% of patients with predisposing disease and 35% of patients without predisposing disease. Pleural effusions occurred in only 5% of all patients.

Bronchoscopy

Despite the absence of sputum production in most patients with a chronic bacterial pneumonia, bronchoscopy usually reveals gross evidence of purulent secretions in the tracheobronchial tree. Purulent secretions and mucosal erythema are seen in nearly 85% of all patients (Kirtland et al., 1994). BAL typically shows an increased total nucleated cell count ranging from 60 to 150 million cells in the total return (normal: 10–15 million) with a striking neutrophil predominance ranging from a mean of 40% in patients with an underlying disease to 74% in those without disease. Thirty-nine percent of patients in a study by Kirtland et al. (1994) had 83% or more neutrophils; 11% had 90% or more. Twenty-one of the 44 BAL specimens from this patient group with chronic bacterial pneumonia were observed by the cell-analysis technician to have significant numbers of intracellular bacteria, but accurate quantitation was not performed. The percent lymphocytes in BAL is also elevated in patients with chronic bacterial pneumonia but to a lesser degree: 8% and 14% in patients with and without predisposing disease, respectively. Twenty-five percent of patients had more than 16% lymphocytes in BAL differential and in five patients the percentage of lymphocytes in BAL fluid exceeded the percentage of neutrophils.

BAL is often used as a diagnostic tool when trying to recognize fungal, mycobacterial, and other infections. These organisms are recognized much more frequently in BAL fluid and tissue biopsies than in expectorated sputum samples. Direct immunofluorescence for *Legionella pneumophilia* and *Pneumocystis carinii* has a sensitivity/specificity of 70%/90% and 80%/100%, respectively (Ng et al., 1990; Meyer & Edelstein, 1987). Fiber-optic evaluation can double the diagnostic yield and may

provide an immediate diagnosis in nearly 50% of patients with tuberculosis (Dannek & Bauer, 1979; Wallace et al., 1989).

In general, transbronchial biopsy provides more information about a predisposing illness than the actual infectious organism. Occasionally, tissue invasion from fungi and atypical bacteria can be seen, but by no means can infection be ruled out in the absence of this finding. In a study of chronic bacterial pneumonia, transbronchial biopsy was performed in 68 of 115 patients (Kirtland et al., 1994). Sixteen biopsies revealed an underlying malignant lesion. Of the remaining 52 biopsies, 38 showed acute or chronic inflammation or both, four showed organizing pneumonia, three showed interstitial fibrosis, two revealed granulomas, and five were interpreted as no pathologic change.

Microbiology

Usual Bacteria

In Kirtland´s series, 133 bacteria were isolated from the 115 patients (Kirtland et al., 1994). Although 25 different species of bacteria were identified, the same five bacteria in the same order of prevalence accounted for 77% and 82% of the isolates from patients with and without predisposing disease (Table 3). *Haemophilus influenzae* (46%), alpha-hemolytic streptococci (22%), *Pseudomonas aeruginosa* (10%), *Staphylococcus aureus* (9%), and *Streptococcus pneumoniae* (4%) were the top five organisms. Polymicrobial infections were found more often in the patients with predisposing disease (16%) than in those without disease (5%).

TABLE 3. Microbiology of Chronic Bacterial Pneumonia in 115 Patients[a]

Microorganism	Number (%) of patients with predisposing disease (n = 75)	Number (%) of patients without predisposing disease (n = 40)
Haemophilus influenzae	31 (41)	22 (55)
α-Hemolytic streptococci (not *Streptococcus pneumoniae* and not enterococci)	18 (24)	7 (18)
Pseudomonas aeruginosa	8 (11)	4 (10)
Staphylococcus aureus	7 (9)	3 (8)
S. pneumoniae	4 (5)	1
Neisseria sp	3 (4)	
β-Hemolytic streptococci		
Group A		1
Not Group A or D	2 (3)	
Coagulase negative *Staphylococcus*	2 (3)	1
Peptostreptococcus	2 (3)	1
Nonhemolytic streptococci		1
Micrococcus		1
Serratia marcescens		1
Pseudomonas maltophila		1
Other *P. non-aeruginosa*		1
Acinetobacter calcoaceticus	1	
Branhamella catarrhalis	1	
Protus mirabilis	1	
Haemophilus parainfluenzae	1	
Bordetella sp. (not pertussis)	1	
Bacteroides sp.	1	
Eikenella corrodens	1	
Pseudomonas florescens	1	
Veillonella	1	
Pasteurella sp.	1	
Diphtheroids	1	

[a]From Kirtland et al., 1994.

H. influenzae was the most common cause of chronic bacterial pneumonia in both patients with an underlying illness (41%) and those without (55%) (Kirtland et al., 1994). Although *H. influenzae* has long been recognized as a serious pathogen in infants and children, with a mortality rate of up to 20%, recent reports note an increasing infection rate in adults as well (Farley et al., 1992; Hirschmann & Everett, 1979; Moxon & Wilson, 1991; Kostman at al., 1993; Quinones it al., 1989). as a major component of the indigenous bacterial flora of the upper respiratory tract, up to 80% of individuals are carriers of *H. influenzae,* most of which are nontypable (Murphy & Apicella, 1987). These nontypable organisms account for approximately 10% of cases of pneumonia in healthy adults (Woodhead & MacFarland, 1982). Knowledge of the epidemiology and pathogenesis of *H. influenzae* is meager. Whether the presence of *H. influenzae* in the lower respiratory tract is a primary event or secondary to other predisposing or concurrent diseases remains unclear. However, underlying disease does not appear to be an absolute cofactor, as up to 50% of *H. influenzae* pneumonia cases have been reported in previously healthy individuals (Kirtland et al., 1994; Quinones et al., 1989).

Multiple virulence determinants promote infection with this saprophytic organism. Genetic diversity allows the organism to perpetuate on mucosal surfaces. Outer membrane proteins and lipopolysaccharides (LPS) are heterogeneous even between nontypable strains (Groeneveld et al., 1988). Furthermore, this organism undergoes a phenotypic shift shortly after introduction into human tissue. This intrastrain and interstrain variability confounds vaccine development (Groeneveld et al., 1988, 1990; Murphy & Sanjay, 1992). Invasion of the parenchyma may follow initial disruption of the bronchial mucosa from underlying disease, prior viral infection, or possibly even cigarette smoke (Murphy & Apicella, 1987). Other factors that inhibit ciliary activity and increase mucus production lead to impaired clearance and/or potentiate penetration of the mucociliary barrier (Farley et al., 1992). Adhesions and immunoglubulin A-l proteases may act to promote adherence, while LPS have been shown to damage respiratory epithelial cells (Moxon et al., 1991). The organism can be destructive, obliterating bronchial walls and causing microabscess formation. It may be the latter which is responsible for the chronic course and the need for prolonged antibiotic therapy. Finally, antimicrobial resistance does not seem to be the reason for chronic infection, as 77% of the isolates in Kirtland's study were β-lactamase-negative (Kirtland et al., 1994).

H. influenzae's prevalence as a saprophyte often makes the diagnosis difficult. Sputum culture often grows only normal respiratory flora (Corley & Winterbauer, 1993). This does not rule out infection, nor does a positive culture establish the presence of infection. Sputum Gram's stain and culture are fraught with diagnostic pitfalls. Quinones, for example, found *H. influenzae* on sputum culture in only 30% of patients with bacteremic *H. influenzae* pneumonia (Quinones et al., 1989).

α-Hemolytic streptococcus is the second most common pathogen in chronic bacterial pneumonia, isolated in 24% of patients with a predisposing disease and in 18% of patients without predisposing disease (Kirtland et al., 1994). This agent was historically regarded as a rare cause of acute community-acquired pneumonia (Pratter & Irwin, 1980). More recent literature suggests that primary pneumonias occur with some regularity (Sarkar et al., 1989). Although most strains are susceptible to penicillin, 17% show moderate resistance (Corley & Winterbauer, 1993). Virulent species, including *Streptococcus milleri* (SMG), *Streptococcus sanguis,* and *Streptococcus mitis* may require higher concentrations of antibiotics (Gossling, 1988). Some evidence even supports promotion of α-streptococcal infections by certain antimicrobial agents such as trimethoprim-sulfamethoxazole and the fluoroquinolones (Elting et al., 1992). In light of increasing patterns of resistance, insufficient dosing or duration of antibiotic therapy may be responsible for a chronic state of infection. The SMG has been recognized to cause a variety of chronic pleural-pulmonary syndromes, including aspiration pneumonia, lung abscess, and empyema (Gossling, 1988). Other investigators have described cases of toxic shock syndrome secondary to *S. sanguis* and *S. mitis* infection (Elting et al., 1992). In addition, α-streptococci are acid-tolerant, which allows them to overgrow in the mildly acidic stomach (Elting et al., 1992). α-Streptococci are considered part of the normal flora and rarely are isolated in sputum culture.

P. aeruginosa, a frequent cause of chronic pneumonia in animals, is isolated in approximately 10% of patients with chronic pneumonia (Kirtland et al., 1994). Although primarily a hospital-acquired pathogen, *P. aeruginosa* can also cause community-acquired pneumonia. Infection may occur hematogenously, associated with hemorrhagic nodules and acute necrotizing vasculitis, or more commonly via inhalation of bacteria from the colonized upper respiratory tract (Winn & Chandler, 1994). Colonization, as well as the development of pneumonia, is associated with age, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, and prior antibiotic therapy (Rose et al., 1973). Long-term inhabitants and employees of nursing facilities are also at risk for colonization of the upper respiratory tract.

P. aeruginosa pneumonia typically spares the apices but may be found in any other area of the lung (Rose et al., 1973). Chronic infections are characterized by multifocal lobular pneumonia with parenchymal necrosis and small abscess formation (Winn et al., 1994). Parenchymal destruction is a result of proteases and exotoxins produced by the organisms. In addition, some strains possess a mucoid layer that inhibits phagocytosis (Corley & Winterbauer, 1993). Because of the destructive nature *of P. aeruginosa* infection and its general resistance to antibiotics, resolution is often prolonged.

S. aureus has been reported to be responsible for 3% to 14% of community-acquired pneumonias (Winn & Chandler, 1994). This rate is similar to the 9% and 8% incidence found in chronic pneumonia patients with and without underlying disease (Kirtland et al., 1994). *S. aureus* pneumonia often follows a viral pneumonia, especially influenza, or sepsis secondary to a nonpulmonary infection. Many patients have an insidious progression of disease. The organism commonly preys on the debilitated patient; infection may occur through aspiration or hematogenous spread (Winn & Chandler, 1994). The organism's presence in up to 40% of sputum samples makes the diagnosis difficult (Johnson & Finegold, 1994). *S. aureus* also causes significant parenchymal destruction, an end result of its various exotoxins and enzymes, including hyaluronidase and coagulase.

Although *S. pneumoniae* is the most common bacterium isolated from patients with classic community-acquired pneumonia, it could only be found in 4% of patents with chronic pneumonia (Kirtland et al., 1994). Perhaps this is due to the bacteria´s characteristic overwhelming growth with attendant host exudative response. It has no identifiable toxin, and pulmonary necrosis is rare. Up to 25% of organisms are now resistant to penicillin (Doern, 1995).

Unusual Bacteria

Many reported atypical or unusual bacteria have been recognized through case reports as causing chronic pneumonia. This type of data tends to overemphasize these organisms as a cause of chronic bacterial infections. Many bacteria were not isolated in Kirtland's series of patients with chronic pneumonia, but are included in this discussion because of their long history of association (Table 4).

Historically, *K. pneumoniae* (Friedländer´s bacillus) was considered a common cause of chronic bacterial pneumonia (Solomon, 1940). However, this community-acquired organism was not isolated in any of the patients in Kirtland's series (Kirtland et al., 1994). It is typically found in alcoholic men, usually in the 40- to 60-year-old group, and is strongly associated with poor oral hygiene (Pierce & Sanford, 1974). Aspiration of contaminated oral secretions introduces the organism into the lung (Fuxench-Lopez & Ramires-Randa, 1978). The affected lung appears consolidated and mucoid. In contrast to pneumococcal pneumonia, pulmonary necrosis is common and is directly proportional to the duration of the disease (Winn & Chandler, 1994). Extensive scarring, necrosis, and abscess formation are invariable features of chronic *K. pneumoniae* infection.

Actinomycosis and mixed anaerobic pulmon-

TABLE 4. Uncommon Bacteria That May Cause Chronic Pneumonia

Klebsiella pneumoniae	*Actinomyces israelii*
Legionella pneumoniae	*Nocardia asteroides*
Mycoplasma pneumoniae	*Brucella melitensis* or *suis*
Chlamydia pneumoniae	*Pasteurella multocida*
Coxiella burnetii	*Rhodococcus equi*
Chalmydia psittaci	

ary infections are similar in many ways and both are notorious causes of a chronic pneumonia syndrome. The organisms responsible are part of the normal oral flora, and infection arises after aspiration (Johnson & Finegold, 1994). Patients generally have poor dental hygiene. Fatigue, low-grade fever, weight loss, and cough may exist for several weeks. Clubbing of the fingers may occur (Winn & Chandler, 1994). Laboratory abnormalities, including leukocytosis, are absent in most patients. Both give rise to necrotizing pneumonias that generally remain confined to the lung (Carrizosa & McNamee, 1984). However, thoracic actinomycosis is notorious for crossing the pleural space. Pleural empyema, cutaneous thoracic sinuses, mediastinitis, pericarditis, and osteomyelitis are not infrequent (Winn & Chandler, 1994). Diagnosis often requires histologic examination. The gram-positive filamentous branching bacilli *Actinomyces israelii* may be observed within sulfur granules (Winn & Chandler, 1994). Prolonged therapy with an appropriate antibiotic such as penicillin G followed by oral penicillin is necessary for cure.

Nocardiosis and actinomycosis are clinically similar infections of the lower respiratory tract. However, nocardiosis has less proclivity for sinus tract formation and a greater tendency for hematogenous dissemination (Peabody & Seaburg, 1960). The clinical presentation of pulmonary nocardiosis is a rapidly progressive pneumonia in the immunocompromised individual but subacute in the immunocompetent patient (Carrizosa & McNamee, 1984; Johnson & Finegold, 1994). The organism most commonly involved in human disease is *N. asteroides.* Physical examination is nonspecific unless sights of dissemination are obvious. Chest radiographs may initially demonstrate a localized bronchial pneumonia; however, as the disease progresses, complete lobar consolidation and eventual cavitation evolve (Balikian et al., 1978). In the chronic pneumonia associated with *Nocardia* infection, multiple abscesses are separated by areas of fibrosis, but are less pronounced and well defined than with actinomycosis (Peabody & Seaburg, 1966). Although the organism occasionally colonizes the upper respiratory tract, recovery of *Nocardia* on sputum culture from a patient with a pulmonary lesion is highly predictive of the diagnosis (Johnson & Finegold, 1994). *Nocardia* has frequently been described as an acid-fast organism. However, it will not stain reliably with the Ziehl-Neelson procedure. While the modified Kinyoun stain will demonstrate the organism to varying degrees, this technique is inferior to the methenamine-silver stain (Winn & Chandler, 1994). Suspicious organisms must be studied carefully when only Gram's stains are used since *Nocardia* is gram-positive and may be confused with darkly staining fibrin fibers (Robboy & Vickery, 1970). Most patients require a minimum of 6 weeks of therapy. Sulfonamide drugs remain the treatment of choice. An unusual association is that with pulmonary alveolar proteinosis, a rare disorder of unknown etiology that may mimic chronic community-acquired pneumonia in its own right. The pathogenic relationship between the two entities is not completely understood. *Nocardia* has a predilection for causing pulmonary infection, and it is likely that alveolar proteinosis provides a favorable condition for growth of the organism. Untreated patients with pulmonary alveolar proteinosis are also susceptible to infections with staphylococci, invasive fungi, and mycobacteria.

Rhodococcus equi and *Pseudomonas pseudomallei* may produce indolent apical infiltrates that progress to cavitation over 2 to 4 weeks (Lasky et al., 1991; Everett & Nelson, 1978). Almost 100 cases of human infection with *R. equi* have been reported in the literature, 85% of which occurred in patients immunosuppressed due to AIDS, corticosteroid therapy, or chemotherapy (Linares et al., 1997) Pneumonia is the most common form of disease in humans, occurring in approximately two thirds of cases (Lasky et al., 1991; Vervilla et al., 1994). The organism is a pleomorphic gram-positive, intracellular bacillus that is an obligatory aerobe and may stain weakly acid-fast. *R. equi* is ubiquitous in soil and in the feces of herbivores, birds, and animals such as the dog (Linares et al., 1997; Prescott, 1991). A history of animal exposure is reported in half of the patients (Lasky et al., 1991). Vancomycin, ciprofloxacin, and the combination of erythromycin and rifampin all have activity against *R. equi.*

P. pseudomallei is a ubiquitous gram-negative organism that contaminates soil, vegetation, and water throughout tropical regions (Everett & Nelson, 1978). The organism is endemic in Southeast Asia (Sanford & Moore, 1971). The organism is acquired through cutaneous inoculation or contact

with contaminated soil or water and it may have a long latent period. A number of cases occurred in U.S. military personnel after their return from the Vietnam war (Gilbert et al., 1968). Serologic data indicate that 1% to 7% of U.S. soldiers contracted the organism while in the endemic area (Sanford & Moore, 1971). The most common form of illness is the chronic pulmonary infection (Everett & Nelson, 1978). Third-generation cephalosporins and imipenen are effective, as is amoxicillin with clavulanic acid and trimethoprim–sulfamethoxazole.

Treatment

Therapeutic outcome in chronic bacterial pneumonia is related to duration of therapy and the presence of predisposing disease (Table 5). In Kirtland´s series, 22 of the 61 (36%) patients with predisposing disease who were evaluable had a recurrence of infection within 6 months, including 8 of 30 (27%) who received 4 weeks or more of antibiotics (Kirtland et al., 1994). In contrast, recurrence of infection was recognized in 10 of the 40 (25%) patients without predisposing illness, including 5 of the 30 (17%) treated for 4 weeks or more. In this group without predisposing illness, there was a significant difference in recurrence rate among those treated less than 4 weeks compared with those treated for 4 weeks or more (P = 0.01). Among the 32 patients with recurrence, the initial and recurrent infections were both the result of the same bacterial species in 7 of 10 patients who had a repeat bronchoscopy to evaluate the recurrence. Three patients recurred with a polymicrobial infection.

Clinical Approach

When presented with a patient with respiratory symptoms and an unresolving parenchymal infiltrate, a thorough clinical evaluation is warranted. Most patients have already failed one or more courses of antibiotics, and invasive diagnostic testing is required. Further empiric trials will generally fail and may create delay in obtaining the proper diagnosis.

The history is important in assessing the patient's immune status, detecting coexistent disease, establishing the risk of exposure to specific pathogens, and looking for extrathoracic symptoms. Thoracic symptoms are nonspecific and generally not helpful. Travel to endemic areas may suggest the possibility of fungal disease or certain bacterial, protozoal, or helminth infections. Occupations and hobbies leading to possible chronic hypersensitivity pneumonitis must not be missed. Although a minority of those exposed to multiple organic antigens develop disease, this syndrome is not rare. Up to 8% of farmers may develop allergic alveolitis to thermophilic actinomycetes; pigeon breeder's disease occurs in 6% to 15% of owners (Grant et al., 1972; Reed et al., 1965). Antecedent medication history must be obtained to determine the risk for drug-induced pulmonary disease. Unfortunately, numerous agents are potential threats and more are being added to the list every year. In addition to chemotherapeutic agents, analgesics, anti-inflammatory, and cardiovascular drugs have all been reported to cause pulmonary disease (Rosenow, 1994). Six percent of cardiac dysrhythmia patients develop an adverse reaction to amiodarone. Ten percent to

TABLE 5. Outcome of Treatment in 101 Patients with Chronic Bacterial Pneumonia Who Survived More Than 6 Months After Treatment[a]

	Patients with predisposing disease (n = 61)		Patients without predisposing disease (n = 40)	
Duration of therapy	Eradication of infection number (%)	Recurrence of infection number (%)	Eradication of infection number (%)	Recurrence of infection number (%)
<2 weeks	10 (56)	8 (44)	1 (25)	3 (75)[b]
2–4 weeks	7 (54)	6 (46)	3 (50)	3 (50)[b]
>4 weeks	22 (73)	8 (27)	25 (83)	5 (17)[b]

[a]From Kirtland et al., 1994.
[b]$P = 0.001$

20% die despite recognition and treatment of the problem (Rosenow, 1994). Amiodarone pneumonitis can be focal or diffuse with either an alveolar or interstitial pattern. A history of a skin rash, muscle pain, Raynaud's phenomenon, sicca syndrome, dysphagia, or synovitis can suggest the presence of underlying collagen vascular disease. Evidence of multisystem disease, especially renal disease, can support this diagnosis as well.

Typically physical examination and laboratory evaluation provide little evidence in support of a specific etiology. Occasionally involvement of one or several extrapulmonary sites may narrow the diagnostic possibilities. Cutaneous lesions are frequently present in disseminated fungal infections and can be seen in 30% of patients with nocardiosis (Johnson & Finegold, 1994; Sarosi, 1991). Tuberculosis, coccidioidomycosis, and blastomycosis can involve the skeletal or genitourinary systems. Routine laboratory studies manifest only nonspecific abnormalities in the majority of cases. In a series of chronic bacterial pneumonia, 80% of patients had a white blood cell count less than 11,000/mm^3 (Kirtland et al., 1994). The minority were anemic and only an elevated erythrocyte sedimentation rate was common to the majority (range, 0–125). Eosinophilia may suggest one of the chronic eosinophilic pneumonias (Alien & Davis, 1994).

The chest radiograph often provides an important clue in diagnosis; however, seldom will the pattern be pathognomonic for any disease. More often, the radiograph will suggest a group of diseases that may produce such a picture. The parenchymal infiltrates found in chronic pneumonias range from interstitial or fibronodular to dense alveolar consolidation (Dismukes, 1990). The propensity for pleural involvement may be characteristic for certain pathogens such as *N. asteroides, A. israelii,* and *M. tuberculosis,* but can be seen in 5% of patients with more typical bacterial infections (Buckner & Walker, 1990). While upper lobe involvement favors tuberculosis, fungal, or unusual bacterial infections (e.g., *R. equi, P. pseudomallei)* and lower lobe disease is more common with other bacterial pneumonias, reliance on this pattern to aid in the diagnosis is fruitless. Finally, the initial roentgenogram interpretation may suggest bronchogenic carcinoma as it did in more than one third of patients with chronic bacterial pneumonia in a study by Kirtland et al. (1994).

Sputum analysis can be helpful, but can be misleading just as often. In Kirtland's study, 25 of 59 patients grew the same organism as was isolated by quantitative culture (Kirtland et al., 1994). However, an equal percentage of patients grew normal respiratory flora, and nine patients had predominant growth of a pathogen not shown by brush quantitative culture. Atypical bacteria may be even more difficult to grow because of their fastidious nature. Sensitivity of sputum analysis in fungal disease varies with the organism and stage of disease (Sarosi, 1991). In cryptococcosis, sputum culture generally has a poor yield with less than 50% of proven cases having positive cultures (Chandler & Watts, 1994). Serology may provide valuable adjunctive information but rarely is sufficient for diagnosis because of the prolonged nature of the illnesses before presentation. Skin testing appears to be of limited value, since a positive reaction only indicates past exposure.

Despite the nonspecific historical, physical examination, laboratory, roentgenographic, and sputum analysis findings, there is still the tendency to want to avoid invasive diagnostic testing, and to give a trial of an antibiotic for a 4- to 6-week course. This course of action is not recommended. Fiberoptic bronchoscopy should be considered essential in the evaluation of patients with chronic pneumonia. Quantitative culture of the lower respiratory tract is known to be sensitive and specific in the diagnosis of community-acquired pneumonia (Winterbauer et al., 1983). In addition to its higher yield with many of the atypical bacteria, mycobacteria, and fungi, up to 14% of patients with chronic bacterial pneumonia may have an underlying previously unrecognized bronchogenic carcinoma, and 3% may have benign endobronchial disease predisposing them to the infection (Kirtland et al., 1994). In a recent study by Feinsilver et al. (1990) fiber-optic bronchoscopy was diagnostic in 86% of patients with nonresolving pneumonia in whom a specific cause was reported (Feinsilver et al., 1990). The yield was especially high in younger, nonsmoking patients with multilobar infiltrates of long duration.

Summary

Chronic bacterial pneumonias are more common than previously recognized. They often pre-

sent in the absence of fever and purulent sputum production. Although cough is the most common symptom, constitutional symptoms such as fatigue and weight loss are also frequent. *H. influenzae* and α-streptococci are the predominant bacterial pathogens in patients both with and without predisposing illness. Sixty-five percent of patients with chronic bacterial pneumonia will have a recognizable predisposing disease. The roentgenographic appearance is variable and nonspecific. Bronchoscopic evaluation is essential. Short courses of therapy have a high incidence of recurrence, despite initial symptomatic improvement. Thus, successful treatment requires prolonged therapy.

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23

Pneumonia Mimics

HENRY SU AND RICHARD H. WINTERBAUER

Introduction

Although infectious pneumonitis is a common illness, known since antiquity, the diagnostic tools used to recognize it have advanced slowly. A positive blood culture, pleural fluid culture, or even a sputum culture with a heavy growth of a recognized pathogen confers varying degrees of confidence in recognizing bacterial pneumonia. However, culture confirmation of pneumonia is rare in patients with community-acquired pneumonia who are treated as outpatients, and 35% to 40% of patients with community-acquired pneumonia treated as inpatients fail to have a specific pathogen identified. Most physicians arrive at a clinical diagnosis based on a patient´s fever, respiratory symptoms, and abnormal chest roentgenogram. This leads to initiation of antibiotic therapy, and improvement with therapy is used as verification of the diagnosis. Unfortunately, the symptoms and signs of infectious pneumonia are mimicked by many noninfectious pulmonary disorders. This chapter discusses the differential diagnosis of the noninfectious entities that mimic pneumonia, identifies the clinical features that raise suspicion of their presence, and reviews the steps necessary for diagnosis.

Clinical Suspicion of Pneumonia Mimics

The disease pattern at presentation may raise an early suspicion of noninfectious mimics of pneumonia. For example, fever, new air space disease, and pulmonary symptoms in a patient just completing thoracic radiation for neoplasm would immediately raise the possibility of radiation pneumonitis, whereas the same patient receiving chemotherapy creates a suspicion of drug-induced pulmonary disease. Collagen vascular diseases and the granulomatous vasculitides commonly present as multisystem diseases, with affected patients exhibiting either skin rash, ocular inflammation, synovitis, renal disease, or central nervous system disease. Peripheral blood eosinophilia suggests eosinophilic pneumonia or the Churg-Strauss syndrome.

A patient's failure to respond to antibiotic therapy is the most common stimulus that pushes the clinician to consider noninfectious mimics of pneumonia. Symptomatic relief and roentgenographic improvement are both important facets of this therapeutic response. The rate of improvement with antibiotics is variable and it is difficult to precisely distinguish patients who are responding slowly from patients who are not responding. Radiographic progression and lack of symptomatic improvement after 1 week of antimicrobial therapy or lack of radiographic improvement after 2 weeks of treatment should raise the possibility of pneumonia mimics. Disease severity plays a strong role in the decision to consider pneumonia mimics. The seriously ill, hospitalized patient provides little or no margin for error diagnostically, and the search for noninfectious mimics of pneumonia should be initiated earlier in these patients than in less seriously ill patients.

Once a noninfectious mimic of pneumonia is suspected, the differential diagnosis is considered (Table 1). The illnesses listed in Table 1 all produce air space disease, fever, and pulmonary symptoms.

HENRY SU AND RICHARD H. WINTERBAUER • Section of Pulmonary and Critical Care Medicine, Virginia Mason Medical Center, Seattle, Washington 98111.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Noninfectious Mimics of Pneumonia

Pulmonary embolism
Pulmonary neoplasm
Obstructive endobronchial neoplasm with distal infection
Bronchoalveolar cell carcinoma
Lymphoma
Kaposi's sarcoma
Radiation pneumonitis
Bronchiolitis obliterans organizing pneumonia
Fibroproliferative phase of late adult respiratory distress syndrome
Collagen vascular disease
Systemic lupus erythematosus
Polymyositis and dermatomyositis
Mixed connective tissue disease
Drug-induced pulmonary disease
Hypersensitivity pneumonitis
Granulomatous vasculitis
Wegener's granulomatosis
Churg-Strauss syndrome
Acute/chronic eosinophilic pneumonia

Many chronic pulmonary syndromes, such as sarcoidosis, idiopathic pulmonary fibrosis, pneumoconioses, pulmonary alveolar proteinosis, and histiocytosis-X, are not listed. In patients with these diseases, the chronicity of the illness and lack of fever guides the clinician away from infectious pneumonia.

Pulmonary Embolism

Pulmonary embolism is a common disease in the United States, with 170,000 to 650,000 patients affected and 50,000 deaths annually (Dalen & Alpert, 1975; Bell & Simon, 1982; National Institutes of Health, 1986; Anderson et al., 1991). Underdiagnosis of pulmonary embolism is common (Goldhaber et al., 1982; Mercer & Talbot, 1985; Gross et al., 1988; Rubenstein et al., 1988). A missed diagnosis of pulmonary embolism has resulted in a mortality rate five to six times greater than that seen in patients promptly diagnosed.

Risk factors for pulmonary embolism, both inherited and acquired, have been well described (Coon, 1984; Moser, 1990; Raskob & Hull, 1990). Although inherited risk factors contributing to a hypercoagulable state are rare, acquired risk factors are not. The more common acquired risk factors include age, previous venous thromboembolism, prolonged immobility or paralysis, malignancy, congestive heart failure, estrogen use, trauma, pregnancy, obesity, and surgery.

Clinical Symptoms and Signs of Pulmonary Embolism

Every study addressing the difficulty in diagnosis of pulmonary embolism comments on the lack of specificity of the symptoms and signs of the disease. The most common symptoms are dyspnea, pleuritic chest pain, apprehension, and coughing. Any or all of these may result from a variety of cardiopulmonary disorders, including infectious pneumonia (Raskob & Hull, 1990). In one series of patients with acute pulmonary embolism, the classic symptom triad of hemoptysis, pleuritic chest pain, and dyspnea was noted in only 20% of patients (Wenger et al., 1972). The recent Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study cited the difficulty of using symptoms to detect the presence of pulmonary embolism (PIOPED Investigators, 1990). The pattern of respiratory symptoms was the same for patients with angiographically proven pulmonary embolus and patients with a negative angiogram (Stein et al., 1991a). Clinical signs in pulmonary embolism are no more specific. Tachypnea, rales, tachycardia, increased intensity of the pulmonic component of the second heart sound, and fever may be present in some combination. The presence of fever with pulmonary embolism may direct initial clinical suspicion toward infectious pneumonia. Although fevers caused by pulmonary embolism are typically of low grade ($\leq$38.5°C) (Moser, 1990), elevations to 40°C may be seen in some patients (Murray et al., 1979).

Laboratory Tests in Pulmonary Embolism

The average peripheral leukocyte count at the time of hospital admission of febrile patients with pulmonary embolism was 11,600/mm^3 in one study (Murray et al., 1979). Among outpatients presenting to the emergency department with pleuritic chest pain and leukocytosis, approximately one third proved to have pulmonary embolism (Hull et al., 1988).

Arterial oxygenation is commonly measured in the evaluation of a patient suspected to have pulmonary embolism. Hypoxemia is common in major pulmonary embolism but is not universal. In the PIOPED study, the mean arterial PO_2 level in patients with pulmonary embolism was 70 ± 16 mm Hg, compared with 72 ± 18 mm Hg in those with similar symptoms but no embolism. Patients with pulmonary embolism had an A-a gradient of 37 ± 17 mm Hg compared to 35 ± 18 mm Hg for patients without embolism (Stein et al., 199la).

The electrocardiogram (ECG) is frequently abnormal in patients with pulmonary embolism, but again, the changes are nonspecific. Most common are depression of the ST segment and/or T-wave inversion (Stein et al., 1991a). The pattern of right axis shift and S1Q3T3 is uncommon (Raskob & Hull, 1990). The ECG may be useful in differentiating pulmonary embolism from myocardial infarction and pericarditis, although ST–T wave changes compatible with early myocardial infarction can be seen in some patients with pulmonary embolism (Moser, 1992).

Chest Radiography in Pulmonary Embolism

The PIOPED study showed that 84% of patients with pulmonary embolism have an abnormal chest radiograph (Stein et al., 1991a). The most frequent abnormalities seen were atelectasis and/or pulmonary consolidation (Stein et al., 1991; Urokinase Pulmonary Embolism Trial, 1973). Other common findings included pleural effusion, diaphragmatic elevation, and prominence of the central pulmonary vasculature. Pulmonary embolism with infarction may result in cavitation on a plain chest radiograph (Libby et al., 1985; Redline et al., 1985).

Pleural effusion is seen on the chest radiograph in up to 51% of patients with pulmonary embolism (Stein et al., 1991; Urokinase Pulmonary Embolism Trial, 1973; Bynum & Wilson, 1978). When present, the effusion almost always occupies less than one third of the hemithorax (Stein et al., 1991; Bynum & Wilson, 1978). The pleural effusion with pulmonary embolism is unilateral in 98% of patients and is associated with parenchymal consolidation in 55% (Bynum & Wilson, 1978). In 86% of patients, the effusion is seen as only costophrenic angle blunting on the chest radiograph (Stein et al., 1991a). Analysis of such effusions shows that a majority are exudates and contain a predominance of polymorphonuclear cells (Bynum & Wilson, 1976). A parapneumonic effusion has similar findings. Only 27% of effusions from pulmonary embolism are hemorrhagic (Bynum & Wilson, 1976).

Diagnosis

Ventilation–perfusion (V/Q) lung scanning is a cornerstone test for the diagnosis of pulmonary embolism (Stein et al., 1993; PIOPED Investigators, 1990). The PIOPED trial showed that the V/Q lung scan is both sensitive and, in some cases, specific for pulmonary embolism (PIOPED Investigators, 1990). Eighty-eight percent of patients with high probability scans had pulmonary embolism demonstrated on pulmonary angiogram. The combination of a high-probability lung scan and a high clinical suspicion of embolism was 96% specific for recognizing pulmonary embolization. This combination should lead to initiation of anticoagulation therapy without further testing.

Patients with prior cardiac or pulmonary disease are more likely to have indeterminate V/Q scans in the face of pulmonary embolism (Stein et al., 1991b). In the patient with suspected pulmonary embolism and a low or intermediate probability lung scan, the diagnostic sequence should be an ultrasound examination of the lower extremities looking for deep venous thrombosis and, if negative, intravenous pulmonary angiography. If this diagnostic sequence is used, pulmonary angiography will be required for approximately one third of patients suspected of having pulmonary embolism.

Spiral computed tomography (spiral CT) has been used to diagnose pulmonary embolism (Chintapalli et al., 1988). The diagnostic finding is an intraluminal filling defect caused by thrombus and the most common parenchymal finding is a neighboring wedge-shaped pleural-based parenchymal infiltrate (Chintapalli et al., 1988). Spiral CT reliably recognizes thromboembolism in large pulmonary vessels but misses disease in pulmonary arteries less than 2 mm in diameter (Gary et al., 1998; Coche et al., 1998; Remy-Jardin et al., 1997). Intravenous pulmonary angiography is recommended as the diagnostic standard.

Pulmonary Neoplasm

Endobronchial Obstruction

Fever is rarely a cardinal manifestation of lung cancer and when present strongly suggests a complicating infection. Pneumonia and lung abscesses both may develop distal to an obstructing endobronchial tumor and the infectious illness may prompt the patient to seek medical help. Small-cell lung cancer and squamous carcinoma typically occur centrally and are more likely to cause endobronchial obstruction (Hyde & Hyde, 1974). Some metastatic neoplasms, including malignant melanoma, adenocarcinoma of the breast and gastrointestinal tract, hypernephroma, and Kaposi's sarcoma, may cause metastatic endobronchial obstruction without apparent pulmonary parenchymal metastases. Abscesses also may develop within a necrotic tumor mass, usually a squamous cell or large-cell undifferentiated carcinoma.

Most neoplasms involving the lung appear on chest radiographs as single or multiple nodular densities. On occasion, lung cancer results in a parenchymal abnormality that may be difficult to distinguish radiographically from pneumonia. The failure of a presumed pneumonia to respond to antimicrobial agents often is the first clue to an underlying neoplastic process. Of particular importance is the presence of hilar or mediastinal adenopathy, which may not be apparent on standard chest radiographs but may be visualized with computed tomography (CT). Although intrathoracic adenopathy may occur with acute pneumonia, the prevalence of adenopathy is greater in patients with neoplasm.

Sputum cytology performed on a patient with pulmonary infection creates difficulties in interpretation. Atypical sputum cytology is common in the presence of bronchial or parenchymal pulmonary infection, and there can be false-positive results for malignancy. Fiber-optic bronchoscopy with transbronchial biopsy is required for accurate diagnosis.

Bronchoalveolar Carcinoma

Bronchoalveolar carcinoma (BAC) is a well-differentiated adenocarcinoma that originates in the pulmonary parenchyma. The tumor spreads by contiguous growth along alveolar surfaces and lymphatic routes (Edwards, 1984). Accepted diagnostic criteria for BAC include the absence of adenocarcinoma elsewhere, the absence of a central bronchogenic focus of tumor, tumor growth along alveolar walls with papillary projections into the alveolar air space, and preservation of the architecture of the interstitium (Liebow, 1960).

Recent evidence suggests that the incidence of BAC is increasing. A retrospective review found that the incidence of BAC relative to the total number of occurrences of lung cancers had increased from 5% to 24% between 1955 and 1990 (Barsky et al., 1994). Much of this increase has been noted in women. BAC has a lower male-to-female ratio than other lung cancer cell types. The association of this cell type with smoking is less than other cell types. BAC has an increased incidence in patients with fibrotic lung diseases such as idiopathic pulmonary fibrosis or scleroderma lung.

As many as 45% of patients with BAC present with an asymptomatic peripheral lesion (Edwards, 1984). More extensive involvement may produce coughing, dyspnea, chest pain, cyanosis, hemoptysis, fever, and weight loss. A unique and characteristic feature of this neoplasm is profuse bronchorrhea, which has been reported in as many as one third of patients. Progressive restriction of lung capacity develops as the tumor extends to previously unaffected areas of the lungs. Severe hypoxemia may develop as a consequence of intrapulmonary shunting when the alveolar surface is filled with tumor infiltration while the circulation is unaffected (Fishman et al., 1974).

A study of 136 patients with BAC revealed that 30% had an area of consolidation on the chest roentgenogram at initial presentation (Hill, 1984). Seven percent of patients had a localized consolidation involving less than one lobe, while 33% presented with multifocal air space disease. Forty-three percent of patients had a single nodule or mass and 27% had multiple nodules. Pleural effusion was reported in 32% of cases (Hill, 1984). Multiple cystic spaces and cavitary infiltrates have been reported.

BAC requires a histologic diagnosis. Diagnostic material is best obtained by fiber-optic bronchoscopy (FOB) with both transbronchial biopsy

(TBBX) and bronchoalveolar lavage having a high diagnostic yield (Tao et al., 1986; Springmeyer et al., 1983). In some, a surgical lung biopsy via thoracoscopy or thoracotomy may be required (Greco et al., 1986).

BAC is managed in a manner similar to other non-small-cell lung cancers. If the tumor is localized, the preferred treatment is surgical removal. Treatment of multicentric or metastatic BAC is generally unsatisfactory. In this form, BAC is an aggressive malignancy with a poor prognosis and median survival of only 4 months in one series (Springmeyer et al., 1983). There are a few successful case reports of double lung transplantation (Etienne et al., 1997).

Hodgkin´s Lymphoma

Primary pulmonary Hodgkin's disease is a rare condition in which the lymphoma is restricted to the lung with no hilar or mediastinal lymph node involvement and no evidence of extrathoracic extent (Yousem et al., 1986). This occurs in less than 1% of patients with Hodgkin's disease and is more frequent in females (Berkman & Bruer, 1993). Some patients are asymptomatic but coughing is a frequent symptom. Weight loss, fever, and night sweats are present in up to 30% of patients (Yousem et al., 1986; Radin, 1990). Other symptoms include dyspnea, chest pain, hemoptysis, and fatigue. The chest radiograph most commonly shows nodules or masses, but may show an alveolar or reticulonodular infiltrate with air bronchograms. The nodules are often multiple and may cavitate. There are no CT scan findings specific for primary pulmonary Hodgkin´s disease (Yousem et al., 1986; Radin, 1990). The presence of B symptoms, bilateral and multilobar disease, cavitation, and advanced age are all associated with a poor prognosis. The diagnosis usually requires surgical lung biopsy. Reed-Sternberg cells must be present on an appropriate cellular background for diagnosis.

Secondary involvement of the lung with Hodgkin's disease is much more common than primary disease. Approximately 50% of patients show pulmonary parenchymal involvement at the time of presentation (Whitcomb et al., 1972). Three radiographic patterns have been described: nodular; bronchovascular-lymphangitic; and pneumonia-alveolar (Bailikian & Herman, 1979). Almost all patients with parenchymal disease will have associated mediastinal involvement and most will have evidence of extrathoracic disease.

Respiratory symptoms are frequently absent and pulmonary involvement is often discovered on screening radiography.

Non-Hodgkin's Lymphoma

Primary pulmonary non-Hodgkin's lymphoma is more common than primary pulmonary Hodgkin´s disease. However, secondary pulmonary involvement is less common than seen in patients with Hodgkin's disease. As many as 50% of patients have no symptoms. However, cough, chest pain, dyspnea, fever, night sweats, and weight loss all may occur (Li et al., 1990). The pattern of symptoms may relate to the specific cell type of the lymphoma (Colby & Yousem, 1985). The most common chest radiographic abnormality is sharply defined single or multiple nodules. Poorly defined single or multiple infiltrates also occur (Li et al., 1990; Turner et al., 1984).

Sixteen percent of patients with lymphoma develop pleural effusion in the course of their disease (Gabriel, 1965). Cytological examination of fluid removed by thoracentesis is nondiagnostic. Needle biopsy of the pleura or visibly directed thoracoscopic biopsy may establish the diagnosis (Berkman & Bruer, 1993).

The diagnosis of primary or secondary pulmonary lymphoma requires an adequate amount of tissue for examination. FOB with transbronchial biopsy is sometimes diagnostic, but most patients will require a surgical biopsy (Berkman & Bruer, 1993).

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis has recently been shown to be a B-cell neoplasm arising from Epstein-Barr virus (EBV)-infected cells. It may produce cough, dyspnea, chest pain, fever, night sweats, weight loss, and skin rash (Fauci et al., 1982). Males are affected more often than women. Typically, the chest radiograph shows multiple bilateral nodules that are frequently cavitary and are most often present in the middle or lower lobe

(Koss et al., 1986). Alveolar and interstitial infiltrates, pleural effusions, hilar adenopathy, and single nodules occur less often. The CT image is not specific.

Radiation Pneumonitis

Clinical Presentation

Radiation pneumonitis is the development of pulmonary infiltrates in a region of irradiated parenchyma accompanied by symptoms which may include fever, dyspnea, and nonproductive cough. The rate of development and severity of the radiation-induced changes are modified by a number of factors. These include the radiation dose, dose fractionation, total volume of lung irradiated, and the simultaneous use of certain chemotherapeutic agents (Phillips et al., 1975a,b). Coincidental discontinuation of corticosteroids may precipitate a severe case of radiation pneumonitis (Castellino et al., 1974; Parris et al., 1979; Pezner et al., 1984). The sequence of pathological events that occurs after pulmonary irradiation has been studied in detail (Gross, 1977; Smith, 1963; Coogle et al., 1986; Guzzon et al., 1993).

The clinical syndrome of radiation pneumonitis develops in only 5% to 15% of patients receiving thoracic radiation. When symptoms do develop, they typically start 1 to 3 months after the completion of therapy (Libshitz & Southard, 1974), but the range is from 2 weeks to 6 months after the completion of radiation therapy (Goldman & Enquist, 1975). A rule of thumb is to expect radiographic changes on the chest film 8 weeks after the delivery of 4000 rads, and 1 week earlier for each additional 1000 rads (Libshitz & Southard, 1974; Boyars, 1990). In general, the early onset of symptoms is indicative of a more serious illness and a protracted clinical course.

Nonproductive cough is often the earliest symptom. Later in the course, small amounts of sputum may be produced. Hemoptysis is unusual. The cardinal symptom of radiation pneumonitis is dyspnea. The onset is usually insidious, initially occurring with exertion. The dyspnea is progressive, and in severe cases may lead to respiratory failure (Boyars, 1990; Gracey, 1975). The degree of fever is variable, but may be $\geq 39°C$. Chest pain is usually musculoskeletal discomfort from cough. The patient may also complain of a sense of fullness in the chest or of a subjective limitation of inspiratory capacity.

On physical examination, the signs of radiation pneumonitis are usually minimal. Atrophy, telangiectasia, and brawny induration over the radiation ports is common (Smith, 1963). However, the severity and extent of the skin change does not correlate with the presence or absence of underlying pneumonitis. Evidence of consolidation in the area of pneumonitis may be appreciated during the physical examination. Moist crackles may be heard, and rarely a pleural friction rub.

Imaging

The earliest chest radiographic changes include parenchymal ground-glass opacification, creating a diffuse haze and indistinctness of the normal pulmonary markings over the irradiated area (Gross, 1977; Libshitz & Southard, 1974; Guzzon et al., 1993; Davis et al., 1992). With mediastinal irradiation, the haziness causes the mediastinal contours to become indistinct or blurred. Later, the chest radiograph may show nodular infiltrates or dense consolidation of the irradiated field. Air bronchograms are usually present (Gross, 1977; Libshitz & Southard, 1974; Guzzon et al., 1993; Davis et al., 1992).

Pleural effusions are sometimes associated with radiation pneumonitis. Such effusions almost always appear within 2 to 6 months after the completion of treatment (Libshitz & Southard, 1974a; Bachman & Macken, 1959; Bate & Guttman, 1957). They are rarely large, usually do not give rise to symptoms, and may persist for years. Although the radiographic changes of radiation pneumonitis may sometimes resolve completely, progression to fibrosis is the usual sequence. With fibrosis, the radiographic appearance changes to streaky opacities radiating from the area of pneumonitis with contraction of lung volume. The cardinal feature of radiation-induced changes on chest radiographs is the sharp borders of the densities corresponding to the margins of the radiation port. The boundaries disregard normal anatomic lung divisions. In a few

cases, extensive changes beyond the field of irradiation have been observed (Bennett et al., 1969).

Recently, CT has found use in the detection of acute radiation pneumonitis (Libshitz & Shuman, 1984). The most characteristic feature of radiation-induced change is its confinement within the irradiated field. The CT patterns in the affected lung include (1) ground-glass opacification corresponding to alveolitis and early interstitial pneumonitis; and (2) homogeneous consolidation corresponding to interstitial pneumonitis with accumulation of desquamated alveolar cells and protein-rich fluid within the alveoli (Libshitz & Shuman, 1984; Ikezoe et al., 1988, 1990). CT can detect changes that are not visible on conventional chest radiography. It is also more specific than chest radiography in the diagnosis of radiation-induced lung injury as the straight-edge effect is clearly seen on CT scans.

Diagnosis/Treatment

Any patient who has received more than 4000 rads of radiation therapy should be suspected of having radiation pneumonitis, especially if there has been a history of concurrent treatment with certain cytotoxic chemotherapeutic agents, or recent discontinuation of steroids. Radiation pneumonitis has an insidious onset, over days or possibly weeks. Laboratory data are rarely helpful in the diagnosis. A peripheral polymorphonuclear leukocytosis may be present, and the erythrocyte sedimentation rate may be elevated (Gross, 1977).

FOB and its attendant procedures (bronchoalveolar lavage, quantitative brush culture, and transbronchial biopsies) should be done. Bronchoalveolar lavage cell populations in radiation pneumonitis are nonspecific, but typically show a significant increase in the lymphocytes (Gibson et al., 1988; Roberts et al., 1993; Massilta et al., 1993). Transbronchial biopsy may be helpful in excluding tumor and infection, but is not specific for radiation pneumonitis. Surgical lung biopsy is rarely necessary. Radiation pneumonitis usually responds rapidly to 40 mg of prednisone daily with prompt defervescence and radiographic improvement in 1 to 2 weeks. Once infection and tumor are excluded by FOB, the next step should be a trial of corticosteroid therapy.

Bronchiolitis Obliterans Organizing Pneumonia

Clinical Presentation

The taxonomy of bronchiolitis obliterans organizing pneumonia (BOOP) is confusing. BOOP may be interpreted as a distinct histologic picture occurring at a specific time in the continuum of lung parenchymal damage and subsequent repair. BOOP is characterized by myxoid fibrous tissue polyps filling the lumen of bronchioles, and adjacent alveoli with coincident organizing intra-alveolar exudate. This histologic response is a sequela of multiple illnesses including infectious pneumonia, collagen vascular disease, toxic fume exposure, and drug-induced parenchymal lung disease. BOOP is associated with a consistent clinical pattern which includes a symptom duration of weeks to months, fever, and prompt improvement with corticosteroid therapy. The syndrome of fibroproliferative phase of late adult respiratory distress syndrome (ARDS) is included in this discussion of BOOP because of its similar histology and clinical features.

Men and women are affected equally. There is no relationship to smoking. A flu-like illness, fever, and increased sedimentation rate occur in 30% to 50% of patients (Alegre-Martin et al., 1991; Flowers et al., 1992; Yamamoto et al., 1992). Coughing is common, dyspnea is variable, and wheezing and hemoptysis are rare. Auscultation reveals crackles in two thirds of patients and finger clubbing is usually absent (Epleret al., 1985). Pulmonary function tests show a decreased vital capacity, normal flow rates, and a decreased diffusing capacity.

Bilateral patchy infiltrates are the most common radiographic finding. Cavities (Epler et al., 1985; Alegre-Martin et al., 1991) and effusions are rare. Chest CT will show that these patchy infiltrates are typically peripheral. Some patients may show focal nodular or mass-like opacities that have either a traversing air bronchogram or penetrating pulmonary vessel (Bouchardy et al., 1993).

Bronchoalveolar lavage in idiopathic BOOP usually shows an increase in all inflammatory cells. Costabel et al. (1992) noted an increase in lymphocytes, neutrophils, and eosinophils. Yamamoto et al. (1992) found a predominance of lymphocytes,

sometimes as high as 80% to 95% and a decrease in the CD4/CD8 ration to ≤1.0.

Diagnosis/Treatment

Histologic diagnosis usually requires a surgical lung biopsy (Epler et al., 1985). Occasionally, a transbronchial biopsy may be enough to establish the diagnosis (Azzam et al., 1993). In many patients, a typical clinical presentation, failure to demonstrate infection, granuloma or neoplasm by FOB with bronchoalveolar lavage, and rapid improvement with corticosteroids (within 1 week) are sufficient to establish a clinical diagnosis.

Prednisone is the treatment of choice for BOOP. The recommended dose is 40 mg daily for 2 weeks, with the dose reduced in 5- to 10-mg increments every 2 weeks. A maintenance dose of 10 to 20 mg daily is continued for at least 3 months. Fifty percent of patients show complete roentgenographic clearing by 2 weeks. Less than 3 months of steroid therapy is frequently followed by relapse. Normalization of the chest radiograph is seen in 65% to 80% of patients treated (Epler et al., 1985; Costabel et al., 1992; Yamamoto et al., 1992). The mortality is approximately 5% (Epler et al., 1985; Yamamoto et al., 1992). Patients with progressive disease despite therapy with 40 mg prednisone daily have a poor prognosis. Cytoxan and other cytotoxic agents are not of proven benefit.

The Fibroproliferative Phase of Late Adult Respiratory Distress Syndrome

The ARDS is a clinical entity characterized by acute, diffuse injury to the endothelial and epithelial surface of the lung that leads to respiratory failure. The fibroproliferative phase of late ARDS refers to a time of lung repair resulting in BOOP histology. Clinical experience has suggested benefit from systemic corticosteroids in some patients with this late fibroproliferative syndrome. The conundrum is to recognize this period of fibroproliferative repair in a patient population frequently too sick for surgical lung biopsy. Corticosteroids at other points in the ARDS disease continuum are of no value.

The chest roentgenogram of fibroproliferative ARDS is characterized by a patchy, dense consolidation progressing to a more diffuse, hazy, less dense, air space pattern (Winer-Muram et al., 1993, 1994). These less dense opacities have a diffuse, ground-glass appearance when imaged with CT.

A study of 13 ARDS patients with histologically proven lung parenchymal fibroproliferation showed a bronchoalveolar lavage fluid with a high percentage of neutrophils and elevated albumin concentration (Meduri et al., 1994). Most patients had fever >38.8°C and leukocytosis, and their illness mimicked nosocomial pneumonia. Progression of fibroproliferation to pulmonary fibrosis produced respiratory death in 15% to 40% of ARDS patients (Zapol et al., 1979; Montgomery et al., 1985; Suchyta et al., 1992).

Collagen Vascular Disease

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) has a prevalence of 15 to 50 per 100,000 population in urban areas of the United States (Fessel, 1974). It is the most likely collagen vascular disease to mimic pneumonia. Lupus-associated pneumonitis has been reported to occur in 1% to 4% of individuals with SLE, with more severe pulmonary disease appearing in younger patients (Weidemann & Mathay, 1989; Cervera et al., 1993).

The syndrome of acute lupus pneumonitis can occur either in patients with chronic or newly diagnosed SLE. Patients present with fever, cough, dyspnea, tachycardia, tachypnea, and hypoxemia (Orens et al., 1994). The chest x-ray shows parenchymal disease which can be unilateral or bilateral (Orens et al., 1994). Effusions from coincident pleural involvement may be present (Good et al., 1983). Infection has to be ruled out before immunosuppressive therapy can be started. FOB with protected specimen brush quantitative culture and bronchoalveolar lavage should be considered early. Transbronchial biopsy will show only nonspecific inflammation in the majority of cases. Pulmonary hemorrhage is a well-recognized complication of SLE pneumonitis. When hemorrhage occurs, the mortality may be as high as 70% (Leatherman et al., 1984). The presence of antiphospholipid antibodies in SLE are associated with an increased incidence

of thromboembolism (Love & Santoro, 1990). In patients with SLE, the prevalence for lupus anticoagulant was 34% and anticardiolipin antibody 44% (Love & Santoro, 1990).

The most characteristic laboratory abnormality is an antinuclear antibody liter $\geq$1:160 which is found in 96% of patients with SLE. The diagnostic serologic finding is an elevation of the percent DNA binding to >15%. SLE pneumonitis is diagnosed when there is an appropriate clinical syndrome and diagnostic serologic tests are positive in the absence of infection and pulmonary edema secondary to congestive heart failure or renal failure. Lupus pneumonitis usually responds rapidly to the administration of prednisone, 1 mg/kg/day. Occasionally, symptoms will recur and azathioprine or cyclophosphamide may have to be used.

Polymyositis and Dermatomyositis

The incidence of polymyositis (PM) and dermatomyositis (DM) is estimated to be 2 to 3 patients per 100,000 population. Women are affected twice as often as men. The most common presentation is an insidious progression of muscular weakness, muscle pain (20% of patients), and dysphagia. The skin changes of dermatomyositis include erythema, maculopapular eruption, eczematous dermatitis, and rarely, exfoliative dermatitis. PM and DM are associated with neoplasia in 8% of cases.

The incidence of lung disease in patients with PM and DM has been reported as high as 45% (Sandbank et al., 1966). Pulmonary involvement has been estimated to precede muscle disease in at least one third of the reported cases and is not correlated with the severity of extrapulmonary manifestations (Weidemann & Matthay, 1989; Dickey & Myers, 1984). Pulmonary symptoms include nonproductive cough and insidiously progressive dyspnea. Fevers may be present and are usually associated with a more acute onset of symptoms (Weidemann & Matthay, 1989). Rales are common, but clubbing is absent (Dickey & Myers, 1984). X-ray findings are most often bilateral, parenchymal infiltrates predominant in the lower lobes (Tazelaar et al., 1990). Pulmonary function testing shows mild to severe decreases in total lung capacity and diffusing capacity (Tazelaar et al., 1990).

The presence of air space disease in a patient with PM or DM raises the possibility of noninfectious inflammation. FOB should be performed to exclude infection and tumor. In a patient with PM or DM that presents with pulmonary infiltrates, a search for skin rash or muscle weakness, including dysphagia, should be undertaken, and serum creatine phosphokinase measured. Electromyography and/or muscle biopsy should be performed in suspect cases. Lung biopsy is nonspecific and does not add materially to FOB in managing these patients.

Mixed Connective Tissue Disease

Mixed connective tissue disease shares clinical characteristics with SLE, progressive systemic sclerosis, PM and DM, and rheumatoid arthritis. Pulmonary disease is common, occurring in up to 85% of patients (Sullivan et al., 1984). Pulmonary involvement can manifest as pneumonitis, severe interstitial disease, pulmonary hypertension, pulmonary embolism, pulmonary hemorrhage, and/or diaphragmatic dysfunction.

Drug-Induced Pulmonary Disease

Patients with drug-induced pulmonary disease frequently present with fever. When fever and infiltrate occur acutely, the illness mimics infection. Table 2 lists most of the drugs known to cause diffuse lung injury (Winterbauer & Hammar, 1988). The clinical presentation begins with fever, followed by nonproductive cough and dyspnea. These symptoms may precede x-ray changes. Anorexia and weight loss are common. The physical examination has few abnormalities. Clubbing is absent. Auscultation of the lungs may be normal or disclose crackles. The chest x-ray may be normal at the onset of symptoms, but then progress in an asymmetrical fashion. The infiltrates frequently localize to one area, mimicking a pneumonia. The progression of pulmonary infiltrate is insidious. A high-resolution CT scan helps to define the parenchymal disease but has little diagnostic specificity. The histology of drug-induced diffuse lung disease is varied and nonspecific. The changes seen include alveolitis, granulomata, myxoid fibroproliferative change, bronchiolitis, and interstitial fibrosis. Vasculitis is rare.

TABLE 2. Pharmacologic Agents That Cause Diffuse Pulmonary Injury[a]

Cytotoxic drugs	Noncytotoxic drugs	
Antiobiotics	Antibacterial agents	Nonsteroidal anti-inflammatory agents
Bleomycin	Nitrofurantoin	Phenylbutazone
Mitomycin	Amphotericin B	Sulindac
Neocarzinostatin	Sulfasalazine	Naproxen
Alkylating agents	Pyrimethamine	Azapropazone
Busulfan	Sulfadimethoxine	Fenbufen
Cyclophosphamide	Penicillin	Antiarrhythmic agents
Melphalan	Ampicillin	Amiodarone
Nitrosoureas	Cephadrine	Lidocaine
Carmustine (BCNU)	Metronidazole	Tocainide
Semustine (methyl-CCNU)	Isoniazid	Miscellaneous
Lomustine (CCNU)	*p*-aminosalicylic acid	Gold salts
Chlorozotocin	Analgesics	Penicillamine
Antimetabolites	Acetylsalicylic acid	Colchicine
Methotrexate	Opiates	Chlorpropamide
Azathioprine	Heroin	Imipramine
Mercaptopurine	Propoxyphene	Methylphenidate
Cytosine arabinoside	Methadone	Hydralazine
Miscellaneous	Sedatives	Dantrolene
Procarbazine	Ethchlorvynol	Cromolyn
VM-26	Chlordiazepoxide	Captopril
Vinblastine	Anticonvulsants	L-Tryptophan
Vindesine	Diphenylhydantoin	Crack cocaine
	Carbamazepine	Diuretics
	Beta-blocking agents	Hydrochlorothiazide
	Nadolol	Major tranquilizers
	Practolol	Haloperidol
	Pindolol	Fluphenazine
	Propranolol	

[a]Modified from Winterbauer & Hammar, 1988.

FOB should be performed in patients suspected of having drug-induced parenchymal lung disease to eliminate the possibilities of tumor and infection. The bronchoalveolar fluid reveals an increase in either neutrophils and/or lymphocytes. Lymphocyte subset analysis shows a predominance of T cells, frequently with a CD4/CD8 ratio < 1.

Hypersensitivity Pneumonitis

Clinical Presentation

Hypersensitivity pneumonitis is a diffuse parenchymal inflammatory disease caused by repeated inhalation of organic dusts containing protein particles of animal or plant origin (Ramazzini, 1940). Although many people are exposed to these antigens, only a few develop disease (Table 3). For example, in some farming communities, the prevalence of farmer's lung, the most common type of extrinsic allergic alveolitis, ranges from 1% to 8% of the population (Grant et al., 1972). This low incidence contrasts with that of pigeon-breeder's disease, which occurs in 6% to 15% of those who raise pigeons (Reed et al., 1965).

Typical symptoms include cough, fever, tightness of the chest, malaise, and body aches (Sharma, 1991). These symptoms appear 8 to 24 hours after the most recent exposure to the offending antigen (Sharma, 1991). Many patients are unaware of a relationship between their symptoms and a specific exposure. Occasionally, the symptom complex is mistaken for an episode of flu or walking pneumonia. Expectoration is scanty and hemoptysis is rare. Examination of the lungs reveals fine crackles. The attack usually lasts 12 to 48 hours.

The chest x-ray may be normal at this stage. A

TABLE 3. Agents Associated with Hypersensitivity Pneumonitis[a]

Disease	Antigen	Source
Related to agriculture		
Farmer's lung	Thermophilic *Actinomyces*	Moldy hay, grain
Bagassosis	Thermophilic *Actinomyces*	Moldy bagasse (sugar cane)
Malt worker's lung	*Aspergillus fumigatus* or *A. clavus*	Moldy barley
Mushroom worker's lung	Thermophilic *Actinomyces*	Mushroom compost
Cheese washer's lung	*Penicillium casei*	Moldy cheese
Coffee worker's lung	Coffee bean dust	Coffee beans
Miller's lung	*Sitophilus granarius* (wheat weevil)	Infested wheat flour
Fish meal worker's lung	Fish meal dust	Fish meal
Compost lung	*Aspergillus*	Compost
Streptomyces albus EAA	*Streptomyces albus*	Contaminated fertilizer
Potato riddler's lung	Thermophilic *Actinomyces*, *Micropolyspora faeni*, *Thermoactinomyces vulgaris*, *Aspergillus* sp.	Moldy hay around potatoes
Tobacco worker's disease	*Aspergillus* sp.	Mold on tobacco
Winegrower's lung	*Botrytis cinerea*	Mold on grapes
Lycoperdonosis	Puffball spores	*Lycoperdon* puffballs
Related to animals		
Bird fancier's, breeder's, or handler's lung	Bird proteins, all types	Avian droppings or feathers
Pituitary snuff taker's lung	Animal proteins	Pituitary snuff
Furrier's lung	Animal fur dust	Animal pelts
Japanese summer house EAA	*Trichosporon cutaneum*	House dust, bird droppings
Related to contaminated water		
Humidifier or air conditioning lung	*Aureobasidium pullulans* or other microorganisms	Contaminated water in system
Sauna taker's lung	*Aureobasidium* sp.	Sauna water
Hot tub lung	*Cladosporium* sp.	Mold on ceiling
Tap water lung	Unknown	Contaminated tap water
Cephalosporium EAA	*Cephalosporium*	Contaminated basement sewage
Related to wood products		
Sequoiosis	*Aureobasidium*, *Graphium* sp.	Redwood sawdust
Woodworker's lung	Wood dust, *Alternaria*	Oak, cedar, and mahogany dust
Maple bark disease	*Cryptostroma corticale*	Maple bark
Suberosis	Cork dust mold	Cork dust
Woodman's disease	*Penicillium* sp.	Oak and maple trees
Wood trimmer's disease	*Rhizopus* and *Mucor* sp.	Contaminated wood trimmings
Thatched roof disease	*Saccharomonospora viridis*	Dried grasses and leaves
Familial EAA	*Bacillus subtilis*	Contaminated wood dust
Related to chemicals		
Chemical worker's lung	Isocyanates	Polyurethane foam, varnish, lacquer
Laboratory worker's EAA	Male rat urine	Laboratory rat
Pauli's EAA	Pauli's reagent	Laboratory reagent
Detergent worker's disease	*Bacillus subtilis* enzymes	Detergent

EAA, extrinsic allergic alveolitis
[a]Modified from Richerson et al., 1989.

study of mushroom worker's lung showed only 8% had an abnormal chest x-ray initially (Stolz et al., 1976). The initial radiograph changes are bilateral ground-glass haziness with loss of definition of the pulmonary vessels, fine nodular shadows varying from 1 mm to 4 mm in diameter, and reticular shadows. High-resolution CT is more sensitive than plain chest roentgenogram in demonstrating the disease. The diffuse ground-glass pattern seen is suggestive of but not specific to hypersensitivity pneumonitis.

In some patients, repeated exposure leads to chronic illness and pulmonary fibrosis. The clinical episodes are less dramatic and the patient experi-

ences only progressive dyspnea with or without coughing. Cyanosis may occur. Finger clubbing is rare. Ultimately, chronic irreversible pulmonary fibrosis may lead to polycythemia and cor pulmonale. This stage is characterized by chronic diffuse interstitial fibrosis with coarse reticulonodular infiltrates, especially in the upper- and mid-lung zones. The lungs shrink and show traction bronchiectasis. Selective upper-lung volume loss was found in 46% of patients in one study (Hapke et al., 1968).

Diagnosis/Treatment

The diagnosis depends on the history of exposure to a recognized antigen, the presence of specific serum precipitating antibodies to the antigen, intermittent or recurrent symptoms, bronchoalveolar lavage fluid demonstrating lymphocytosis with a CD4/CD8 ratio <1, and a good response to antigen avoidance and/or corticosteroids. Skin tests are of no value. Inhalational challenge with the offending antigen is diagnostic, but rarely necessary, and may be dangerous. Such tests should be performed only by experts in the technique. The potential dangers of challenge combined with lack of commercially available standardized antigens preclude routine use of the technique. Avoidance of exposure followed by absence of symptoms may be evidence of cause and effect. In the rare situation where the diagnosis remains obscure, open-lung biopsy could be performed.

The most important treatment is avoidance of the antigen. Minor symptoms can be treated with anti-inflammatory drugs and bronchodilators. In severe cases, corticosteroids for 2 to 4 weeks can achieve resolution of clinical, functional, and radiological findings. A small number of patients will develop cor pulmonale from progressive parenchymal fibrosis.

Granulomatous Vasculitis

Wegener´s Granulomatosis

Wegener's granulomatosis (WG) consists of a triad of (1) necrotizing granulomatous inflammation and vasculitis involving the upper and lower respiratory tract, (2) a generalized vasculitis affecting arteries and veins, and (3) glomerulonephritis. Classic Wegener's granulomatosis commonly presents with upper respiratory tract disease which may include destructive lesions of the nasal septum, sinusitis, chronic otitis media, and occasionally laryngitis. The most frequent lower respiratory tract symptoms are cough, chest pain, dyspnea, and occasionally hemoptysis. Patients with Wegener´s granulomatosis are often febrile and may have arthralgias, skin rashes, conjunctivitis, pericarditis, and central nervous system disease.

These patients characteristically have a high erythrocyte sedimentation rate, leukocytosis, elevated serum IgG and IgA levels, a low titer rheumatoid factor, and occasionally cryoglobulins in their serum. An initial presentation with renal failure is relatively uncommon, although an abnormal urinary sediment is a common finding. Chest radiographs most frequently show multiple well-demarcated peripheral nodules, but multiple patterns can be seen, including segmental or lobar consolidalion and diffuse reticulonodular infiltrates.

The diagnosis of Wegener's granulomatosis was advanced significantly with recognition of antineutrophil cytoplasmic autoantibodies (ANCAs). These antibodies react against lysosomal enzymes present in myeloid cells (Goldschmeding et al., 1989). Using indirect immunofluorescent techniques on alcohol-fixed neutrophils, two types of immunofluorescent staining patterns have been identified: (1) a pattern in which the staining is predominantly in a cytoplasmic distribution (Anti-PR-3); and (2) a perinuclear fluorescent pattern which is an artifact of ethanol fixation that results in rearrangement of positively charged granules around and on negatively charged nuclear membrane (anti-MPO). PR-3 antibodies recognize a soluble 29-kd serine protease (proteinase-3) in the lysosomal granules of neutrophils and monocytes (Jennette et al., 1990). MPO antibodies recognize other lysosomal antigens, including myeloperoxidase, elastase, cathepsin-G, lactoferrin, and lysozyme (Roberts, 1992). Anti-PR-3 has a high specificity for Wegener´s granulomatosis (Specks & Homburger, 1994). Anti-MPO has been observed in a wide spectrum of disease, including inflammatory bowel disease, autoimmune liver disease, and rheumatoid arthritis (Gal et al., 1994).

Diagnosis

The diagnosis of WG is established when a characteristic clinical syndrome is accompanied by typical pathologic features on a biopsy specimen. The American College of Rheumatology criteria for WG is a patient with vasculitis (tissue or angiographically demonstrated) and any two of the following four findings: (1) painful or painless oral ulcers or purulent or bloody nasal discharge; (2) chest radiograph showing the presence of nodules, fixed infiltrates, or cavities; (3) microhematuria (> five red blood cells per high power field) or red cell casts in urine sediment; and (4) histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (Gaulard et al., 1988). These criteria had a sensitivity of 88% and specificity of 92% in recognizing WG (Gaulard et al., 1988). ANCA was not used in developing these criteria. The presence of anti-PR-3 appears to be a highly specific and moderately sensitive marker of WG, and when present in a patient with typical clinical features it may obviate the need for histologic confirmation.

For histologic confirmation an open-lung biopsy is the procedure of choice. The patchy nature of the infiltrate makes diagnosis difficult. The kidney is a poor site to sample for it rarely yields diagnostic histology. Biopsy of an upper airway lesion can confirm WG, but nonspecific inflammation does not rule out the diagnosis.

Treatment

The best treatment for WG currently is oral cyclophosphamide (2 mg/kg/day) and prednisone (initially 1 mg/kg/day) (Fauci et al., 1983; Guinee et al., 1994). Among patients who achieve remission after receiving standard therapy, conversion from daily to alternate-day prednisone usually occurs at approximately 3 months (Hoffman et al., 1992). Cyclophosphamide should be continued for at least one full year after the patient is in complete remission (Fauci et al., 1983; Hoffman et al., 1992). This treatment results in marked improvement or partial remission in 91% of patients and complete remission in 75% of patients (Hoffman et al., 1992). Although some patients achieve complete remission within a few months, the median time to achieve remission is 12 months (Hoffman et al., 1992).

Churg-Strauss Syndrome

Patients with Churg-Strauss Syndrome (CSS) have a triad of asthma, blood eosinophilia, and systemic vasculitis (Churg & Strauss, 1951). The central/peripheral nervous system and gastrointestinal tract are common extrathoracic sites of involvement. Three clinical phases of CSS have been postulated (Lanham et al., 1984). The first is a prodromal allergic phase, which may persist for years, consisting of allergic rhinitis, nasal polyposis, and asthma. The second phase is characterized by the onset of peripheral blood and tissue eosinophilia, frequently causing a syndrome resembling Löffler's syndrome, or chronic eosinophilic pneumonia. The eosinophilic infiltrative disease may remit and recur over years before the third phase, consisting of systemic vasculitis, is reached. Men and women are equally affected. Chest radiographs usually show pulmonary infiltrates that are patchy and sometimes transient, although occasionally large and small noncavitary nodules or diffuse pulmonary infiltrates are seen. Pleural effusions occur in about one third of the patients, and hilar lymph node enlargement has also been noted. In some patients, angiograms show hepatic or renal aneurysms resembling those seen in polyarteritis nodosa.

There is often a significant elevation in IgE level, and it may correlate with disease activity. Low titers of rheumatoid factor have also been noted, and most patients have an elevated erythrocyte sedimentation rate and mild anemia. Complement levels are usually in the normal range.

Diagnosis

The histologic triad of tissue infiltration with eosinophils, necrotizing vasculitis, and extravascular granuloma formation does not need to be present if one or more of these features are documented in patients with typical clinical features (Lanham et al., 1984). The American College of Rheumatology developed six diagnostic criteria for the diagnosis of CSS in a patient with documented vasculitis: (1) asthma, (2) eosinophilia >10% on differential

white blood cell count, (3) mononeuropathy (including multiplex) or polyneuropathy, (4) nonfixed pulmonary infiltrates on roentgenography, (5) paranasal sinus abnormality, and (6) biopsy containing a blood vessel with extravascularеosinophils (Masi et al., 1990). The presence of four or more of these criteria in a patient with documented vasculitis yielded a sensitivity of 85% and a specificity of 99% in recognizing CSS (Masi et al., 1990). In a patient with well-documented systemic vasculitis the combination of asthma, eosinophilia >10% on differential white blood cell count, and history of documented allergy (allergic rhinitis, food or contact hypersensitivity) other than asthma or drug sensitivity was 95% sensitive and 99% specific for CSS (Masi et al., 1990). In cases of suspected CSS, extrathoracic biopsy sites such as skin, gastrointestinal tract, or peripheral nerve should be considered prior to lung biopsy.

Treatment

CSS responds well to steroids. Allergic symptoms and eosinophilia improve rapidly with the vasculitic component requiring treatment for several weeks to subside. A short time interval from onset of asthma to development of vasculitis is associated with a worse prognosis (Chumbley et al., 1977; Lanham et al., 1984). Asthma usually persists after the resolution of the vasculitic illness with corticosteroids. The therapy of choice is prednisone with an initial dose of 1 mg/kg/day until a clinical response is attained. At that point the dose is tapered. Some patients will require the addition of oral cyclophosphamide at a dose of 2 mg/kg/day (Leavitt & Fauci, 1986).

Chronic Eosinophilic Pneumonia

Clinical Presentation

Women are affected by chronic eosinophilic pneumonia twice as often as men, with a peak incidence in the third decade of life. Preexisting atopic disease occurs in 50% of patients, with asthma being the most common manifestation. Asthma typically exists for years prior to symptoms of chronic eosinophilic pneumonia. Many patients are cigarette smokers. Most patients will present with a subacute respiratory illness of approximately 6 months' duration, with symptoms of nonproductive cough (90%), dyspnea (57%), fever (87%), and weight loss (57%) (Matsuse et al., 1997). The pathologic changes seen on open-lung biopsy are an intra-alveolar accumulation of eosinophils and histiocytes (Jederlinic et al., 1988).

Diagnosis/Treatment

Peripheral pulmonary infiltrates, an increase in blood eosinophils, bronchoalveolar lavage fluid eosinophilia, and transbronchial biopsy showing an eosinophilic parenchymal infiltrate are strongly supportive of chronic eosinophilic pneumonia. The presence of >30% eosinophils in the bronchoalveolar lavage cell differential is consistent with, although not diagnostic of, chronic eosinophilic pneumonia, but parenchymal infiltration with eosinophils on transbronchial biopsy is diagnostic. An open-lung biopsy is rarely needed (Carrington et al., 1969).

These patients usually respond promptly and completely to corticosteroids. Their response to low-dose corticosteroids is so dramatic that 10 mg of prednisone daily has been suggested as a therapeutic trial. If chronic eosinophilic pneumonia is present, there should be a dramatic, immediate response, usually within 3 to 5 days. Therapy of at least 6 months duration is often required to avoid relapse.

Summary

Infectious pneumonia and noninfectious pneumonia mimics frequently have overlapping symptom complexes and chest roentgenographic patterns. The initial evaluation of such patients should include a careful search for extrathoracic disease manifestations, exposure to hypersensitivity antigens, and recent medications, as well as recognition of risk factors for venous thrombosis/pulmonary embolism. Failure of the patient to respond to antibiotic therapy frequently is the first clue to the presence of a pneumonia mimic. Patients who demonstrate roentgenographic progression and fail to show symptomatic improvement after 1 week of

antimicrobial therapy or roentgenographic improvement after 2 weeks of treatment should be evaluated for mimics of pneumonia.

The diagnostic sequence to search for pneumonia mimics does not lend itself to a simple algorithm. Patients with multi-system disease should have serologic testing to check for collagen vascular disease and Wegener´s granulomatosis. The recommended diagnostic sequence for pulmonary embolism is ultrasound of the lower extremities (to detect deep venous thrombosis), ventilation–perfusion lung scans, and pulmonary angiography. Anticoagulation may be started at any point along the three-test sequence depending on the results. Imaging techniques are of limited help in the diagnosis of mimics of pneumonia. The exceptions are a thoracic CT scan which may be helpful in recognizing radiation pneumonitis by defining the sharp borders of the radiodensities corresponding to the margins of the radiation port, the high-resolution CT ground-glass appearance of hypersensitivity pneumonitis, and pulmonary angiograph for pulmonary embolism. FOB with bronchoalveolar lavage, transbronchial biopsy, and cultures for multiple pathogens should be done in many patients suspected of having pneumonia mimics. A surgical lung biopsy will be necessary in only a small fraction of patients. Recognition of pneumonia mimics is imperative. Most of the diseases described show a good response to appropriate therapy. The therapies used are widely disparate and proper selection requires accurate diagnosis.

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24

Lung Abscess

CHRISTOPHER W. H. DAVIES, FERGUS V. GLEESON, AND ROBERT J. O. DAVIES

Introduction

Lung abscess is a disorder whose clinical presentation and microbiology has changed in the face of varying antimicrobial efficacy, resistance, and host immunity. It might be best defined as a localized area of suppuration within lung tissue that leads to destruction of the lung parenchyma. As air enters the destroyed tissues, cavitation presents as an air-fluid level on the chest radiograph. Ultimately, in the absence of effective treatment, a fistula develops with a bronchus, resulting in airway drainage. Lung abscesses can be single or multiple; prior to cavitation, a necrotic lung abscess is indistinguishable from pneumonitis, pneumonia, or a lung mass on radiological imaging.

Lung abscesses are most frequently caused by bacterial infection, but similar radiographic appearances can occur with other infections with agents such as *Aspergillus fumigatus* and *Mycobacterium tuberculosis,* as well as with noninfectious pathology such as malignancy. The pathological and radiological lesions associated with tuberculosis are not usually considered lung abscesses.

CHRISTOPHER W. H. DAVIES, FERGUS V. GLEESON, AND ROBERT J. O. DAVIES • Osier Chest Unit and Department of Radiology, The Churchill Hospital, Oxford Radcliffe Hospitals, Headington, Oxford OX3 7LJ, England.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

Epidemiology and Etiology

There are no systematic studies of the epidemiology of what is now an uncommon condition in large unselected modern populations. Lung abscess has traditionally been associated with the aspiration of oropharyngeal bacteria into the lung in middle-aged men with a history of alcoholism or dental caries. In the pre-antibiotic era, when lung abscess was common, studies of several large cohorts of patients were reported. Cutler and Schlueter (1926) described 1908 cases from the literature and examined the clinical features in this large sample. These reports provide the basis for the traditional view of lung abscess, with the majority of patients having dental caries and excessive alcohol intake. The introduction of antibiotics has markedly reduced the prevalence of the suppurative lung diseases, reducing lung abscess to the infrequent condition seen in the developed world today. Estrera et al. (1980) reviewed the experience of a major U.S. cardiothoracic center in the 1970s and found an average incidence of only 11 cases of primary lung abscess per year, even in this tertiary center. Hagan and Hardy (1983) reported 184 cases of lung abscess over a 22-year period, an average of eight cases per year. The most accurate estimate of a modern incidence comes from Chidi and Mendelsohn (1974), who estimated that between 4.0 and 5.5 per 10,000 hospital admissions per year were due to lung abscess. The reduced incidence of lung abscess means that few clinicians now have a substantial personal experience in its diagnosis and management.

Despite the reduced incidence of lung abscess, the reported mortality from this disease has changed

little. The mortality rate was 22% in the 1960s (Hagan & Hardy, 1983) and 28% in the early 1980s; these rates are comparable to the rates of 10% to 29% reported in other modern studies (Pohlson et al., 1985; Andersen & McDonald, 1960; Chidi & iMendelsohn, 1974). Deaths related to lung abscess are nearly always in patients with comorbid disease (Alexander & Wolfe, 1980; Chidi & Mendelsohn, 1974; Andersen & McDonald, 1960; Pohlson et al., 1985), and it is unusual for otherwise healthy patients to die as a direct result of lung abscess (Chidi & Mendelsohn, 1974).

As modern intensive inpatient care has developed, some presentations of lung abscess have become more frequent. The frequency of nosocomial abscess has increased (Irwin et al., 1981), particularly during prolonged hospitalization. Therapeutic or acquired immunosuppression and illnesses causing periods of altered consciousness are also risk factors for nosocomial abscess.

TABLE 1. Precipitating and Predisposing Factors Contributing the Development of Lung Abscess

Factors associated with impaired cough reflex and/or aspiration
Alcoholism
Drug abuse
Anesthesia
Epilepsy and seizure disorders
Dental caries and dental extraction/oropharyngeal surgery
Stroke
Gastric surgery
Laryngeal/esophageal abnormality
Factors associated with immunosuppression
Diabetes
Malignancy
Steroids and immunosuppressive drugs
HIV and AIDS
Miscellaneous
Bronchial carcinoma
Bronchiectasis
Chronic obstructive pulmonary disease
Pulmonary infarction
Trauma

Risk Factors

Lung abscess occurs most commonly in men after the fifth decade and is usually associated with a history of oropharyngeal dysfunction and aspiration. The reason for male preponderance in the development of lung abscess is not entirely clear, but it is presumably due to an association with alcoholism and poor dentition. Aspiration is often due to preexistent conditions that impair pharyngeal function or alter the state of consciousness (Table 1). These include many forms of neurological diseases, epilepsy and seizure disorders, alcoholic stupor, and anesthesia (Nield et al., 1985; Hammond et al., 1995; Sosenko & Glassroth, 1985; Estrera et al., 1980; Chidi & Mendelsohn, 1974; Groskin et al., 1991; Hagan & Hardy, 1983; Bartlett et al., 1974). Surprisingly, lung abscess following stroke is uncommon (Hagan & Hardy, 1983; Pohlson et al., 1985). This may reflect good management of stroke and particularly bulbar dysfunction, or underreporting of lung abscess in stroke patients (Table 1).

Other conditions that may predispose an individual to lung abscess include bronchial carcinoma (Hagan & Hardy, 1983), septic embolization (Christensen et al., 1993), diabetes (Hagan & Hardy, 1983; Chidi & Mendelsohn, 1974), and trauma (Rice et al., 1987). The severity of the underlying disease greatly influences the mortality associated with lung abscess. Increasingly, immunosuppressive illnesses, in addition to diabetes, are recognized as predisposing factors in the development of lung abscess in developed communities. In a recent series of cases from South Africa (Hammond et al., 1995), all cases were associated with traditional risk factors, including alcoholism, a history of aspiration, and dental caries. In contrast, Pohlson et al. (1985) found that alcoholism was less frequently related to abscess in Hawaii; instead 24 of 89 (28%) cases were in patients receiving steroids or who were immunosuppressed.

Dental caries have also been recognized as a risk factor for many years and a direct pathogenic role is supported by animal models. Smith (1927) was able to produce lung abscesses in animals by the transtracheal inoculation of material and debris from the teeth of patients with pyorrhea. These abscesses contained the same organisms found in the culture of the carious debris, indicating that aspiration of organisms from the mouth and pharynx can play a direct role in causing lung abscess. In an early series by Andersen and McDonald (1960), 63 of 90 patients with lung abscess had significant dental caries. Lung abscess, however, still occurred in 16 patients with teeth in good repair and 11 edentulous patients, and no data is presented

about the prevalence of caries in the general population at that time.

Classification of Lung Abscesses

There are no general classification schemes for lung abscess, but a classification by precipitating category has the advantage of suggesting the likely pathogens involved, which aids investigation and management. With such a classification system, lung abscess can be considered as secondary to aspiration pneumonitis or bronchial obstruction, complicating pneumonia, hematogenous, or due to HIV and AIDS.

Aspiration

Aspiration is the most common precipitant of lung abscess and is usually associated with risk factors for oropharyngeal aspiration and/or causes of altered conscious state (Table 1). Infection is caused by organisms within the particulate matter of oropharyngeal secretions, and initially results in pneumonitis, followed by necrosis and cavitation. Consequently, greater than 50% of aspiration lung abscesses are due to a combination of aerobic and anaerobic bacteria (Table 2) (Hammond et al., 1995; Estrera et al., 1980; Cesar et al., 1975; Bartlett et al., 1974; Lorber & Swenson, 1974; Bartlett, 1993). This accounts for the often fetid odor of sputum and halitosis in these patients. The anaerobes most commonly identified are those that colonize the gingival crevice, including gram-negative bacilli (*Bacteroides* and *Prevotella* species), *Fusohacterium* species, and anaerobic gram-positive *Peptostreptococcus* species (Bartlett, 1991; Marina et al., 1993; Nield et al., 1985; Estrera et al., 1980; Jerng et al., 1997; Bartlett, 1993). The frequency with which these groups of anaerobes are implicated in lung abscess has changed little (Bartlett et al., 1974; Marina et al., 1993). These frequently identified organisms have a number of important features. Peptostreptococci grow optimally in an anaerobic environment, but are also aerotolerant and frequently resistant to metronidazole, whereas many of the *Bacteroides* and *Prevotella* species are β-lactamase producers and are therefore resistant to penicillin (Bartlett, 1993; Marina et al., 1993).

Anaerobic bacteria are found concurrently with aerobic organisms in many cases (Hammond et al., 1995; Bartlett, 1991; Cameron et al., 1980; Nield et al., 1985; Estrera et al., 1980; Jerng et al., 1997; Wong et al., 1995). These are most commonly *Streptococcus milleri, Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus,* and in cases of nosocomial aspiration, *Pseudomonas* species. The coexistence of aerobes and anaerobes may be advantageous for the bacteria. Shinzato and Saito (1994) described synergy between *S. milleri* and *Prevotella intermedia* when cultured together, and Eftimiadi et al. (1990) demonstrated that short-chain fatty acids from anaerobic bacterial metabolism inhibit the phagocytosis of *S. aureus.* These laboratory observations are consistent with clinical data since mixed bacterial infections are associated with a poorer prognosis (Andersen & McDonald, 1960; Hagan & Hardy, 1983).

TABLE 2. Principal Organisms Associated with Lung Abscess Associated with Aspiration of Oropharyngeal Contents[a]

Aerobic bacteria	Anaerobic bacteria
Streptococcus milleri group (32%–41%)	*Bacteroides* species (34%–41%)
Haemophilus influenzae (9%–11%)	*B. fragilis* group
Streptococcus pneumoniae (6%–13%)	*B. gracilis*
Staphylococcus aureus (8%)	*Prevotella* species (11%–54%)
Pseudomonas aeruginosa (6%)	*P. intermedia*
Escherichia coli (5%–8%)	*P. denticola*
	P. melaninogenica
	P. oralis
	Fusobacterium species (12%–50%)
	F. nucleatum
	Peptostreptococcus species (33%–42%)
	P. micros
	P. anaerobius
	P. magnus

[a]Adapted from Bartlett et al., 1974; Estrera et al., 1980; Lorber & Swenson, 1974; Marina et al., 1993; and Nield et al., 1985.

Bronchial Obstruction

Lung abscess may be seen in patients with an endobronchial obstruction due to bronchial carcinoma or a foreign body. Obstruction is followed by atelectasis, stasis, and subsequent mixed aerobic

and anaerobic infection causing necrosis. Organisms are, therefore, usually similar to those associated with aspiration. Treatment, however, is different and requires relief of the bronchial obstruction or resection of the affected bronchus and necrotic lung tissue. Occasionally, it is possible to drain abscesses due to obstruction by passing a catheter distal to the obstructing lesion using a fiber-optic bronchoscope (Schmitt et al., 1988).

Postpneumonic Abscess

Pulmonary infections with isolated aerobic organisms such as *S. aureus, Klebsiella pneumoniae,* or *Pseudomonas* species may lead to cavitating lung disease. Characteristically *S. aureus* occurs after viral lower respiratory tract infections, especially during outbreaks of influenza; is more common in older patients with concomitant illnesses; and may be nosocomial. Cavitation may be seen in about 16% of cases of *S. aureus* pneumonia (Kaye et al., 1990). *Pseudomonas aeruginosa* is also typically nosocomial, and infection with *K. pneumoniae* can present as an acute pneumonia, often affecting the upper lobes, leading to cavitation in some cases (Alexander & Wolfe, 1980; Bartlett el al., 1974).

Hematogenous

A relatively uncommon cause of lung abscesses is the hematogenous dissemination of septic emboli from the heart, septic venous thrombophlebitis, or head and neck infections such as mastoiditis. The use of nonsterile needles by intravenous drug abusers leads to endocarditis, which affects the tricuspid valve and septic emboli, commonly due to *S. aureus* and gram-negative organisms (O'Donnell, 1996). A similar clinical picture can occur in patients with arteriovenous shunts or those receiving chemotherapy with long-term indwelling central lines.

Lemierres disease (necrobacillosis) is a rare pharyngotonsillar infection caused by the anaerobic organism *Fusobacterium necrophorum.* The clinical presentation of this disorder is highly characteristic so a clinical diagnosis should usually be possible. Unfortunately the diagnosis is often delayed because the possibility of this disorder is not considered due to its rarity. Patients are usually young and present with a painful pharyngitis, identical to the more usual viral diseases. Bacteremia and systemic illness follows due to septic thrombophlebitis of the jugular veins, which is clinically evident as an inflamed mass along the border of the sternocleidomastoid. Metastatic septic emboli develop after approximately 9 days, most commonly in the lungs, bone, joints, liver, and kidneys (Currie et al., 1994; Moreno et al., 1989). Spread of lung abscesses to the pleural cavity is a common complication. Despite its dramatic course, most patients survive this disorder after intensive treatment, probably because of its predilection for young adults without significant comorbidity.

HIV/AIDS

There has also been an increase in the number of cases of lung abscess in patients with HIV (Furman et al., 1996). These patients are at risk of lung abscess related to common pneumonia pathogens, but also from a number of unusual opportunistic infections leading to lung abscess. This may be explained by the use of prophylactic antibiotics in this group of patients. Opportunistic lung abscess in HIV-positive patients due to *Pneumocystis carini* (Furman et al., 1996), *Rhodococcus equi* (Shapiro et al., 1992), *Legionella micdadei* (Johnson & Huseby, 1997), and *Cryptococcus neoformans* (Furman et al., 1996) has been described and is associated with a poor outcome, with up to 36% recurrences and the need for longer duration of antibiotic therapy.

In patients with AIDS, despite the widely different spectrum of pathogens causing lung abscess, the clinical presentation is remarkable similar to that in HIV-negative patients, with fever (90%), cough (87%), and dyspnea (36%), occurring most frequently (Furman et al., 1996). Lung abscess may also be the first HIV-associated diagnosis in a small number of patients.

Clinical Features

Patients with lung abscess may present with a wide spectrum of clinical features that are influenced by the precipitating cause and the organism(s) involved (Table 3). The most common lung

TABLE 3. Clinical Features Associated with Lung Abscess[a]

Freatures of lung abscess	Frequency
Clinical features	
Productive cough	75%–94%
Fever and rigors	46%–88%
Pleuritic pain	25%–88%
Breathlessness	30%–44%
Hemoptysis	17%–37%
Weight loss	6%–64%
Malaise	22%
Clubbing of fingers	4%–12%
Laboratory features	
Neutrophil leukocytosis	
Anemia	
Elevated C-reactive protein	

[a]Adapted from Estrera et al., 1980; Groskin et al., 1981; Hammond et al., 1995; Nield et al., 1985; Pohlson et al., 1985; and Sosenko & Glassroth, 1985.

abscesses develop secondary to oropharyngeal aspiration and have a characteristically insidious onset. This indolent presentation is shared with patients with pleural empyema due to mixed organisms (Bartlett et al., 1974). The presumed oropharyngeal aspiration is usually undetected clinically, but a pneumonitis occurs in the dependent segments of the lung (Alexander & Wolfe, 1980; Sosenko & Glassroth, 1985; Estrera et al., 1980; Groskin et al., 1991; Ha et al., 1993; Hagan & Hardy, 1983; Cesar et al., 1975; Bartlett et al., 1974; Bartlett, 1993). In those patients where this is not self limiting, tissue necrosis leading to abscess formation occurs after 1 to 2 weeks (Bartlett, 1993). In animal models, transtracheal injections of pyorrheal pus leads to the development of pneumonitis over 4 to 7 days. At necropsy, the macroscopic appearances of this process are indistinct from other forms of pneumonitis, but microscopically, the various pyorrheal organisms can be identified in association with an inflammatory process (Smith, 1927). Those animals who survived for 2 weeks or longer developed either a pulmonary abscess or had normal lungs.

In humans, the presentation history characteristically lasts for 1 to 6 weeks. Nield et al. (1985) found that 88% of patients had symptoms for more than 7 days and Hammond et al. (1995) reported a median symptom duration of 21 days. Although this protracted presentation is typical of anaerobic abscess, it is not absolutely consistent, as some patients present with an acute illness. Bartlett et al. (1974) reported that 9 of 26 patients with mixed aerobic and anaerobic lung abscess had symptoms for less than week. A shorter presentation may be more likely in those with a documented loss of consciousness (Nield et al., 1985), in those developing lung abscess during hospital stay for other medical problems (Estrera et al., 1980) and in those with an associated pneumonia (Alexander & Wolfe, 1980). The most common symptoms associated with an acute or subacute illness are listed in Table 3. Initially, shortness of breath, fever, malaise, and pleuritic chest pain are associated with a cough. When the predominant pulmonary lesion is pneumonitis, cough is usually nonproductive (Bartlett, 1993), but when an abscess communicates with a bronchus, copious amounts of purulent sputum result. In patients with radiographically evident cavitation, a productive cough is almost universal and affects 75% to 94% of patients (Estrera et al., 1980; Hammond et al., 1995; Nield et al., 1985). The sputum is often foul-smelling when anaerobes are involved (Bartlett, 1993). Hemoptysis may occur in 11% to 38% of patients (Thoms et al., 1970; Hagan & Hardy, 1983; Hammond et al., 1995; Nield et al., 1985; Estrera et al., 1980), but is usually limited to minimal blood streaking. However, even minor hemoptysis should be taken seriously since it may be a "sentinel" hemoptysis (Philpott et al., 1993) preceding a major hemorrhage. Massive hemoptysis is rare, but has an associated mortality of up to 70% with medical management (Garzon et al., 1970) and is an indication for surgery (discussed under interventional therapy). Pleuritic chest pain is a relatively common symptom and reflects the peripheral nature of most lung abscesses. This peripheral situation also risks pleural abscess extension and empyema, which may affect 18% of patients (Groskin et al., 1991).

Weight loss and constitutional symptoms are common in patients with the usual insidious presentation, and patients may lose as much as 5 to 10 kg before presentation (Estrera et al., 1980; Nield et al., 1985). It may therefore be difficult to distinguish those with infective lung abscess from those with pulmonary malignancy. Sosenko and Glassroth (1985) compared the features of patients with benign and malignant lung abscesses, finding similar

histories of weight loss, smoking, poor dentition, and cough in the two groups. However, patients with infective lung abscess were more likely to have systemic symptoms such as fever, rigors, sweats, or general malaise, and a predisposing factor for aspiration.

The physical findings in lung abscess are nonspecific and resemble those of a localized pneumonia, with dull percussion and bronchial or reduced breath sounds, occasionally with a pleural rub. As cavitation develops with bronchial communication, breath sounds may acquire a resonating *amphoric* quality, resembling the sound produced by blowing across the top of a bottle (Macleod & Munro, 1987). Lung abscess is often described as a cause of clubbing of the finger nails, but is only found in 4% to 12% of patients (Estrera et al., 1980; Sosenko & Glassroth, 1985).

Apart from microbiological and radiological investigations (discussed below), most other investigations are diagnostic-ally unhelpful. Many patients will demonstrate a nonspecific neutrophil leukocytosis ($10–20 \times 10^9$/L), but this may help distinguish malignant from benign abscesses (Sosenko & Glassroth, 1985). Anemia is seen in some patients, but the degree of anemia does not correlate with the length of the history (Nield et al., 1985). Recently, Lin et al. (1990) measured the C-reactive protein (CRP) in 207 cases of pulmonary infection, including 16 cases of lung abscess. CRP was elevated in all causes of infection, most significantly with bacterial pneumonia (241 ± 72 μg/mL), bacterial pneumonia with parapneumonic effusion (225 ± 65 μg/mL), and lung abscess (169 ± 50 μg/mL). The test is therefore neither sensitive nor specific enough to distinguish lung abscess from other bacterial pneumonia, but may help to distinguish bacterial lung abscess from other causes of a cavitating lesion on the chest radiograph and is invaluable as a biochemical marker of response to treatment.

Diagnostic Imaging

Chest Radiograph

The diagnosis of lung abscess may be made in some patients post mortem, but for the majority of patients, recognition and diagnosis is based on the findings seen on the chest radiograph. The early pneumonic stage of abscess development resembles any other form of consolidation and is usually in the dependent segments of the lung. Cavitation and an air-fluid level develop as air enters the abscess cavity and may indicate the development of a communication with the bronchial tree, which is also evidenced by voluminous purulent and often foul-smelling sputum. As it is common for patients who are critically ill to have a chest radiograph taken in the supine or semi-erect position, it may not be possible to detect an air-fluid level, and in this setting, recognition of lung abscess is easily overlooked.

The majority of lung abscesses related to aspiration occur in the posterior segment of the right upper lobe and/or the apical basal (superior) segments of the lower lobes. At least 50% of abscesses will occur in these three segments (Sosenko & Glassroth, 1985; Groskin et al., 1991; Estrera et al., 1980; Hagan & Hardy, 1983). If the apicoposterior segment of the left upper lobe is included, over 80% of abscesses will be in these four segments (Bernhard et al., 1962); an abscess in any other segment should arouse suspicions regarding the pathogenesis. In particular, lesions located in an anterior segment of the lung may be more likely to be malignant (Wallace et al., 1979). Abscesses may be single or multiple, and are more likely to be multiple when due to septic emboli.

Lung abscesses can be of variable size ranging from 1.0 to 13.0 cm (Sosenko & Glassroth, 1985; Weiss, 1973; Groskin et al., 1991) and most cavitating lesions due to infection are surrounded by an area of extensive parenchymal infiltrate, reflecting the underlying pneumonitis. Sosenko and Glassroth (1985) found that 83% of lung abscesses had extensive infiltrates (although there is no definition of the criteria used) compared to 17% in those with malignant cavitating lesions. There were no differences in the mean diameter of lesions or the presence of thickened irregular cavity walls between the benign and malignant groups. Similarly, Wallace et al. (1979) found that chest radiographs could not accurately distinguish carcinomatous abscess from benign lung abscess (sensitivity, 70%). Again, in this study, the only significant radiological clue in favor of carcinomatous abscess was a location in an anterior lung segment or the demonstration of obvious bone erosion or metastasis from a carcinoma. In

reality, it is frequently impossible to distinguish benign and malignant abscesses radiologically.

Once bronchial communication is established with a lung abscess, providing there is continuing internal drainage and antibiotic therapy, the air-fluid level, if present, often disappears rapidly (Weiss, 1973). A rising air-fluid level may be an indication of hemorrhage and should be taken seriously in any patient with lung abscess and hemoptysis (Groskin et al., 1991); it may also indicate ineffective defervescence, evident by a deteriorating clinical course. Weiss (1973) studied cavity behavior on chest radiographs in 60 patients with lung abscess that were treated by antibiotics alone. By 28 to 41 days, 75% of cavities will have disappeared, and by 92 days, 95%. As resolution of the cavity occurs, there is a reduction in the wall thickness, and not surprisingly smaller cavities (<3 cm) will resolve more quickly.

Computerized Tomography

Computerized tomography (CT) scanning has three significant roles in the management of primary lung abscess and should be considered in every case.

First, CT will confirm the presence of lung abscess and help to define the exact anatomical position of the collection. In particular, it often helps differentiate a lung abscess from pleural empyema. A lung abscess usually appears as a rounded intrapulmonary mass, often with an indistinct boundary between the lung parenchyma and the collection, and it does not usually compress adjacent lung. In contrast, an empyema usually has a lenticular shape and compresses the surrounding lung parenchyma (Stark et al., 1983; Muller, 1993). The wall of an abscess is usually thick and irregular and makes contact with the chest wall at an acute angle, compared to the smooth (pleural) margins of an empyema which create obtuse angles as they follow the contour of the chest wall (Stark et al., 1983; Klein et al., 1995). In addition, pleural thickening is seen in 86% to 100% of empyemas (Aquino et al., 1994; Waite et al., 1990; Takasugi et al., 1991) and there is usually pleural enhancement (Waite et al., 1990), with increased attenuation of extrapleural subcostal fat and tissues (Aquino et al., 1994; Waite et al., 1990; Takasugi et al., 1991; Muller, 1993). The "split pleura" sign, caused by enhancement of both parietal and visceral pleural surfaces separated by infected fluid in empyema, may be the most reliable distinguishing sign to aid in the differentiation of empyema from lung abscess (Stark et al., 1983). The radiographic features of a typical abscess and a typical pleural empyema are shown in Figures 1 through 4.

The second role of CT in lung abscess is to examine for obstructing endobronchial disease. Bronchi and pulmonary vessels may terminate abruptly at the wall of an abscess (Stark et al., 1983), but more proximal obstruction may be due to a foreign body or neoplastic lesion. Thus, CT may help select those patients who definitely require bronchoscopy to further assess for endobronchial disease, and help avoid unnecessary bronchoscopy in those who are recovering with antibiotics alone.

The third main indication for CT scan is to plan for percutaneous aspiration and drainage, which is discussed later in this chapter.

Ultrasound

Ultrasound imaging may be used to check for the presence of lung abscess, but is more useful as a guide to percutaneous transthoracic aspiration. The advantages include ready availability, low costs, and portability, allowing bedside needle aspiration if the patient is unable to move. The use of ultrasound, however, is limited to patients with abscesses abutting the pleural surface, and the findings with ultrasound are not specific for infective lung abscess, typically demonstrating the presence of a hypoechoic lesion, with an irregular wall, central necrosis, and an air-fluid level (Yang et al., 1991; Lin et al., 1992; Chen et al., 1993). Ultrasound can also identify cavitation when the chest radiograph appearances show only consolidation (Yang et al., 1991) and will also confirm that the abscess abuts the pleura, enabling identification of a "window" for safe needle aspiration. Yang et al. (1991) described the use of ultrasound-guided aspiration in 35 patients. Pleural apposition was demonstrated in 71% of abscesses, and aspiration using an 18- or 20-gauge needle was well tolerated, with two self-resolving pneumothoraces as the only complications.

Patients with Lemierres disease usually develop a septic thrombophlebitis of the tonsillar and

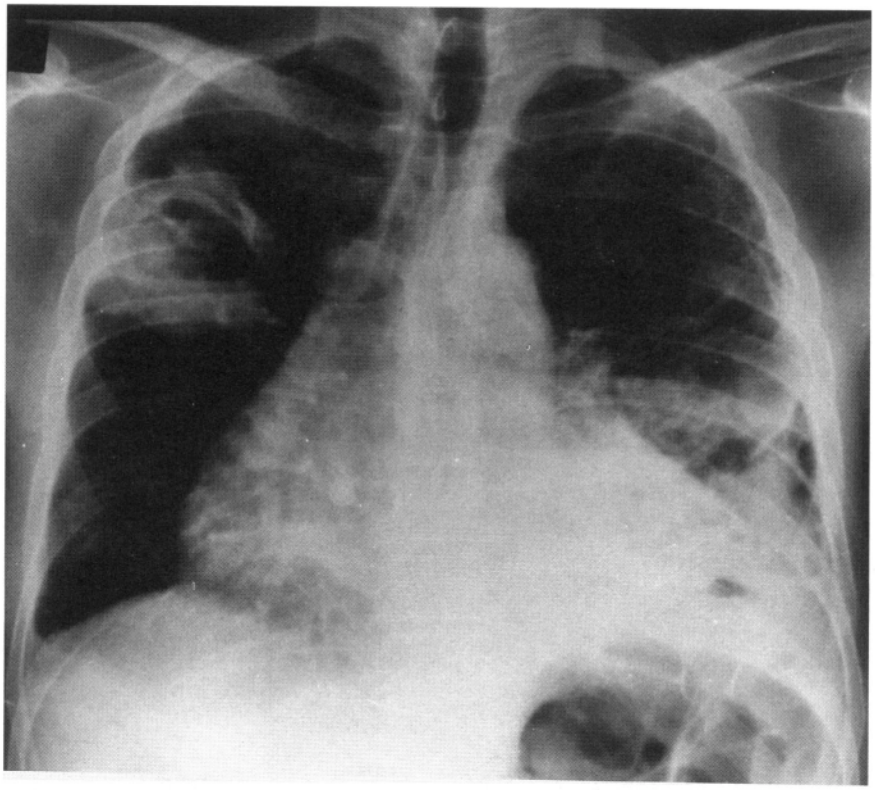

FIGURE 1. Chest radiograph showing cavitating abscess with air-fluid level and extensive parenchymal infiltrate in the right upper lobe, and necrotizing cavitating pneumonia and in the left lower lobe, with associated pleural fluid.

external jugular veins. Although this is easy to detect clinically by a tender palpable mass along the border of the sternocleidomastoid muscle, venous thrombosis may be confirmed on ultrasound (Currie et al., 1994; Moreno et al., 1989). It may be necessary occasionally to ligate the internal jugular vein to reduce septic embolization if thrombosis is confirmed by ultrasound.

Other Imaging

A small study by Saverymuttu et al. (1985) assessed the kinetics of granulocyte localization in patients with pneumonia and lung abscess. In lung abscess, there was an intense accumulation of labeled leukocytes at the pulmonary site, in contrast to no accumulation with pneumonia. The test is, however, unlikely to be helpful in the management of patients. Similarly, magnetic resonance imaging has not been assessed in patients with lung abscess and is unlikely to have any advantage over CT scanning.

Medical Therapy

The main determinants of successful treatment for lung abscess are appropriate antimicrobial drugs and the effective drainage of pus. The predisposing cause for abscess may be apparent after clinical history and examination, and this will enable a choice of antibiotics based on the likely pathogens involved.

Differential Diagnosis

A number of diseases and pathological processes may cause cavitation on the chest radiograph. It is important to consider these alternative diagnoses at all stages of management (Table 4). As

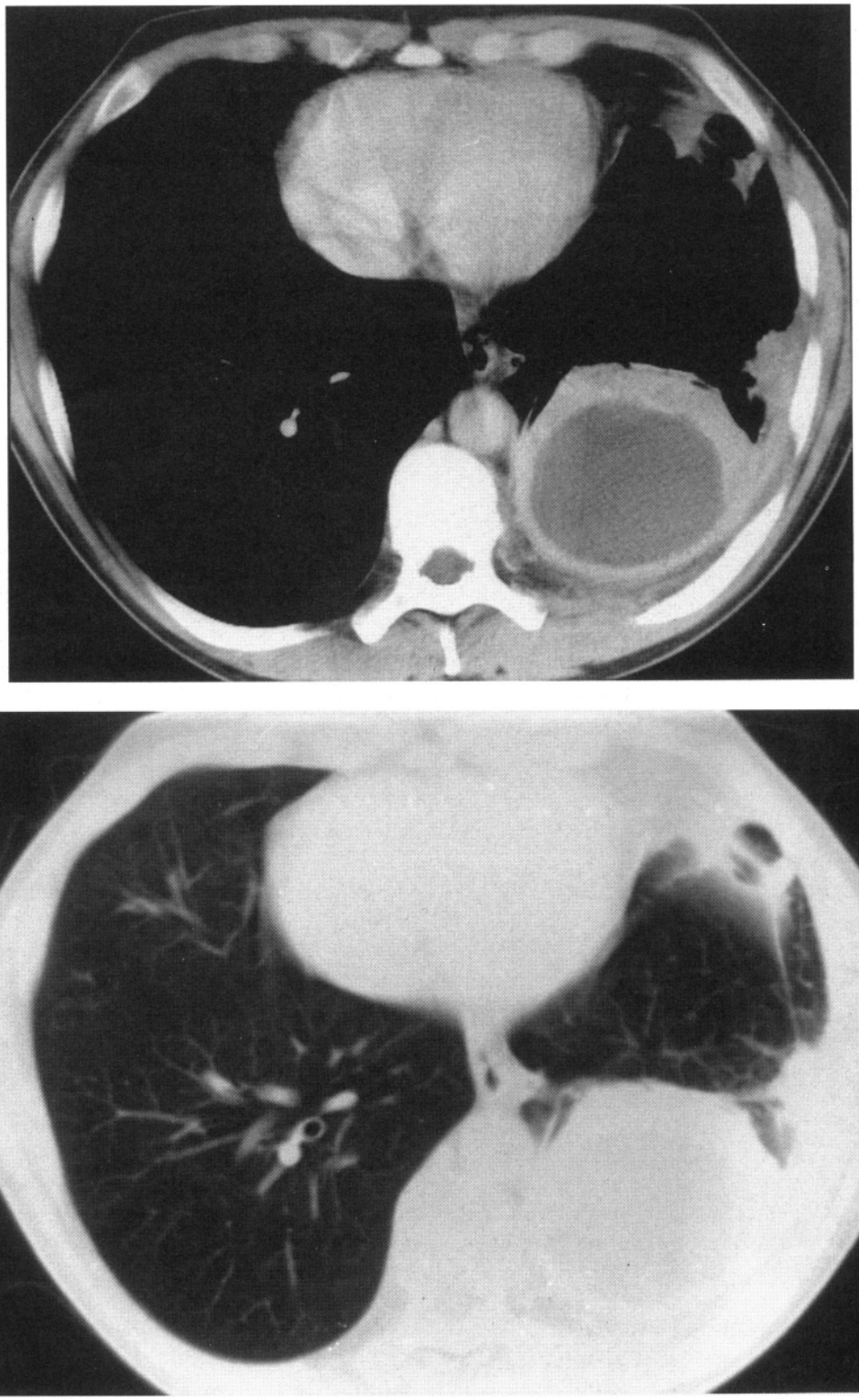

FIGURE 2. Lung abscess on CT scan: (a) thick-walled rim enhancing abscess in left lower lobe (mediastinal windows); (b) no significant compression of lung adjacent to the abscess (lung windows).

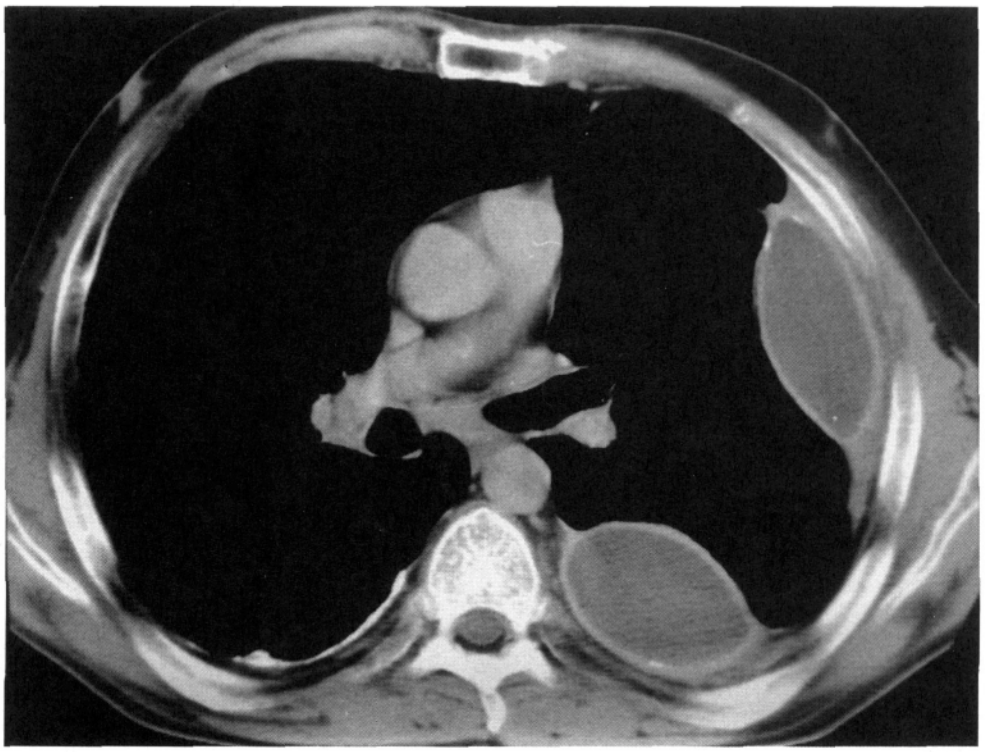

FIGURE 3. Empyema, loculated on CT (post-contrast) demonstrating "split pleura" sign, and increase in extrapleural fat attenuation. Note pleural calcification on the right due to asbestos pleural plaque.

discussed previously, the most significant, and often difficult, differential diagnosis is between a benign and malignant abscess. The clinical and radiological diagnoses are similar, and histological specimens are usually required to confirm malignancy.

The important infective causes for a cavitating lesion other than bacterial lung abscess include tuberculosis and fungal diseases, and these lesions may also be indistinguishable on clinical grounds. *Cryptococcus, Aspergillus, Blastomyces, Histoplasma,* and *Mucor* species typically lead to abscess formation. Mucormycosis particularly affects diabetic patients with severe metabolic acidosis and may have a rapidly fatal outcome if not promptly treated, often due to direct erosion into the pulmonary vasculature (Anonymous, 1987). *Nocardia asteroides* and *Actinomyces israelii* are rare causes of abscess, but are likely to be overlooked because they are difficult to confirm microbiologically. Both organisms are branching, gram-positive, weakly acid-fast anaerobic bacteria, and are difficult to culture after prior exposure to antibiotics.

Microbiological Diagnosis

Establishing a microbiological diagnosis is important and should be attempted before commencing empirical antibiotics when the clinical context allows it. Microbiological samples can be obtained from expectorated sputum, transtracheal aspirates, bronchoscopic lavage, protected brush specimens, or aspirates from percutaneous transthoracic needle aspiration, but all of these methods can potentially produce false-positive cultures from contamination at specimen collection. There are obvious risks and benefits associated with the more invasive tests such as transtracheal aspiration, and these need to be considered for individual cases.

The most satisfactory method of obtaining specimens with minimal possibility of contamination is by percutaneous aspiration (Pena Grinan et al., 1990; Irwin et al., 1981; Yang et al., 1991). The technique can be performed using fluoroscopy, ultrasound, or CT guidance. Pena Grinan et al. (1990) used a 22-gauge needle to aspirate 50 lung ab-

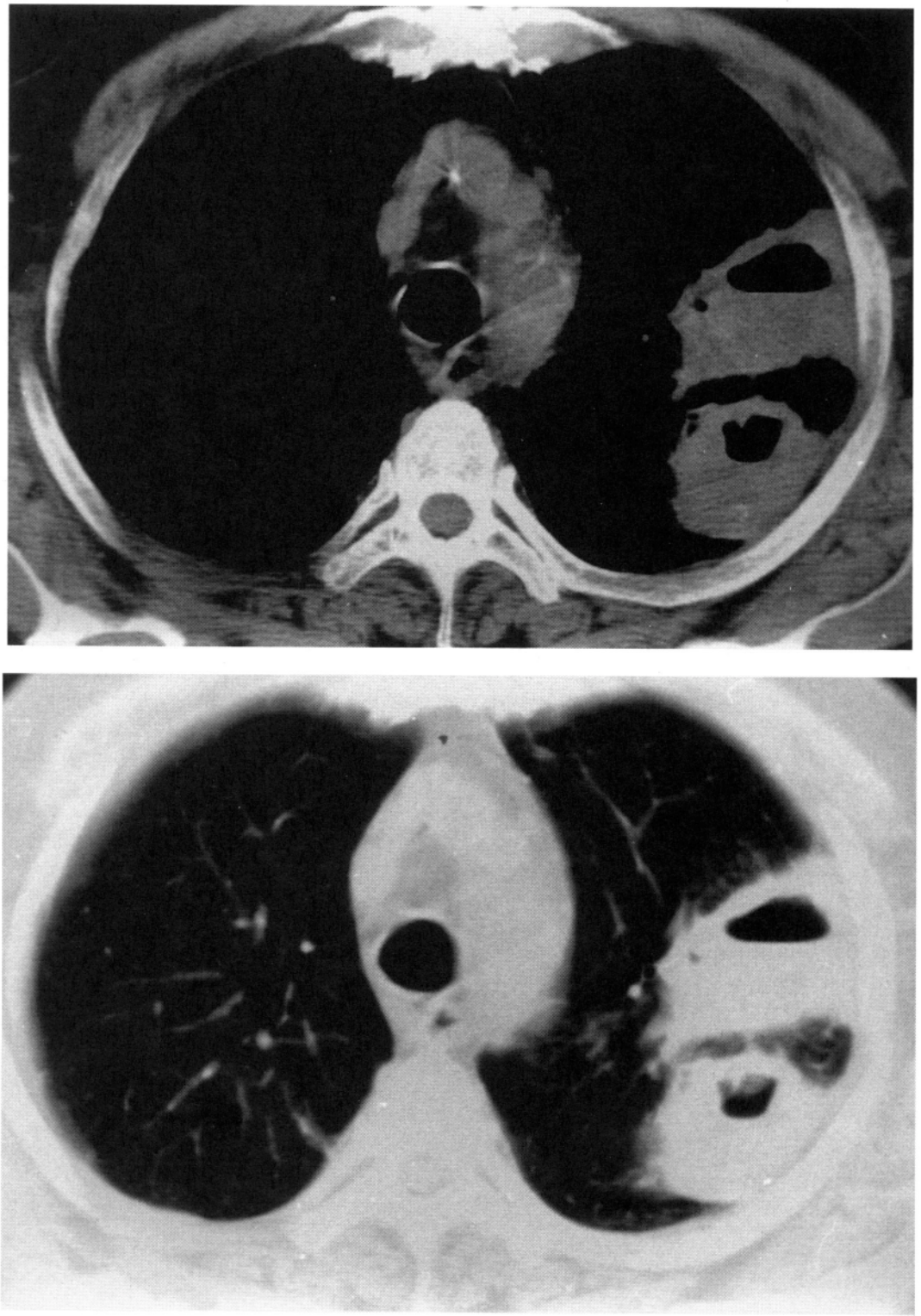

FIGURE 4. Multiple lung abscesses on CT: (a) mediastinal and (b) lung windows, in left upper lobe, demonstrating air-fluid levels, thick rim, and adjacent parenchymal infiltration.

TABLE 4. Differential Diagnosis of Lung Abscess

Cavitating carcinoma
Cavitary tuberculosis
Fungal disease
Aspergillus fumigatus
Cryptococcus neoformans
Blastomyces dermatitidis
Histoplasma capsulatum
Nocardiosis and actinomycosis
Wegener's granulomatosis
Infected pulmonary cyst or bulla
Pulmonary infarct
Rheumatoid nodule
Metastatic carcinoma
Pulmonary lymphoma
Chronic pulmonary sarcoidosis
Saccular bronchiectasis

scesses and obtained positive cultures from 82% of patients, which changed the antibiotic choice in 47% of those who were culture-positive. Despite its microbiological accuracy, needle aspiration has a significant complication rate. In this series, pneumothorax occurred in 7 (14%) cases. Other reports have confirmed similar complication rates with percutaneous aspiration (Chen et al., 1993; Irwin et al., 1981; Hammond et al., 1995). Percutaneous transthoracic needle aspiration has also been reported in a series of HIV-positive patients, who are at higher risk of pneumothoraces associated with *P. carinii* infection (Gruden et al., 1993). Complications, predominantly small pneumothoraces, occurred in 28% of patients; one major intrapleural hemorrhage requiring blood transfusion also occurred. Generally, complications from percutaneous abscess aspiration are minimal when the abscess has formed a lesion-pleura symphysis, and aspiration should be considered in all patients with a peripheral collection.

In a small and highly selected group of 10 patients with lung abscess, Irwin et al. (1981) compared the relative accuracy of expectorated sputum, wire-brushing under direct vision through a fiberoptic bronchoscope, transtracheal aspiration, and percutaneous needle lung aspiration. All patients underwent all four procedures, without complications. Using percutaneous aspiration as a standard cultural method, the investigators found that the next most sensitive method of sampling the lower respiratory tract was transtracheal aspiration, followed by bronchoscopic brushing and expectorated sputum. None of the techniques had 100% sensitivity. Transtracheal aspiration can yield both false-positive and negative results, primarily due to sampling above the carina, the small quantity of aspirate obtained, and the uneven distribution of organisms throughout the larger airways. Bronchoscopic sampling may be contaminated by organisms from the nose, mouth, or in the case of ventilated patients, the endotracheal tube, and excessive use of topical anesthetic agents such as lignocaine can have antibacterial properties (Bartlett, 1987).

The rapid transportation and processing of specimens is essential to increase the likelihood of obtaining positive microbiological cultures, particularly for anaerobic culture (Bartlett et al., 1974). Ideally, the time from specimen collection to incubation should not exceed 20 minutes.

Antibiotics

Antibiotic therapy is dictated by the type of abscess being treated, and usually must be initiated before definitive microbiology is available. It is usually aimed at covering gram-positive and gram-negative aerobes, as well as anaerobes (Table 5). Several studies (Tally et al., 1975; Eykyn, 1983; Perlino, 1981) have found a high failure rate with

TABLE 5. Antibiotics for Lung Abscess

Active against majority of aerobic and anaerobic organisms
Imipenem
β-lactam with β-lactamase inhibitor
Chloramphenicol
Cefoxtin
Third-generation cephalosporins
Antipseudomonal penicillins
Clindamycin
Active against most anaerobic organisms
Metronidazole (often used in combination with anti-aerobic antibiotics)
Unreliable or ineffective alone against anaerobic organisms
Aminoglycosides
Penicillins (other than antipseudomonal penicillins)
Macrolides
Quinolones
Aztreonam

metronidazole as anaerobic monotherapy, which was often corrected by the addition of a penicillin, confirming the importance of the aerobic component in lung abscess. The in vitro penicillin resistance of many anaerobes suggests β-lactamase-resistant drugs might be more effective, as up to 65% of *Bacteroides* and 41% of *Fusobacterium* species produce β-lactamase (Bartlett, 1991). However, older studies suggest that most lung abscesses may respond to penicillin alone, even when β-lactamase-producing anaerobes are present (Weiss, 1973; Bartlett, 1993), which casts doubt on the clinical relevance of in vitro sensitivity studies in these patients.

A small number of clinical trials have attempted to clarify the ideal in vivo antibiotic for lung abscess, but these studies are now outdated and do not include more modern antimicrobial agents. Until comparative studies are performed for the new generation of drugs, the results of in vitro susceptibility will be the main guide for clinicians to choose antibiotics. Two studies have compared penicillin and clindamycin (Levison et al., 1983; Gudiol et al., 1990). In both trials, patients were randomized to initial intravenous therapy, followed by an oral equivalent for 4 to 6 weeks. Both studies showed significant benefits with clindamycin with a combined failure rate of 45% in the penicillin groups, often due to β-lactamase-producing *Bacteroides* (Gudiol et al., 1990).

Four groups of drugs are active against the majority of significant anaerobic bacteria and are approved for the treatment of anaerobic infections. These drugs are the nitroimidazoles such as metronidazole, carbapenems such as imipenem, chloramphenicol, and combinations of β-lactam drugs with a β-lactamase inhibitor (Finegold & Wexler, 1996). Other drugs that have good anti-anaerobic activity, but are less active than the above four groups, include the cephamycin agent cefoxitin, the third-generation cephalosporins, clindamycin, and broad-spectrum antipseudomonal penicillins such as piperacillin (Finegold & Wexler, 1996). Drugs which have virtually no activity against anaerobes in vitro include aminoglycosides, quinolones [newer quinolones such as trouafloxacin and moxifloxacin do have activity against anaerobic bacteria], and the monobactam agent aztreonam (Bartlett, 1991). The aminoglycosides are also unsuitable for lung abscess therapy because of their poor efficacy in acidotic environments (Shohet et al., 1987; Hughes & Van Scoy, 1991). Many of these drugs will also have significant activity against the common aerobic and facultative organisms found in mixed infections. Viridans streptococci, including the common *S. milleri* group of organisms, are nearly always susceptible to penicillin (Jerng et al., 1997; Wong et al., 1995). In the recent series of community-acquired lung abscesses reported by Hammond et al. (1995), all aerobic and anaerobic isolates were susceptible to amoxicillin-clavulanate, chloramphenicol, or a combination of metronidazole and penicillin. For patients with nosocomial infection, imipenem is the drug of choice. Clearly, clinicians must maintain close contact with their microbiology service to obtain information about local resistance patterns.

Drainage

Spontaneous drainage is common in lung abscess and occurs early in the illness, with bronchial communication and the production of copious purulent sputum. Antibiotic therapy combined with postural drainage and physiotherapy will often lead to successful defervescence, but can be unsuccessful in some patients. Alternative approaches to drainage can be used including bronchoscopy, percutaneous drains, and surgery.

Interventional Therapy

The following sections discuss interventional methods for lung abscess drainage. However, it should be noted that the majority of lung abscess patients will recover with conservative therapy comprising antibiotics and internal abscess drainage alone. Since all these interventional techniques carry some risk of morbidity and mortality, their use should be limited to selected patients who do not improve with a conservative approach.

Bronchoscopy

Bronchoscopy, most commonly fiber-optic bronchoscopy (FOB), has been used to aid internal drainage of lung abscess. However, there are no randomized controlled data to allow thorough as-

sessment of the efficacy of this approach, and bronchoscopy is associated with morbidity and perhaps mortality in patients with lung abscess (Harber & Terry, 1981). Attempts to locate an abscess with FOB can be aided by using fluoroscopy, but commonly the affected bronchus is edematous and narrowed, making it impossible to enter and dilate the bronchus to promote drainage (Sosenko & Glassroth, 1985; Wallace et al., 1979; Hammond et al., 1995). In a study comparing malignant and infective abscesses, Wallace et al. (1979) found that FOB was not helpful in distinguishing tumor from the edema associated with infection, although excessive bronchial secretions are more common with nonmalignant abscesses. Occasionally, sudden and massive evacuation of an abscess can occur with FOB, and adequate suction capacity must be available to limit the aspiration of infective debris into the remaining lung (Harber & Terry, 1981; Alexander & Wolfe, 1980). Patients with large abscesses and incompetent airway reflexes are at higher risk for aspiration during FOB, and the procedure should be undertaken with the cautious use of sedative drugs, and with the abscess in a dependent position (Harber & Terry, 1981; Alexander & Wolfe, 1980).

Several observational reports have described the use of angiography catheters passed via the bronchoscope through the leading segmental bronchus and into the cavity (Connors et al., 1975; Estrera et al., 1980; Hagan & Hardy, 1983; Schmitt et al., 1988). The small-caliber (8–10 French) and semi-rigidity of angiography catheters makes it easier to penetrate inflamed bronchi, and placement in the cavity can be confirmed by fluoroscopy before aspiration. The procedure can be repeated if fluid reaccumulates within the cavity or alternatively, the catheter can be left in position after removing the bronchoscope, and irrigation performed regularly with suction until the cavity is <4 cm in diameter. During bronchoscopy, successful drainage may be aided by the use of local bronchodilating drugs such as ephedrine applied to the edematous bronchial opening (Connors et al., 1975). These techniques have only been reported in a small number of cases and their use cannot be routinely recommended, and careful patient selection is required when using these novel approaches.

Percutaneous Catheter Drainage

External drainage can be performed by a percutaneous catheter placed under radiological guidance (Vainrub et al., 1978; Rice et al., 1987; Parker et al., 1987; Yang et al., 1991; Ha et al., 1993; vanSonnenberg et al., 1991; Klein et al., 1995; Lambiase et al., 1992). The technique is best reserved for those with peripheral lung abscesses and where radiological imaging confirms pleural apposition. The largest series reported is by vanSonnenberg et al. (1991), who performed CT-guided drainage under local anesthesia in 19 patients with lung abscess. Indications for percutaneous drainage included persistent sepsis despite antibiotic therapy, physiotherapy, and in 11 cases attempted FOB drainage. In 17 of 19 cases, the catheter was placed without traversing aerated lung. There was one hemothorax in a patient whose abscess was approached via aerated lung, and two smaller catheters became blocked and were changed to 20 French catheters, but there were no pneumothoraces or episodes of pleural infection. Improvement in fever and leukocytosis was seen within 48 hours in most patients, and catheters were irrigated every 8 hours until the fluid became clear, remaining in place for an average of 9.8 days. Successful drainage was achieved in 16 (84%) patients, avoiding the need for surgery.

Catheters can be placed by either a trocar or Seldinger technique. The Seldinger technique is favored when traversing aerated lung to reach the abscess cavity (Klein et al., 1995) and although experience is limited, larger drains (at least 12 French) are less likely to become blocked and obstructed (Parker et al., 1987; vanSonnenberg et al., 1991). As with bronchoscopy, the abscess should be placed in a dependent position to avoid the aspiration of its contents into the other lung. Failure of percutaneous drainage is more likely if pus is loculated within the abscess cavity and when a thickened wall prevents collapse of the draining cavity (vanSonnenberg et al., 1991). If a lesion-to-pleura symphysis has not occurred prior to drain insertion, stay sutures can be placed on lung tissue after a small intercostal incision to avoid spillage of infected fluid into the pleural cavity (Weissberg, 1984). Contrast media can be injected through the catheter to determine the presence of bronchial

communications (vanSonnenberg et al., 1991), although these will usually heal without intervention (Rice et al., 1987).

Surgery

Prior to the use of antibiotics, surgery was considered the treatment of choice for lung abscess, and a number of patients underwent segmentectomy or lobectomy to remove suppurating lung. The incidence of surgery for lung abscess has now decreased significantly and in the survey of cases by Hagan and Hardy (1983), only 3.5% of cases were treated with surgery in the 1980s, compared to 10% in 1960. Surgery may still be necessary for those patients who do not respond to antimicrobial therapy and medical drainage, those with suspected malignancy, patients with severe hemorrhage, and those with recurrent disease.

The timing and type of surgery will depend on the presence of underlying comorbidity, the duration of antibiotic therapy, and local expertise. Surgical authorities recommend surgery for patients who are still toxic despite 6 to 8 weeks of organism-specific antibiotics (Estrera et al., 1980; Chidi & Mendelsohn, 1974) and in those with both empyema and lung abscess. Early surgery in neutropenic patients with acute leukemias may be life-saving (Rice et al., 1987), and intrapulmonary abscesses secondary to hematomas following gunshot wounds usually require resection (Rice et al., 1987). Lobectomy is less likely to lead to spillage of infected material or persistent air leaks into the pleural cavity than is a segmentectomy (Hagan & Hardy, 1983).

Complications

The most significant complication of lung abscess is hemorrhage, which may lead to significant morbidity and sometimes death. As the inflammatory process extends into the lung parenchyma, erosion of blood vessels inevitably occurs. This accounts for the streaky hemoptysis seen in 11% to 38% of patients (Thorns et al., 1970; Hagan & Hardy, 1983; Hammond et al., 1995; Nield et al., 1985; Estrera et al., 1980). Occasionally hemorrhage can be massive and life-threatening due to contralateral pulmonary obstruction and anoxia, as well as hypovolemic shock (Thorns et al., 1970). The quantity of evident bleeding is not a reliable indicator of the seriousness of the hemorrhage, and any significant hemoptysis should prompt the consideration of a surgical opinion. Other features associated with hemorrhage include a varying level in the cavity meniscus or emptying and refilling of the cavity on chest radiograph. Major hemorrhage is more common in dependent locations and will often cease spontaneously at least once, allowing the clinician time to plan further therapy. Careful positioning of the patient onto the dependent side and antitussive agents may prevent contamination of the contralateral lung. If proceeding to a surgical assessment, it is advisable to intubate the patient with a biluminal endotracheal tube (Thoms et al., 1970) before performing bronchoscopy to identify the bleeding source. It may be possible to control bleeding by inflating a balloon catheter in the bronchus before proceeding to thoracotomy. Alternatively, in patients who are unsuitable for anesthesia, pulmonary and bronchial artery angiography may identify the bleeding vessel, allowing embolization.

Erosion of an abscess into the pulmonary veins can result in embolic spread of infection, although with modern antibiotics, metastatic cerebral abscess is now uncommon. Patients may occasionally develop multiple systemic abscesses from the primary lung abscess (Andersen & McDonald, 1960). Generalized sepsis may occur due to spillage of infected material into the contralateral lung or pleural cavity; empyema and bronchopleural fistula are not infrequent complications of lung abscess; management of these conditions is discussed elsewhere.

Prognosis

Mortality rates of 10% to 29% are still reported in patients with lung abscess, but the survival rate is high for patients without underlying comorbid conditions (Hagan & Hardy, 1983; Pohlson et al., 1985; Andersen & McDonald, 1960; Chidi & Mendelsohn, 1974). Andersen and McDonald (I960) identified several unfavorable prognostic factors, in-

eluding increasing age (>50 years), presence of comorbidity, abscesses in the lower lobes, large cavities (>6 cm), and infection with *S. aureus.* Lung abscess itself usually contributes to the cause of death; death is rarely directly attributable to the primary abscess. In patients with HIV and abscess, a poorer prognosis is seen in women and those with infection from *Pseudomonas* species.

Summary

Lung abscess has become an uncommon disease in the modern antibiotic era. Despite this low incidence it is associated with a mortality rate of about 20%, and as with most septic disorders, mortality is most closely related to the presence of comorbidity. The diagnosis is usually made from cavitation on the chest radiograph, with the additional use of CT to aid location of the abscess, differentiate abscess from empyema, and assess complications and bronchial obstruction. Unlike pleural empyema, where interventional drainage is a mainstay of therapy, most lung abscesses respond to conservative medical therapy with antibiotics and postural drainage. Antibiotic therapy must cover both aerobic and anaerobic bacteria, including both penicillin-sensitive and resistant organisms. In the event of failure to respond to conservative treatment, bronchoscopic or percutaneous drainage may improve recovery.

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Nonresolving Pneumonia

DAVID OST, ANNA ROZENSHTEIN, AND ALAN FEIN

Introduction

Pneumonia that fails to respond to treatment is a common problem. Although quantification of the frequency of this problem is difficult, Feinsilver et al. (1990) reported that approximately 15% of pulmonary consultations and 8% of bronchoscopies were done to evaluate nonresolving pneumonia. In the intensive care unit (ICU) up to 90% of patients will have persistent radiographic infiltrates on chest x-ray (Augustine et al., 1992). Clinicians are confronted with a complex challenge when this occurs. First, it is difficult to define normal resolution, delayed resolution, and progression of disease. A specific pathogen cannot be identified in up to 50% of cases of community-acquired pneumonia (CAP), and two or more etiologies are identified in up to 5% of cases (Marston et al., 1997; British Thoracic Society, 1993; Fang et al., 1990; Marrie et al., 1989; Mundy et al., 1995). This leads to significant diagnostic uncertainty when patients fail to respond to empiric therapy. As a result, when pneumonia fails to respond to treatment, the question becomes whether or not the diagnosis of pneumonia is even correct, since many conditions can mimic pneumonia. It is therefore more precise to use the term nonresolving pneumonia syndrome when approaching these cases, since a nonresolving pneumonia may not even be infectious.

DAVID OST, ANNA ROZENSHTEIN, AND ALAN FEIN • Columbia University College of Physicians & Surgeons, St. Luke's–Roosevelt Hospital Center, New York, NY 10025.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

The first goal in evaluating nonresolving pneumonia is to discriminate between normal and nonresolving pneumonia in order to avoid unnecessary diagnostic tests. This requires a clear definition of what is normal and what is abnormal resolution. If abnormal resolution is identified, the next step is to consider the most common infectious and noninfectious factors associated with the nonresolving pneumonia syndrome. Finally, the utility of various tests in developing a diagnostic approach must be assessed.

Definitions

The difficulty in defining the nonresolving pneumonia syndrome is that the normal resolution of pneumonia is not a clearly defined process. Given this uncertainty, it is useful to consider the resolution of pneumonia as a spectrum, including normal resolution, slowly resolving pneumonia, and progressive pneumonia. The parameters used to describe this spectrum include both clinical and radiographic criteria.

Clinical criteria that have been studied include fever, cough, crackles, white blood cell count, PO_2 level, and C-reactive protein (Lehtomaki, 1988; Bartlett et al., 1998; American Thoracic Society, 1993). Subjective response is usually noted within 3 to 5 days of starting treatment (Bartlett et al., 1998). Most studies of resolution of pneumonia have not focused on symptoms, however, but instead on radiographic resolution (Lehtomaki, 1988; Marrie, 1992; Imboden et al., 1961; MacFarlane et al., 1984; Jay et al., 1975; Finnegan et al., 1981). Fein et al. (1991) defined this as at least 10 days of antibiotic therapy alone with "a radiographic infiltrate that

has not resolved in an expected period of time based on the presumptive diagnosis." Kirkland and Winterbauer (1991) defined slowly resolving pneumonia as less than 50% clearing at 4 weeks associated with clinical improvement on antibiotics. Most investigators have chosen an arbitrary definition of 1 month, but in all instances slowly resolving infections have been defined by the persistence of radiographic abnormalities in a clinically improved host (Lehtomaki, 1988; Imboden et al., 1961; MacFarlane et al., 1984; Jay et al., 1975; Finnegan et al., 1981; Kirkland & Winterbauer, 1991; Israel et al., 1956; Gleichman et al., 1949).

Although the ideal transition point for defining slowly resolving pneumonia varies, from a clinical standpoint the critical distinction lies in differentiating pneumonias that are progressive from those that are merely slow to resolve. The latter can be observed without further testing, whereas the former requires further investigation. The clinical decision that a patient has a nonresolving and progressive pneumonia must therefore take into account factors that affect the expected rate of resolution. These factors include comorbidities, age, severity, and type of infectious agent.

Comorbidities and Resolution of Community-Acquired Pneumonia

Pneumonia frequently occurs in patients with comorbidities or advanced age. The comorbidities most commonly associated with CAP that affect the rate of resolution include chronic obstructive pulmonary disease (COPD), alcoholism, diabetes mellitus, neurological disorders, ischemic heart disease, malignancy, renal failure, immunosuppression, and HIV infection (Fein et al., 1991; Israel et al., 1956; Marrie, 1990). While patients without comorbidities will usually demonstrate clearing of radiographic infiltrates by 4 weeks, only 20% to 30% of patients with these comorbidities will clear by 4 weeks (MacFarlane et al., 1984; Jay et al., 1975). The frequency of these comorbidities increases with age and thus concurrent comorbidities are more common in the elderly. For example, in patients less than 50 years of age, COPD is present in 5.7% of CAP cases. In patients older than 50 years, COPD is present in greater than 30% of CAP cases (Marrie, 1990).

Age and Resolution of Community-Acquired Pneumonia

Despite the concurrence of comorbidities and advanced age, several studies have demonstrated that age itself is an independent risk factor for delayed clearing (MacFarlane et al., 1984; Jay et al., 1975; Israel et al., 1956; Van Metre, 1954). Approximately 90% of patients younger than 50 years show radiographic resolution by 4 weeks (MacFarlane et al., 1984; Jay et al., 1975; Israel et al., 1956; Van Metre, 1954). However, Jay et al. (1975) demonstrated that only 30% of patients older than 50 years without concurrent disease had radiographic resolution by 4 weeks. Similarly, MacFarlane et al. (1984) found that even by 9 weeks only 50% of older patients had radiographic resolution. In a study of CAP by Israel et al. (1956), only one third of patients were over 50 years but this group accounted for two thirds of the cases of nonresolving pneumonia. Thus, age is among the most important factors associated with delayed resolution.

Severity and Resolution of Community-Acquired Pneumonia

Age is also associated with an increased risk for more severe pneumonia (American Thoracic Society, 1993; Research Committee of the British Thoracic Society, 1987; Zweig et al., 1990; Fine et al., 1990). However, severity of disease remains an independent risk factor for delayed resolution (Marrie et al., 1989; Research Committee of the British Thoracic Society, 1987; Fine et al., 1990). The time to radiographic resolution for severe CAP has been estimated at 10 weeks, compared with 3 to 4 weeks for mild to moderate pneumonia (Marrie, 1992). Indeed, definitions of normal resolution vary significantly in the literature, in part because of wide variations in the severity of illness triggering admission (McMahon et al., 1989; Roos et al., 1988; Wennberg et al., 1987). This has an impact on the expected "normal" rate of resolution, since severity of disease affects the rate of resolution (Marrie et al., 1989; Mundy et al., 1995; Marrie, 1992; Research Committee of the British Thoracic Society, 1987; Zweig et al., 1990; Sullivan et al., 1972; White et al., 1981).

Impact of Infectious Agents on Rate of Resolution

The rate of radiographic and clinical improvement also varies with the infectious agent. While a full review of each infectious agent associated with CAP is beyond the scope of this chapter, this section will focus on the features that are relevant to resolution of pneumonia with respect to the most common microorganisms. These include *Streptococcus pneumoniae, Legionella, Mycoplasma, Chlamydia pneumoniae,* and *Haemophilus influenzae.*

Streptococcus pneumoniae

Pneumococcal pneumonia accounts for up to 65% of CAP infections, and therefore accounts for most cases of infectious nonresolving pneumonia syndromes (Bartlett et al., 1998; American Thoracic Society, 1993; Marrie, 1990; Pennington, 1986). It is also the best studied of the infectious etiologies in terms of the rate of resolution and the factors that affect resolution. In normal individuals without predisposing illnesses, clinical improvement precedes radiographic improvement.

Clinical improvement is relatively rapid in uncomplicated cases. When auscultation was the primary tool for assessing response to therapy, clinicians were able to detect abnormal findings on physical examination in only 8% of patients at 1 month (Chatard, 1910; McRae, 1910; Lord, 1925). Similarly, Van Metre (1954) demonstrated that fever resolved rapidly, with only 6% of patients demonstrating fever beyond 20 days. Risk factors for delayed resolution of auscultatory findings and fever in this study included more severe presentation and multilobar disease.

In contrast, radiographic improvement is often much slower. Despite relatively rapid clinical improvement, approximately 20% to 30% of patients will have no improvement on chest radiograph at one week (MacFarlane et al., 1984). Initial worsening of the chest radiograph has also been frequently reported (MacFarlane et al., 1984; Jay et al., 1975; Graham & Bradley, 1978). Risk factors for delayed radiographic resolution include bacteremia, persistent fever or leukocytosis beyond 6 days, age greater than 50 years, COPD, and alcoholism (MacFarlane et al., 1984; Jay et al., 1975; Israel et al., 1956). Radiographic clearing occurs by 1 to 3 months in nonbacteremic cases and in 3 to 5 months for bacteremic cases (Fein et al., 1987). Residual radiographic abnormalities are rare in nonbacteremic cases but are present in up to 35% of bacteremic cases (MacFarlane et al., 1984; Jay et al., 1975; Israel et al., 1956; Fein et al., 1987). Importantly, bronchogenic carcinoma was not found to be a common cause of nonresolving pneumonia in any of these studies (Jay et al., 1975; Israel et al., 1956).

Legionella pneumophila

Legionella is increasingly recognized as an important pathogen in patients with severe CAP (Bartlett et al., 1998; American Thoracic Society, 1993; Marrie, 1990). Indeed, *Legionella* is one of the three most frequent etiologic agents that cause rapidly progressive pneumonias (Torres et al., 1991; VanEeden et al., 1988). It is frequently encountered in the compromised host and in the elderly, with the established risk factors for *Legionella* being cigarette use, alcoholism, age greater than 65 years, immunosuppression with corticosteroids, dialysis, and bone marrow transplantation (England et al., 1980; Gump & Keegan, 1986). Many of these predisposing conditions are likewise risk factors for delayed resolution, so it is not surprising that the rate of resolution for *Legionella* is slower than that of other organisms.

Ninety percent of *Legionella* infections are due to *Legionella pneumophila,* and 80% of these are due to serogroup 1 (Bartlett et al., 1998; American Thoracic Society, 1993; England et al., 1980; Gump & Keegan, 1986; Fang et al., 1989). Thus, most of the literature on the natural history of *Legionella* infections is based on this one serogroup. As in pneumococcal infections, clinical improvement precedes radiographic improvement. The radiographic infiltrates and clinical picture are usually indistinguishable from severe pneumococcal infections (Helms et al., 1979). There is usually an initial patchy infiltrate that subsequently becomes confluent and even bilateral, often despite appropriate antibiotic therapy (Dietrich et al., 1978; Edelstein & Meyer, 1984; Kroboth et al., 1983; Lo et al., 1983).

The distinguishing features of *Legionella* infections are the propensity for initial radiographic deterioration, the prolonged resolution of radio-

graphic infiltrates, and the prolonged convalescence associated with this infection. MacFarlane et al. (1984) noted radiographic deterioration in up to two thirds of patients with *Legionella,* compared with 4% of patients with nonbacteremic pneumococcal pneumonia. In addition, after this initial deterioration, resolution is slower than with pneumococcal infections. Radiographic clearing only begins after 2 to 3 weeks, with 50% of radiographs abnormal at 10 weeks (MacFarlane et al., 1984; Lo et al., 1983). Resolution may take as long as 6 to 12 months, with residual fibrosis evident in up to 25% of patients (Dietrich et al., 1978; Edelstein & Meyer, 1984). Even after radiographic resolution, generalized weakness and fatigue may persist for months. In the initial description of Legionnaires' disease in Philadelphia, patients frequently complained of fatigue and shortness of breath when surveyed up to 2 years after the event, with half demonstrating residual abnormalities on pulmonary function testing (Lattimer et al., 1979).

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of respiratory tract infections; however, it is a relatively rare cause of severe pneumonia (Foy et al., 1979). *M. pneumoniae* infection is generally less severe and occurs in a younger population, so it is not surprising that the rate of resolution is faster than with other types of pneumonia. Clinically apparent pneumonia occurs in only 3% to 13% of patients infected, with most patients being young adults (Cassell & Cole, 1981; Luz et al., 1984; Murray et al., 1975; Foy et al., 1971). *Mycoplasma* accounts for approximately 5% of hospitalized pneumonias, but is unusual in those older than 65 years (Marrie, 1993).

The initial radiographic pattern is one of interstitial infiltrates with progression to air space disease with consolidation. Multilobar involvement is common, occurring in 50% to 60% of cases (Finnegan et al., 1981). Radiographic deterioration on treatment is rare, occurring in less than 25% of cases (Fein et al., 1987). Acute respiratory distress syndrome (ARDS) is a rare complication of *Mycoplasma* pneumonia; in one series of hospitalized patients with *Mycoplasma* pneumonia, only seven of 64 patients (10.9%) required mechanical ventilation (Marrie, 1993).

In contrast to Legionnaires' disease, rapid resolution of *Mycoplasma* pneumonia is common (Marrie, 1992; Fein et al., 1987). There is usually a rapid clinical improvement that occurs in the first 2 weeks, in part reflecting the predominantly young population affected. Radiographic resolution may take anywhere from 2 weeks to 2 months (Fein et al., 1987). Shames et al. (1970) demonstrated an average duration of radiographic abnormalities of 1 to 2 weeks, depending on the use of antibiotics. Finnegan et al. (1981) and MacFarlane et al. (1984) found that 40% had complete radiographic resolution at 4 weeks and 90% at 8 weeks. Residual scarring and fibrosis were rare in both studies.

Chlamydia pneumoniae

C. pneumoniae infection is common, with 30% to 50% of young adults having serological evidence of infection (Grayston, 1992). Distinguishing features of *Chlamydia* infection include an increased frequency of hoarseness, lack of fever, and a prolonged period before seeking medical attention. Extrapulmonary manifestations include erythema nodosum, encephalitis, and Guillain-Barré syndrome.

The disease is relatively mild and mortality is rare, with prompt resolution common in younger patients. However, relapse is common when erythromycin is given for only 2 weeks, and it is therefore advisable to treat with either 3 weeks of erythromycin or 2 weeks of a tetracycline (Grayston, 1992). Radiographically, *Chlamydia* pneumonia is indistinguishable from other forms of pneumonia, with lobar and interstitial infiltrates being common. Initial radiographic deterioration is rare, with radiologic clearing requiring 1 to 3 months (Marrie, 1992; MacFarlane et al., 1984). In MacFarlane's (1984) series, resolution was intermediate between *Mycoplasma* and *Legionella.* Fifty percent of chest radiographs were normal by 4 weeks and up to 20% took longer than 9 weeks to clear (MacFarlane et al., 1984; Stengstrom et al., 1962). Residual radiographic scarring and fibrosis is seen in 10% to 20% of cases (Fein et al., 1987).

Haemophilus influenzae

Haemophilus influenzae has become an increasingly common cause of pneumonia and is now recognized as a common pathogen in the elderly, in hospitalized patients, and in cigarette smokers

(Niederman, 1998). Risk factors for severe infection include COPD, malignant disease, diabetes, alcoholism, and immunosuppression (Takala et al., 1990; Musher et al., 1983; Levin et al., 1977). In a surveillance study in Finland, 71% of cases occurred in patients who were severely immunocompromised, and 55% of invasive cases occurred in those over the age of 50 years (Takala et al., 1990). Invasive cases are more commonly caused by encapsulated strains, which are also associated with a higher risk for severe sepsis and mortality (Williams & Verghese, 1991; Fein et al., 1993). Unencapsulated strains are less frequently associated with mortality but are more often associated with a prolonged febrile tracheobronchitis (Williams & Verghese, 1991).

The clinical presentation of *Haemophilus* pneumonia is not unique and it is therefore impossible to reliably differentiate it from other pneumonias, particularly pneumococcal pneumonia (Niederman, 1998; Takala et al., 1990; Musher et al., 1983; Levin et al., 1977; Williams & Verghese, 1991; Fein et al., 1993). A multilobar pattern of bronchopneumonia with a pleural effusion is considered "classic" but this finding is by no means specific.

The natural history of *Haemophilus* infection has not been well studied and there are no distinguishing features regarding the rate of resolution. Based on its propensity to infect the immunocompromised and elderly, the rate of resolution can be expected to be slow. Clinical improvement is also slow, with many patients hospitalized for up to 2 to 3 weeks, with only half returning to their previous level of function by 6 weeks (Takala et al., 1990; Fein et al., 1993; Venkatesan et al., 1990). Similarly, radiographic resolution can be expected to be slow relative to other pneumonias.

Pneumonia of Unknown Etiology

Since half of all pneumonias will have no isolated pathogen, it becomes clear that the possible upper limit of normal resolution will be quite high (Marston et al., 1997; British Thoracic Society, 1993; Fang et al., 1990; Marrie et al., 1989; Mundy et al., 1995). Because *S. pneumoniae* and *L. pneumophila* are both common in severe CAP, the normal resolution time for severe CAP may be expected to range from 3 to 12 weeks. However, in many cases no pathogen will be identified.

Based on these studies, it is apparent that the normal time to resolution for severe CAP has a broad distribution curve, depending on a variety of factors. Many patients with a nonresolving pneumonia will actually be within the limits of normal resolution once these other factors are taken into consideration. Those patients with slow radiographic resolution but a good clinical response can be defined as having slowly resolving pneumonia. At some point in this spectrum, however, the patient crosses into the area of nonresolving pneumonia. Those patients with clinical deterioration under therapy can be defined as having progressive pneumonia. These two categories have significant overlap, but are useful clinical definitions, since patients with progressive disease are more likely to warrant additional diagnostic testing. Importantly, the term pneumonia in this situation does not necessarily equate with infection, since many patients with clinical deterioration may have a noninfectious disorder. Progressive disease in these cases may be due to factors associated with infectious or noninfectious etiologies.

Infectious Etiologies

If the initial diagnosis of an infectious etiology is correct, then factors that can lead to a progressive or nonresolving pneumonia need to be assessed. These factors include those associated with the pathogen, the host, or the therapy.

Pathogen Factors

Alternative or unusual pathogens need to be considered in the patient who fails to respond to treatment. Although there are a potentially unlimited number of "unusual" pathogens that may cause a nonresolving pneumonia, several warrant special attention. The most important are tuberculosis, fungi, *Nocardia* and *Actinomyces, Coxiella burnetii,* and *Pneumocystis carinii.* In addition, the possibility of a relatively "common" pathogen with resistance needs to be considered.

Tuberculosis

There has been an increase in the incidence of tuberculosis recently, and in certain populations tuberculosis remains a significant concern (Ameri-

can Thoracic Society, 1994; Centers for Disease Control, 1990a). In particular, the suspicion of tuberculosis should be particularly high in immigrant populations, those with a history of intravenous drug abuse, and in patients with AIDS (Block et al., 1989; Centers for Disease Control, 1990b). In addition, the elderly should also be considered at higher risk for tuberculosis, since the elderly still represent one of the largest repositories of tuberculosis in the United States. Most infections in the elderly will represent reactivation disease, since the majority were infected 50 to 70 years ago. However, recent studies of epidemic spread in nursing homes indicate that new infections are also possible, so a high index of suspicion is necessary (American Thoracic Society, 1994; Centers for Disease Control, 1990a; Creditor et al., 1988).

The clinical presentation of tuberculosis as a cause of nonresolving pneumonia will often be "atypical," especially in the elderly. Nine out of ten cases of unsuspected tuberculosis in a community teaching hospital occurred in elderly patients (Counsell et al., 1989). In a review of 93 patients over the age of 60 years, Morris found atypical findings such as nonspecific mid- or lower-lobe changes to be common (Morris, 1989). Similarly, Kahn et al. (1977) found that one third of adult patients with newly diagnosed tuberculosis had "atypical" findings, irrespective of age. Thus, the classic presentation of a cavitary infiltrate in the apical or posterior segments of one or both upper lobes may not always be present.

In this setting, the diagnosis of tuberculosis may be difficult. Tuberculin testing may be negative in 10% to 20% of patients with active disease, and in an even higher percentage of the elderly and patients with AIDS (American Thoracic Society, 1994; Kent & Schwartz, 1967). A two-step tuberculin test should be considered in the elderly to overcome this waning of delayed hypersensitivity. Sputum acid-fast cultures are positive in up to 80% of cases, but sputum is not always easy to obtain, especially in the elderly (American Thoracic Society, 1994; Katz et al., 1987). Because culture results may take up to 6 weeks, newer methods, including the BAC-TEC system, are recommended to decrease the time needed to establish a diagnosis (Ellner et al., 1988). Polymerase chain reaction testing has been approved for smear-positive specimens to allow confirmation of tuberculous disease, but its role in smear-negative patients remains to be determined (Chin et al., 1995; Brisson-Noel et al., 1991).

Fungi

Both opportunistic as well as endemic fungi mimic bacterial pneumonia. Of the opportunistic fungi, *Aspergillus* is the most important. The spectrum of pulmonary *Aspergillus* infections includes benign mycetomas, chronic necrotizing aspergillosis, and invasive pulmonary aspergillosis. Of these various forms, it is the chronic necrotizing and invasive forms of disease that are most likely to be mistaken for bacterial pneumonia.

Chronic necrotizing aspergillosis represents a semi-invasive form of infection and is most commonly seen in patients with preexisting chronic lung disease, often in the setting of chronic corticosteroid use (Binder et al., 1982). It may also be seen at the interface of a mycetoma and the normal lung. From a pathophysiologic standpoint, this syndrome represents the result of a host immune response that is barely able to hold the infection in check but not strong enough to eradicate it. The radiographic appearance is usually chronic and progressive, affecting the upper lobes more frequently.

Invasive aspergillosis is classically described as affecting neutropenic patients taking multiple antibiotics for several days. However, it is important to realize that aspergillosis is being increasingly recognized in two new groups of patients. The first group is older patients with chronic lung disease who are taking corticosteroids. In these cases *Aspergillus* may mimic a bacterial infection, leading to significant delays in therapy. In one series, patients with invasive aspergillosis were treated an average of 18 days with multiple antibiotics before the diagnosis was made. In many of these cases the diagnosis was only established post mortem (Rodriguez et al., 1992).

The second new group at risk for *Aspergillus* infection is the AIDS population. Patients with advanced AIDS are at increased risk for invasive aspergillosis (Miller et al., 1994; Denning et al., 1991). In addition, patients with less advanced HIV infection may develop one of three different patterns of tracheobronchitis that may mimic nonresolving

pneumonia. These three patterns are obstructive bronchial aspergillosis, ulcerative tracheobronchitis, and pseudomembranous tracheobronchitis. Obstructive bronchial disease is characterized by thick mucous plugs filled with *Aspergillus* in the airways, with little mucosal involvement (Denning et al., 1991). Ulcerative tracheobronchitis is characterized by additional mucosal and cartilaginous involvement (Kemper et al., 1993). Pseudomembranous tracheobronchitis develops when there is extensive inflammation and invasion of the tracheobronchial tree with formation of a pseudomembrane of hyphae and necrotic debris (Pervex et al., 1985). Thus, in addition to the traditional neutropenic patient, the diagnosis of *Aspergillus* as a cause of nonresolving pneumonia should be considered in elderly immunocompromised patients and in patients with advanced AIDS.

The other major group of fungal infections that need to be considered as a cause of nonresolving pneumonia are the endemic fungi. The endemic fungi share many common clinical characteristics, but the most important element in establishing the diagnosis is a careful history, since each fungus can be found in certain geographic areas. *Histoplasrrui capsulatum* can be found in the Mississippi River valley, *Coccidioides immitis* in the southwestern United States, and *Blastomyces dermatitidis* in the Southeast and Midwest. In the case of both histoplasmosis and coccidioidomycosis, most inhabitants of these areas will have immunologic evidence of prior exposure (Davies & Sarosi, 1987). These fungi can cause a nonspecific acute febrile illness, which is usually self-limited and may easily be confused with CAP.

The more difficult cases involve those patients who develop chronic and progressive disease, which involves the upper lobes and may be cavitary, often leading to a misdiagnosis of tuberculosis (Goodwin et al., 1981). Although blastomycosis is classically described as mass-like and coccidioidomycosis is described as producing thin-walled cavities, none of these fungi can be reliably distinguished on the basis of their chest radiograph findings.

In general, when the chest radiograph suggests tuberculosis but smears are negative for acid-fast organisms, these fungal infections should be considered. In addition, patients with HIV infection are at particularly high risk of disseminated infection with both histoplasmosis and coccidioidomycosis, so early consideration of these possibilities is essential in this group (Wheat et al., 1990; Sarosi & Johnson, 1992; Ampel et al., 1993; Grossman et al., 1970).

A combination of potassium hydroxide smear and culture of sputum may make the diagnosis. Serology is generally not useful for histoplasmosis and blastomycosis. IgM antibodies for coccidioidomycosis may be clinically useful, and tilers typically rise in the first 2 weeks, disappearing by 1 month (Davies & Sarosi, 1987). Skin testing is available for histoplasmosis but is not useful since active infection cannot be distinguished from prior exposure and 90% of inhabitants in an endemic area can be expected to lest positive (Davies & Sarosi, 1987; Goodwin el al., 1981).

Nocardia and Actinomyces

Although *Nocardia* and *Actinomyces* are classified as higher-order bacteria, both behave in a manner more consistent with the pulmonary mycoses. Both result in a chronic pulmonary disease that is difficult to diagnose because of the difficulty in isolating these pathogens. *Nocardia* can only be grown aerobically if cultures are kept and examined for up to 4 weeks, whereas *Actinomyces* requires strict anaerobic conditions with enriched media. Both are gram-positive organisms with branching filamentous pseudohyphae. *Nocardia* frequently stains positive on acid–fast smear, but *Actinomyces* is rarely positive. Because these organisms have relatively specific culture requirements and are difficult to stain, communication with the microbiology laboratory is essential when there is clinical suspicion of either disease.

Patients with *Nocardia* present with a subacute or chronic syndrome, including cough, purulent sputum, and night sweats. Infection frequenlty occurs in the setting of underlying malignancy or pulmonary alveolar proteinosis. Disseminated infection may occur, with the most serious consequence being central nervous system involvement with brain abscess. The most common radiographic presentation is that of a localized alveolar infiltrate that is usually homogenous, nonsegmental, and often cavilary (Grossman el al., 1970). Actinomycosis has similar clinical and radiographic features, but

tends to extend across fissures and to involve the chest wall.

Coxiella burnetii (Q Fever)

Coxiella burnetii, also known as Q fever, is a zoonosis, with infected cattle, goats, sheep, and cats as its primary reservoirs (Babudieri, 1959). Infection occurs when *C. burnetii* is aerosolized at the time of parturition (Marrie et al., 1988). Most infections are self-limited febrile illnesses, with pneumonia, hepatitis, and endocarditis being rare complications (Sawyer et al., 1987).

The pneumonia caused by Q fever is generally mild but rarely may present as a rapidly progressive pneumonia that is refractory to antibiotics. Cases may be part of an outbreak or may occur sporadically. In cases involving exposure to animals or during a recognized outbreak there is usually little diagnostic difficulty. Sporadic cases are much more difficult to diagnose. Signs and symptoms that should raise the suspicion of Q fever include mild to moderate pneumonia with a nonproductive cough associated with a severe headache. Radiographic findings include pleural based opacities, single or multiple rounded opacities, atelectasis, and hilar adenopathy. The mean time to radiographic resolution is 30 days with a range from 10 to 70 days (Gordon et al., 1984; Millar, 1978). Mortality is very uncommon with Q fever.

Pneumocystis carinii

P. carinii pneumonia (PCP) is most likely to occur as a nonresolving pneumonia in the setting of unrecognized HIV infection, chronic steroid use, chemotherapy, or bone marrow transplantation. The course of PCP infection is less acute and the mortality lower in HIV-positive patients than in HIV-negative patients. Patients with HIV have a longer duration of symptoms (28 days vs. 5 days), lower respiratory rate (23.4 vs. 30), and higher PO_2 (69 vs. 52) (Kovacs et al., 1984). In a study by Gerrard (1995), the mortality rate among HIV-positive patients was 8% versus 32% among HIV-negative patients. Among HIV-negative patients infection develops almost exclusively in the setting of combined corticosteroid and immunosuppressive therapy. Notably, in Gerrard's (1995) series, all cases of HIV-negative PCP occurred within 6 months of the initiation of immunosuppressive therapy, indicating that the risk for PCP infection may be higher shortly after initiation of immunosuppression. In this study, PCP occurred in 12% of patients with Wegener's granulomatosis, 6% of patients with renal transplants, and 4% of liver transplants.

The radiographic findings associated with PCP are quite varied. The characteristic pattern of perihilar interstitial infiltrates is seen in two thirds of patients, but up to 10% will have normal chest radiographs (Katz et al., 1991). There is usually progression to widespread air space disease over a 2- to 5-day period. Other unusual but not uncommon findings include unilateral focal infiltrates, nodules, mediastinal and hilar adenopathy, and pleural effusions. Thin-walled cysts are observed in 10% of patients and therefore pneumothorax may be a complication of recurrent infections. In patients who have undergone prior pentamidine prophylaxis, the radiographic findings can be expected to be atypical, with up to 40% demonstrating upper lobe disease. This is in contrast to a rate of 7% for patients not taking pentamidine (Coblentz, 1992).

Resistant Pathogens

An important consideration in the approach to any pneumonia is the possibility of antibiotic resistance. In particular, the possibility of penicillin-resistant *S. pneumoniae* (PRSP) must be considered when evaluating patients with nonresolving pneumonia. PRSP was first described in the 1960s in Australia and New Guinea. In recent surveys from Europe, approximately 40% to 60% of pneumococci demonstrate intermediate or high-level resistance (Linares et al., 1992; Marton, 1992). In the United States resistance rates are lower but are rising, mimicking the trends seen previously in Europe. Among isolates of invasive pneumococcal disease, 25% to 35% of cases currently demonstrate penicillin resistance (Hofmann et al., 1995).

The clinical impact of penicillin resistance on immediate mortality is unclear. Bacteremia occurs in 15% to 30% of patients with pneumococcal pneumonia and carries a mortality of 36% to 43% (Afessa et al., 1995). This mortality is unaffected by antibiotic administration in the first 5 days. Thus, risk factors at presentation and other comorbidities may

outweigh antibiotic resistance as predictors of early mortality. Studies from Spain demonstrated no significant difference in mortality between patients infected with resistant or sensitive strains of pneumococci (Pallares et al., 1995). Penicillin was equivalent to other therapies as long as the minimum inhibitory concentration (MIC) was 2 μg/mL or less. Other retrospective studies have demonstrated a higher mortality in bacteremic patients with PRSP but this was in association with other risk factors known to affect prognosis (Pallares et al., 1987).

In patients with nonresolving pneumonia who have by definition survived the initial 5 days, it is reasonable to investigate the possibility of drug resistance as a contributing factor. The suspicion of PRSP should be especially high in cases of nonresolving pneumonia associated with risk factors for drug resistance. The risk factors for infection with PRSP include prior β-lactam therapy within 6 months, pneumonia within 1 year, hospitalization in the prior 3 months, and nosocomial infection (Bedos et al., 1996; Moreno et al., 1995; Nava et al., 1994). Of these factors, the most significant in both univariate and multivariate analyses is prior β-lactam use.

Once a PRSP is either suspected or isolated, it becomes important to determine the level of penicillin resistance and the sensitivity pattern of the organism. The majority of PRSP strains have intermediate resistance to penicillin, defined as an MIC >0.1 and <2.0 μg/mL. In the setting of intermediate resistance to penicillin, increasing the dose of penicillin to 12 to 18 million units per day is effective. Isolates with an MIC >2 μ/mL are defined as having high-level resistance, and these cases should be treated with agents other than penicillin based on their susceptibility testing.

Alternative agents include cefotaxime, ceftriaxone, imipenem, macrolides, newer fluoroquinolones, and vancomycin. Importantly, sensitivity patterns for cephalosporins do not necessarily follow penicillin susceptibility patterns. Pneumococcal isolates that have intermediate resistance to penicillin may have high-level resistance to cephalosporins (Jacobs, 1992; John, 1994). Therefore, sensitivity to cephalosporins and imipenem should be confirmed in cases of PRSP. Similarly, since macrolide resistance is less prevalent, these drugs may be useful alternatives but their use still requires confirmation of sensitivity. If erythromycin resistance is demonstrated, then clarithromycin, azithromycin, and clindamycin should not be used, since there is significant cross-resistance. Newer fluoroquinolones, such as trovofloxacin and levofloxacin, have demonstrated excellent activity against PRSP and may be considered in cases of PRSP. Finally, vancomycin is the most reliable treatment for PRSP since resistance to vancomycin has not yet been demonstrated.

Host Factors

The effect of various host factors, including comorbidities such as alcoholism, diabetes, COPD, and age on the normal rate of resolution of pneumonia has been discussed above. Most host factors cannot be altered and therefore do not necessarily directly affect treatment. However, certain disorders of immune function warrant special attention because the underlying defect can be at least partially treated if recognized. These include AIDS and syndromes associated with deficiencies of humoral immunity.

AIDS

With the experience gained from the HIV epidemic, most physicians are aware of PCP as a cause of respiratory compromise in the HIV-infected patient. Indeed, PCP was among the most common diseases associated with AIDS, being the initial manifestation in approximately two thirds of cases in older series (Centers for Disease Control, 1989). With the use of widespread prophylaxis, the dominance of PCP among the pulmonary pathogens associated with HIV has decreased, but it remains an important consideration (Martin et al., 1992). Bacterial pneumonia is now the most common initial lower respiratory tract infection in AIDS patients (Wallace et al., 1993); therefore, it is important to consider the possibility of HIV infection in patients with nonresolving pneumonia. If the diagnosis of unrecognized HIV is made, the spectrum of possible pathogens changes dramatically. Indeed, the Infectious Disease Society of America (Centers for Disease Control, 1989) recommends routine testing for HIV infection in patients between the ages of 15 and 54 with CAP that occurs in hospitals where the

rate of newly diagnosed HIV infection exceeds one case per 1000 discharges. Conditions that are much more likely in this setting and that need to be considered in these cases include cryptococcal pneumonia, endemic fungal infection, tuberculosis, and PCP.

Primary Humoral Immune Deficiencies

Primary humoral immune deficiencies are due to inherited defects in antibody production. While there are many diseases associated with secondary disorders of humoral or cellular immunity, the importance of identifying primary humoral immune deficiency syndromes lies in the fact that treatment with intravenous immune globulin has an effect on the incidence and resolution of pneumonia. The disorders most commonly associated with hypogammaglobulinemia in which intravenous immune globulin (IVIG) is indicated include X-linked agammaglobulinemia, common variable immune deficiency (CVID), selective IgG subset deficiency, and hypogammaglobulinemia with hyperimmunoglobulin M.

All these disorders are characterized by defects in the production of immunoglobulins, from intrinsic defects within the B cell to problems with B cell/T cell interactions. The resulting deficiencies in immunoglobulin production lead to impaired opsonization and complement activation. Thus, patients with relative or absolute hypogammaglobulinemia are prone to recurrent and refractory sinopulmonary tract infections with encapsulated organisms leading to nonresolving pneumonias. Infections typically begin in infancy or early childhood so that most cases are recognized by the time patients reach adulthood. Importantly, certain disorders, most notably CVID and IgG subclass deficiency, may present in an atypical manner at a later age. The most common pathogens in these patients include 5. *pneumoniae* and *H. influenzae,* with *Mycoplasma* and *P. carinii* being less common.

Monthly IVIG maintenance therapy markedly reduces the incidence and severity of pneumonia in these patients (Skull & Kemp, 1996; Buckley & Schiff, 1991; World Health Organization, 1982). Currently, protocols require maintenance infusions every 2 to 4 weeks to maintain a trough level greater than 400 mg/dL (Buckley & Schiff, 1991). When patients with primary humoral immune deficiencies develop pneumonia, additional supplemental IVIG is warranted for treatment of the acute disease and facilitates resolution and decreases severity.

Another situation in which humoral immunity is commonly compromised is chronic lymphocytic leukemia (CLL). Progressive hypogammaglobulinemia is common in CLL, and results in an increased incidence of respiratory tract infections. IVIG has been demonstrated to decrease the incidence of these infections by nearly 50% (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, 1988). However, some investigators have questioned the utility of IVIG in this setting based on its high cost. It has been estimated that IVIG in CLL results in a gain of 0.8 quality-adjusted days per patient per year at a cost of $6 million per quality-adjusted life-year gained (Weeks et al., 1991). Thus, the routine maintenance use of IVIG in CLL is probably not warranted. However, in an individual patient with CLL with nonresolving pneumonia and hypogammaglobulinemia, IVIG should be considered.

Therapy-Related Factors

When pneumonia fails to respond appropriately to treatment, certain aspects related to therapy need to be considered, including possible medication errors as well as the concentrations of antibiotics used.

With respect to medication errors, it is especially important to carefully check dosing schedules, compliance, and when appropriate, drug levels. If intermediate-level resistant PRSP is present, higher doses of penicillin will be required as previously discussed. Similarly, if PCP is suspected, higher doses of trimethoprim–sulfamethoxazole will be required. When aminoglycosides are used it is important to check levels and adjust the dosing regimen accordingly. Similarly, as renal function changes, drug doses may similarly require readjustment. In addition, aminoglycosides do not penetrate the lung well so it may be necessary to aim for higher peak concentrations when using a traditional dosing regimen, especially when treating pseudomonal pneumonia. The effect of decreased pulmonary penetration on aminoglycoside efficacy using a once-daily dosing regimen has not yet been studied for pneumonia.

It is also important to ensure that adequate levels of drug are reaching the site of infection by ruling out sequestered foci of infection. The two main forms of sequestered foci that may prevent adequate resolution of pneumonia are empyemas and lung abscesses. Empyema evaluation can be facilitated by a variety of imaging techniques, including chest CT and ultrasound. In the patient with nonresolving pneumonia, demonstration of any significant amount of pleural fluid should lead to consideration of a diagnostic thoracentesis to rule out empyema. Although the exact criteria for defining an empyema remains controversial, in the setting of a nonresolving or progressive pneumonia it is prudent to aggressively evaluate all effusions for possible chest tube drainage. A pH less than 7.20, positive gram stain, positive culture, or demonstration of grossly purulent fluid should prompt chest tube placement.

Pulmonary abscesses can also lead to nonresolving pneumonia. Predisposing factors that should raise the suspicion of abscess formation include alcoholism, seizures, poor oral hygiene, and previous aspiration. Chest x-ray typically will demonstrate an air-fluid level but chest CT is more sensitive and can confirm the diagnosis in difficult cases. Because most patients with lung abscesses do well with only conservative management and a prolonged course of antibiotics, it is important to identify those factors associated with increased abscess-related mortality that may warrant a more aggressive approach. Factors that adversely affect the prognosis in patients with lung abscess include increased age, pediatric age, large cavity size, longer duration of symptoms prior to therapy, lower lobe location, multiple abscesses, and association with malignant disease (Perlman et al., 1969; Sosenko & Glassroth, 1985; Wallace et al., 1979; Harber & Terry, 1981). The importance of intrabronchial aspiration as a contributing factor in fatal cases of lung abscess has also been emphasized in several reports (Harber & Terry, 1981). This has led several investigators to recommend controlled drainage and improved physical measures to avoid intrabronchial spread. Thus, although routine drainage is not necessary in all patients, it should be considered in those at high risk and in those with nonresolving pneumonia drainage.

A variety of techniques have been used to drain abscesses. These include bronchoscopic aspiration, CT-guided aspiration, and ultrasound-guided aspiration. However, some attempts at bronchoscopic aspiration have actually led to intrabronchial aspiration and ARDS (Harber & Terry, 1981). Thus, if bronchoscopic aspiration is considered, it should probably be limited to carefully selected patients in whom all other methods of drainage are not possible. When bronchoscopy is done for either diagnostic or treatment purposes, there should be minimal use of depressant drugs and careful use of lidocaine to minimize the risk of intrabronchial spread.

Noninfectious Etiologies

Many noninfectious diseases may mimic pneumonia by presenting pulmonary infiltrates. The major categories of disease that warrant consideration as mimics of pneumonia include neoplastic, immunologic, drug-induced, and vascular diseases.

Neoplastic Diseases

Neoplasms may cause a nonresolving pneumonia syndrome either by causing a postobstructive pneumonia or abscess or by appearing as infiltrative processes with air bronchograms. Neoplasms that cause postobstructive pneumonias and abscesses are most commonly bronchogenic carcinomas. Those that present as alveolar infiltrates include lymphoma and bronchoalveolar cell carcinoma.

Postobstructive Pneumonias

In cases of postobstructive pneumonia, the tumor occludes the bronchi either by endobronchial involvement or extrinsic compression. Bronchoscopy remains the method of choice for detecting endobronchial obstruction, since it allows for the simultaneous collection of biopsy and cytology specimens that are >95% sensitive and specific for endobronchial malignancies. However, the overall frequency of endobronchial carcinoma as a cause of nonresolving pneumonia is surprisingly low, ranging from 0% to 8% (Feinsilver et al., 1990; Israel et al., 1956; Gleichman et al., 1949). Despite this low prevalence, the relatively low risk associated with bronchoscopy makes it an appropriate considera-

tion in those at especially high risk for lung cancer (e.g., cigarette smokers older than 50 years).

Carcinomatous Lung Abscess

It has been recognized for many years that a significant proportion of lung abscesses are associated with bronchogenic carcinomas, so-called carcinomatous lung abscesses (Perlman et al., 1969; Sosenko & Glassroth, 1985; Wallace et al., 1979). The reported incidence of carcinoma in this setting is high, ranging from 7.6% to 17.5% (Sosenko & Glassroth, 1985; Wallace et al., 1979). The identification of this subset of nonresolving pneumonias is particularly important, since identification of concurrent carcinoma may allow for curative resections and since carcinomatous lung abscess is associated with greater mortality than is simple lung abscess. Unfortunately, distinguishing carcinomatous from simple abscesses can be difficult.

Although a number of radiographic findings have been described as being suggestive of carcinomatous abscess, such as mural nodules and ipsilateral hilar node enlargement, none of these radiographic criteria have been demonstrated to clearly distinguish between carcinomatous and simple lung abscesses. Indeed, when Wallace et al. (1979) applied radiographic criteria to cases of lung abscess, the diagnostic accuracy was only 70%, with a 16% false-negative rate and a 14% false-positive rate. Radiographic location is also not helpful, since lobes that are classic for aspiration (i.e., posterior segments of the upper lobes or superior segments of the lower lobes) account for 50% to 60% of carcinomatous abscesses. The exception to this is the rare occurrence of an anterior segment abscess, which strongly suggests the possibility of carcinoma (Sosenko & Glassroth, 1985; Wallace et al., 1979).

Direct visual findings at the time of bronchoscopy are similarly not helpful in identifying most cases of carcinomatous lung abscess, with only 15% to 21% of cases demonstrating an endobronchial lesion (Perlman et al., 1969; Sosenko & Glassroth, 1985; Wallace et al., 1979). The most common finding is nonspecific inflammation and edema of the affected bronchus. Although bronchoscopy in the setting of lung abscess can be associated with significant risk, cytology and transbronchial biopsy have diagnostic yields as high as 80% (Wallace et al., 1979). Thus, the best test to identify carcinomatous abscess remains bronchoscopically obtained cytology and transbronchial biopsy samples. Given the risk of bronchoscopy in this setting, it is advisable to attempt bronchoscopy only in those patients with carcinomatous lung abscesses and to avoid bronchoscopy in those with simple abscesses.

Clinical features associated with carcinoma abscess include older age, rapid onset, lack of systemic symptoms, no predisposition to aspiration, lower white blood cell count, lower oral temperature, and less extensive infiltrates on chest radiograph. Patients with three or more of these factors can be considered at high risk for carcinoma, and bronchoscopic examination should be considered (Sosenko & Glassroth, 1985). Similarly, those with mediastinal or hilar adenopathy or very limited infiltrates surrounding the abscess should also be considered for bronchoscopy. Patients without any of these risk factors, especially if they are less than 45 years of age and are nonsmokers, are at relatively low risk for carcinoma and can be managed conservatively unless healing is delayed or the course is otherwise atypical of anaerobic infection (Sosenko & Glassroth, 1985).

Bronchoalveolar Cell Carcinoma

Bronchoalveolar cell carcinoma is traditionally characterized as a subtype of adenocarcinoma of the lung that is slow-growing and frequently associated with the small peripheral airways and alveolar spaces. It may present as a focal alveolar infiltrate, often with air bronchograms, mimicking the radiographic appearance of pneumonia. Consolidation occurs in up to one third of cases, involving both segmental and lobar areas (Ludington et al., 1972). Other radiographic appearances include pulmonary nodules and diffuse or multicentric alveolar infiltrates. The nodular form has a good prognosis, whereas the resectable diffuse and multicentric forms have a worse prognosis (Dumont et al., 1998).

Lymphoma

Lymphoma in the lung may present as focal alveolar infiltrates with air bronchograms, mimicking the radiographic appearance of pneumonia. When lymphoma affects the lung parenchyma, it

may occur either as part of a systemic disease or as a true primary pulmonary lymphoma. Lymphoma rarely presents with radiographic evidence of pulmonary parenchymal involvement; only 10% of Hodgkin's and 4% of non-Hodgkin's lymphomas present with initial parenchymal pulmonary involvement (Berkman & Breuer, 1993). However, in both cases, as the disease progresses, lung involvement becomes progressively more common, rising to 38% of Hodgkin's and 24% of non-Hodgkin's cases (Berkman & Breuer, 1993). If pulmonary Hodgkin's lymphoma is suspected, CT scan of the chest may be especially useful, since mediastinal lymphadenopathy is almost invariably present. Importantly, in cases of non-Hodgkin's lymphoma as well as Hodgkin's disease associated with HIV, mediastinal lymphadenopathy may be absent in up to 50% of cases (Berkman & Breuer, 1993; White & Matthay, 1989). Confirming the diagnosis of pulmonary lymphoma requires an adequate core of tissue for histologic examination; thus, percutaneous fine-needle aspirates are frequently nondiagnostic. Similarly, bronchoscopy with transbronchial biopsy may provide the diagnosis but only if an adequate sample size can be obtained. In this setting, immunophenotyping, immunoelectrophoresis, and analysis of monoclonal markers may be of diagnostic benefit when traditional light microscopy is not definitive (Oka et al., 1988; Schwaiger et al., 1991). If these tests are still nondiagnostic, open-lung biopsy may be required to establish the diagnosis.

Immunologic Diseases

Many immunologic diseases can be associated with some pulmonary manifestations, but this discussion will be limited to diseases that present with an acute onset, have frequent pulmonary manifestations, and present with few extrapulmonary symptoms. These include systemic vasculitis, bronchiolitis obliterans organizing pneumonia, the eosinophilic pneumonia syndromes, acute interstitial pneumonia, pulmonary alveolar proteinosis, and sarcoid.

Systemic Vasculitis

Fever, dyspnea, and pulmonary infiltrates may be the initial manifestation of systemic vasculitis or a connective tissue disorder and may be easily mistaken for CAP. In most patients, extrapulmonary symptoms will be prominent and a prior history of vasculitis will be present. However, when extrapulmonary symptoms are lacking, differentiating pulmonary vasculitis from severe CAP may be difficult. Furthermore, patients with a previously established diagnosis of vasculitis are frequently on immunosuppressive therapy for their vasculitis and are therefore prone to opportunistic infections. Distinguishing a nonresolving infectious process from worsening vasculitis can be especially difficult in these immunocompromised patients.

While many types of vasculitis have varying degrees of pulmonary involvement, this discussion will focus only on those that have a propensity to involve the lung and that may mimic CAP. These include Wegener's granulomatosis and the alveolar hemorrhage syndromes.

Wegener´s Granulomatosis. Wegener's granulomatosis (WG) is a form of small- and medium-vessel granulomatous vasculitis that primarily involves the upper and lower respiratory tracts and kidneys. Other organ systems that may be involved include the joints, eyes, skin, nervous system, and heart. Less commonly involved are the gastrointestinal tract, subglottic area, trachea, thyroid, and liver (Hoffman et al., 1992). The "limited" form of WG accounts for up to 25% of cases and is characterized by isolated upper respiratory tract and lung involvement (Hoffman et al., 1992; Duna et al., 1995). WG typically occurs in middle-aged men, but it has been noted in all age groups.

Upper respiratory tract involvement is the most common manifestation, and pulmonary symptoms are rare in the absence of upper respiratory tract symptoms. A history of recurrent upper respiratory tract problems should raise the possibility of WG when evaluating patients with a nonresolving pneumonia syndrome. Common upper respiratory tract manifestations of WG include sinusitis, rhinorrhea, purulent nasal discharge, oral and nasal ulcers, and otitis (Hoffman et al., 1992).

Extrapulmonary manifestations may be especially useful in distinguishing WG from an infectious etiology of nonresolving CAP. The most common extrapulmonary manifestations include segmental necrotizing glomerulonephritis, ocular involvement with uveitis, joint manifestations with arthralgias and arthritis, central or peripheral nervous

system involvement, and cardiac involvement. Skin involvement may be evident as well, including palpable purpura, ulcers, vesicles, papules, or subcutaneous nodules (Hoffman et al., 1992). Importantly, many or all of these extrapulmonary findings may be absent in the limited form of WG.

Lower respiratory tract manifestations of WG are nonspecific and include cough, hemoptysis, dyspnea, and pleuritic pain. Pulmonary function is also nonspecific and may demonstrate either a restrictive or obstructive pattern. Chest radiographic findings are variable, including nodules, diffuse hazy infiltrates, alveolar infiltrates, and pleural opacities (Cordier et al., 1990; Buschman et al., 1990). The nodules encountered in WG may be either well circumscribed or hazy, and up to one half will be cavitary. Nodules range in size from several millimeters up to several centimeters.

Laboratory findings are generally nonspecific in WG and include leukocytosis, thrombocytosis, anemia, and an elevated sedimentation rate, any of which can be seen in other causes of nonresolving pneumonia. The most useful diagnostic laboratory test in differentiating WG from infectious causes of nonresolving pneumonia is the antineutrophil cytoplasmic antibody (ANCA) test (Kallenberg et al., 1994). WG is now classified as one of the ANCA-associated vasculitides. There are two main forms of ANCA, cytoplasmic or c-ANCA and perinuclear or p-ANCA. Most patients with WG have the c-ANCA form, which is directed against a serine proteinase. Ninety percent of patients with active WG with both renal and pulmonary involvement will be ANCA-positive (Duna et al., 1995; Kallenberg et al., 1994). However, in patients with limited WG without glomerulonephritis, or in inactive disease, the sensitivity of c-ANCA decreases to 65% (Rao et al., 1995). Similarly, false-positive tests do occur, most notably with microscopic polyarteritis, polyangiitis overlap syndrome, idiopathic crescenteric glomerulonephritis, Churg-Strauss syndrome, or classic polyarteritis nodosa (Kallenberg et al., 1992). Thus, it remains controversial whether the diagnosis of WG can be established with just an abnormal radiograph, the clinical history, and a positive ANCA. Some clinicians advocate treating in these instances even without histologic confirmation. Since the disorders most likely to cause a false-positive ANCA are generally treated with immunosuppressive regimens similar to that for WG, this is often a reasonable option. However, when concurrent infection is a concern, tissue biopsy becomes imperative.

Alveolar Hemorrhage Syndromes. The syndrome of diffuse alveolar hemorrhage (DAH) may be a manifestation of a wide variety of diseases, including Goodpasture's syndrome, connective tissue disorders, systemic vasculitis, drug toxicity, coagulopathy, mitral stenosis, and a variety of pulmonary infections. The clinical presentation of alveolar hemorrhage is relatively similar irrespective of the cause and includes fever, dyspnea, and alveolar infiltrates that are easily mistaken for pneumonia. Differentiating DAH from infectious etiologies of nonresolving pneumonia is critical because the treatment for many of the syndromes associated with DAH includes immunosuppressive agents. This discussion will focus on those features of DAH that distinguish it from other causes of nonresolving pneumonia and the etiologies of DAH that are most likely to mimic pneumonia.

DAH may present at any age because of the wide variety of diseases that lead to the syndrome. The typical onset is fairly rapid, with cough, fever, and dyspnea being common but nonspecific symptoms. Physical examination and routine laboratory tests are nonspecific and reflect the extrapulmonary manifestations of the underlying cause of the DAH. Respiratory distress may be severe, leading to rapid deterioration and the need for mechanical ventilation. Hemoptysis is common but is not necessarily massive and is absent in up to one third of patients, so careful attention to the serum hemoglobin level is important. A rapidly falling hemoglobin in the absence of gastrointestinal bleeding with diffuse pulmonary infiltrates should raise the possibility of DAH. When hemoptysis is not obvious, bronchoscopy with sequential bronchoalveolar lavage (BAL) will demonstrate progressively hemorrhagic fluid characteristic of DAH. This finding is not specific for any particular etiology of DAH and is seen irrespective of the cause of DAH.

Radiographic findings are nonspecific, with patchy bilateral alveolar infiltrates being the most common finding. If the patient has had previous

episodes of DAH an interstitial infiltrate secondary to pulmonary fibrosis may also be present. Similarly, chest CT scan is usually nonspecific, often reflecting the underlying disease associated with the DAH.

After the presence of DAH is established, it is imperative to establish the specific underlying cause. A careful history and physical along with some specific serologic tests will rule out most causes of DAH, including drug use, exposure to cytotoxic agents, bone marrow transplantation, and vasculitis or collagen vascular disease. In most cases, extrapulmonary manifestations of disease will be present to help in establishing the diagnosis. This is particularly helpful in differentiating DAH from infectious causes of nonresolving pneumonia.

However, in some cases the clinician will only be able to rule out drug exposures, environmental factors, coagulopathy, and neoplasms, and there will be no extrapulmonary findings to help guide the diagnostic evaluation. These cases are most likely to be mistaken for pneumonia because of the paucity of extrapulmonary manifestations. In these cases, in the absence of other systemic findings, there are four causes of DAH that need to be considered. These include p-ANCA-associated vasculitis, isolated pulmonary vasculitis without associated antibodies, anti-glomerular basement membrane disease, and idiopathic pulmonary hemosiderosis.

p-ANCA-associated vasculitis and isolated pulmonary vasculitis are truly forms of pulmonary capillaritis (Mark & Ramirez, 1985; Leatherman, 1988; Travis et al., 1990). Both syndromes are distinct from the usual classification of vasculitis syndromes. Indeed, follow-up evaluation of isolated pulmonary capillaritis indicates no evidence of subsequent systemic disease. Both are treated similar to WG, with cytoxan and corticosteroids.

Anti-glomerular basement membrane disease (anti-GBM), or Goodpasture's syndrome, is distinct from these two forms of pulmonary capillaritis and represents the classic form of immune-mediated pulmonary injury. Patients with Goodpasture's syndrome usually present with concurrent renal involvement, but isolated lung injury can occur without renal disease (Tobler et al., 1991). In these cases, in contrast to typical anti-GBM disease, circulating anti-GBM antibodies are often absent. The only way to establish the correct diagnosis in these cases of limited Goodpasture's syndrome is to demonstrate linear immunofluorescence in lung tissue.

Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) is characterized by the proliferation of granulation tissue in the respiratory bronchioles and alveolar ducts associated with chronic inflammation in the adjacent alveoli (Cordier, 1993). BOOP may occur in association with a variety of other disorders, in which case it is a secondary form of BOOP. It may also occur in an isolated form, idiopathic BOOP, also referred to as cryptogenic organizing pneumonia. This discussion will focus on the idiopathic form of BOOP, emphasizing those points that help to distinguish it from other mimics of pneumonia.

BOOP typically occurs in the fifth or sixth decade of life, with men and women equally affected. The onset is typically subacute, with 75% of patients having symptoms for less than 2 months at the time of diagnosis (Cordier, 1993; Cordier et al., 1989). The typical presentation of BOOP begins with a flu-like illness mimicking CAP, with fever, malaise, fatigue, dyspnea, and dry cough. Rales are common and are present in approximately 75% of patients, but wheezes are rare as is clubbing (Cordier et al., 1989). Laboratory tests are nonspecific, with an elevated sedimentation rate and leukocytosis the most common findings.

The chest radiograph demonstrates bilateral, diffuse alveolar infiltrates, often with a peripheral distribution. Up to half of all patients will have recurrent or migratory infiltrates. Linear, interstitial, and cavitary lesions are rare, as are pleural effusions and pleural thickening. The CT scan typically reveals patchy, alveolar infiltrates with consolidation, ground-glass changes, and bronchial wall thickening (Cordier et al., 1989; Muller et al., 1990).

The diagnosis of BOOP requires demonstration of the characteristic histologic pattern in the absence of other concurrent disease. Transbronchial biopsy is often insufficient to establish this diagnosis, since the histologic features of BOOP

can be seen with a variety of other disorders. Therefore, open-lung biopsy remains the gold standard tor diagnosing BOOP.

Eosinophilic Pneumonia Syndromes

The common pathologic feature of the eosinophilic pneumonia syndromes is the collection of eosinophils in the interstitial and alveolar spaces. Other pathologic findings that may be present to varying degrees include lymphocytic interstitial pneumonia, bronchiolitis obliterans organizing pneumonia, and usual interstitial pneumonia. The hypereosinophilic syndrome as well as allergic angiitis and granulomatosis (Churg-Strauss syndrome) both belong to this category of disease. However, both of these rare disorders have prominent extrapulmonary symptoms that serve to differentiate them from infectious pneumonia. Only two diseases within this category are rapidly progressive and limited to the pulmonary system such that they are frequently mistaken for CAP. These are chronic eosinophilic pneumonia and acute eosinophilic pneumonia.

Chronic Eosinophilic Pneumonia. The term "chronic eosinophilic pneumonia" (CEP) was first used by Carrington et al. (1969) to describe a syndrome of concurrent blood eosinophilia and pulmonary eosinophilic infiltrates. CEP may often present as a fulminant illness with cough, fever, dyspnea, weight loss, wheezing, night sweats, and radiographic infiltrates (Jederlinic et al., 1988). With this constellation of findings, it is frequently mistaken for CAP.

CEP occurs most commonly in middle-aged adults, although it can occur at any age. Women are affected twice as often as men. Atopy is common, occurring in up to 50% of patients. Asthma or asthmatic symptoms occur in 30% to 50% of patients, and are usually of recent onset (Jederlinic et al., 1988; Allen & Davis, 1994). The onset is insidious and the course variable, with symptoms present for weeks prior to the time of diagnosis. Peripheral blood eosinophilia is present in more than 80% of patients and may be very severe. Other nonspecific laboratory abnormalities include an elevated sedimentation rate and IgE levels, thrombocytosis, and iron deficiency anemia.

The chest radiograph demonstrates patchy, nonsegmental, alveolar infiltrates that tend to spare the central and basilar regions, resulting in a pattern termed the "photographic negative of pulmonary edema" (Gaensler & Carrington, 1977). CT scan sometimes better delineates this peripheral pattern of disease, but the pattern is not pathognomonic and is not always present (Ebara et al., 1994). However, this photonegative pulmonary edema pattern is sufficiently rare that its presence should at least prompt consideration of the diagnosis of CEP. Other radiographic patterns that can be seen in CEP include diffuse bilateral infiltrates and lobar consolidation.

The diagnosis of CEP is usually suspected on clinical grounds based on the chest x-ray pattern, blood eosinophilia, and clinical history. However, tissue is still necessary to confirm the diagnosis. The distinctive feature of CEP is elevated BAL eosinophilia, typically in the 20% to 70% range (Allen & Davis, 1994). Transbronchial biopsy usually demonstrates interstitial and alveolar eosinophils and histiocytes. Multinucleated giant cells with a granulomatous component may be present as well. The sensitivity of BAL eosinophilia and transbronchial lung biopsy is such that open-lung biopsy is rarely needed to establish the diagnosis.

Less than 10% of patients will improve without treatment (Allen & Davis, 1994; Yoshida et al., 1994; Naughton et al., 1993). Corticosteroids are the mainstay of therapy, with complete remission being the rule. Radiographic and clinical improvement can be expected within 2 to 3 days, and radiographic resolution by 3 weeks. Lack of a prompt response to corticosteroids should prompt reevaluation and consideration of alternative diagnoses. Relapse occurs in up to 80% of cases after either cessation or tapering of steroids (Jederlinic et al., 1988). Thus, corticosteroids often have to be continued for prolonged periods after the initial treatment period.

Acute Eosinophilic Pneumonia. Acute eosinophilic pneumonia (AEP) as a cause of acute respiratory failure was first described by Badesch et al. (1989). Although it is characterized by eosinophilic infiltration of the lung parenchyma similar to that seen in CEP, the two syndromes seem to be distinct clinical entities.

AEP occurs most commonly from the ages of

20 to 40 years, although it can occur at any age. Men are affected twice as often as women. There is no relationship to smoking, and unlike CEP, most patients do not give a history of asthma or atopy (Badesch et al., 1989; Allen et al., 1989). In contrast to CEP, the onset of AEP is rapid, usually manifesting in less than 7 days. AEP typically presents with the onset of fever, nonproductive cough, dyspnea, and pleuritic chest pain. Constitutional symptoms are common, including malaise, myalgias, and night sweats. The most common findings on physical examination are fever, tachypnea, occasional rhonchi, and bibasilar crackles. Laboratory findings are similarly nonspecific. The peripheral eosinophil count usually becomes markedly elevated during the course of disease, but may be normal at presentation (Umeki & Soejima, 1992). Erythrocyte sedimentation rate and IgE levels are also elevated in the majority of patients but are nonspecific (Umeki & Soejima, 1992; Pope-Harman et al., 1996).

Early in AEP, the chest radiograph may only show subtle reticular or ground-glass infiltrates. High-resolution CT is more sensitive, demonstrating progressive, bilateral, patchy, ground-glass infiltrates, often located along the bronchovascular bundles. As the disease progresses, bilateral diffuse alveolar and reticular changes are seen (Umeki & Soejima, 1992; Pope-Harman et al., 1996). Unlike CEP, the infiltrates are not localized to the periphery. Small effusions occur in up to two thirds of patients and are frequently bilateral. If a thoracentesis is done, these effusions typically demonstrate a high pH with marked eosinophilia (Allen & Davis, 1994).

The distinctive feature of AEP is the markedly elevated number of eosinophils in the BAL fluid. Typically >25% of BAL cells are eosinophils, along with an increased proportion of BAL lymphocytes and neutrophils (Allen & Davis, 1994; Umeki & Soejima, 1992; Pope-Harman et al., 1996). Transbronchial biopsy usually demonstrates extensive eosinophilic parenchymal involvement, frequent diffuse alveolar damage, an organizing fibrinous exudate, hyaline membranes, type II cell hyperplasia, and the absence of granulomas or hemorrhage. As with CEP, open-lung biopsy is rarely necessary to establish the diagnosis, given the good sensitivity of BAL and transbronchial biopsy.

The diagnosis of AEP is a diagnosis of exclusion. In addition to BAL eosinophilia and biopsy evidence of eosinophilic parenchymal infiltrates, other known causes of eosinophilic pneumonia syndromes should be ruled out. These include drug reactions, asthma, and infections (Allen & Davis, 1994). In addition, the diagnosis is in part established by the rapid and complete response to treatment, which consists of corticosteroids. Response to corticosteroids is frequently dramatic, occurring within 48 hours, and failure to respond should prompt the consideration of alternative diagnoses. In contrast to CEP, there should be no further episodes of relapse during long-term follow-up.

Acute Interstitial Pneumonia

Acute interstitial pneumonia (AIP) is a rare, idiopathic form of diffuse alveolar damage. Hamman and Rich (1935) classified it with idiopathic pulmonary fibrosis. However, it is now recognized that AIP is separate and distinct from idiopathic pulmonary fibrosis and probably corresponds to a subset of idiopathic ARDS.

AIP typically occurs in young healthy adults. There are no known risk factors and both sexes are affected equally. The median age is 43 years (range, 7–83 years). AIP typically presents after a prodromal period of up to 14 days with the abrupt onset of fever, cough, and dyspnea (Olson et al., 1990). Chest radiographs usually demonstrate bilateral air space disease. CT scan of the chest typically reveals patchy or diffuse areas of ground-glass attenuation (Primack et al., 1993). The disease is similar to ARDS but unlike ARDS there are none of the usual risk factors such as sepsis, shock, trauma, or pneumonitis. Unlike idiopathic pulmonary fibrosis, the onset and progression of the disease is very rapid. Most patients develop hypoxic respiratory failure, and mechanical ventilation is often required. Mortality is high, ranging from 60% to 100% in several series, with an average of approximately 70%. It is unclear whether or not corticosteroids are beneficial in AIP, although most clinicians would favor a trial of corticosteroids once infectious etiologies have been ruled out (Olson et al., 1990).

The distinguishing features of AIP are the clinical syndrome of idiopathic ARDS without risk factors and pathologic evidence of diffuse alveolar damage. Thus, AIP requires an open or thoraco-

scopic lung biopsy to confirm the diagnosis. The most common findings on biopsy are diffuse alveolar damage, including alveolar-septal thickening, inflammatory cellular infiltration, type II cell hyperplasia, collapse of adjacent alveoli, and hyaline membranes (Katzenstein et al., 1986). These features of diffuse alveolar damage are nonspecific and other diagnoses must be ruled out.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP), also known as pulmonary alveolar phospholipoproteinosis, is a rare diffuse lung disease characterized by the abnormal accumulation of lipoproteinaceous fluid in the distal air spaces (Wang et al., 1997; Prakash et al., 1987). PAP probably represents a histopathologic syndrome caused by multiple etiologies. Histopathologic findings similar to PAP can be found in cases of silicoproteinosis, aluminum dust exposure, titanium exposure, hematologic malignancies, immunosuppressive disorders, and opportunistic infections. However, despite these associations, the majority of cases of PAP are not associated with any of these risk factors and fall into the category of idiopathic PAP.

Tests that can help differentiate PAP from other causes of nonresolving pneumonia include chest radiography, high-resolution CT, serum surfactant proteins, BAL fluid analysis, and either open-lung biopsy or transbronchial biopsy. Chest radiographs typically demonstrate nonspecific central alveolar opacities in the mid- and lower-lung zones with marked sparing of the areas adjacent to the diaphragm and heart. High-resolution CT will often reveal a ground-glass appearance with thickening of the intralobular and interlobular septa in a pattern of polygonal shapes, frequently referred to as a "crazy paving" appearance. Elevated serum levels of surfactant proteins A and D have been demonstrated in PAP (Honda et al., 1993, 1995; Kuroki et al., 1993). These are not specific to PAP and can also be found in idiopathic pulmonary fibrosis. While none of these findings are diagnostic of PAP, they should raise the suspicion of PAP and can narrow the diagnostic possibilities.

BAL, transbronchial biopsy, or open biopsy can make the diagnosis. BAL demonstrates characteristic findings of PAP, including milky appearing, periodic acid-Schiff (PAS)-positive fluid, macrophages filled with PAS-positive material, and acellular eosinophilic granules. Transbronchial biopsy is distinctive for preserved alveolar architecture with minimal thickening of the septa and scant inflammatory infiltrates. Terminal bronchioles and alveoli are flooded with a PAS-positive lipoproteinaceous fluid consisting of phospholipids.

In contrast to many of the other noninfectious mimics of pneumonia, there is no role for immunosuppressive agents or corticosteroids in PAP. The most effective treatment is whole lung lavage (Hoffman et al., 1989). Indeed, PAP may exist with concurrent infections and predisposes patients to superinfections with *Nocardia*, opportunistic fungi, and mycobacteria. It is therefore critical to rule out concurrent infection, and corticosteroids should be avoided since there have been reports that they may increase mortality.

Sarcoidosis

Sarcoidosis is a chronic granulomatous disease of unknown etiology that affects multiple organ systems, most frequently the lungs, skin, and eyes. Because sarcoidosis usually has extrapulmonary organ system involvement, it is rarely confused with other causes of nonresolving pneumonias. Evidence of extrapulmonary disease that should raise the suspicion of sarcoidosis includes extrathoracic lymphadenopathy, skin lesions such as erythema nodosum, lupus pernio, or sarcoid plaques, and uveitis. Clinically significant extrapulmonary involvement in other organ systems is much less common, with asymptomatic histologic evidence of involvement being the rule. Chest radiographs typically demonstrate hilar adenopathy in more than 70% of cases but parenchymal infiltrates in the absence of adenopathy may be present in up to 25% of cases (Thomas & Hunninghake, 1987). Histology typically demonstrates a nonspecific pattern of noncaseating granulomas with multinucleated giant cells and lymphocytes. In contrast to many other interstitial lung diseases, bronchoscopy with transbronchial biopsy has an excellent diagnostic yield, in the range of 75% to 95%. The natural history of sarcoidosis is quite variable, with many patients undergoing spontaneous remissions. Other patients may have a chronic relapsing course. Hunninghake

et al. (1994) demonstrated that withholding therapy until there is objective evidence of deterioration does not adversely affect outcome. Since the finding of noncaseating granulomas is relatively nonspecific and may be found in other infectious and noninfectious granulomatous disorders, reserving therapy for those patients with severe or progressive disease is prudent. Therapy in such cases typically consists of corticosteroids given for several weeks to months. The optimal dose and duration are not known. Other infectious etiologies should be excluded prior to initiating corticosteroid treatment.

Drug-Induced Pneumonitis

The number of drugs and therapeutic agents that may cause pulmonary toxicity is large and ever growing. Mechanisms of injury include direct toxic effects, idiosyncratic reactions, and immune-mediated mechanisms. With some exceptions, the diagnosis of drug-induced lung disease is one of exclusion. Clinical findings, histology, chest radiographs, and even high-resolution CT scans are relatively nonspecific. Most reactions are not dose-related but some reactions can occur weeks to years after the medication is discontinued. Thus, to effectively rule out drug-induced lung disease in the setting of a nonresolving pneumonia requires careful evaluation of every drug that the patient is receiving or has recently received. This section focuses on a few of the classic agents that produce unusual or characteristic patterns that may mimic pneumonia. These include amiodarone, methotrexate, and bleomycin.

Amiodarone

Amiodarone is associated with a wide variety of pulmonary presentations, including interstitial pneumonitis, mass lesions, BOOP, hypersensitivity pneumonitis, eosinophilic pneumonitis, diffuse alveolar hemorrhage, asthma-like syndromes, pleural effusions, and lymphocytic interstitial pneumonitis (Rosenow et al., 1992). One unusual association of amiodarone toxicity is that with postoperative ARDS. There are a number of reports of ARDS occurring after surgery in patients taking amiodarone, typically within 18 to 72 hours (Kennedy, 1990). Some investigators have observed unilateral lung injury postoperatively, with only the ventilated lung being involved. Whether or not this represents potentiation of amiodarone toxicity by supplemental oxygen remains unclear.

The exact incidence of these complications is difficult to define, with most estimates around 5% in the literature. There are no good ways to identify those patients at particularly high risk for amiodarone toxicity. Males are affected more commonly than females, and pulmonary toxicity is more common in those with other pulmonary comorbidities. Most patients who develop toxicity are taking 400 mg per day or more for 2 or more months (Kennedy, 1990). As with most forms of drug toxicity, clinical and radiographic findings are otherwise nonspecific. Symptoms may be acute or insidious in onset. Pleurisy is uncommon, occurring in 10% of cases, with pleural effusions also uncommon but reported. The chest radiograph is nonspecific, ranging from focal alveolar infiltrates to peripheral infiltrates to mixed alveolar-interstitial patterns. Because amiodarone is an iodinated compound, its density on noncontrast high-resolution CT scan may be increased (Rosenow et al., 1992; Kennedy, 1990). Although it is not sensitive, this is one of the few highly specific radiographic findings that when present can definitively establish a diagnosis. Treatment for suspected amiodarone toxicity is corticosteroids and discontinuation of the drug. In those rare instances where there are no suitable alternative antiarrhythmic agents, administration of corticosteroids combined with reducing amiodarone to the lowest possible dose may be effective.

Methotrexate

Methotrexate has been associated with many syndromes that may mimic pneumonia, including bronchospasm, BOOP, pleural effusions, eosinophilic pulmonary infiltrates, noncardiogenic pulmonary edema (from intrathecal methotrexate), and a hypersensitivity type of pneumonitis (Rosenow, 1994). Because opportunistic infection is a well-documented complication with even low-dose methotrexate, it is particularly important to rule out concurrent infection and to look for signs that may differentiate drug toxicity from infection. In patients receiving chemotherapeutic doses of methotrexate there are well-described cases of a hypersensitivity pneumonitis-like reaction, with about

half of patients reporting both lung and blood eosinophilia (Zitnick & Cooper, 1990). Granulomas are also frequently associated with this reaction, and occasionally hilar adenopathy has been reported. Patients receiving lower doses of methotrexate for anti-inflammatory purposes have a slightly different presentation. About 5% of patients receiving chronic low-dose methotrexate develop a subacute interstitial process with fever, hypoxia, rales, and cough (Carson et al., 1987). Eosinophilia in this syndrome is rare, but poorly formed granulomas are still seen on biopsy. Nitrofurantoin potentiates this syndrome, and deaths have been reported (Rosenow, 1994; Carson et al., 1987). Treatment consists of withdrawal and corticosteroids.

Bleomycin

Bleomycin has been associated with a wide variety of complications, including pulmonary fibrosis, BOOP, eosinophilic infiltrates, pulmonary veno-occlusive disease, and an acute pneumonitis reaction similar to hypersensitivity. Up to 20% of patients taking bleomycin develop pulmonary reactions, and 1% die of pulmonary complications (Rosenow, 1994). Risk factors include age above 70 years and dose greater than 450 units. There is a marked synergy between bleomycin and high levels of inspired oxygen. This is often encountered after general anesthesia, typically manifesting about 18 hours later as ARDS. Other reported synergistic insults include the concurrent use of granulocyte colony-stimulating factor (GCSF) (Rosenow et al., 1992; Rosenow, 1994). Treatment in all cases includes minimizing inspired oxygen content and administer corticosteroids.

Vascular Syndromes

Vascular conditions that may mimic pneumonia include pulmonary embolism and congestive heart failure. Pulmonary embolism (PE) is a common problem with radiographic and clinical findings that may easily be mistaken for pneumonia. There are no specific or typical clinical signs and symptoms. Dyspnea is observed in 80% of patients, pleuritic pain in up to 75%, hemoptysis in 20%, and wheezing in 15% (PIOPED Investigators, 1990; Stein, 1996). Chest radiographs show infiltrates in up to 30% of cases, with effusions in 20% (PIOPED Investigators, 1990). Other radiographic findings include diaphragmatic elevation in 60%, focal oligemia in 10%, enlarged pulmonary arteries in 20%, and normal radiographs in 30%. The classic Hampton's hump is rarely seen (PIOPED Investigators, 1990; Stein, 1996). Infiltrates from PE may take several weeks to resolve and thus are easily mistaken for slowly resolving pneumonias. Although the chest radiographic does not correlate with the severity of PE, the alveolar–arterial gradient on blood gas correlates linearly with the severity of PE (Stein et al., 1995). The possibility of PE as the cause of a nonresolving pneumonia syndrome should be raised when hypoxia is out of proportion to radiographic findings and fails to improve despite lack of radiographic progression.

Although the diagnosis of congestive heart failure is usually apparent, occasionally unusual radiographic patterns of cardiogenic pulmonary edema may mimic pneumonia. In particular, atypical pulmonary edema patterns have been well described in patients with bullous lung disease and in patients with mitral regurgitation. Because pulmonary edema principally develops in areas of maximal perfusion, patients with marked COPD may manifest asymmetric pulmonary edema patterns. Similarly, if the regurgitant jet associated with mitral valve insufficiency is directed at one of the pulmonary veins, unilateral and focal pneumonia edema patterns may occur. In this setting echocardiography may be of help to identify the severity and direction of the mitral regurgitation. In borderline cases, Swan–Ganz catheterization may be necessary to further clarify the issue and is usually definitive.

Approach to Nonresolving Pneumonia

In developing a diagnostic approach, it is important to first understand the capabilities as well as the limitations of the most commonly used diagnostic tests. Careful consideration of the diagnostic yield, risks, and benefits is critical in deciding whether additional invasive tests are warranted. The diagnostic tests that are most commonly used in evaluating nonresolving pneumonia are chest radiographs, chest CT scans, and fiber-optic bronchoscopy.

Radiographic Differential Diagnosis

As is clear from the previous descriptions, radiographic findings alone are almost never specific for any one diagnosis. However, radiographic studies are useful in narrowing the differential diagnosis and suggesting groups of diagnostic possibilities for consideration. The primary radiographic tools in assessing nonresolving pneumonia are chest radiographs and chest CT scans. The evaluation of nonresolving pneumonia has further benefitted from the development of high-resolution chest CT (HRCT). HRCT involves using thin-section scanning at 1- to 2-mm collimation combined with a high spatial reconstruction algorithm. HRCT is superior to conventional techniques in several key areas that affect the management of nonresolving pneumonia. Compared to conventional chest x-ray, HRCT allows superior detection of parenchymal abnormalities including emphysema, air space disease, interstitial disease, and nodules. Detection of these structural abnormalities may narrow the differential diagnosis or suggest new possibilities. Certain conditions, such as amiodarone toxicity and lymphangitic spread of malignancy have specific HRCT characteristics that may suggest a diagnosis with reasonable specificity. In addition, the greater sensitivity of HRCT allows for better precision in assessing a patient's response to therapy over time. This is especially useful when there is preexisting lung disease, such as in idiopathic pulmonary fibrosis, that makes it difficult to distinguish acute from chronic changes. CT also improves detection of localized collections, such as abscesses and empyemas. Finally, the ability to better localize disease helps direct biopsy procedures and may improve diagnostic yield.

Bronchoscopy

The role of fiber-optic bronchoscopy (FOB) in the diagnosis of nonresolving pneumonia depends largely on the clinical scenario. The best accepted indication for FOB in the diagnosis of pneumonia is in the immunocompromised host with diffuse pulmonary infiltrates. In this setting different organisms that require markedly different treatments may have similar or indistinguishable clinical presentations. While clinical and radiographic patterns may narrow the set of diagnostic possibilities, abnormal host factors, poor baseline cardiopulmonary reserve, and the wide spectrum of possible pathogens often make an empiric trial risky and therefore justify early FOB. Similarly, in cases of nonresolving pneumonia, the relative ease and low risk of FOB make this an appealing diagnostic procedure in a population of patients with a similarly wide spectrum of possible infectious and noninfectious etiologies.

Despite the frequency of its use for this indication, there are few studies that document the diagnostic yield of FOB for nonresolving pneumonia. In a retrospective analysis of FOB for nonresolving pneumonia, Feinsilver et al. (1990) demonstrated that FOB successfully diagnosed 86% of patients who eventually had a specific diagnosis established. FOB was more likely to establish a specific diagnosis in younger, nonsmoking patients with multilobar involvement and prolonged duration of disease. Patients older than 55 years, smokers, and those with immune defects were more likely to have a nondiagnostic bronchoscopy and were subsequently shown to have slowly resolving pneumonia.

The utility of FOB in nonresolving pneumonia also depends on the disease possibilities being considered and the population being studied. FOB is most useful in diagnosing unusual pathogens, some immunologic disorders such as chronic and acute eosinophilic pneumonia, and neoplastic diseases. Depending on the diseases being considered, transbronchial biopsy may or may not be necessary. In other situations, FOB may have a relatively low diagnostic yield but may provide useful information in ruling out infectious processes. This is especially important if immunosuppressive therapy is being considered.

The role of bronchoscopy in ruling out bacterial infections in the setting of nonresolving pneumonia is unclear. Most recommendations are based on extrapolating data from studies of CAP and nosocomial pneumonia. Since the causative organism in CAP is not isolated in more than 40% of cases, the initial rule of FOB is limited (British Thoracic Society, 1993; Bartlett et al., 1998; Baselski & Wunderink, 1994). FOB for CAP, particularly if done prior to antibiotic therapy, increases the percentage of cases with a defined etiology. How-

ever, the additional pathogens that are isolated are almost always covered by routine empiric antibiotic therapy. Therefore, the role of FOB in identifying bacterial pathogens in nonresolving CAP is not easily defined. Unless unusual pathogens such as *Mycobacterium tuberculosis* are present, the diagnostic sensitivity and specificity for pathogens in this population is probably limited.

Based on studies of ventilator-acquired pneumonia (VAP), however, several recommendations can be made. First, unprotected collection techniques, such as tracheal aspirates and unprotected BAL, are of little value for identifying bacterial pathogens. Physician accuracy on predicting VAP based on unprotected endotracheal aspirates and clinical information ranges from 71% to 82% (Fagon et al., 1993). Diagnosis with protected bronchoscopic techniques demonstrates sensitivity and specificity in excess of 85% (American Thoracic Society, 1995). While multiple protected bronchoscopic techniques have been used, each with its own particular advantages and disadvantages, it is unclear whether any one technique is markedly superior. Techniques include protected specimen brush and protected BAL with quantitative culture. The important point with all of these techniques is to obtain specimens from the distal alveolar or respiratory bronchiole with minimal proximal airway contamination. Controversy exists as to whether diagnostic bronchoscopy should be performed on all patients with VAP, since multiple studies have shown no survival benefit compared to empiric therapy alone (American Thoracic Society, 1995). Whether this applies to nonresolving pneumonia is unclear. Certainly FOB that detects noninfectious etiologies would be expected to alter therapy and presumably affect survival. Given this limited data, it still best to use a protected specimen technique if bacterial pathogens are suspected, realizing the limitations of the technique.

Summary

The diagnostic evaluation of nonresolving pneumonia begins with a careful history, physical examination, and review of the medical record. The goal is to determine whether the rate of resolution is within the range of expected norms, taking into consideration the patient's underlying host factors, comorbidities, severity of illness, and any known pathogens. If the patient is stable or slowly improving and has other comorbidities or host factors that are known to delay the rate of resolution of pneumonia, careful observation and continued therapy is warranted for 4 to 8 weeks. If there is no resolution or progression of disease, then a more aggressive diagnostic approach is warranted.

The physician must first determine whether the nonresolving pneumonia is due to an infectious or noninfectious etiology. The initial evaluation should include a chest CT to look for unsuspected nodules or localized collections of fluid. Any significant pleural collections should be biopsied or drained. If this is unrevealing, bronchoscopy should be considered.

Several factors should be considered when deciding on whether to proceed with FOB. As mentioned previously, in patients with stable but nonresolving pneumonia with impaired host defenses it is reasonable to observe the patient, since the infection can be expected to take a longer time to clear. When infection fails to resolve in a patient without impaired host defenses or if there is clinical progression, FOB should be pursued. Similarly, if noninfectious etiologies or unusual pathogens are suspected. FAB is warranted. Positive results from FOB can serve to modify or optimize treatment regimens. Similarly, a negative result has significant value. Patients with a negative FOB have a good chance of merely having a slowly resolving pneumonia and if they are stable can be observed. Similarly, a negative FOB will narrow the differential diagnosis for patients with progressive disease. Diseases that typically are not diagnosed with FOB that are progressive include pulmonary vasculitis syndromes, BOOP, and the various forms of diffuse alveolar damage. In these cases a negative bronchoscopy with progressive symptoms should prompt consideration of an open-lung biopsy.

While definitive recommendations on the decision to proceed to open-lung biopsy cannot be made, several factors need to be considered when deciding whether to proceed with open-lung biopsy. These factors include disease progression, the diagnostic possibilities being considered, and the effect that a positive open-lung biopsy will have on treatment. In general, if the disease is relatively

stable, a period of careful observation may be warranted. If there is a high likelihood for a disease that would necessitate a dramatic change in therapy, then open-lung biopsy is warranted. Diseases in this category generally include most vasculitis syndromes (WG) and inflammatory lung diseases (AIP) that require immunosuppressive therapy. In these cases, the risk of immunosuppression in a patient who is currently infected requires a specific tissue diagnosis. The more potent the immunosuppression required, the more the open-lung biopsy is warranted. Similarly, FOB in these cases can help to rule out concurrent infection, but open-lung biopsy remains the gold standard to establish the diagnosis.

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26

Community-Acquired Pneumonia Associated with Exposure to Contaminated Water

TODD F. HATCHETTE

Introduction

> After conception, each developing human being spends approximately nine months completely immersed in a sterile environment of amniotic fluid without ordinarily drowning or contracting any bacterial infection. From the time of birth, however, each infant, child, adolescent and adult is at risk for these upon subsequent re-entry into any natural saline fluid milieu, whether salt water oceans, seas, bays, springs, harbors, lagoons or lakes. (Sims et al., 1983)

Since many believe that it was the seas which provided the media from which primordial life began, it is not surprising that aquatic environments including drinking water can sustain many microorganisms, many of which are capable of producing human disease (Table 1) (Sims et al., 1983; Auerbach et al., 1987; Rusin et al., 1997). A number of bacterial and fungal pathogens have been associated with pneumonia due to aspiration of contaminated water as a result of near-drowning episodes (Table 2). The temperature and chemical composition of the aquatic environment (i.e., pH, salinity, turbidity, inorganic and organic substrates) will influence the type of microorganisms found there. Patients who suffer a near-drowning episode, particularly in shallow water, will also aspirate mud and sediment, which harbor potential pathogens (Auerbach et al., 1987; Ender & Dolan, 1997). Knowing whether the exposure was in fresh water, marine, or stagnant aquatic environments can provide clues as to the etiologic organism causing the pneumonia (Ender & Dolan, 1997).

Massive aspiration of contaminated water is not required for pulmonary infection to occur; more subtle mechanisms of exposure can result in pneumonia. Small amounts of water may be aspirated (realized or unnoticed) during recreational activities in aquatic environments such as swimming or canoeing (Turner et al., 1990). Inhalation of aerosolized contaminated water has also been associated with community-acquired pneumonia due to a number of different organisms (Rose et al., 1983; Harris et al., 1984; Bernstein et al., 1989; Hubert et al., 1991; Straus, 1996).

In addition to the respiratory tract, microorganisms like *Leptospira* and *Chromobacterium* may gain entry into the bloodstream through mucosal membranes and abrasions or breaks in the skin and hematogenously seed the lungs, causing pulmonary infection (Farr, 1995; Ender & Dolan, 1997).

Legionella pneumophila and other *Legionella* species are the most common cause of pneumonia following exposure to contaminated water, however, a number of other aquatic microorganisms are also capable of producing pulmonary infections. This chapter reviews the different bacterial species that have been implicated in such infections. Many of the examples come from limited case series,

TODD F. HATCHETTE • Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Potential Bacterial Pathogens Isolated in Drinking Water[a]

Pseudomonas spp.	*Moraxella* spp.
Acinetobacter spp.	*Mycobacterium avium*
Stenotrophomonas maltophilia	*Legionella* spp.
Aeromonas spp.	

[a]From Rusin et al., 1997.

while others such as *Legionella* have been extensively studied and are reviewed elsewhere. Other microorganisms that have also been implicated in pneumonia due to exposure to contaminated water include *Pseudomonas aeruginosa, Burkholderia pseudomallei, Scedosporium apiospermum* and *Aspergillus* are reviewed in detail in other chapters.

Aeromonas

Aeromonas species are oxidase-positive, gram-negative rods that live in aquatic environments (fresh water or sea water). *Aeromonas* species have been considered members of the family Vibronaceae, however, molecular studies suggest that they are distinct and therefore a separate family has been proposed. There are ten *Aeromonas* species that can be further divided into 13 different genomospecies based on DNA hybridization. They can be differentiated from *Vibrio* species by their failure to grow in media containing 6% sodium chloride and the lack of ornithine decarboxylase (except for *A. veronii* biotype *veronii)* (Koneman, 1997a).

TABLE 2. Microorganisms Associated with Pneumonia in Near-Drowning Victims[a]

Bacteria	Fungi
Aeromonas species	*Aspergillus* species
Chromobacterium violaceum	*Pseudoallescheria boydii*
Burkholderia pseudomallei	
Francisella philomiragia	
Klebsiella pneumoniae	
Legionella species	
Neisseria mucosa	
Pseudomonas aeruginosa	
Shewanella putrefaciens	
Vibrio species	
Streptococcus pneumoniae	
Staphylococcus aureus	

[a]From Ender & Dolan, 1997

Aeromonas species are more commonly identified as causal agents in cellulitis and acute diarrheal disease but have been associated with pneumonia (Koneman, 1997b; Ender & Dolan, 1997). Baddour and Baselski (1988) reported eight cases of pneumonia due to *A. hydrophila* and reviewed the eight additional cases reported in the literature at that time. Nine of the 19 patients (56%) had risk factors for aspiration including depressed levels of consciousness, alcohol consumption, general anesthesia, or cerebral vascular accidents. Five patients (31%) were previously healthy and developed pneumonia following near-drowning episodes. The remaining patients had underlying medical conditions including alcoholism; chronic liver, cardiac, renal, or lung disease; and malignancy. Bilateral pneumonia was present in five cases (31%) and pleural effusion was seen in only one patient. *Aeromonas* was recovered from blood (six patients), sputum (eight patients), tracheal suction (four patients) and from postmortem lung tissue (two patients). Overall nine of 13 patients with available data (69%) had community-acquired *Aeromonas* pneumonia, with a mortality rate of 44% (four of nine patients). One of the previously healthy patients was a 29-year-old male who died from a rapidly progressive hemorrhagic *Aeromonas* pneumonia. There was no indication of any exposure to environmental sources, and only 15 hours had elapsed from the time he first developed acute onset of pleuritic chest pain to death (Scott et al., 1978). A similar fatal infection was seen in a previously healthy 24-year-old male who presented with an 18-hour history of severe pleuritic chest pain, fever, dyspnea, cough, and hemoptysis. He had been swimming in the ocean 24 hours prior to the onset of his symptoms and died 3 hours after admission of generalized necrotizing hemorrhagic *Aeromonas* pneumonia (Goncalves et al., 1992). Ender and Dolan (1997) reviewed cases of *Aeromonas* pneumonia after near drowning episodes and found that 70% of patients were bacteremic with a progressive pneumonia that developed within the first 24 hours after submersion. Invasive infection with *Aeromonas* have been found more commonly in patients with underlying liver disease or malig-

nancy but the majority of the patients developing pulmonary infections after near-drowning episodes were previously healthy. *Aeromonas hydrophila* was the most common species associated with pneumonia and mortality was estimated to approach 60% (Ender & Dolan, 1997).

Aeromonas species produce β-lactamases and are thus resistant to ampicillin; the addition of a β-lactamase inhibitor does not enhance susceptibility. Most *Aeromonas* species are susceptible to chloramphenicol, third-generation cephalosporins, quinolones, aminoglycosides, tetracycline, trimethoprim-sulfamethoxazole, and carbapenems. However, resistance is emerging and susceptibility can be unpredictable; therefore treatment choices should be dictated by susceptibilities determined by in vitro testing (Ko & Chuang, 1999).

Chromobacterium violaceum

Chromobacteria are motile, facultative anaerobic gram-negative bacilli that may be confused with *Vibrio* or *Aeromonas* species. *Chromobacterium violaceum,* previously classified as *Bacillus violaceus, B. violaceus manilae,* and *C. janthinum,* is the most common species isolated and produces a characteristic water-insoluble violet-colored pigment (violacein) that diffuses into the surrounding media. *C. violaceum* produces small quantities of hydrogen cyanide, giving cultures the distinct aroma of cyanide. The microorganism is present in the environment and has been isolated off the southeastern coast of the United States but is typically confined to tropical and subtropical areas, thriving at temperatures of 20°C to 30°C. Infection tends to occur in June through September in patients who have a history of water exposure (Holmes et al., 1995; Lang & Morris, 1999).

Hubert and coworkers (1991) described 35 cases of pneumonia among persons attending a hot spring spa in France in 1987. There were no cases in individuals less than 50 years of age and the attack rate increased for those older than 70 years. Patents presented with fever, chills, pleuritic chest pain, and hemoptysis, with radiographic findings of lobar consolidation. Six patients had blood cultures positive for an unusual gram-negative rod initially thought to be a *Pseudomonas* or *Flavobacterium* species. Risk factors associated with infection included spa treatments early in the morning on the first day of care (odds ratio [OR], 4.8) and participation in vapor baths (OR, 10.7). Twenty-six patients were hospitalized but there were no deaths. Subsequent studies failed to definitively identify the microorganism but it was thought to most closely resemble *Chromobacterium violaceum* or *Aquaspirillum serpens* (Casalta et al., 1989; Hubert et al., 1991). This organism was susceptible to penicillin and other β-lactams as well as sulfonamides, aminoglycosides, chloramphenicol, and quinolones, but resistant to clindamycin and vancomycin (Casalta et al., 1989; Hubert et al., 1991).

Midani and Rathore (1998) reviewed the 34 published cases of *C. violaceum* in the literature and found nine of the 34 patients (26.5%) had pneumonia or lung abscesses. There appears to be an association with chronic granulomatous disease (Macher et al., 1982; Midani & Rathore, 1998). *Chromobacterium* has been implicated in pneumonia in patients who have survived near-drowning episodes (Ender & Dolan, 1997). In the four cases reviewed by Ender and Dolan (1997), 75% developed more than 1 month after the near-drowning episode, suggesting that the delay reflects a different mechanism of infection. Pneumonia may not be secondary to aspiration but result from hematogenous spread of *Chromobacterium* species that have gained entry to the bloodstream through the skin. This microorganism should be suspected when there is a delay in onset of pneumonia in patients with a history of near-drowning in stagnant water in the southeastern United States (Ender & Dolan, 1997).

With improved medical treatment the overall mortality from *C. violaceum* infection has dropped from 81% (1937–1979) to 41% (1980–1994) (Midani & Rathore, 1998). The microorganism is typically resistant to penicillin, cephalosporins, and vancomycin. Susceptibilities to chloramphenicol, tetracycline, and aminoglycosides vary, but *C. violaceum* generally remains susceptible to quinolones, imipenem, and doxycycline. The combination of chloramphenicol and an aminoglycoside has been the most common treatment cited in the literature but in vitro data suggest that neither agent is particularly effective in treating *C. violaceum* infections (Lang & Morris, 1999). Initial treatment with

ciprofloxacin in combination with gentamicin for 3 to 4 weeks followed by prolonged oral ciprofloxacin suppression therapy for 8 to 12 weeks to prevent fatal relapse is currently the therapeutic regimen of choice (Lang & Morris, 1999).

Cyanobacteria

Cyanobacteria are the largest group of photosynthetic bacteria. They were once referred to as "blue-green algae" because of their ability to conduct photosynthesis. Although their biochemical and structural properties are closer to those of bacteria they are often not considered true bacteria (VanDemark & Batzing, 1986; Alcamo, 1997). *Microcystis* species, *Planktothrix* species, *Tychonema* species, and *Nostoc* species all belong to this group (Rudi et al., 1998a). These microorganisms may exhibit bacilli, cocci, or filamentous, branching forms. Some species are immobile while others have a gliding motility. They can colonize rock and volcanic ash and can be found in soil and in freshwater or marine environments, often tolerating otherwise hostile conditions such as those in hot springs, snow fields, and deserts. Lichen is an example of how these microorganisms can live in symbiotic relationships with other organisms such as fungi. Photosynthesis is conducted within membrane-bound organelles called thylakoids that contain light-absorbing pigments including chlorophyll-*a* and carotenoids. Fertilizers and other wastes can pollute aquatic environments, increasing the nutrients available (e.g., inorganic phosphates) and establishing a fertile breeding ground for cyanobacteria. The explosive increase in the cyanobacterial population is referred to as a "bloom" which often gives a foul smell and greenish color to the contaminated water (VanDemark & Batzing, 1986; Alcamo, 1997). These microorganisms can produce several toxins that can be potentially harmful to humans and livestock, including a leucine- and arginine-containing pentapeptide that has been shown to induce pulmonary thrombosis in mice (Slatkin et al., 1983). Using primers corresponding to sequences in cyanobacterial 16S rDNA, polymerase chain reaction can be used to identify Cyanobacteria in water samples to detect potentially toxic "blooms" (Rudi et al., 1998b).

The cyanobacterium *Microcystis aeruginosa* has been implicated in cases of community-acquired pneumonia in two young army recruits (Turner et al., 1990). These patients presented with malaise, sore throat, blistering around the mouth, pleuritic chest pain, and dry cough and were diagnosed with pneumonia. Both patients had taken part in canoeing on a reservoir contaminated with *Microcystis aeruginosa.* Subsequently 16 more soldiers developed the same symptoms. These symptoms were attributed to cyanobacterial toxins and the pneumonia was attributed to cyanobacterial infection (Turner et al., 1990).

Francisella philomiragia

Francisella philomiragia was formerly classified as *Yersinia philomiragia*, but biochemical studies of its fatty acid profile and DNA homology found that it was closely related to *Francisella tularensis.* Identification can be difficult. *Francisella philomiragia* has been misidentified as *Yersinia* species, *Neisseria* species and *Actinobacillus* species (Wenger et al., 1989). Both *F. tularensis* and *F. philomiragia* are small, coccobacillary, gram-negative rods. A positive oxidase and weak or delayed hydrogen sulfide production when inoculated to a triple sugar iron agar help differentiate *F. philomiragia* from *F. tularensis.*

Wenger et al. (1989) reviewed 14 isolates of *F. philomiragia* that were sent to the Centers for Disease Control and Prevention between 1975 and 1987. Five of the 14 patients (36%) had chronic granulomatous disease (CGD); five patients (36%) suffered near-drowning episodes; two patients had underlying hematological malignancies; the remaining two patients did not have any obvious underlying illness. All five episodes of near-drowning occurred in salt water or estuary environments with the patients becoming bacteremic with presumed pneumonitis (as indicated by chest radiographs) 4 to 5 days after their exposure to water. No follow-up information was available for one of these victims, but three of the remaining four survived their infections. The fifth patient died 7 days after antibiotic therapy and autopsy revealed multilobar pneumonia and multiple abscesses.

Of the patients with CGD, two of five had

pneumonia due to *F. philomiragia* diagnosed by open-lung biopsy. One of the patients responded to chloramphenicol, and the outcome of the second patient was not indicated. The other pulmonary infection occurred in a 39-year-old male who was being investigated for a 3-year history of chronic pleural effusions. Although no obvious underlying illness was found he had *F. philomiragia* isolated from pleural fluid samples. There was no indication of direct exposure to sea water in any of the remaining patients; however, 12 of the 14 patients (85.7%) lived within 50 miles of a saltwater coastline suggesting that there was exposure to contaminated water that predisposed them to *F. philomiragia* infection.

All of the 14 isolates produced β-lactamase and were resistant to ampicillin. Only 79% of isolates were intermediately susceptible to erythromycin. All were susceptible to aminoglycosides, tetracycline, cefotaxime, cefoxitin, and chloramphenicol (Wenger et al., 1989).

Leptospira

Leptospirosis refers to the disease caused by slow-growing, motile, aerobic, helical-shaped spirochetes called *Leptospira.* Originally two species were recognized, *L. interrogans* and *L. biflexa.* Through comparison of genomic homology, the genus was reorganized and now contains at least eight pathogenic species, including *L. interrogans,* L. borpetersenii, *L. inadai*, *L. kirscheri, L. noguchii*, *L. santarosai*, *L. grippatyphosa*, and *L. weilii* encompassing over 200 different serovars (Faine, 1999). The serovars responsible for human disease belonged to the *L. interrogans* species and were divided into 23 serogroups (Koneman et al., 1997b). *Leptospira* species cannot be seen on gram stain but may stain lightly with Giemsa or Wright's stain. On dark-field microscopy they exhibit a terminal hook that helps to differentiate *Leptospira* from other spirochetes. Successful culture of these microorganisms often requires prolonged incubation (up to 4 weeks) using special media containing 10% rabbit serum or 1% bovine serum albumin, and long-chain fatty acids with a 5-fluorouracil analogue added to suppress the growth of other organisms (Farr, 1995).

Epidemiology

Leptospirosis is a worldwide zoonosis in which humans are terminal hosts. *Leptospira* have been isolated from various animals, including reptiles, amphibians, birds, fish, and invertebrates, but the mammalian host is the most important. These microorganisms can persist in many different mammalian hosts, both wild and domestic, and are excreted in the urine where they can persist in moist soil and water. Wild animals represent an important reservoir for perpetuating the infection in domesticated animals such as cattle and dogs (Farr, 1995). This zoonosis is frequently associated with rats and is traditionally described in tropical areas, particularly in the Far East but can be found in countries throughout the world including large endemic areas within North America (O'Neil et al., 1991). It is usually associated with occupational exposure to infected urine or animal tissues but has been associated with contaminated rainwater collected for household use (Sasaki et al., 1993). Farmers working in moist conditions such as rice or sugar cane fields are at greatest risk. People who milk cattle, veterinarians, abattoir workers, sewer workers, trappers, loggers, and military personnel are all at risk of exposure to contaminated water, infected urine, or animal tissues (Farr, 1995; Faine, 1999). Between 1964 and 1978, there were 50 to 150 cases reported annually in the United States, most frequently in the southern Atlantic, Gulf, and Pacific states (Im et al., 1989; Farr, 1995). Less than 20% of cases in the United States report direct contact with possible animal hosts (rats, raccoons, and opossums), with another 20% of cases reported to be related to recreational exposure to infected urine through kayaking, canoeing, swimming, or wading in contaminated water (Im et al., 1989; Farr, 1995). Leptospirosis was reported in 9 of 26 people who went whitewater rafting in Costa Rica in 1996 (CDC, 1997). Outbreaks of leptospirosis have occurred in Nicaragua, Korea, and Hawaii (Park et al., 1989; Sasaki et al., 1993; CDC, 1997; Trevejo et al., 1998). During a 2-month period in 1995, following heavy tropical rain storms, an epidemic of leptospirosis associated with pulmonary hemorrhage was reported in rural Nicaragua. During this period, 2259 patients presented to clinics with symptoms of a non-malaria febrile illness consistent with lepto-

spirosis. The estimated cumulative incidence was 6.1%, with a minimum case–fatality rate from pulmonary hemorrhage of 0.7% (Trevejo et al., 1998). Patients with leptospirosis were more likely to have walked in creeks, been exposed to rodents in the home environment, or owned dogs that had titers of greater than 1:400 to *Leptospira* species (Trevejo et al., 1998).

Clinical Features

Leptospira can gain access to the bloodstream through conjunctival or mucus membrane exposure to water contaminated with infected urine, but the usual portal of entry for the spirochete is through abraded skin (usually on the feet) (Farrar, 1995; Farr, 1995). Once in the bloodstream they migrate to the liver and reproduce. After an incubation period of 7 to 12 days the patient begins to display signs and symptoms of the infection during which time the spirochetes can be isolated from the blood, urine, and cerebrospinal fluid (O'Neil et al., 1991). Subclinical infection with *Leptospira* has been described. While some suggest that it is uncommon, others suggest that the incidence can be as high as 20% of cases (cited in Perani et al., 1998). Men are more commonly infected than are women and the infection typically can manifest as two possible clinical syndromes with two distinct phases. The more common, milder form is anicteric leptospiro--sis and is the presentation in 85% to 90% of cases. This self-limiting illness is first characterized by a septicemic phase in which the patient develops acute onset of mild flu-like symptoms including headache, remitting fever, chills, nausea, vomiting, abdominal pain, severe muscle aches, and sometimes circulatory collapse; death rarely ensues. The most common sign is conjunctival suffusion withoul purulent discharge. Muscle tenderness, maculopapular rash, hepatosplenomegaly, and pharyngeal injection can also occur. After 3 to 7 days the second or "immune" phase of anicteric leptospirosis may begin. Its presentation is variable, and the headache and fever are less prominent. The hallmark of this phase is the development of aseptic meningitis (Farr, 1995). Pulmonary manifestations can occur in this phase, with hemoptysis and pulmonary infiltrates seen in 20% to 70% of patients. Studies of epidemics in China, Brazil, Korea, and Nicaragua have reported patients who had severe pulmonary hemorrhage without the presence of jaundice (Trevejo et al., 1998).

More severe pulmonary manifestations are usually seen in the more severe or "icteric" form of leptospirosis or Weil's syndrome (Farrar, 1995). This is a potentially fatal manifestation of leptospiral disease. It is characterized by renal and hepatic dysfunction, with hemorrhage, vascular collapse, and mental status changes probably reflecting a severe vasculitis (Farr, 1995). The exact mechanism of endothelial injury is unknown. Immunohistochemical studies on autopsy specimens in patients that died from leptospirosis demonstrated the presence of *Leptospira* antigen on endothelial surfaces. This suggests that vascular injury is due to toxigenic products from the microorganism or an immune-mediated mechanism triggered against leptospiral antigen adherent to the endothelial cell membrane (Nicodemo et al., 1997). Anuria during this stage is a poor prognostic sign, with mortality rates varying from 2% to 14% (Im et al., 1989; Farr, 1995). Hyperventilation, hypoxia, and hypocarbia are common findings in these patients and an increase in the diffusing capacity of carbon monoxide (CO) is consistent with the hemorrhagic etiology of the pulmonary disease (O'Neil et al., 1991). The diffusion capacity is the calculated difference in measured concentrations of inspired and expired CO, reflecting the proportion of CO that diffuses across the alveolar membrane and binds to the hemoglobin of circulating erythrocytes. Since carbon monoxide has a high affinity for hemoglobin blood in the alveoli from hemorrhage can aggressively bind to the carbon monoxide, leading to a decreased amount of expired CO and causing a falsely elevated diffusion capacity (Drazen & Weinberger, 1998). Although unusual, acute respiratory failure has been described secondary to massive hemorrhage or adult respiratory distress syndrome (ARDS) (O'Neil et al., 1991).

Pulmonary Manifestations

In a prospective survey of patients presenting with community-acquired pneumonia to a hospital in Italy, the prevalence of leptospiral infection over a 1-year period was 12%, with an annual incidence of 0.5% (Perani et al., 1998). Perani et al. (1998)

found that 10 of 176 patients (5.6%) had antibodies to *Leptospira* species. However, in only one of these patients was pneumonia determined to be secondary to acute *Leptospira* infection. A case-control study of 51 patients with leptospirosis during the Nicaraguan outbreak of 1995 revealed that 39% of patients had hemorrhagic manifestations including fatal pulmonary hemorrhage (21.5%; 11/51 patients) and hemoptysis (7.8%; 4/51 patients) (Trevejo et al., 1998). O'Neil et al. (1991) reviewed the pulmonary manifestations of leptospirosis. Twenty percent to 70% of patients have pulmonary findings. These are usually mild but can be the "most dramatic" feature of the infection. Common pulmonary symptoms include cough, hemoptysis (which mimics many other hemorrhagic pulmonary syndromes), and plerutic chest pain (which is felt to be musculoskeletal in origin due to the intercostal muscle involvement of *Leptospira).* A productive cough, minimal at first, often becomes blood-tinged and can progress to massive hemoptysis leading to asphyxiation in severe cases. Despite the presence of pulmonary symptoms, the clinical pulmonary examination is frequently normal and signs of consolidation are rare.

Pulmonary radiographic findings in leptospirosis can mimic a number of infectious and non-infectious pulmonary diseases including viral or bacterial pneumonia, miliary tuberculosis, ARDS, and hemorrhagic pulmonary syndromes. Im et al. (1989) reviewed the radiographic pulmonary manifestations in 58 patients with leptospirosis and found that 64% of the patients developed abnormal findings on chest radiograph. Of these patients, 57% developed their radiographic abnormalities 3 to 7 days after the onset of their symptoms. Although findings tended to change during the course of infection, all were bilateral in distribution with three distinct patterns. Fifty-seven percent of patients developed multiple nodular densities ranging from 1 to 7 mm in diameter, 16% developed large areas of consolidation, and 27% developed an ill-defined ground-glass appearance on chest radiograph. In 62% of the patients with abnormal chest radiographs there was progression from either nodular densities (85%) or consolidation (15%) to a ground-glass appearance. In general, the abnormalities resolved in 5 to 15 days. There was a correlation between time to resolution and severity of the pulmonary process. The more severe manifestations took longer to resolve. Small pleural effusions, Kerley B lines, cardiomegaly, miliary and atelectatic patterns were other abnormal findings seen on chest radiographs. The findings tended to be in the peripheral regions of the lower lobes, corresponding to the areas of greatest blood flow (O'Neil et al., 1991; Im et al., 1989).

Although *Leptospira* species are occasionally found in the lung tissue, there is a notable lack of the usual inflammatory infiltrates seen in other types of pneumonia (O'Neil et al., 1991). Animal models suggest that the pulmonary infiltrates seen in leptospirosis are due to hemorrhagic pneumonitis caused by endothelial damage and increased vascular permeability. Since progression of pulmonary findings is present in a significant proportion of patients with leptospirosis, Im et al. (1989) suggest that the different histological patterns produced in the lungs of guinea pigs infected with *Leptospira interrogans* correspond to the three different radiographic presentations seen in human infection. Small foci of intra-alveolar hemorrhage correspond to the small nodules seen on early pulmonary radiographs. These hemorrhages increase in size, reaching their maximum size 5 or 6 days after the onset of symptoms. The greater degree of hemorrhage corresponds to the consolidation pattern sometimes seen in patients with leptospirosis. By 12 to 15 days there is no fresh blood, but areas of resolving hemorrhage are present, corresponding with the ground-glass appearance seen prior to resolution. Hemorrhage is not due to disseminated intravascular coagulation but appears to be the direct result of endothelial damage caused by intact organisms or secondary to antigenic proteins or toxins released by the Leptospira (Nicodemo et al., 1997). The ARDS seen in some patients may be a result of the infection or supportive measures such as high oxygen concentrations, shock, secondary bacterial infection, or uremia (Nicodemo et al., 1997).

Diagnosis

The diagnosis of leptospirosis is often overlooked. In an outbreak in Hawaii in 1988-1989, only 30% of the patients who had confirmed disease had this diagnosis entertained at the time of presentation (Sasaki et al., 1993). Im et al. (1989) suggests

that the diagnosis of leptospirosis should be considered in patients with the appropriate symptoms, environmental exposure, and typical evolving radiographic findings. *Leptospira* can be recovered from tissue samples, cerebrospinal fluid, and blood during the first 7 days of infection and from urine after the first week. Definitive diagnosis can be made by isolation of the microorganism from a clinical specimen. However, the special media requirements and prolonged incubation period (up to 2 months) can often delay diagnosis (Merien et al., 1995). Demonstration of the organisms in blood and urine using dark-field microscopy or agglutination techniques is insensitive and can lead to misdiagnosis (Paganin et al., 1996). Paganin et al. (1996) showed that the spirochetes could be identified by direct examination of bronchoalveolar lavage (BAL) specimens using dark-field microscopy in patients with icteric leptospirosis, suggesting that BAL may be a rapid method of diagnosis. Diagnosis has traditionally been made serologically, most commonly through the microscopic agglutination test (MAT). This test uses 23 different *Leptospira* antigens that correspond to the most common pathogenic serogroups of *Leptospira* species. Two samples are required to confirm seroconversion. Seroconversion is defined as a titer of 0 to 50 in the first (acute) serum sample, a titer of greater than 200 in the second (convalescent) serum sample, or a >4-fold rise in antibody titer in the convalescent sera compared to the acute sera of suspected patients (Merien et al., 1995). MAT is not widely available, is time-consuming, and uses live organisms, which requires the maintenance of a viable stock, posing a risk of exposure and infection to laboratory personnel (Winslow et al., 1997). In addition, serological diagnosis is often not possible until the 6th to 12th days of disease, and early antibiotic treatment can inhibit the antibody response so a 4-fold rise in antibody titer may not be evident (Im et al., 1989; Merien et al., 1995). Rapid methods such as enzyme-linked immunosorbent assays and dipstick assays for detection of *Leptospira*-specific IgM in patients suspected of having leptospirosis are currently being developed (Winslow et al., 1997; Gussenhoven, 1997). These tests are easier to perform and may become useful as a more widely available screening test. With primers specific for the 16S rRNA gene or sequences in conserved repetitive elements of *Leptospira* species, polymerase chain reaction (PCR) has been found to be a sensitive technique for the identification of low levels of *Leptospira* in clinical specimens as well as for differentiating serovars (Merien et al., 1992, 1993; Savio et al., 1994). To examine its clinical application, Merien et al. (1995) prospectively compared PCR with microagglutination assay to diagnosis leptospirosis. Over a 1-year period, 200 suspected cases of leptospirosis were seen in clinics in New Caledonia in the South Pacific. Using PCR, 28 cases were identified, 14 of which were confirmed using culture and the microagglutination assay. The remaining 14 represented patients who had *Leptospira* DNA present but had a decreasing or stable serologic titer. On average, a median of 13 days was required for seroconversion compared with PCR, which was able to detect infection on average by day 5.

Treatment

The treatment of choice for leptospirosis is penicillin (1.5 million units iv every 6 hours) and it is most effective when started early, often empirically before the diagnosis is confirmed. Alternative treatments include ampicillin (500–750 mg every 6 hours), amoxicillin (500 mg every 6 hours), erythromycin (250 mg every 6 hours for 5 days), doxycycline (100 mg twice daily), tetracycline, cephalosporins, and aminoglycosides. The microorganism is resistant to chloramphenicol, vancomycin, metronidazole, and rifampin (Faine, 1999). Imipenem has been used successfully in one case (Perani et al., 1998). Combination antimicrobial therapy is not indicated, and defervescence can be expected in 24 hours. Tetracycline is less favorable in the presence of renal insufficiency and is contraindicated in pregnant women and young children (Faine, 1999). Supportive measures are often necessary in severely infected individuals with pulmonary hemorrhage, renal failure, and hypotension (Farr, 1995). Patients respond better when the appropriate antibiotic is started early, but there is evidence that administration of high doses of penicillin late in the icteric disease also improves outcome. The Jarisch–Herxheimer reaction has been documented after penicillin treatment. Although this reaction is potentially fatal, treatment is supportive, and the occurrence of a Jarisch–Herxheimer reaction should not be consid-

ered a contraindication to continued antibiotic therapy (Farr, 1995; Faine, 1999).

A number of approaches have been used to prevent leptospirosis. Prophylaxis with a 200-mg oral dose of doxycycline once weekly has been shown to be effective in preventing infection in persons traveling to endemic areas with potential exposure to contaminated water (Takafuji et al., 1984). Vaccines have been developed for domestic animals, but some vaccinated dogs will continue to shed the leptospira in their urine, causing human disease. Public health measures such as educating people to avoid urine-contaminated water or to use protective measures such as water-resistant boots are also complementary components to effective treatment and prevention of disease (Farr, 1995). Antibodies generated during the infection will protect the individual from subsequent infections with the same serovar, but they do not protect against infection with different serovars of *Leptospira.*

Although leptospirosis does not result in a community-acquired pneumonia in the classical sense, the pulmonary manifestations represent an important presentation of acute pulmonary syndromes. *Leptospira* infection should be considered in the differential diagnosis of community-acquired pneumonia, particularly in any individual with occupational or environmental exposure who presents with hemoptysis (Turner & Willcox, 1989; Paganin et al., 1996; Perani et al., 1998).

Vibrio

Koch once referred to *Vibrio* species as "Kommabacillus," referring to their distinctive curved comma-shape (cited in Koneman et al., 1997a). Like *Aeromonas* species, *Vibrio* species are gram-negative rods whose natural habitat is aquatic. Although they may be isolated from fresh water, they are halophilic and are more commonly isolated from saltwater or brackish environments (Ender & Dolan, 1997). They have been associated with a number of infections in patients with a history of saltwater exposure (Hlady & Klontz, 1996). Typically infections manifest as gastroenteritis, wound infections, or septicemia. There have been only six documented cases of pneumonia due to *Vibrio* species (*Vibrio vulnificus* [2 cases], *V. alginolyticus* [2 cases], and *V. cholerae* non-O1 [2 cases]), all of which occurred in patients who had near-drowning episodes in sea water (Kelly & Avery, 1980; Chuang et al., 1992; Hlady & Klontz, 1996). Both patients with pneumonia due to *V. vulnificus* died between 2 to 9 days after the near-drowning event despite treatment with a cephalosporin and or an aminoglycoside (Kelly & Avery, 1980; Chuang et al., 1992). Treatment and outcome information is unknown for the other four cases (Hlady & Klontz, 1996). Treatment of other infections using third-generation cephalosporins, tetracycline, and quinolones in combination with an aminoglycoside have been successful (Seas & Gotuzzo, 1999). In vitro data suggest that trimethoprim-sulfamethoxazole may be an effective alternative (Chuang et al., 1992).

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Pneumococcal Pneumonia

ÅKE ÖRTQVIST

Introduction

In 1881, Pasteur in France and Sternberg in the United States independently isolated, cultured, and described the pneumococcus (Heffron, 1939). Although the clinical presentation of pneumonia had then been known for more than 2000 years, this was the first time an organism was associated as a causative agent of this disease. During the following years several other investigators, including Fränkel and Weichselbaum, established the pneumococcus as the common cause of lobar pneumonia. At that time, pneumonia was probably the most common cause of death overall, and was accordingly named "captain of the men of death" by Sir William Osier (Stratton, 1986). Since then, the overall morbidity and mortality of this disease has decreased significantly. However, *Streptococcus pneumoniae* remains the most common cause of community-acquired pneumonia (CAP) in patients admitted to hospital (British Thoracic Society, 1987; Örtqvist et al., 1990a; Fang et al., 1990; Burman et al., 1991; Lieberman et al., 1995; Bohte et al., 1995), is the most common cause of pneumonia requiring intensive care treatment (Örtqvist, 1994), and accounts for more deaths than any other pathogen among patients with CAP (Fine et al., 1996). Furthermore, the global spread of antibiotic-resistant pneumococci, which has accelerated during the past two decades (Tomasz, 1997), has led to an increasing impact of pneumococcal disease. More widespread use of the current polysaccharide pneumococcal vaccine and the development of new, more immunogenic vaccines will likely help in the continuing battle against pneumococcal disease.

ÅKE ÖRTQVIST • Department of Infectious Diseases, Karolinska Institutet, Karolinska Hospital, S-171 76 Stockholm, Sweden.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

Microbiology

S. pneumoniae is typically a lancet-shaped, gram-positive diplococcus, surrounded by a polysaccharide capsule, that usually occurs in pairs or in short chains (Table 1). There are several similarities between the pneumococcus and other streptococci, including morphology, cell-wall composition, and metabolism. There is also a nucleic acid homology between the pneumococcus and several other streptococcal species, and genetic material can be transferred from one species to another. *S. pneumoniae* ferments glucose by the hexose monophosphate pathway with lactic acid as the end product. Pneumococci are facultative anaerobes and should be incubated under anaerobic conditions, or with 5% to 10% of CO_2 for optimal growth. Colonies of pneumococci grown on blood agar in air or CO_2 produce an alpha-hemolytic zone. The optochin disk sensitivity test is the most common way to discriminate pneumococci from other streptococcal species, since optochin inhibits growth of pneumococci, but not of other streptococcal species. Another more reliable, but also more laborious, identification method for pneumococci is the bile solubility test, since bile (2% sodium deoxycholate) causes lysis of pneumococci but not of other streptococci.

The capsule consists of polymers made up of units of repeating oligosaccharides. The capsular polysaccharides are antigenic and form the basis of

TABLE 1. General Characteristics of *Streptococcus pneumoniae*

Gram-positive diplococcus
Surrounded by polysaccharide capsule, 90 distinct serotypes
Facultative anaerobe, 5–10% CO_2 may be required
Alpha-hemolytic colony type
Optochin-sensitive
Bile-soluble

classifying pneumococci into different serotypes. The Danish nomenclature is now generally accepted, and to date 90 different serotypes have been identified (Henrichsen, 1995). Some types are antigenically related to each other and have been included into groups. A number (e.g., 1, 2, 3) is given to separate types, whereas antigenically related types are given a number and in addition a letter for the subtype (e.g., 6A, 6B).

The major cell-wall component of the pneumococcus, in addition to peptidoglycan, is the cell-wall polysaccharide (CWPS). The CWPS contains phosphorylcholine and galactosamine and is specific for the species *S. pneumoniae*, but not type-specific. The cell wall also contains several proteins. The M-protein is type specific rather than species-specific, but is, unlike the M-protein in *Streptococcus pyogenes,* not known to be related to virulence or immunity. Surface protein A (PspA) is one of several proteins that has received recent attention as a possible pneumococcal virulence factor, particularly in view of the potential of these proteins as vaccine candidates (Paton et al., 1997). The function of PspA is not clear, but it has been suggested as an inhibitor of complement activation (AlonsoDeVelasco et al., 1995). The molecule is highly immunogenic, and antibodies to PspA have been shown to prevent pneumococcal infections in mice (Briles et al., 1996; Wu et al., 1997; Nayak et al., 1998). Pneumococcal surface adhesin A (psaA), choline-binding protein A (cbpA), and *S. pneumoniae* secretory IgA binding protein (SpsA) are surface proteins that seem to be involved in the process of bacterial adherence (Sampson et al., 1994; Hammerschmidt et al., 1997; Rosenow et al., 1997). Autolysin (N-acetylmuramic acid-L-alanine amidase), an enzyme involved in cell division, cleaves the peptidoglycan, but induces lysis of pneumococci under certain conditions such as during prolonged incubation (AlonsoDeVelasco et al., 1995). The lipoteichoic acid, or Foreman antigen, is a powerful inhibitor of this autolysin. Pneumolysin (Rubins et al., 1995) and neuraminidase (Paton et al., 1997) are two proteins released upon lysis of pneumococci that also may be important for the virulence of the bacteria.

Pathogenesis

The typical pathogenesis of pneumococcal pneumonia in a nonimmune host begins with the organism's entry, colonization of the nasopharynx, and aspiration into the lower airways. A prolonged carriage in the nasopharynx preceding a pneumonia caused by the same pneumococcal serotype is less common, probably because carriage leads to a type-specific antibody response (Gwaltney et al., 1975; Gray et al., 1980; Musher et al., 1997). A direct invasion into the bloodstream, or a continuous spread to adjacent tissues, seems also to be less common than aspiration. In the absence of an effective local defense in the lower airways, the pneumococci rapidly multiply in the alveolar spaces, leading to local hyperemia, edema, and mobilization of neutrophils (congestion). Congested capillaries, and alveoli filled with bacteria, red cells, and fluid, lead to a significant increase in the lung weight after 2 to 3 days (red hepatization). Neutrophils begin to invade the alveoli and trap bacteria against pulmonary cells and fibrin, so-called surface phagocytosis, and the infected part of the lung becomes gray-white in color (gray hepatization). Resolution begins when complement and anticapsular antibodies appear in the alveoli, permitting the neutrophils and macrophages to phagocytize the opsonized pneumococci. The healing of the lung is in general complete, without scarring or evidence of tissue necrosis.

From the time of entry of the organism into the host to the healing of the pneumonia, several different virulence and defense mechanisms are involved, many of which are still incompletely understood, or have been studied only in vitro or in animal experiments. The proposed mechanisms, based mainly on reviews by AlonsoDeVelasco et al. (1995), Tuomanen et al. (1995), and Watson et al. (1995), are

TABLE 2. Proposed Pneumococcal Virulence Factors and Mechanisms for Host Defense[a]

Pneumococcal pathogenic pathway	Proposed virulence factors and mechanisms for virulence	Proposed defense mechanisms
Nasopharyngeal colonization	IgA proteases Pneumococcal surface proteins (adhesins)	Secretory IgA, type-specific IgG
Progression to lower respiratory tract (or directly to the bloodstream)	Epithelial and cilial damage by previous viral infection, or release of pneumolysin or hydrogen peroxide	Cough reflexes, mucosal secretion, ciliary transport Secretory IgA, type-specific IgG
Proliferation within alveoli and spread within the lung or to the bloodstream	Capsule: resistance to phagocytosis, lack of activation of alternative complement pathway, deposition of opsonically inactive complement compounds, poor ability to induce antibodies in some serotypes	Opsonization by alveolar macrophage and PMNs + type-specific antibodies or complement C-reactive protein
	Cell wall or C-polysaccharide: inflammatory effects, such as IL-1 production, activation of alternative complement pathway resulting in anaphylactic reaction, PMN activation, enhanced vascular permeability	
	Complement factor H-binding component: inhibition of complement and phagocytosis	
	PspA: inhibition of phagocytosis?	
	Autolysin: releases pneumolysin and cell wall products	
	Pneumolysin: cytolytic or cytotoxic to most cells in the lung, activates complement	
	Hydrogen peroxide: lung injury?	

PMN, polymorphonuclear leukocyte; PspA, surface protein A.
[a]Adapted from AlonzoDeVelasco et al., 1995; Tuomanen et al., 1995; and Watson et al., 1995.

listed in Table 2. The capsule is the major virulence factor for *S. pneumoniae,* supported by the fact that encapsulated bacteria are at least 10^5 times more virulent than strains lacking the capsule (Watson & Musher, 1990). At an early stage of infection, pneumococcal surface proteins such as PspA and factor H-binding component may inhibit the activity of complement and thus enhance the capsule's resistance to phagocytosis (AlonsoDeVelasco et al., 1995). Later, at the stage of bacterial disintegration and lysis, cell-wall components, especially the CWPS and pneumolysin, induce inflammation due to the release of one or more cytokines. The phosphorylcholine residue of the CWPS binds to the C-reactive protein (CRP), an acute-phase reactant β-globulin of human serum. CRP is a potent activator of the classical pathway of complement and promotes opsonization of pneumococci. Animal models indicate that CRP may play an important role in the host defense against pneumococcal disease (Szalai et al., 1995). If pneumococci are spread into the bloodstream they are normally rapidly cleared in the presence of anticapsular antibodies, mainly by the liver and to a lesser extent by the spleen. However, complement deposition on the capsule is essential for effective clearance. An intact complement system is even more important if anticapsular antibodies are lacking, but in this case the macrophages of the spleen seem to be superior to those in the liver for clearance of the pneumococci.

In the immunocompetent host, colonization or infection with pneumococci elicits an antibody response against several bacterial structures, including the capsular polysaccharide, the CWPS, pneumolysin, and different surface proteins (AlonsoDeVelasco et al., 1995). However, only type-specific capsular polysaccharide antibodies are known to be important in the defense against pneumococcal disease in humans (Musher et al., 1992). The capsular polysaccharides, similar to other pure polysaccharides, induce a T-cell-independent antibody re-

sponse. This response is characterized by long-lasting antibodies, mainly of IgM, IgA, and IgG_2 isotypes, in immunocompetent adults, but no immunogenic memory and no booster effect on re-exposure (Byrun & van Furth, 1991; AlonsoDe-Velasco et al., 1995). These antigens also elicit a poor response, especially from IgG_2, in children less than 2 years of age, who have immature immune systems; the IgG_1 response is relatively stronger. However, for some serotypes, especially 6A, 14, 19F, and 23F, the antibody response continues to be poor up to about 5 years of age.

Epidemiology

Carriage

Disease caused by *S. pneumoniae* is endemic in all areas of the world. A high percentage of the population are asymptomatic carriers of pneumococci in their upper respiratory tract. The rate of carriage varies with age, environment, season, and the presence of respiratory tract infections. The carriage rates are the highest in preschool children, among whom it may be >50%, and the lowest, <5%, in adults without children who live in industrialized parts of the world (Hendley et al., 1975; Aaronson et al., 1996; Musher et al., 1997). The mean duration of carriage of a specific serotype may be as long as 3 to 5 months in infants (Gray et al., 1980). In older children and adults the mean duration of carriage seems to be shorter, about 2 months, with a median of less than 1 month (Hendley et al., 1975; Ekdahl et al., 1997).

Epidemic Outbreaks

In the pre-antibiotic era epidemics of pneumococcal disease were not uncommon, especially in settings where people lived in crowded conditions, such as military camps and jails (Heffron, 1939). Such outbreaks, although infrequent, continue to occur. During the last 10 years there have been reports of outbreaks of pneumococcal pneumonia serotype 1 in two men's shelters (Mercat et al., 1991), serotype 12F in a large urban jail (Hoge et al., 1994), and serotypes 7F and 8 in a military camp (Musher et al., 1997). In the study by Musher et al. (1997), even soldiers without any symptoms of lower respiratory disease had a high carriage rate of pneumococci, about 25%, reflecting the capability of the pneumococcus to spread in crowded conditions. During epidemics, person-to-person transmission occurs via droplets.

Serotypes

Of the 90 serotypes now recognized (Henrichsen, 1995), those with the lower numbers are generally the most pathogenic for humans (Table 3). During the first half of the century, serotypes 1, 2 and 3 were the most common, and were together responsible for approximately 75% of bacteremic disease (Tilghman & Finland, 1937). Now serotype 2 is rarely found, whereas serotype 3 remains a common cause of invasive disease. In a study of 7000 episodes of invasive pneumococcal disease obtained by combining 13 existing datasets from Europe, South America, and North America, 12 serotypes (or groups) accounted for 80.9% of all

TABLE 3. Rank Order of Serotypes (Serogroups) Causing Invasive Pneumococcal Disease

Study	Serotype/serogroup									Percentage of all isolates
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	
Scott et al., 1996; N = 7010; Europe, North and South America; all age groups	14	6	19	3	23	1	9	4	8	70
Nielsen & Henrichsen, 1992; N = 6209; Europe (81%); Adults (>14 years of age)	3	1	14	7	19	4	6	9	8	64
Nielsen & Henrichsen, 1992; N = 2304; Europe (81%); Children (≤14 years of age)	6	14	19	18	1	7	23	4	5	77
Nielsen & Henrichsen, 1996; N = 495; Denmark; all age groups	1	9	4	14	6	7	3	12	8	68

isolates (Scott et al., 1996). Serotypes 14, 6, 19, and 3 were the most common and accounted for nearly 40%; serotypes 23, 1, 9, and 4 for approximately 25%; and types 8, 18, 7, and 5 for approximately 15% of isolates. This study also demonstrated that there are important geographic variations and that significant variations in the distribution of serotypes can be found among different age groups. The majority of serotypes were most prevalent in the first decade of life. For some (e.g., serotypes 6, 19, 14, and 23), there was an abrupt reduction in risk of disease beyond the first decade, whereas for others (e.g., serotype 1), the relative risk declined steadily throughout life. Only with serotypes 3 and 8 was there an increased risk of disease past middle age. However, there may be significant temporal variations in the epidemiology of serotypes in one geographic location. For example, a pronounced increase in serotype 14, especially in the elderly, occurred in Sweden, from 8% of invasive isolates in 1987 to 18% in 1992 (Hedlund et al., 1995).

The serotypes included in the current 23-valent pneumococcal polysaccharide vaccine are types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. In developed countries these 23 serotypes represent approximately 90% of the types that have been responsible for invasive disease (Hedlund et al., 1995; Nielsen & Henrichsen, 1996; Plouffe et al., 1996; Sankilampi et al., 1997).

Incidence of Pneumococcal Pneumonia

The highest incidence of CAP is seen in the very young and in the elderly. The total incidence of CAP is approximately 10 per 1000 inhabitants per year, but may reach approximately 35 per 1000 inhabitants per year in those less than 5 or more than 74 years of age (Jokinen et al., 1993) (Fig. 1). *S. pneumoniae* is the most common cause of CAP, and accounts for approximately 50% of cases requiring treatment in hospital (Macfarlane et al., 1982; Holmberg 1987; British Thoracic Society, 1987; Örtqvist et al., 1990a; Levy et al., 1988; Fang et al., 1990; Burman et al., 1991; Lieberman et al., 1995; Bohte et al., 1995).

The exact incidence of pneumococcal pneumonia is not known. However, it can be estimated that 5 to 10 per 1000 persons 65 years of age or more had a pneumococcal pneumonia in Sweden in 1995. The basis for this estimation is that approximately 65% to 70% of patients with pneumonia in this age group will require hospital treatment (Jokinen et al., 1993; Örtqvist et al., 1998), that the incidence of pneumonia as a first-listed diagnosis requiring treatment in hospital was 11.7 per 1000 in 1995 (register data, Swedish National Board of Health), and that pneumococcus is the cause of CAP in 32% to 54% of all cases of CAP admitted to hospital in Sweden (Berntsson et al., 1985, Holmberg, 1987; Örtqvist et al., 1990a; Burman et al., 1991).

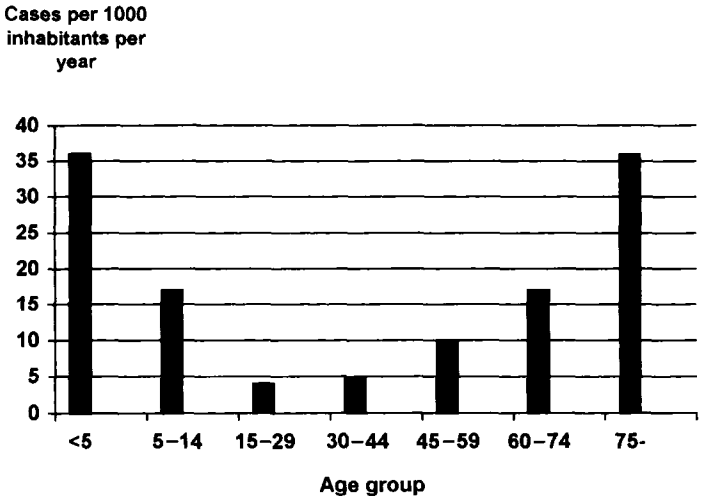


FIGURE 1. Incidence of community-acquired pneumonia. Adapted from Jokinen et al., 1993.

Incidence of Invasive Pneumococcal Disease

In developed countries the incidence of invasive disease, defined as isolation of the bacteria from blood, liquor, or another normally sterile site, is about 10 to 20 per 100,000 inhabitants of all ages, and up to about 50 per 100,000 (range, 30–80) in those 65 years or older (Fedson et al., 1999). Bacteremic pneumococcal pneumonia is the predominant clinical syndrome and accounts for approximately 60% to 80% (compared with 5% to 10% for meningitis) of all cases of invasive pneumococcal disease (Mufson et al., 1982; Burman et al., 1985; Jetté et al., 1989; Davidson et al., 1994; Zangwill et al., 1996). Whereas meningitis is relatively more common in the very young, pneumonia may account for up to 90% of all invasive pneumococcal disease in the elderly. Between countries, and also within a single country, there may be substantial differences in the observed rates of invasive disease (Fedson et al., 1999). There may be several reasons for this observation—differences in the frequency with which blood cultures are obtained in CAP patients, different blood culturing techniques, or true variations in the incidence.

During the last decade, there have also been several reports of an increase in the incidence of invasive pneumococcal disease (Hedlund et al., 1995; Magnus & Andersen, 1995; Plouffe et al., 1996; Nielsen & Henrichsen, 1996; Giesecke & Fredlund, 1997; Ekdahl et al., 1998). This increase seems to have been most pronounced for bacteremia in the elderly, and in Sweden it has coincided with a substantial increase in the number of serotype 14 isolates (Hedlund et al., 1995). In Sweden, the incidence of pneumococcal bacteremia increased from 5 per 100,000 in 1990 to nearly 15 per 100,000 in 1995, while the incidence of pneumococcal meningitis remained just above 1 per 100,000. Figure 2 shows the increase of invasive disease in different age groups in Sweden. Some of this increase may be due to better ascertainment of cases of invasive disease (Schönheyder & Sörensen, 1997), but there are also data indicating that it may represent a true increase in the incidence of disease (Hedlund et al., 1995; Giesecke & Fredlund, 1997; Ekdahl et al., 1998).

Underlying Conditions

In most studies of pneumococcal disease (Burman et al., 1985; Davidson et al., 1994; Scott et al., 1996; Sankilampi et al., 1997), but not all (Örtqvist et al., 1988; Nielsen & Henrichsen, 1996), a predominance of males is found, with a typical male: female ratio of about 1.5–2:1. One reason for this may be that some other underlying conditions, such as smoking and alcoholism, have been more common among males.

Defects in any of the proposed nonspecific or specific defense mechanisms listed in Table 2 are associated with an increased risk for pneumococcal disease. Decreased cough reflex (e.g., in neurological disease or alcoholism) and poor ciliary function (e.g., in chronic bronchitis) would result in a decreased clearance of aspirated bacteria, and thus a higher bacterial load in the alveoli. Defects in the

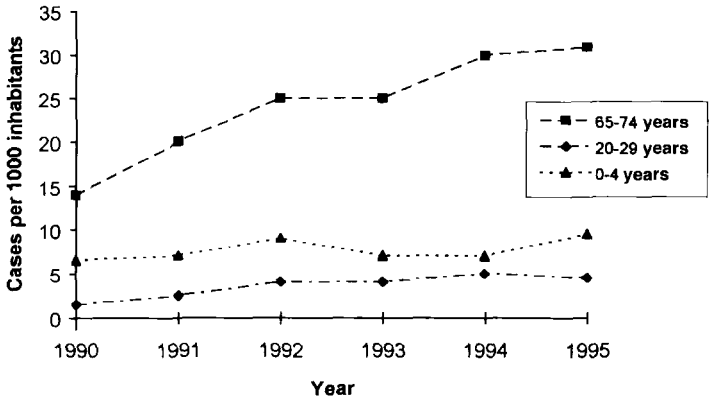


FIGURE 2. Incidence of invasive pneumococcal disease in different age groups in Sweden, 1990–1995.

immune system (e.g., gammaglobulinemia; hypogammaglobulinemia; secondary Ig deficiency as in myeloma; complement defects, especially C3; or leukopenia or diminished leukocyte migration) can lead to poor opsonization and phagocytosis of the pneumococci. The spleen has a high capacity for clearance of nonopsonized organisms; thus, patients with functional or anatomical asplenia have a higher risk for developing severe pneumococcal infection. Liver cirrhosis would also increase the risk for serious pneumococcal infections due to reduced phagocytosis.

These theoretical risk factors have been found among patients with pneumococcal disease in many clinical studies (Austrian & Gold, 1964; Mufson et al., 1982; Burman et al., 1985; Gransden et al., 1985; Örtqvist et al., 1988; Davidson et al., 1994; Watanakunakorn & Bailey, 1997). The most common predisposing conditions observed in clinical practice are listed in Table 4. The incidence of pneumococcal disease is up to 50 times higher in children younger than 2 years and in adults older than 65 years than in adolescents (Davidson et al., 1994). Lipsky et al. (1986) demonstrated in a case-control study that dementia, seizure disorders, current cigarette smoking, congestive heart failure, cerebrovascular disease, institutionalization, and chronic obstructive pulmonary disease were statistically independent risk factors for pneumococcal pneumonia in male patients admitted to hospital. Cigarette smoking was recently demonstrated to be the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults (Nuorti et al., 2000). Alcoholism has been associated with a higher risk for pneumonia and for developing severe pneumococcal disease (Brayton et al., 1970; Burman et al., 1985; Perlino & Rimland, 1985; Örtqvist et al., 1988; Davidson et al., 1994; Jaero et al., 1996). In addition to the higher risk for aspiration, this association with alcoholism is probably due to decreased neutrophil mobilization and perhaps the effect of ethanol on the neutrophil bactericidal mechanisms. The highest risk for pneumococcal infection is seen in patients with asplenia, especially in young children with sickle-cell disease (Austrian, 1981). Following splenectomy, the risk is higher in patients with malignant disease than in those in whom surgery was necessary because of trauma. In a follow-up study of nonvaccinated patients subjected to staging splenectomy for Hodgkin's disease in Norway, from 1969 to 1980, the risk for systemic pneumococcal disease was 20 times that in the general Norwegian population (Foss Abrahamsen et al., 1997). The deficient clearance of pneumococci from the bloodstream in asplenic patients often results in overwhelming infection with a rapid progression to septic shock, and is associated with a high mortality. *S. pneumoniae* is the most commonly identified bacterial pathogen causing pneumonia in patients with HIV infection, and this patient group has 10 to 100 times higher risk for pneumococcal pneumonia and bacteremia than do non-HIV-infected persons (Redd et al., 1990; Janoff et al., 1992, 1993; Garcia-Leoni et al., 1992; Hirschtick et al., 1995). Although HIV infection primarily affects the cell-mediated immune system, multiple components of the immune response to pneumococcal infection, such as IgG, complement, phagocytosis, and clearance, may also be impaired. The clinical course of pneumococcal pneumonia is more often complicated by bacteremia in HIV-infected persons, compared with HIV-negative controls. Despite this, the mortality in invasive pneumococcal disease does not seem to be higher in HIV-infected than in noninfected persons, perhaps because the former most often are young, do not have other underlying diseases, and receive prompt medical care (Janoff et al., 1993; Hirschtick et al., 1995; Gilks et al., 1996).

TABLE 4. Common Predisposing Factors for Pneumococcal Disease

Age <2 years or >65 years
Institutionalization
Cigarette smoking
Alcoholism
Chronic heart and lung disease
Congestive heart failure
Chronic obstructive pulmonary disease
Liver cirrhosis
Neurological disease
Cerebrovascular disease
Dementia
Seizure disorders
Decreased cough reflex
Immune deficiencies
Hypogammaglobulinemia, agammaglobulinemia, or secondary Ig deficiency
Complement defects, especially C3
Leukopenia
Functional or anatomical aplasia
HIV infection

Resistance to Penicillin and Other Antibiotics

According to the current classification, pneumococci with a minimum inhibitory concentration (MIC) for penicillin of ≤0.06 μg/mL are defined as susceptible; those with MIC 0.1 to 1 μg/mL are intermediately resistant, and those with MIC ≥2 μg/mL are resistant (National Committee for Clinical Laboratory Standards [NCCLS], 1995). For practical reasons all pneumococcal strains with MIC ≥0.1 μg/mL are often referred to as "resistant." However, a majority of such strains are not resistant, but have a decreased susceptibility to penicillin that may be overcome by an increased dosage of this drug. Furthermore, for treatment of pneumococcal pneumonia, the current NCCLS values are overly conservative, and penicillin remains a first-line drug in a majority of cases.

For the first 25 years of penicillin use in clinical practice *S. pneumoniae* was highly susceptible to that drug, with MICs of approximately 5 to 10 ng/mL. However, in 1967, the first "penicillin-resistant," pneumococcus (MIC 0.5 μg/mL) was isolated from a patient in Papua New Guinea (Tomasz, 1997). During the next 10-year period pneumococcal strains that were penicillin-resistant, but susceptible to other common antibiotics, were reported from several parts of the world. In 1977, multidrug-resistant (defined as resistant to three or more antibiotics) pneumococci were isolated for the first time during an outbreak of pneumococcal disease in South African hospitals, and these strains showed greatly increased MICs to penicillin, tetracycline, erythromycin, chloramphenicol, clindamycin, streptomycin, and occasionally also rifampin.

The decreased susceptibility to penicillin is caused by a reduced capacity of one or more of the five pneumococcal penicillin-binding proteins (PBPs) to bind the antibiotic molecules (Tomasz, 1997). Alterations of PBP1a and PBP2x typically leads to a low-level resistance, while the additional acquisition of an altered PBP2b results in highly penicillin-resistant isolates (Baquero, 1996a). There is a considerable variation in the molecular PBP pattern of resistant isolates. However, isolates that share a unique PBP pattern also tend to share other properties, such as resistance pattern to other antibiotics and serotype, and have been shown to represent a genetically distinct lineage of pneumococcal clones (Tomasz, 1997). The reason for this clonality may be that the PBP genes of resistant isolates are "mosaic" in nature, that is, nonpneumococcal nucleotide sequences are incorporated within the genes. The heterologous DNA, thought to originate from *viridans* streptococci in the oral flora, has been imported by the pneumococci and integrated in the structural genes of PBPs through recombination (Baquero, 1996a; Tomasz, 1997). Penicillin-resistant pneumococci are to a varying degree resistant also to other β-lactam antibiotics, since the PBPs are common targets for these drugs. Third- or fourth-generation cephalosporins for parenteral treatment (e.g., cefotaxime, ceftriaxone, cefpirom and cefepim, and imipenem) are generally more active than penicillin or amoxicillin (Tables 5, 6) (Hoffman et al., 1995; Goldstein et al., 1996). However, cephalosporin-resistant, penicillin-susceptible pneumococci do occur and may be an increasing problem. Of the oral β-lactam antibiotics, amoxicillin remains the most active.

Penicillin-resistant isolates (MIC ≥0.1 μg/mL) often also carry resistance genes for other antibacterial agents, such as chloramphenicol, trimethoprim–sulfamethoxazole, erythromycin, tetracycline, and aminoglycosides (Tables 6, 7). Table 7 illustrates

TABLE 5. Minimum Inhibitory Concentrations (MIC_{90}) for Commonly Used Antibiotics Against 1812 Strains of *Streptococcus pneumoniae* Isolated from Patients with Lower Respiratory Tract Infections in Europe and the United States, 1992–1993[a]

Drug	MIC_{90}	Range
Penicillin	2	0.008–4
Amoxicillin	1	0.004–8
Cefaclor	64	0.06–≥128
Cefuroxime	4	≤0.015–≥32
Cefixime	16	0.06–≥128
Ceftriaxone	1	≤0.004–≥4
Erythromycin	≥32	≤0.06–32
Doxycycline	4	≤0.26–16
Chloramphenicol	1	0.5–0.32
Ciprofloxacin	1	0.12–16
Ofloxacin	2	0.25–>16
Trimethoprim/sulfamethoxazole	4	<0.5–≥64

[a]From Goldstein et al., 1996.

TABLE 6. Antibiogram in 59 Penicillin-Resistant Invasive Pneumococcal Strains Isolated from Children, Washington, D.C.[a]

	MIC (range)	MIC_{90}	Percentage susceptible
Cefotaxime	0.03–4	1	85
Chloramphenicol	2–32	16	69
Imipenem	0.015–0.5	0.5	53
Meropenem	0.015–1	0.5	51
Rifampicin	0.015–0.06	0.06	100
Vancomycin	0.125–0.25	0.25	100

[a]From Pikis et al., 1997.

that resistance to erythromycin (and other macrolides) and tetracycline is very common among penicillin-resistant isolates. Furthermore, it can be seen that the intermediately resistant populations are very small, compared to those that are susceptible or resistant. Because of this bimodal distribution, either susceptible or resistant, of pneumococcal strains against these classes of drugs, few, if any, truly intermediate strains occur (Jacobs, 1992). In contrast to the β-lactams, it is unlikely that a nonsusceptible strain can be effectively treated by increasing the dose of macrolides or tetracyclines. Ciprofloxacin and ofloxacin have borderline MICs, but have shown a relatively low rate of resistance (Tables 5, 7) (Hoffman et al., 1995; Goldstein et al, 1996). Newer quinolones, such as sparfloxacin, trovafloxacin, grepafloxacin, clinafloxacin, gatifloxacin, and moxifloxacin, have improved activity against pneumococci with MICs ≤ 0.25 μg/mL (Lode et al., 1995; Ortqvist et al., 1996; George & Morrissey, 1997; Barry & Fuchs, 1997; Klugman & Gootz, 1997; Bauernfiend, 1997). However, in the study by Goldstein et al. (1996), seven (of 1812) pneumococcal strains had MICs ≥ 16 μg/mL to ofloxacin and ciprofloxacin, which indicates that they may not have responded to any of the newer quinolones designed for improved activity against *S. pneumoniae*. This fear has been confirmed by recent studies showing a clear correlation between increasing usage of quinolones and an increase of resistance in *S. pneumoniae* for these drugs, including newer "respiratory tract quinolones" (Chen et al., 1999; Ho et al., 1999; Linares et al., 1999). Vancomycin is today the only antibiotic on the market that is universally active against *S. pneumoniae*. Recently, clinical isolates of pneumococci tolerant to vancomycin have been described (Novak et al., 1999). Theoretically, vancomycin tolerance could contribute to therapy failure in some clinical situations (e.g., meningitis), but it is not known whether it may also facilitate the acquisition of vancomycin resistance.

Resistance is most frequently found in serotypes 6, 9, 14, 19, and 23. This may be due to the high rates of carriage of these strains in the nasopharynx of small children. The high rate of carriage is probably related to the good mucosal adher-

TABLE 7. Resistance against Different Antibiotics in Invasive Pneumococcal Isolates (N = 527) from Atlanta, Georgia, 1994[a]

	All pneumococcal isolates		Penicillin-resistant (MIC ≥ 0.1 μg/mL) isolates
	Intermediate resistance (%)	High-level resistance (%)	Intermediate or high-level resistance (%)
Penicillin	18	7	—
Cefotaxime	5	4	34
Chloramphenicol	—	3	12
Trimethoprim-sulfamethoxazole	18	7	75
Tetracycline	0.2	8	24
Erythromycin	3	12	41
Ofloxacin	1	0	1
Imipenem	4	2	23

[a]From Hoffman et al., 1995.

TABLE 8. Prevalence Rates of Penicillin-Resistance in Healthy Carriers, Patients with Noninvasive Pneumococcal Disease, and Invasive Disease in Reports from Four Countries, 1994–1998

Country	References	Carriage (%)	Noninvasive disease (%)	Invasive disease (%)
Sweden	Henning et al., 1997 Christensson et al., 1997 Ekdahl et al., 1998	2–9	1.5–4	1.5
Spain	Nava et al., 1994 Garcia-de-Lomas et al., 1997 Garcia-Martos et al., 1997 Clavo-Sanchez et al., 1997	68	50–89	18
United States	Stanek & Mufson, 1995 Duchin et al., 1995 Hoffman et al., 1995 Fairchok et al., 1996 Zangwill et al., 1996	48–53	36	11–25
Australia	Gratten et al., 1996 Skull et al., 1996 Gratten et al., 1997 McLaughlin et al., 1997	40	4	2[a]

[a]20% reported among aborigines.

ence properties of these serotypes and the poor immune response they induce in this age group (Baquero, 1996a). The prevalence of resistant strains is generally higher in healthy carriers (mostly children) than in patients with clinical disease, and higher in patients with noninvasive than invasive pneumococcal disease (Table 8).

The spread of resistant organism in the community is enhanced by many factors (Table 9) (Nava et al., 1994; Duchin et al., 1995; Bédos et al., 1996; Fairchok et al., 1996; Reichler et al., 1996; Clavo-Sánchez et al., 1997). Such horizontal spread seems to be especially effective in areas with a large population of "colonizable humans" or crowded conditions, such as day-care centers, and areas with high antibiotic consumption (Baquero, 1996a,b; Kristinsson, 1997). In addition, clonal spread of pneumococcal strains that are indistinguishable in terms of overall relatedness and relatedness of their PBP genes, within as well as between countries, has been well documented. In the 1990s several distinct resistant clones spread throughout the world. Two early clones are both supposed to have originated from Spain, a 23F strain that has spread to several countries in Europe, the United States, South Africa, and Korea (Munos et al., 1991; Tomasz, 1997), and a 6B strain that spread to Iceland (Soares et al., 1993). That a significant spread over large geographical areas may occur also for penicillin-susceptible pneumococci has recently been shown for a type 14 clone causing invasive disease (Henriques et al., 2000).

TABLE 9. Factors Associated with Carriage or Infection with Penicillin-Resistant Pneumococci

Age <5 years or >65 years
"Pediatric" serotypes (i.e., serotypes 6, 9, 14, 19, 23)
Day-care attendance
Previous hospitalization
Nosocomial infection
Recent antibiotic treatment, especially with β-lactams and trimethoprim-sulfamethoxazole
Underlying conditions (e.g., immunosuppression, alcoholism)

During the last 10-years there has been an extensive spread of β-lactam-resistant and multiresistant *S. pneumoniae* strains. The map in Figure 3 shows a world image of the estimated prevalence of penicillin resistance (MIC $\geq$0.1 μg/mL)[1]. The included data are based on the highest prevalence rate reported for these countries, obtained from approximately 50 publications published from 1996 to

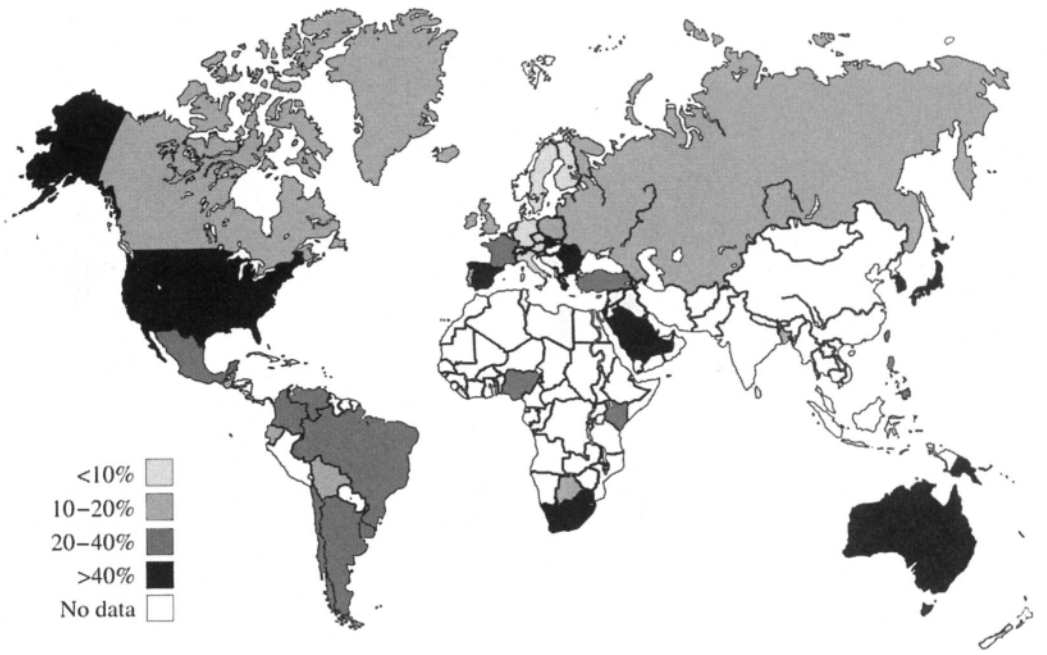


FIGURE 3. Global prevalence of penicillin resistance (MIC >0.1 μg/mL) in reports published 1995–1998.

1998. Although these data may not be representative for each country as a whole (Bedos et al., 1996; Trupl et al., 1997), and may not always be comparable between countries, they reflect the fact that the possibility of penicillin resistance, and also resistance to other antibiotics, must be taken into account in the management of pneumococcal disease throughout the world. A very high prevalence of pneumococci with decreased susceptibility to penicillin (60%-90%) has been reported from Spain (Garcia-Martos et al., 1997; Garcia-de-Lomas et al., 1997), Slovakia (Reichler et al., 1996), Romania (Appelbaum et al., 1996), South Korea (Kirn et al., 1996), and Papua New Guinea (Lehmann et al., 1997). In areas with a high prevalence of nonsusceptible pneumococci, there is also a shift toward a higher percentage (often more than 50%) of strains with MIC for penicillin of >1 μg/mL and of multiresistant strains. However, so far pneumococcal isolates with penicillin MICs ≥4 μg/mL, seem to be uncommon, and those with MICs ≥8 μg/mL are rare (Goldstein et al., 1996; Appelbaum et al., 1996; Kim et al., 1996; Trupl et al., 1997; Garcia-de-Lomas et al., 1997). In contrast, a very low prevalence of resistance, often below 5%, exists in the Nordic countries (except for Iceland) (Nielsen & Henrichsen, 1996; Manninen et al., 1997; Kristinsson, 1997; Henning et al., 1997; Ekdahl et al., 1998), the Netherlands (Hermans et al., 1997), and Austria (Mittermayer et al., 1996; Georgopoulos et al., 1998).

Clinical Features

Symptoms, Signs, and Physical Examination

Case Presentation A 45-year-old man presents at the emergency room on a February evening with cough, fever, and left-sided pleuritic chest pain. The patient's medical history is notable only for a mild ulcerative colitis for the past 8 years, which is being treated with a low dose of sulfasalazine (500 mg twice daily). He has been smoking approximately five cigarettes per day for many years. He works full-time in an office and lives at home together with his wife and a 15-year-old son. His son developed a runny nose and cough about 10 days ago, and is now recovered, and his wife developed an intense cough about 2 days ago. There is a limited outbreak of influenza in the community.

The symptoms began 5 days ago with a sudden onset of high temperature (39°–40°C), a single shaking chill, pleuritic chest pain in the left side and a productive cough with expectoration of rusty sputum. He has been slightly nauseous, but has not vomited. On physical examination, the patient's temperature is 39.5°C, pulse is 120 bpm, blood pressure is 135/70 mm Hg, and respiratory rate is 28 breaths per minute. The patient is not confused, and there is no evidence of cyanosis, jugular venous distention, swelling of the feet, or clubbing. Oral examination is within normal limits and there is no palpable cervical adenopathy. Cardiac examination is within normal limits, except for the tachycardia. There are no crackles, but a coarse bronchial breathing is heard over the apical/frontal part of the left lung and percussion reveals dullness over the same area. Laboratory data on admission include a hemoglobin 113 g/L, white blood cell count 22.5×10^9/L with 23% band forms and 70% neutrophils, C-reactive protein 375 mg/L, serum sodium 132 mmol/L, serum potassium 3.9 mmol/L, serum albumin 26 g/L, serum creatinine 122 μmol/L, and serum alanine aminotransferase 1.69 μ/L. Chest x-ray shows lobar infiltration of the left upper lobe (Fig. 4). The preliminary diagnosis is pneumococcal pneumonia, and after cultures from blood, sputum, and nasopharynx are obtained the patient is given benzylpenicillin 3 g three times daily. He responds rapidly to therapy and fever has resolved after 36 hours. By then, cultures have shown growth of *S. pneumoniae* in blood, nasopharyngeal secretions, and sputum ($>10^5$ cfu/mL, and gram-positive diplococci in a representative sputum sample). The patient is switched to penicillin V on day 3 and discharged on day 6. The day before discharge a laboratory analysis shows hemoglobin 127 g/L, white blood cell count 11.4×10^9/L with no band forms, and C-reactive protein 103 mg/L. At follow-up 6 weeks later the patient has regained his previous health and laboratory and radiographic abnormalities have resolved.

Comment

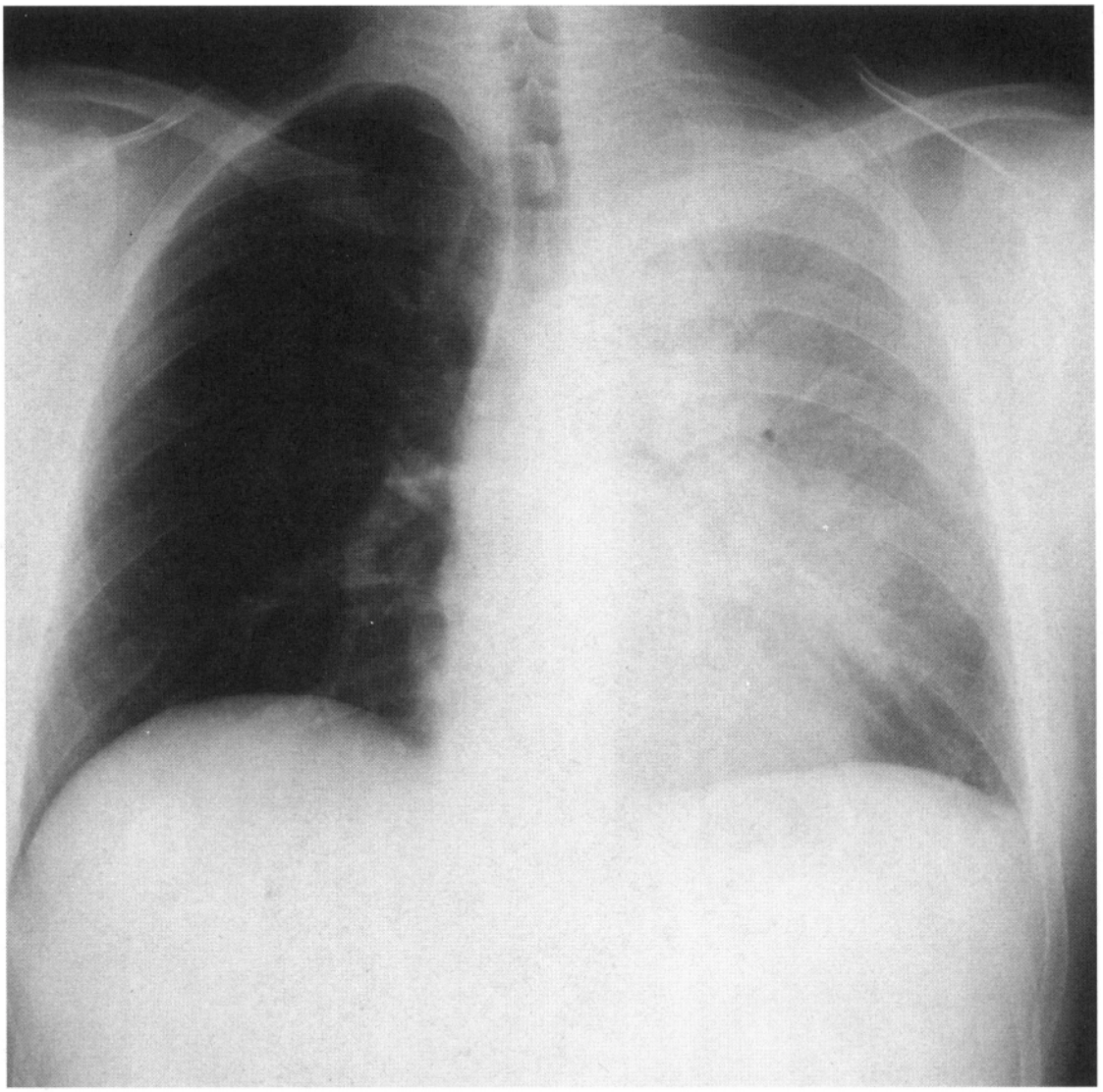
This patient's history is typical of a pneumococcal pneumonia. He has a moderately severe bacteremic disease with tachypnea, tachycardia, an intense inflammatory reaction, and slightly elevated serum creatinine and hepatic enzyme values. The response to penicillin is rapid and the patient recovers completely within 6 weeks without any complications.

However, the clinical presentation of pneumococcal pneumonia is variable. It is not uncommon that patients, and especially those with bacteremic disease, lack respiratory tract symptoms. In up to 50% of patients with bacteremic pneumococcal pneumonia, respiratory tract symptoms are seen late in the course or not at all (Örtqvist et al, 1988). The dominating symptoms in bacteremic patients may instead be chills, diarrhea, vomiting, and muscle or joint pain. Contusion is common, and fever may be absent in elderly patients and in otherwise immunocompromised patients (Gleckman & Hibert, 1982; Perlino & Rimland, 1985). Atypical presentation of pneumonia may also be associated with specific locations of the pneumonia. A pneumonia located in the apical part of the lung may present as a meningitis with severe headache and stiffness of the neck, and a basal pneumonia causing diaphragmatic pleuritis may result in symptoms suggesting an acute abdominal surgical condition.

During the first 24 hours of disease the physical findings may be slight. Inspection may reveal diminished motion of the affected side, tachypnea, and shallow breathing. The typical findings of a lobar pneumonia gradually become apparent over the next 2 to 3 days, with dullness on percussion, bronchial breathing, and crackling rales over the consolidated lobe. If the patient has severe pleuritic pain, the restricted movement of the affected lung may result in only weak breathing sounds and no crackles on auscultation. However, percussion findings may suggest the possibility of a pneumonia diagnosis and the need to proceed with further investigations, especially a chest x-ray. Focal findings may be sparse also in those who have difficulties in cooperating fully, such as elderly persons or severely toxemic patients.

Laboratory Findings

During the first 24 hours of disease, the chest x-ray may be normal, but then typically reveals a homogeneous lobar or segmental alveolar infiltrate (Austrian & Gold, 1964; Jay et al., 1975; Ort et al., 1983; Örtqvist et al., 1988) (Figs. 5-8). Bilateral

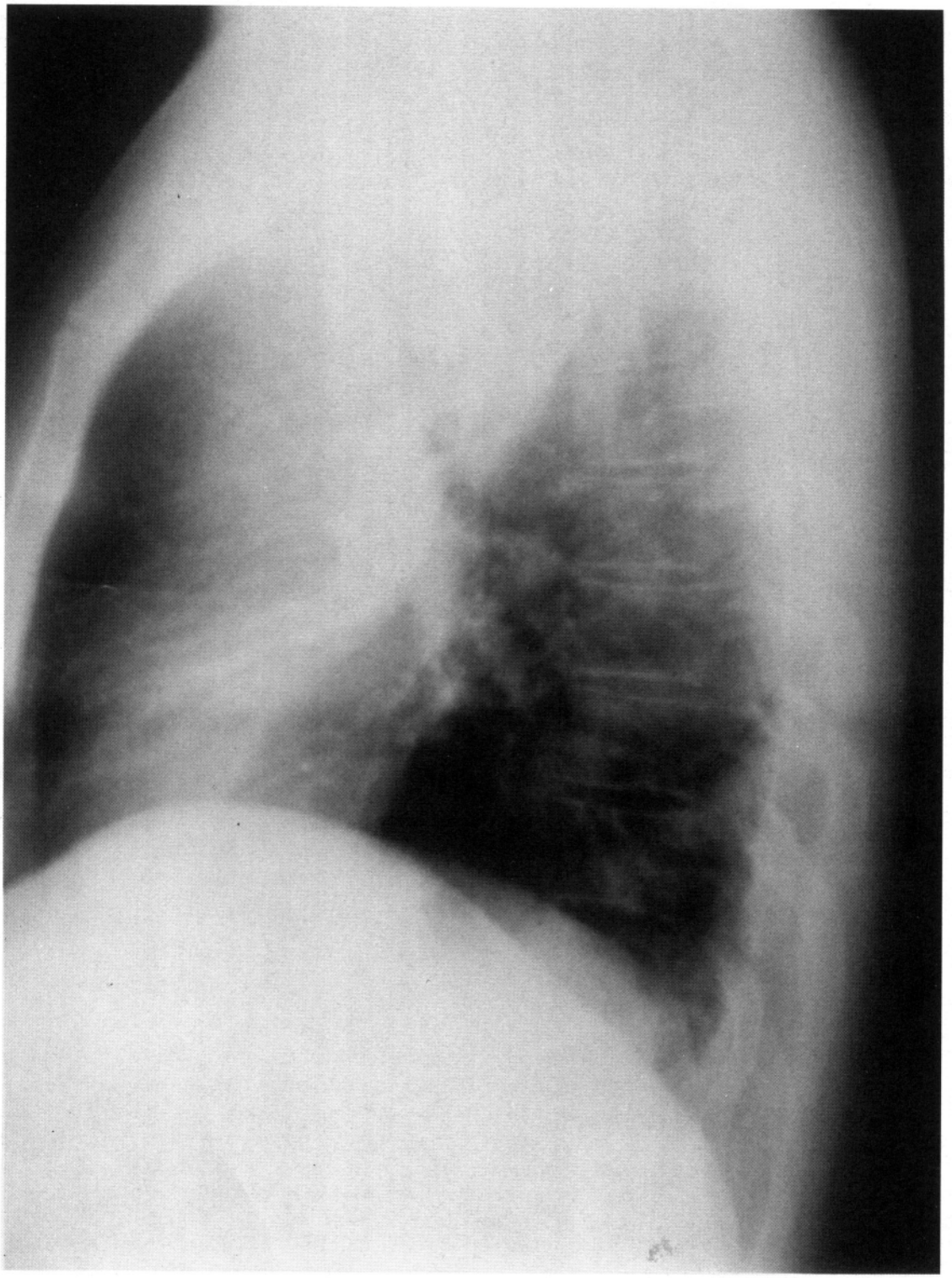


A

FIGURE 4. Bacteremic pneumococcal pneumonia. Chest radiograph (A) posterior–anterior and (B) lateral views showing a dense, almost lobar, alveolar infiltrate of the left upper lobe. (*Continued*)

changes are not uncommon and a small amount of pleural fluid may be present in one fifth to one third of cases (Fig. 5). Along with clinical improvement, the chest x-ray changes gradually disappear and in most cases resolve completely in 6 to 8 weeks.

Significant polymorphonuclear leukocytosis ($\geq 15 \times 10^9$/L) is a common finding, but there is no white blood cell count finding that can exclude the diagnosis of pneumococcal pneumonia (Austrian & Gold, 1964: Ort et al., 1983; Örtqvist et al., 1988). Leukopenia ($< 4 \times 10^9$/L) on admission is found in a minority (5%-10%) of patients, most often in chronic alcoholics, and is associated with a poor prognosis (Austrian & Gold, 1964; Perlino & Rimland, 1985; Örtqvist et al., 1988). The release of inflammatory mediators such as interleukin-6 (IL-6) from activated mononuclear phagocytes as a response to the infection induces a rapid and marked elevation of C-reactive protein (CRP) (Örtqvist et al., 1995). CRP values on admission will commonly



B

FIGURE 4. (*Continued*)

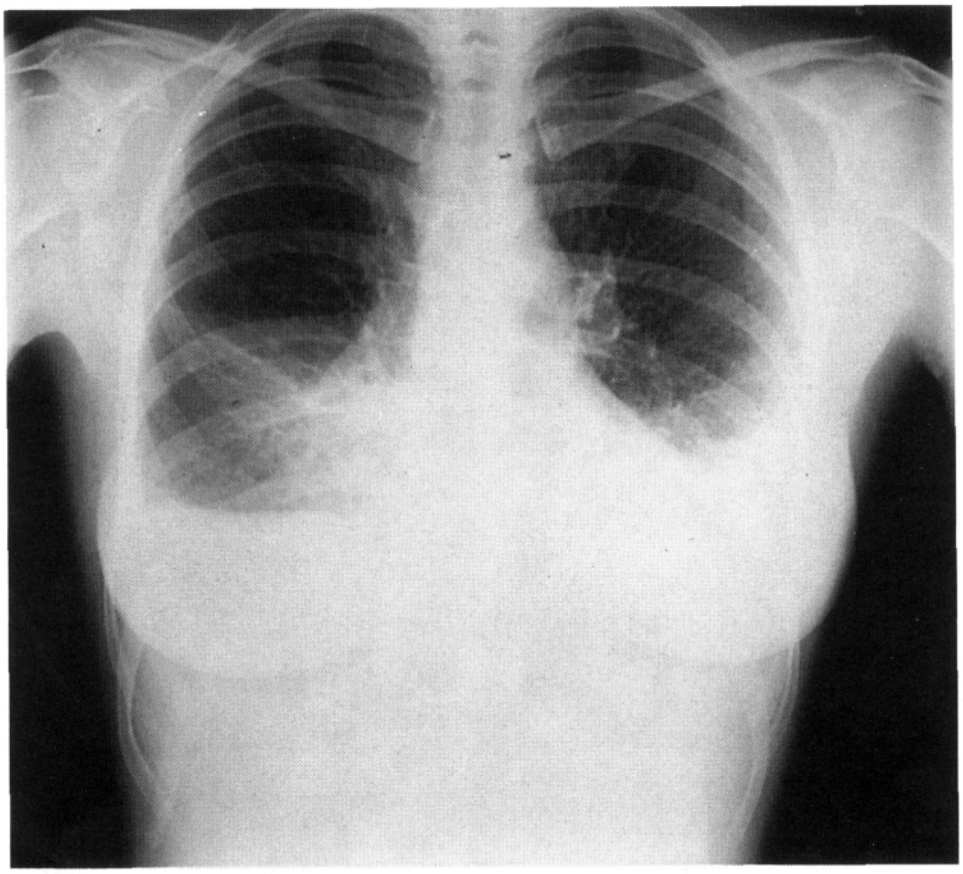


FIGURE 5. Posterior–anterior chest radiograph of a 40-year-old female with bacteremic pneumococcal pneumonia. Note the bilateral opacities and the small pleural effusions.

be approximately 150 to 300 mg/L, but may reach as high as 400 mg/L, and are significantly higher than in patients with atypical or viral pneumonia. The short half-life of CRP makes repeated tests a useful complement to physical examination for monitoring the treatment response. IL-6 seems to have even better discriminatory diagnostic potential and prognostic utility than CRP, but this test is still too laborious to be used routinely (Örtqvist et al., 1995).

Several clinical features (e.g., advanced age, sudden onset of symptoms, leukocyte count $\geq 15 \times 10^9$/L, and CRP >150 mg/L) are more common in patients with pneumococcal pneumonia than in those with pneumonia caused by other common pathogens such *as Mycoplasma pneumoniae.* However, the ability of these features, singly or in combination, to predict the microbial etiology is unfortunately rather poor (Woodhead & Macfarlane, 1987; Farr et al., 1989).

Microbiological Diagnosis

There are several methods available for the etiologic diagnosis of pneumococcal pneumonia, some of which can be recommended for routine clinical use (Table 10). The result of a diagnostic test should be available in a few hours. In theory this is possible with gram stain and pneumococcal antigen detection on lower respiratory samples, but in most hospitals the results of such tests unfortunately often take 24 hours or more to reach the physician in charge of the patient.

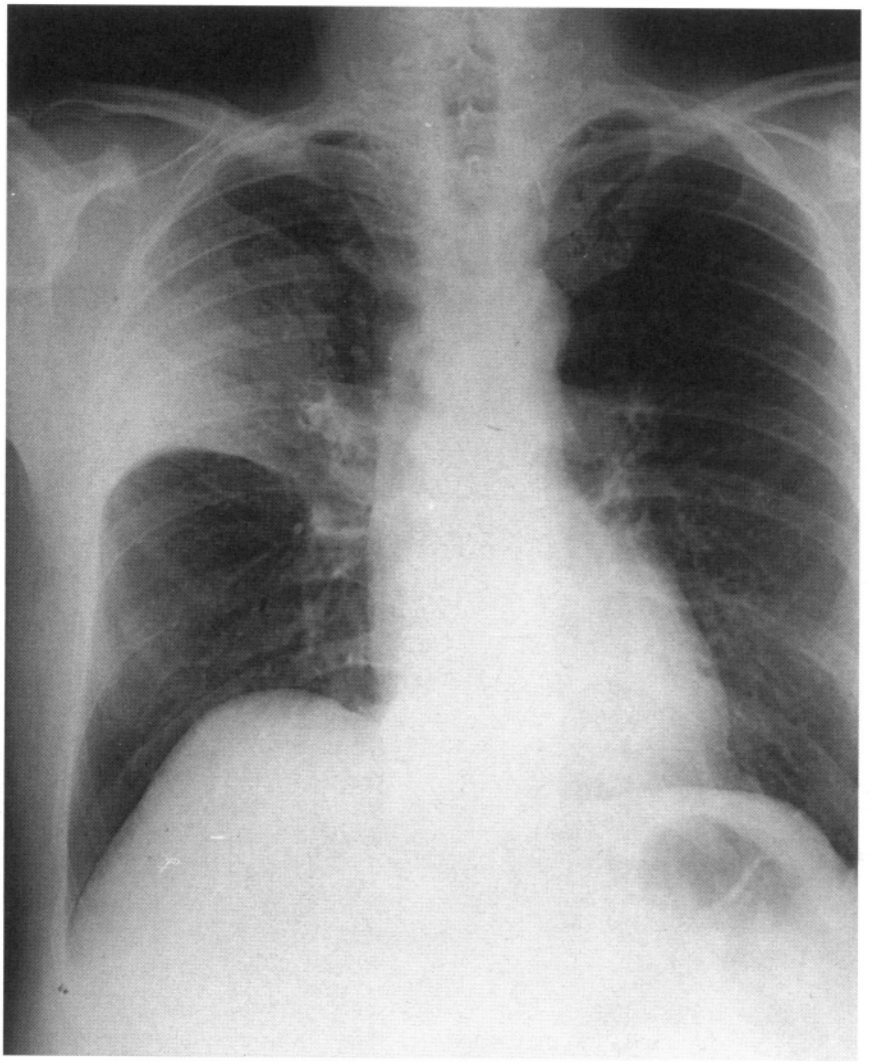


FIGURE 6. Posterior–anterior chest radiograph of a 65-year-old man with upper right lobe pneumonia. Sputum culture was positive for *Streptococcus pneumoniae*.

A definite pneumococcal etiology can be established by culture of the organism from a normally sterile site. Blood cultures therefore remain valuable for the diagnosis of pneumococcal pneumonia, although the sensitivity is only about 25% (Heffron, 1939). Pneumococcal antigen can be detected in blood, but the sensitivity is much lower than in sputum. Polymerase chain reaction methods for detection of specific nucleotide sequences in blood have shown promising results (Salo et al., 1995; Boersma & Holloway, 1996), but are time-consuming and not yet commercially available.

In the case of a significant pleural exudate visible on chest x-ray, a sample of pleural fluid for culture should be aspirated before antibiotic treatment is started since this may lead to a definite diagnosis in a few additional cases.

In an adult patient with pneumonia, nasopharyngeal cultures provide a fairly specific, but not very sensitive (~30%), test for pneumococcal pneu-

TABLE 10. Recommended Methods for Establishing a Pneumococcal Diagnosis in Patients Admitted with Pneumonia

Moderately severe pneumonia
Antibiotics given prior to tests
Blood culture
Sputum, for gram stain and pneumococcal antigen detection
Culture if pleural fluid (if present)
No antibiotics given prior to test—add
Sputum culture
Nasopharyngeal culture
Severe pneumonia
All of the above, plus consider
Bronchoscopy with protected brush and bronchoalveolar lavage

monia (Hedlund et al., 1990). Since this test is inexpensive and provides a definite result within 24 hours it may be a valuable supplement in the diagnostic arsenal.

The value of gram stain and sputum culture in the diagnosis of pneumonia is still controversial (Bartlett & Finegold, 1978; Kalin & Lindberg, 1983; Lentino & Lucks, 1987). The differing results are probably due to differences in the material cultured, the choice of sputum samples cultured, and the culture methods used. The gram stain can provide a specific (90%) and fairly sensitive (60%-85%) means for a pneumococcal diagnosis in a patient who has not been treated with antibiotics and who can produce a purulent sputum. Purulence must be evaluated by microscopy, and only purulent samples (>5 leukocytes/epithelial cell) should be cultured. The sample should be washed to eliminate contaminating oral flora, then homogenized and cultured quantitatively. A culture with growth of $>10^5$ cfu/mL can be considered positive, but should always be evaluated together with the result of the gram stain.

Pneumococcal antigen detection in sputum is highly specific (75%-100%) and probably the most sensitive (70%-95%) method for the diagnosis of pneumococcal pneumonia in patients who can provide a sputum sample (Örtqvist et al., 1989; Woodhead et al., 1990; Boersma & Holloway, 1996). Of the existing methods for pneumococcal antigen detection, co-agglutination or latex agglutination tests directed against capsular polysaccharide or C-polysaccharide antigen seem to be optimal. The agglutination methods are as sensitive and specific as counterimmunoelectrophoresis or enzyme immunoassays, but much faster and technically simpler. Antigen detection has the advantage, compared to culture, of a high specificity in all types of sputum samples, even in samples consisting of mostly saliva, and high sensitivity, that is, pneumococcal antigen may be detected up to several days after antibiotic therapy has been initiated. The method may not be ideal in patients with chronic obstructive pulmonary disease who have heavy bronchial colonization with pneumococci. However, 10^6 to 10^7 cfu/mL of pneumococci are needed to be detectable with agglutination methods, which reduces the risk for false-positive tests (Holloway et al., 1992). A positive antigen detection test in a patient with an infiltrate on chest x-ray or clinical symptoms of pneumonia will therefore strongly indicate a pneumococcal infection requiring treatment. Capsular polysaccharide antigens can be detected also in urine, but these tests have shown a low sensitivity and are not recommended for routine diagnostic use.

In the severely ill pneumonia patient, an etiologic diagnosis is crucial, and the use of an invasive diagnostic technique should therefore always be considered. Fiber-optic bronchoscopy, using a protected brush (PB) or bronchoalveolar lavage (BAL), is safe and probably the most feasible way to obtain an accurate diagnosis. The PB technique with quantitative culture of the respiratory sample, introduced by Wimberley et al. (1979), is highly specific and has a good sensitivity in previously untreated patients, but the diagnostic sensitivity is lower in patients who have undergone bronchoscopy because of therapy failure (Ortqvist et al., 1990b). The diagnostic thresholds for pneumonia are 10^3 cfu/mL for the PB culture and 10^4 cfu/mL for the BAL culture, both corresponding to approximately 10^5 to 10^6 cfu/mL in respiratory secretions (Wimberley et al., 1979; Meduri & Baselski, 1991).

Percutaneous lung needle aspiration is one of the most specific respiratory diagnostic methods and has a fair sensitivity, but the use of this technique has been limited because of fear of severe complications, such as bleeding and pneumothorax

(Davidson et al., 1976; Torres et al., 1990; Boersma & Holloway, 1996).

Treatment

In the majority of cases of pneumococcal pneumonia, penicillin is the drug of choice despite the increase in strains with decreased susceptibility to that drug. This recommendation is based on the low incidence of pneumococcal strains with high-level resistance (MIC ≥4 μg/mL), the high concentration of penicillin that may be reached at the site of infection, and the favorable clinical experience of penicillin use for treatment of pneumonia caused by pneumococci with decreased susceptibility to this drug (Sanchez et al., 1992; Tan et al., 1992; Friedland, 1995; Pallares et al., 1995; Gress et al., 1996; Cabellos et al., 1998).

With intravenous penicillin G, peak serum levels are reached that are more than 100 times the MIC of most pneumococcal strains (Table 11). The drug concentration at the site of infection is approximately 50% to 75% of the serum level, and the amount of free active drug will be adequate even when plasma-protein binding is considered. However, the short half-life of penicillin poses a problem, since for optimal effect the concentration of β-lactam drugs should remain above the MIC for as much of the dosing interval as possible. A 3-g dose (5 million units) of penicillin G given intravenously will, despite an immediate peak of 300 to 400 μg/mL, result in a serum concentration after 4 hours of ≤4 μg/mL, and after 6 hours of ≤1 μg/mL. Thus, in an area where high-level penicillin resistance (≥4 μg/mL) is common, patients with severe pneumococcal pneumonia should be treated with a frequent intermittent dosing of penicillin G (e.g., 2-3g every 4 hours). Continuous infusion of penicillin G may be an alternative (e.g., 10 g every 12 hours after a loading dose of 2 g to a person with normal renal function) (Bryan et al., 1997). Since penicillin G has to be added to solutions containing sodium before infusion, salt overload may be a problem in patients treated with continuous infusion of this drug. Patients with mild to moderately severe pneumococcal pneumonia may be treated with procaine penicillin 1.2 g intramuscularly every 12 hours or oral amoxicillin 0.5 to 1.0 g every 8 hours (Cabellos et al., 1998). Although amoxicillin provides a broader spectrum than is necessary, its better absorption, longer half-life, and slightly higher activity makes it a better choice than penicillin for treatment of pneumococci with decreased susceptibility (Musher, 1992; Garau, 1996).

In areas where resistance is uncommon, oral penicillin V 3 to 4 g per day in three to four divided doses will be adequate initial treatment for mildly to moderately severely ill patients, whereas penicillin G 2 to 3 g intravenously every 6 to 8 hours is recommended for those with more severe disease.

The alternative to penicillin/amoxicillin for treatment of patients who are allergic to penicillin or who are infected with highly penicillin-resistant pneumococci depends on the antibiogram. If the antibiogram is unavailable, it is important to know the local resistance patterns. For parenteral treatment, a third- or fourth-generation cephalosporin is

TABLE 11. Approximate Half-Lifes and Peak Concentrations of Different Penicillin Regimens[a]

Drug	Dose (g)	$T_{1/2}$ (hours)	Serum concentration (μg/mL) after 1–2 hours
Penicillin V, oral	1.0	0.5	1–3
Amoxicillin, oral	0.5	1–1.3	6–7
	1.0		9–10
Benzylpenicillin, intramuscular	0.75 (1.2 million units)	0.4–0.8	2–2.5
Benzylpenicillin, intravenous	0.6 (1 million units)		10
	1.5 (2.5million units)		30
	3.0 (5 million units)		60–70

[a]From Gerdon et al., 1998; Bryan et al., 1997; Cabellos et al., 1998.

most often the primary alternative. However, it should be noted that pneumococcal strains that are more resistant to cephalosporins than to penicillins have become more common during the last few years (Garau, 1996). Other alternative drugs include the carbapenems, newer quinolones, and vancomycin (and other glycopeptides). Of the available alternative drugs on the market today, only vancomycin is universally active (Tables 5–7). However, for epidemiological reasons vancomycin should be used only as a last resort, or in pneumonia with resistant pneumococci complicated by meningitis.

Currently available cephalosporins are not alternatives to penicillin or amoxicillin for oral treatment of resistant pneumococci, since the latter two drugs have generally lower MIC values and are more bactericidal (Garau, 1996). For non-β-lactam oral drugs there is a wide local variation in the resistance pattern among both penicillin-susceptible and penicillin-resistant pneumococcal strains, and no single drug can be recommended. The newer quinolones have shown promising results and may be useful as second-line drugs for the treatment of pneumococcal pneumonia when penicillin resistance is known or suspected (Lode et al., 1995; Örtqvist et al., 1996). However, pneumococci that are highly resistant to ciprofloxacin or ofloxacin have a decreased susceptibility also to the newer quinolones; thus resistance may occur even before new drugs are on the market (Chen et al., 1999). Quinolones are today used extensively for a variety of diagnoses, and with an inappropriate and extensive prescription of the newer drugs also for respiratory tract infections (especially if indications are extended to include children) there is a definite risk for a rapid increase in quinolone resistance (Chen et al., 1999; Ho et al., 1999; Linares et al., 1999).

Several new drugs with improved activity against penicillin-resistant pneumococci are now in clinical trials for treatment of gram-positive pneumonia, and some may already be available in certain countries. These new drugs include β-lactams, e.g., the cephalosporin cefditoren (Spangler et al., 1996), but more importantly also new classes of drugs, streptogramins, oxazolidones, ketolides, and evernomicins (Spangler et al., 1996; Urban et al., 1996; Agouridas et al., 1997). Finally, a combination of a β-lactam and an aminoglycoside may be used as treatment for a severe pneumonia with penicillin-resistant pneumococci, since such a combination has been shown to be synergetic and bactericidal (Schlegel et al., 1997).

Clinical Course, Complications, and Prognosis

If antimicrobial agents or serum therapy are not given, the patient with severe pneumococcal pneumonia will typically continue to be toxic with sustained high fever for about 5 to 9 days (Heffron, 1939). After this time, most patients who survive will experience a "crisis," which is characterized by a sudden drop in temperature to normal or below normal, and a marked subjective sense of relief, with disappearance of the toxemia.

The response to adequate antibiotic therapy is most often prompt, with significantly lowered fever and improvement of symptoms and signs within 24 to 48 hours. However, it is not uncommon for a low-grade fever to continue for a few more days. In bacteremic pneumonia the median total duration of fever is approximately 5 days (Örtqvist et al., 1988). Several possible factors may contribute to a failure to respond to treatment, including failure of the drug to reach the site of infection (the drug is not administered correctly or not absorbed), presence of resistant pneumococci, mixed infection, extrapulmonary spread of the infection (especially empyema or meningitis), sterile pleural effusion, atelectasis, nosocomial infection, or other complications of hospitalization, such as a deep venous thrombosis. All these complications should be considered, adequately diagnosed, and treated. However, some patients seem to be "slow responders," and no particular reason can be found to the slowly yielding symptoms, such as a sustained fever (Örtqvist et al., 1990b).

Focal infections secondary to lobar pneumonia were not uncommon in the pre-antibiotic era, especially infections in the pleura (5%), pericardium (1%–5%), endocardium (1%), meninges (0.5%–2%), joints (0.2%–0.6%), and the peritoneum (0.2%) (Heffron, 1939). However, despite adequate antibiotic treatment, patients with bacteremic pneumococcal pneumonia still seem to have about the same risk for developing pyogenic complications, except for pericarditis which is rarely

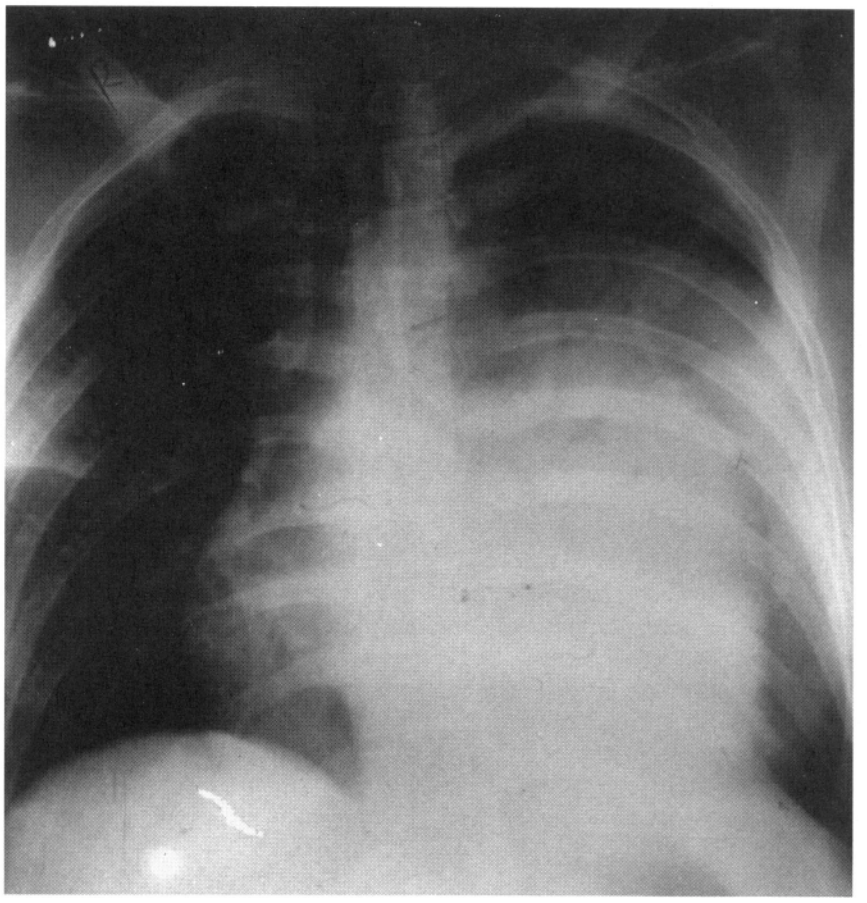


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FIGURE 7. (A) Chest radiograph of a 31-year-old man with fatal bacteremic pneumococcal pneumonia. Most of the left lower lobe and part of the left upper lobe is involved. (B) Chest radiograph of same patient 3 days later. Note the complete opacification of the left lung. Also note the air bronchograms in (A) and (B).

seen today (Austrian & Gold, 1964; Örtqvist et al., 1988). One possible explanation to this fact is that the spread of infection, and establishment of the pyogenic complication, often take place several days before antibiotic therapy is instituted.

Nosocomial infection are also a definite threat to patients with severe pneumococcal disease. In a recent multi-center study in five countries—Sweden, Great Britain, Spain, United States, and Canada—34 (7%) of 460 patients with pneumococcal bacteremia (82% with pneumonia) developed a nosocomial infection during their hospital stay (Kalin et al., 2000). Of these, approximately one half had a secondary pneumonia and 40% a urinary tract infection.

The outcome for patients with nonbacteremic pneumococcal pneumonia is often favorable. In a study of 100 nonbacteremic patients, the case–fatality rate was only 1% (Örtqvist et al., 1990a), and in a meta-analysis of approximately 2000 patients with pneumococcal pneumonia that included both bacteremic and nonbacteremic cases, the total death rate was 8.3% (Fine et al., 1996).

In patients with invasive pneumococcal disease, however, the outcome is much more uncertain (Figs. 7 and 8). In the pre-antibiotic era, the case-fatality rate of bacteremic pneumococcal pneumonia was very high, approximately 80% with symptomatic therapy and 45% with serum therapy (Tilghman & Finland, 1937). In 1964, Austrian and

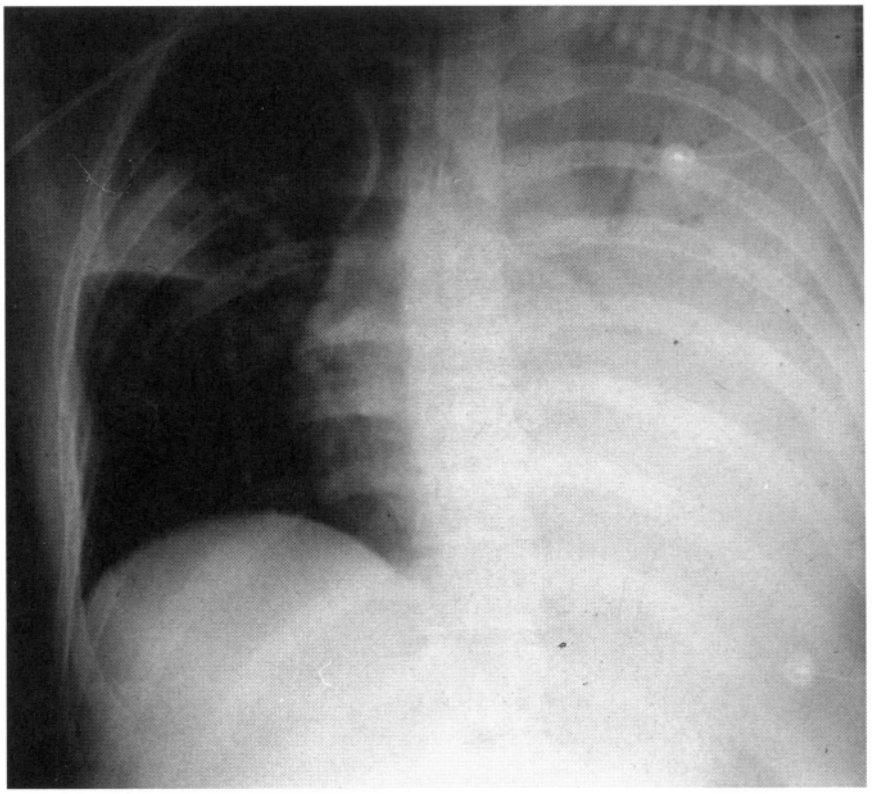

FIGURE 7. (*Continued*)

Gold reported that this figure, despite adequate antibiotic treatment, was still as high as 23% in approximately 500 patients with bacteremic pneumococcal pneumonia. A high case-fatality rate (≥20%) has also been reported in more recent studies (Marfin et al., 1995; Lääveri et al., 1996; Mirzanejad et al, 1996; Watanakunakorn & Bailey, 1997). However, in some studies much lower case-fatality rates (0%-12.5%) have been found (Örtqvist et al., 1993; Davidson et al., 1994; Gilks et al., 1996; Kalin et al., 2000). In two of these studies (Örtqvist et al., 1993; Kalin et al., 2000) the outcome was compared between study sites in different countries. These comparisons showed that some of the differences in outcome could be explained by differences in underlying conditions or severity of illness. In the study by Kalin et al. (2000), a multivariate analysis demonstrated that the case-fatality rate was closely correlated to the severity of illness score (APACHE II score) on admission (Fig. 9). With an APACHE II score ≤12 (median value), the death rate was only 2.6%, compared to 21% among those who had a score >12 on admission. Other independent negative prognostic factors were advanced age, presence of chronic pulmonary disease, and residence in a nursing home.

One important reason that the case-fatality rate for bacteremic pneumococcal pneumonia has remained approximately the same during the last 35 years is that a high percentage (25%–50%) of deaths occur during the first 24 to 48 hours after admission to hospital, indicating that a "point of no return" has already been reached when antimicrobial and supportive therapy begins (Austrian & Gold, 1964; Örtqvist et al., 1988; Kalin et al., 2000). These early deaths, together with the significant overall morbidity of pneumococcal disease and the increasing problems of antimicrobial resistance, emphasize the need for widespread effective prevention against pneumococcal disease.

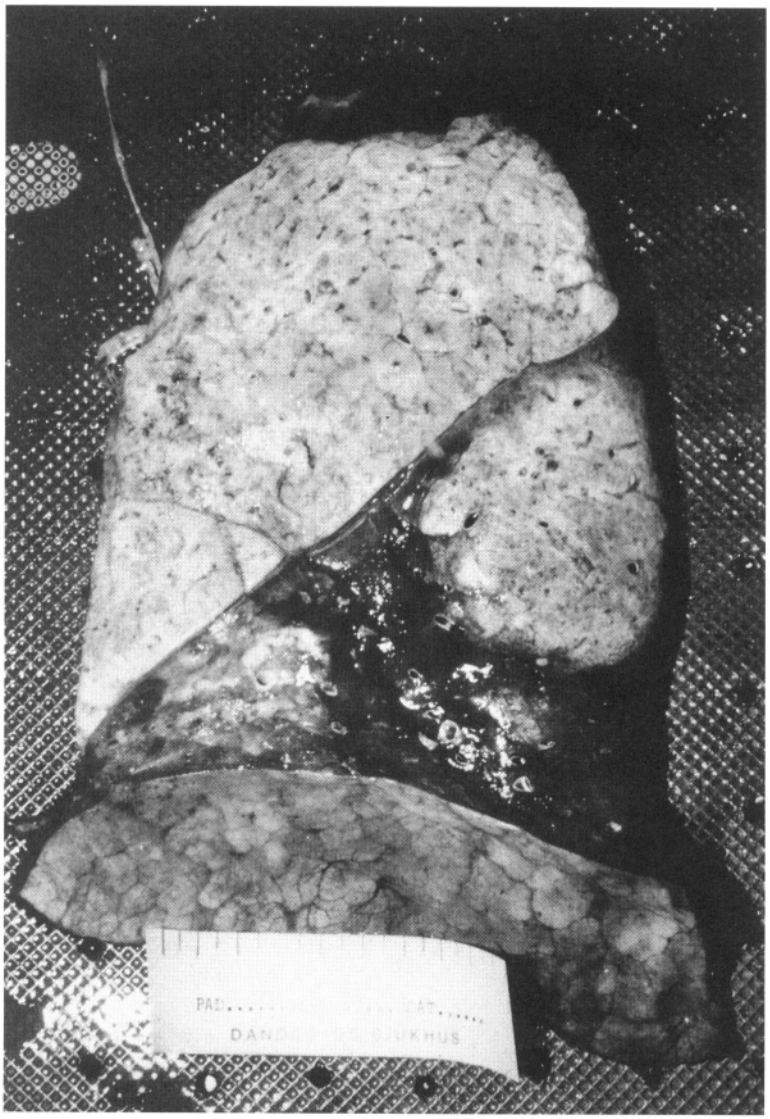

FIGURE 8. Gross appearance of lung in a patient who died from pneumococcal pneumonia. Dense consolidation of the lung is evident. This allows correlations with the radiographic appearance of pneumonia.

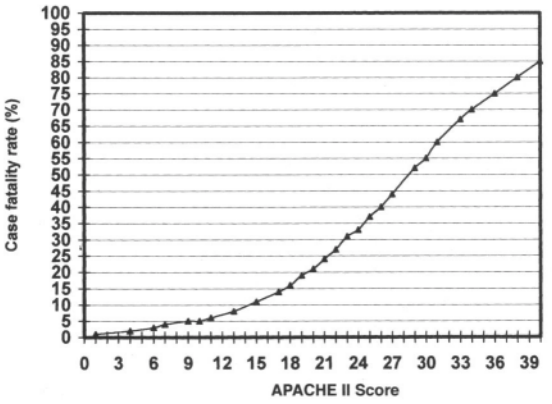

FIGURE 9. Relationship between severity of illness score (APACHE II) on admission and case-fatality rate in pneumococcal bacteremia.

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Haemophilus influenzae

LARRY J. STRAUSBAUGH

Introduction

Haemophilus influenzae was described first in 1892 by Pfeiffer, who recovered it from the sputa and lungs of patients dying of influenza during the pandemic of 1889–1892 (Ward & Zangwill, 1998; Turk & May, 1967). Though his contention that this bacterium caused influenza eventually proved false, the species name reflects the circumstances of the original isolation. The genus name relates to the organism's requirements for growth factors that can be supplied by erythrocytes. Through most of the 20th century, *H. influenzae* has been recognized as a major pathogen in children, especially as a cause of meningitis. It has been observed, albeit much less frequently, as a cause of pneumonia in children. Although the evidence suggests that Sir William Osler died of bronchopneumonia and empyema caused by *H. influenzae* (Hirschmann & Everett, 1979), its role as a cause of pneumonia in adults was not established until 1942 (Keefer & Rammelkamp, 1942). Even so, cases of *H. influenzae* pneumonia in adults were not commonly reported in the United States until the 1960s. Since then, however, it consistently has ranked among the top five causes of community-acquired pneumonia (CAP) in adults. Cases have been reported in a number of other countries as well (Ashworth et al., 1985; Bohte et al., 1995; Lieberman et al., 1996; Pareja et al., 1992; Neill et al., 1996; Marrie et al., 1989). Nosocomial pneumonia in adults has been described too. Following the introduction of conjugated vaccines for *H. influenzae* type b in the late 1980s, this microbe's role in pneumonia and other diseases of childhood has shrunk dramatically in the countries where the vaccines have been widely deployed (Schuchat et al., 1997; Clements, 1998; Petola et al., 1999; Bisgard et al., 1998). Accordingly, this chapter focuses largely on *H. influenzae's* role as a cause of pneumonia in adult patients.

Properties

Bacteriology

H. influenzae is a small (1 × 0.3 μm), nonmotile, non-spore-forming, facultatively anaerobic bacterium (Campos, 1995; Ryan & Falkow, 1994). On gram-stained smears of clinical specimens, it usually appears as a gram-negative coccobacillus but, occasionally, filamentous forms are noted; hence, it is often described as pleomorphic. *H. influenzae* has fastidious nutritional requirements and needs complex, well-supplemented media for cultivation in the laboratory (Moxon, 1995; Lieberman & Ward, 1994; Murphy, 1998). Aerobic growth in vitro requires two growth factors, historically termed X and V factors. The heat-stable X factor, usually supplied by hemoglobin, provides protoporphyrins essential for catalases, peroxidases, and cytochromes of the electron-transport system. The heat-labile V factor may be supplied by nicotinamide-adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), or by nicotinamide

LARRY J. STRAUSBAUGH • Infectious Disease Section, Medical Service, Veterans' Affairs Medical Center, and the Division of Infectious Diseases, Department of Medicine, School of Medicine, Oregon Health Sciences University, Portland, Oregon 97201.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

nucleoside. Although present in erythrocytes, V factor must be released from cells to support growth; consequently, *H. influenzae* usually does not grow on standard blood agars.

Virulence Factors

The most important virulence factor of *H. influenzae* is the type b polysaccharide capsule. Following Pittman's description of six *H. influenzae* capsular serotypes in 1931, which are designated types a, b, c, d, e, and f, type b strains were recognized as the most common causes of invasive disease, especially in children (Turk, 1982; Dajani et al., 1979; Fraser, 1982). A variety of experimental and epidemiologic data attest to the virulence of the type b strains. The type b capsule, composed of repeating units of ribosyl and ribitol phosphate, is antiphagocytic (Ward & Zangwill, 1998; Moxon, 1995). Opsonization is facilitated by type-specific antibody, which also appears to activate complement-mediated bactericidal and opsonic activity. Fothergill and Wright (1933) demonstrated that children aged 3 months to 3 years generally lack bactericidal antibody against the type b capsule. Furthermore, they correlated antibody titers with frequency of meningitis caused by type b strains. Children without antibody had much higher rales of meningitis than older children and adults who had substantial antibody liters. Until conjugated vaccines against this type were released a decade ago, type b strains accounted for more than 95% of all systemic *H. influenzae* infections in children (Clements, 1998). Type b strains have caused invasive disease in adults infrequently, presumably because most adults—even before the release of the conjugated vaccines—have possessed antibodies against this serotype. Data relating to this contention, however, are conflicting (LeFrock et al., 1984; Smith, 1994).

The extent to which other capsular polysaccharides function as virulence factors is unclear. *H. influenzae* strains with serotypes a or c through f account for a small percentage of invasive disease (Ward, 1996; Waggoner-Fountain et al., 1995; Slater et al., 1990; Urwin et al., 1996; Parley et al., 1992; Wallace et al., 1981). This observation suggests that the other capsules may be important factors in individuals lacking antibody. However, these capsular serotypes have not been subjected to the same degree of experimental scrutiny as type b strains, and their incidence has not risen appreciably since the type b vaccines were released (Ward, 1996).

With the success of the type b conjugated vaccines and with the recognition that unencapsulated strains of *H. influenzae* account for much of the clinical caseload in adult patients, attention has turned toward other putative virulence factors (Murphy & Apicella, 1987; Murphy & Sethi, 1992). Candidates include the fimbriae or pili on the bacterium's surface, which may mediate attachment to human epithelial cells (Murphy, 1998). Neutrophil defensins also may facilitate attachment to epithelial cells (Gorter et al., 1998). The three types of IgA-1 proteases secreted by *H. influenzae* are potential virulence factors (Ward & Zangwill, 1998). They can cleave different peptide bonds within the IgA-1 hinge region, which may nullify this important mucosal defense. Substances that interfere with the ciliary activity of human epithelial cells are potential candidates too. Lipooligosaccharide (LOS) from *H. influenzae* exhibits this property in vitro as does another low-molecular-weight factor, possibly a heat-stable glycopeptide (Moxon, 1995). Although the physicochemical properties of LOS from *H. influenzae* differ considerably from the lipopolysaccharide of enteric gram-negative bacilli, it demonstrates similar biologic activity. Hence, LOS may be considered a virulence factor (Ward & Zangwill, 1998). Lastly, the outer membrane protein (OMP) also appears to play an important role in pathogenesis (Murphy & Sethi, 1992). Antibodies against OMP, especially the P6 component, have protected animals against infection by nontypable strains in experimental studies (Murphy, 1998; Ward, 1996).

Typing Systems

The polysaccharide capsular antigen permits typing of *H. influenzae* into six serotypes. Historically, this system was useful to establish the primacy of type b strains. Molecular methods such as OMP subtyping and DNA fingerprinting, have been used to subtype strains in epidemiologic studies (Lagos et al., 1991).

As attention has shifted to the unencapsulated (nontypable) strains, six different systems have been developed to differentiate these strains (Murphy

& Sethi, 1992). These systems include the following: OMP subtype, LOS subtype, OMP serotype, biotype, electrophoretic type, and DNA fingerprinting. None is clearly superior to the others. For example, biotypes have failed to distinguish isolates from infected and colonized patients (Brabender et al., 1984; Wallace et al., 1981). The utility of the newer methods in the study of pneumonia caused by *H. influenzae* remains to be established.

Epidemiology

General Considerations

H. influenzae colonizes or infects humans exclusively. It has no reservoir in animals or other parts of the environment. For the most part *H. influenzae* colonizes the nasopharynx of adults and children. Colonization begins in the first months of life, and by the age of 5 years, 90% of children harbor this organism (Smith, 1994). Nontypable strains predominate in this population as they do in adults. Cultures of pharyngeal secretions have yielded nontypable strains from up to 80% of asymptomatic adults (Murphy, 1998; Turk, 1982; St. Geme, 1997; Hirschmann & Everett, 1979; Kuklinska & Kilian, 1984). Virtually all patients with chronic obstructive pulmonary disease (COPD) carry nontypeable strains of *H. influenzae* in their respiratory secretions (Murphy & Sethi, 1992). Carriage of type b strains generally occurs in 3% to 5% of the population; however, rates may be two or three times higher in some populations, such as native Alaskan children or household contacts of patients with type b disease, and in day care centers (Galil et al., 1999; Murphy et al., 1989; Lagos et al., 1991). Carriage of other encapsulated strains occurs in only 1% to 2% of the population. The colonization of all segments of the human population helps to explain the diversity of groups afflicted by *H. influenzae* pneumonia.

Colonization with *H. influenzae* is ordinarily a dynamic process (Spinola et al., 1986; Murphy, 1998; Kuklinska & Kilian, 1984). New strains are acquired from time to time. They persist for variable periods measured in days to months, and then disappear for long intervals before re-appearing or being replaced by other strains. Transmission from one person to another occurs via respiratory droplets released by colonized individuals and by direct contact with respiratory secretions or fomites (St. Geme, 1997). Nasal mucus from children colonized with type b strains has demonstrated large concentrations of *H. influenzae,* and items contaminated with nasal mucus from such children have yielded viable organisms for up to 5 hours (Murphy et al., 1989). Ordinarily, transmission results only in colonization of the exposed individual.

Infrequently, transmission leads to pneumonia or other syndromes. This may not occur for weeks to months after receipt of a new strain because development of pneumonia requires aspiration of large numbers of sufficiently virulent *H. influenzae* particles into the lower airway by individuals with impaired systemic or pulmonary defense mechanisms (Smith, 1994). The timing of such events is unpredictable; hence, the variable interval between acquisition and infection. Rarely, cases of CAP are linked to other cases of *H. influenzae* disease, such as epiglottitis, in the family (Manji & Reeve, 1990).

Of note, creation of a fatal, bacteremic pneumonia in adult C57BL/6 mice, the only experimental model described for this type of pulmonary infection, requires intratracheal instillation of 3×10^9 colony-forming units of type b *H. influenzae* (Esposito & Pennington, 1984). This observation may provide a glimpse of the magnitude of aspiration required to precipitate pneumonia in humans, especially in those with normal immunologic function. Generally, persons with only impaired local defenses of the lung (e.g., decreased mucociliary clearance) will develop bronchopneumonia without bacteremia or other foci of infection (Smith, 1994; Klein, 1997). In contrast, individuals lacking antibody who aspirate encapsulated strains that can grow faster than local clearance mechanisms can remove them will likely develop bacteremia and, possibly, metastatic foci of infection as well.

Population-Based Studies

During the last 15 years several population-based studies have provided information on the epidemiology of invasive *H. influenzae* infections, including pneumonias accompanied by bacteremia or culture-positive pleural effusions. Invasive disease is defined by the isolation of bacteria from a normally sterile site such as blood or cerebrospinal

fluid. Studies examining type b disease generally emphasize the pediatric dimension, which has predominated historically. For example, a population-based study in Wales established an annual incidence of 3.2 cases of invasive *H. influenzae* type b infections per 100,000 population in Gwynedd during the period 1980-1990 and an incidence of 2.5 cases per 100,000 population for all of Wales during the period 1988-1990 (Howard et al., 1991). The majority of these cases occurred in children less than 5 years of age (annual incidence 43.8 and 34.6 per 100,000 population in Gwynedd and all of Wales, respectively), with the highest incidence being observed in children less than 1 year of age. Only 15% of invasive infections in Gwynedd and only 7% of cases in all of Wales occurred in persons ≥16 years of age (annual incidence 0.61 and 0.18 per 100,000 population in Gwynedd and all of Wales, respectively). Although pneumonia accounted for less than 10% of all infections, it accounted for more than 40% of those occurring in adults (Howard et al., 1991).

These data correspond to those reported from other locations. A national surveillance program for invasive diseases caused by type b *H. influenzae* conducted in Finland during the period 1985 through 1988 found an annual incidence of 0.22 cases per 100,000 population in persons ≥16 years of age (Takala et al., 1990). Bacteremic pneumonias accounted for 23% of these cases. Similarly, a population-based study of invasive type b *H. influenzae* in children ≤5 years of age in Minnesota and Dallas County, Texas, during the period 1983–1984 found an annual incidence of 64 and 98 cases per 100,000 populations, respectively (Murphy et al., 1992). Once again pneumonia accounted for a small percentage of the disease in children—3% of cases in Minnesota and 11% of cases in Dallas County. Although the conjugated type b vaccines have altered the epidemiology of *H. influenzae* in children dramatically, limited data suggest that the traditional pattern prevails in developing nations that have not yet begun widespread immunizations (Greenwood, 1992).

Few population-based studies have examined the frequency of other *H. influenzae* serotypes as a cause of human disease. However, Urwin et al. (1996) provided such data on invasive disease caused by serotype f in a multistate population during the 6-year period from 1989 to 1994. Altogether 91 cases of invasive disease were identified in the 6-year period. The annual incidence ranged from 0.5 cases per 1 million population in 1989 to 1.9 cases per 1 million population in 1994. Seventy-two percent of cases occurred in adults, and respiratory tract infections accounted for 82% of adult cases. Pneumonia accounted for 40% of pediatric cases. Overall mortality was 30% among adults and 21% among children. These data raised concerns about the effect that widespread vaccination against type b strains might have on the epidemiology of other strains of *H. influenzae.*

Population-based studies examining invasive disease caused by all strains of *H. influenzae,* not just type b strains, have been reported for adult populations. Not surprisingly, rates generated in these studies are considerably higher than those in studies focusing only on type b strains. A retrospective study from two regions of Sweden reviewing all isolates of *H. influenzae* recovered during the period from 1971 to 1983 determined an annual incidence for invasive infections of 1.1 per 100,000 in persons ≥16 years of age (Trollfors et al., 1984). Cases of pneumonia with positive blood or pleural fluid cultures accounted for 48% of the total. Similarly, a study conducted in metropolitan Atlanta during the period 1988-1990 yielded an annual incidence of 1.7 cases per 100,000 populations in persons ≥18 years of age (Farley et al., 1992). From these data the authors estimated that there are 4000 cases of invasive disease caused by *H. influenzae* in adults each year in the United States. Since bacteremic pneumonias accounted for 70% of cases in this study, the number of bacteremic pneumonias caused by *H. influenzae* may exceed 2800 per year. Comparable data for the pediatric age groups are not available.

In summary, population-based studies indicate that invasive *H. influenzae* type b infection is predominantly a pediatric disease, but pneumonia accounts for less than 10% of pediatric cases. Although type b disease is rare in adults, pneumonia is a common manifestation. When invasive disease caused by other serotypes and unencapsulated strains is considered, the incidence of infection in adults is substantially higher, and pneumonia accounts for a majority of these infections. Since most patients with *H. influenzae* pneumonia do not have

positive blood or pleural fluid cultures, the incidences and projections considered above represent only a fraction of the true incidence.

Case Series of Community-Acquired Pneumonia

Case series of adult patients with CAP give ample evidence of the leading role played by *H. influenzae.* In a prospective study of 359 cases of CAP seen at three facilities in Pittsburgh between 1986 and 1987, *H. influenzae* accounted for 11% of all cases and was second only to *Streptococcus pneumoniae* in frequency (Fang et al., 1990). Of the patients with pneumonia caused by *H. influenzae,* 15% were admitted to the intensive care unit, 8% required respiratory support, and 5% died. These investigators also reviewed 15 series of CAP with more than 100 cases that had accumulated between 1960 and 1985. *H. influenzae* ranked second in five of these series and ranked among the top five causes in eight of the other ten series.

A similar range of frequencies is noted in other case series of CAP not covered in the review by Fang et al. (1990). For example, Marrie and colleagues (1989), reporting on 719 consecutive patients requiring hospital admission for CAP in Halifax, found that *H. influenzae* accounted for 1.4% to 9.4% of the cases during each of the 5 years—overall mean for the 5-year period was 3.7%. Similarly, in a meta-analysis performed by Fine et al. (1995), who reviewed 27 case series of CAP to evaluate prognostic factors, *H. influenzae* was second only to *S. pneumoniae* as the etiology of pneumonia in these series, accounting for 4% of cases with a known etiology. The overall case-fatality rate for pneumonia caused by *H. influenzae* in these series was 7.4%. Levy and coworkers (1988), studying CAP in Paris during the period 1983–1984, found that *H. influenzae* ranked second in frequency, accounting for 12% of cases. Lastly, six case series of CAP in adult patients requiring hospitalization, which were published after 1992, provide data from four different countries to the same effect (Pareja et al., 1992; Lieberman et al., 1996; Bohte et al., 1995; Neill et al., 1996; Gomez et al., 1996; Rello et al., 1996). The percentage of cases attributed to *H. influenzae* ranged from 2% to 19% (median, 8%), and cases caused by this bacterium ranked among the top three causes in four of the six series (Table 1).

In case series of adult patients with CAP it is apparent that *H. influenzae* affects adults of all ages, with or without comorbidities. For example, in the series of 346 patients reported by Lieberman and colleagues (1996), the percentage of patients in the 17–44, 45–54, 55–64, 65–74, and 75+ age groups with pneumonia caused by *H. influenzae* was 5%, 3%, 11%, 4%, and 4%, respectively. In another series of 95 patients ⩾65 years of age requiring admission to intensive care units, *H. influenzae* accounted for 7% of the cases (Rello et al., 1996). Verghese and Berk (1983) also found *H. influenzae* to be a common cause of bacterial pneumonia in elderly patients.

In three series of generally younger patients with CAP not requiring hospital admission, *H. influenzae* accounted for 10% to 18% of cases (Berntsson et al., 1986; Woodhead et al., 1987; Cassell et al., 1991). Not surprisingly, in the 1993 guidelines on CAP from the American Thoracic Society (Niederman et al., 1993), *H. influenzae* is viewed as a potential threat in all adults regardless of age, underlying comorbidities, setting, and severity of illness. Guidelines from the British Thoracic Society express a similar perspective (British Thoracic Society, 1993).

Because documentation of the etiology of pneumonia in infants and young children is difficult, case series of CAP in these age groups often have little information on the role of *H. influenzae* (Isaacs, 1989). Nevertheless, other sources of data suggest that *H. influenzae* plays an important role in this age group. Series of bacteremic cases, especially those caused by type b strains, appear in the medical literature from time to time (Jacobs & Harris, 1979; Ginsburg et al., 1979). Moreover, studies from developing nations using lung punctures for diagnosis frequently identify both type b and nontypable strains of *H. influenzae* as common causes of pneumonia in children (Klein, 1998).

H. influenzae Case Series

Generic case series of infections caused by *H. influenzae* shed additional light on its role as a cause of pneumonia. For example, a review of invasive disease occurring in persons ⩾9 years of age in

TABLE 1. Role of *H. influenzae* in Community-Acquired Pneumonia—Hospital Series from the 1990s

Reference	No. of months	Country (years)	No. of cases	% *Haemophilus influenzae*	Rank	Comment
Pareja et al., 1992	30	Granada, Spain[a]	165	2	10	Etiologic diagnosis in 71% of cases
Bohte et al., 1995	28	Leiden, The Netherlands (1991–1993)	334	8	2	Etiologic diagnosis in 32% of cases
Gomez et al., 1996	40	Murcia, Spain (1991–1994)	100	19	3	Etiologic diagnosis in 100% of cases—etiology required as part of case definition; 5% case–fatality rate in *H. influenzae* cases
Neill et al., 1996	12	Christchurch, New Zealand (1992–1993)	255	11	3	Etiologic diagnosis in 71% of cases; 9% case–fatality rate in *H. influenzae* cases
Rello et al., 1996	12	Several cities in Spain (1991–1992)	95	7	2	All patients >65 years of age and admitted to ICU; etiologic diagnosis in 39%; 57% case–fatality rate in *H. influenzae* cases
Leiberman et al., 1996	12	Israel (1991–1992)	346	5.5	6	Etiologic diagnosis in 81% of cases

[a]Years not stated in text.

Seattle area hospitals for the 11-year period from 1980 to 1990 identified 79 bacteremic cases and 40 nonbacteremic cases (Kostman et al., 1993). Pneumonia accounted for 52% of the bacteremic cases. Lung abscesses and empyema accounted for 18% of the nonbacteremic cases. Only 17 isolates were typed, of which 13 were type b. Four cases of pneumonia were caused by type b strains. A similar type of review conducted in four hospitals in Houston and one in Atlanta during the period 1974 to 1980 identified 96 episodes of bacteremia caused by H. *influenzae* (Wallace et al., 1981). Pneumonia accounted for 60% of the cases. Of the serotypes that were confirmed, nine were type b, three were type f, and 12 were nontypable. In a 5-year study conducted at the Hartford hospital during the period from 1979 to 1983, 29 cases of invasive disease caused by *H. influenzae* were detected (Crowe & Levitz, 1987). Seventeen (59%) of these patients presented with bacteremic pneumonia. Type b strains were isolated from seven of these patients. Thus, these data buttress conclusions reached in population-based studies that pneumonia is the most common form of invasive disease caused by *H. influenzae* in adults and that type b strains do not predominate. Of note, case series of adult patients with *H. influenzae* pneumonia not requiring positive blood or pleural fluid cultures for diagnosis have strengthened the assertion that nontypable strains account for the vast majority of cases (Berk et al., 1982; Musher et al., 1983; Woodhead & MacFarlane, 1987).

The generic case series of *H. influenzae* infections also elaborate the varied clinical settings in which pneumonia appears. For example, a case series of unusual presentations of *H. influenzae* infections in immunocompromised children described the occurrence of pneumonia caused by a nontypable strain in a 5-year-old child recovering from acute lymphocytic leukemia (Bartlett et al., 1983). Similarly, Fainstein et al. (1989), reviewing their experience with *Haemophilus* bacteremia at a large cancer center over a 13-year period, found that *H. influenzae* was the isolate most frequently recovered (67% of cases) and that 50% of their patients presented with pneumonia. Of the six *H. influenzae* isolates available for typing, one was type f and the others were nontypable. Finally, Simon et al. (1980) studied 100 consecutive adult patients with positive sputum cultures for *H. influenzae* over an 18-month

period. Analysis of clinical features indicated that 65 patients were merely colonized, 10 had bronchitis, and 25 had pneumonia. Eleven of the 35 isolates causing bronchopulmonary infection were serotyped and only one was type b. Ten of the 65 isolates responsible for colonization were typed and none were type b. Contact with children was not a risk factor for colonization or infection. Lastly, *H. influenzae* appeared to be hospital-acquired in 29% of the infected patients and 43% of the colonized patients.

Nosocomial Pneumonia Caused by H. *influenzae*

H. influenzae easily gains access to the hospital environment via colonized individuals. Not surprisingly, it accounts for a small percentage of nosocomial pneumonias, presumably developing after in-hospital aspiration of nasopharyngeal flora. Data from the hospital-wide component of the Centers for Disease Control and Prevention (CDC) National Nosocomial Infections Surveillance (NNIS) system indicated that *H. influenzae* accounted for 5% of the isolates recovered from patients with nosocomial pneumonia from October 1986 to April 1996 (CDC NNIS System, 1996). Data from adult and pediatric intensive care units for the same period indicated that *H. influenzae* was isolated from 4.9% of patients (CDC NNIS System, 1997). These results, which were generated largely from cultures of expectorated sputum, find their counterpart in studies with more stringent requirements for diagnosis. For example, Taylor and coworkers (1995) found that *H. influenzae* was responsible for 2% of isolates recovered during 149 episodes of bacteremic nosocomial pneumonia occurring over an 89-month period in a Canadian teaching hospital. Likewise, studies of nosocomial pneumonia using bronchoscopic techniques for diagnosis have identified *H. influenzae* in 5% to 10% of cases (Strausbaugh, 1999; Mayhall, 1997). For this reason *H. influenzae* is included as a "core organism" in the American Thoracic Society (1995) guidelines for treatment of hospital-acquired pneumonia.

Person-to-person spread of *H. influenzae* has been documented within healthcare facilities. Smith et al. (1988) reported a cluster of six cases of type b infections occurring among adults over the course of 1 month in a nursing home and adjoining hospital. Five of these patients had pneumonia, and person-to-person spread appeared to be the likely mode of transmission. Sturm and coworkers (1990) reported an outbreak caused by a multiresistant, nonencapsulated strain that affected 15 of 21 individuals with chronic obstructive pulmonary disease residing in a Dutch pulmonary rehabilitation center. The outbreak strains showed identical OMP patterns and harbored the same plasmid that conferred resistance. This strain had initially been isolated from three patients on the same hospital ward, two of whom were later transferred to the pulmonary rehabilitation center. Over the next 2 months, 13 other patients in the center acquired the outbreak strain, presumably as a result of person-to-person spread.

Gough and colleagues (1990) described a similar outbreak affecting 18 patients admitted to an acute medical chest ward in the United Kingdom. Here again, the outbreak strain was unencapsulated. There was strong circumstantial evidence that a spirometer was a common iatrogenic source of the cross-infection. Finally, Goetz et al. (1994) reported a cluster caused by an unencapsulated strain of *H. influenzae* involving three patients with pneumonia, one patient with bronchitis, and four roommates with nasopharyngeal colonization. Analysis of the recovered isolates indicated that a single clone of unencapsulated *H. influenzae* was present in the four patients and in three of seven close contacts. Asymptomatic carriage of *H. influenzae* in the three contacts was terminated with rifampin therapy. The authors speculated that person-to-person spread was the most likely means of nosocomial transmission.

Case series featuring selected populations of hospitalized patients further delineate the spectrum of nosocomial pneumonias caused by *H. influenzae*. Campognone and Singer (1986), for example, reported 19 cases of neonatal sepsis seen during a 4-year period that were caused by nontypable strains. Disease occurred within 48 hours of birth and 15 infants had pneumonia at the time of diagnosis. Spain and colleagues (1995) have drawn attention to the role of *Haemophilus* spp. as a cause of pneumonia and early pulmonary dysfunction following major trauma. In their series of 257 consecutive patients with blunt or penetrating trauma treated for pneumonia, 37% had *Haemophilus* spp. isolated from sputum cultures. Compared with patients who had pneumonia caused by other organisms, these

patients were younger and more severely injured. Lastly, Rello et al. (1992) prospectively studied the frequency of *H. influenzae* as a cause of ventilator-associated pneumonia (VAP) in the intensive care unit. During a 3-year period they found that *H. influenzae* accounted for 22% of 91 episodes of VAP. Other etiologic agents were isolated from about half of these patients. On average, *H. influenzae* pneumonia developed 10.8 days after intubation. Thirteen potential risk factors for development of *H. influenzae* VAP were evaluated but the only variable to achieve statistical significance was absence of prior antimicrobial therapy.

Association with HIV Infection

H. influenzae commonly causes CAP in persons infected with HIV. In an early series describing CAP in patients with AIDS, *H. influenzae* accounted for 8 of the 18 episodes occurring in 13 individuals (Polsky et al., 1986). Schlamm and Yancovitz (1989) reported that 34 of 51 adult patients with *H. influenzae* pneumonia seen at the Beth Israel Medical Center in New York during the period 1984–1986 occurred in young persons with AIDS, AIDS-related complex, or risk factors for AIDS. A more recent series from Baltimore that included 180 patients with concurrent HIV infection of varying degrees of severity found that *H. influenzae* accounted for 7% of cases (Mundy et al., 1995). A Spanish study describing 68 episodes of bacterial pneumonia in 55 patients with HIV infection found that *H. influenzae* was responsible for 18% of cases (Falco et al., 1994). A six-center study of bacterial pneumonia in HIV-infected patients conducted during the period 1988–1990 identified *H. influenzae* as the third leading cause, accounting for 15% of isolates (Hirschtick et al., 1995).

In a series of CAP in injection drug users, the relative risk for pneumonia caused by *H. influenzae* in persons with concurrent HIV infection was 13.62 (95% confidence interval [CI], 3.81–48.77) (Boschini et al., 1996). In a review from a New York hospital of 15 cases of bacteremia caused by type b *H. influenzae* during the period 1983–1991, ten cases occurred in individuals with AIDS or at high risk for AIDS (Casadevall et al., 1992). All but one patient had pneumonia. Lastly, a study of invasive *H. influenzae* infections conducted in San Francisco during the period 1989–1991 yielded annual incidences of 16.2 (95% CI, 5.8–45.2) and 24.1 (95% CI, 10.8–53.6) per 100,000 population in HIV-infected men without AIDS and all HIV-infected men in the 20–49-year age group, respectively (Steinhart et al., 1992). In this study pneumonia occurred in 5 of the 17 men with invasive disease. In summary, these diverse data suggest that defects in humoral immunity associated with HIV infection predispose this population to invasive disease caused by *H. influenzae,* especially pneumonia.

Risk Factors

Although risk factors for invasive disease caused by type b strains in children have been studied in considerable detail (Makela et al., 1992), similar attention has not been given to H. *influenzae* pneumonia. In particular, there are no prospective studies of *H. influenzae* pneumonia that use multivariate techniques that define the relative risk associated with certain patient characteristics. Nevertheless, as implied in previous sections, the absence of bactericidal antibody for type b (and presumably for other encapsulated strains) is an important risk factor for invasive disease, as are conditions associated with impaired humoral immunity, such as hypogammaglobulinemia, multiple myeloma, and HIV infection. Takala et al. (1993) have provided evidence suggesting that previous viral respiratory tract infections predispose children to invasive type b infections. Observations from case series of *H. influenzae* pneumonia in adults also suggest that antecedent respiratory tract infections may be important in pathogenesis (Quintiliani & Hymans, 1971; Johnson et al., 1968; Tillotson & Lerner, 1968; Levin et al., 1977). Finally, as will be seen from the characteristics of patients with *H. influenzae* pneumonia, conditions associated with aspiration and impaired pulmonary defenses appear to be important in pathogenesis as they are in CAP caused by other etiologic agents.

Clinical Features

The limited number of physiological responses to acute inflammation within the lung parenchyma dictate a clinical picture for H. *influenzae* pneumonia that is indistinguishable from that associated with pneumonia due to other pyogenic bacteria

such as *S. pneumoniae* (Klein, 1998; Smith, 1994; LeFrock et al., 1984). The spectrum of disease severity runs the gamut from mild to fulminant and life-threatening. The former is usually encountered in younger, healthier patients without serious underlying disease, whereas the latter is generally seen in adults with significant comorbidities. In extreme cases, patients may present with hypotension and respiratory failure (Eveloff & Braman, 1990; Martinella, 1997). As a rule and not surprisingly, pneumonia accompanied by bacteremia is a more severe illness with substantial case–fatality rates.

Patient Characteristics

Thirteen case series with five or more cases of *H. influenzae* pneumonia in adult patients have been published since 1967 (Goldstein et al., 1967; Tillotson & Lerner, 1968; Johnson et al., 1968; Quintiliani & Hymans, 1971; Everett et al., 1977; Levin et al., 1977; Wallace et al., 1978; Stratton et al., 1980; Berk et al., 1982; Musher et al., 1983; Pearlberg et al., 1984; Woodhead & MacFarlane, 1987; Quinones et al., 1989). A review of the 190 cases included in these series indicates that all age groups and both sexes are affected by this disease (Table 2). Persons greater than 45 years of age, however, appear to be affected more frequently. Although individuals without underlying lung disease can develop *H. influenzae* pneumonia, this factor is frequently cited as a descriptor of patients in the 13 case series (Table 2). These underlying diseases include chronic obstructive pulmonary disease, asthma, tuberculosis, bronchogenic carcinoma, and bronchiectasis. Series involving younger adults without underlying lung disease indicate that a history of tobacco smoking is frequent in such cases (Woodhead & MacFarlane, 1987). Alcoholism is also frequently mentioned as a patient characteristic in case series (Table 2). A number of other comorbidities are mentioned too, but none reach the frequency of either antecedent pulmonary disease or alcoholism. Moreover, most series also include individuals judged to be otherwise healthy.

Observations about patient characteristics in pediatric cases differ, reflecting the primacy of type b disease in the age group lacking antibody. In one series of 65 cases of type b pneumonia collected over a 14-year period at one urban hospital in Texas, patient ages ranged from 2 weeks to 7 years; 83% were younger than 2 years (Ginsburg et al., 1979). In another series from Chicago that collected 34 cases during a 4-year period, ages ranged from 2 months to 9 years, with a median age of 9.5 months (Jacobs & Harris, 1979). In this latter series, males outnumbered females 23 to 11. For the most part, *H. influenzae* pneumonia occurs in children without underlying lung disease or other comorbidities.

History

In adults, *H. influenzae* pneumonia is an acute illness with a symptomatic history measured in days at the time of presentation. In those patients with an antecedent viral respiratory infection the symptomatic history may seem to be a week or two longer. The vast majority of adult patients present with fever, cough, and sputum production (Table 3). Sputum has been described as thick, copious, purulent, and yellow or yellow to green (Tillotson & Lerner, 1968). A smaller percentage of patients complain of chest pain, which is invariably pleuritic, or hemoptysis (Table 3). Shortness of breath is present in up to one half of patients at the time of presentation. The frequency of this complaint probably reflects the status of pulmonary reserves and the extent of pulmonary involvement. Although the natural history of untreated *H. influenzae* pneumonia in adults has not been described, progression to chronic pulmonary disease appears to be rare (Henry et al., 1983).

Fever and cough are the typical symptoms observed in children with *H. influenzae* pneumonia (Ginsburg et al., 1979). These symptoms are often preceded by several days of coryza. Other symptoms may include anorexia, malaise, and fussiness (Smith, 1994). Parents may note the child's failure to improve and the development of tachypnea. The transition from coryza can be abrupt, with rigors, productive cough, and pleuritic pain appearing with the transition. In a small percentage of children the course is more indolent with 2 or 3 weeks of cough preceding presentation.

Physical Findings

Adult patients with *H. influenzae* pneumonia usually present with fever, tachycardia, tachypnea, and localized pulmonary findings (Table 3). These

TABLE 2. Case Series of *H. influenzae* Pneumonia

Reference	Diagnostic criteria	No. of cases	Age range in years (mean)	Male: female ratio	% Underlying lung disease	% with alcoholism	Case–fatality rate
Goldstein et al., 1997	Positive blood and sputum cultures	6	32–84 (68)	2:1	83	17	33
Tillotson & Lerner, 1968	Positive blood or pleural fluid cultures	6	30–78 (55)	2:1	100	50	0
Johnson et al., 1968	Positive blood cultures	5	36–73 (49)	1:4	20	NS	0
Quintiliani & Hymans, 1971	Positive blood or pleural fluid cultures	7	34–62 (47)	0:7	43	14	0
Everett et al., 1977	Positive blood, pleural fluid, or transtracheal aspirate culture	18	17–87 (NS)	NS	61	—	17
Levin et al., 1977	Positive blood or pleural cultures	24	23–81 (54)	2:1	54	50	33
Wallace et al., 1978	Positive blood culture	23	(54)	1.3:1	57	26	57
Wallace et al., 1978	Positive pleural fluid or transtracheal aspirate culture	18	(50)	5:1	28	28	11
Stratton et al., 1980	Positive blood, transtracheal aspirate, or expectorated sputum culture	5	33–78 (59)	2:3	20	NS	20
Berk et al., 1982	Positive transtracheal aspirate	12	60–80 (67)	All men	50	NS	25
Musher et al., 1983	Positive blood and expectorated sputum cultures	30	(57)[a] (47)	Mostly men	80	27	7
Pearlberg et al., 1984	Positive blood cultures	11	18–80 (48)	7:4	27	45	NS
Woodhead & MacFarlane et al., 1987	Positive blood or expectorated sputum culture	15	13–67 (NS)	2:3	0	NS	0
Quinones et al., 1989	Positive blood culture	10	27–77 (46)	7:3	40	0	0

NS, not stated in text
[a]Mean in bacteremic group and mean in expectorated serum group.

findings frequently include rales and rhonchi (Smith, 1994; LeFrock et al., 1984). Signs of consolidation are unusual. Pleural friction rubs are rare. Various degrees of systemic toxicity accompany these findings. Although fever is present in a majority of patients at the time of presentation, its absence does not exclude the diagnosis.

Fever, tachypnea, and localized lung findings are the predominant signs of *H. influenzae* pneumonia in children (Smith, 1994). In two large series of pediatric cases, localized lung findings were present in 82% and 56% of patients (Ginsburg et al., 1979; Jacobs & Harris, 1979).

Laboratory Findings

The most frequent laboratory abnormality in patients with *H. influenzae* pneumonia is leukocytosis. Usually the total white blood cell count is elevated as is the percentage of neutrophils (Table

TABLE 3. Clinical Features of *H. influenzae* Pneumonia

Reference	% Fever	% Chills	% Cough	% Sputum production	% Hemoptysis	% Dyspnea	% Chest pain	% Localized chest findings[a]	Range of white blood cells count[b] (mean)
Goldstein et al., 1997	100	100	100	NS	33	NS	33	NS	Elevations in 17%
Tillotson & Lerner, 1968	83	83	83	83	NS	83	NS	NS	8.1–82.5 Leukemia in one case
Johnson et al., 1968	60	20	80	60	80	60	60	80	12.9–29.0 (19.1)
Quintiliani & Hymans, 1971	43	14	86	86	28	43	57	100	5.9–30.7 (12.9)
Everett et al., 1977	67	61	94	78	6	44	61	NS	2.2–17.3 (NS)
Levin et al., 1977	58	33	38	NS	8	38	17	NS	1.7–20.5 (11)
Stratton et al., 1980	40	40	80	60	NS	NS	60	60	4–15.5 (11.5)
Berk et al., 1982	75	17	83	NS	8	NS	33	67	Elevations in 83%
Musher et al., 1983	NS	NS	NS	NS	NS	NS	NS	NS	2.6–24.9 (13.4)
Pearlberg et al., 1984	60	20	60	NS	0	20	40	NS	7.1–18.1 (NS)
Woodhead & MacFarlane et al., 1987	60	NS	100	NS	7	47	60	67	Elevations in 53%

NS, not stated in text.
[a]Localized rales, rhonchi, tubular breath sounds
[b]In thousands.

3). In some cases the total white blood cell count may be within normal limits, but in such cases the percentage of neutrophils and their precursors is generally elevated (Goldstein et al., 1967). Other laboratory abnormalities (e.g., anemia or hypoxemia) in patients with *H. influenzae* pneumonia generally reflect antecedent conditions or the extent of pulmonary involvement.

Radiographic Findings

Chest roentgenograms demonstrate a range of abnormalities in adult patients with *H. influenzae* pneumonia (Table 4). Published series of adult cases exhibit considerable variation in the frequency of lobar and bronchopneumonia patterns, possibly reflecting the lack of uniform criteria for evaluation. Pearlberg et al. (1984) observed an alveolar pattern in 8 of their 11 bacteremic cases. Three of their patients demonstrated a mixed alveolar-interstitial pattern. Lobar consolidation was present in four patients and segmental consolidation was present in four patients.

Although a majority of adult patients present with a single lobe involved, multiple lobe involvement is not uncommon (Table 4). Pleural effusions are present in about 20% of patients. Cavitation and abscesses are decidedly rare. As with the other clinical features of *H. influenzae,* the radiographic picture is not distinctive.

A similar range of radiographic abnormalities has been described in children with pneumonia caused by *H. influenzae* type b. Segmental infiltrates tend to be most common in frequency, and

TABLE 4. Radiolgoic Features of *H. influenzae* Pneumonia

Reference	% with lobar infiltrate	% with bronchopneumonia	% with only one lobe involved	% with more than one lobe involved	% with pleural effusion
Goldstein et al., 1997	67	33	50	30	NS
Tillotson & Lerner, 1968	0	100	NS	NS	NS
Johnson et al., 1968	100	0	80	20	20
Quintiliani & Hymans, 1971	86	14	43	57	43
Everett et al., 1977	100	0	61	39	0
Levin et al., 1977	25	75	NS	NS	46
Wallace et al., 1978	22	78	22	78	30
Wallace et al., 1978	NS	NS	22	78	44
Stratton et al., 1980	100	0	80	20	0
Berk et al., 1982	NS	NS	67	33	17
Musher et al., 1983	23	77	87	13	10
Pearlberg et al., 1984	73	27	45	55	56
Woodhead & MacFarlane et al., 1987	27	73	80	20	NS
Quinones et al., 1989	90	10	40	60	40

NS, not stated in text.

early pleural reactions appear in more than 50% of cases (Smith, 1994). Ginsburg et al. (1979) observed pleural effusions in 75% of the 65 cases studied. They further noted consolidation in one or more lobes of 75% of their cases and bronchopneumonia in 25%. Disease was unilateral in 57% of patients with consolidation and in 69% of patients with bronchopneumonia. In the 34 patients reported by Jacobs and Harris (1979), 23 had pneumonia localized to one lobe without involving the entire lobe. Thirteen patients had roentgenographic evidence of pleural effusion; seven were large, obscuring a third or more of the hemithorax.

Natural History

Although pleural effusions are common in *H. influenzae* pneumonia, these are generally parapneumonic effusions. Empyema is uncommon in adult patients, but complicates approximately 10% of pediatric cases, generally occurring in the later stages (Smith, 1994). Prior to the advent of the conjugated vaccines, it accounted for approximately 6% of empyemas in children. It is generally recognized as a loculated effusion several days or even weeks into the infection, and it is infrequently symptomatic.

Approximately 5% of children with *H. influenzae* pneumonia develop lung abscesses (Smith, 1994). It is generally associated with mild symptomatology: low-grade fever, slight cough, malaise, and failure to gain weight. Chest x-rays disclose an air-fluid level and a pleural reaction. Therapy may require thoracostomy tube placement. Although reported, this complication is rare in adult patients with *H. influenzae* pneumonia (Smith, 1994).

Diagnosis

Because *H. influenzae* is often part of the normal human flora, establishment of its pathogenic role in patients with pneumonia is not always easy, especially in patients with chronic obstructive pulmonary disease who are frequently colonized with this organism (Murray & Sethi, 1992). In previously healthy individuals or those without underlying lung disease, the diagnosis of *H. influenzae* pneumonia may be suggested by the results of a gram-stained smear of sputum, demonstrating a uniform population of pleomorphic, gram-negative coccobacilli. Musher et al. (1983) required gram-stained specimens with many neutrophils, less than one epithelial cell per five to ten oil immersion fields, and "... gram-negative, pleomorphic coccobacilli as the overwhelming predominant form, outnum-

bering other organisms by greater than 50 to 1." Cultural confirmation is required since other organism such as *Acinetobacter* spp. can mimic this picture (LeFrock et al., 1984). Although other stains, including Wayson and acridine orange, can improve the detection of H *influenzae* in clinical specimens, they are seldom used outside of research studies (Campos, 1995).

Luxurious growth of *H. influenzae* from respiratory tract secretions in the absence of other respiratory pathogens is highly suggestive of the diagnosis, especially when coupled with compatible morphologic findings on a high-quality gram stain of the same specimen. Such results are less helpful in patients with chronic obstructive pulmonary disease and other chronic pulmonary conditions. For these patients, positive cultures from blood, pleural fluid, or other normally sterile body fluids probably offer the surest handle on the etiologic diagnosis. In patients with nosocomial pneumonia, especially those who have undergone endotracheal intubation, quantitative cultures of specimens obtained with bronchoscopic techniques probably offer the greatest likelihood of a convincing etiologic diagnosis (Strausbaugh, 1999; Mayhall, 1997).

Culture

Specimens submitted for culture need to be processed quickly since *H. influenzae* is fastidious. Virtually all commercially available blood culture media support its growth, but other specimens such as sputum or pleural fluid should be plated directly on chocolate agar or a semisynthetic media containing heme and NAD (Ward & Zangwill, 1998). Although chocolate agar is the traditional favorite for the isolation of *H. influenzae,* GC agar base plus 5% chocolatized sheep blood and 1% yeast autolysate promote the best growth (Campos, 1995). *H. influenzae* will not grow on sheep blood agar; consequently, isolation of a small gram-negative coccobacillus on chocolate agar, and not on blood agar, strongly suggests *Haemophilus.* Of note, if X and V factors are applied to the surface of blood agar via paper disk or strip, this media will support the growth of *H. influenzae.* These factors may be supplied also by cross-streaking the plate with *S. aureus.*

Since the small, translucent colonies of *H. influenzae* are easily obscured by the growth of other bacteria after overnight incubation on chocolate agar, several selective media have been developed to facilitate isolation (Campos, 1995), but they are not commonly used in clinical microbiology laboratories. Candidate isolates are identified definitively as *H. influenzae* by demonstration of the organism's dependence on heme and NAD for growth. Isolates can be serotyped with agglutination, counterimmunoelectrophoresis, and other techniques. These tests are infrequently performed in most clinical microbiology laboratories.

Serology

Serologic tests to detect rising antibody tilers against various antigens of *H. influenzae* have been developed, but they are rarely used outside of research settings. Theoretically, radioimmunoassays or enzyme immunoassays developed to document the response to *H. influenzae* type b could be used to document infections such as pneumonia caused by type b strains. Burman et al. (1994) described an enzyme-linked immunosorbent assay using antigens derived from ten different strains of nonencapsulated *H. influenzae.* Eleven (7%) of the 158 adult patients with CAP demonstrated significant increases in antibody titer to the antigen preparation used. Three of these patients had positive transtracheal aspirates and seven of these patients had cultures of sputum, nasopharynx, or both that were positive for *H. influenzae.* In contrast, six patients whose transtracheal aspirates were positive failed to demonstrate an antibody increase, suggesting that this approach to diagnosis lacked sensitivity. Additional study of this approach is warranted. Use of the P6 component of the OMP as the antigen might improve the results (Murphy et al., 1986; Nelson et al., 1991).

Antigen Detection

Examination of pleural fluid, serum, or urine for antigen has been used in the diagnosis of type b infections in children, albeit, usually for the diagnosis of meningitis (Lieberman & Ward, 1994; Murphy, 1998). Latex particle agglutination, countercurrent immunoelectrophoresis, and coagglutination are the techniques used most frequently (Ward & Zangwill, 1998). False-positive reactions with cerebrospinal fluid specimens are rare; how-

TABLE 5. Susceptibility of *H. influenzae* to Antimicrobial Agents

	Doern et al., 1988	Jacobs & Jerris, 1991	Jorgensen et al., 1990	Tremblay et al., 1990	Barry et al., 1994	Ostroff et al., 1996	Doern et al., 1997[a]
Years of study	1986	1987–1989	1987–1989	1985–1987	1992–1993	1991–1993	1994–1995
Sources	30 US medical centers	Decatur, GA medical center	15 US medical centers	14 Canadian hospitals	19 US clinical laboratories	2 fever hospitals in Egypt	30 US medical centers
No. of strains	2811	325[b]	564	2503	890	353	1537
% β-lactamase positive	20	24	16	17	30	NT	36
% Susceptible to							
Ampicillin	97[c]	NT	99[c]	81	NT	93	>90[c]
Ampicillin/clavulanate	NT	100	100	98	99	NT	>90
Trimethoprim/sulfamethoxazole	99	96	99	96	93	85	>90
Ampicillin/sulbactam	NT	100	99	NT	NT	NT	NT
Cefaclor	94	100	98	99	91	NT	<90
Cefuroxime	NT	100	99	99	98	NT	>90
Cefotaxime	NT	100	NT	99	NT	NT	NT
Azithromycin	NT	NT	NT	NT	99	NT	>90
Ciprofloxacin	NT	NT	NT	NT	100	NT	NT

NT, not tested

[a]Presentation of data in this article do not permit a more precise estimate of susceptibility

[b]Only 71 strains were tested against the antimicrobial agents specified.

[c]% of β-lactamase-negative strains tested that were susceptible.

ever, they occur with some frequency with serum and urine specimens. Whether any of these assays for type b antigens would substantially increase the diagnostic yield in children is uncertain and probably unimportant, given the dramatic decline in the incidence of this infection.

Because of the lesser frequency of type b strains in adults with pneumonia, there has been little interest in using antigen detection assays in adults. Burman et al (1991) did include an enzyme-linked immunosorbent assay for capsular antigens a, b, c, d, e, and f in their evaluation of 196 hospitalized adults with CAP. *H. inftuenzae* was isolated from transtracheal aspirates, sputum, or nasopharynx of 28 patients, but all strains were nonencapsulated. Not surprisingly, capsular antigens were not detected in sputum or urine of these patients, and none of these patients had an antibody response to the type b capsular antigen. Tests using common antigens from nontypable strains have yet to appear.

Treatment

In vitro Susceptibility Data

Until the early 1970s virtually all strains *of H. inftuenzae* were susceptible to ampicillin, which was considered the drug of choice. Since then, however, ampicillin resistance has become widespread (Doern et al., 1988, 1997; Jacobs & Jerris, 1991; Jorgensen et al., 1990; Tremblay et al., 1990; Barry et al., 1994; Ostroff et al., 1996). Most ampicillin resistance is due to production of β-lactamases. The TEM-1 β-lactamases predominate; ROB-1 β-lactamases are five to eight times less frequent (Cunha & Shea, 1998). A small percentage of *H, influenzae* strains owe their ampicillin resistance either to alterations in their penicillin-binding proteins or to diminished membrane permeability. Although the percentage of resistant isolates varies from one locale to another, in recent years it has exceeded 30% in many areas (Table 5). It has been estimated that in less than a year, 45% to 50% of clinical isolates in the United States will be β-lactamase producers (Doern, 1995).

The vast majority of clinical isolates of *H. influenzae,* including β-lactamase-producing strains, are susceptible to β-lactam/β-lactamase inhibitor combinations (e.g., ampicillin/sulbactam), second- and third-generation cephalosporin antibiotics, azithromycin, and fluoroquinolone antimicrobial agents (Table 5). Most strains are also susceptible to trimethoprim–sulfamethoxazole, but resistant strains that produce dihydrofolate reductases have been described (Cunha & Shea, 1998). Although rarely used in the United States, chloramphenicol possesses excellent activity against *H. influenzae.* To date, resistant strains expressing chloramphenicol acetyltransferase have been detected infrequently. Though seldom used to treat *H. influenzae* infection, tetracycline antibiotics and rifampin demonstrate potent activity in vitro against most clinical isolates of this bacterium (Doern et al., 1988, 1997; Jorgensen et al., 1990; Tremblay et al., 1990).

Therapeutic Options

The treatment choices for patients with *H. influenzae* pneumonia correspond to the possibilities identified in susceptibility tests (Table 5). Some of

TABLE 6. Therapeutic Options for Empirical Treatment of *H. influenzae* Pneumonia

Clinical situation	Class of antimicrobial agent	Examples
Moderate to severe disease—parenteral therapy desired	Second- or third-generation cephalosporin antibiotic	Cefuroxime, cefotaxime, ceftriaxone
	β-lactam/β-lactamase inhibitor combination	Ampicillin/sulbactam
	Fluoroquinolone	Ciprofloxaxin, levofloxacin
Milder disease—oral therapy possible	β-lactam/β-lactamase inhibitor combination	Ampicillin/clavulanic acid
	Inhibitors of folic acid synthesis	Trimethoprim/sulfamethoxazole
	Second- or third-generation cephalosporin antibiotic	Cefuroxime axetil, cefpodoxime proxetil
	Macrolide	Azithromycin

the options available for empirical therapy are listed in Table 6. These conform to recommendations offered in recent guidelines (British Thoracic Society, 1993; Niederman et al., 1993; Bartlett et al., 1998; Bartlett & Mundy, 1995). Although some have questioned whether β-lactamase resistance results in treatment failures in patients with pneumonia (Klugman, 1996), coverage of such resistant strains is a priority in the recommendations. Specific selections for individual patients will require consideration of unique patient variables (e.g., a history of β-lactam allergy or concurrent meningitis), desired coverage of other etiologic agents (e.g., *S. pneumoniae* or *Mycoplasma pneumoniae),* local resistance patterns, drug costs, and drug toxicities. Once the etiologic diagnosis is confirmed and susceptibility data are available, it is often possible to narrow the spectrum of therapy. For example, if the isolate of *H. influenzae* is not resistant to ampicillin, then therapy with ampicillin or amoxicillin may be safely substituted for the initial agent. In general, patients with *H. influenzae* pneumonia only require 7 to 10 days of antimicrobial therapy.

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Community-Acquired Pneumonia: *Staphylococcus aureus*

SANTIAGO EWIG AND ANTONI TORRES

Introduction

Staphylococcus aureus represents an uncommon etiology of community-acquired pneumonia (CAP). Accordingly, only three large series of staphylococcal CAP have been published, two originating from the pre-antibiotic era (Chickering & Park, 1919; Finland et al., 1942) and only one more recent series (Woodhead et al., 1987b). Nevertheless, the majority of studies of hospitalized patients with CAP do report this etiology, especially those investigating severe CAP. Since *S. aureus* can cause excess mortality, this etiology should be taken into account when evaluating patients with CAP. In this chapter, we describe pathogenesis, incidence, risk factors, outcome and prognostic factors, clinical features, diagnostic evaluation, and antimicrobial treatment of staphylococcal CAP.

Pathogenesis

S. aureus is a member of the normal flora of the human skin and the respiratory and gastrointestinal tracts. Nasal carriage occurs in approximately 50% of humans. The pathogenic potential of *S. aureus* is the combined effect of extracellular substances (enzymes and toxins) together with the invasive properties of the strain. Focal suppuration is typical of staphylococcal infection. Hematogenous spread may occur from any focus to any other part of the body. Infection with influenza virus with subsequent necrosis of the ciliated and goblet cells represents a well recognized factor that favors staphylococcal adherence and superinfection.

It is important to recognize that CAP due to *S. aureus* may be acquired via the airways as well as the bloodstream. These types of staphylococcal pneumonia are sometimes referred to as primary and secondary staphylococcal pneumonias, respectively.

Incidence

Ambulatory Setting

S. aureus has been found only rarely in patients with mild to moderate CAP who are treated as outpatients. In a British series, it accounted for 1% of pneumonias (Woodhead et al., 1987a), and in a Swedish one, not a single case was identified (Berntsson et al., 1985). A more recent British series on lower respiratory tract infections reported *S. aureus* in 1% of those studied (MacFarlane et al., 1993).

Hospital Setting

In hospitalized patients with CAP, the incidence of *S. aureus* infection is higher. A study from the United States originating from the early 1970s

SANTIAGO EWIG • Medizinische Universitatsklinik und Poliklinik Bonn, Innere Medizin–Pneumologie, Sigmund Freud Str. 25, 53105 Bonn, Germany. **ANTONI TORRES** • Hospital Clinic i Provincial, Servei de Pneumologia i Allergia Respiratoria, Villarroel 170, 08036 Barcelona, Spain.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

found *S. aureus* in 10% of cases, representing the third most common pathogen (Sullivan et al., 1972). Since this study, only three other series (also conducted in the United States) have reported a similarly high incidence of 7% (Bates et al., 1992), 8% (Klimek et al., 1983) and 9% (Farr et al., 1991). All other studies from the United States (Yu et al., 1982; Fang et al., 1990; Mundy et al., 1995), Canada (Marrie et al., 1989), Europe (United Kingdom: White et al., 1981; MacFarlane et al., 1982; McNabb et al., 1984, British Thoracic Society, 1987; Sweden: Holmberg, 1987; örtqvist et al., 1990; France: Aubertin et al., 1987, Levi et al., 1988; Spain: Blanquer et al., 1991; Pareja et al., 1992; Germany: Steinhoff et al., 1996), Australia (Lim et al., 1989), New Zealand (Karalus et al., 1991; Neill et al., 1996), Hong Kong (Chan et al., 1992), Israel (Lieberman et al., 1996), and Saudi Arabia (Kurashi et al., 1992) found incidences of approximately 1% to 5%. A German series comparing incidences of causative pathogens of CAP during a 10-year period found a stable incidence of *S. aureus* of approximately 2% to 3% (Allewelt et al., 1997). In a recent series of 395 patients during an 18-month period, Ruiz et al. (1998) found an incidence of 3%. Of note, only two studies did not find any cases of CAP due to *S. aureus* (Kauppinen et al., 1995; Gomez et al., 1996). Thus, it seems that the incidence of *S. aureus* in hospitalized patients with CAP is 2% to 4%. Only a few studies report the proportion of cases associated with influenza virus infection. In a study by Sullivan and coworkers (1972) reporting the highest incidence, none of these cases was associated with influenza virus infection. British authors have reported corresponding concomitant influenza virus infection rates ranging from 38% to 75% (White et al., 1981; MacFarlane et al., 1982; McNabb et al., 1984; British Thoracic Society, 1987).

Special Populations: Children

The highest incidence of staphylococcal CAP in children occurs during the first 3 months of life. Typical clinical features are acute onset and rapid progression. Pneumothorax, lung abscess, and pneumatoceles are the most characteristic complications (Fisher et al., 1958; Joosten et al., 1995). In the remainder of childhood, pneumonia due to *S. aureus* is rare (Chartrand & McCracken, 1982). One series comparing the etiology of CAP in children and adults did not find any *S. aureus* cases in children (Ausina et al., 1988).

Special Populations: Elderly and Residents of Nursing Homes

The incidence of pneumonia due to *S. aureus* does not seem to be higher in the elderly. Two large studies of CAP in the elderly did not find any cases (Venkatesan et al., 1990; Riquelme et al., 1996). In contrast, in a study comparing patients aged 65 and less than 65 years, the incidence of *S. aureus* pneumonia was 4% and 3%, respectively (Marrie et al., 1989). Two studies have addressed the incidence of CAP due to *S. aureus* in patients admitted from nursing homes. Since head injury is a clear risk factor for nosocomial pneumonia due to *S. aureus* (Rello et al., 1990; Ewig et al., 1998a), one might expect that pneumonia due to this microorganism may be more frequent in a population with an increased proportion of patients with severe neurological disorders. In one case–control study, *S. aureus* was found to be significantly more common in nursing home patients than in community patients (26% vs. 14%) (Garb et al., 1978). Conversely, others comparing both populations in an exceptionally large series (131 nursing home-acquired and 588 community-acquired pneumonias) could not find a corresponding difference (5% vs. 4%) (Marrie et al., 1989).

Special Populations: HIV-Infected Patients

Bacterial pneumonia acquired in the community has been recognized as a frequent complication during the course of HIV infection (Wallace et al., 1993; Hirschtick et al., 1995). *S. aureus* has been repeatedly described as a cause of bacterial pneumonia in this population (Levine et al., 1990; Wallace et al., 1993). Moreover, staphylococcal infections were found to be the leading bacterial infection in one autopsy series (Nichols et al., 1989). All of these infections involved the lungs. In two large series, *S. aureus* was the third and fourth most common pathogen, respectively, reaching an incidence of 5% (Burack et al., 1994; Hirschtick et al., 1995). The attack rate of staphylococcal pneumonia (mostly community-acquired) was recently esti-

mated to be as high as 8.3 per 1000 HIV-related hospital admissions in a case–control study (Tumbarello et al., 1996). In this study, intravenous drug abuse and previous *Pneumocystis carinii* pneumonia were identified as independent risk factors. However, in several series evaluating microbial patterns in HIV-infected patients with pneumonia, the incidences ranged from 0% to 2%, independent of the proportion of intravenous drug abusers included (Magnenat et al., 1991; Ferrer et al., 1992; Falco et al., 1994; Ewig et al., 1998b). Thus, there is currently no convincing evidence that staphylococcal CAP is more frequent in these patients versus the general population. Nevertheless, *S. aureus* represents an important etiology of pneumonia acquired in the community in this population.

Intensive Care Unit Setting

As reported from series involving patients with severe CAP, the incidence appears to be more variable in this population compared with the general population. The highest incidences have been reported from Nottingham, England, accounting for 10% of cases (Woodhead et al., 1985) and 12% of cases in a follow-up study (Hirani & MacFarlane, 1997). Several authors from different regions have reported similarly high incidences of 8% (Italy: Cosentini et al., 1996; South Africa: Potgieter & Hammond, 1992), 7% (Singapore: Tau et al., 1998), and 6% (United Kingdom: Alkhayer et al., 1990). Conversely, there are also several series with very low incidences of 1% to 2% (United Kingdom: British Thoracic Society, 1992; Spain: Pachon et al., 1990; Torres, 1991; Rello et al., 1993). Moreover, two studies did not find any patients with *S. aureus* pneumonia (Almirall et al., 1995; Rello et al., 1996). Intermediate incidences of 3% to 5% have also been reported from Spain (Oleachea et al., 1996); France (Moine et al., 1994); South Africa (Feldman et al., 1989, 1995). One group from Lille, France, reported excess incidences for *S.* spp. as high as 19% and 18% (Leroy et al., 1995, 1996). However, the authors did not specify how many cases were attributable to *S. aureus.* Unfortunately, in these populations, the number of concomitant infections with influenza virus is usually not reported. In the aforementioned series from Nottingham, co-infection with influenza virus was demonstrated in 40% (Woodhead et al., 1985) and 57% (Hirani & MacFarlane, 1997) of cases. Only a single case has been reported to be due to an oxacillin-resistant strain (Potgrieter & Hammond, 1992).

Risk Factors

Fifty percent of the cases of staphylococcal CAP occur in previously healthy patients (Woodhead et al., 1987b). The majority of these cases are associated with influenza virus infection (Schwarzman et al., 1971). No studies have specifically addressed risk factors for CAP due to *S. aureus.* Nevertheless, from the current literature some conditions that most probably represent risk factors can be inferred.

With regard to inhalational pathogenesis, influenza virus infection probably represents one of the most common predisposing factors for staphylococcal CAP. Accordingly, the first description of staphylococcal CAP was in the wake of the 1918 influenza epidemic (Chickering & Park, 1919). In one recent study, it has been argued that even the 52% rate of coincident infection with influenza virus found is probably an underestimate since the seasonal distribution of staphylococcal CAP follows the same distribution as that of annual influenza epidemics (Woodhead et al., 1987b). In this case, risk factors for influenza virus pneumonia, such as advanced age, residence in a nursing home, chronic cardiopulmonary disorders, and other chronic disabling conditions, would in part also represent risk factors for staphylococcal CAP. Chronic respiratory diseases were reported to be present in 23% of cases in the study by Woodhead et al. (1987b). However, in a recent Spanish multicenter study specifically addressing patients with chronic obstructive pulmonary disease (COPD), *S. aureus* was detected in only one of 124 patients, indicating that this underlying condition is probably not a risk factor for this etiology (Torres et al., 1996). Cystic fibrosis is frequently associated with tracheobronchial colonization with *S. aureus* and, therefore, may represent a risk factor for staphylococcal CAP.

Patients with traumatic and medical head injury frequently develop early onset ventilator-

associated pneumonia. *S. aureus* has been repeatedly demonstrated to be the leading pathogen in these patients (Rello et al., 1992; Sirvent et al., 1997; Ewig et al., 1998b). The predominant pathway of infection by *S. aureus* and other community endogenous pathogens (such as *Haemophilus influenzae* and *Streptococcus pneumoniae)* in this setting is oropharyngeal or gastric colonization followed by high-inoculum aspiration of oropharyngeal secretions. Patients may aspirate oropharyngeal secretions shortly after brain injury, during resuscitation, or as a consequence of intubation. Similarly, *S. aureus* was the most frequent pathogen of upper and lower airway colonization at the initial evaluation as well as of early-onset ventilator-associated pneumonia in a series of 48 patients with traumatic or medical head injury (Ewig et al., 1998b). An especially high colonization rate with *S. aureus* was observed in the upper airways (nose and pharynx). The precise reasons for the high incidence of staphylococcal colonization in these populations are not known.

Hematogenous spread frequently occurs in intravenous drug abusers. Nevertheless, primary bacteremia with subsequent pneumonia, but without identifiable focus, can be observed (Table 1).

Outcome and Prognostic Factors

The reported mortality rates of staphylococcal CAP in hospitalized patients differ considerably. Sullivan and colleagues found a mortality rate of 41%, 6-fold higher than the mortality due to pneumococcal pneumonia. The rate was 25% in younger patients and 75% in the elderly (Sullivan et al., 1972). Comparable rates of 38% to 50% were reported in several other series (White et al., 1991; Örtqvist et al., 1990; Fang et al., 1990). This rate is clearly higher than that reported for the general population, which ranges from 5% to 10%. In the largest series of staphylococcal CAP available in the antibiotic era, mortality was found to be 30% (Woodhead et al., 1987b). In our recent experience, only one of seven patients with staphylococcal CAP died (Ruiz et al., 1998). Similarly, no patient died in two reports of eight and seven patients (Blanquer et al., 1991; Neill et al., 1996). In studies of severe CAP, mortality ranged from 60% to 100% (Moine et al., 1994; Woodhead et al., 1985; Hirani & MacFarlane, 1997). Thus, although staphylococcal CAP may be associated with excess mortality, it appears that there are additional factors that determine the outcome.

Factors associated with death in patients with staphylococcal pneumonia in a univariate analysis of one large series were age >45 years, mental confusion, reduced level of consciousness, blood urea nitrogen >7 mmol/L, arterial pH <7.35, and bacteremia (Woodhead et al., 1987b). These factors do not appear to be different from those associated with mortality in the general population with CAP. However, it seems that bacteremia is one of the major adverse factors, comparable only to the adverse prognostic potential of pneumococcal bacteremia and bacteremia in CAP due to *Klebsiella pneumoniae* (Feldman et al., 1989; Woodhead et al., 1985). In a study of 44 patients with bacteremic staphylococcal pneumonia, mortality was 84% (Watanakunakorn, 1987). Influenza virus seems to be an adverse prognostic factor. In the series cited previously, 64% of patients with evidence of concomitant influenza virus infection died (Woodhead et al., 1985). In the British Thoracic Society (1992) study, all patients with concomitant influenza virus infection died (Table 2).

The impact of methicillin resistance on the outcome of staphylococcal CAP is not known. Nevertheless, in patients with ventilator-associated pneumonia, mortality directly related to pneumonia was

TABLE 1. Risk Factors for Staphylococcal Community-Acquired Pneumonia

Influenza virus infection	Chronic cardiopulmonary disorders
Advanced age	Cystic fibrosis
Nursing home residence	Intravenous drug abuse

TABLE 2. Prognostic Factors for Staphylococcal Community-Acquired Pneumonia

Advanced age	Arterial pH <7.35
Mental confusion	Bacteremia
Reduced consciousness	Influenza virus infection
Blood urea nitrogen >7 mmol/L	Methicillin resistance

significantly higher among patients with episodes of methicillin resistant *Staphylococcus aureus* (MRSA). Similarly, the presence of bacteremia and septic shock was more frequent in the MRSA group (Rello et al., 1994).

Clinical Presentation

The clinical and laboratory features of staphylococcal CAP are similar to those seen in the general population with CAP. The presentation is variable, with a clinical course ranging from subacute to fulminant (Kaye et al., 1990; Woodhead et al., 1987b). Laboratory abnormalities were only infrequently studied. Notable features include a high incidence of lymphopenia (33%), abnormal liver function (55%), and serum albumin <25 g/L (59%) (Woodhead et al., 1987b). Radiographic patterns are more specific. In one series of 34 patients with staphylococcal CAP (including eight children), bilateral patchy shadowing, cavitation, pneumatoceles, and pneumothorax were features of this etiology in both adults and children. Radiographic deterioration after hospital admission was frequently observed (64% of cases), comparable only to the corresponding frequency seen in legionellosis (65%) (MacFarlane & Rose, 1996). In a series that included 25 nosocomial and six community-acquired staphylococcal pneumonias, patients frequently presented with multilobar (65%) and bilateral (48%) involvement; pleural effusions (48%), half of which were empyemas; and abscess formation (16%) (Kaye et al., 1990). Others have described abscess formation and cavitations in 20% to 70% of cases (Hausmann & Karlish, 1956; Fisher et al., 1958; Wiita et al., 1961; Woodhead et al., 1987b), and pneumothorax in 10% (Woodhead et al., 1987b). These patterns are clearly more frequent than in the general population with CAP. Thus, any of these patterns should lead the clinician to suspect staphylococcal CAP (Table 3). Typical examples of extensive consolidating primary as well as secondary staphylococcal CAP are shown in Figures 1 and 2. Although these features are typical for staphylococcal CAP, due to the low frequencies of these features, the absence of these findings does not rule out this etiology (MacFarlane & Rose, 1996). Any case with staphylococcal bacteremia should be evaluated for extrapulmonary foci, especially for cutaneous infections, thrombophlebitis, and tricuspid valve endocarditis in intravenous drug abusers.

TABLE 3. Clinical Features of Staphylococcal Community-Acquired Pneumonia

Clinical presentation
Variable: subacute to fulminant
Laboratory abnormalities
Lymphopenia
Abnormal liver function
Low serum albumin
Radiographic patterns
Multilobar involvement
Bilateral involvement
Pleural effusions (empyemas)
Abscess formation, cavitation, pneumatoceles
Pneumothorax

Microbiological Diagnosis

Staphylococcal CAP may be diagnosed by sputum Gram stains and cultures, blood cultures, pleural fluid, tracheobronchial aspirates, and other invasive techniques, such as transthoracic needle aspiration or bronchoscopically retrieved protected specimen brush and bronchoalveolar lavage. Most cases reported in the literature are diagnosed by sputum cultures (Woodhead et al., 1987b). Gram stains of sputum typically show gram-positive cocci in clusters, suggesting staphylococci (Fig. 3). The diagnostic yield of sputum cultures is not precisely known. Since staphylococci may be normal inhabitants of the upper respiratory tract in approximately one third of adults, there are concerns about the specificity of the sputum culture. Nevertheless, the appearance of *S. aureus* in pure culture of a sputum sample is usually thought to be evidence for a causal role of this pathogen (Fisher et al., 1958; Woodhead et al., 1987b). In the general population of hospitalized patients with staphylococcal CAP, 9% to 34% patients had positive blood cultures (Sullivan et al., 1972; Woodhead et al., 1987b; Kaye et al., 1990; Farr et al., 1991). In severe staphylococcal CAP, the corresponding rates are 25% to 100% (Feldman et al., 1989, 1995; Woodhead et al., 1985;

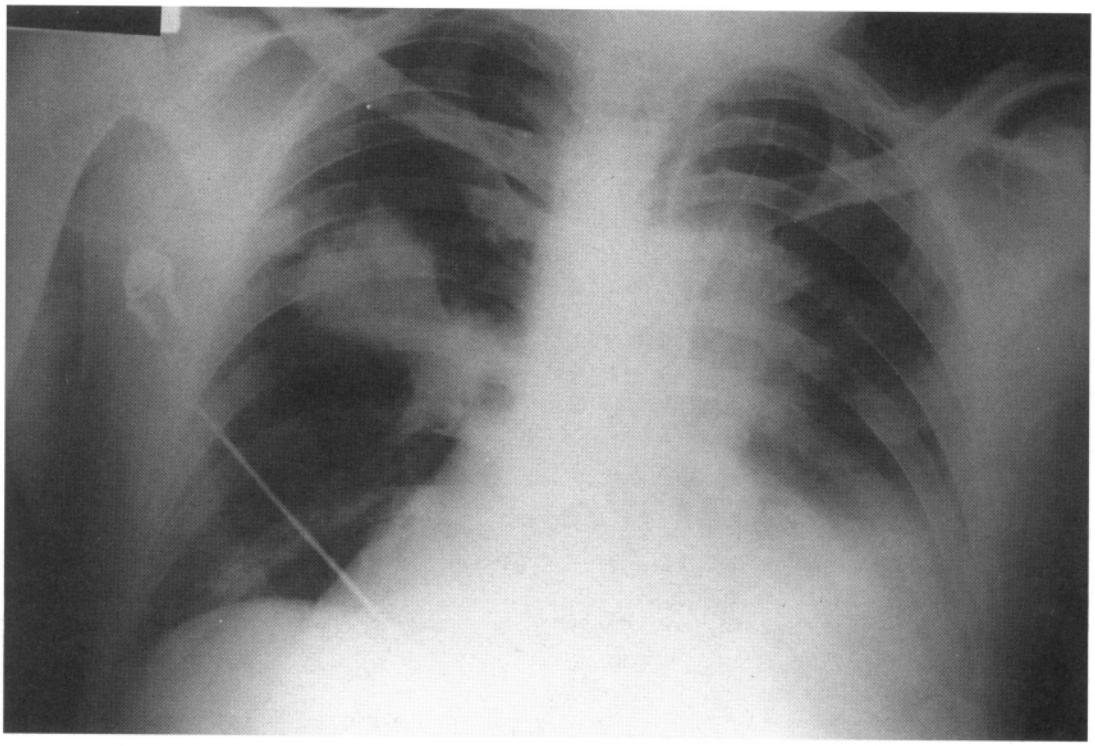

FIGURE 1. Chest radiograph of a patient with severe staphylococcal community-acquired pneumonia showing extensive bilateral areas of consolidation and left-sided pleural effusion.

Tau et al., 1998). Other techniques have only sporadically been reported. In one recent series, diagnosis of staphylococcal CAP was made by sputum culture in 29% (2/7), blood culture in 29% (2/7), and tracheobronchial aspirates in 43% (3/7) (Ruiz et al., 1998). For practical purposes, sputum Gram stains and cultures (or tracheobronchial aspirates in mechanically ventilated patients) and two sets of blood cultures should be obtained from any patient presenting with severe CAP. In nonsevere CAP, diagnostic evaluation may be restricted to patients not responding to the initial empiric antimicrobial treatment. Any pleural effusion extending beyond the costophrenic angle should be investigated in order to exclude empyema.

Antimicrobial Treatment

Suspected staphylococcal CAP may be safely treated with antimicrobial agents that exhibit antistaphylococcal activity against β-lactamase negative and positive strains while awaiting culture and susceptibility results. These drugs include second-generation cephalosporins (e.g., cefuroxime 3 × 2 g/day), antistaphylococcal penicillins (e.g., cloxacillin 3–4×l–2g/day), aminopenicillins/β-lactamase inhibitors (e.g., amoxicillin/clavulanic acid 3–4 × 1.2–2.2 g/day), erythromycin (3–4 × 1 g/day), clindamycin (4 × 300–600 mg/day, and carbapenems (e.g., imipenem 3 × 0.5–1 g/day). The response to antimicrobial treatment may be slow, in part due to reduced penetration of antimicrobial agents into necrotic areas (Woodhead et al., 1987b). Therefore, the duration of antimicrobial treatment must be individualized. It may be necessary to administer antimicrobial treatment for 2 to 4 weeks. The presence of pneumatocele and/or lung abscess may require prolonged antimicrobial treatment for up to 6 weeks.

Nevertheless, community-acquired MRSA infections, including pneumonia, have been reported

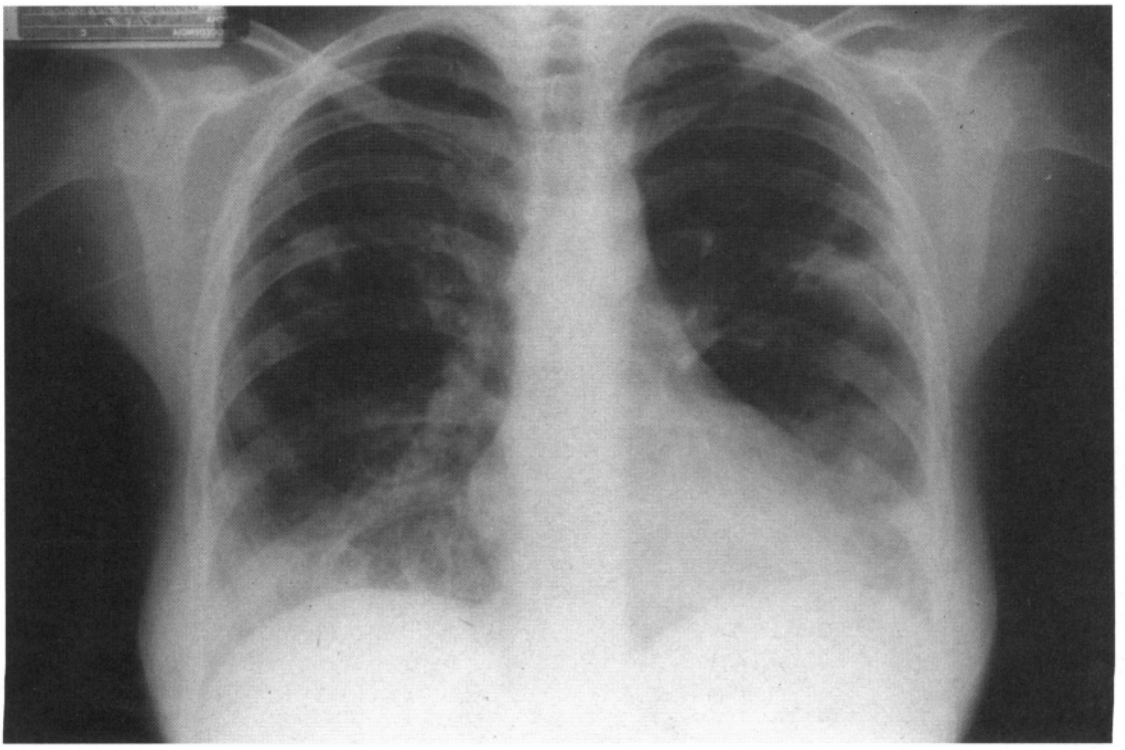

FIGURE 2. Chest radiograph of a patient (intravenous drug abuser) with metastatic staphylococcal community-acquired pneumonia showing multiple bilateral peripheral lung abscesses.

(Saravolatz et al., 1982). During a community outbreak of MRSA in Detroit, surveillance studies revealed that 14% of staphylococcal infections were caused by MRSA. The majority (61%) occurred in intravenous drug abusers. While skin and soft tissue infections were the most common manifestation, pneumonia was the fourth most common infection, and the second most common in non-intravenous drug abusers. Bacteremia was present in 29% of pneumonias. Most of the non-intravenous drug abusers had been hospitalized within the last year, half of them in units where MRSA had been documented. These findings suggest that MRSA should be considered in intravenous drug abusers and patients with recent hospitalization in a unit where MRSA is endemic. Residents of nursing-homes may also be at increased risk. Vancomycin (2 x 1 g/day) and teicoplanin (3 x 400 mg every 12 hours, followed by 1 × 200–400 mg/day) remain the treatment of choice for infections due to MRSA. Drugs that may be effective in a combination regimen include rifampin (1 × 450–600 mg/day) and ciprofloxacin (2 × 200 mg/day).

Measures of infection control should include good hygiene and handwashing as well as isolation to prevent transfer of MRSA. In case of readmission to the hospital, the patient should be investigated for nasal carriage and may be a candidate for local nasal antimicrobial treatment (mupirocin).

Conclusions

S. aureus accounts for 3% to 5% of all cases of CAP. The clinical presentation is variable, ranging from subacute to fulminant illness. The presence of risk factors such as current influenza epidemics, age, residence in nursing homes, cardiovascular comorbidity, as well as certain radiographic characteristics represent the main clues for suspicion of staphylococcal etiology. In view of the potential for an excess mortality of approximately 30% to 50%,

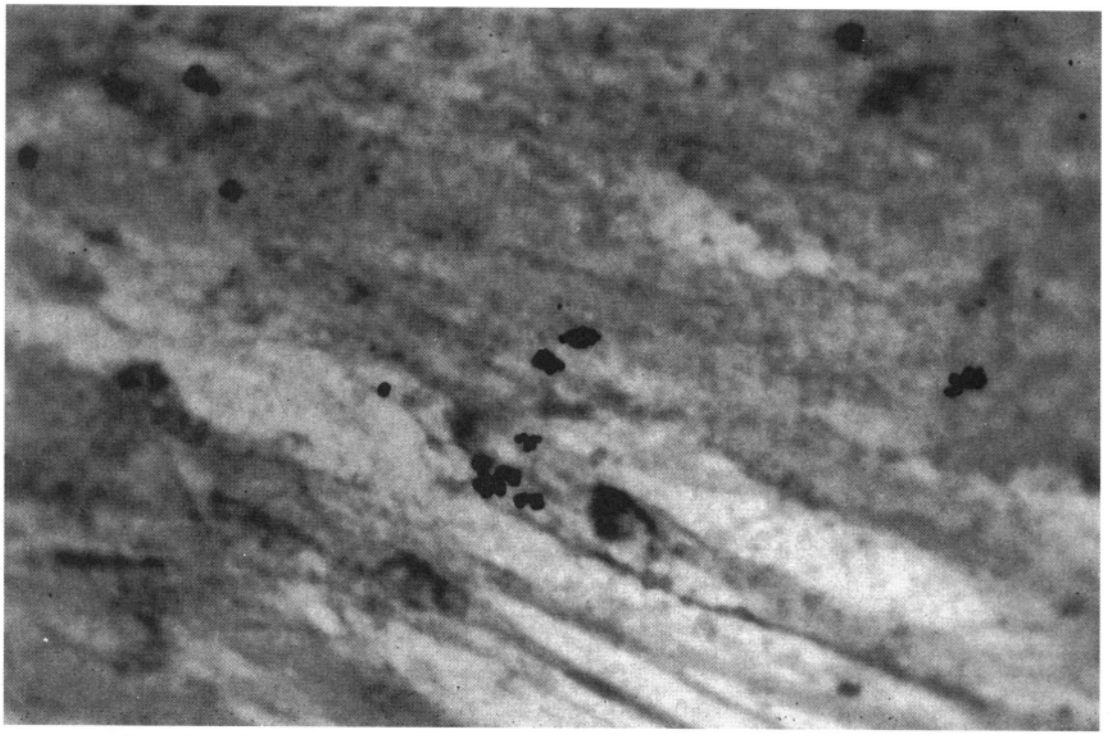

FIGURE 3. Gram stain disclosing clusters of gram-positive cocci. Provided by Jorge Puig de la Bellacasa, Department of Microbiology, Hospital Clinic i Provincial Barcelona.

appropriate antimicrobial treatment should be initiated immediately. Although still a rarity, community-acquired methicillin-resistant staphylococcal pneumonia should be taken into account in patients at risk for the acquisition of methicillin-resistant strains.

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Mycoplasma pneumoniae Pneumonia

THOMAS M. FILE, JR. AND JAMES S. TAN

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia (CAP). Results of recent studies indicate this pathogen may cause 5% to 30% (in selected populations) of cases of CAP (Table 1). Although most often described as a respiratory pathogen associated with mild disease and primarily in young patients, *M. pneumoniae* may cause pneumonia in all age groups and can be fatal; in some persons the organism has the ability to produce invasive infection resulting in serious complications (Cassell, 1995).

Microbiology and Pathogenesis

M. pneumoniae is a cell wall-deficient bacterium with a sterol-containing plasma membrane (Baseman & Tully, 1997). Mycoplasmas will grow on cell-free media but they require a sterol-containing medium supplemented with horse serum and fresh yeast extract for growth (Liu, 1994). *M. pneumoniae* is facultatively microaerophilic and differs from other mycoplasmas in that it ferments glucose and hemolyses erythrocytes. Isolation from clinical specimens is relatively slow, requiring 2 to 3 weeks for visible growth.

Mycoplasma infects the respiratory tract extracellularly as filamentous forms that adhere to epithelial cells (Baseman & Tully, 1997; Baum, 1995). Cell injury which occurs after attachment can lead to ciliostasis, which may account for the prolonged paroxysmal cough that often occurs. Pathological findings in fatal cases of *M. pneumoniae* pneumonia include diffuse pneumonia associated with alveolar infiltrates, hyaline membrane formation, and pulmonary infarcts. Other pathological findings have been adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and interstitial fibrosis (Baum, 1995). Open-lung biopsies in six patients with nonfatal *M. pneumoniae* pneumonia reported in a recent review revealed infiltration of bronchiolar walls with acute and chronic inflammatory cells (cellular bronchiolitis) in two patients, bronchiolitis obliterans with organizing pneumonia in three patients, and an active pneumonitis in one patient (Chan & Welsh, 1995).

The exact pathogenesis of *M. pneumoniae* infection in humans is unclear. Two mechanisms for development of disease may play a major role: tissue reaction directly as a result of microbial invasion or an autoimmune-mediated process.

In experimental animal models of intranasally inoculated *Mycoplasma* infection the organism quickly attaches to the epithelial cells of the upper respiratory tract, which appears to serve as a nidus of infection from which the organism can be transmitted to other animals or spread to the lower respiratory tract (Cassell, 1982). *Mycoplasma* can be readily isolated from the lung tissue of these infected animals (Cartner et al., 1995). Lung findings included neutrophil-rich exudate in airways; hyperplasia and dysplasia of the airway epithelium; submucosal lymphoid hyperplasia; peribronchiolar, bronchial, and perivascular infiltrates; luminal occlusion; and parenchyorial pneumonia (Cartner et al., 1995; Wubbel et al., 1998). Evidence indicates that mycoplasmas cause direct cell injury following

THOMAS M. FILE, JR AND JAMES S. TAN • Northeastern Ohio Universities College of Medicine, Rootstown, Ohio, and Summa Health System, Akron, Ohio 44272-0095.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Percent of Community-Acquired Pneumonia Cases Caused by *Mycoplasma pneumoniae*

Study	No. of patients	Type of patients	Method of diagnosis	% due to *M. pneumoniae*
Marrie et al., 1989	301	Hospitalized adults	Serology	5.6
Fang et al., 1990	359	Hospitalized adults	Serology	2 (1)
Mundy et al., 1995	385[a]	Hospitalized adults	PCR	0.8 (0.8)[b]
Lieberman et al., 1996a	348	Hospitalized adults (HIV excluded)	Serology	29.2
Gray et al., 1997	88	Hospitalized adults; military recruits	Serology, culture, PCR	36.4
Marston et al., 1997	2775	Hospitalized adults	Serology	31 (5.3)
Cassell et al., 1991	120	Adult outpatients	Serology, culture	13
Block et al., 1995	260	Pediatric outpatients	Cultures, serology, PCR	27
Marrie et al., 1996	149	Adult outpatients	Serology	26

PCR, polymerase chain reaction.
[a]45% with HIV infection.
[b]Parentheses indicate percentage with definite diagnostic criteria, see text.

attachment. Ciliostasis, loss of cilia, distention of intracellular spaces, cytoplasmic vacuolization, disruption of mitochondria, and epithelial hyperplasia and metaplasia have been observed in animal models (Cassell, 1982).

Immune mechanisms may also be important in the pathogenesis of *M. pneumoniae* pneumonia. One of the properties of *Mycoplasma* attachment-related proteins is their extensive homology to mammalian structural proteins. An immune response to these cytoadherence proteins may trigger an autoimmune response (Baseman & Tully, 1997). Patients with documented *M. pneumoniae* respiratory infection demonstrate seroconversion to myosin, keratin, and other tissue proteins, and often manifest extrapulmonary findings such as immune hemolytic anemia, exanthems, and cardiac and central nervous system abnormalities. The multi-organ protean manifestations of *Mycoplasma* infection are consistent with the pathogenesis of autoimmunity (Murray et al., 1975; Baseman & Tully, 1997). The relative importance of direct *Mycoplasma* damage as opposed to immune inflammatory reactions in infection has not been determined.

Prevalence and Epidemiology

In clinical practice, *M. pneumoniae* is often suspected but confirmatory tests are seldom performed. Cases of these infections, therefore, tend to be underdiagnosed. The relative prevalence of CAP attributed to *M. pneumoniae* is derived from the results of numerous studies that have evaluated the etiologic agents of CAP using various bacteriologic and immunologic tests. As indicated in Table 1, the percentage of cases of CAP caused by *M. pneumoniae* ranged from 0.8% of cases requiring hospitalization at a tertiary medical center (Mundy et al., 1995) to 36% of cases among U.S. military personnel in training (Gray et al., 1997). The relative rates for these studies will vary depending on the criteria for diagnosis (loosely or strictly applied), age group, geographic location, and whether an epidemic is occurring at the time of evaluation. Only a few studies classify etiologic diagnosis as definite, probable, or possible based on specification of the diagnostic method. Diagnosis based on a single-titer IgG antibody result is less definitive than a 4-fold rise and may falsely include a case. Therefore, an attempt to compare various studies can be problematic. Two recent series illustrate these differences. Mundy et al. (1995) prospectively evaluated 385 patients hospitalized at Johns Hopkins Hospital (45% were infected with HIV). At 0.8%, the incidence of *M. pneumoniae* was very low. However, the diagnosis was based solely on positive culture or polymerase chain reaction. Leiberman et al. (1996a) evaluated 346 CAP patients in a hospital in southern Israel and reported that *M. pneumoniae* was identified in 29.2% of the patients—in many patients more than one pathogen was identified. A large proportion of cases were diagnosed by serologic means (with a single elevated titer as a

criterion). In this study *M. pneumoniae* was the most common cause of CAP in patients 17 to 44 years of age, accounting for 43.2% of cases in this age group. In a recent prospective study of 2776 adult patients hospitalized with CAP from Ohio, *M. pneumoniae* accounted for 5.3% (using criteria for definite diagnosis) to 31% (including criteria for possible diagnosis) of patients (Marston et al., 1997).

In general, *M. pneumoniae* is a common cause of CAP in ambulatory patients and is implicated in 13% to 27% of cases of CAP in the studies reviewed. Although some studies have found *M. pneumoniae* to be an uncommon case of CAP in adults requiring hospitalization (Janssens et al., 1996), the Ohio study observed this to be an important cause of CAP in both persons younger than 50 years as well as in older age groups (Marston et al., 1997). This study found that the incidence of *M. pneumoniae* in older adults increased with age (Fig. 1), with an incidence in the 65–84 year age group of 25 per 1000 and in the ⩾85 year age group of 45 per 1000 (Marston et al., 1997). Others have also reported *M. pneumoniae* as a significant cause of pneumonia in older adults and pneumonia requiring hospitalization (Lim et al., 1989; Lieberman et al., 1996b).

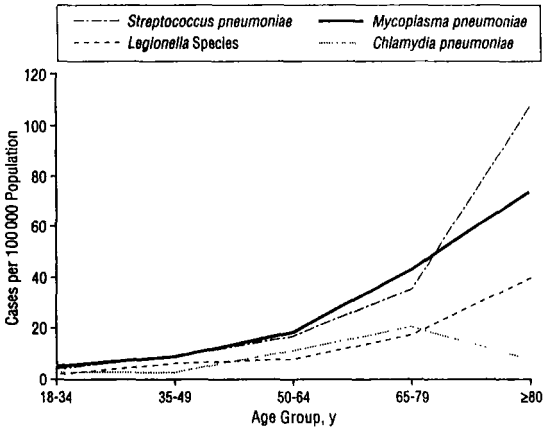

FIGURE 1. Age-specific rates of hospital admission for community-acquired pneumonia due to *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella*. Reproduced, with permission, from Marston et al., 1997.

M. pneumoniae infections are ubiquitous and must be considered as a potential cause of CAP in virtually all age groups in both urban and rural settings. Early longitudinal studies found that the rate of infection of *M. pneumoniae* was highest among school children and second highest among children <5 years of age (Foy et al., 1970). Recent studies have also found *M. pneumoniae* to be a common cause of pneumonia in children aged 3 through 12 (Block et al., 1995). Including patients treated within or outside the hospital, Foy et al. (1979) reported the incidence of *M. pneumoniae* pneumonia as 500/100,000 per year for the age 10 population, with a steady reduction in incidence to less than 100/100,000 per year for the population older than age 70 (Foy et al., 1979).

Although objective confirmation is often difficult, *M. pneumoniae* can be associated with pneumonia caused by mixed infection. The incidence of CAP caused by more than one apparent etiology that includes *M. pneumoniae* varies among different studies and, to a certain extent, depends on the definition (i.e., definite vs. presumed) of the diagnosis. The mixed infections observed in studies are often caused by *M. pneumoniae* and a bacterial agent such as *S. pneumoniae.* In such cases, *M. pneumoniae* may be the initiating pathogen and, after immobilizing the ciliated cells lining the respiratory tract, permit a secondary invader, such as *Streptococcus pneumoniae,* to gain access to the lungs. Cimolai et al. (1995) reviewed studies of dual infections that possibly involved *M. pneumoniae.* Co-pathogens predominantly included typical respiratory viruses but also *Haemophilus influenzae,* Epstein-Barr virus, *Coxiella burnetii,* and *Leptospira* spp. (Cimolai et al., 1995). Two recently published trials found very different results concerning the incidence of mixed infections including *M. pneumoniae.* Lieberman et al. (1996a) found mixed infections with *M. pneumoniae* and other pathogens in 48 of 385 (13%) patients with CAP requiring hospitalization. The most common associated pathogen was *S. pneumoniae* in 43 cases. Using a stricter criteria for the definition of etiology, Mundy et al. (1995) found only I of 380 (0.3%) patients with pneumonia due to *M. pneumoniae* and another apparent cause *(Legionella).* It is unclear from such studies whether these mixed infections represent true co-infection, possible sequential infection, or

false-positive findings from serologic tests (particularly when only a single elevated titer is used as the criterion). It is also unclear whether such mixed infections are associated with a worse outcome; Cimolai et al. (1995) describe cases of severe CAP caused by *M. pneumoniae* with other co-pathogens, suggesting more severe disease when more than one pathogen is implicated.

In urban areas, infection tends to be endemic and usually occurs throughout the year; epidemics often occur in cyclical 4- to 7-year intervals. Person-to-person transmission occurs via respiratory droplets. Spread is slow and occurs more often in closed populations such as families or the military. The incubation period is approximately 2 to 3 weeks. Risk factors such as smoking or the presence of comorbid conditions (which are associated with most causes of CAP) are not as significant for *M. pneumoniae.* Several reports have emphasized an unusually increased severity of *M. pneumoniae* infection in patients with sickle cell disease or related hemoglobinopathies, and in children with Down syndrome (Shulman et al., 1972; Solanki & Berdoff, 1979; Orlieck et al., 1992).

Perspectives on the Classification of Atypical Pathogens

M. pneumoniae has been classified with other organisms (e.g., *Chlamydia pneumoniae* and *Legionella* species, and occasionally *Coxiella burnetii)* as pathogens causing atypical pneumonia and has been designated an atypical pathogen (distinct from typical pneumonia pathogens such as *S. pneumoniae).* This designation is controversial in relationship to scientific merit, and it has been suggested by many authorities that the term *atypical* be discontinued (Fang et al., 1990). However, the term remains popular among clinicians of all disciplines.

The term *atypical pneumonia* was first coined by Rieman (1938) when he described several cases of pneumonia caused by an unknown agent and characterized by constitutional symptoms, upper and lower respiratory tract symptoms and signs, and a protracted course with gradual resolution. These cases differed from pneumococcal pneumonia by the lack of typical findings of consolidation and lack of response to penicillin therapy. Since no causative agent could be identified at that time the word *primary* was eventually added, creating the term known for many years as *primary typical pneumonia* (PAP). In the 1940s Eaton et al. (1944) ultimately identified an agent that was the principal cause of PAP, which was eventually identified as *M. pneumoniae.* Subsequently other pathogens have been linked with atypical pneumonia because of similar clinical presentation, including a variety of respiratory viruses, *Chlamydia psittaci, C. burnetii,* and most recently, *C. pneumoniae.* In addition, pneumonia caused by *Legionella* species, although often significantly different in clinical presentation, is also included.

Originally the classification of pneumonia into atypical and typical forms arose from the observation that the clinical presentation of patients were different compared with standard pneumococcal infection. The potential to differentiate the etiology on the basis of presenting manifestations has clinical relevance since rapid diagnostic tests are not readily available for many of these respiratory pathogens and antimicrobial therapy differs from that for standard bacterial pneumonia. The designation of specific clinical features to an etiologic agent has been common practice. Nonetheless, recent data have cast doubt on the specificity of these observations when comparing individual clinical manifestations, concluding that there is excessive overlap of clinical manifestations of specific infectious and noninfectious causes of lung infiltrates, thus, therapeutic decisions cannot be made on the basis of this information (Fang et al., 1990; Farr et al., 1989; Lieberman et al., 1996b). The optimal method of differentiating the increasing number of possible pathogens will be the development of rapid, easily accessible, and cost-effective diagnostic tests.

Clinical Characteristics

M. pneumoniae is a common cause of respiratory infections ranging from asymptomatic infection to upper respiratory tract infection, tracheobronchitis, and pneumonia (Foy, 1993). It is estimated that only 3% to 10% of infected persons develop pneumonia (Clyde, 1993). The majority of patients with symptomatic *M. pneumoniae* infection probably develop

upper respiratory tract infection or tracheobronchitis syndrome.

Pulmonary Manifestations

M. pneumoniae pneumonia is considered to be the classic atypical pneumonia. Early descriptions of the clinical course were based on definite diagnostic criteria (i.e., culture or 4-fold antibody titer rise) and therefore likely represent valid association of findings (Alexander et al., 1986; Foy et al., 1970). The onset is often insidious, over several days to a week. Constitutional symptoms include headache (usually worse with cough), malaise, myalgias, and sore throat. Cough is typically dry, paroxysmal, and worse at night and may produce mucopurulent sputum. Sinus and ear pain are occasionally reported. The physical findings often are minimal, seemingly disproportional to the patient's complaints. Auscultation of the lungs usually reveals variable scattered rales or wheezes. An association between respiratory infection with *M. pneumoniae* and exacerbation of asthma has been established (Laitinen et al., 1992). Abnormalities of ventilatory function as measured by spirometry is likely to be prolonged for several months in patients with *M. pneumoniae* pneumonia (Laitinen et al., 1992). Bullous myringitis, first described in volunteer subjects infected with *M. pneumoniae,* is infrequent in naturally occurring infection. Table 2 lists the clinical manifestations, as reported in reviews and individual studies, of patients with *M. pneumoniae* pneumonia.

Chest radiographic findings are variable and can mimic a wide variety of other conditions. Radiographic findings are related to the pathologic changes, including peribronchial interstitial infiltrates as well as alveolar space neutrophilic infiltration. Common findings include peribronchial pneumonia and localized lower-lobe patchy and consolidating infiltrates. Other patterns include atelectasis, nodular infiltrates, and hilar adenopathy. Clyde (1993) described the most common radiographic findings as peribronchial pneumonia characterized by thickened bronchial shadows, interstitial streaking, and small areas of subsegmental atelectasis. In a series of 76 patients (aged 9 months to 72 years) hospitalized for *M. pneumoniae* pneumonia, Hwang et al. (1993) described peribronchial and perivascular interstitial infiltrates in 18.4%, nonhomogeneous patch consolidation in 22.4%, homogeneous acinar consolidation in 27.6%, and mixed interstitial and alveolar infiltrates in 31.6% of patients. Twenty percent were bilateral and 33% were described as multilobar (Hwang et al., 1993). In a series of 101 adult patients admitted for *M. pneumoniae* pneumonia, a homogeneous infiltrate was found in 45.5%, a patchy infiltrate in 52.5%, and an interstitial infiltrate in 2.0% of patients. The infiltrate was in the right lung in 51.5%, in the left lung in 38.6, and bilateral in 10% of patients; 13% had involvement of more than one lobe (Lieberman et al., 1996b). Although pleural effusion was previously thought to be uncommon in *M. pneumoniae* pneumonia, small effusions can be demonstrated in 2% to 10% of patients with the use of lateral decubitus chest radiographs (Cassell, 1995).

The mortality associated with *M. pneumoniae* pneumonia is low. In a meta-analysis of studies of CAP by Fine et al. (1996), the mortality rate from *M. pneumoniae* infection was 1.4% (compared to 10% for all cases of CAP). Although the clinical course of *M. pneumoniae* pneumonia is usually mild, significant pulmonary complications can occur and include lung abscess, pneumothorax, pneumatocele, bronchiectasis, interstitial fibrosis, and respiratory distress syndrome (Baum, 1995; Chan & Welsh, 1995; Chiou et al., 1997). *M. pneumoniae* has also been reported as a cause of bronchiolitis obliterans organizing pneumonia (Llibre et al., 1997). Chan and Welsh (1995) reviewed 39 cases of *M. pneumoniae* pneumonia that resulted in respiratory failure or death. Most patients were less than 40 years of age, had no underlying disease, and were previously healthy. The reviewers reported a spectrum of small airways disease, including cellular bronchiolitis and bronchiolitis obliterans with and without organizing pneumonia. ARDS and/or DIG was evident in several patients. The incidence of pulmonary thromboembolic disease was increased in fatal cases. The authors suggested that because of the high frequency of acute infection with *M. pneumoniae,* severe cases are probably undiagnosed due to a lack of awareness of such cases. In an additional analysis of *M. pneumoniae* pneumonia requiring hospitalization, with emphasis on infection in the elderly, Marrie (1993) described six patients who were $\geq$65 years of age.

TABLE 2. Symptoms and Findings in Patients with *Mycoplasma pneumoniae* Pneumonia

	Foy et al., 1970	Mansel et al., 1989	Hwang et al., 1993	Marrie, 1996
No. of patients	385	148	76	
Age group studied	6 months–66 years (15% adults)	3 months–77 years (10% >40 years)	Mean 16–20 years	
Diagnostic methods	Culture: 4-fold antibody rise	Culture: serology	Complement fixation; cold agglutinins	
Symptoms				
Cough	99	97	100	95
Fever	94	—	100	90
Productive cough	45	—	37	83
Anorexia	—	—	—	80
Chills	58	32	33	75
Headache	66	33	30	60
Myalgia	—	24	29 (or arthralgia)	53
Chest pain	NS	25	20	43
Sore throat	54	52	—	33
Arthralgia	—	—	—	30
Nausea	29 (or vomiting)	42	55 (or vomiting)	30
Vomiting	—	—	—	25
Abdominal pain	—	—	—	10
Diarrhea	15	—	—	5
Hoarseness	37	—	NS	NS
Malaise	89	—	NS	NS
Earache	31	—	NS	NS
Rash	15	—	7	NS
Rhinorrhea	29 (coryza)	22	37	NS
Findings				
Temperature	94% >37.8°C	85% >37°C	Mean 37.7°C	92% >37°C (mean = 38.3°C)
WBC >10,000	27% (5% >15,000)	—	—	NS
Crackles	—	—	100	88
Wheezing	—	—	50	20
Consolidation	—	26	33	23
Pharyngeal erythomia	—	47	—	—
CNS involvement	—	7	—	—
Rash	—	6	—	—

NS, not stated or studied; WBC, white blood cell count; CNS, central nervous system.

None of the elderly patients had a discharge diagnosis of *M. pneumoniae* pneumonia. The clinical features of these elderly patients did not allow distinction from other causes of pneumonia. Of the patients that were ≤64 years of age in this series, Marrie (1993) described several underemphasized features of *M. pneumoniae* infection such as prolonged thrombocytopenia, recurrent pulmonary hemorrhage, or thrombostasis. Although not commonly considered, *M. pneumoniae* can be a causative agent of pneumonia in the immunocompromised host (Perez & Heigh, 1991).

In general, while these signs and symptoms are typical of *M. pneumoniae* pneumonia, they are not specific and can be seen with other causes of pneumonia, especially *C. pneumoniae.* However, in one large study of CAP in Seattle, Foy et al. (1970) compared the clinical manifestations of patients

from whom *M. pneumoniae* was isolated to those from whom it was not. Positive correlations with *M. pneumoniae* infection included the presence of headache, rash, sore throat, and a family with more than four members.

Extrapulmonary Manifestations

M. pneumoniae pneumonia is associated with several extrapulmonary manifestations (Table 3) (Murray et al., 1975; Cunha & Ortega, 1996; File et al., 1998; Baum, 1995).

Skin manifestations include maculopapular eruptions, vesicular eruption, toxic epidermolysis, urticaria, erythema nodosum, erythema multiforme, and leukocytoclastic vasculitis (Cherry, 1993; Perez et al., 1997). Mucocutaneous lesions occur in approximately 25% of serologically or culturally documented cases (Cassell, 1995). Erythematous maculopapular or vesicular exanthems are most common. The development of erythema multiforme (including Stevens–Johnson syndrome) associated with CAP is very suggestive of *M. pneumoniae.*

Central nervous system (CNS) complications associated with *M. pneumoniae* infection have been frequently described (Koshiniemi, 1993; Pellegrini et al., 1996; Tjhie et al., 1997). Neurologic manifestations include aseptic meningitis, meningoencephalitis, cerebral ataxia, Guillain-Barré syndrome, and transverse myelitis. The precise incidence has not been determined. Recovery from neurologic dysfunction has often been slow, requiring many months. Up to 10% of cases have been fatal, and about one third who have recovered have permanent neurologic deficit. It has been estimated that 0.1% of all patients with *M. pneumoniae* infection and 7% requiring hospitalization have CNS complications (Cassell, 1995; Koshiniemi, 1993). Although infection has been documented in the CNS by cultural isolation of *M. pneumoniae* from cerebrospinal fluid and from brain tissue, the relationship of *M. pneumoniae* infection and CNS manifestations is unclear.

In 33% to 76% of patients with *M. pneumoniae,* IgM autoantibody that agglutinates with human erythrocytes at 40°C (cold agglutinins) is evoked (Cassell, 1995), which may result in hemolytic anemia (Cherry, 1993). Significant hemolysis usually occurs only with high titers from cold agglutinin. In general, patients with *M. pneumoniae*-associated hemolytic anemia have a higher median age than patients without this complication (Cherry, 1993). Other complications possibly related to a hemagglutinin response include paroxysmal cold hemoglobinuria, Raynaud's disease, peripheral gangrene, diffuse intravascular coagulation, thrombocytopenia, and renal failure.

TABLE 3. Respiratory and Nonrespiratory Complications of *M. pneumoniae* Infections[a]

General
Skin rashes
Erythema multiforme
Maculopapular eruptions
Vesicular eruption
Toxic epidermolysis
Erythema nodosum
Arthritis
Glomerulitis
Pulmonary
Adult respiratory distress syndrome
Bronchial asthma exacerbation
Bronchiectasis
Bronchiolitis obliterans
Hyperlucent lung syndrome
Interstitial fibrosis
Lung abscess
Pleuritis
Pneumatocele
Pneumothorax
Pulmonary embolism
Hematologic
Anemia (including hemolytic)
Disseminated intravascular coagulation
Thrombocytopenia
Cardiac
Pericarditis
Myocarditis
Neurologic
Encephalitis
Meningitis, aseptic
Poliomyelitis-like syndrome
Guillain-Barré syndrome
Brain-stem syndrome/cerebellar ataxia
Psychosis
Transverse myelitis
Cerebral infarction
Other
Glomerulonephritis
Nephrotic syndrome
Uveitis

[a]Modified from File et al., 1998; Marrie, 1996.

Cardiac involvement in *M. pneumoniae* is generally considered to be uncommon, but in one prospective study occurred in as many as 4.5% of patients (Farraj et al., 1997; Kenney et al., 1993). Myopericarditis is the most common cardiac manifestation, but hemopericardium and heart block have been described. *M. pneumoniae* has been isolated in pure culture from pericardial and cardiac tissue (Kenney et al., 1993). Polyarthritis is another extrapulmonary manifestation. While arthralgias are common in patients with *M. pneumoniae* infection, arthritis is uncommon. A review by Pönkä (1979) of 1259 patients with *M. pneumoniae* infection identified only 11 patients with associated arthritis.

Diagnosis

A definitive diagnosis of pneumonia caused by *M. pneumoniae* is no frequently obtained (File et al., 1996). The techniques currently used to obtain a laboratory diagnosis of *M. pneumoniae* pneumonia include culture, detection of specific antibodies, and, more recently, direct detection of the organism in respiratory secretions (i.e., DNA sequences by polymerase chain reaction [PCR]) (Table 4; Quinn, 1996; File et al., 1998).

Culture

M. pneumoniae can be isolated from both upper and lower respiratory tract specimens from individuals with pneumonia. Throat swabs, nasopharyngeal swab, throat washes, sputum, tracheal aspirates, bronchoscopy specimens, and lung tissue have all yielded the organism (Lehtomäki et al., 1987; Loo et al., 1991; Nagayama et al., 1987; Hammerschlag, 1995; Quinn, 1996). Because the organism is fastidious, culture media should be inoculated as soon as possible. Culture media dispensed into small vials are often used as transport media. However, culture is not available in most clinical laboratories, and since it requires 1 to 3 weeks to complete, this information is generally not helpful for prospective management of patients.

Serology

Serologic tests that are available in most clinical laboratories include cold agglutinins (nonspecific) and evaluation of specific antibodies by complement fixation (CF) tests or enzyme immunoassay (EIA). Serologic tests have potential drawbacks either because of low sensitivity or requirement of convalescent sera for accurate interpretation. Part of the uncertainty with the laboratory diagnosis of

TABLE 4. Diagnostic Tests for *Mycoplasma pneumoniae*[a]

Test	Specimen	Sensitivity (%)	Specificity (%)	Comments
Culture	Throat or nasopharyngeal swab, sputum, bronchial washings, tissue	>90	50–90	Not routinely available; slow-growing organism (7–10 days for preliminary growth); need DNA probe for speciation
PCR	Throat or nasopharyngeal swab, sputum, bronchial washings, tissue	95	95–99	Not commercially available; available from reference and research laboratories; potentially useful as rapid diagnostic test
Serology	Cold agglutinins	50	<50	Nonspecific; takes several weeks to develop
	Serum, complement fixation, ELISA	75–80	80–90	Paired acute-convalescent sera preferred; takes 4–9 weeks for seroconversion (therefore retrospective); IgM may be present after 1 week but can persist 2–12 months. Diagnostic criteria: Definite: 4-fold increase in titer Possible: IgG = 1:64 (complement fixation); IgM = 1:16 (ELISA)

PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.
[a]Data from Ferraro, 1997; Quinn, 1996.

M. pneumoniae infection is related to the insidious nature of the disease. The patient may not be evaluated for weeks or more after infection. By this time the organisms might not be as readily isolated or the serological response may have already reached an elevated titer, precluding the possibility of meeting the criterion for a current infection of a 4-fold or greater rise in antibody titer.

Elevated cold agglutinins may be an early indication of acute *M. pneumoniae* disease. A titer of 1:64 is supportive of the diagnosis of *M. pneumoniae* but is found in only 30% to 50% of cases (Jacobs, 1993). A positive but low titer may not be due to *M. pneumoniae* because cold agglutinins are also found in several other respiratory diseases, such as infection due to adenovirus, respiratory syncytial virus, mumps virus, and influenzae virus, and several other diseases, including cardiovascular diseases, myelomas, and tropical diseases. Therefore, in the absence of hemolytic anemia, this test appears to have poor clinical utility.

The CF test measures predominantly "early" IgM antibodies to *M. pneumoniae* and, only to a minor extent, IgG antibodies to *M. pneumoniae;* thus the diagnostic value of the CF test may be limited to the initial *M. pneumoniae* infection and may not reveal antibody responses with *M. pneumoniae* re-infection.

The antigen for the CF test is a chloroform-methanol glycolipid extract of *M. pneumoniae* cells. A 4-fold rise in antibody titer of paired sera is considered evidence of recent or current infection. An elevated single titer (i.e., >16) is often considered evidence of probable recent infection, but is not as definitive as a 4-fold or greater rise. The comparability of CF antibodies and culture was evaluated in a detailed 12-year study that included more than 3000 cases of pneumonia (Kenny et al., 1990). The organism was isolated from 360 of 525 patients who showed a 4-fold or greater antibody increase in their paired sera, resulting in a sensitivity of 68%. When persons with titers of greater than 32 but without a 4-fold rise were included, the sensitivity was 58%. In contrast, 4-fold antibody increases were found in 360 of 674 persons with positive cultures. An additional 247 persons with positive culture showed a titer greater than 32, resulting in a combined sensitivity of 90% for serology for the detection of antibody in a culture-positive person.

An EIA measures specific IgM antibodies directed against *M. pneumoniae.* Specific IgM appears in patients approximately 7 days after the onset of symptoms, with peak titers occurring between 4 to 6 weeks (Jacobs, 1993). As with the CF test, titers fall slowly to usually undetectable levels at an estimated 12 to 26 weeks after the onset of symptoms. A rapid IgM assay lest is offered in many laboratories for early serologic evidence of acute infection. However, since *M. pneumoniae*-reactive IgM can persist for 2 months to 1 year after infection (especially in children), detection of specific IgM does not necessarily indicate the time of infection. In general, the absence of specific IgM antibodies in serum collected 10 to 20 days after the onset is relative evidence against pneumonia due to *M. pneumoniae.*

Direct Detection

Efforts to improve the early laboratory diagnosis of infection due to *M. pneumoniae* have involved efforts at direct detection of *Mycoplasma* antigen in respiratory secretions (Marmion et al., 1993; Abele-Horn et al., 1998). Antigen detection by particle agglutination or antigen capture of sputum, throat swabs, or nasopharyngeal aspirates is under development, but is not yet satisfactory for clinical application. DNA amplification using PCR offers a promising lest of potential clinical utility (de Barbeyrac et al., 1993; Falguera et al., 1997; Talkington et al., 1998; Narita et al., 1998). PCR is available through reference laboratories but currently is not easily accessible. There is no kit approved by the U.S. Food and Drug Administration. Nevertheless, several recent studies have evaluated this technique and found it to be useful. One study of 155 patients found that PCR on a single throat swab specimen is a rapid, sensitive, and specific test that may greatly simplify the diagnosis of CAP caused by *Legionella, M. pneumoniae,* or *C. pneumoniae* (Rameriz et al., 1996). *M. pneumoniae* throat swab PCR proved to be more sensitive than acute IgM serology in this study. PCR assays were positive in eight of the nine patients with serologic evidence of *M. pneumoniae* infection (four had

4-fold antibody titer rise and four had positive acute IgM serology).

Therapy

In general, the tetracyclines, macrolides, and fluoroquinolones are active in vitro against *M. pneumoniae* (Table 5) (McCormak, 1993; McMillan, 1998; File et al., 1998). Because *M. pneumoniae* lacks cell walls, these pathogens are not effectively treated with β-lactam agents. In vitro susceptibility testing indicates that *M. pneumoniae* is most sensitive to the macrolides and tetracyclines. In general, the minimum inhibitory concentrations (MICs) are lower for the macrolides than for tetracycline and there is little variability between erythromycin and the newer macrolides (clarithromycin, azithromycin). The MICs of tetracycline and doxycycline are similar. Macrolide-resistant strains have been described but appear to be uncommon; resistance to tetracycline has not been encountered (McCracken, 1986; McMillan, 1998). In an animal model of *Mycoplasma* infection, both erythromycin and tetracycline inhibited, but did not kill, *M. pneumoniae.* The data from this model indicated that early treatment with tetracycline or erythromycin after inoculation delayed, but did not prevent, the development of pneumonia.

TABLE 5. In Vitro Activity of Various Antibiotics against *Mycoplasma pneumoniae*[a]

Drug	*M. pneumoniae* MIC (μg/mL)
Erythromycin	<0.002–0.004
Tetracycline	0.25
Doxycycline	0.25
Azithromycin	<0.001–0.004
Clarithromycin	<0.004–0.125
Ciprofloxacin	1–8
Ofloxacin	1–2.0
Levofloxacin	0.5
Sparfloxacin	0.06–0.25
Grepafloxacin	0.06–0.25
Trovafloxacin	0.12–0.25

MIC, minimum inhibitory concentration.
[a]From Renaudin & Bébéar, 1990; Hammerschlag, 1995; Kenny & Cartwright; 1996; File et al., 1997; Ridgeway et al., 1997; McMillan, 1998.

Isolates of *M. pneumoniae* are also susceptible to the fluoroquinolones, although MICs are not as low as for the macrolides or tetracyclines. The newer fluoroquinolones with enhanced activity against *S. pneumoniae*—levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin—are more active in vitro against *M. pneumoniae* than prior fluoroquinolones.

Therapy of *M. pneumoniae* has been the subject of some conjecture. A prevailing view is that it really does not matter whether antibiotics are given for most infections since the mortality is low, infections are often self-limiting, and there may be ambiguity of diagnosis (prompt etiologic confirmation is difficult to establish). However, studies have shown that treatment reduces the morbidity of pneumonia and shortens duration of symptoms. In a large placebo-controlled clinical trial of antimicrobial agents for therapy of *M. pneumoniae* pneumonia, Shames et al. (1970) studied 317 military recruits who received one of six different antibiotics (Table 6). Forty-three trainees with serologically proven *M. pneumoniae* received either no therapy or penicillin G, which served as controls. All antibiotics were more effective in reducing clinical illness as well as resolving abnormalities on chest radiograph than no therapy or therapy with penicillin G. These investigators also evaluated the effect of therapy on shedding of *Mycoplasma* in respiratory secretions. Cultures were positive in a variable number of patients at the beginning of therapy as well as after therapy. The clinical and radiographic responses to therapy were similar, regardless of *Mycoplasma* recovery after completion of therapy. Other studies evaluating erythromycin or tetracycline have found that *M. pneumoniae* may persist in respiratory secretions despite good clinical response to therapy (Smith et al., 1967). Cultures may remain positive for weeks to months even after symptoms have resolved (McMillan, 1998).

In a randomized controlled treatment of clarithromycin versus erythromycin in 260 children with CAP, Block et al. (1995) observed that 69 (29%) had evidence of *M. pneumoniae* (most detected by PCR or culture). Treatment with clarithromycin or erythromycin eradicated *M. pneumoniae* in both treatment groups. Azithromycin has also been found to be effective against *M. pneumoniae* in recent studies and may allow a shorter duration

TABLE 6. Clinical Effect of Therapy for *Mycoplasma pneumoniae* Pneumonia[a]

Drug	No. of patients treated	Days febrile (mean)	Days of abnormal chest x-ray (mean)	No. of positive cultures pretherapy	Total cultured[b] after therapy (%)
Controls	39	4.2	14.8	12/19 (63)	1/3 (33)
Demedocycline	26	1.8	6.7	28/72 (39)	2/29 (7)
Tetracycline	89	2.4	9.3	8/37 (22)	2/37 (5)
Erythromycin stearate	76	2.4	7.2	32/89 (40)	2/27 (7)
Erythromycin ethyl succinate	43	3.0	11.3	11/25 (44)	4/22 (18)

[a]Data from Shames et al., 1970.
[b]Patients without positive culture had diagnosis confirmed by serologic methods.

of therapy (Gregory et al., 1997; Plouffe et al., 2000).

The newer fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin) are more active in vitro than ciprofloxacin against *M. pneumoniae* and have been shown to be effective in early trials in *M. pneumoniae* infections (Bébéar et al., 1993; Plouffe et al., 1996; File et al., 1997). These studies have predominantly relied on serologic means of diagnosis but have shown good efficacy.

Recommendations for therapy of *M. pneumoniae* pneumonia are included in Table 7. The recommended duration of therapy for adults for *M. pneumoniae* pneumonia is 10 to 14 days of doxycycline or erythromycin. Clarithromycin 1 g/day for 10 days has been shown to be effective as has azithromycin 1.5 g administered over 5 days. The studies of fluoroquinolones to date indicate that a schedule of 7 to 10 days is appropriate for the treatment of *M. pneumoniae* infection. Choice of regimens depends on patient compliance, tolerance, and cost. Further prospective studies using microbiologic techniques may provide additional information concerning the best therapeutic regimen for treatment of respiratory infections caused by *M. pneumoniae.*

It must be acknowledged that most patients with *M. pneumoniae* infection are treated empirically. Recently published guidelines for the treatment of CAP suggest that empiric therapy should include antimicrobial agents effective against *M. pneumoniae* and other atypical pathogens as well as the standard pyogenic common causes (*S. pneumoniae, H. influenzae*) (Niederman et al., 1993; Bartlett et al., 1998). Based on present data, the decision to use therapy specific for *M. pneumoniae* in the management of patients with CAP will depend to a great extent on clinical judgment as well as the recommendations of various guidelines.

The role of therapy other than antimicrobials

TABLE 7. Antimicrobial Therapy for *Mycoplasma pneumoniae* Pneumonia

Antibiotic	Oral dose	Duration
Erythromycin	Adults: 1–2 g/day divided 4 times a day	10–14 days
	Children: 40 mg/kg/day divided 4 times a day	10–14 days
Clarithromycin	Adults: 250–500 mg/day divided twice a day	10 days
	Children: 15 mg/kg/day divided twice a day	10 days
Azithromycin	Adults: 500 mg/day divided twice a day × 1 day, followed by 250 mg/day × 5 days	5 days total
	or 500 mg/day	3 days total
	Children: 10 mg/kg/day divided twice a day × 1 day, followed by 5 mg/kg/day × 4 days	5 days total
Tetracycline	1–2 g/day divided 4 times a day	10–14 days
Doxycycline	200 mg/day divided 4 times a day	10–14 days
Levofloxacin	500 mg/day	7–14 days
Sparfloxacin	400 mg (first day), then 200 mg/day	7–14 days
Gatifloxacin	400 mg/day	7–14 days
Moxifloxacin	400 mg/day	7–14 days

in the management of pulmonary complications and the extrapulmonary manifestations of *M. pneumoniae* infection has not been well defined. While immune mechanisms may have a role in such conditions as hemolytic anemia and CNS involvement, the role of corticosteroid therapy remains unresolved (Koshiniemi et al., 1997; McMillan, 1998). Based on favorable results from anecdotal reports and small series of patients, corticosteroid therapy has been recommended for complications such as bronchiolitis obliterans and hemolytic anemia (Cherry, 1993; Chan & Walsh, 1995; Llibre et al., 1997).

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Community-Acquired Pneumonia Due to *Chlamydia pneumoniae*

JULIO A. RAMIREZ AND JAMES T. SUMMERSGILL

Introduction

Chlamydia pneumoniae causes upper and lower respiratory tract infections. The organism has been identified as the etiology of otitis, sinusitis, pharyngitis, bronchitis, and community-acquired pneumonia (CAP). Although CAP is the most frequently recognized illness, asymptomatic or mild disease is the most common result of *C. pneumoniae* infection (Grayston, 1992).

Before the recognition of *C. pneumoniae,* all epidemic respiratory tract infections associated with chlamydial organisms were considered to be produced by *C. psittaci,* although in several reported epidemics an avian contact could not be identified. Retrospective sero-epidemiological investigations established *C. pneumoniae* as the etiologic agent of these past epidemics of chlamydial respiratory tract infections not associated with birds (Saikku et al., 1985; Kleemola et al., 1988). These studies indicate that *C. pneumoniae* is not a new respiratory pathogen but a newly recognized pathogen and that *C. pneumoniae* has always been a significant etiologic agent in patients with CAP. The association of *C. pneumoniae* with respiratory infections was demonstrated by culture in a study of seroconverting patients in Seattle in 1984. (Grayston et al., 1986).

Microbiology

C. pneumoniae is a member of the genus *Chlamydia,* which includes *C. trachomatis, C. psittaci,* and *C. pecorum* (Kuo et al., 1995). *C. pneumoniae* is an obligate intracellular gram-negative bacterium with a unique biphasic life cycle. The extracellular smaller form is known as the elementary body, and the larger replicating intracellular form is known as the reticulate body. The elementary bodies attach to susceptible host cells, gain access to the intracellular environment via a membrane-bound phagosome, and transform within the phagosome into reticulate bodies. The reticulate bodies replicate via binary fission with the help of host cell energy stores and form characteristic cytoplasmic inclusions. The reticulate bodies revert to the elementary body form prior to cell lysis (McClarty, 1994).

Pathogenesis

Most of the steps in the pathogenesis of *C. pneumoniae* pneumonia in humans are unknown. In the mouse model, intranasal inoculation of *C. pneumoniae* produces a leukocytic infiltrate of the alveolar space (Yang et al., 1994). Once the organism reaches the lower respiratory tract, it has the ability to invade and multiply in epithelial cells, human

JULIO A. RAMIREZ AND JAMES T. SUMMERSGILL • Division of Infectious Diseases, Department of Medicine, School of Medicine, University of Louisville, Louisville, Kentucky 40292.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

alveolar macrophages, smooth muscle cells, and endothelial cells (Gaydos et al., 1996). Infection of endothelial cells with *C. pneumoniae* in vitro is associated with local production of chemokines and recruitment of leukocytes (Molestina et al., 1998). Since *C. pneumoniae* has the capability to produce ciliostasis (Shemer-Avni & Lieberman, 1995), a patient with an episode of bronchitis due to *C. pneumoniae* may be predisposed to a secondary bacterial pneumonia by a blockage of mucociliary clearance. In clinical practice it is not uncommon for a patient with CAP to have a positive serology for *C. pneumoniae* and positive blood cultures for *Streptococcus pneumoniae.* In this type of patient it is unclear whether *C. pneumoniae* and *S. pneumoniae* are co-pathogens causing CAP, or whether *C. pneumoniae* is the etiology of bronchitis and *S. pneumoniae* is the etiology of CAP.

C. pneumoniae has the capability to produce persistent lung infection in mice (Malinverni et al., 1995). A persistent infection of lower respiratory tract epithelial cells may trigger an immunopathologic process in the lung. Chronic airway inflammation due to a persistent infection has been suggested as the pathogenesis for adult patients who develop asthma after an episode of *C. pneumoniae* infection.

The spread of the organism from the respiratory tract to other organs is thought to be mediated by its ability to survive in monocyte-macrophages. Dissemination of infected pulmonary monocyte-macrophages via the bloodstream with incorporation into other tissues would allow *C. pneumoniae* to be delivered to different organs. In a mouse model of pulmonary infection, transmission of the organism to healthy animals was demonstrated after transfusion of circulating monocytes from infected animals (Moazed et al., 1998).

Epidemiology

It is believed that *C. pneumoniae* is spread from person to person by respiratory droplets. The lack of a recognized animal reservoir for the organism supports the concept of person-to-person transmission. There is no correlation of severity of disease with the ability of the patient to transmit the organism. Many patients with severe disease are ineffective transmitters. On the other hand, patients with mild or even asymptomatic disease may play an important role in transmission (Grayston, 1992). The mean interval between primary infection and secondary cases is 30 days (Grayston, 1992).

Antibodies to *C. pneumoniae* in the IgG serum fraction are present in approximately half of the adults throughout the world (Grayston et al., 1990). This indicates that past respiratory tract infection due to *C. pneumoniae* is very common. Since the IgG antibody titer tends to decline after infection but the prevalence of antibody rises steadily throughout life, it has been estimated that all persons have been infected at some point and that reinfection is common (Grayston et al., 1990; Aldous et al., 1992).

C. pneumoniae infection is infrequent in preschool-age children. Most primary infections occur during school age and the early teenage years. The incidence of infection among schoolchildren, estimated on the basis of seroconversion, is 6% to 9% annually (Aldous et al., 1992).

Outbreaks of respiratory infection have been reported in families, schools, nursing homes, and military barracks. Among military trainees, approximately 10% of those infected develop clinical manifestations of CAP (Kleemola et al., 1988). The average annual incidence of CAP in a defined population in Seattle from 1963 to 1975 was 1.2/100 (Grayston, 1992). CAP due to *C. pneumoniae* is more common among the elderly and less common among persons younger than 20 years (Grayston, 1992). Pneumonia is more likely to affect males than females; however, the reason for this gender difference cannot be explained on the basis of smoking.

In ten published studies of adult patients with CAP performed outside of epidemic situations, *C. pneumoniae* was considered the etiologic agent in 1% to 15% of all cases (Grayston et al., 1986; Marrie et al., 1987; Thom et al., 1990; Fang et al., 1990; Karalus et al., 1991; Bates et al., 1992; Sundelöf et al., 1993; Örtqvist, 1996; Steinhoff et al., 1996; Ramirez & Ahkee, 1997). In most of these studies the diagnosis was based on serology. At the reference laboratory of the University of Louisville the authors studied 1517 cases of CAP in adults. *C. pneumoniae* was identified as the etiology of CAP in 5% of the cases. During epidemics, *C. pneumoniae* may account for as much as 40% of hospitalized patients with CAP (Kauppinen et al., 1995).

The importance of *C. pneumoniae* as etiology of CAP in children has been documented in two clinical trials. In one study involving 240 pediatric patients with CAP, *C. pneumoniae* was considered the etiologic agent in 28% of the patients (Block et

al., 1995). In a second study of 456 pediatric patients with CAP, *C. pneumoniae* was considered the etiologic agent in 8% of the patients (Roblin & Hammerschlag, 1998).

Besides the capability of the organism to cause sporadic or epidemic disease, some of the variation seen in reported studies in relation to the etiologic role of *C. pneumoniae* in CAP may be due to the lack of standardization of laboratory techniques for diagnosis, the probable geographic distribution of the organism, and the year-to-year variation in prevalence of the disease.

There is no increased frequency of C. *pneumoniae* infections in patients with AIDS (Comandini et al., 1997; Dalhoff & Maass, 1996). In patients with cystic fibrosis, *C. pneumoniae* was found in 12% of acute pulmonary exacerbations (Emre et al., 1996). In two published studies of patients with nosocomial pneumonia, *C. pneumoniae* was identified by serologic criteria in 11 patients (Grayston et al., 1989; Bates et al., 1992). These studies indicate that *C. pneumoniae* may cause hospital-acquired pneumonia.

Clinical and Laboratory Manifestations

The spectrum of clinical manifestation in patients with CAP ranges from mild disease to severe disease associated with sepsis and multi-organ failure. As with other etiologic agents, no group of signs and symptoms can be considered characteristic of CAP due to *C. pneumoniae.* Patients with CAP may have upper respiratory tract symptoms such as sore throat, hoarseness, or nasal discharge due to associated *C. pneumoniae* pharyngitis or sinusitis. Sore throat preceding the onset of pulmonary symptomatology has been reported in 20% to 50% of university students with CAP (Grayston et al., 1986). The patient may have signs and symptoms of upper respiratory tract infection for 1 to 4 weeks before developing clinical evidence of pneumonia. Fever and cough, initially nonproductive, are the most common symptoms in patients with CAP (Saikku et al., 1985; Grayston et al., 1986; Kleemola et al., 1988). These symptoms typically have a gradual onset over several days. Rhonchi and rales are common findings at physical examination. Some patients have a biphasic clinical illness characterized by an upper respiratory infection with spontaneous resolution that is followed by an episode of pneumonia. Patients with a primary infection due to *C. pneumoniae* are more likely to develop CAP than patients with episodes of reinfection (Ekman et al., 1993).

Several factors influence the severity of *C. pneumoniae* CAP at presentation. Pneumonia in the elderly is frequently more severe than in healthy young adults, but severe disease in healthy adults complicated with multi-organ failure has been reported (Marik & Iglesias, 1997). Another factor that will influence the clinical presentation of CAP produced by *C. pneumoniae* is the presence of a copathogen. CAP due to *C. pneumoniae* and *S. pneumoniae* is a more severe disease compared to CAP produced by *C. pneumoniae* as a single pathogen and is associated with prolonged hospital stay (Kauppinen et al., 1996). In patients with CAP who are serologically positive for *C. pneumoniae,* coinfection with a second pathogen has been reported in almost 50% of the cases (File et al., 1997).

The most common laboratory abnormalities at the time of presentation in young patients are an elevated erythrocyte sedimentation rate and mild elevation of C-reactive protein and white blood cell count (Kleemola et al., 1988; Kauppinen et al., 1996b). The time to complete resolution of clinical manifestations may be prolonged, with persistent cough and general malaise for several weeks, even in patients with mild CAP and appropriate antimicrobial therapy. In some patients, the convalescent period is characterized by a syndrome of cough, shortness of breath, and wheezing. It has been suggested that *C. pneumoniae* respiratory infections may trigger acute episodes of asthma in children (Emre et al., 1994) or may be the cause of new onset of asthma in adults (Hahn et al., 1991). Persistent infection with *C. pneumoniae* characterized by chronic cough, low-grade fever, and malaise lasting for many months may complicate episodes of acute pharyngitis, sinusitis, or bronchitis (Hammerschlag et al., 1992).

Radiographic Manifestations

Although a patchy alveolar or reticular infiltrate that involves a single subsegmental area is the most common radiographic presentation, *C. pneumoniae* can produce a lobar infiltrate such as that associated with typical or bacterial pneumonia (Marrie et al., 1987; McConnell et al., 1994). The

pulmonary infiltrates are located mainly in the lower lobes. A radiographic pattern of multilobar bilateral infiltrates can be seen in severe disease. The type of pulmonary infiltrate at presentation cannot be used to differentiate *C. pneumoniae* from *S. pneumoniae* (Kauppinen et al., 1996a). Pleural fluid due to a parapneumonic effusion can be seen (Marrie et al., 1987; Augenbraun et al., 1991). The authors treated a young healthy adult who required chest tube placement for drainage of extensive empyema. Resolution of chest x-ray abnormalities occurs over 2 to 4 weeks in the younger population (Saikku et al., 1985; Grayston et al., 1986).

Extrapulmonary Manifestations

Owing to the ability of *C. pneumoniae* to produce infections outside the respiratory tract, patients may have several extrapulmonary manifestations of disease. Some of these manifestations occur at the time of or immediately following an episode of CAP and can be defined as complications of pneumonia. Patients may have extrapulmonary manifestations due to pneumonia complicated with endocarditis, myocarditis, pericarditis, erythema nodosum, hepatitis, meningitis, or encephalitis (Norton et al., 1995; Gran et al., 1993; Haidl et al., 1992).

Other extrapulmonary clinical syndromes that are probably due to *C. pneumoniae* infection are not temporally related to a respiratory infection. *C. pneumoniae* has been associated with coronary artery disease and other atherosclerotic syndromes (Saikku et al., 1988). The organism has been isolated from atheromatous plaques present in coronary artery (Ramirez et al., 1996a) and carotid artery (Jackson et al., 1997). Although the role of *C. pneumoniae* in the pathogenesis of atherosclerosis is unknown, the spread of the organism to the arterial wall after a respiratory infection, with the local production of a persistent infection, has been suggested as a possible mechanism of arterial damage.

Laboratory Diagnosis

Since no clinical or radiographic manifestations of CAP due to *C. pneumoniae* are specific for this organism, the etiologic diagnosis should be based on laboratory criteria. This can be difficult for the clinician, as diagnostic assays for this organism are not widely available, being restricted to regional reference and research laboratories.

C. pneumoniae identification in patients with CAP can be obtained by serology, culture, or molecular detection. As with other etiologic agents of CAP, if a laboratory test is positive, the next step is to define the organism as a definitive etiology or a presumptive etiology of pneumonia. There are no standard criteria to define when *C. pneumoniae* should be considered a presumptive or definitive etiology in patients with CAP. In this section, the criteria that are currently used at the Infectious Diseases Reference Laboratory of the University of Louisville are discussed.

Serology

The microimmunofluorescence (MIF) assay is used for serological confirmation of *C. pneumoniae* infection (Wang et al., 1979). It requires considerable expertise for proper interpretation and at present there is no commercially available diagnostic kit that has received Food and Drug Administration approval for use in the United States. Most testing is done using "in-house" reagents, and tests are not standardized among laboratories. Rheumatoid factor needs to be removed from serum specimens prior to testing for specific IgM (Verkooyen et al., 1992).

C. pneumoniae is considered a definitive etiology of CAP in a patient with documented 4-fold increase in IgM or IgG antibody titer. *C. pneumoniae* is considered a presumptive etiology of CAP in a patient with a single IgM titer of $\geq$1:16 or a single IgG titer of $\geq$1:512. The serologic diagnosis may be associated with false-negative and false-positive results. False-negative serologic diagnosis was reported in pediatric patients with CAP due to *C. pneumoniae* confirmed by culture (Block et al., 1995). It has been suggested that the MIF assay may not be sufficiently sensitive in children. Since prompt treatment of pneumonia may depress antibody response (Kleemola et al., 1988), false-negative serologic diagnosis may occur in a patient who is managed with early and effective antibiotic therapy. During primary infection the appearance

of MIF antibody can be delayed for 3 weeks in the IgM fraction and for more than 6 weeks in the IgG fraction (Kleemola et al., 1988). A false-negative serologic diagnosis may occur if the convalescent serum sample is obtained less than 3 weeks after onset of illness. A false-positive serologic diagnosis can occur owing to the background antibodies in subjectively healthy adults who may fulfill criteria for presumptive etiology.

Culture

Recovery of viable *C. pneumoniae* from clinical specimens remains the gold standard for laboratory diagnosis. Several cell lines have been used for recovery of this organism from clinical specimens, including HL (Kuo & Grayston, 1990), HEp-2 (Roblin et al., 1992), and BGMK (Freidank et al., 1996). Procedurally, the respiratory specimen (i.e., oropharyngeal or nasopharyngeal swab) is centrifuged on to a cell monolayer in either 1-dram shell vials or a 96-well microtiter plate. These cells have been treated with cycloheximide, an inhibitor of eukaryotic protein synthesis, in order to give the bacterium access to intracellular nutrients. Following a 72-hour incubation period, monolayers are stained with a *Chlamydia-specific* FITC-labeled antibody and examined under epifluorescent microscopy for the presence of typical inclusion bodies indicative of *C. pneumoniae.* A recent review of three commercially available monoclonal antibody preparations for use in cell culture confirmation indicates there was little difference in intensity of staining of *C. pneumoniae* inclusions (Montalban et al., 1994). New alternative culture conditions have been suggested to improve the recovery of *C. pneumoniae* from clinical specimens (Maass et al., 1993; Tjhie et al., 1997; Kazuyama et al., 1997; Berlau et al., 1996), but these new methodologies need to be confirmed.

C. pneumoniae is considered a definitive etiology of CAP in a patient with a positive culture from any respiratory specimen. A false-positive diagnosis by culture may occur in the very rare situation of a healthy carrier of the organism in the respiratory tract (Gaydos et al., 1994). False-negative results are expected, considering the difficulty in recovering the organism from clinical specimens.

Molecular Detection

The hope for improved rapid diagnosis of *C. pneumoniae* infection may rest with the use of molecular techniques, specifically nucleic acid amplification methods such as the polymerase chain reaction (PCR). Several of these procedures have been described in the literature, using diverse specimens, and showing promising sensitivity and specificity. To date, however, no commercially available diagnostic kit using amplification technology is on the market.

In patients with CAP, *C. pneumoniae* has been detected by PCR in upper respiratory tract secretions obtained by nasopharyngeal swabs and throat swabs (Ramirez et al., 1996b; Gaydos et al., 1992). The most common targets for amplification are a 463-bp fragment of the 16S rRNA gene (Gaydos et al., 1992) and a 474-bp fragment of an unknown gene (Campbell et al., 1992). A combined PCR amplification step with an enzyme immunoassay (EIA) step has been reported to increase the sensitivity of detection. This methodology was successfully applied to diagnose *C. pneumoniae* using oropharyngeal swabs in patients with CAP (Gaydos et al., 1993a) and bronchoalveolar lavage specimens from an immunocompromised patient population (Gaydos et al., 1993b). An internal positive control consisting of a lambda-phage DNA segment has been introduced into this PCR-EIA protocol (Pham et al., 1998) to allow for the detection of inhibitors of amplification.

Sputum has also been examined as a clinical specimen using PCR-based methods. Good concordance has been reported between sputum PCR, direct immunofluorescence assay, and serological assays for anti-C. *pneumoniae* antibody by ELISA and MIF testing. In a study using a nested, touchdown PCR-EIA protocol comparing sputum, oropharyngeal, and nasopharyngeal specimens, the sputum sample showed the highest diagnostic efficacy (Boman et al., 1997).

Peripheral blood mononuclear cells (PBMC) have recently been used as specimens for PCR detection of *C. pneumoniae* (Boman et al., 1998). Although this study was aimed at determining the prevalence of *C. pneumoniae* DNA in PBMCs of patients with cardiovascular disease and middle-aged blood donors, its methodology could certainly

be applied to the rapid diagnosis of acute respiratory infection. A positive PCR from a PBMC specimen in a patient with CAP would be an indication of bacteremic pneumonia.

C. pneumoniae is considered a definitive etiology of CAP in a patient with a positive PCR from any respiratory specimen. A false-positive diagnosis by PCR may occur because of laboratory contamination of the sample or in the very rare situation of a healthy carrier of the organism in the respiratory tract. A false-negative diagnosis by PCR may occur because of poor technique in the collection of respiratory samples or because of the presence of inhibitors of amplification.

Antibiotic Therapy

In cell culture, the best bactericidal activity against *C. pneumoniae* is obtained with tetracyclines, macrolides, and quinolones (Chirgwin et al., 1989; Cooper et al., 1991; Kuo & Grayston, 1988; Hammerschlag et al., 1992). β-lactam antibiotics failed to kill *C. pneumoniae* owing to their poor intracellular penetration. In most prospective controlled studies, the clinical effectiveness of a new antimicrobial agent has been compared to erythromycin. Comparable clinical effectiveness has been achieved with clarithromycin (Block et al., 1995), azithromycin (Roblin & Hammerschlag, 1998), ofloxacin (Lipsky et al., 1990), and levofloxacin (File et al., 1997). Intravenous tetracycline, macrolides, or quinolones should be used for the hospitalized patient with *C. pneumoniae* CAP. Once the patient reaches clinical stability it is appropriate to switch from intravenous to oral antibiotics (Ramirez, 1995).

Some patients remained persistently culture-positive and clinically symptomatic despite courses of tetracycline, doxycycline, or erythromycin (Hammerschlag et al., 1992a). A previously healthy young nurse from the University of Louisville remained clinically symptomatic and culture-positive, despite treatment with azithromycin, clarithromycin, and levofloxacin. It is unclear whether the variation between self-limited disease, severe disease, and chronic or relapsing disease is entirely due to host factors or different virulent factors that may be present in some organisms. In view of the reported cases of relapsing or chronic infections after short or conventional courses of appropriate antibiotics, a duration of therapy of 14 days is recommended for patients with CAP due to *C. pneumoniae.* If the signs and symptoms persist or relapse, a second course of 14 to 21 days of therapy is recommended.

A problem with the evaluation of antibiotic therapy in the management of pneumonia due to *C. pneumoniae* is that in some patients a clinical cure is achieved even with the use of antibiotics with poor in vitro susceptibility. Clinical responses have been reported with the use of amoxicillin–clavulanic acid (Roblin & Hammerschlag, 1998), cefuroxime (File et al., 1997), and ceftriaxone (File et al., 1997). The good clinical responses observed in some patients with the use of β-lactam antibiotics may be due to spontaneous resolution of infection or due to some clinical activity of the antibiotics. Penicillin and ampicillin fail to prevent the first passage of *C. pneumoniae* in cell culture, but cause aberrant inclusions whose infectivity on second passage is decreased (Kuo & Grayston, 1988). This capability of β-lactam antibiotics to inhibit infectivity in vitro may explain the good clinical response reported with the use of β-lactams in some patients with CAP due to *C. pneumoniae.*

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Legionnaires' Disease

JOSEPH F. PLOUFFE

Introduction

Legionnaires' disease is a pneumonia caused by environmental gram-negative bacilli, the Legionella. Legionnaires' disease was first discovered as an epidemic at the Legionnaires' convention in Philadelphia in 1976. *Legionella pneumophila,* the causative agent, did not grow on standard media used for isolation of respiratory pathogens. Investigators from the Centers for Disease Control and Prevention (CDC) identified the organism, developed diagnostic studies, and developed culture media that would support growth. In the ensuing quarter of a century we have learned much about Legionella. It has been estimated that more than 12,000 cases of Legionnaires' disease occur annually in the United States. Only a fraction of these cases are diagnosed and reported to public health authorities. Legionnaires' disease can occur as epidemics in the community or in the hospital setting. It can occur sporadically and appears to occur more commonly in certain geographical areas. The disease remains an elusive diagnostic entity.

Microbiology

Legionnaires' disease is caused by strains of the newly identified family Legionellaceae (Fraser et al., 1977; McDade et al., 1977). There are currently 42 described species with 64 serogroups within the genus *Legionella* (Table 1; Benson & Fields, 1998). The organisms are aerobic, gram-negative bacilli that usually contain flagellae. L-cysteine-HCl and iron salts are required for extracellular growth. The cell wall contains abundant branched chain fatty acids (Brenner et al., 1984; Benson & Fields, 1998).

Legionella sp. do not grow on routine media used by the clinical microbiology laboratory for respiratory pathogens. Charcoal yeast extract (CYE) agar that contains L-cysteine-HCl and iron salts is used to isolate *Legionella.* Unfortunately, most clinical microbiology laboratories do not offer this service or have little experience with culturing *Legionella* (College of American Pathologists, 1989). Some isolates *of Legionella* do not grow well extracellularly on CYE agar but grow intracellularly in amoeba (Legionella-like amoebal pathogens [LLAP|) (Drozanski, 1991; Rowbotham, 1993). LLAP 3 has been isolated from the respiratory secretions of a patient with pneumonia by co-cultivation with amoeba (Rowbotham, 1993). Serologic studies have implicated other LLAPs in patients with community-acquired pneumonia (CAP) (Butler et al., 1995; McNally et al., 1998). Additional studies are needed to isolate these strains from patients and to define the amount of cross-reactivity in serologic assays.

Approximately half of the isolates of *Legionella* have been associated with human disease. *L. pneumophila* has been associated with 80% of clinical cases of Legionnaires' disease. *L. pneumophila* serogroup 1 accounts for the majority of these cases.

Benson and Fields (1998) provide an excellent discussion of biochemical identification, analysis of cell-wall fatty acids and ubiquinones, proteins, and carbohydrates.

The organisms have been isolated from spu-

JOSEPH F. PLOUFFE • Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio 43210.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Type Strains of *Legionella* Species and Serogroups

Name of species	Serogroup	Reference strain	ATCC No.	Name of species	Serogroup	Reference strain	ATCC No.
L. pneumophila				*L. santicrucis*	1	SC-63-C7	35301
ssp. *pneumophila*				*L. steigerwaltii*	1	SC-18-C9	35302
ssp. *fraseri*				*L. parisiensis*	1	PF-209C-C2	35299
ssp. *pascullei*	1	Philadelphia 1	33152	*L. spirtensis*	1	Mt St Helens 9	35249
	1	Knoxville 1	33153		2	ML 76	12082[a]
	2	Togus 1	33154	*L. hackeliae*	1	Lansing 2	35250
	3	Bloomington 2	33155		2	798-PA-H	35999
	4	Los Angeles 1	33156	*L. maceachernii*	1	PX-1-G2-E2	35300
	5	Dallas 1	33216	*L. jamestowniensis*	1	JA-26-G1-E2	35298
	6	Chicago 2	33215	*L. cherrii*	1	ORW	35252
	7	Chicago 8	33823	*L. rubrilucens*	1	WA-270A-C2	35304
	8	Concord 3	35096	*L. erythra*	1	SE-32A-C8	35303
	9	IN-23-G1-C2	35289		2	LC 217	
	10	Leiden 1	43283	*L. israelenis*	1	Bercovier 4	43119
	11	797-PA-H	43130	*L. birminghamensis*	1	1407-AK-H	43702
	12	570-CO-H	43290	*L. cincinnatiensis*	1	72-OH-H	43753
	13	82A3105	43736	*L. quinlivanii*	1	1442-AUS-E	43830
	14	1169-MN-H	43703		2	LC 870	12434[a]
	15	Lansing 3	35251	*L. moravica*	1	316-36	43877
L. bozemani	1	WIGA	33217	*L. brunensis*	1	441-1	43878
	2	Toronto 3	35545	*L. tucsonensis*	1	1087-AZ-H	49180
L. dumoffii	1	NY-23	33279	*L. gratiana*	1	Lyon 8420412	49413
L. gormanii	1	LS-13	33297	*L. fairfieldensis*	1	1725-AUG-E	49588
L. micdadei	1	TATLOCK	33218	*L. adelaidensis*	1	1762-AUS-E	49625
L. longbeachae	1	Long Beach 4	33462	*L. shakespearei*	1	214	49655
	2	Tucker 1	33484	*L. lansingensis*	1	1677-MI-H	49751
L. jordanis	1	BL-540	33623	*L. quateirensis*	1	1335	49507
L. oakridgensis	1	Oak Ridge 10	33761	*L. worsleinsis*	1	1347	49508
L. wadsworthii	1	81-716	33877	*L. geestiana*	1	1308	49504
L. feeleii	1	WO-44C-C3	35072	*L. nautarum*	1	1224	49506
	2	691-WI-H	35849	*L. londiniensis*	1	1477	49505
L. sainthelensi	1	Mt St Helens 4	35248	*L. waltersii*	1	2074-AUS-E	51914
	2	1489-CA-H	49322	*L. genomospecies*	1	2055-AUS-E	51913
L. anisa	1	WA-316-C3	35292	*L. lytica*	1	PCM 2298	

ATCC, American Type Culture Collection.
[a]National Collection of Type Cultures, Central Public Health Laboratory, London, England

tum cultures. Acid pretreatment of the sputum enhances recovery (Bopp et al., 1981; Buesching et al., 1983). *Legionella* can be isolated from blood cultures by subculturing to buffered CYE agar.

The natural habitat for *Legionella* appears to be the intracellular environment. In nature, *L. pneumophila* live in fresh water and replicate as intracellular parasites of amoeba, but may exist as free-living organisms in the environment. Heller et al. (1998) recently reported isolation of *Legionella* from salt water. *L. pneumophila* causes pneumonia by replicating in alveolar macrophages. Recent studies have better defined the process of cell attachment, entry into cells, and inhibition of fusion of phagosomal and lysosomal vacuoles associated with intracellular survival (Gardumo et al., 1998; Brieland et al., 1996).

Antimicrobial Susceptibility

Legionella are susceptible to a wide range of antimicrobial agents. However, because of the intracellular location of the organisms, only antibiotics that achieve high intracellular concentrations are clinically useful. Once a class of agents

has been proven efficacious, in vitro studies (i.e., Etest) can be useful in monitoring susceptibility (Schrock et al., 1997; Schulin et al., 1998). New agents including quinupristin/dalfopristin and linezolid, which have been shown to be active in vitro (Schulin et al., 1998), must be tested in cell culture systems and animal studies (Stout et al., 1998; Edelstein et al., 1996a, b). Clinical data from the initial outbreak in 1976 suggested that erythromycin and tetracycline were useful therapeutically. Recently, newer macrolides such as azithromycin and clarithromycin and the fluoroquinolones (Marco et al., 1997) have been shown to have better activity than erythromycin. Animal experiments suggest superior activity of the fluoroquinolones and newer macrolides (Garcia-de-Lomas et al., 1998; Edelstein et al., 1996a, b; Pechere & Gootz, 1998; Walz et al., 1997). There are no controlled clinical trials in Legionnaires' disease.

Epidemiology

The epidemiology of Legionnaires' disease is distinct from other etiologies of pneumonia. The natural habitat for *Legionella* is not man, but the aquatic environment. *Legionella* has evolved to survive in nature by its association with freshwater amoeba. The amoeba ingest *Legionella* as a food source. However, *Legionella* escape digestion within the amoeba and use the intracellular locale to survive and actually multiply, consuming the intracellular nutrients present in the protozoa.

Legionnaires' disease is a disease of modern technology. Bringing the natural water in proximity to man (through cooling towers, whirlpools, recirculating water systems in multistory buildings) is the first necessary condition. Conditions must be appropriate for *Legionella* multiplication (i.e., warm temperatures, lack of biocides, and the presence of adequate nutrients [presence of amoebae]). In general, the organism must then be aerosolized in droplets small enough to penetrate to the alveoli. Aerosols are generated from sinks, showers, cooling towers, respiratory therapy devices, and whirlpools. Alternatively, the organisms can be aspirated through exposure to water that is contaminated with *Legionella.* Aspiration appears to be the pathogenic mechanism in the postoperative patient on the ear, nose, and throat service. Muder et al. (1986) reviewed the potential mechanisms of acquiring Legionnaires' disease.

The final link in the chain is a susceptible host. Patients who have compromised cell-mediated immunity have a higher incidence of Legionnaires' disease. However, the majority of patients presenting with Legionnaires' disease do not show any evidence of underlying immunodeficiency. A major risk factor is cigarette smoking. Travel and recent plumbing work in the home have been associated with increased risk of Legionnaires' disease. The clinician should not exclude Legionnaires' disease from consideration in the normal host presenting with CAP.

Epidemics

Much of the epidemiology that we understand has come from the investigation of outbreaks. The outbreak in Philadelphia during the Legionnaires' convention in 1976 was the first time *Legionella* was identified as a cause of pneumonia. In most outbreaks the attack rate appears to be low. The incubation period has been reported to range from 2 to 14 days. Recent outbreaks in the community have been associated with cooling towers in the northeastern and midwestern United States (Keller et al., 1996; Whitney et al., 1997; Fiore et al., 1998) and in Spain (Ramon et al., 1997), and with whirlpool spas (Tolentino et al., 1996), a shopping center display (CDC, 1997), and a cruise ship (Jernigan et al., 1996; Pastoris et al., 1999; Edelstein & Cetron, 1999). *Legionella* may not be as ubiquitous in the environment as initially thought, as only 2 of 60 thermal springs contained *Legionella* in Italy (Sommese et al., 1996).

One case of Legionnaires' disease in a calf was reported from Italy. Environmental investigation found *L. pneumophila* in an electric water heater used to supply water to calves (Fabbi et al., 1998).

Investigations of outbreaks involve environmental sampling for *Legionella* as well as epidemiological studies to define exposure. Newer techniques have allowed comparison of environmental and clinical isolates to help define the source (Benson & Fields, 1998).

Travel remains a risk factor for Legionnaires' disease (Straus et al., 1996; Jernigan et al., 1996;

Joseph et al., 1996). Joseph et al. (1997) reported that 100 of 202 cases reported in the United Kingdom were associated with travel either abroad or within the United Kingdom. A variety of sources have been implicated, including water from hotels and whirlpool spa water from a cruise ship. A whirlpool spa display in a shopping mall (CDC, 1997a) was associated with spread of Legionnaires' disease. It is also possible that prolonged absence from the home with resultant stagnation of the home water system may be a risk factor. *Legionella* has been isolated from water in dental units (Pankhurst et al., 1998).

In series of cases of community-acquired pneumonia the proportion of cases ascribed to *Legionella* varies considerably. Part of this discrepancy is due to geographic variation. An additional confounder is the battery of diagnostic studies used by investigators. In areas where Legionnaires' disease has been recognized, 1% to 16% of cases of CAP requiring hospitalization will be due to *Legionella* infection: northern India 0%, New Zealand 11%, Israel 16%, Spain in patients with chronic obstructive pulmonary disease (COPD) 9% (Bahl et al 1997; Porath et al., 1997; Torres et al., 1996; Lieberman et al., 1996). It must be noted that most diagnostic tests are aimed at identifying disease due to *L. pneumophila* (especially serogroup 1). Identification of other *Legionella* species is suboptimal at best.

Nosocomial Legionnaires disease continues to occur (Green et al., 1996; Harrington et al., 1996; Jack et al., 1996; CDC, 1997b; Goetz et al., 1998). Clinical suspicion needs to be high. An interesting recent observation by Kool et al. (1999) is that nosocomial outbreaks were more likely to occur if the water supplying the hospital was disinfected with chlorine rather than monochloramine. Additional studies addressing the issues of community treatment of water and the prevalence of Legionnaires' disease in the community are warranted.

Clinical Manifestations

The classical clinical picture was described by Kirby et al. (1980) from patients with nosocomial Legionnaires' disease at a hospital in Wadsworth, Virginia. The patients had hectic fevers, confusion, gastrointestinal symptoms, relative bradycardia, and worsening clinical findings while on "standard therapy with betalactams and aminoglycosides." Laboratory abnormalities included hyponatremia and increase in liver enzymes.

Cunha et al. (1998) have emphasized the extrapulmonary manifestations of Legionnaires' disease. They have constructed a scoring system to identify patients in whom Legionnaires' disease should be considered. Keller et al. (1995) also developed a scoring system to identify patients in whom specific testing for Legionnaires' disease should be undertaken. Others have suggested that Legionnaires' disease cannot be differentiated from other causes of pneumonia on clinical grounds. At one medical center physicians were more likely to start therapy appropriate for Legionnaires' disease on the day of admission in patients eventually proven to have Legionnaires' disease compared to a variety of control groups (pneumococcal pneumonia, bacteremic pneumococcal pneumonia, *Haemophilus influenzae* pneumonia) (Plouffe et al., 1995). One reason that the clinical manifestations of Legionnaires' disease may not be distinguishable is that the group of cases of Legionnaires' disease is tainted by pneumonia cases that use single titers as the sole method of diagnosis. These false-positive Legionnaires' disease cases make the group heterogeneous and mask the true positives.

Sopena et al. (1998) studied 392 patients with CAP. There were 48 patients with Legionnaires' disease and 125 patients with other bacterial etiologies (50% caused by *S. pneumoniae).* Univariate analysis showed that Legionnaires' disease was more frequent in middle-aged, healthy (but alcohol-drinking) male patients. Lack of response to previous lactam drugs, headache, diarrhea, severe hyponatremia, and elevation in serum creatine kinase (CK) levels on presentation were more frequent in Legionnaires' disease, whereas cough, expectoration, and thoracic pain were more frequent in CAP due to other bacterial etiology. Multivariate analysis only confirmed these differences with respect to lack of underlying disease, diarrhea, and elevation in the CK level. Ebiary et al. (1997) from Spain looked at 84 Legionnaires disease patients requiring intensive care unit (ICU) admission. They compared the nosocomial cases to community-acquired cases. Nosocomial cases were more likely to have underlying diseases such as COPD, cardiac disease, renal failure, alcoholism, and septic shock.

Crude mortality was 30% and similar in the two groups.

Increased APACHE scores and sodium <137 mg/dl were associated with increased mortality. Pedro-Botet et al. (1998) separated Legionnaires' disease cases into those receiving immunosuppressive therapy, those with chronic underlying diseases, and others. They were unable to define statistical differences in clinical presentation and mortality risk factors, although there were trends toward greater complications and increased mortality rates in the immunocompromised population.

Ostergaard et al. (1996) recognized relative bradycardia in patients with Legionnaires' disease, typhoid fever, and pneumonia caused by *Chlamydia* sp. Endocarditis has been reported with Legionnaires' disease (Chen et al., 1996; Berbari et al., 1997). Since blood is rarely cultured for *Legionella,* endocarditis may be more common than recognized. *Legionella* has been cultured from blood. Subcultures of routine blood cultures on buffered CYE agar may grow *Legionella.*

Domingo et al. (1996) reviewed cases of spontaneous rupture of the spleen in pneumonia, with Legionnaires' disease and Q fever being the most common etiologies.

Acute renal failure can develop with Legionnaires' disease. Renal biopsies have revealed tubulointerstitial nephritis (Verhaeverbeke et al., 1995; Ivanyi et al., 1996) and rapidly progressive crescentic glomerulonephritis (Pai et al., 1996).

Several cases of Legionnaires' disease in pregnancy have been reported (Eisenberg et al., 1997; Tewari et al., 1997) and pediatric cases of Legionnaires' disease have been examined (Levy & Rubin, 1998).

Diagnosis

The diagnosis of Legionnaires' disease can be made by culturing the organism from respiratory secretions, identifying the organisms by staining with fluorescein-tagged antibody (direct fluorescent antibody [DFA]), identifying byproducts of the organism excreted in the urine (*Legionella* urinary antigen assay [LUA]), or identifying a host response to the organism with serologic assays. The use of polymerase chain reaction (PCR) methods for diagnostic purposes is still experimental.

Culture methods of respiratory secretions remains one of the best methods of diagnosing Legionnaires' disease. Isolation of the organism is crucial in epidemiological studies. The organism can be isolated from expectorated sputum by plating on buffered CYE agar with and without supplement antibiotics or dyes. The use of acid pretreatment of expectorated sputum decreases the growth of contaminating oropharyngeal flora. The organism may not induce a pyogenic reaction; thus laboratories should not discard respiratory specimens lacking a polymorphonuclear response (Ingram & Plouffe, 1994). Respiratory samples obtained by bronchoalveolar lavage (BAL) are excellent specimens as there is less oropharyngeal flora contamination (Chiba et al., 1998). The lack of a positive culture for *Legionella* should not exclude the diagnosis as many clinical laboratories are not able to perform these cultures. The specificity of a positive culture approaches 100%. The real sensitivity of culture is actually relatively low owing to lack of adequate specimens in many patients and laboratory variability. Sensitivity of culture improves in laboratories experienced with Legionnaires' disease.

Most clinical laboratories do not use DFA staining on expectorated sputum because of low sensitivity and specificity. With respiratory specimens obtained by BAL or biopsy, the sensitivity and specificity are better.

The laboratory diagnosis of Legionnaires' disease due to *L. pneumophila* serogroup 1 has improved with greater use of the LUA test. The original radioimmunoassay (RIA) has been replaced with an EIA, which allows more laboratories to perform the test (Plouffe et al., 1995; Chang et al., 1996a,b; Schrock et al., 1997; Hackman et al., 1996). Kazandjian et al. (1997) found the sensitivity of the LUA test significantly greater than that of the direct fluorescent antigen test and similar to that of culture and serology. Although the LUA has been reported to remain positive for prolonged periods, this phenomenon occurs rarely. Most patients will clear the urinary antigen rapidly. There is a need for LUA tests with the ability to detect *Legionella* other than *L. pneumophila* serogroup 1. Tang and Toma (1986) have used a broad-spectrum assay, but the assay is not yet available.

The use of PCR to make the diagnosis of Legionnaires' disease has been reported. Unfortunately, there have been no large studies reported to

determine sensitivity and specificity. Ramirez et al. (1996) reported positive PCR of throat swabs in live of six patients with Legionnaires' disease. Weir (1998) reported positive PCR in four respiratory specimens from patients with Legionnaires' disease.Murdochetal.(1996) reported that *Legionella* DNA was detected in urine and/or serum samples from 18 (64%) of 28 patients with Legionnaires' disease and from zero of 28 patients with other etiologies.

Serologies

The vast majority of patients presenting with acute Legionnaires' disease have negative acute serological tests.

A 4-fold rise between acute and convalescent specimens appears to he fairly specific, especially for *L. pneumophila* serogroup 1. The sensitivity has been reported to he 80%. There are no large scries with other *Legionella* isolates to verily specificity. Cross-reactions with other organisms have been reported, including *Campylobacter* and *Coxiella* (Musso & Raoult, 1997). The specificity of single titers is variable. The use of specific IgM titers has been reported to be helpful in some laboratories, but these assays are not generally available. Confirmatory tests should he performed in these cases.

Treatment

Since *Legionella* is an intracellular pathogen, appropriate antimicrobial agents must achieve high intracellular concentrations. Erythromycin, historically, has been the most widely used antimicrobial agent. Newer macrolides such as azithromycin or clarithromycin achieve even better intracellular concentrations than erythromycin, thus it has been recommended that the newer agents supplant erythromycin. The fluoroquinolones have excellent in vitro activity and achieve high intracellular concentrations. Fluoroquinolones may he more advantageous in immunocompromised patients. There are no comparative trials with various new antimicrobial agents. Azithromycin, levofloxacin, and trovafloxacin were approved by the FDA for the treatment of Legionnaires' disease. Doxycycline has been used successfully in cases of Legionnaires' disease. Heath (et al., 1996) reported that delays in beginning appropriate antimicrobial therapy were associated with increased mortality.

Duration of therapy has not been systematically studied. In immunocompromised patients, 3 weeks of therapy seems reasonable. Since azithromycin has a prolonged half-life, 10 days is probably an appropriate duration. In nonimmunocompromised patients, 7 to 14 days appears to be successful, the shorter courses being used in rapid responders.

The addition of rifampin to erythromycin has been suggested to produce better intracellular killing as seen in experimental studies. No clinical data are available. The addition of rifampin is not suggested with newer regimens.

Control

Legionnaires' disease can be prevented by controlling the environmental proliferation of *Legionella*. Various biocides are available for cooling towers. Measures to control *Legionella* in hospitals and other large buildings have included heat and Hush procedures, hyperchlorination, copper and silver ionization, ultraviolet light treatment, and avoidance of large water storage tanks (Yu-sen et al., 1998; Liu et al.. 1998; Stout et al., 1998b).

The CDC's hospital infection control practices advisory committee recommends that laboratory testing for the diagnosis of Legionnaires' disease should he available in all hospitals and that clinicians should maintain a high index of suspicion for Legionnaires' disease particularly among patients who are at high risk because of underlying illness, immunosuppressive therapy, or advanced age. If a case of laboratory-confirmed nosocomial Legionnaires' disease is identified or two cases of possible nosocomial Legionnaires' disease occur during a 6-month period, an epidemiologic and environmental investigation should he conducted to identify a potential source of infection for decontamination. An alternative approach advocated by Yu (1998) is periodic sampling of hospital water systems. Water systems should be decontaminated if more than 30% of sites sampled are colonized or if cases of nosocomial Legionnaires' disease are identified.

This approach advocates applying *Legionella* tests for hospital-acquired pneumonia only in patients residing in hospitals colonized with *Legionella* so as to derive a reasonable yield. Yu in 1998 proposed a large-scale prospective observational study to help determine the utility of these strategies.

Pontiac Fever

There has not been much new information regarding the nonpneumonic form of Legionnaires' disease, Pontiac fever. This influenza-like illness has been associated with high attack rates, short incubation periods, fevers, myalgias, normal chest x-rays, and resolution of symptoms in a lew days without specific antimicrobial therapy. Cases have been associated with building air conditioning systems, whirlpool spas, decorative fountains, and steam turbine condensers. *L. pneumophila, L. micdadei,* and *L. anisa* have been associated with outbreaks of Pontiac fever. Luttichau et al. (1998) investigated an outbreak of Pontiac fever due to a contaminated whirlpool. The authors isolated *L. pneumophila* serogroup OLDA from one child and believe this represents the first reported culture-proven case of Pontiac fever. The outbreak was characterized by a short incubation period, influenza-like symptoms, and rapid recoveries, all features typical of Pontiac fever. The median incubation period for the children was shorter (43 hours) than for adults (70 hours). The median duration of the illness was 87 hours for the children versus 61 hours for the adults. Chest x-rays were normal. Ear pain and rash were more common in children. Antibody seroconversion was documented to both *L. pneumophila* and *L. micdadei,* suggesting a dual infection. Girod et al. (1982) reported two maintenance workers exposed to a contaminated cooling tower. One developed severe pneumonia and the other a self-limited Pontiac fever-type illness.

The pathophysiology of Pontiac fever is not understood. Possibilities include exposure of an immune host to viable or nonviable organisms, exposure of a nonimmune host to nonviable organisms, hypersensitivity response, or response to another organism such as amoeba.

Clinical infection with *Legionella* spp. other than *L. pneumophila* are relatively infrequently reported. *L. paracinesis, L. micdadei,* and *L. longbeachae* were isolated from transplant patients (Korman et al., 1998; Ernst et al., 1998). Harris et al. (1998) described three patients with AIDS and *L. bozemanii* pneumonia. LoPresti et al. (1998) reported the first isolation in Europe of *L. feeleii* from two cases of pneumonia. Baty et al. (1997) reported a case of *L. jordanis* pneumonia that was difficult to treat. Lung abscesses were caused by *L. micdadei* (Johnson & Huseby, 1997). An interesting association of positive serologies for *L. longbeachae* in patients with adult respiratory distress syndrome was made by Konecny and Bell (1996). *L. longbeachae* has been associated with contaminated potting soil.

One of the problematic areas is the lack of diagnostic tests for *Legionella* species other than *L. pneumophila.* The organism must be cultured to establish the diagnosis and better tests must be developed to identify this organism.

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Community-Acquired Aerobic Gram-Negative Bacillary Pneumonia

JAMES S. TAN

Introduction

Community-acquired pneumonia (CAP) among healthy young adults is usually a mild disease and patients seldom require hospitalization. However, in the elderly and in those with comorbid illness, pneumonia is more serious and is an important cause of hospitalization and death. *Streptococcus pneumoniae* remains the most common bacterial agent isolated in CAP. Other common bacterial etiologies are *Haemophilus influenzae, Moraxella catarrhalis,* and "atypical" pneumonia agents such as *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* species. *H. influenzae* and *M. catarrhalis* are more commonly found in patients with underlying lung disease and are frequently mild. *M. pneumoniae* and *C. pneumoniae* are seldom severe enough to require hospitalization. In contrast, patients with pneumonia caused by *Legionella* have a more severe illness and are more frequently hospitalized. The above six organisms are responsible for less than two thirds of the established etiologies of CAP. Aerobic gram-negative bacilli (AGNB) are responsible for a minority of CAP cases depending on geography, patient demographics, and diagnostic criteria used in the report. AGNB, most commonly *Klebsiella pneumoniae* and *Escherichia coli*, *Acinetobacter* species, and *Pseudomonas aeruginosa*, have been reported to cause pneumonia in the community setting (Garb et al., 1978; Berk et al., 1982; Harris et al., 1984; Molavi & LeFrock, 1984; Reines & Cook, 1981; Rudin et al., 1979; Tillotson & Lerner, 1966, 1967, 1968a, b; Ishida et al., 1998). These bacteria do not commonly cause pneumonia in healthy adult patients, but are more likely to cause pneumonia in the elderly, in patients who are chronically ill, in alcoholics, in the debilitated, or in immunocompromised patients (Tillotson & Lerner, 1966). Patients with AGNB pneumonia have higher mortality than those with pneumonia caused by other etiologies. Fine et al. (1996) reported on patient mortality based on their meta-analysis on previously reported CAP series: *P. aeruginosa* 61.1%, *Klebsiella* species 35.7%, *E. coli* 35.3%, *Proteus* species 8.3%, and mixed bacterial species 23.6%. *S. pneumoniae* has a reported mortality of 12.3%, *S. aureus* 31.8%, and unknown etiology 12.8%. Aspiration of microorganisms in the oropharyngeal secretions and less commonly through airborne or hematogenous routes are modes of acquiring pneumonia. Increased pharyngeal colonization has been reported in nursing home residents (Johanson et al., 1979), diabetics (Mackowiak et al., 1978), and alcoholics (Mackowiak et al., 1978; Fuxench-Lopez & Ramirez-Ronda, 1978; Rosenthal & Tager, 1975). Airborne transmission may be seen in contaminated aerosols and humidifiers. Hematogenous spread of AGNB may emanate from pyelonephritis or intra-abdominal infection. Table 1 lists the modes of acquisition of AGNB. The paper discusses the controversies in the diagnosis of these pneumonias and

JAMES S. TAN • Infectious Disease Section, Department of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, and Department of Medicine, Summa Health System, Akron, Ohio 44272-0095.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

TABLE 1. Mode of Acquisition of Aerobic Gram-Negative Bacilli[a]

Aspiration of oropharyngeal flora
Klebsiella pneumoniae
Escherichia coli
Enterobacter sp.
Proteus sp.
Pseudomonas aeruginosa
Acinetobacter sp.
Aerosolization from contaminated nebulizer
Serratia marcescens
Pseudomonas
Acinetobacter calcoaceticus
Klebsiella pneumoniae (infrequent)
Bacteremia from other sites
Escherichia coli
Pseudomonas aeruginosa

[a]Modified from Reyes, 1980

the recommend antimicrobial treatment for these serious infections. Other gram-negative bacilli such as *Francisella tularensis* (tularemia), *Yersinia pestix* (plague), and *Pseudomonas pseudomallei* (melioidosis) will not be included in this presentation.

Incidence

Less than 5% to 15% of cases of bacterial pneumonia are caused by AGNB (Molavi & LeFrock, 1984; Chase & Trenholme, 1986). The relative incidences of specific pathogens causing CAP vary from study to study depending on local demographics (age, inclusion of nursing home patients, patients recently hospitalized), presence of underlying disease (chronic lung disease, alcoholism, immunosuppression), seasonal variations, and criteria used for the diagnosis of pneumonia and its etiologic agent. There is no convincing evidence that age or residence in the nursing home per se is a risk factor for CAP. However, the association is more likely with comorbid conditions (Venkatesan et al., 1990; Riquelme et al., 1996). Marrie et al. (1985) found no difference in the incidence of pneumonia due to gram-negative bacilli in elderly patients in contrast to young hospitalized patients.

Table 2 lists the reported incidences of CAP in hospitalized patients and those in the intensive care units from different countries. The incidence of AGNB among those who were admitted to the intensive care unit in the ten studies ranged from 2% to 42%. Five of these studies reported incidences between 11% and 16%. The incidence among the less severely ill hospitalized patients ranged from 1% to 9%. Reports from the British Thoracic Society had the lowest percentages.

TABLE 2. Incidences of Aerobic Gram-Negative Bacilli (AGNB) among Patients with Community-Acquired Pneumonia

Author (country)	AGNB (%)[a]	Number of patients studied
Hospitalized patients		
Fang et al., 1990 (United States)	6	359
Mundy et al., 1995 (United States)	7	205
Marrie et al., 1989 (Canada)	3	588
Levy et al., 1988 (France)	7	116
Lim et al., 1989 (Australia)	9	106
Karulus et al., 1991 (New Zealand)	5	92
Steinhoff et al., 1996 (Germany)	8	236
British Thoracic Society, 1992	1	453
Burman et al., 1991 (Sweden)	1	196
Ishida et al., 1998 (Japan)	8.6	318
Critical care patients		
Pachon et al., 1990 (Spain)	25	67
Rello et al., 1993 (Spain)	11	58
Rello et al., 1996 (Spain)	16	95
Torres et al., 1991 (Spain)	9	92
Moine et al., 1994 (France)	15	299
Leroy et al., 1995 (France)	15	132
Feldman et al., 1995 (South Africa)	42	259
Potgieter et al., 1992 (South Africa)	15	178
British Thoracic Society, 1992	2	60
Lee et al., 1996 (Singapore)	39	59

[a]Percent of patients with known etiology.

Klebsiella pneumoniae

K. pneumoniae is the most frequent AGNB causing community-acquired pneumonia and is responsible for a significant proportion of nosocomial

pneumonia as well. *Klebsiella* is an encapsulated gram-negative rod found as part of normal oropharyngeal flora in 1% to 6% of healthy individuals (Levison & Kaye, 1985). It accounts for less than 6% of all bacterial pneumonias (Lerner & Jankauskas, 1975). In the reports from Japan, South Africa, and Singapore, 4.3% of 326 CAP patients, 8% of 225 CAP patients, and 15% of 59 CAP patients, respectively, had *K. pneumoniae* pneumonia (Ishida et al., 1998; Hammond et al., 1990; Lee et al., 1996). Pneumonia due to this organism most commonly occurs among alcoholics, debilitated patients, and those with chronic underlying disease (Hammond et al., 1990; Jong et al., 1995; Carpenter, 1990; Blinkhorn, 1998).

In the older literature, *Klebsiella* lung infection was commonly referred to as Friedländer's pneumonia. *Klebsiella* species types 1 through 6 (formerly Friedländer's bacillus types a through f) have been known to be more virulent in mice (Blinkhorn, 1998). Friedländer's pneumonia was characteristically found in a middle-aged alcoholic patient with chronic lung disease presenting acutely with fever, rigor, pleuritic chest pain, and cough productive of nonputrid, thick, sticky, gelatinous, brick-red expectoration that may be blood-streaked or grossly bloody (Finland, 1948). This presentation of primary Friedländer's pneumonia is rare in modern-day practice. In present-day practice, *K. pneumoniae* when isolated is more often part of mixed flora from respiratory secretions of a patient with a chronic lung condition, a hospitalized patient, a patient with swallowing difficulty, or an immunocompromised patient. Most clinical microbiology laboratories do not serotype *K. pneumoniae* when it is isolated from clinical specimens.

Although certain radiologic findings such as upper lobe consolidation and bulging interlobar fissure are suggestive, they are by no means diagnostic (Lerner & Jankauskas, 1975; Felson et al., 1949). Half of the patients may have multilobar involvement and abscess formation (Lerner & Jankauskas, 1975). Empyema may be found in up to one third of the cases. The findings described above may be found in other cases of acute pyogenic pneumonia as well as tuberculosis (Carpenter, 1990).

Microbiologic diagnosis is made by gram stain and culture of sputum, bronchial sampling, or pleural fluid culture. Gram stain of respiratory secretions shows many polymorphonuclear leukocytes and a high number of encapsulated short, fat, gram-negative rods. Culture of respiratory secretions yields mucoid colonies of *Klebsiella.* Carpenter (1990) reviewed the experience of *Klebsiella* pulmonary infection at Parkland Memorial Hospital in Dallas, Texas, from 1965 to 1986. He found that the criteria used for diagnosis of *Klebsiella* lung infections were not strict. The frequency of infection was much lower when *Klebsiella* infection was defined more narrowly than the mere presence of *Klebsiella* in the expectorated sputum and the presence of pulmonary infiltrates. Complications include lung abscess (it is debated that many of the previously reported cases of lung abscess were due to *Klebsiella* alone, or due to mixed aerobic–anaerobic infection following aspiration) (Carpenter, 1990), empyema, metastatic visceral abscess (liver, brain, and eye), and chronic pneumonia. *Klebsiella* infection is believed to be a more common cause of lung abscess than other bacterial causes of CAP, with the exception of the anaerobes. A rare complication is massive pulmonary gangrene that is attributed to vascular compromise resulting in rapid and total destruction of part of the lung (Carpenter, 1990).

Blood cultures are seldom positive among patients with pneumonia due to *Klebsiella* (Carpenter, 1990). Lee et al. (1996) from Singapore in their review of 59 patients with severe CAP noted that 9 (15%) had *K. pneumoniae* infection and only one had bacteremia. Jong et al. (1995) reported that bacteremic cases are more common among alcoholic patients and are rapidly fatal. Patients from public municipal hospitals have been observed to have higher frequency of bacteremic pneumonia than those from private hospitals (Carpenter, 1990). Lung abscess and empyema are relatively common among these bacteremic patients (Carpenter, 1990).

Korvick et al. (1992) reported their prospective study on the treatment of *Klebsiella* bacteremia. Only 19 of their 230 patients had respiratory infection as the source of bacteremia. They found that monotherapy using a susceptible β-lactam or aminoglycoside is sufficient for patients with less severe bacteremia. For the severely ill patient, an antibiotic combination of a β-lactam plus aminoglycoside has been recommended (Hammond et al., 1990; Korvick et al., 1992). Because of the poor lung penetration of aminoglycosides, a fluoro-

quinolone may be substituted. The added value of combination therapy is still debatable. The current recommended treatment is a third-generation cephalosporin, an imipenem, an aminoglycoside, or a fluoroquinolone after the susceptibility is known (Paterson & Trenholme, 1999). If a β-lactam plus aminoglycoside combination is chosen based on susceptibility testing, maximum doses of aminoglycoside should be used to avoid subtherapeutic levels. The choice of antimicrobial agents for the treatment should be based on knowledge of susceptibility testing especially with the increasing awareness of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae*. These organisms are susceptible to carbapenems. Mortality was lower when a carbapenem was used (Paterson et al., 1999).

Escherichia coli

E. coli the is second most common AGNB causing CAP. Pneumonia develops following aspiration of oropharyngeal flora or bacteremia from the genitourinary or gastrointestinal tract (Berk et al., 1982; Tillotson & Lerner, 1967). The incidence of pneumonia caused by *E. coli* is reported to be 1.2% in the Ohio study and 1.6% in the PORT study (Marston et al., 1997; Marrie et al., 1998). These infections are usually found in older nursing home residents who are confused and severely ill. Ninety percent of patients have comorbid conditions.

The clinical manifestations are difficult to differentiate from those of other acute bacterial pneumonia. Chest radiograph shows a patchy lower-lobe bronchopneumonia pattern and in some cases lobar consolidation and abscess formation. Empyema is common. Bacteremia is found in about a third of the patients. Mortality rate is high (29%–60%) especially in the presence of bacteremia (Tillotson & Lerner, 1967; Jonas & Cunha, 1982). The diagnosis is based on the presence of pulmonary infiltrates on chest radiograph, purulent sputum, and the presence of the bacteria in the pulmonary secretions, pleural fluid, or blood. Gram stain of respiratory secretions shows inflammatory cells and a predominance of fat gram-negative bacilli.

When a patient has a severe CAP with concomitant risk factors, therapy should also include coverage of AGNB. When *E. coli* pneumonia is suspected, one should not fail to look for sources of infection, including urinary tract infection and intra-abdominal infection. Therefore, antibiotic coverage should include agents with activity against mixed flora. The therapeutic regimen should be based on susceptibility testing because of increasing antimicrobial resistance among the penicillins and gentamicin. *E. coli* is more consistently sensitive to imipenem, third-generation cephalosporins, and ciprofloxacin.

Pseudomonas aeruginosa

P. aeruginosa is the third most common AGNB causing CAP. It is found primarily in water, vegetables, and moist soil. *P. aeruginosa* may be found in low counts in healthy adult human oropharynx, skin, and colonic flora (Rosenthal and Tager, 1975), and this organism accounts for only 1% to 2% of cases of CAP (Fang et al., 1990; Blanquer et al., 1991; Steinhoff et al., 1996). Most *Pseudomonas* pneumonias encountered in clinical practice are nosocomial in origin. Primary CAP due to *P. aeruginosa* in previously healthy adults with no underlying risk factors is rarely observed. The reported cases of pneumonia are usually fulminant with high mortality (Ishihara et al., 1995; Henderson et al., 1992). Risk factors include chronic lung disease, especially cystic fibrosis, exposure to home humidifiers or improperly maintained whirlpool spas, parenteral drug use, and immunosuppression (Harris et al., 1984; Hoogwerf & Kahn, 1981). Chronic obstructive pulmonary disease (COPD) is the predominant determinant of *Pseudomonas-associated* CAP (Torres, 1998). Other predisposing factors are advanced age, debilitation, underlying cardiopulmonary disease, neutropenia, and impaired pulmonary mucociliary clearance. Pneumonia usually follows aspiration of oropharyngeal secretions containing the organism.

Most patients present acutely with fever, rigor, confusion, and cough productive of yellowish expectoration (Malovi & LeFrock, 1984). Culture of respiratory secretions and blood frequently yields the causative agent. Radiographic findings show diffuse often bilateral infiltrates but are not characteristic except for the rapid progression to abscess

formation (Tillotson & Lerner, 1968a). These infiltrates are often nodular with multiple small areas of radiolucency suggesting microabscesses. The prominent histologic finding is alveolar wall necrosis with resulting abscesses of various sizes scattered throughout the affected lung. When pneumonia is accompanied by bacteremia, the bacteria invade the arterial walls, causing vascular thrombosis and infarcts. In nonbacteremic pneumonia, pulmonary vessels are patent with no evidence of necrotizing vasculitis.

Patients with pneumonia plus bacteremia are seriously ill with fever, dyspnea, cyanosis, and marked toxicity. Ecthyma gangrenosum of the skin may be seen. In patients with severe pneumonia and underlying chronic lung disease such as COPD and bronchiectasis, *Pseudomonas* infection should be strongly considered especially when respiratory secretion yields this organism. These patients should be promptly and aggressively treated because their mortality rate approaches 100% (Tillotson & Lerner, 1968a; Torres, 1998). Randomized controlled studies on the treatment of *Pseudomonas* pneumonia are not available. Because of increasing antimicrobial resistance, the choice of antimicrobial agents should be guided by susceptibility testing. The current recommendation is a combination of an anti-pseudomonal β-lactam agent with an aminoglycoside or ciprofloxacin (Yu & Paterson, 1999). Aminoglycosides have the disadvantages of ototoxicity and nephrotoxicity as well as poor ability to penetrate lung tissues. The use of ciprofloxacin over aminoglycosides is preferred.

Acinetobacter Species

Acinetobacter species is widely distributed in nature and can be found in fresh water or soil. *Acinetobacter* can be isolated from the throat in as many as 7% of normal persons. Pulmonary infections are infrequent. *Acinetobacter* is a gram-negative coccobacillus and can easily be misread on gram stain as *Haemophilus*. Anstey et al. (1992) reported 11 cases of *Acinetobacter* bacteremic pneumonia in the Northern Territory of Australia and reviewed 34 previously reported cases of CAP due to *Acinetobacter*. The risk factors identified among the 11 bacteremic patients were cigarette smoking, alcoholism, chronic obstructive airway disease, and diabetes mellitus.

Nonbacteremic CAP due to *Acinetobacter* is found in younger patients, whereas bacteremic pneumonia is found predominantly among men over the age of 50 years. The most common clinical presentation is a rapid onset of fever, dyspnea, pleuritic chest pain, and cough productive of purulent blood-stained sputum (Lee et al., 1996; Anstey et al., 1992; Bick & Semel, 1993; Bilgic et al., 1995). About half of the bacteremic patients progress to shock. This disease has a high mortality. Factors predicting fatal outcome are neutropenia, empyema, and inappropriate antimicrobial therapy. Chest radiographic changes arc not distinctive. The infiltrates start with lobar or bronchopneumonic distribution and rapidly progress to bilateral disease. Pleural effusion is found in about half of the cases.

When pneumonia is suspected, imipenem or ceftazidime with or without amikacin is recommended (Bergogne-Berezin, 1999). If resistant organisms are found, susceptibility to other antimicrobials including the new fluoroquinolones should be considered.

Aeromonas hydrophilia and Other Gram-Negative Bacteria

Aeromonas hydrophila is a motile bacillus that stains gram-negative and is usually found in contaminated water. The spectrum of infections includes diarrhea, wound and soft tissue infection (but rarely respiratory infections), intra-abdominal infections, urinary tract infections, and thrombophlebitis (McGowan & Steinberg, 1995). Pneumonia has been reported in those patients who have suffered near-drowning episodes and aspirated a large inoculum of the microorganism (Reines & Cook, 1981; Ender et al., 1996; Goncalves et al., 1992). Community-acquired pneumonias due to *Proteus*, *Enterobacter*, and *Serratia* are uncommon. Alcoholism, chronic lung disease, and aspiration may he predisposing factors. CAP due to Proteus usually occurs in persons with underlying conditions, particularly chronic obstructive lung disease or diabetes mellitus (Tillotson & Lerner, 1968b). Clinically, the presentation is not specific. Patients

have chills, fever, pleuritic chest pain, dyspnea, and cough productive of tenacious yellow sputum. Chest radiographs show dense lobar infiltrates, usually with multiple abscesses. The right upper lobe is more commonly involved, and the associated volume loss produces ipsilateral tracheal shift. The radiologic appearance resembles *Klebsiella. Enterobacter* pneumonia commonly arises from aspiration of oropharyngeal flora. Sputum is yellow and purulent. Chest radiograph has a bronchopneumonia pattern usually involving more than one lobe. *Serratia* pneumonia is more commonly associated with hospital-acquired pneumonia related to contaminated ventilation equipment. Radiographic findings may be characterized by diffuse alveolar infiltrates with specific site of predilection, rapid progression to abscess formation, and empyema.

Pneumonia plus Bacteremia

When AGNB pneumonia is accompanied by bacteremia, the illness usually takes on a more aggressive course and the mortality rate is higher (Jonas & Cunha, 1982; Anstey et al., 1992; Karnad et al., 1985; Leroy et al., 1995). Karnad et al. (1985) studied patients with both community-acquired and nosocomial AGNB pneumonias. Pneumonia was defined by positive roentgenographic evidence, isolation of bacteria from the pulmonary secretions obtained by the transtracheal route in nonbacteremic patients or isolation of the same organism from the blood and sputum, and a confirmatory gram stain showing inflammatory response and gram-negative rods. They reported that *Pseudomonas* (10 of 12 patients) and *Serratia* (7 of 10 patients) were more often associated with bacteremia. *E. coli* (5 of 16), *Klebsiella* species (5 of 14), *Enterobacter (2* of 7), *Proteus* (0 of 5), *and Acinetobacter* (1 of 3) were bacteremic less often. Most of the bacteremic patients had nosocomial pneumonia. Yinnon et al. (1996) studied 241 patients with *Klebsiella* bacteremia. Thirteen (3 community-acquired and 10 nosocomial) had pneumonia. The overall mortality rate of bacteremia was 32%. Cases of *Klebsiella* bacteremia published from 1973 to 1996 showed mortality rates ranging from 20% to 62%. The higher percentage was that reported in 1973. Anstey et al. (1992) reported that *Acinetobacter* bacteremic pneumonia patients had a fulminant course and high mortality.

Diagnosis

Using the results of sputum culture for the etiologic diagnosis of respiratory infections has many pitfalls. Many patients are unable to expectorate. Sputum samples, no matter how carefully obtained, are invariably contaminated with pharyngeal flora that can mask the isolation of the real pathogen on culture. Since *S. pneumoniae* and *H. influenzae* are components of normal pharyngeal flora, their presence in the sputum culture does not indicate that they are the infectious cause. AGNB are known to colonize pharyngeal flora in the elderly and those with chronic illness. The presence of AGNB in sputum samples is difficult to interpret even in the presence of compatible clinical findings. A definitive diagnosis of AGNB pneumonia is made only if pneumonia is present and AGNB is isolated from the blood, pleural fluid, or direct sampling of the lung tissue (Levison & Kaye, 1985). Bates et al. (1992) believe that studies that use more aggressive approaches to diagnosis will uncover more gram-negative bacillary infections.

The Guidelines from the Infectious Disease Society of America (IDSA) on CAP in adults states that confidence in the accuracy of the diagnosis depends on the pathogen and on the diagnostic test as follows (Bartlett et al., 1998):

1. Etiologic diagnosis definite:

- a compatible clinical syndrome plus
- recovery of a likely etiologic agent from an uncontaminated specimen (blood, pleural fluid, a transtracheal aspirate, or a transthoracic aspirate) or recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *M. tuberculosis, Legionella* species, influenza virus, or *Pneumocystis carinii*). (Some serological tests are regarded as diagnostic, although the results are usually not available in a timely manner and the diagnostic criteria are controversial.)

2. Etiologic diagnosis probable:

- a compatible clinical syndrome plus
- detection (by stain or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, a bronchoscopic aspirate, or a bronchoalveolar lavage (BAL) or brush-catheter specimen that has been cultured). With semiquantitative culture, the pathogen should be recovered in moderate to heavy growth.

In clinical practice, blood cultures usually show no growth, a specimen from lung or pleural fluid is not routinely obtained, and even tracheal or bronchial sampling is rarely performed. Gram stain examination of a properly collected sputum sample can still provide valuable guidance to the clinician in the diagnosis of AGNB pneumonia. The sputum culture can further confirm the initial suspicion provided by the microscopic examination. To improve the value of examination of the sputum, both gram staining and culture should be performed and the results integrated (Murray & Washington, 1975; Geckler et al., 1977). If a properly collected respiratory secretion contains gram-negative bacilli and if these bacilli are found inside the leukocytes, the clinician should be highly suspicious of a gram-negative bacillary pneumonia. This suspicion is further reinforced if the culture yields AGNB. Levison and Kaye (1985) stated, "in our opinion, the use of sputum culture results alone for etiologic diagnosis has led to reports of unbelievably high cure rates in series of patients with putative gram negative bacillary pneumonia treated with various new antibiotics."

Treatment

The initial choice of antimicrobial therapy for a patient with pneumonia is based on the knowledge of common etiologic agents in the community setting. In the outpatient setting, AGNB have seldom been reported as significant pathogens. The IDSA guidelines did not include AGNB as important pathogens (Bartlett et al., 1998). On the other hand, the role of AGNB in CAP among hospitalized patients is controversial. Some studies have shown that AGNB is relatively common (Feldman et al., 1989; Pachon et al., 1990; Potgieter & Hammond, 1992; Pareja et al., 1992; Rello et al., 1993) but others have not (Bartlett et al., 1998; Woodhead, 1992; Woodhead et al., 1985). Empiric therapy need not be designed to cover AGNB (Bartlett et al., 1998; Neiderman et al., 1993; Plouffe, 1998) when the patient does not have risk factors such as immunosuppression, chronic lung disease, or alcoholism.

With the increasing problems of resistance among AGNB, every effort should be made to isolate the infecting organism and perform susceptibility testing when AGNB pneumonia is suspected. Table 3 lists the recommended therapy for the four common AGNB. Empiric therapy should include two antimicrobial agents that are effective against *E. coli*, *Klebsiella*, and *Pseudomonas*. The empiric antimicrobial agent used should also have activity against *S. pneumoniae*.

Summary

AGNB are uncommon causes of CAP. Infections with these organisms should be suspected among patients with comorbid factors or in those who fail to respond to conventional therapy. Clinical manifestations and radiological manifestations are not specific. When abscess or cavitation is suspected on chest radiograph, AGNB should be in-

TABLE 3. Recommended Antimicrobial Therapy for Common Aerobic Gram-Negative Bacilli Causing Pneumonia

Aerobic gram-negative bacilli	Recommended antimicrobial therapy
Klebsiella pneumoniae and *Klebsiella* sp.	Imipenem, third-generation cyclosporins, aminoglycoside, fluoroquinolone
Escherichia coli	Imipenem, third-generation cephalosporins, fluoroquinoline, aminoglycoside
Pseudomonas aeruginosa	Anti-pseudomonal β-lactam (imipenem, ceftazidime, piperacillin) plus aminoglycoside or ciprofloxacin
Acinetobacter sp.	Imipenem, ceftazidime

cluded in the differential diagnosis. Sputum examination may be helpful but can often lead to overdiagnosis. When AGNB is suspected, blood and pleural fluid culture should be obtained whenever possible. Aggressive attempts should be made to obtain a good respiratory sample that bypasses the oropharyngeal region. Empiric treatment with at least two antimicrobial agents should be started as soon as possible after appropriate cultures have been obtained.

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Community-Acquired Pneumonia Due to Nonfermenting Gram-Negative Bacilli

TODD F. HATCHETTE

Introduction

The members of the genus *Acinetobacter* and those belonging to the family *Pseudomonadaceae* both can be generally classified as nonfermentative gram-negative bacilli. As their name suggests, these organisms do not derive their energy requirements from the fermentation of carbohydrates. Members of this group are generally considered nosocomial pathogens. However, nonfermenters have been documented as causal agents in community-acquired pneumonia.

Pseudomonadaceae

The family *Pseudomonadaceae* has been divided into five different groups based on rRNA nucleic acid homology. The most common clinical isolates include members from the genus *Pseudomonas* (Group I), members of the genus *Burkholderia* (Group II), and members of the genus *Stenotrophomonas* (Group V).

Burkholderia

Members of the rRNA homology group II in the family *Pseudomonadaceae* have been given the genus name *Burkholderia.* The genus was named in honor of Burkholder who was the first to isolate and describe the gram-negative rod (*Burkholderia cepacia*) as the cause of soft onion rot in 1950 (cited in Butler et al., 1995). Members of this genus include *B. cepacia, B. gladioli, B. picketti,* and *B. pseudomallei,* which all have similar cellular fatty-acid compositions that differentiate them from other members of the *Pseudomonadaceae* (Dees et al., 1983; Ross et al., 1995). Members of this genus are becoming increasingly identified as pathogens particularly in patients with cystic fibrosis (CF) and chronic granulomatous disease.

Burkholderia cepacia

B. cepacia has had several different names since its first description in 1950. In 1965, King at the Centers for Disease Control described a gram-negative, *Pseudomonas-like* organism that she called Eugonic oxidizer-1 (EO-1). Subsequent studies confirmed that this organism was the same as *Pseudomonas cepacia* (King, 1965, cited in Ederer & Matsen, 1972). This microorganism has also been named *Pseudomonas multivorans* and *P. kingii* (Burdon & Whitby, 1967; Gilardi, 1970; Ederer & Matsen, 1972; Poe et al., 1977). *B. cepacia* is ubiquitous and has been isolated from such unlikely places as antiseptic solutions (Burdon & Whitby, 1967). In addition, this organism has the potential to colonize respiratory equipment, resulting in nosocomial outbreaks of *B. cepacia* pneumonia (Poe et

TODD F. HATCHETTE • Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

al., 1977; Yamagishi et al., 1993). In a review of 115 isolates of *P. cepacia (B. cepacia)* from 41 patients, Ederer and Matsen (1972) concluded, "hospitalized persons with serious underlying disease appear to be the only population susceptible to infections with *P. cepacia."* Many of the patients had an underlying malignancy. Only one of the 115 isolates was from a nonhospitalized patient.

B. cepacia has been implicated in recurrent pneumonitis in patients with chronic granulomatous disease (CGD) (Bottone et al., 1975; Denney et al., 1975; O'Neil et al., 1986). These patients are at increased risk for infection with *B. cepacia* due to decreased intracellular killing of phagocytized microorganisms secondary to a defect in hydrogen peroxide production. This defect along with the ability of *B. cepacia* to produce catalase allows intracellular survival of the microorganism (Bottone et al., 1975; Denney et al., 1975). In a review of *B. cepacia* infections in patients with CGD, O'Neil et al. (1986) found that pneumonia was present in 11 of 12 cases. Most patients had no prior history of pneumonia and presented with insidious onset of fever, malaise, and chest pain. When it occurred, cough was usually nonproductive, but it was not a common early feature in most patients. Lung abscess and pleural effusions were also seen in some of these patients. None of the patients had positive sputum samples, and bacteriological diagnosis was made from material obtained with bronchoscopy, pleural fluid, percutaneous aspiration of consolidated pulmonary tissue, or surgical biopsy of pulmonary lesions. Trimethoprim–sulfamethoxazole was the most effective antibiotic used in these patients.

Patients with CF are particularly prone to colonization and infection with *B. cepacia.* The presence of increasing severity of lung disease, increasing age, prior hospitalizations, and a sibling at home with CF who is colonized with *B. cepacia* are all associated with increasing risk for colonization (Thomassen et al., 1985; Smith et al., 1993). In addition, the adherence of *B. cepacia* to respiratory epithelium is enhanced by *P. aeruginosa* (Saiman et al., 1990). In CF patients colonized with *B. cepacia* one of three scenarios occurs. Some patients may have a rapid decline in pulmonary function with death within 6 months of acquiring the microorganism; others show a slower rate of decline; still others show no adverse effects (Thomassen et al., 1985; Smith et al., 1993). Some clinicians view *B. cepacia* as a marker of seventy of disease rather than the cause of deterioration of the respiratory status of CF patients (Govan et al., 1993). Females are at risk for more rapid decline in pulmonary functional status after colonization compared to males (Thomassen et al., 1985). Colonization with *B. cepacia* leads to longer hospital stays and higher mortality rates (Tablan et al., 1987). The environment does not appear to be a source of infection for CF patients. This may be explained by differences in clinical and environmental strains (Butler et al., 1995). Although the source and mode of transmission is not well defined for most patients, ribotyping has confirmed that person-to-person transmission does occur (LiPuma et al., 1990; Smith et al., 1993; Govan, et al., 1993). This has led to segregation of patients colonized or infected with *B. cepacia* at CF clinics, meetings, and summer camps. Smith et al. (1993) advise against any social contact between patients who are *B. cepacia-positive* and those who are *B. cepacia-negative.* Furthermore, Ledson et al. (1998) suggest that patients who posses a particularly virulent strain (such as the UK epidemic strain) should be segregated from other *B. cepacia*-positive patients.

There have been two reports of *B. cepacia* pulmonary infections in previously healthy individuals (Pujol et al., 1992, Ledson et al., 1998). The first involves a 14-year-old boy who had a history of acne conglobata for which he was treated with multiple courses of antibiotics and a synthetic retinoid preparation. He came to hospital with a 10-day history of fever, cough, and pleuritic chest pain with clinical and radiographic findings of a right upper lobe pneumonia. Despite treatment with erythromycin his condition deteriorated with bilateral progression of pneumonia and the development of a right pleural effusion. On the third day of hospitalization he required mechanical ventilation because of respiratory failure. Subsequent cultures of blood, pleural fluid, bronchial washings, and a transthoracic needle aspiration all were positive for *B. cepacia.* He was successfully treated with 4 weeks of aztreonam and trimethoprim–sulfamethoxazole (Pujol et al., 1992). Although the boy had normal levels of T cells and T-cell subsets, Cohen et al. (1993) argued that *B. cepacia* infection in this 14-

year-old boy should be regarded as a red flag for underlying disease, and other investigations evaluating his lung function and immunity should be considered.

The second case involves a previously healthy 47-year-old female who developed chronic *B. cepacia* bronchiectasis following an acute pulmonary infection. This woman was the mother of two children with cystic fibrosis, both of whom were colonized with *B. cepacia.* The *B. cepacia* recovered from the woman was identical to those isolated from her children, suggesting that transmission of *B. cepacia* from patients with CF to "immunocompetent adult individuals" is possible (Ledson et al., 1998a). The mother was heterozygous for the DF508 mutation in the CF gene. Although her sweat test was within the low normal range, perhaps her heterozygous state placed her at an increased risk for *B. cepacia* infection.

Burkholderia is intrinsically resistant to polymyxin, aminoglycosides, first- and second-generation cephalosporins, carbenicillin, azlocillin, and ticarcillin. Resistance is due to reduced permeability, aminoglycoside-modifying enzymes, alteration of penicillin-binding proteins, and β-lactamases including a metallo-enzyme capable of inactivating imipenem (Pegues, 1999). β-lactamase production can be chromosomally mediated (constitutively expressed or inducible) or plasmid mediated. Trimethoprim–sulfamethoxazole, ceftazidime, chloramphenicol, ciprofloxacin, ureidopenicillins, and carbepenems all have been shown to have variable degrees of activity against this microorganism, ranging from inhibition of 45.2% of strains with imipenem to 94.8% with trimethoprim–sulfamethoxazole (Pegues, 1999). Isolates from CF patients tend to be more resistant, and current antibiotic choices will not eradicate colonization in these patients. Data suggest that monotherapy leads to emergence of resistant strains; therefore combination therapy should be administered. In vitro synergy has been shown with combinations of ticarcillin/tobramycin and ciprofloxacin/imipenem. Visalli et al. (1997) demonstrated in vitro synergism against *B. cepacia* with the combination of trovafloxacin and imipenem. However, clinical data to demonstrate the effectiveness of these combinations are lacking and no studies have demonstrated which antibiotic combinations are most effective (Pegues, 1999).

Antibiotic therapy, physiotherapy, and bronchodilators are important in managing infectious exacerbations in patients with CF (Ramsey, 1996). Although ceftazidime and piperacillin are the most active antibiotics in vitro against *B. cepacia* strains from CF patients, treatment results have been disappointing (Pegues, 1999). It is important to obtain appropriate cultures on the first day of therapy to determine the appropriate antibiotic combination (Hamer & Parker, 1996). Recommendations for antibiotic management of exacerbations of pulmonary infections in patients with CF include treatment with up to three active antibiotics against *B. cepacia* based on previously obtained sputum culture results (Noni MacDonald, 1999, personal communication). Appropriate antibiotic coverage for stains of *P. aeruginosa* should be chosen on the basis of susceptibility testing (Ramsey, 1996; Pegues, 1999). However, if culture results are not available empiric treatment should include trimethoprim–sulfamethoxazole (5 mg/kg of trimethoprim; 25 mg/kg of sulfamethoxazole every 6 hours) combined with ciprofloxacin and imipenem or ticarcillin and tobramycin for 14 to 21 days to cover strains of *B. cepacia.* Empiric treatment of patients with CGD and pneumonia should include ceftazidime in combination with trimethoprim–sulfamethoxazole (Pegues, 1999).

Burkholderia gladioli

B. gladioli, previously known as *Pseudomonas gladioli, P. marginatum*, and *Bacterium marginatum,* is a plant pathogen that has also been identified in the sputum of CF patients and as a causal agent of pneumonia in patients with CGD (Christenson et al., 1989; Ross et al., 1995; Kanj et al., 1997). Although the clinical significance of colonization is not known, *B. gladioli* tends to be more susceptible to antibiotics than *B. cepacia* and does not appear to be associated with the decline in respiratory status seen with *B. cepacia* colonization in patients who have CF (Christenson et al., 1989).

Stenotrophomonas maltophilia

S. maltophilia, previously classified as *Pseudomonas maltophilia*, was later classified in the genus *Xanthomonas* after genetic, enzymatic, and fatty-acid composition homology revealed a greater

similarity to *Xanthomonas* species than *Pseudomonas* species. However, using polymerase chain reaction (PCR) amplification of specific 16S rDNA sequences, *X. maltophilia* showed discordance with other members of the *Xanthomonas* genus. To resolve the dispute, a new genus, *Stenotrophomonas*, was created and subsequent restriction mapping of PCR-amplified 16S rRNA genes have confirmed the unique character of *Stenotrophomonas. Stenotrophomonas* is derived from the Greek "a unit *(monad)* feeding *(trophos)* on few *(steno* = narrow) substrates." *S. maltophilia* is the only member of group V in the family *Pseudomonadaceae* (Denton & Kerr, 1998). *Stenotrophomonas* is a straight or slightly curved, aerobic, motile, gram-negative rod that occurs alone or in pairs. It can be distinguished from other members in the family *Pseudomonadaceae* by characteristic biochemical properties, including a negative oxidase reaction and a positive DNAase and lysine decarboxylase reaction (Koneman et al., 1997). It is a microorganism that is widely distributed in the environment and has traditionally been implicated in nosocomially acquired infection, most frequently involving the respiratory tract.

Stenotrophomonas is adherent to plastics, glass, and teflon. Although it has a number of enzymes that may be considered virulence factors (elastase, protease, DNAase, lipase, fibrinolysin, cell wall-associated immunoglobulin G binding protein), their role in the pathogenesis of pulmonary infections is yet to be determined (Denton & Kerr, 1998). The microorganism has been isolated from the stool of healthy patients, and there is some evidence that it may colonize the oropharynx (cited in Denton & Kerr, 1998). The frequency with which *Stenotrophomonas* is isolated from clinical specimens is increasing. Chronic respiratory disease, malignancy, neutropenia, immunosuppressive therapy, admission to the intensive care unit, length of intubation, indwelling vascular catheters, and prior treatment with antibiotics (including ampicillin, piperacillin, cefotaxime, gentamicin, tobramycin, and metronidazole) are all considered risk factors for the acquisition of *Stenotrophomonas* (Heath & Currie, 1995; Muder et al., 1996; VanCouwenberghe et al., 1997). Heath and Currie (1995) found that there was an increase in the number of *Stenotrophomonas* isolates during the "wet season" and suggested that the increased use of ceftazidime and imipenem in the treatment of other "seasonal infections" due to *B. pseudomallei* and *Acinetobacter baumanii* leads to an increased rate *of Stenotrophomonas* colonization. The number of community-acquired isolates ranges from 22% to 50% (Heath & Currie, 1995; Muder et al., 1996; VanCouwenberghe et al., 1997; Denton & Kerr, 1998). One study found that the primary site of infection was pulmonary in 11% of patients but did not state how many were community-acquired or nosocomially acquired cases (Muder et al., 1996).

Although *Stenotrophomonas* may account for up to 5% of nosocomial pneumonias (Denton & Kerr, 1998), there have only been three cases of community-acquired *S. maltophilia* pneumonia published in the literature. The first case involved a 71-year-old male who presented with a 2-day history of fever, chills, weakness and fatigue. There were no complaints of cough, dyspnea, or chest pain, but clinical and radiographic findings were consistent with a right upper lobe pneumonia. Cultures were negative, but the patient did not respond to empiric penicillin therapy and had bronchial washings taken 6 days after admission that grew *S. maltophilia.* He was successfully treated with 14 days of chloramphenicol (Sakar et al., 1979). The second case was a 41-year-old female with bronchiectasis who was assessed for increasing sputum production and was found to have a right lower-lobe pneumonia. Sputum cultures grew a mucoid stain of *S. maltophilia* and she was successfully treated with minocycline (Irifune et al., 1994). The third case involved a 56-year-old female with rheumatic heart disease who was admitted with a right upper-lobe pneumonia. Blood cultures grew *S. maltophilia* and she was successfully treated with penicillin and streptomycin (Sonnenwirth, 1970).

Although *S. maltophilia* has been implicated as the causal agent in nosocomial pneumonia in patients with HIV (Franzetti, 1992), there are no documented cases of community-acquired pneumonia due to this pathogen in this patient population. Nagai (1984) found that 50 of 82 patients who had a positive culture for *S. maltophilia* had an underlying malignancy. He suggests that any patient with a positive culture for *S. maltophilia* who does not have underlying risk factors for *Stenotrophomonas* infection should be considered for

screening for an underlying malignancy. The prevalence of *Stenotrophomonas* in the sputum specimens of patients with CF has been increasing since it was first isolated in 1975. Prevalence rates vary from 1.8% to 8.7% in centers in the United States and 19% to 30% in European centers (Denton & Kerr, 1998). The clinical significance of isolating *S. maltophilia* from the sputum of patients with CF is controversial. Some studies suggest there are no adverse effects, whereas others suggest that there is a deterioration of respiratory status in patients colonized with high levels of the bacteria for prolonged periods of time. However, unlike *B. cepacia,* no person-to-person transmission of *Stenotrophomonas* has been documented (cited in Denton & Kerr, 1998). *Stenotrophomonas* has been misidentified as *B. cepacia* in the sputum of some patients with CF (Burdge et al., 1995).

Treatment of *Stenotrophomonas* can be difficult, as it is intrinsically resistant to a number of antimicrobials used to treat other gram-negative infections. There are a lot of in vitro data examining the susceptibility patterns of *Stenotrophomonas*, but clinical trials are lacking. Susceptibility testing is difficult, as many methods are not standardized. The broth or agar dilution method is currently the method recommended by the National Committee for Clinical Laboratory Standards (cited in Poulos et al., 1995). Muder (1999) recommends the agar dilution method, because of its high degree of correlation with time-kill studies, as the most reliable way to test for susceptibility. *Stenotrophomonas* has decreased permeability to a number of antibiotics and has two different inducible β-lactamases (a cephalosporinase and a metallopenicillinase) that make them resistant to extended-spectrum penicillins, third-generation cephalosporins, and imipenem. Strains also tend to be resistant to aminoglycosides and have variable susceptibility to the fluoroquinolones (Spangler et al., 1996; Vartivarian et al., 1994; Muder, 1999). *Stenotrophomonas* strains tend to have the greatest susceptibility to trimethoprim–sulfamethoxazole, minocycline, and ticarcillin–clavulanic acid, although resistance to trimethoprim–sulfamethoxazole is increasing (Vartivarian et al., 1994; Spangler et al., 1996; Muder et al., 1996; Muder, 1999). There is also anecdotal evidence of successful treatment with chloramphenicol (cited in Denton & Kerr, 1998). In vitro synergy has been demonstrated with the combination of trimethoprim–sulfamethoxazole and ticarcillin–clavulanic acid and with the combination of ciprofloxacin and ceftazidime or piperacillin despite the microorganism displaying resistance to these antibiotics when used alone (Chow et al., 1988; Poulos et al., 1995). However, synergy occurred in many isolates at levels that cannot be achieved clinically (Chow et al., 1988). Newer quinolone agents such as trovafloxacin and levofloxacin are more active against *S. maltophilia* than ciprofloxacin (Visalli et al., 1997). Visalli et al. (1997) demonstrated in vitro synergism against *S. maltophilia* with the combination of trovafloxacin and ceftazidime. When quinolone-β-lactam, quinolone–gentamicin combinations were used, synergism was only demonstrated at 12 hours, whereas after 24 hours regrowth was evident. The clinical significance of this finding is not clear at this time (Visalli et al., 1998). Combination therapy has also been associated with a reduced mortality rate in bacteremic patients (Muder et al., 1996). Although the in vitro studies mentioned demonstrate promise with combination therapy, proper clinical trials are needed to confirm their effectiveness. Muder et al. (1996) suggest a combination of trimethoprim–sulfamethoxazole (10 mg/kg of the trimethoprim component) and ticarcillin–clavulanic acid or a third generation cephalosporin in the treatment of *Stenotrophomonas* bacteremia. The trovafloxacin and ceftazidime combination represents a possible effective alternative.

Acinetobacter

Like *Pseudomonas*, *Acinetobacter* has become an increasingly important pathogen, most commonly associated with nosocomial respiratory infections. Although uncommon, *Acinetobacter* can cause community-acquired infections, particularly pneumonia.

Acinetobacter is a gram-negative aerobic, non-spore-forming, nonmotile coccobacillus. Although they are true gram-negative microorganisms, *Acinetobacter* species are often difficult to decolorize and can occur in pairs or clusters. These features, along with their coccobacillary shape, cause them to be confused with *Moraxella* species, *Haemophilus* species, *Neisseria* species, or over-

decolorized pneumococci (Goodhart et al., 1977; Henderson et al., 1987; Bick & Semel, 1993). *Acinetobacter* is oxidase-negative, which can distinguish it from *Neisseria* species and other nonfermenting microorganisms (Levison & Kaye, 1985; Von Graevenitz, 1995). The microorganism possesses a number of virulence factors including the production of a polysaccharide capsule, the generation of enzymes that are harmful to tissue, and the presence of endotoxin (Bergogne-Berezin & Towner, 1996).

In the past, many different names including *Bacterium antiratum*, *Herellea vaginicola*, *Mima polymorpha*, *Micrococcus calcoaceticus*, *Diplococcus*, and *Cytophagia* have been used to refer to the members of the *Acinetobacter* genus (Bergogne-Berezin & Towner, 1996). With the use of DNA hybridization techniques the genus has been divided into 19 species, many of which are yet to be named. Clinically the most important species is *Acinetobacter baumanii,* which is the cause of 3% to 24% of nosocomial pneumonia cases (Bergogne-Berezin & Towner, 1996). The genetic homology between *A. calcoaceticus* and *A. baumanii* is so close that many refer to a broader A. *calcoaceticus–A. baumanii* complex. This group encompasses the older species designation *A. calcoaceticus* subsp. *antiratus,* as well as those mentioned above (Bergogne-Berezin & Towner, 1996). Unfortunately, because of the confusion caused by taxonomy changes, it is difficult to be certain what species is being discussed in the older literature.

Acinetobacter is the second most common nonfermenting microorganism isolated from humans after *P. aeruginosa.* The microorganism is quite hardy and can persist for days on dry inanimate objects and in dust (Bergogne-Berezin & Towner, 1996). Like *Pseudomonas* spp. it is present in soil and water and may colonize healthy individuals. *Acinetobacter* colonization of the skin is fairly common, with up to 25% of normal individuals carrying the microorganism on the axilla, groin, and the web spaces of the toes (Bergogne-Berezin & Towner, 1996). *Acinetobacter* species have been isolated from the pharynx in infants up to 6 months of age, and from 9% of healthy adults (Rosenthal & Tager, 1975; Baltimore et al., 1989; Mengistu & Gedebou, 1986).

Community-acquired pneumonia due to *Acinetobacter* species has been reported in the literature since 1959 and accounts for up to 10% of the community-acquired pneumonia in some regions (Anstey et al., 1992). Anstey et al. (1992) reviewed 45 cases of community-acquired *Acinetobacter* pneumonia. Of the 34 cases reported until 1992, most were male (91%), greater than 40 years of age (79%, mean age, 51 years), with a history of smoking (68%) and alcoholism (60%). Although there have been some cases where patients did not have any underlying disease, the majority of patients had some comorbid illness including diabetes, chronic obstructive pulmonary disease, congestive heart failure, steroid therapy, pneumoconiosis, and chronic renal failure (Anstey et al., 1992; Bick & Semel, 1993). Cordes et al. (1981) reported three cases of community-acquired *Acinetobacter* pneumonia in patients who worked in a steel-casing foundry. They were able to isolate *Acinetobacter* (the same serotype as from the patients) from air samples and suggested that airborne spread of the bacteria and chronic inhalation of metallic dust were predisposing environmental factors leading to disease in these workers.

Anstey et al. (1992) found that the most common clinical presentation in community-acquired *Acinetobacter* pneumonia is one of acute onset with fever, pleuritic chest pain, dyspnea, and a productive cough with blood-stained sputum. The mean duration of symptoms was 2 to 3 days prior to assessment and the majority of the patients presented with hypoxia and unstable blood pressure. While some case reports did not provide exact details, of those that provided arterial blood gases, nearly all patients had a Pao_2 of <80 mm Hg and 78% had a Pao_2 of <60 mm Hg. Thirty-eight percent of the patients were described as in shock and many of those who were "normotensive and noncyanosed" on presentation developed shock and respiratory failure at some point during their admission. Thirty-six percent were leukopenic (white blood cell count [WBC] $<4.0 \times 10^9$/mL) and 82% (9/11) of the patients in the northern Australian report were lymphopenic (WBC $<1.5 \times 10^9$/mL) (Anstey et al., 1992).

Radiological findings in community-acquired *Acinetobacter* pneumonia are nonspecific. There is no predilection for any particular lobe of the lung. These patients can present with infiltrates in one or

multiple lobes and may have an effusion. The majority of patients with community-acquired pneumonia due to *Acinetobacter* are bacteremic (68%, 38/45) whereas in nosocomial pneumonia this is not a characteristic feature (Anstey et al., 1992). Due to *Acinetobacter*'s coccobacillary shape, and its sometimes poor decolorization on gram staining, *Acinetobacter* pneumonia has been misdiagnosed as pneumococcal pneumonia, which has led to delays in treatment and increased mortality (Goodhart et al., 1977; Henderson et al., 1987). The overall mortality in the review by Anstey et al. (1992) was 55%, with a strong association between mortality and inappropriate antibiotic treatment, a finding common to other reviews (Barnes et al., 1988; Anstey et al., 1992; Bick & Semel, 1993). However, when all cases were reviewed, more than 50% of the patients who died did so despite receiving the appropriate antibiotic therapy (Anstey et al., 1992). Shock at presentation appears to be a predictor of mortality. Small case series have suggested that leukopenia is a risk factor for fulminant disease and increased mortality (Wallace et al., 1976; Rudin et al., 1979). However, this risk factor could not be substantiated when all of the reported cases were reviewed (mean WBC 9.67×10^9/mL in fatal cases vs. 11.24×10^9/mL in survivors) (Anstey et al., 1992).

Since Anstey's review (1992) there have been 10 other reported cases of community-acquired *Acinetobacter* pneumonia (Patel et al., 1991; Achar et al., 1993a,b; Bick & Semel, 1993; Bernasconi et al., 1993; Currie et al., 1994; Bilgic et al., 1995; Domingo et al., 1995; Yang et al., 1997), including a patient with underlying human immunodeficiency virus infection (Domingo et al., 1995) and a case involving a healthy 74-year-old woman who lacked any of the mentioned risk factors and survived with the appropriate treatment (Bick & Semel, 1993).

It is difficult to compare treatments in the cases documented above because they span a 30-year period during which newer, more effective antibiotics have been developed. However, the development and use of broader-spectrum antibiotics has led to increasing resistance among many bacteria including *Acinetobacter.* Most of our information on treatment of *Acinetobacter* pneumonia is from studies of nosocomial pneumonia. Earlier these organisms were susceptible to antibiotics such as gentamicin, ampicillin, or carbenicillin. Now, from most accounts, these antibiotics are ineffective and there is increasing reliance upon the broader coverage given by drugs such as imipenem, third-generation cephalosporins, amikacin, tobramycin, and the fluoroquinolones (Bergogne-Berezin & Towner, 1996). Trovafloxacin and levofloxacin are more active than ciprofloxacin against *Acinetobacter,* but *Acinetobacter baumanii* strains are more resistant to fluoroquinolones than other strains (Visalli et al., 1997). Unlike other bacteria, *Acinetobacter* has the ability to rapidly adapt to the antibiotic selective pressures in the environment. The mechanisms responsible for resistance include poor penetration of antimicrobials, as well as more specific mechanisms such as plasmid and chromosomally mediated production of -lactamases. The resistance pattern of the microorganism will depend largely on the antibiotic presence in the community, and, as the microorganisms continue to evolve in the presence of these broad-spectrum agents, the effective minimum inhibitory concentrations of these drugs continue to increase. To limit the development of resistant strains, combination therapy is recommended. At present, various combinations of an extended-spectrum penicillin, fluoroquinolones, imipenem, and an aminoglycoside are the recommended treatment for nosocomial pneumonia. The first-line treatment is imipenem and amikacin or ceftazidime and an aminoglycoside. However, the combination of ciprofloxacin and imipenem demonstrates synergistic bactericidal activity in vitro and is the first choice in some institutions. In vitro studies have also shown the combination of trovafloxacin and imipenem to be synergistic in some strains (Visalli et al., 1997). Rifampicin may also be effective as part of a synergistic combination (Bergogne-Berezin, 1999).

Community-acquired isolates may not be subjected to the same antibiotic-induced selection pressure and thus may not be as resistant. However, it is reasonable to treat for the more resistant possibilities and similar suggestions have been made for the treatment of community-acquired *Acinetobacter* pneumonia (Anstey et al., 1992). No specific duration of treatment has been formally recommended, but the majority of successfully treated infections in the literature were treated with antibiotics for 2 to 3 weeks.

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35

Miscellaneous Bacterial Causes of Community-Acquired Pneumonia

TODD F. HATCHETTE

Many species of bacteria have been implicated as causes of community-acquired pneumonia (CAP). This chapter summarizes the literature describing CAP due to *Clostridium* species, *Listeria monocytogenes, Neisseria* species, and *Eikenella corrodens.*

Clostridium

Introduction

Of the 100 different species of *Clostridium* only 26 have been associated with disease in humans. Disease caused by *Clostridium* species can be divided into three categories; noninvasive (secondary to toxin production), invasive or histotoxic, and purulent diseases (where *Clostridium* species are involved in abscess formation often as part of a polymicrobial infection). Members of the genus *Clostridium* are anaerobic, spore-forming, catalase-negative, gram-positive bacilli that may have tapered, rounded, or blunt ends. *Clostridium* can sometimes falsely stain gram-negative after prolonged periods of growth. Although there are some species that can be aerotolerant (including *C. tertium* and some strains of *C. perfringens*), better growth is observed under strict anaerobic conditions (Onderdonk & Alien, 1995). *Clostridium* species produce a number of toxins and the different strains can be differentiated on the basis of the toxin they produce. For example, *C. perfringens* produces an alpha toxin (the most commonly found toxin in the strains that produce human disease), which is a potent phospholipase that can interact with the membrane of erythrocytes and a variety of cells, leading to the necrosis seen in myositis and hemolysis. Other toxins include beta toxin, which is important in the pathogenesis of necrotizing enteropathies, epsilon lethal toxin, iota toxin, a protease, hyaluronidase, neuraminidase, DNAase, and a collagenase (Hatheway, 1990; Onderdonk & Alien, 1995). A novel IgA protease has also been recently isolated from some *Clostridium* species, which may help circumvent local humoral immunity in humans (Fujiyama et al., 1985). (For a good review on toxigenic *Clostridium* species see Hatheway, 1990).

The majority of *Clostridium* species are harmless saprophytes found as natural inhabitants of the bowel. However, under the right conditions these organisms can invade and cause infection in tissues throughout the body. Apart from botulism, tetanus, *C. perfringens* food-borne illness, and traumatic gas gangrene, the majority of *Clostridium* infections arise from endogenous flora. The most frequently isolated *Clostridium* species is *C. perfringens* (referred to as *C. welchii* in older literature). Although most commonly isolated from the bowel, *C. perfringens* can be recovered from the genital tract of 1% to 9% of females and historically has been associated with gas gangrene of the uterus as a consequence of illegally performed abortions (Onderdonk & Alien, 1995). However, Ramsey described *C. perfringens* as a "harmless saprophyte" of the female

TODD F. HATCHETTE • Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

genital tract as it was observed as a self-limiting, relatively asymptomatic bacteremia in women often following septic abortion (cited in Gorbach & Thadepalli, 1975). During a 14-month period one hospital processed a total of 16,314 blood cultures. *Clostridium* species represented only 2.6% of the 2168 positive blood cultures and *C. perfringens* accounted for 57% of these. From these 114 patients, 152 strains of *Clostridium* representing 20 different species were identified. *Clostridium* infections have been associated with hematological and gastrointestinal malignancies and neutropenia (Bretzke et al., 1988; Tanabe et al., 1989; Larson et al., 1995; Bar-Joseph et al., 1997). *C. perfringens* is the most common *Clostridium* species to cause bacteremia in cancer patients, and C. *septicum* and *C. tertium* are often associated with neutropenic patients who present with typhlitis (Bodey et al., 1991). Bretzke et al. (1988) suggest that a search for occult malignancy should be conducted on any patient presenting with a *C. septicum* infection.

Clostridium Pleuropulmonary Infections

Although fairly rare now, *Clostridium* pleuropulmonary infections are well-recognized complications of penetrating chest trauma. Eighty-seven cases of *C. perfringens* empyema were reported in 1917. Either alone or as part of a polymicrobial infection, these microorganisms are estimated to have accounted for 10% of hemothorax infections during World War I (cited in Poppe, 1944; O'Donnell, 1952; Bentley & Lepper, 1969). Fargo (1939) demonstrated the presence of *C. perfringens* in cavities of patients with tuberculosis. Twelve percent of these patients had *C. perfringens* isolated from their sputum. The clinical significance of this finding is not clear. Finland and Barnes (1978) reviewed all cases of empyema diagnosed at Boston City Hospital during 12 selected years from 1935 to 1972. Although the incidence of certain causes of empyema decreased with the development of antibiotics, the incidence of *Clostridium* empyema was relatively constant. This infection tended to be posttraumatic or occur after intrathoracic surgery and was usually part of a polymicrobial infection. Overall, *Clostridium* species were isolated from 2.9% of the cases of empyema. Eight patients in a series of 144 patients with *Clostridium* infection reviewed by Gorbach and Thadepalli (1975) had *Clostridium* species isolated from infected pleural fluid (including *C. ramosum* (three isolates), *C. subterminate, C. limosum, C. innocuum, C. sporogenes,* and *C. perfringens* (one isolate each)). In six of the eight cases *Clostridium* species were isolated as part of a polymicrobial infection. Bartlett and Finegold (1974) reviewed 143 cases of anaerobic pleuropulmonary infections. Over 70% of lung abscesses, necrotizing pneumonia, and empyema were community-acquired, whereas 50% of cases of pneumonitis were nosocomial. Two of 45 cases of lung abscess were due to *C. perfringens,* with only one isolated in pure culture. Seven of 44 cases of pneumonitis were due to *Clostridium* species (including *C. perfringens, C. sordellii, C. sporogenes, C. bifermentans,* and one *Clostridium* sp.), and six of those seven were associated with polymicrobial infections. Of the cases of empyema, only 2 of 47 were due to *Clostridium* species (both *C. perfringens*), both of which were part of a polymicrobial infection (Bartlett & Finegold, 1974).

In addition to these cases reported as part of large series, a number of case reports and smaller reviews of *Clostridium* pleuropulmonary infections have been published. Tables 1 through 4 summarize these reports.

Clinical Features

Of the 39 cases of *Clostridium* pleuropulmonary infection reported from 1935 to 1993, 57.9% of patients were male with an average age of 50.3 years (range 2–95 years). Only 23.1% (9/39) cases were polymicrobial, which is in contrast to the 82% (9/11) of cases reported by Bartlett and Finegold (1974). Seventy-nine percent (31/39) of cases summarized in Table 1 were due to *C. perfringens.* The remaining cases were due to a variety of *Clostridium* species, including *C. sordellii* (cases 17, 35), *C. bifermentans* (case 18, 23), *C. paraputrificum* (case 21), *C. tertium* (case 31), and *C. innocuum* (case 32). Predisposing factors for anaerobic lung infection include conditions that predispose to aspiration: periods of unconsciousness with aspiration of gastric contents; aspiration of foreign bodies during dental extraction; tuberculosis; cavitation; carcinomatosis; and dysphagia (Seriki et al., 1970; Bartlett & Finegold, 1974).

A previous review of the literature suggested that *Clostridium* pleuropulmonary infections were caused by either aspiration of oropharyngeal contents or contamination of the pleural space by instrumentation (Bekemeyer, 1986). Of the 39 cases of *Clostridium* pleuropulmonary infection summarized (Table 1), 79.5% of patients had an underlying medical problem, 38.5% had risk factors for aspiration, 20.5% had a history of alcohol abuse, and one patient developed aspiration pneumonia during treatment for alcohol withdrawal (case 31). Six of the 39 patients (15.4%) developed postoperative clostridial infections. Nine of the 39 patients (23.1%) had a thoracentesis 2 to 10 days prior to the diagnosis of *Clostridium* empyema. The majority of these were diagnostic taps that failed to reveal the cause of a presenting plural effusion with subsequent aspirates yielding the diagnosis of a *Clostridium* infection. Bayer et al. (1975) suggest that these may represent an iatrogenic cause in some cases, while others may represent a reactive effusion due to an underlying pulmonary infection that became secondarily infected. One patient (case 14) may have seeded a malignant pleural effusion during a *Clostridium* bacteremia induced by biopsy of a friable adenocarcinoma lesion in the sigmoid colon (Bentley & Lepper, 1969). Bentley and Lepper (1969) suggest that the preparation for gastrointestinal investigations with cathartics may have altered the flora sufficiently that *C. perfringens* was allowed to proliferate to numbers that could predispose to bacteremia when the integrity of the mucosa was compromised. Eight of the 39 patients (20.5%) in Table 1 had a pulmonary embolus. The necrotic, ischemic tissue distal to the embolus is a good environment for the growth of *Clostridium* species (Raff et al., 1984). Hematogenous spread may also explain the association of *Clostridium* pleuropulmonary infections in patients with pulmonary embolus. Although several of the patients with *Clostridium* pleuropulmonary infections were noted to have poor dental hygiene, a recognized risk factor in other causes of anaerobic pleuropulmonary infections, *Clostridium* species are not commonly found in the mouths of patients with dental caries (Johnson 1947; Morris 1954; Sullivan et al., 1973; Listgarten et al., 1993). The median duration of symptoms in *Clostridium* pleuropulmonary infections was 7 days, which is roughly similar to what was seen in pleuropulmonary infections due to other anaerobic organisms (Bartlett & Finegold, 1974).

The most common presenting symptoms of *Clostridium* pleuropulmonary infection were pleuritic chest pain (67.7%) and dyspnea (54.8%). Cough, fever, chills, and hemoptysis were present in 30% to 40% of patients (Table 4). These symptoms are nonspecific and are found in patients with bacterial empyema of all causes or in patients presenting with pulmonary embolus (Vianna, 1971). Others have noted mild jaundice or tachycardia out of proportion to the degree of fever (Goldberg & Rifkind, 1965). The mean leukocyte count was 15.5 $\times 10^9$/L, similar to that seen in other causes of bacterial empyema (Vianna, 1971). Foul-smelling specimens are considered to be hallmarks of anaerobic infections. However, the lack of the characteristic foul-smelling sputum does not rule out the possibility of an anaerobic infection (Bartlett & Finegold, 1972). Only 2 of 39 patients (6.5%) had foul-smelling sputum as a presenting complaint (cases 9 and 13). This is consistent with other causes of anaerobic pneumonitis where only 9% of patients present with foul-smelling sputum (Bartlett & Finegold, 1974). Ninety-four percent of patients presented with pleural effusion that varied in size but on occasion was large enough to cause hemodynamic compromise (Goldberg & Rifkind, 1965). Characteristics of the pleural fluid can often give clues as to the cause. The fluid in *Clostridium* empyema was more commonly on the right side. It was described as bloody, dark, brown, or cloudy in 50% (13/26) of patients and purulent in 34.6% (9/26) of the patients. The fluid was foul-smelling in 14 of 26 patients (53.8%) and gas was released at the time of chest tube insertion in 2 of the 26 patients (7.7%) (Table 3).

Pleural effusion was the most common radiological presentation in clostridial pleuropulmonary infections, with effusion being the sole manifestation of infection in two patients (cases 15 and 27). The anatomic position of the right mainstem bronchus facilitates right lower-lobe involvement in cases of aspiration. In clostridial infections, parenchymal infiltrates can involve both the right and left lungs. However, the right side was more commonly involved than the left. Pneumonitis (parenchymal disease without cavitation) was present in 51.6% of patients, commonly involving the right

TABLE 1. Published Reports of Nontraumatic *Clostridium* Pleuropulmonary Infections

	Patient gender and age	Duration of symptoms	Organism	Predominant symptoms	Underlying illness	History of aspiration risk factors	Procedure history
Ghormley, 1935			*C. perfringens*				
Badet & Muller, 1939	Female, 54 years	3 months	*C. perfringens*	Pleuritic chest pain Fever/chills	None		Multiple thoracentesis prior to empyema
Glaser et al., 1941	Male, 41 years	1 week	"Gas bacillus" *C. perfringens*	Weakness, dyspnea, hemoptysis, pleuritic chest pain	Loss of teeth due to trauma (fist fight), carious teeth, BC, PC	LOC × 2–3 hours	—
Poppe, 1944	Female, 28 years	3 days post-op	*C. perfringens Staphylococcus Viridans Streptococcus*		BC, recurrent pneumonia	Post-op GA	LLL lobectomy
	Female, 15 years		*C. perfringens Klebsiella* spp *Staphylococcus aureus*		Chronic cough, BC	Post-op GA	Lobectomy, RML, RLL
	Female, 48 years		*C. perfringens*		Recurrent empyema	Post-op GA	Lobectomy 4 months previous
Johnson, 1947	Male, 38 years	6 months	*C. perfringens* gnb		Tuberculosis, empyema		Thoracentesis 4 days prior to empyema
Jacox & Dionne, 1951	Female, 30 years	3 days	*C. perfringens*	Pleuritic chest pain, cough, blood-streked sputum, chills	Nil (?tender area over malleolus 6 weeks prior) Pulmonary TB	None	Thoracentesis 4 days prior to pneumonia
O'Donnell, 1952	Female, 52 years		*C. perfringens*		PUD, nasal catarrhalis	Surgery 3 days prior to diagnosis, chronic vomiting	Thoracentesis 4 days prior to empyema diagnosis
Sweeting & Rosenberg, 1959	Female, 45 years	7–10 days	*C. perfringens*	Dyspnea, ankle swelling	Nil[b]	Nil	Nil
Haughland & Krohn, 1960 (cited in Goldberg & Rifkind, 1965)	Female, 61 years		*C. perfringens* with: *S. aureus, Enterococcus, Alcaligines faecalis*		Pulm. TB, BC		Thoracentesis and closed chest tube drainage several wks prior to empyema
Goldberg & Rifkind, 1965	Male, 42 years	3 weeks	*C. perfringens*	Pleuritic chest pain (no history of fever, chills, cough, or hemoptysis)	Multiple sclerosis AAA repair *E. coli* pyelo. 3 months before		Thoracentesis 10 days prior to empyema
	Male, 65 years	3 weeks	*C. perfringens* Coagulase negative *Staphylococcus*	Pleuritic chest pain, dyspnea, cough, brown/ blood sputum (foul smelling)	Alcoholism, dental extraction 2 months prior, CHF	Alcoholism	Nil

TABLE 1. (*Continued*)

White blood cell count	Effusion (gram stain)	X-ray	Pleural effusion	Sputum gram stain/culture	Culture	Treatment	Outcome (time to death/ discharge)
		Pneumonia[a]			Sputum		
	Right side, brown pus, foul smelling, gpb				Pleural fluid	Rib resection, antitoxin	Survived (4 days)
9.7	Right side, dark, foul smell, gpc/gpb	RLL infiltrate (? aspiration)	No	Pus cells	Pleural fluid		Death (4 days)
8.7	Left side		No		Pleural fluid	Penicillin (160,000 u/day), open drainage	Survived (35 days)
30.0					Pleural effusion	Penicillin × 18 days (2.3 mlu total), open drainage	Survived (5 weeks)
30.0	Right side, thick pus				Pleural effusion	Penicillin, open drainage	Survived (6 months)
	Pyopneumonia, foul small, pus, gnb				Pleural fluid	Rib resection/ thoracoplast, penicillin	Survived
33.5	Right side, gpr	RML infiltrate, progression to abscess	Yes	*Streptococcus viridans*	Pleural fluid	Penicillin + surgical drainage	Survived (39 days)
4.5	Left side, clear 1st tap, "stinking" pus on 2nd tap, gnb	LLL infiltrate		Thick, foul smell, gpc/gpb, grew *Streptococcus pneumoniae*/ coliforms/*C. perfringens*	Sputum, pleural fluid	Penicillin, anti-gas gangreen serum, repeated aspirations of effusion	Survived (52 days)
20.6	Right side, foul smell, bloody, gnp	RML/RLL necrotizing pneumonia			Pleural fluid, blood, lung		Death (30 hours)
	Right side (foul smell), pyopneumonia				Pleural fluid	Pneumothorax	Death BPF
11.1	Left side, 1st blood, 2nd brown and foul smell, gpb	LLL consolidation	Yes	*Streptococcus pneumoniae*	Pleural fluid	Oxacillin then penicillin/ chloramphenicol, chest tube drainage	Survived (44 days)
7.9	Left side, hydropneumothorax, small right side (foul smell/brown/ gpb)	LUL/RML/RUL infiltrates			Pleural fluid	Erythromycin/ chloramphenicol × 19 days, chest tube drainage	Survived (40 days)

(*continued*)

TABLE 1. (*Continued*)

	Patient gender and age	Duration of symptoms	Organism	Predominant symptoms	Underlying illness	History of aspiration risk factors	Procedure history
Bentley & Lepper, 1969	Male, 74 years		*C. perfringens* *E. coli*		Carcinoma of cecum	SBO, fecal contamination, aspiration, surgery	Cathartics for GI prep, thoracentesis 7 days prior to empyema
	Male, 53 years	1 month	*C. perfringens*	Dry cough, pleuritic chest pain, weight loss	Colonic cancer with lung/pleural metastases		Sigmoidoscopy + biopsy, cathartics for GI prep, thoracentesis 2 and 6 days prior to empyema
Malmborg et al., 1970	Male, 25 years		*S. sporogenes*	Pleuritic chest pain, fever, hemoptysis		Post-op following orto./ surgery	Nil
Seriki et al., 1970; Bohrer & Williams, 1970	Male, 2 years	6 weeks	*C. perfringens* Coliforms Anaerobic *Streptococcus*	Fever, cough, weight loss, soreness of mouth	Nil	Nil ?poor oral hygiene	
Hardison, 1970	Males, 56 years	1 week	*C. perfringens*	Pleuritic chest pain, fever, night sweats, hemopysis	Diabetes, poor oral hygiene	LOC 1 week PTA	
Bayer et al., 1975	Male, 48 years	12 hours	*C. perfringens*	Pleuritic chest pain	CAD (CABG), pulmonary embolism, HTN, chronic bronchitis		Diagnostic thoracentesis 2 days prior
File et al., 1977	Male, 55 years	"Acute"	*C. sordelli*	Dyspnea, cough, hemoptysis, pleuritic chest pain	Rheumatic heart disease	No	No
Mirsa & Hurst, 1980	Female, 41 years	1 week	*C. bifermentans*	Fatigue weakness, dyspnea, cough, hemoptysis, pleuritic chest pain	CHF		
Spagnuolo & Payne, 1980	Female, 84 years	Several weeks	*C. perfringens*	Increasing dyspnea, orthopnea, edema	CHF	Depressed gag reflex	
Spagnuolo & Payne, 1980	Female, 25 years		*C. perfringens*	Dyspnea, fever	DD, SLE, steroid therapy		

TABLE 1. (*Continued*)

White blood cell count	Effusion (gram stain)	X-ray	Pleural effusion	Sputum gram stain/culture	Culture	Treatment	Outcome (time to death/ discharge)
	Right side, 1st yellow, 2nd thick pus, foul smell	Right lung abscess (?aspiration)			Sputum, pleural fluid, bronch.	Antimicrobials, chest tube drainage	Survived (45 days)
	Right side (bloody/ foul smell), gpb	No pneumonia				Penicillin/ cephalothin, chest tube drainage × 12 days	Survived (18 days)
13.2	Right side, brown-red, hemolized	LLL infiltrate	No	Culture: *E. coli*/*Klebsiella* spp.	Pleural fluid	Penicillin, streptomycin	Survived
	Left side (blood/ pus), gpc	LLL infiltrate/ abscesses, LUL collapse			Sputum	Penicillin/ polymixin and cloxacillin, antitoxin, thoracotomy, pneumonectomy	Survived (>1 month)
	Right side, red/ brown (gas and foul smell)	RML/RLL infiltrates		Gram-negative/ gram-positive organisms	Pleural fluid, bronchial washing	Penicillin, chest tube drainage, BPF: open thoracotomy	Survived (87 days)
8.3	Right side, foul smell (bloody)*, *gpc*	Multiple infiltrates in RLL, Necrotizing pneumonia	?		Transtracheal aspirate, pleural fluid, lung tissue	Ampicillin × 3 days, penicillin/ gentamicin × 3 weeks, right thoracotomy decortication	Survived (3 weeks)
19.2	Left side, blood-tinged, gpb	LLL consolidation	?	Mixed flora (grew *Streptococcus*, *Neisseria* sp., considered oral contaminants)	Pleural fluid	Penicillin (18 miu/d × 3 weeks, chest tube drainage	Survived (50 days)
15.8	Right side/ pneumothorax	LUL infiltrate/ cavitation, RLL infiltrate/ cavitation	Yes		Pleural fluid, blood, lung tissue		Death (4 days) Multiple pulmonary emboli
12.8	Right side, cloudy, negative gram stain	RLL infiltrate		Gram-variable pleomorphic rods	Sputum, blood	Ampicillin/ gentamicin, changed to penicillin, chest tube drainage	Survived (2 weeks)
20.7	Right side (bloody/ purulent)	LLL/RLL infiltrates, RLL abscess	Yes		Blood, sputum, pleural fluid	Clindamycin/ gentamicin, penicillin	Death (15 days)

(*continued*)

TABLE 1. (*Continued*)

	Patient gender and age	Duration of symptoms	Organism	Predominant symptoms	Underlying illness	History of aspiration risk factors	Procedure history
Nachamkin et al., 1982	Male, 65 years	2–3 days	*C. paraputrificum*	Cough, hemoptysis, dyspnea, fever, chills, vomiting	Alcoholism, malnourishment, poor dental hygiene	Head trauma and LOC	
Silpa et al., 1982	Male, 49 years		*C. perfringens* Light growth of *H. influenzae*		PVD with foot ulcer, CHF, alcoholism, alcohol cardiomyopathy, poor dental hygiene	Altered LOC	
Jonsson et al., 1983	Male, 60 years	1 week	*C. bifermentans Bacillus cereus*	Dyspnea, fever, productive cough, pleuritic chest pain	Alcoholism, HTN, a. fib, CHF		
Kwan et al., 1983	Female, 19 years	1 week	*C. perfringens*	Pleuritic chest pain, malaise, night sweats	Nil		
Raff et al., 1984	Male, 44 years		*C. perfringens*	Pleuritic chest pain, hemoptysis	ESRD, analgesic-induced neuropathy, ascites	Vomiting post AV fistula surgery	
	Male, 60 years	3 days	*C. perfringens*	Dyspnea, cough, whitish sputum, edema, nausea/vomiting	Alcoholism, ulcer on left ankle, a. fib, chronic liver disease		
	Male, 59 years	1 week	*C. perfringens*	Chest pain, diaphoresis, SOB, PND	CHF, rib fractures, acute MI, VT		
Raff et al., 1984	Male, 51 years		*C. perfringens*	Cough, chills, sweats, chest pain, dyspnea, hemoptysis, orthopnea	Alcoholism, HTN, cardiomyopathy, CHF, CVA	Previous CVA	
	Female, 68 years	2 months	*C. perfringens*	Nausea, vomiting, fever/ chills, cough	CVA, HTN, alcoholism, smoker		
Bekemeyer, 1986	Female, 81 years	2 days	*C. perfringens*	Pleuritic chest pain, dyspnea	PUD, vagotomy, gastroenterostomy, HTN, RA, bil. TKR, THR, penicillin allergy		
Johnson & Tenover, 1988	Male, 48 years	4 days after admission for AW	*C. tertium*	Fever, respiratory distress	Alcoholism	Sedation	

TABLE 1. (*Continued*)

White blood cell count	Effusion (gram stain)	X-ray	Pleural effusion	Sputum gram stain/culture	Culture	Treatment	Outcome (time to death/ discharge)
8.3	Nil	LLL infiltrate, RLL involved (aspiration)	No	gpc, gnc, grew *Streptococcus/ Neisseria* spp./ *Streptococcus pneumoniae*	Blood	Ampicillin/ gentamicin changed to penicillin	Survived (>14 days)
22.0	Loculated right side (serosanguine, foul smell)				Pleural fluid	Penicillin/ gentamicin changed to cefoxitin Thoractomy	Survived BPF
24.4	Right side (serosanguine/ purulent/foul smell), gpb	Right sided infiltrates/cavities, necrotizing pneumonia	No		Pleural fluid, lung tissue	Chloramphenicol changed to penicillin/ vancomycin, chest tube drainage, thoracotomy/ decortication	Survived (26 days)
13.8	Left side (serosanguine), no bacteria seen, pleural Bx, gpb	No pneumonia	No		Pleural fluid, pleural bx	Penicillin × 6 weeks, chest tube drainage, hyperbaric O_2	Survived (3 weeks)
16.9	Left hydropneumothorax, gas on intubation, gbp	Multiple densities in the left side	No	Nil	Pleural fluid	Cephalothin/ gentamicin changed to penicillin, chest tube drainage	Death from GI hemorrhage
	Right hydropneumothorax, blood/purulent, gpb	RLL infiltrates		Tracheal aspiration, gpb	Pleural fluid, tracheal aspiration	Penicillin, chest tube drainage	Survived (1 month)
9.0	Right side, gpb	RML density	Yes		Pleural fluid		Death due to cardiac arrest (7 days)
20.0	Left side, right side				Pleural fluid	Cefoxitin, chest tube drainage	Survived
12.4	Right side, negative gram stain	Atelectasis on right side	No		Pleural fluid	Penicillin, chest tube drainage	Survived
7.8	Right hydropneumothorax, gpb	RLL infiltrate/ cavitation	No	gnp, gpc (grew *P. aeruginosa/K. oxytoca*)	Pleural fluid	Erythromycin changed to vancomycin, chest tube drainage	Death (25 days) BPF Systemic candidiasis
	Nil	RUL infiltrate, ? aspiration pneumonia	No	Mixed, gnb with "squarish" ends, culture: *E. coli/H. influenzae*	Blood	Cefaxolin/ gentamicin/ clindamycin, changed to cefazolin alone	Survived (20 days)

(*continued*)

TABLE 1. (*Continued*)

	Patient gender and age	Duration of symptoms	Organism	Predominant symptoms	Underlying illness	History of aspiration risk factors	Procedure history
Domej et al., 1990	Female, 29 years	3 months	*C. innoculum* *Streptococcus viridans* *P. mirabilis* *Staphylococcus aureus* *Enterobacter* *K. pneumoniae* Group D streptococcus *Bifidus* bacteria Fungi	Dyspnea, productive sputum, recurrent fevers (chronic LLL pneumonia/left pleural effusion)	Chrohn's colitis, comp. deficiency, low protein		
Bashir & Benson, 1990	Male, 66 years	3 weeks	*C. perfringens*	Pleuritic chest pain, dyspnea, hemoptysis	Smoking		
Patel & Mahler, 1990	Male, 82 years	10 days after admission for diagnosis and treatment of PUD	*C. perfringens*	Pleuritic chest pain, hemoptysis	CAD	Vomiting, ?SBO	
Buchman et al., 1991	Female, 95 years		*C. sordelli*	Admitted to hospital with chest pain and hypotension	Aortic stenosis, anemia, NYD, CHF		
Baldwin et al., 1993	Male, 53 years	2 days	*C. perfringens*	Dyspnea, cough, pleuritic chest pain	Heavy smoker		

LOC, loss of consciousness; BC, bronchiectasis, PC, pneumoconiosis; RLL, right lower lobe; GA, general anesthesia; LLL, left lower lobe; RML, right middle lobe; TB, tuberculosis; PUD, peptic ulcer disease; gpc, gram-positive coccobacilli; gpb, gram-positive bacilli; gnb, gram-negative bacilli; gpr, gram-positive rods; BPF, bronchopleural fistula; AAA, adbominal aortic aneurysm; CHF, congestive heart failure; LUL, left upper lobe; RUL, right upper lobe; SBO, small bowel obstruction; GI, gastrointestinal; CAD, coronary artery disease; CABG, coronary artery bypass graft; HTN, hypertension; DD, developmentally delayed; SLE, systemic lupus erythematosus; gnc, gram-negative coccobacilli; PVD, peripheral vascular disease; ESRD, end-stage renal disease; SOB, shortness of breath; PND, paroxysmal noctural dyspnea; MI, myocardial infarction; VT, ventricular tachycardia; CVA, cerebral vascular accident; RA, rheumatoid arthritis; TKR, total knee replace; THR, total hip replacement; AW, alcohol withdrawal; NYD, not yet diagnosed.

lower lobe (Table 2). Ten of the 39 patients (25.6%) with *Clostridium* pleuropulmonary infections were described as having hydropneumothoraces or pyopneumothoraces (cases 7, 11, 13, 18, 21, 28, 29, 33, 36, 39). Of these patients, two were described as developing a bronchopulmonary fistula (BPF) (cases 11 and 33), and one developed a pneumothorax after mechanical ventilation was started (case 39). Autopsy findings in another patient (case 21) revealed necrotizing pneumonia of the left upper lobe, corresponding to an area on chest radiography that communicated with the pneumothorax. These findings suggest that the presence of gas in the pleural space was secondary to the parenchymal damage produced by the clostridial microorganism. Although BPF cannot be ruled out in the remaining seven patients, an alternative explanation is that gas production by the organism resulted in the accumulation of gas in the pleural space. It may be difficult to differentiate a true pneumothorax from gas produced by the organism (Bentley & Lepper, 1969).

TABLE 1. (*Continued*)

White blood cell count	Effusion (gram stain)	X-ray	Pleural effusion	Sputum gram stain/culture	Culture	Treatment	Outcome (time to death/ discharge)
11.0	Left side	LLL infiltrates, colobronchial fistula	No	Mixed flora	Sputum	Imipenem/ metronidazole, partial colectomy, LLL resection	Survived (3 months)
	Right side	RLL infiltrate/ cavitation, subpulmonary gas collection	V/Q high, probable		Pleural fluid	Penicillin/ metronidazole, chest tube drainage	Death
14.0	Left side	LLL infiltrate	No		Lung tissue	Ampicillin	Death due to cardiac arrest[d]
13.5	Right side, thin yellow	RLL infiltrate	No	Yeast, gpc, gpb	Pleural fluid	Clindamycin/ metronidazole, clindaycin/ vancomycin	Death
14.1	Left side	LLL infiltrate/ abscess, pneumothorax (after ventilation started)	No		Bronchial washing	Penicillin/ erythromycin, chest tube drainage, thoracotomy/ LLL resection	Survived (28 days)

[a]Described in report as having "pneumonia," no further details.
[b]Patient clinically in congestive heart failure on admission.
[c]Spontaneous hemothorax or pulmonary embolus.
[d]Patient died 4 hours after onset of respiratory symptoms, 10 days into hospital admission (autopsy revealed bowel infarction).

Diagnosis

Diagnosis of clostridial pleuropulmonary infections can be difficult. Sputum examination revealing gram-positive bacilli suggesting the presence of *Clostridium* was seen in only 12.8% (5/39) of patients. Only 20.5% (8/39) of patients with *Clostridium* pleuropulmonary infections had *Clostridium* species isolated from sputum specimens. Examination of the pleural fluid revealed organisms suggestive of *Clostridium* in 13 of 39 (33.3%) patients. Pleural fluid cultures positive for *Clostridium* species were present in 75% of patients. *Clostridium* species were also identified in bronchial washings (7.7%), transtracheal aspirates (5.1%), and the blood of 15.4% (6/39) of patients. Tracheal aspiration has been suggested as a method of obtaining the appropriate respiratory specimen without oropharyngeal contamination (Bartlett & Finegold, 1974). However, Lorber and Swenson (1974) demonstrated that oropharyngeal contents could still contaminate transtracheal aspirates. They con-

TABLE 2. Patient Characteristics in *Clostridium* Pleuropulmonary Infections

Age	range 2–95 years (mean 50.3)
Male	57.9% (22/38)
Mean duration of symptoms prior to diagnosis	26.0 days (range 12 hours to "several weeks")
Median duration of symptoms	7 days
Underlying illness	79.5% (31/39)
Risk factors for aspiration	38.5% (15/39)
Thoracentesis prior to development of emphysema	23.1% (3/39)
Pulomonary embolism	20.5% (8/39)
Chest x-ray	
Right lung parenchymal disease[a]	70.0% (21/30)
Lower lobe	57.1% (12/21)
Middle lobe	23.8% (5/21)
Upper lobe	9.5% (2/21)
Left lung parenchymal disease[a]	43.3% (13/30)
Upper lobe	15.3% (2/13)
Lower lobe	76.9% (10/13)
Diagnosis	
Abscess/cavitation	29/0% (9/31)
Necrotizing pneumonia	12.9% (4/31)
Pneumonitis	51.6% (16/31)
Empyema	92.1% (36/39)
Pneumothorax[b]	25.6% (10/39)
Mortality	
Overall	28.9% (11/38)
Infection-related[c]	18.4% (7/38)

[a]Some patients had more than one lung/lobe involved.
[b]Includes pyopneumothorax and hydropneumothorax.
[c]Noninfection-related deaths from acute myocardial infarction, GI hemorrhage, and pulmonary embolism.

TABLE 3. Characteristics of Pleural Fluid

Right side	65.7% (23/35)
Foul smell	53.8% (14/26)
Bloody/dark/brown	50.0% (13/26)
Purulent	34.6% (9/26)
Gas released on insertion of chest tube	7.7% (2/26)
Cloudy	3.8% (1/26)
Hydropneumothorax[a]	20.5% (8/35)
Pyopneumothorax	5.7% (2/35)

[a]Case 39 developed a pneumothorax after initiation of mechanical ventilation.

sidered an anaerobic organism to be responsible for pulmonary disease if it could be isolated from transtracheal aspirates at quantities of 10^6 cfu/mL or more. Respiratory specimens are not routinely set up for anaerobic culture, so failure to culture a microorganism from an obviously purulent specimen under aerobic conditions suggests the possibility of an anaerobic agent. Although examination of gram stains of specimens is not a reliable way to diagnose *Clostridium* infections, specimens containing the characteristic morphology of *Clostridium* in patients at risk may be useful in guiding empiric treatment and should direct the specimen to be processed so as to facilitate the recovery of anaerobic microorganisms. Bartlett and Finegold (1974) concluded "that the failure to obtain appropriate specimens and to utilize optimal techniques for their transport and cultivation accounted for a common failure to identify cases involving anaerobes."

Prognosis

Unlike the overwhelming sepsis picture seen in *Clostridium* myonecrosis (renal failure, hemolysis, and shock) infections of the pulmonary system tend to be more benign. This may be due to inactivation of the toxins by metabolically active lung tissue, sequestration of the toxins in the pleural cavity, or less toxin production by the strains responsible for infection (Kwan et al., 1983; Patel & Mahler, 1990). The mortality rate from all causes of bacterial empyema has ranged from 4% to 30% and has reached 46% depending on the case series (Sullivan et al., 1973; Finland & Barnes, 1978). The overall mortality rate in patients with *Clostridium* pleuropulmonary infections (Table 1) was 28.9% (11/38). However, it is likely that the one patient who died within 30 hours of presentation developed his empyema secondary to a pulmonary embolism

TABLE 4. Presenting Symptoms in *Clostridium* Pleuropulmonary Infections

Pleuritic chest pain	67.7% (21/31)
Dyspnea	54.8% (17/31)
Cough	41.9% (13/31)
Hemoptysis	38.7% (12/31)
Fever/chills	38.7% (12/31)
Constitutional symptoms (weight loss/night sweats)	16.3% (5/31)
Foul-smelling sputum	6.5% (2/31)

and that it was the embolism and not the infection that caused his death (Sweeting & Rosenberg, 1959). Similarly another patient died within 4 days of multiple pulmonary emboli (Mirsa & Hurst, 1980). Two other patients died of noninfectious related causes including gastrointestinal hemorrhage and a myocardial infarction. The overall infection-related mortality in *Clostridium* pleuropulmonary infections (92.1% of which were empyema) was 18.4%. The median length of stay in patients who survived their infection was 41 days (range 14-168 days), which is consistent with other causes of bacterial empyema (45.25 days; range, 1-90 days) (Vianna, 1971). Generally there was almost complete resolution of pulmonary findings on chest radiograph, only mild residual pleural thickening in a few cases (Bayer et al., 1975), and a mild restrictive defect demonstrated by pulmonary function testing (Kwan et al., 1983).

Treatment

Although decreased susceptibility of *C. perfringens* to penicillin has been demonstrated (Marrie et al., 1981; Silpa et al., 1982), penicillin-G (20 million units per day administered every 6 hours) is the treatment of choice for severe infections (including pulmonary) due to *C. perfringens, C. sordellii,* and *C. septicum* (Schwartzman et al., 1977; Brook, 1999). Certain species of *Clostridium,* including *C. ramosum, C. butyricum,* and *C. clostridiforme,* produce β-lactamases and therefore should not be treated with penicillin. Alternative choices include chloramphenicol, clindamycin, metronidazole, and vancomycin (Brook, 1999). There is evidence that treatment with agents that suppress toxin production are more rapidly bactericidal than cell-wall active agents (Stevens et al., 1987; Brook, 1999). Tetracycline, which may be inactivated in the biochemical environment of an anaerobic *Clostridium* infection, may not be the best alternative choice (Schwartzman et al., 1977). Imipenem is also considered an alternate choice, but a breakthrough has been reported during treatment of a strain of *C. septicum,* which was called "tolerant" to imipenem (Eron, 1985), and two of the strains of *C. septicum* isolated at our institution in the last year were resistant to imipenem (unpublished data). Some strains of *C. ramosum* are resistant to erythromycin and clindamycin (Tally et al., 1974). Some strains of *C. innocuum* have shown resistance to cephalosporins and have been only moderately susceptible to vancomycin (Alexander et al., 1995). Metronidazole is an antibiotic often used in the treatment of anaerobic infection. Although *Clostridium* species are generally susceptible to metronidazole, studies have shown *C. perfringens* and *C. ramosum* to have resistance rates of 17% and 24%, respectively (Staneck & Washington, 1974; Tally et al., 1974; Marrie et al., 1981; Alexander et al., 1995). Baldwin et al. (1993) suggested that the combination of metronidazole and penicillin is more efficacious than penicillin alone. Depending on the susceptibility pattern of *Clostridium* species in the hospital and community, penicillin or clindamycin are good choices for empiric therapy. However, with the increasing resistance of *Clostridium* species to various antimicrobials, susceptibility testing should be done with all isolates obtained from normally sterile sites.

All of the studies reviewed agree that the most important treatment for *Clostridium* empyema is effective surgical drainage of the infected fluid from the pleural space (Goldberg & Rifkind, 1965; Vianna, 1971; Bartlett & Finegold, 1972, 1974; Sullivan et al., 1973; Gorbach & Thadepalli, 1975; Raff et al., 1984; Bekemeyer, 1986; Patel & Mahler, 1990). Of the 29 patients who underwent treatment for *Clostridium* empyema (some patients died before treatment could be instituted), only 2 (6.9%) were effectively managed with antibiotics and repeated thoracentesis. Fourteen of the 29 (48.3%) were managed with antibiotics and closed chest tube drainage, three of whom died. Eight of the 29 (27.6%) required surgical procedures to definitively manage their infections (including thoracotomy, decortication, and lobe/lung resection). The use of hyperbaric oxygen is also controversial (Brook, 1999), but it may enhance treatment through direct bactericidal effects or enhancement of oxygen-dependent killing (Kwan et al., 1983).

Eikenella

The genus *Eikenella* has a single member, *Eikenella corrodens,* which is a gram-negative, nonmotile, capnophilic, fastidious, slow-growing, facultative

anaerobe that produces a characteristic colony (Holmes et al., 1995). Henriksen (1948) and later Holm (1950) reported isolation of "the corroding bacillus," so named because "its colonies when seen with the naked eye, resemble small, mat, corroded patches on the glistening surface of the blood agar" (cited in Eiken, 1958). Eiken (1958) was the first to fully characterize this corroding bacillus from various oral isolates and sputum and gave it the name *Bacteroides corrodens.* There were actually two organisms in this group, which had different growth conditions and were genetically distinct. One of the organisms described by Eiken was a facultative anaerobe and had different guanine-cytosine ratios within its genome, compared to the *Bacteroides* spp. It was therefore given its own genus designated *Eikenella* (Joshi et al., 1991). The other species, an obligate anaerobe, was later renamed *Bacteroides ureolyticus.* By using 16S rRNA sequencing and DNA–RNA hybridization techniques, a phylogenic relationship between *Neisseria* species and *Eikenella* was identified, leading to *Eikenella's* inclusion in the Neisseriaceae family (Koneman et al., 1997a).

Eikenella is a normal part of human oral flora and is often associated with dental plaque (Chen et al., 1989; Listgarten et al., 1993). It has a number of virulence factors that enhance pathogenicity. The generation of hemagglutinins and pili facilitate adherence to the surface of epithelial cells, and the production of a slime layer may inhibit phagocytosis. Like other gram-negative bacteria, it has endotoxin as part of its membrane. It also possesses an outer membrane protein that is able to precipitate the release of lysosomal enzymes by macrophages (Koneman et al., 1997a). *Eikenella* has been implicated as a cause of periodontal pathology, endocarditis, meningitis, subdural abscess, sinusitis, and osteoarthritis and human bite wound infections (Dudley et al., 1978; Sinkovics et al., 1979; Chen et al., 1989; Holmes et al., 1995). Its association with pulmonary infections is more controversial because of its infrequent isolation, particularly in pure culture. Of the 140,000 samples processed in a Boston hospital laboratory over a 1-year period there were 72 patients who had samples from which *Eikenella* was isolated, only one of which yielded *Eikenella* in pure culture. This may be due to its fastidious nature and tendency to become overgrown by other flora. Isolation and identification is further complicated by the fact that the characteristic colony morphology is seen in only approximately 45% of *Eikenella* isolates. Despite this, more than 175 pleuropulmonary isolates were reported in the literature up until 1979 (Goldstein et al., 1979).

Joshi et al. (1991) reviewed all the published reports of *Eikenella* pleuropulmonary infections since 1970. Only 24 reports gave enough detailed clinical information to allow an appropriate review. *Eikenella* pulmonary infections occurred in a bimodal age distribution in individuals who were at risk for aspiration and had underlying immunosuppression or diseases that compromise local defense mechanisms within the lung. Of the 24 cases, 72% were over 44 years of age and 20.8% were between 6 months and 14 years. The majority of children were free of any underlying medical conditions; however, *Eikenella* pneumonia was seen in children with Down syndrome or cerebral palsy (St. John et al., 1981; Joshi et al., 1991). In adults only 15.7% (3/19) were without any obvious predisposing factors. The most common underlying condition was malignancy (42%), particularly pleuropulmonary malignancy (31.5%). Other associated conditions included alcoholism, chronic lung disease, steroid use, polymyositis, and cerebrovascular accidents. None of these patients were intravenous drug users, which has been an associated risk factor for *Eikenella* skin infections and endocarditis (Silpa & D'Angelo, 1980). Although this organism is a common member of normal oral flora, periodontal disease or recent dental manipulation was not mentioned as a risk factor for pneumonia (Joshi et al., 1991).

Eikenella was identified most commonly in empyema fluid (54.2%) but was also found in tracheal aspirates (29.2%), blood (8%), lung biopsy, and lung abscess specimens. Most of the time (58%), it was present in mixed culture with one or more of the following microorganisms: microaerophilic streptococcus, Viridans streptococci, *Staphylococcus aureus,* or *Prevotella melaninogenicus. Eikenella* was isolated in pure culture in only 42% of cases. Pathologically, its association with other bacterial species in mixed infections may be coincidental. However, there is evidence of a synergistic action between microaerophilic and Viridans streptococci and *Eikenella* in infection, particularly

in abscess formation (Joshi et al., 1991; Stone, 1992).

Clinically, patients with *Eikenella* pneumonia presented with fever, cough, and pleuritic chest pain. Only 8.3% were described as producing sputum. There were four common radiological presentations including pneumonia, pleural effusion/empyema, cavitation, or a combination of these findings. Although these findings were acute, Killen et al. (1996) reported a case of *Eikenella* causing a chronic infection extending from the pleural space to the soft tissues in the chest wall that required chronic suppressive antibiotic therapy.

Seventy-four percent of patients improved with treatment and 26% died. However, of the five patients who died, three died from their underlying illness rather than from *Eikenella* infection (Joshi et al., 1991).

Eikenella is resistant to clindamycin, metronidazole, aminoglycosides, anti-staphylococcal penicillins, and first-generation cephalosporins (Joshi et al., 1991). It is usually resistant to erythromycin and clarithromycin but is sensitive to azithromycin (Chen et al., 1999). Despite the rare isolation of strains that produce β-lactamase (Trallero et al., 1986, Lacroix & Walker, 1991), the vast majority of strains are sensitive to penicillin which remains the treatment of choice for *Eikenella* infections (Goldstein & Citron, 1984; Goldstein et al., 1980, 1986). *Eikenella* that are resistant to penicillin owing to β-lactamase production can be effectively treated with antibiotics containing β-lactamase inhibitors (Lacroix & Walker, 1991) or third-generation cephalosporins. Alternative treatment choices include fluoroquinolones, trimethoprim–sulfamethoxazole, chloramphenicol, tetracycline, and rifampin (Goldstein et al., 1986; Chen et al., 1999).

Listeria

Introduction

Listeria are facultative, anaerobic, nonspore-forming, short, gram-positive bacilli that have a characteristic "tumbling" motility. *Listeria* was first described by Murray et al. in 1924 as *Bacterium monocytogenes* after it was shown to induce a monocytosis in infected rabbits (a manifestation that is rarely seen in humans). In 1929 this organism was isolated from a patient who was believed to have infectious mononucleolus, leading to the conclusion that *Bacterium monocytogenes* could be the causal agent in this disease (Buchner & Schneierson, 1968). In honor of Lord Joseph Lister, the name was changed to *Listeria* monocytogenes in 1940 (Gellin & Broome, 1989). The appearance of *Listeria* in gram stains can be pleomorphic and assume palisade forms or may present as coccobacilli in pairs. These variable morphological features can cause them to be mistaken for diphtheroids or *S. pneumoniae.* In addition, if the gram stain is overdecolorized *Listeria* can be mistaken for Haemophilus species (Lorber, 1997; Koneman et al., 1997c). Group B streptococci can also be confused with *Listeria.* Both microorganisms are isolated in similar clinical situations, produce similar colonies with a small zone of β-hemolysis on blood agar, and hydrolyze sodium hippurate. Although both microorganisms are CAMP test positive with CAMP, group B *Streptococcus* typically produce an arrowhead zone of accentuated hemolysis, whereas *Listeria* produces a rectangular reaction. Other key distinguishing features that differentiate *Listeria* from group B *Streptococcus* are a positive catalase test and its ability to grow at 4°C. Although the genus *Listeria* contains seven species, *L. monocytogenes* is the predominant human pathogen. *L. monocytogenes* can be divided into 16 serotypes based on different cellular (O) and flagellar (H) antigens, with serotypes 1/2a, 1/2b and 4b being responsible for the majority of human diseases (Lorber, 1997).

Pathophysiology

Listeria are intracellular pathogens and have a number of essential virulence factors including internalin, listeriolysin O, Act A, and iron. Internalin is a cell surface protein that interacts with receptors on epithelial surfaces resulting in phagocytosis of the microorganism. Once internalized, a hemolytic and cytolytic protein (listeriolysin O) binds to cholesterol and disrupts the membrane of the phagosome, leading to release into the cytoplasm. The release of iron from ferritin-like proteins during the breakdown of these membranes will enhance the intracellular growth of the organism (Lamont et al.,

1988). Once in the cytoplasm, *Listeria* uses Act A to promote actin filament assembly leading to the formation of filopods. Filopods are finger-like projections of the cell membrane that contain bacteria that can be ingested by cells belonging to the monocyte-macrophage lineage. This sequesters *Listeria* from the immune system and allows infection to be perpetuated from cell to cell fashion (Lorber, 1997).

Epidemiology

Listeria has can be found throughout the environment in soil, decaying vegetable matter, sewage, water, and animal feeds. It has been considered a zoonosis. *Listeria* has been isolated from wild and domestic mammals and avian species and is the causal organism in "circling disease" of sheep (Gellin & Broome, 1989). Human disease is rare. Cutaneous infection has been reported in a veterinarian following occupational exposure to the microorganism (Buchner & Schneierson, 1968). In 1983, foodborne transmission was clearly established when a *Listeria* outbreak was traced to contaminated coleslaw (Schlech et al., 1983). Since that time *Listeria* infection has been implicated with the ingestion of a variety of contaminated foods including unpasteurized milk or cheeses, processed meats or coleslaw, shellfish, or raw fish (Gellin & Broome, 1989; Lorber, 1997). This relationship was further consolidated by studies from the Centers for Disease Control and Prevention (CDC), which involved an active surveillance of listeriosis in a population of 18 million people. Eleven percent of all foods sampled had positive cultures for *L. monocytogenes.* During an outbreak, 63% of the infected patients had *Listeria* isolated from food in their refrigerators, with half of these isolates matching those recovered from the patients. Soft cheeses, deli meats (ready-to-eat foods), and raw or undercooked chicken had the highest rates of contamination. Consumption of undercooked chicken was a particular risk factor in immunosuppressed patients (Schuchat et al., 1992; Pinner et al., 1992).

Listeria is capable of colonizing the human gastrointestinal tract and 1% to 5% of healthy people can be asymptomatic carriers. Close contacts of infected patients can have carriage rates of 11%. Up to 21.6% of healthy renal transplant recipients and 26% of symptomatic patients have been shown to shed *Listeria* in their stool (Stamm et al., 1982; Schlech et al., 1983; Armstrong, 1995). *Listeria* has occasionally been isolated from the vagina, cervix, and pharynx (Lamont et al., 1988). Although not the most common mode of transmission, patient-to-patient transmission has been implicated in some outbreaks (Stamm et al., 1982). The incidence of infection varies with the season. Animals develop *Listeria* infections in late winter and early spring, whereas humans tend to develop them from July to October. This seasonal variation remains unexplained (Stamm et al., 1982). The annual incidence of listeriosis is 7.4 cases per million population but it occurs more commonly in neonates and the elderly (Schuchat et al., 1992).

Listeria probably causes infection after first successfully colonizing the bowel. Not surprisingly, the higher the inoculum of *Listeria,* the higher the chance for developing disease (Pinner et al., 1992). Infection may be enhanced by elevation of gastric pH (secondary to surgery or medications such as antacids or H_2 blockers), laxative use (Schuchat et al., 1992), or concurrent infection with another gastrointestinal pathogen that may facilitate passage across the mucosa (Mascola et al., 1988; Lorber, 1997). However, a preexisting defect in the mucosa is not necessary for the organism to enter the host. As mentioned above, internalin facilitates entry into epithelial cells when the mucosa is intact.

Clinical Features

Listeriosis typically manifests as sepsis or central nervous system disease with meningitis or meningoencephalitis. Although pleuropulmonary *Listeria* infections are common in newborn infants (secondary to aspiration of infected amniotic fluid), they are rare in adults (Gellin & Brome, 1989). In 1066 cases of pleural infection published in the literature from 1971 to 1987 there were no cases secondary to *L. monocytogenes* infection. Mazzulli and Salit (1991) reviewed nine cases of pleural fluid infection caused by *L. monocytogenes* reported in the literature to 1990. Eighty-nine percent of the patients had an underlying hematological malignancy including leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. Eighty-nine percent (8/9) of the patients were male and 78% were older than 58 years of age. The effusions were nonspecific and

could be either unilateral or bilateral. The majority of patients had fever and respiratory symptoms and 71% were bacteremic. The overall mortality was 44% (4/9 patients), which is significantly higher than the mortality rate seen with other causes of empyema (15%). Interestingly, all patients with acute presentations survived, whereas those with a more chronic course died. In general pleural infections are most commonly secondary complications to an underlying pulmonary infection; however, 44% (4/9) of patients with *Listeria* pleural infection had effusions with no evidence of parenchymal disease (Mazzulli & Salit, 1991). The underlying etiology of these effusions was malignant and Mazzulli and Salit (1991) suggested that a transient bacteremia seeded these effusions, leading to infection.

As with pleural infections, pneumonia is also quite rare. Only 13 cases have been reported in the literature. Of the seven adult patients who developed *Listeria* infections during an outbreak in the Maritime Provinces of Canada, one had pneumonia documented as the primary site of infection. All seven patients had been previously healthy (Schlech et al., 1983). Pneumonia was identified as the primary site of 2 of 11 cases of invasive *Listeria* infections in the results of a recent population-based surveillance study (Senzilet et al., 1998). Domingo et al. (1992) reviewed eight cases of *Listeria* pneumonia published up to 1992. Only one of the eight patients was previously in good health. The remaining patients had underlying medical conditions including malignancy (Hodgkin's disease, lung and colon carcinoma), pregnancy, alcohol abuse, diabetes, and AIDS. The clinical presentation was non-specific and similar to pneumonia due to other bacterial pathogens. Although there was a slight predisposition for involvement of the right lower lobe (4/6 who had location described), other areas of the right and left lung were involved. Effusion was a complicating finding in 37.5% (3/8) of patients. The predominant serotype was *L. monocytogenes* 4b and the overall mortality was 12.5%. The most important prognostic factor was the degree of underlying immunosuppression. Although age is considered a risk factor for *Listeria* infections (Hedderwick et al., 1997), the average age of these patients was only 39 years (range 20–74 years).

In contrast, Hedderwick et al. (1997) published a case report *of Listeria* pneumonia in a 74-year-old man who had been receiving high-dose prednisone for the treatment of temporal arteritis, and Garcia-Montero et al. (1995) reported a case of *Listeria* pneumonia in an 87-year-old woman who was previously healthy. The incidence of *Listeria* infections in patients 70 years of age is up to 21 cases per million population (Hedderwick et al., 1997). Mazzulli and Salit (1991) suggest that the increase in *Listeria* infection with increasing age is multifactorial. The incidence of atrophic gastritis, malignancies, use of immunosuppressive agents, and pleural effusion increases with advancing age. On admission the elderly woman described by Garcia-Montero et al. (1995) had a low total lymphocyte count and she was anergic. Garcia-Montero et al. suggest that malnutrition could have contributed to the cutaneous anergy and abnormal lymphocyte count. Animal studies, however, have demonstrated that protein deprivation did not affect the hosts' ability to deal with intracellular pathogens including *Listeria* (Jakab et al., 1981).

Although patients with HIV infection are prone to infections that depend on the cell-mediated arm of the immune system, *Listeria* is not a common pathogen in these patients. Up until 1991 there had been only 20 published reports of listeriosis in HIV patients, with no cases of pneumonia as the primary infection (Berenguer et al., 1991). Domino et al. (1992) has described the only case *of Listeria* pneumonia in a patient with AIDS. Despite the low incidence of *Listeria* infections in patients with HIV, it is higher than that in the general population. Juardo et al. (1993) estimated the incidence of *Listeria* infection in HIV patients in the Atlanta area to be 52 cases per 100,000 HIV-infected patients per year, which is more than 60 times that in the general population. The incidence in individuals with AIDS was 115 cases per 100,000 per year. The majority of infections were due to serotype 4b and the average CD4 count in the HIV-infected patients was 40/μL. The mortality in this group of HIV patients was 29%, compared with 17% among *Listeria* infections in the general population. With the routine use of trimethoprim–sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia (PCP), the incidence of other bacterial infections that are susceptible to trimethoprim-sulfamethoxazole has decreased. This factor along with avoidance of high-risk foods

may explain the low incidence of *Listeria* infections in patients with HIV. None of the patients with HIV and *Listeria* infections in one series were receiving trimethoprim–sulfamethoxazole prophylaxis (Juardo et al., 1993). There is some suggestion that factors other than CD4 T-cell immunity that contribute to protection against *Listeria* infections may still be intact in patients with HIV. Animal models of *Listeria* pneumonitis suggest that both specific and nonspecific immunity are important in combating infection (Lefford et al., 1978). Dunn and North (1991) demonstrated that thymectomized mice that were depleted of $CD4^+$ and $CD8^+$ lymphocytes were capable of resisting *Listeria* infection, suggesting that a T-cell subset other than the CD4 cells affected by HIV may be responsible for combating *Listeria* infections. Beckerman et al. (1993) showed that macrophages were capable of being activated in a T-cell-independent manner that is important in combating *Listeria* infections in mice.

An important group of patients that are predisposed to *Listeria* infections are those who have undergone organ transplantation. Stamm et al. (1982) reviewed 102 cases of listeriosis in renal transplant patients published in the literature between 1971 and 1980, including six cases discovered during a nosocomial outbreak. Pneumonia was present in 7% (7/102) of these patients, with a 71.4% (5/7) mortality rate. Radiographic manifestations included consolidation with cavitation, focal or interstitial infiltrates, or a miliary pattern. Histology revealed varying manifestations including necrotizing granulomas and infarction, bronchopneumonia, abscess formation, and miliary disease. Concurrent pulmonary infection with cytomegalovirus was identified at autopsy in one patient. Graft rejection and its management were identified as risk factors for developing listeriosis (Stamm et al., 1982). Transplant recipients are subjected to substantial amounts of immunosuppressive medications, including prednisone, cyclosporin, FK-506, methylphenidate, rapamycin, azathioprine, and anti-lymphocyte antibodies. The cumulative effect of these medications is to prevent graft rejection by blunting the host's immune response. As an intracellular pathogen, *Listeria* can persist in members of the monocyte-macrophage lineage. The cell-mediated arm of the immune system, particularly sensitized T lymphocytes, are essential in activating the macrophage system to allow efficient phagocytosis and killing of these microorganisms. Many of these medications inhibit the cell-mediated arm of the immune system (Stamm et al., 1982). Patients who did not receive cotrimoxazole prophylaxis during OKT3 treatments were at increased risk for *Listeria* infections (Oh et al., 1988). Lambertus et al. (1990) reported a case of listeriosis in a patient with AIDS that developed 1 week after completion of glucocorticoid therapy as part of treatment for PCP. Animal experiments have demonstrated that local cell-mediated immunity in the lung is essential in overcoming *Listeria* infection. Using a guinea pig model *of Listeria* pneumonia, Blackwood and Pennington (1982) demonstrated that glucocorticoids had a dose-dependent effect on pulmonary defenses. The animals that received high-dose steroids were unable to limit the infection to the lungs, the alveolar macrophages had a reduced killing capacity compared to an equal number of control animals infected with the same number *of Listeria* organisms, and all the animals receiving the high dose died. The animals that received the low-dose steroids were eventually able to mount a defense against the microorganisms but it was delayed compared to the steroid-free controls. Miller and Hedburg (1965) showed that the LD_{50} in mice could be reduced from 10^4–10^5 *Listeria* to <50 microorganisms with only 12 to 16 mg of hydrocortisone.

Diagnosis

Diagnosis *of Listeria* pneumonia is difficult, as sputum samples are unreliable. The morphologic characteristics of *Listeria* are variable and can resemble diphtheroids, microorganisms that are typically disregarded in clinical respiratory specimens (Buchner & Schneierson, 1968). In the eight patients reviewed by Domingo et al. (1992), only two were diagnosed with positive respiratory cultures. Only two of seven renal transplant patients with *Listeria* pneumonia had positive sputum or lung cultures (Stamm et al., 1982). The majority of patients had clinical radiographic and histological evidence of an acute pulmonary infection with positive blood cultures. Cold enrichment (growth at 4°C) and the use of selection media can be used to isolate this microorganism from a polymicrobial sample.

Using DNA hybridization techniques, a DNA probe specific for a unique sequence in the 16S rRNA region is available for rapid identification of colonies suspected of being *Listeria* (Ninet et al., 1992). Truncated forms of the listeriolysin O protein have been developed and are sensitive and specific when used in the serologic diagnosis of listeriosis. In the future, these proteins may be incorporated into solid-phase enzyme immunoassays to help facilitate diagnosis of *Listeria* infection (Gholizadeh et al., 1996). Polymerase chain reaction technology is being used to identify *Listeria* in cerebrospinal fluid (CSF) and tissue. The anti-listeriolysin gene, the invasion-associated protein gene *(iap),* or sequences of the 16S rRNA have been used as potential amplification targets (Jaton et al., 1992; Greisen et al., 1994).

Treatment

The mortality for untreated *Listeria* infections exceeds 70% (Whitelock-Jones et al., 1989). There have been no clinical trials examining the treatment *of Listeria* pneumonia. In fact there is a distinct lack of clinical trials examining the appropriate duration and type of treatment in any *Listeria* infection (Parkas & Armstrong, 1999). Ampicillin has been the antibiotic of choice in treating *Listeria* infections (Lober, 1997). Both ampicillin and penicillin are bacteriostatic against *Listeria.* The combination of ampicillin and gentamicin has been shown to be synergistic (Moellering et al., 1972; Azimi et al., 1979; Scheld, 1983). Despite the fact that gentamicin is often a poor antibiotic for the treatment of intracellular pathogens, clinical experience has been favorable with this combination (Hof et al., 1997). There is in vitro evidence of a delayed bactericidal activity of these antibiotics in CSF (Winslow et al., 1983; Lorber, 1997). Combination therapy with ampicillin and an aminoglycoside is the regimen of choice for meningitis, rhomboencephalitis, endocarditis, neonatal infection, and bacteremia in immunosuppressed patients. However, ampicillin can be used alone in the treatment of bacteremia in immunocompetent individuals. In patients who cannot be treated with penicillin, trimethoprim–sulfamethoxazole (15 mg/kg/day divided every 6 hours), which has equivalent bactericidal activity against *Listeria* compared to ampicillin and aminoglycoside combination therapy, is an appropriate second choice (Hof et al., 1997; Lober, 1997; Parkas & Armstrong, 1999). Although vancomycin is bacteriostatic alone, it is synergistic and bactericidal in combination with an aminoglycoside (Parkas & Armstrong, 1999). There is some clinical evidence that this combination is also successful in treating *Listeria* infections, but treatment failures have also been reported (Hof et al., 1997; Parkas & Armstrong, 1999). Chloramphenicol, tetracycline, and erythromycin are all bacteriostatic against this microorganism. Chloramphenicol should no longer be used to treat listeriosis, as there is an increased rate of failure and a high mortality rate. Due to their bacteriostatic nature, macrolides and tetracycline are also not recommended (Parkas & Armstrong, 1999). Cephalosporins are not active against this microorganism and are associated with clinical failure and therefore contraindicated. There are data that suggest that imipenem/cilastatin has some activity against *Listeria* in vitro, but animal data suggest that imipenem/cilastatin is not as efficacious as ampicillin (Kim, 1986). Ciprofloxacin is not very effective against *Listeria* (Andriole, 1989). Rifampin is bactericidal against *Listeria* and is an antibiotic with good intracellular killing capability; however, clinical experience with it is limited (Gellin & Broome, 1989; Parkas & Armstrong, 1999). Data from animal models suggest that the combination of rifampin and penicillin was no better than penicillin alone, while other data indicate that the combination is antagonistic (Winslow et al., 1983; Scheld, 1983). A similar antagonistic effect has been shown with the combination of rifampin and trimethoprim–sulfamethoxazole (Winslow et al., 1983).

Antibiotic resistant *Listeria* strains are rare. Plasmid-mediated antibiotic resistance was first described by Poyart-Salmeron et al. (1990). Between 1988 and 1994, 70 strains were reported resistant to tetracycline, streptomycin, erythromycin, and trimethoprim–sulfamethoxazole (MacGowan et al., 1990; Charpentier et al., 1995). Charpentier et al. (1995) screened 1100 *Listeria* specimens collected worldwide and found 57 isolates of *L. monocytogenes* that were resistant to tetracycline and monocycline, 3 isolates resistant to low levels of streptomycin, and one resistant to trimethoprim–sulfamethoxazole. The tetracycline-resistant strains were found to

contain *tet*(M), a gene that may have been transferred from other more common gastrointestinal bacteria such as streptococci or enterococcal species via conjugative transposons (Charpentier et al., 1995). The trimethoprim–sulfamethoxazole resistance was secondary to a yet undefined gene and could not be transferred to other *Listeria.* The resistance to streptomycin was due to ribosomal mutations.

The duration of treatment is not well established. In a small case series, HIV-infected patients with listeriosis were effectively treated with 20 days of antibiotic therapy. None of these patients developed a relapse (Mascola et al., 1988). Lorber (1997) suggests that *Listeria* bacteremia can be treated with 2 weeks of therapy, meningitis with 3 weeks of therapy, and endocarditis and rhomboencephalitis or brain abscess with 4 to 6 weeks of treatment. In a review of eight patients who were cured with trimethoprim–sulfamethoxazole the average treatment duration was 28.8 days (range, 14–49 days) (Spitzer et al., 1986).

Listeria pneumonia should be considered in any patient who has underlying immune deficiency (particularly hematological malignancy) presenting with a clinical picture suggestive of a bacterial pneumonia. Isolation of gram-positive bacilli in the sputum of these patients should be viewed with suspicion and the sputum should be tested for *Listeria.* The treatment of *Listeria* pneumonia should consist of high-dose ampicillin or trimethoprim–sulfamethoxazole (15 mg/kg/day divided every 6 hours). The duration of treatment should be a minimum of 3 weeks. Since iron is a virulence factor and iron excess is associated with an increased incidence of *Listeria* infection, iron supplementation should be withheld during the treatment period (Lorber, 1997). To prevent infection with *Listeria,* prophylaxis with trimethoprim–sulfamethoxazole in patients taking immunosuppressants should be considered (Oh et al., 1988). To prevent acquisition and subsequent infection, high-risk patients (patients with malignancies or HIV, those taking corticosteroids, or pregnant patients) should avoid exposure to *Listeria.* The CDC has established dietary restrictions for patients at risk for *Listeria* infection (Schuchat et al., 1992):

- Avoid eating raw or partially cooked foods of animal origin.
- Avoid cross-contamination between raw and cooked foods during food preparation and storage.
- Reheat leftovers until they are too hot to touch.
- Avoid soft cheeses such as feta and Mexican-style cheeses. Hard cheese, cottage cheese, and cream cheese can be eaten without concern about the risk of listeriosis.
- Wash raw vegetables thoroughly before eating.

Neisseria

Introduction

Bacteria within the family *Neisseriaceae* are nonmotile, oxidase-positive, capnophilic, gram-negative coccobacilli, occurring in short chains or pairs that can be "kidney-shaped." Both pathogenic and nonpathogenic species are commonly isolated as part of the normal flora of the upper respiratory tract and genital tract. The so-called nonpathogenic species include *N. lactamica, N. cinerea, N. mucosa, N. sicca, N. subflava,* and *N. flavescens.* The most common pathogenic species in this genus are *N. meningitidis* and *N. gonorrhoeae.* Both organisms possess hair-like proteins called pili that are essential for adherence to epithelial surfaces in the nasopharynx and genital tract. If these proteins are absent or blocked by antibodies, attachment and thus infection are prevented. Other virulence factors produced by pathogenic *Neisseria* spp. include a protease capable of splitting and potentially neutralizing immunoglobulin A as well as enzymatic methods of releasing iron and a hemoglobin-binding protein, both of which are essential requirements for the establishment of infection (Koneman et al., 1997b). The capsular polysaccharide, another important virulence factor in *N. meningitidis,* surrounds the microorganism and prevents opsonization and phagocytosis. The variation in the antigenic composition of this capsule is used to separate *N. meningitidis* into 13 serogroups, which can be divided further into serotypes based on distinct antigenic outer membrane proteins. The polysaccharide component in serogroup B is antigenically homologous to neuraminic acid found in

the human central nervous system and is therefore not recognized by the immune system.

Although *Neisseria* species are common commensal organisms within the human oropharynx and are often disregarded in clinical respiratory tract specimens, both nonpathogenic and pathogenic species of *Neisseria* have been implicated in CAP. *Neisseria* species have been isolated as part of a polymicrobial infection in patients with suspected aspiration pneumonia (Jordan et al., 1976; Gonzalez & Calia, 1975; Marrie, 1993). *N. cinerea* was isolated from the blood in a young boy with pneumonia who was otherwise healthy (Southern & Kutscher, 1987). Three cases of pneumonia caused by *N. sicca* were reported in patients who were relatively immunosuppressed (Gilrane et al., 1985), and *N. mucosa* has been implicated as the causal agent in cases of pneumonia and empyema (Herbert & Ruskin, 1981; Manser & Warner, 1987). *N. gonorrhoeae,* typically associated with sexually transmitted disease, has been reported as the causal agent in a fatal case of CAP and empyema in a 62 year old woman with underlying emphysema and coronary artery disease (Enos et al., 1980). The most common member of the genus *Neisseria* isolated in cases of pneumonia is *N. meningitidis.*

Neisseria meningitidis Pleuropulmonary Infections

Clinical Presentation *N. meningitidis* is found only in humans and is transmitted by respiratory droplets (Koneman et al., 1997b; Cartwright, 1999). The microorganism must first colonize the nasopharynx. If the host generates an immune response against the microorganism, asymptomatic colonization is the result; otherwise an infection ensues (Cohen et al., 1979). The microorganism can be identified in the nasopharynx of asymptomatic individuals. Carriage rates are 4.9% to 31% in nonmilitary personnel, up to 20% in homosexual males, and 40% to 60% in military recruits (Putsch et al., 1970; Canby, 1970; Cohen et al., 1979; Nitta et al., 1993). *N. meningitidis* has been recovered by transtracheal aspiration of endobronchial secretions in patients with chronic bronchitis and no evidence of acute illness or pneumonia (Jordan et al., 1976).

Primary meningococcal pneumonia has been defined as "a pneumonia caused by *N. meningitidis* without evidence of concomitant meningeal involvement or the Waterhouse-Friderichsen syndrome" (Jones et al., 1997). The first case reports of pneumonia secondary to *N. meningitidis* date back to 1906 (Putsch et al., 1970). Traditionally it was believed that meningococcal pneumonia was the result of secondary metastatic spread from a transient bacteremia in a patient with pharyngeal colonization. However, evidence now suggests that infection occurs from inhalation rather than hematological spread (Irwin et al., 1975). Although often severe, community-acquired meningococcal pneumonia is considered rare. Studies examining the epidemiology and prognostic factors in severe CAP requiring intensive care admissions do not identify *N. meningitidis* as a causal agent (Dahmash & Chowdhury, 1994; Torres et al., 1991; Almirall et al., 1995).

Stephens et al. (1995) conducted a prospective population-based surveillance in the Atlanta metropolitan area from 1988 to 1993 of cultures of sterile sites that were positive for *N. meningitidis.* They found that 23% (10/44) of the sporadic cases of meningococcal disease in adults were due to meningococcal pneumonia. Seventy percent of these patients were over 50 years of age and all were diagnosed on the basis of typical signs and symptoms for pneumonia with positive blood cultures. Using previous data that suggested that only 30% of patients with cases of *N. meningitidis* pneumonia are bacteremic, they estimated the incidence of meningococcal pneumonia to be approximately 0.4 cases/100,000 adults per year. Pneumonia did not occur in patients aged 18 to 24 years and none of the patients were described as "septic" or exhibited a rash typical of meningococcemia. The lack of the typical purpuric rash seen in meningococcemia is a common theme in the cases described in the literature (Meltzer & Kneeland, 1957; Paine et al., 1967; Ball & Young, 1974; Jacobs & Norden, 1974; Irwin et al., 1975; Koppes et al., 1977; Hersh et al., 1979; Brandstetter et al., 1981; Witt & Olans, 1982; Hanson & Lawson, 1985; Jones et al., 1997). Stephens et al. (1995) suggest that absence of the rash may be due to lower levels of bacteremia or less virulent strains. Although leukocytosis is the predominant finding, neutropenia has been found and is associated with severe disease (Koppes et al., 1977). Ball and Young (1974) reported a case of *N. meningitidis* pneu-

monia associated with leukopenia. They suggested that the leukopenia was likely the result of overwhelming sepsis and may represent a poor prognostic sign as it does in pneumococcal pneumonia.

The presentation of *N. meningitidis* pneumonia is nonspecific and cannot be distinguished from other causes of pneumonia based on clinical or radiological findings (Knoppes et al., 1977; Rose et al., 1981). Patients typically present with fever, cough, chest pain, and dyspnea with radiological evidence of alveolar infiltrates (rather than interstitial involvement) in either or both lungs (Koppes et al., 1977; Berkman, 1980). Lung cavitation and effusion may also be found (Koppes et al., 1977; Berkman, 1980). The prevalence of serogroups has evolved with time. Initially group A was predominant, followed by B and C. The majority of reports after 1970 suggest group Y is the most common, but group W-135 has been increasingly more common (Galaid et al., 1980; Berkman, 1980; Brandstetter et al., 1981; Witt & Olans, 1982; Stephens et al., 1995; Jones et al., 1997; Koppes et al., 1977). In a review of 58 cases of meningococcal pneumonia reported in the literature from 1974 to 1998, 44.2% were identified as serogroup Y; 19.2% were serogroup W-135; 17.3% were serogroup B; 15% were serogroup C; and 3.85% were serogroup Z (Winstead et al., 2000). Koppes et al. (1977) suggest that pneumonia is the predominant manifestation of group Y disease and that this group may be less virulent than other serogroups. The mortality rate for patients in this series with serogroup Y meningococcal pneumonia was 1.1% compared with 4% to 7% in other reports of pneumonia due to serogroups B or C. Since up to 90% of incoming military recruits have bactericidal antibodies to serogroup Y *N. meningitidis* (Smilack, 1974), Yee et al. (1975) suggest that a higher prevalence of group Y antibodies in the community may protect against more severe systemic disease.

Predisposing conditions to *N. meningitidis* pneumonia include aspiration and immunosuppression (Stephens et al., 1995; Jones et al., 1997). Meningococcal pneumonia has been found in patients with hypogammaglobulinemia (Salit, 1981), systemic lupus erythematosus (Brandstetter et al., 1981), malignancy (Cohen et al., 1979), selective IgA deficiency (Hersh et al., 1979), multiple myeloma (Righter, 1981; Hanson & Lawson, 1985), and HIV infection (Winters et al., 1991). Stephens et al. (1995) estimated the annual incidence of sporadic meningococcal disease in patients with HIV to be 11.2 per 100,000 adults, with a relative risk of 28.2 compared to the general population. However, there have only been three documented cases of *N. meningitidis* pneumonia in patients with HIV (Winters et al., 1991; Nitta et al., 1993; Stephens et al., 1995). The reasons for this are not clear. Patients with HIV are known to have deficiencies in the humoral arm of the immune system that put them at risk for pneumococcal disease (Nitta et al., 1993). However, Nitta et al. (1993) suggest that complement-mediated bacteriolysis of gram-negative organisms such as *N. meningitidis* in patients with HIV and normal complement levels may be more important than the humoral aspect of immunity. It is well known that patients who have complement deficiencies for any reason are predisposed to meningococcal disease (Apicella, 1995). However, complement deficiency was not identified as a predisposing condition in 58 cases reviewed by Winstead et al. (2000).

The association of meningococcal pneumonia in patients with underlying viral illness is well documented. During the "Spanish flu" pandemic of 1918-1919, 121 cases of N. *meningitidis* pneumonia were reported in patients with underlying influenza A, with a 48% (53/121) mortality rate (Putsch et al., 1970). *N. meningitidis* has since been implicated as one of the causal agents in bacterial pneumonia superinfecting patients with influenza, measles, or adenoviral pneumonia, particularly among military recruits (Young et al., 1972; Ellenbogen et al., 1974; Olson & Hodges, 1975; Gremillion & Crawford, 1981). Young et al. (1972) suggest that influenza may "enhance the acquisition" of pathogenic *N. meningitidis,* thus predisposing to colonization and infection. Gremillion and Crawford (1981) reviewed 106 cases of measles pneumonia in military recruits and found that 30.3% of cases became superinfected with bacterial pneumonia. *N. meningitidis* was the causal agent in 26% of the cases of documented bacterial pneumonia, the second most common etiology after *H. influenzae.* Bacterial superinfection typically occurred 5 to 10 days after onset of rash. The association of meningococcal pneumonia and viral illness is not fully understood. Adenoviral infection impairs the polymorpho-

nuclear (PMN) cell's ability to kill *N. meningitidis* (Silva et al., 1972). PMN cell defense is important in fighting a meningococcal infection and thus patients with adenoviral infection are more susceptible to meningococcal infection (Paine et al., 1967; Silva et al., 1972).

Diagnosis

Diagnosis can be difficult as identification of the microorganism in sputum may not necessarily distinguish colonization from infection (Putsch et al., 1970). Although meningococcal pneumonia has been correctly diagnosed from sputum cultures (Brandstetter et al., 1981), most *Neisseria* species are common members of normal pharyngeal flora so they are often disregarded in sputum cultures. In the majority of cases the diagnosis of meningococcal pneumonia is made by the isolation of N. *meningitidis* from the blood of a patient with signs and symptoms of pneumonia (Jones et al., 1997; Stephens et al., 1995; Gremillion & Crawford, 1981). If underdecolorized during gram staining, *N. meningitidis* can be mistaken for pneumococcal pneumonia (Sacks, 1986). These circumstances may result in cases of N. *meningitidis* pneumonia being missed (Witt & Olans, 1982). The probability that the isolated bacterial species is a true pathogen increases if it is seen inside the PMN cells on the gram stain of the sputum (Putsch et al., 1970). Pleural fluid and lung tissue can also be used to make the diagnosis (Witt & Olans, 1982). Transtracheal aspiration has also been used to establish the diagnosis (Irwin et al., 1975; Koppes et al., 1977), but this method is invasive and may still lead to false-positive results (Ellenbogen et al., 1974). Transthoracic lung aspirations have also been used to diagnose meningococcal pneumonia. However, due to the risk of pneumothorax, this procedure is not a part of the routine work-up and is usually reserved for severely ill individuals who are not improving with treatment (Koppes et al., 1977). PCR has been used with good results in CSF samples and recently it has proven effective in detecting *N. meningitidis* in blood (Newcombe et al., 1996). This may be particularly helpful in patients who have received antibiotic therapy prior to specimen collection, which may cause a false-negative culture result. Serum adenosine deaminase, an enzyme involved in the degradation pathway for purines, has been shown to be low in meningococcal pneumonia; however, the utility of this assay as a diagnostic test for *N. meningitidis* pneumonia remains unclear (Klockars et al., 1991).

Treatment and Prophylaxis

There are no clinical trials that have specifically studied the treatment or prevention of *N. meningitidis* pneumonia. The majority of trials deal with the treatment and prevention of meningococcal meningitis. Sulfonamides were the first antibiotics used in the treatment of meningococcal disease. However, resistance against sulfonamides is now widespread, with approximately 30% of isolates being resistant (Oppenheim, 1997). Penicillin has traditionally been the antibiotic of choice for treatment of meningococcal disease, with minimum inhibitory concentrations (MICs) of less than 0.05 mg/L. Until the 1970s the microorganism had always been fully susceptible to penicillin, but over the past 25 years there have been increasing reports of strains that are relatively resistant to penicillin, with MICs ranging from 0.1 to 1.28 mg/L. The term "moderately susceptible" is now used to refer to those strains with MICs between 0.12 and 1 mg/L. These strains have been isolated around the world, with a prevalence rate of 4% in the United States (Woods et al., 1994; Jackson et al., 1994), 8% in the United Kingdom, and up to 46% in Spain (Oppenheim, 1997). Resistance in these strains appears to be secondary to the gradual alteration of penicillin-binding proteins through genetic recombination with other *Neisseria* species (Spratt et al., 1989; Oppenheim, 1997). None of these isolates have been found to harbor β-lactamase enzymes. In vitro studies have demonstrated that transfer of β-lactamase-containing plasmids can occur between *N. meningitidis* and other *Neisseria* species (Brett, 1989). There have been only four reports of β-lactamase-producing strains of *N. meningitidis*. These are considered resistant to penicillin, with MICs up to 256 mg/L (Oppenheim, 1997). Of the moderately susceptible strains isolated in the United Kingdom in 1988, 61% were also resistant to sulfonamides, but they remained sensitive to rifampin, chloramphenicol, aminoglycosides, erythromycin, and tetracycline (Sutcliffe et al., 1988). There have been no reports

of treatment failures with appropriate dosages of penicillin. Rifampin resistance is rare but can be suspected in chemoprophylaxis failures (Oppenheim, 1997).

Response to antibiotic treatment is prompt. In one case series, 43% of patients were afebrile within 24 hours, with 76% achieving defervescence in 72 hours. Resolution of radiological abnormalities occurred in 10 days in 79% and by 3 weeks in 93% (Koppes et al., 1977).

Chemoprophylaxis is an important component of meningococcal treatment. It is well known that *N. meningitidis* can colonize the pharynx of healthy adults, and there is evidence that nosocomial transmission of the microorganism can occur. Rose et al. (1981) reported a case of nosocomial *N. meningitidis* pneumonia in a patient who was the roommate of *a* patient admitted with community-acquired *N. meningitidis pneumonia.* The two isolates were found to be identical. Rose et al. (1981) suggest that the transmission was by direct contact from hospital personnel carrying the microorganism on their hands. There have also been reported cases of *N. meningitidis* transmitted via respiratory droplets (Cohen et al., 1979). In meningitis, secondary attack rates can reach 20.8%. Therefore, prompt recognition is important so that appropriate interventions such as respiratory isolation can be started to limit the spread to close contacts and hospital personnel (Irwin et al., 1975). Respiratory isolation for 24 hours after the initiation of therapy is recommended in patients with *N. meningitidis* pneumonia (Cohen et al., 1979). Systemic therapy with β-lactam antibiotics may not eradicate carriage in patients presenting with meningococcal disease. Abramson and Spika (1985) found that 28.6% of patients had persistently positive cultures from the respiratory tract 1 week after the completion of initial therapy. Whether or not to treat this small group is debatable; however, it is common practice for patients in the United Kingdom recovering from meningococcal disease to receive chemoprophylaxis and this has been suggested in the guidelines published by the Canadian Medical Association (CCDR, 1994; Cartwright, 1999). Current recommendations are for prophylaxis to be administered to household contacts; day-care center contacts; medical personnel who are exposed to respiratory secretions when performing resuscitation, intubation, or suctioning before treatment is initiated; and others who have had contact with the patients' oral secretions (Sacks, 1986; CDC, 1997). The possible choices for chemoprophylaxis are rifampin (adults: 600 mg oral twice daily for 2 days; children: 10 mg/kg every 12 hours for four doses), ciprofloxacin (500 mg in a single oral dose), or ceftriaxone (250 mg intramuscularly in a single dose; 125 mg in children) (Cartwright, 1999). (Note: Ceftriaxone can be diluted with 1% lidocaine to reduce the pain at the site of injection (CDC, 1997).) Cuevas et al. (1995) conducted a randomized comparative study of rifampin and ciprofloxacin for eradication of nasopharyngeal carriage of *N. meningitidis* in adults and children in Africa. They found that a 2-day course of rifampin was 96.5% effective at 7 days and 97.7% effective at 14 days. A single oral dose of 750 mg of ciprofloxacin was 88.6% effective at 7 days and 91.1% effective at 14 days. In the same study another group of patients also received a single intramuscular dose of ceftriaxone, which was 95.1% and 97.6% effective at days 7 and 14 respectively. Any of the described regimens are more than 90% effective. However, ceftriaxone and ciprofloxacin have the advantage of a single-dose administration, thereby increasing compliance, and ciprofloxacin also has the advantage that it is oral and therefore easier to administer. This has led some to suggest that ciprofloxacin or ceftriaxone should be considered first-line agents for prophylaxis (Martin et al., 1996).

In cases of meningitis secondary to *N. meningitidis* serogroup A or C, the meningococcal vaccine can be offered to close contacts as a strategy to prevent disease. There was an estimated reduction of 86% in the number of infections in military recruits who underwent vaccination against group C *N. meningitidis* between 1969 and 1971 (Smilack, 1974); however, efficacy of this intervention in meningococcal pneumonia is not known (Cartwright, 1999).

Primary community-acquired *N. meningitidis* pneumonia is not as rare as it was once thought to be. Problems with isolation of the organism, the nonspecific clinical presentation, and its response to the antibiotics recommended for the treatment of CAP contribute to the underestimation of its prevalence. Although immunosuppressed and healthy individuals are at risk, military recruits are at particular risk. Diagnosis of meningococcal pneumonia

should be considered in these patients, particularly in patients with underlying viral pneumonia who suffer a deterioration in their respiratory status.

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36

Q Fever

THOMAS J. MARRIE

Background

In August 1935, E. H. Derrick, a pathologist who was Director of the Laboratory of Microbiology and Pathology at the Queensland Health Department, Brisbane, Australia, was contacted by Sir Raphael Cilento, Director General of Health and Medical Services for Queensland (McDade, 1990). Cilento had learned of an outbreak of an undiagnosed febrile illness among workers at the Cannon Hill abattoir in Brisbane. He also informed Derrick that such cases had been occurring since 1933 and that the outbreak was ongoing (McDade, 1990).

Derrick first carefully described the clinical illness. He noted that it lasted 7 to 24 days and was characterized by fever, headache, malaise, anorexia, and myalgia. Blood cultures were negative and serum samples had no antibodies to influenza, typhus, leptospirosis, typhoid, and paratyphoid. He named the illness Q (for query) fever (Derrick, 1937).

Derrick next inoculated blood or urine from his febrile patients into guinea pigs. The guinea pigs became febrile, and tissues from these animals when injected into uninfected guinea pigs resulted in fever. Derrick was unable to isolate a microorganism. In October 1936, he sent a saline emulsion of infected guinea pig liver to Frank MacFarlane Burnet, a virologist (and later a Nobel laureate) who was working at the Walter and Eliza Hall Institute in Melbourne. Burnet and his research associate Mavis Freeman found oval areas about the size of a nucleus in sections of spleen from a mouse that had been inoculated with Derrick's specimen. When these smears were stained by Castaneda's method, "bodies which appeared to be of rickettsial nature were found, sometimes in enormous numbers" (Burnet & Freeman, 1937). As often happens in scientific endeavor, seemingly unrelated investigations converged. In the spring of 1935, Laurence Humble, a laboratory attendant at the Rocky Mountain Laboratory in Hamilton, Montana, collected 200 *Dermacentor andersoni* ticks and brought them to Gordon Davis, who was working at the laboratory on various aspects of Rocky Mountain spotted fever (McDade, 1990). Davis was able to isolate an organism from these ticks. By 1938 it was apparent that the tick agent and the Q fever agent were identical. Herald Rea Cox, a Rocky Mountain Laboratory scientist, worked with Davis and characterized "the nine mile agent." He was able to cultivate this agent in embryonated eggs.

Rolla Dyer (Director of National Institutes of Health from 1942 to 1950) visited Cox to review his data. He left convinced about the validity of the results. A few days later he developed fever and retroorbital headache. The nine mile/Q fever agent was isolated from his blood (McDade, 1990). As is often the case with microorganisms there have been a series of names for this agent. Initially it was called *Rickettsia diaporica* (diaporica, Greek for having the property or ability to pass through, describing the filterability of this agent) and then *R. burnetii* was proposed. It was later elevated to a subgenus, *Coxiella* (McDade, 1990). The agent is know known as *Coxiella burnetii.* Cox and Burnet both died in 1986.

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

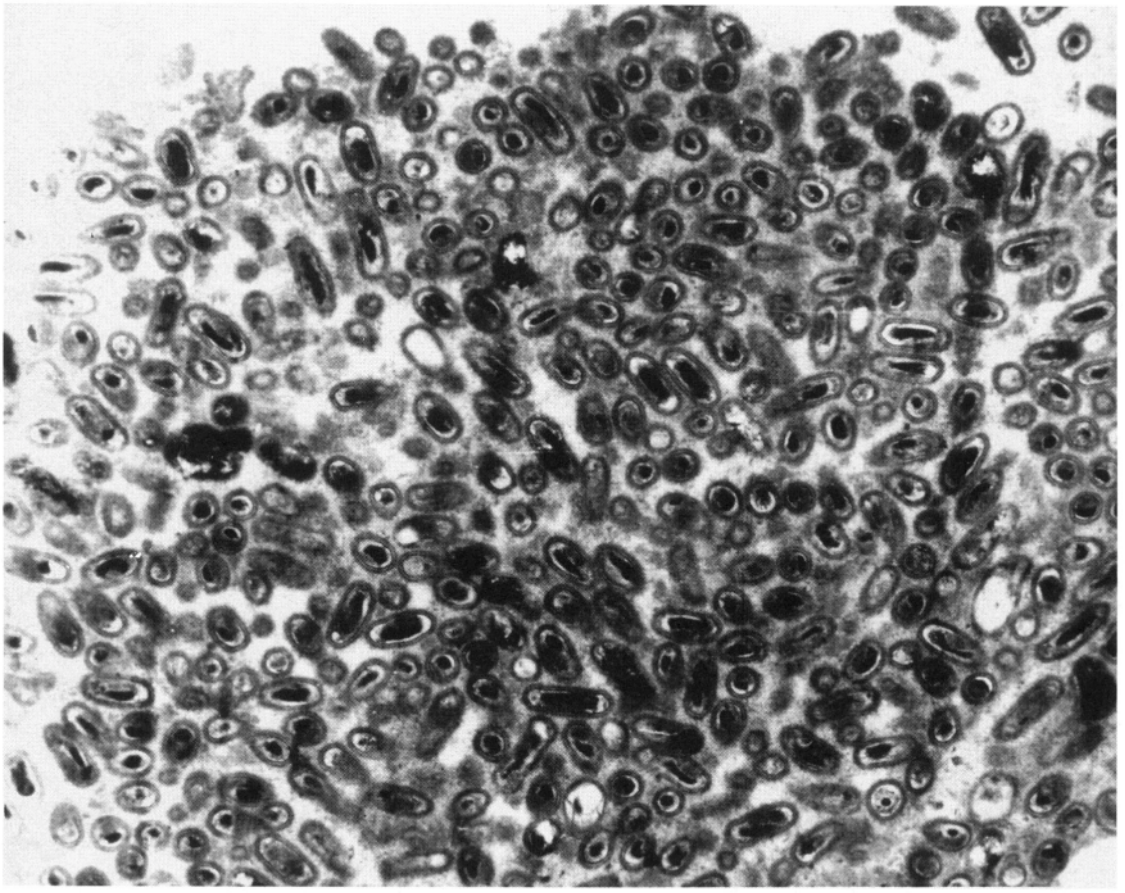

FIGURE 1. Transmission electron micrograph of *Coxiella burnetii*. Magnification × 35,000. The dark material in the center of each cell is condensed DNA.

Coxiella burnetii

C. burnetii (Fig. 1) is a pleomorphic coccobacillus with a gram-negative cell wall (Baca & Paretsky, 1983). It measures 0.2×0.7 μm. *C. burnetii* is an obligate intracellular microorganism. It is this feature which has contributed most to our lack of knowledge of many of the basic features of *C. burnetii.* We do know there is a developmental cycle in which there is a large and small cell variant (McCaul, 1991). The small cell variant attaches to the host cell (the receptor has not yet been identified) and is ingested. The acid pH of the phagolysosome is necessary for development of *C. burnetii* since the low pH activates its metabolic enzymes (Thompson, 1991). Following maturation of the large cell variant, sporogenesis begins (McCaul & Williams, 1981). Spore formation explains why *C. burnetii* is so successful as a pathogen. It can survive for 7 to 10 months on walls at 15°C to 20°C, for more than 1 month on meat in cold storage, and for more than 40 months in skim milk at room temperature (Christie, 1974). Following the identification of plasmid DNA in *C. burnetii* it was hypothesized that this was a virulence factor (Samuel et al., 1985), since the plasmid type was different in the two prototype strains: Nine mile, a strain obtained from a tick but determining acute pulmonary infection in a laboratory animal model, and Priscilla, obtained from the placenta of a goat, which was considered representative of "chronic infection." In fact, in humans the disease type (acute or chronic)

is clearly determined by the host status, and in animal models so far the distinction between acute and chronic strain types has never been confirmed. Moreover, the diversity of *C. burnetii* plasmids is wider than expected and the plasmid virulence theory has not been confirmed. However, this does not mean that strain diversity is not correlated with variations in clinical presentation.

C. burnetii undergoes phase variation, which is akin to the smooth-to-rough transition of lipopolysaccharides (LPS) of gram-negative bacteria (Stoker & Fiset, 1956). In nature and in laboratory animals it exists in the phase I state in which organisms react with late (45 days) convalescent guinea pig sera and only slightly with early (21 days) sera (Stoker & Fiset, 1956). Studies by Hackstadt (1988) and Lukacova et al. (1994) have shown that in experimentally infected animals the first antibody production is to *C. burnetii* protein phase II antigen and later antibody is produced to *C. burnetii* LPS phase I antigen. Hyperimmunization of animals suggests that phase I LPS exerts an adjuvant effect on antibody response (Lukacova et al., 1994). In humans, high antibody titers ($\geq$1:800) to phase I antigen are suggestive of chronic Q fever, while phase II antibodies predominate in acute Q fever. There is no morphological difference between phase I and phase II cells, although they do differ in the sugar composition of their LPS (Schramek & Mayer, 1982), their buoyant density in cesium chloride, and their affinity for basic dyes. The LPS of *C. burnetii* is nontoxic to chick embryos at doses of $>$80 μg/embryo in contrast to *Salmonella typhimurium* LPS, which is toxic in nanogram amounts (Lukacova et al., 1993). Hackstadt et al. (1985) and Lukacova et al. (1993) believed that there was also a phase intermediate between phase I and phase II. They also noted that there was no basic difference in the phase variation phenomenon between prototype *C. burnetii* strains isolated from a tick (Nine mile) and a goat (Priscilla) during their first 30 passages in eggs, that is, in their transition through the intermediary phase II (Lukacova et al., 1993).

Plasmids have been found in both phase I and phase II cells (Samuel et al., 1985). At one point it was thought that certain plasmids were associated with acute or chronic Q fever (Samuel et al., 1985). However, further studies have shown that this is not so (Thiele et al., 1993). Table I lists the plasmids of *C. burnetii* described to date. It also appears that some plasmidless isolates contain inverted repeats common to both ends of plasmid homologous DNA, integrated into the host chromosome (Stein et al., 1993). Others have also found chromosomally integrated sequences with homology to a Q fever plasmid (Minnick et al., 1991). DNA fragments (obtained by digestion with ECOR1) from QpH1, QpDG, and Q4DV are remarkably similar (Valkova & Kazar, 1995). Stein and Raoult (1992a) used primers for the gene CbhE (unique to QpH1 plasmid) obtained from strain Nine mile to examine 30 French isolates of *C. burnetii.* This "acute Q fever" plasmid was found in 3 of 8 acute Q fever isolates and 7 of 21 chronic Q fever isolates.

TABLE 1. Plasmids of *Coxiella burnetii*

Plasmid	Size	Source strain	Reference
QpH_1	36 kb	Nine mile	Sekeyova et al., 1995
QpRs	39 km	Priscilla	Samuel et al., 1985; Stein & Raoult, 1992a
QpDg	51 kb	Dugway	Minnick et al., 1991; Valkova & Kazar, 1995
	40 kb	Unnamed, chronic Q fever isolates	
QpDV	33.5 kb		Heinzen et al., 1990
	56 kb	Chinese isolates	

Heinzen et al. (1990) examined eight *C. burnetii* isolates by pulsed field gel electrophoresis following digestion with NotI and SfiI. They classified these isolates into four groups. Examination of 30 isolates from diverse geographic regions allowed Thiele et al. (1993) to describe nine different patterns. The European strains were different from the North American strains.

Stein et al. (1993) sequenced the 16S rRNA segments (1418 bases) of six strains of *C. burnetii* and found very high levels of sequence similarity among all strains. Only three base substitution points in the sequences were identified and only three strains differed from the type strain sequence. The entire 16S/23S spacer region of *C. burnetii* Nine mile phase I was sequenced by Thiele et al. (1994). They noted that there were two tRNA coding regions for $tRNA^{Ile}$ and $tRNA^{Ala}$. There was significant homology with tRNA from the spacer

region that was unique to *C. burnetii* based on database alignment (Thiele et al., 1994).

Epidemiology

The initial description of Q fever as an outbreak of a febrile illness in an abattoir (Derrick, 1937) clearly indicated several features about the epidemiology of Q fever. Q fever is a zoonosis (Babudieri, 1959). *C. burnetii* has been identified in arthropods, fish, birds, rodents, marsupials, and livestock (Baca & Paretsky, 1983). Indeed it naturally infects more than 40 species (including 12 genera) of ticks found on five continents (Baca & Paretsky, 1983). Lice, mites, and parasitic flies are also infected (Ormsbee, 1965). Bandicoots, rats, rabbits, mice, porcupines, hedgehogs, tortoises, cattle, sheep, goats, dogs, cats, swine, camels, buffaloes, baboons, leopards, hyenas, chickens, ducks, geese, turkeys, pigeons, bats, shrews, and birds have been infected (Ormsbee, 1965; Babudieri, 1959). Babudieri (1959) in a classical review of Q fever in 1959 raised the first four of the following questions:

1. Why is Q fever endemic in some countries and why does it undergo cyclic epidemic patterns in other countries?
2. Why is airborne transmission from person to person so rare?
3. In what form does the pathogenic agent survive in the organs of carrier animals?
4. By what mechanism does birth mobilize the *Coxiella* present in the organism and lead to their abundant emission with excretions?
5. Why does Q fever endocarditis develop only in humans?
6. Why does Q fever endocarditis develop in a minority of those humans who develop Q fever?
7. Why do the predominant manifestations of Q fever vary from country to country?

Coxiellosis in Laboratory Animals

The term coxiellosis is used for *Coxiella* infection in animals other than man (Lang, 1990). Clinical manifestations of *C. burnetii* in infected animals could theoretically vary depending on species, age, sex, strain, and immunological status of the challenged animal and the strain of *C. burnetii,* inoculum size, and route of inoculation.

Guinea pigs infected with *C. burnetii* via the intraperitoneal route develop hyperthermia ($\geq$40°C) following an incubation period of 5–12 days. *C. burnetii* is excreted in the urine over many months (Franti et al., 1974). Death is rare unless $\geq 10^8$ ID_{50} is used (Franti et al., 1974). Lesions are seen in spleen, testes, inguinal and mesenteric nodes, and liver. Degenerative myocarditis is frequently found in guinea pigs dying during convalescence. Pulmonary congestion is seen even in animals infected via the peritoneal route.

The strain of *C. burnetii* used may result in a different response in different species of animals. Franti et al. (1974) found that the Hopland strain did not cause an increase in mouse spleen size, whereas the Hergerling strain did. Mice were more resistant to first passage material and male mice were more severely affected than female mice. Baumgartner et al. (1993) infected 8- to 16-week-old female C57 BL/GJ ($H\text{-}2^b$) and Balb/CJ ($H\text{-}2^d$) mice with 3.85×10^6 infectious units of *C. burnetii* intraperitoneally. They noted hepatosplenomegaly 3 days after infection. No significant lesions were seen in lungs, brain, or spinal cord. Moderate to severe lesions were seen in the uterus, pancreas, mediastinum, heart, kidneys, and lymph nodes. Neutrophils predominated up to day 8, and thereafter macrophages predominated. Microabscesses were prominent in the liver up to day 8. Multifocal granulomas were present in the bone marrow. Most inflammatory changes had resolved by 150 days. There was no difference in the manifestations caused by the two strains. Infection of pregnant mice with *C. burnetii* results in a 50% stillbirth rate and a 42% abortion rate. Pyometritis and endometritis are evident (Baumgartner & Bachman, 1992).

Surprisingly, fetuses in utero and aborted, stillborn, or perinatally dying offspring were immunocytochemically negative for *C. burnetii.* However, mice killed 9 days after birth had *C. burnetii* antigen-positive cells in lung, liver, and spleen (Baumgartner & Bachman, 1992).

C. burnetii remains in phase I while in experimental animals but changes to phase II following serial passage in the yolk sac of chicken embryos

(Stoker & Fiset, 1956). *C. burnetii* grows in the yolk sac's endodermal cells, attains maximum growth by day 7, and degrades rapidly thereafter so that 24 hours later only half the population remains (Ormsbee, 1952).

Domestic Animals

Cattle, sheep, and goats are the primary reservoirs of Q fever for humans. *C. burnetii* localizes to the uterus and mammary glands of infected animals (Babudieri, 1959). Infected cows have shed *C. burnetii* in milk for up to 32 months (Grist, 1959).

Infected sheep shed the organism in feces for 11 to 18 days post-partum (Welsh et al., 1958). Large concentrations of *C. burnetii* are present in the infected placenta, and aerosols are created during parturition (Welsh et al., 1958). Inhalation of these contaminated aerosols by a susceptible human results in Q fever.

C. burnetii infection has caused outbreaks of abortion in goats (Babudieri, 1959) and sheep (Palmer et al., 1983; Raju et al., 1988; Polydorou, 1981). The placentas of infected sheep can contain 10^9 guinea pig infective doses of *C. burnetii* per gram of tissue (Welsh et al., 1953).

The stillbirth rate among infected cats is about 70% compared with the usual rate of 10% for uninfected cats (Pratt, 1983).

Dairy cows are important in the spread of Q fever, while beef cows are rarely infected (Luoto & Pickens, 1961). Once *C. burnetii* is introduced into a heard, it spreads rapidly: 80% of the cows are positive within a few months (Luoto & Pickens, 1961). Infected wildlife may be important in infecting cattle, since in a large portion of newly infected herds a source of infection is not found (Luoto & Pickens, 1961; Enright et al., 1971).

Hares and rabbits in many areas have the highest rate of infection among wild animals (Enright et al., 1971; Marrie et al., 1993).

Infected ticks are probably most important in perpetuating the cycle of *C. burnetii* infection (Stoker & Marmion, 1955). These infected ticks have been found on rabbits, goats, cattle, sheep, and many other animals (Stoker & Marmion, 1955).

However, the pattern of maintenance of *C. burnetii* in animal or tick hosts differs in different parts of the world (Marmion & Stoker, 1958). in some countries infection among domestic or wild animals results in considerable infection among humans in contact with these animals, whereas in other areas little if any transmission to humans occurs (Marmion & Stoker, 1958).

Man

C. burnetii has been an extraordinarily successful pathogen. From its humble beginnings in an Australian abattoir in 1935, by 1955 *C. burnetii* was found in 51 countries on five continents (Kaplan & Bertagna, 1955). In the 1990s, New Zealand (Hilbink et al., 1993) is one of the few countries that is free of *C. burnetii* infection.

The epidemiology of Q fever in man is closely related to the activity of *C. burnetii* in wild and domestic animals. However, the manifestations of Q fever (e.g., fever, pneumonia, hepatitis) differ from country to country. In addition, Q fever in a geographic area may be endemic or epidemic.

Within a short time after *C. burnetii* was isolated in the laboratory, laboratory-acquired Q fever was noted at the National Institutes of Health from 1940 to 1946 (Hornibrook, 1940; Huebner, 1947; Huebner et al., 1948; Spicknall et al., 1947).

The next major outbreak of Q fever was among British and American troops during World War II (Robbins & Regan, 1946a; Robbins et al., 1946; Feinstein et al., 1946; Commission on Acute Respiratory Diseases, 1946).

Shortly thereafter (1946–1950), outbreaks of Q fever were observed at meat packing plants in Texas and Chicago (Irons & Hooper, 1947; Irons et al., 1946, 1947; Topping et al., 1947; Cox et al., 1947; Shepard, 1947). While studying these outbreaks, Shepard implicated aerosols as the route of transmission of Q fever (Shepard, 1947).

Careful studies of the epidemiology of Q fever in California led to the conclusion that Q fever was associated with exposure to sheep and goats (Lennette et al., 1949; Lennette & Welsh, 1951). During the course of these studies *C. burnetii* was recovered from the air of premises with infected goats (Lennette & Welsh, 1951), from raw milk (Huebner et al., 1948), and from the placentas of infected cows (Luoto & Huebner, 1950). Thus, by 1951 much was known about the microepidemiology of Q fever.

One of the first studies of the microepidemiology of Q fever was conducted during February and April 1949 when 1.5% of the 3000 residents in a small rural community in northern California developed a flu-like illness that was shown to be due to Q fever (Clarke et al., 1951). Most (40/41) of those affected were males and cases were clustered by place of occupation.

Two outbreaks provide additional information about the epidemiology of Q fever. British residents who lived along a road over which farm vehicles traveled developed Q fever as a result of exposure to contaminated straw, manure, or dust from farm vehicles (Salmon et al., 1982). In a Swiss valley, 415 residents who lived along a road over which sheep traveled to and from mountain pastures developed Q fever (Dupuis et al., 1987).

Our experience in Nova Scotia illustrates the evolution of Q fever in one geographic area over a 17-year period. Nova Scotia is located on the eastern seaboard of Canada. There are just under 1 million inhabitants split equally between urban and rural areas. The land mass is 55,000 km^2, of which 70% is forested and 14% is farmland. Q fever was first recognized in Nova Scotia in 1979 during the course of a study of atypical pneumonia (Marrie et al., 1981). In 1982 the first of many small outbreaks, usually involving a single family unit, was recognized (Kosatsky, 1984). A case–control study detailed 13 cat-related outbreaks of Q fever and showed that exposure to stillborn kittens was the major risk factor for acquisition of Q fever (Marrie et al., 1988). A dose-effect response was evident in these cat-related outbreaks. Those who cleaned up the products of conception had the shortest incubation period and were most seriously affected (Marrie et al., 1988). The number of cases in this province peaked at 58 in 1985 (Marrie, 1990a).

While these cases were occurring we determined the seropositivity rate to *C. burnetii* of several species of domestic and wild animals in Nova Scotia (Table 2; Marrie et al., 1985, 1993).

Despite the high seroprevalence of infection in cattle we have observed only one small outbreak of Q fever involving four family members, secondary to exposure to an infected cow that gave birth to a stillborn calf and retained the placenta for 3 days. However, in a seroepidemiological study of a random sample of 492 Nova Scotian volunteers, we noted that the highest seroprevalence was in six contiguous counties around the Bay of Fundy. This area of the province comprises the major agricultural area and most of the animal husbandry in the province (Marrie & Pollak, 1995). The overall seroprevalence rate was 14.8%, and the rates for the six Bay of Fundy counties ranged from 18% to 28%. Another observation from this study was that those who were ≤34 years old had a low stable seroprevalence that increased with increasing age from 11.8% for those 35 to 39 years old to 66.7% for those 70 to 75 years old (Marrie & Pollak, 1995). Cases of Q fever occur throughout the year in Nova Scotia (Marrie, 1990a).

TABLE 2. Seroepidemiology of *Coxiella burnetii* in Various Animals in Nova Scotia as Measured by Antibodies to *C. burnetii* Phase I and Phase II Antigens[a]

Animal	No. tested	Percent positive IFA test	
		Phase I	Phase II
Domestic			
Sheep	329	0	6.7
Cattle	214	24.2	23.8
Goats	39	3.5	7.0
Cats	216	6.0	24.1
Dogs	447	0	0
Wild			
Snowshoe hare (*Lepus americanus*)	730	49	12
Moose (*Alces alces americana Clinton*)	243	16.5	11.5
White-tailed deer (*Odocoileus virginianus*)	68	1.5	4.4
Raccoon (*Procyon lotor*)	42	7.1	9.5

IFA, indirect fluorescence antibody.
[a]Data from Marrie et al., 1985, 1993.

The mean age of 174 Nova Scotians with acute Q fever was 40.17 years, with range of 17 to 80 years. Most (68.9%) of the cases occurred in the 20-to-49-year age group (Marrie, 1990a). These findings are consistent with the seroepidemiological data (Marrie & Pollak, 1995). However, in contrast to the seroprevalence data where the positivity rate was equal among males and females, in our cases of acute Q fever males outnumbered females 2:1—69% vs 31% (Marrie, 1990a).

We have also observed cases of Q fever following exposure to infected wild hares (Marrie et al., 1986).

In 1990, outbreaks of Q fever in Nova Scotia seemed to cease. Sporadic cases continue to occur and in a study of ambulatory patients with pneumonia in the Halifax area from December 1991 until March 31, 1994, we found that 4 of 149 (2.7%) had Q fever (Marrie et al., 1996a).

In 1995 we noted the first outbreak of Q fever due to exposure to an infected parturient dog (Buhariwalli et al., 1996). Since then there has been one other case of dog-related Q fever. Our previous serosurvey (Table 2) failed to show even one antibody-positive dog among the 447 tested.

In many countries Q fever is not a reportable disease so it is difficult to know how many cases occur. Furthermore, sporadic cases are rarely identified. With these qualifications it is useful to note that 6479 cases of Q fever were diagnosed in Australia from 1960 to 1986 (Marrie, 1990a). From 1980 to 1987 there were 328 cases in Canada and in Uruguay there were 1358 since 1975. France, Spain, Israel, and the United Kingdom continue to have considerable Q fever activity (Marrie, 1990a); this is due in part to active case finding. From 1984 to 1994, 1117 cases of Q fever were reported in England and Wales (Peabody et al., 1996) and 1018 cases (731 acute and 287 chronic Q fever) have been diagnosed at the French National Reference Center from 1985 to 1995 (unpublished data). The mean age of the 1117 patients from England and Wales was 45 years, and 71% were men. Sixty percent reported contact with animals. Forty-seven percent of cases presented with respiratory symptoms, 7% with heart disease, and 5% with hepatitis. Fifty of the cardiac cases had endocarditis, 9 had myocarditis, and 18 had pericarditis. Ten patients were immunocompromised: two had Hodgkin's disease, two had leukemia, one had lung cancer, one a renal transplant, and one a heart transplant. In three cases the cause of the immunosuppression was unspecified.

Modes of Transmission of Q Fever to Man

Inhalation of Contaminated Aerosols

There is good experimental and epidemiological evidence that the inhalation of contaminated aerosols is the major mechanism by which Q fever is transmitted to man (Tigeret & Benenson, 1979; Gonder et al., 1979; Laughlin et al., 1991; Marrie et al., 1989a, b; Abinanti et al., 1953; Oliphant et al., 1949). Human volunteers who inhaled one infectious dose had an incubation period of 16 days, whereas those who were exposed to 1500 infectious doses had an incubation period of 10 days. Indirect exposure to contaminated material may also lead to Q fever, such as when contaminated clothing from the Rocky Mountain Laboratory in Montana led to cases of Q fever among laundry workers (Oliphant et al., 1949). Even a game of poker may result in Q fever if an infected cat delivers during the game (Langley et al., 1988). There have been several outbreaks of Q fever in research institutions when infected pregnant animals, especially sheep, were transported through the building to the laboratory (Langley et al., 1988; Schachter et al., 1971;Meiklejohn et al., 1981; Hall et al., 1992; Curet & Paust, 1972).

Oral Route

There is a suggestion from epidemiological studies that ingestion of contaminated milk is a risk factor for Q fever infection (Marmion et al., 1956; Fishbein & Raoult, 1992). However evidence from experiments where contaminated milk was fed to volunteers is contradictory (Benson et al., 1963; Editorial, 1950; Krumbiegel & Wisniewski, 1970).

The route of infection may explain the difference in the manifestations of Q fever in some countries (e.g., pneumonia in Nova Scotia, Canada, versus hepatitis in Marseilles, France). We used five different strains of *C. burnetii* to infect mice via the intraperitoneal or intranasal route. Those infected intranasally developed pneumonia only, while those infected intraperitoneally developed hepatitis, splenomegaly, and pneumonia. Bronchiolar changes were seen only in mice inoculated intranasally (Marrie et al., 1996b). These data have been reproduced in a guinea pig model of Q fever (La Scola et al., 1997).

Percutaneous Route

Crushing a tick between the fingers has resulted in Q fever (Eklund et al., 1947), as has intradermal inoculation (Editorial, 1950) and blood transfusion (Editorial, 1977).

Vertical Transmission

Vertical transmission rarely occurs (Fiset et al., 1975; Raoult & Stein, 1994); however, increased surveillance may reveal additional cases.

Person-to-Person Transmission

Despite the fact that pneumonia is a common manifestation of Q fever in humans there have been only a few cases of person-to-person transmission (Raoult & Stein, 1994; Harman, 1949; Gerth et al., 1982; Deutch & Peterson, 1950). There are two reports of transmission of Q fever to attendants during autopsies (Harman, 1949; Gerth et al., 1982) and one report of transmission of infection from a patient to hospital staff. Raoult and Stein (1994) described a case where an obstetrician developed Q fever pneumonia following delivery of an infected pregnant woman. Since infected parturient cats, sheep, and cattle readily spread infection to humans, one wonders why more cases of Q fever do not develop in obstetrical staff who assist at the delivery of infected pregnant women. We observed two pregnant women with large numbers of *C. burnetii* in the placenta, yet Q fever did not develop in any of the obstetrical attendants.

Sexual Transmission

There is a suggestion that sexual transmission can occur in animals (Kruszewska & Tyleswka-Wierzbanowska, 1993). Whether or not it occurs in humans is not known.

Clinical Manifestations of Q Fever

Q fever is commonly divided into acute and chronic forms. This is a useful clinical distinction since the course of the illness and treatment differ markedly for the two disease forms.

Acute Q Fever

Fifty percent of *C. burnetii* infections are asymptomatic (Dupuis et al., 1987). There are three distinct manifestations of acute Q fever: (1) a self-limited febrile illness, (2) pneumonia, and (3) hepatitis. There are a variety of other manifestations including neurological manifestations, miscellaneous manifestations, Q fever in the immunocompromised host, and Q fever in pregnancy. In this chapter we discuss acute Q fever, with an emphasis on Q fever pneumonia.

Self-Limited Febrile Illness

Self-limited febrile illness is the most common manifestation of Q fever. Even though 10% to 15% of some populations are seropositive for C. *burnetii,* most of these individuals do not recall an illness that could be attributed to this infection. Viciana et al. (1992) examined 505 Spanish adults who had fever lasting more than 1 week and less than 3 weeks. They found that 108 (21%) had Q fever. All had normal chest radiographs. Derrick (1973) described the course of infection in 173 patients with *C. burnetii.* The duration of fever was 5 to 57 days, with a median of 10 days. He noted that the duration of fever increased with increasing age and in 28% of cases fever recurred.

Pneumonia

Pneumonia is one of the most commonly recognized forms of acute Q fever. As mentioned previously, this is the major manifestation of acute Q fever in Nova Scotia, while in France hepatitis is the predominant manifestation (Tissot-Dupont et al., 1992). In the Basque region of Spain both pneumonia and hepatitis due to *C. burnetii* occur (Errasti et al., 1984).

We studied all patients with community-acquired pneumonia (CAP) admitted to a tertiary-care teaching hospital in Nova Scotia over a 5-year period: 3.7% of all cases were due to *C. burnetii* (Marrie et al., 1989a). Lieberman et al. (1995) studied 346 patients with CAP who were admitted to the Soroka Medical Center, which serves southern Israel: 5.8% were due to *C. burnetii.* There is a remarkable report from Japan in which To et al. (1996) studied 58 acute-phase serum samples from children with atypical pneumonia. Twenty-three (39.7%) were positive for *C. burnetii* DNA by polymerase chain reaction. Twenty-one of the 23 had the organism isolated following injection of the serum samples into mice. In the remaining two, the mice serocenverted.

TABLE 3. Symptoms Reported by Patients with Acute Q Fever[a]

Symptom	Percent of patients (N = 1993)	Symptom	Percent of patients (N = 1993)
Fever	88–100	Cough	24–90
Fatigue	97–100	Nausea	22–49
Chills	68–88	Vomiting	13–42
Headache	68–98	Chest pain	10–45
Mylagia	47–69	Diarrhea	5–22
Sweats	31–98	Rash	4–18

The symptoms of acute Q fever are given in Table 3 (Marrie et al., 1988; Clark et al., 1951a,b; Spelman, 1981; Dupuis et al., 1985; Somma-Moreira et al., 1987; Smith et al., 1993). We prospectively studied patients with radiographically confirmed pneumonia and found that only 28% complained about cough (Marrie et al., 1988). The cough is usually nonproductive of mucoid sputum. In most cases Q fever pneumonia is of mild to moderate severity. However, it can be rapidly progressive, resulting in respiratory failure. The radiological manifestations of Q fever pneumonia are shown in Table 4 and in Figures 2 through 4. Rounded opacities are very suggestive of this entity in an endemic area. In Tables 5 through 8, pneumonia due to *C. burnetii* is compared with that due to *Mycoplasma pneumoniae* and *Legionella pneumophila.* Patients with Q fever pneumonia who required hospitalization were younger than those with Legionnaires' disease. Mortality is rare in acute Q fever; in our series, only 1 of 200 Q fever pneumonia patients (0.5%) died. This patient had aspirated stomach contents and had *Escherichia coli* bacteremia with septic shock as well as undiagnosed hypertrophic cardiomyopathy (Table 5). One other patient who underwent coronary artery bypass grafting 1 month after treatment for Q fever pneumonia died. This patient became hypotensive immediately after surgery and died despite intra-aortic balloon support. Derrick (1937) reported a 1.5% mortality rate (4/273), and the same mortality rate was reported from France.

TABLE 4. Radiographic Manifestations of *Coxiella burnetii* Pneumonia in 272 Patients[a]

Feature[b]	Number	Percent of patients with feature
Rounded opacity	17	6.3
Multiple rounded opacities	7	0.3
Pleural effusion	27	9.9
Atelectasis	12	4.4
Bilateral opacities	21	7.7
Air bronchogram	70	25.7
Lower lobes involved	100	36.7
Segmental consolidation	17	6.3

[a]From Gordon et al., 1984; Sobradillo et al., 1989; Pickworth et al., 1991; Smith et al., 1991.
[b]Not all features were examined in each report.

The radiographic manifestations of *C. burnetii* pneumonia are given in Table 4. Unfortunately, not all radiographical features are commented upon in each report. In our experience multiple rounded opacities (Figs. 2 and 4) are suggestive of Q fever pneumonia. One must remember to rule out septic pulmonary emboli due to right-sided endocarditis in the setting of multiple rounded opacities. Often, however, the radiographic features are not specific for Q fever pneumonia. The resolution time ranges from 10 to 90 days (mean, 30 days). Table 8 shows laboratory data for patients with Q fever pneumonia compared with those with pneumonia due to other causes. The white blood cell count is usually normal but liver enzymes are mildly elevated in about half the patients.

The histology of Q fever pneumonia in man has rarely been studied (Janigan & Marrie, 1983, 1990; Perrin, 1949; Lille et al., 1941). Interstitial edema and infiltration by lymphocytes and macrophages occur. Alveolar spaces are filled with macrophages (Figs. 5, 6). Giant cells and plasma cells were seen in a pulmonary pseudotumor due to *C. burnetii* (Janigan & Marrie, 1990). In rhesus monkeys (Lille et al., 1941), the consolidation was peribronchial or peribronchiolar.

The white blood cell count is usually normal, 25% have an elevated WBC ranging from 14 to 21×10^9/L. Liver enzymes are mildly elevated to the same magnitude as seen in *Mycoplasma pneumoniae.* About 20% of patients have an elevated creative phosphokinase level. Twelve percent of patients with Q fever pneumonia are thrombocytopenic at the time of admission. Most striking, however, is that 53% demonstrate thrombocytosis ($>400 \times 10^9$/L)

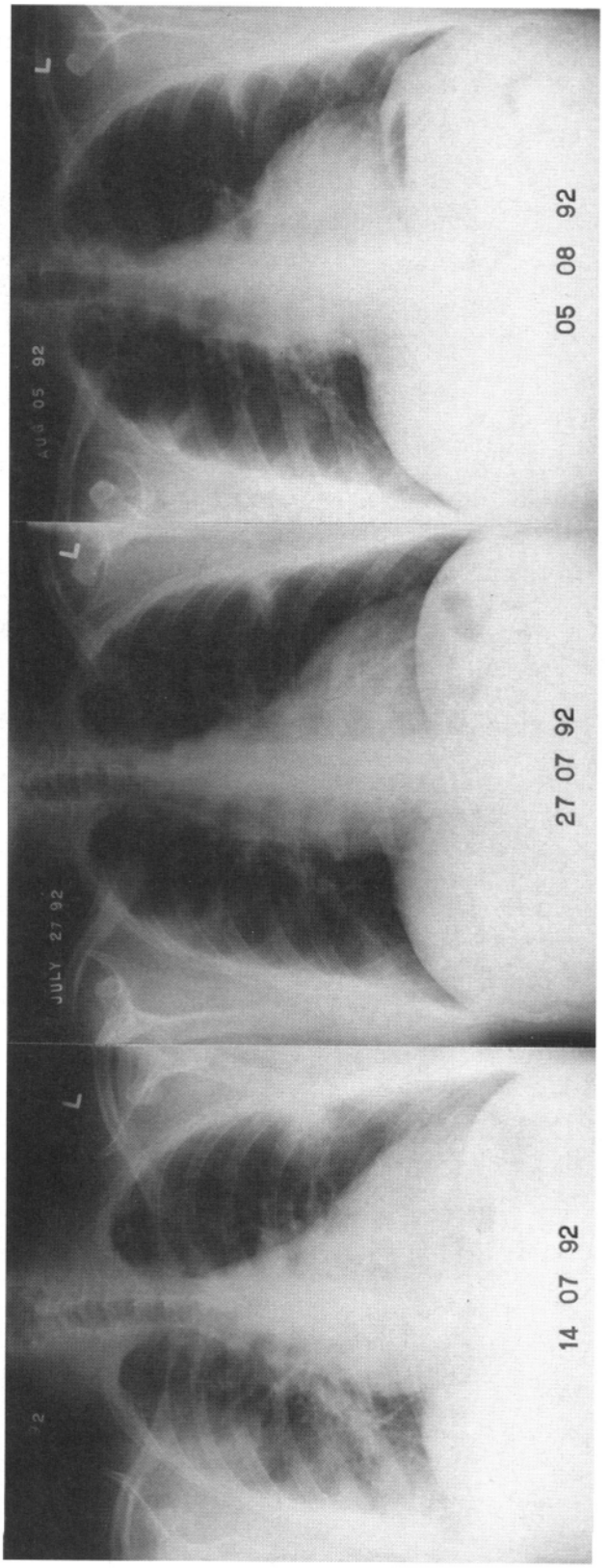

FIGURE 2. A series of chest radiographs showing the evolution of *Coxiella burnetii* pneumonia. Note the multiple rounded opacities on the radiograph dated 14.07.92. Substantial resolution (with treatment) occurred 2 weeks later.

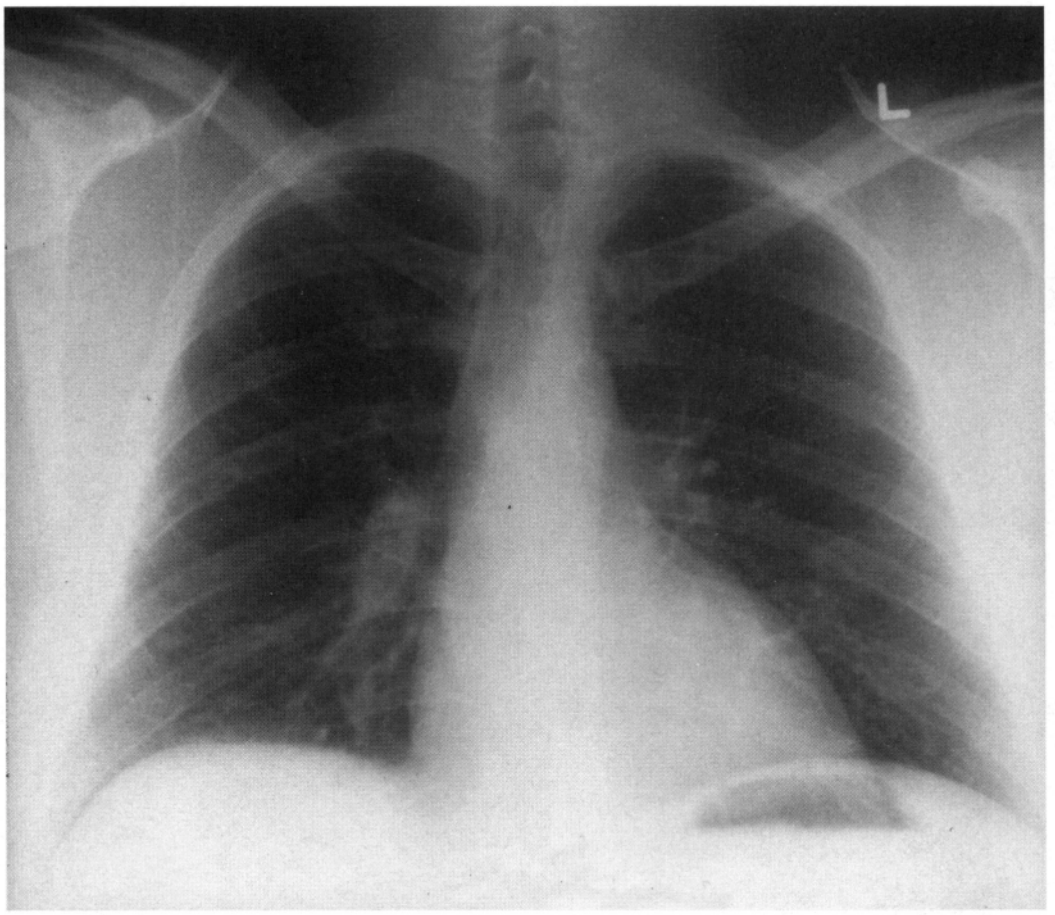

FIGURE 3. Right-sided hilar adenopathy due to *Coxiella burnetii* infection.

at some time during convalescence. We have observed several patients with platelet counts of $>1000 \times 10^9$/L during convalescence. Microscopic hematuria is common, occurring in up to 50% of the patients. Rarely the syndrome of inappropriate secretion of antidiuretic hormone complicates Q fever pneumonia (Biggs et al., 1984).

Hepatitis

There are three main menifestations of Q fever hepatitis: (1) infectious hepatitis-like picture, (2) hepatitis as an incidental finding, and (3) fever of unknown origin with characteristic granulomas on liver biopsy (Dupont et al., 1971; Qizilbash, 1983).

The hepatic granuloma of Q fever hepatitis, the so-called doughnut granuloma, consists of a dense fibrin ring surrounded by a central lipid vacuole (Dupont et al., 1971). These granulomas are not specific for Q fever, since they have also been seen in Hodgkin's disease and infectious mononucleosis. Most cases of hepatitis represent the acute form of the disease, although an occasional patient with hepatitis can have the serological profile of chronic Q fever. These patients should be treated for longer than 2 weeks. Some patients with hepatitis present with prolonged fever despite appropriate antibiotic therapy. These patients exhibit anti-smooth muscle antibodies and are rapidly cured by short-term corticosteroid therapy.

Neurological Manifestations

Severe headache is the most common neurological manifestation of Q fever (Marrie, 1985). Aseptic meningitis and/or encephalitis complicate 0.2% to 1.3% of cases of Q fever. Eight of 16 patients with Q fever meningoencephalitis had an

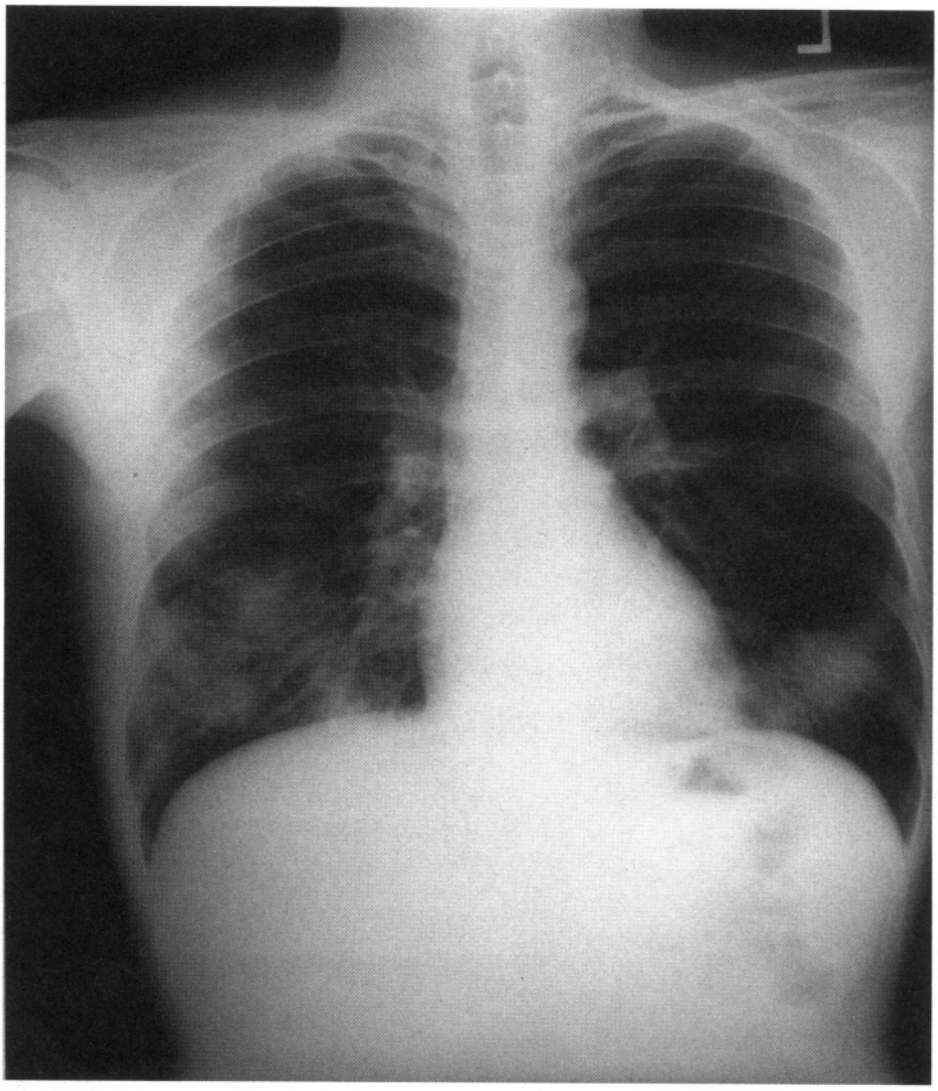

FIGURE 4. Chest radiograph showing multiple rounded opacities. This patient developed *Coxiella burnetii* pneumonia following exposure to an infected parturient cat that gave birth to kittens in his house.

elevated cerebrospinal fluid WBC count ranging from 18 to 1392 cells/mm^3 (Marrie & Raoult, 1992). The electroencephalogram was abnormal in five of six patients with Q fever meningoencephalitis in whom this investigation was carried out. Two recent studies from the United Kingdom report a very high incidence of neurological manifestations of Q fever infection. In a study from Plymouth, Reilly et al. (1990) reported a 22% incidence of neurological complications among 103 patients with Q fever. Forty-six of the patients had acute Q fever, 5 had chronic Q fever, and 52 had remote infections. Six of the 45 patients with acute Q fever had residual neurological impairment including weakness, recurrent meningismus, blurred vision, residual parasthesias, and sensory loss involving the left leg. In the study from the West Midlands (Smith et al., 1993), 23 of 101 patients reported neurological symptoms. Eight complained of hallucinations: in six these were visual, in one auditory, and in one

TABLE 5. A Comparison of the Demographic Data for Patients with Pneumonia[a]

	Coxiella burnetii	*Mycoplasma pneumoniae*	*Legionella pneumophila*
No. studied	21	40	14
No. males	14	25	10
Mean age (years)	47.1	42.3	61.9
No. (%) died	1 (5)	1 (3)[b]	5 (36)[c]
Mean length of stay (days)	11.5	13.6	15.8
No. (%) who had blood cultures done	19 (90)	29 (73)	10 (71)[c]
Positive blood cultures	1 (5)	1 (3)	1 (10)
Microorganisms isolated from blood			
Escherichia culture	1	0	0
Salmonella montevideo	0	1	0
Haemophilus influenzae	0	0	1

[a]Reproduced, with permission from Marrie, 1990b.
[b]$P < 0.02$, *C. burnetii* vs *L. pneumophila*.
[c]$P < 0.003$, *M. pneumoniae* vs *L. pneumophila*.

TABLE 6. A Comparison of the Incidence of Signs and Symptoms in Patients with Pneumonia[a]

	Percentage of patients		
	Coxiella burnetii (N = 21)	*Mycoplasma pneumoniae* (N = 40)	*Legionella pneumophila* (N = 14)
Symptoms			
Fever	95	90	71
Chills	71	75	29
Rigors	38	20	7
Pleuritic chest pain	57	43	50
Headache	71	60	21[b]
Nausea	38	30	36
Abdominal pain	5	10	14
Diarrhea	10	5	14
Sore throat	14	33	0[c]
Anorexia	81	80	43
Myalgia	43	53	36
Arthralgia	33	30	7
Cough	71	95	71
Productive cough	33	83	43
Confusion	43	18	29
Signs			
Temperature >37°C on admission	90	92	100
Rales	52	88	79
Rhonchi	5	20	29
Consolidation	29	23	43

[a]Reproduced, with permission, from Marrie, 1990b.
[b]*L. pneumophila* significantly different from *C. burnetii*.
[c]*L. pneumophila* significantly different from *M. pneumoniae*.

TABLE 7. Complications of Pneumonia due to *Coxiella burnetii, Mycoplasma pneumoniae,* and *Legionella pneumophila*[a,b]

	No. (%) of patients		
	C. burnetii (N = 21)	*M. pneumoniae* (N = 40)	*L. pneumophila* (N = 14)
Renal failure	1 (5)[c]		3 (21)
Congestive heart failure	1 (5)[c]		3 (21)
Hemolysis	0	3 (8)	0
Pulmonary embolism	1	1 (3)	0
Ataxia	0	0	1 (7)
Deep vein thrombophlebitis	1 (5)	0	0
Respiratory failure	1 (5)	0	0
Stroke	0	1 (3)	1 (7)
Urinary tract infection	1 (5)	0	0
Gastrointestinal hemorrhage	0	1 (3)	0
Diarrhea	0	1 (3)	0
Pneumothorax	0	1 (3)	0
Seizures	0	1 (3)	5 (36)[d]
Hypothermia	1 (5)[c]	0	0
Myocardial infarction	1 (5)	0	0
Death	1 (5)[c]	1 (3)	5 (36)[d]

[a]Reproduced, with permission, from Marrie, 1990b.
[b]Mean number of complications was 0.38 for the *C. burnetii* group, 0.53 for the *M. pneumoniae* group, and 1.21 for the *L. pneumophila* group.
[c]All these complications occurred in the same patient.
[d]*L. pneumophila* significantly different from *M. pneumoniae* ($P < 0.08$) and *C. burnetii* ($P < 0.06$).

TABLE 8. Clinical and Laboratory Findings in Patients wth Atypical Pneumonia due to *Coxiella burnetii, Mycoplasma pneumoniae,* and *Legionella pneumophila*[a]

	C. burnetii (N = 21)	*M. pneumoniae* (N = 40)	*L. pneumophila* (N = 14)
Mean WBC × 10^9/L	8.95	12.52	10.40
Mean ALT (IU/L)	54.35	71.85	72.38
Mean AST (IU/L)	48.1	142.0	20
Mean bilirubin (mmol/L)	14.1	10.7	4.0
Mean CPK (IU/L)	912	154	527
Mean platelet count × 10^9/L			
Day 1	259.95	330.5	261.42
Day 5–7	317.63	335.67	235.00
No. (%) with pO_2 < 60 torr on admission	4/15 (26.6)	12/32 (37.5)	7/13 (53.8)
No. (%) with creatine > 110 mmol/L	6 (29)	4 (10)	7 (50)[b]
No. (%) in whom creatine increased by >100 mmol/L from day 1 to day 7	0	1 (2.5)	2 (14)
No. (%) with WBC >10 × 10^9/L on admission	6 (29)	20 (50)	6 (42.8)
No. (%) with CPK > 200 IU/L on admission	6 (29)	7 (17.5)	6 (42.8)
No. (%) with alkaline phosphatase >104 IU/L	12 (57)	19 (47.5)	9 (64)
No. (%) with ALT >29 IU/L	9 (42.8)	15 (37.5)	8 (57)
No. (%) with AST >41 IU/L	10/19 (52.6)	11 (27.5)	4/13 (30.7)
No. (%) with total bilirubin >16 mmol/L	3 (14.3)	8 (20)	3 (21)

[a]Reproduced, with permission, from Marrie, 1990b.
[b]*L. pneumophila* significantly different from *M. pneumoniae* and *C. burnetii*.

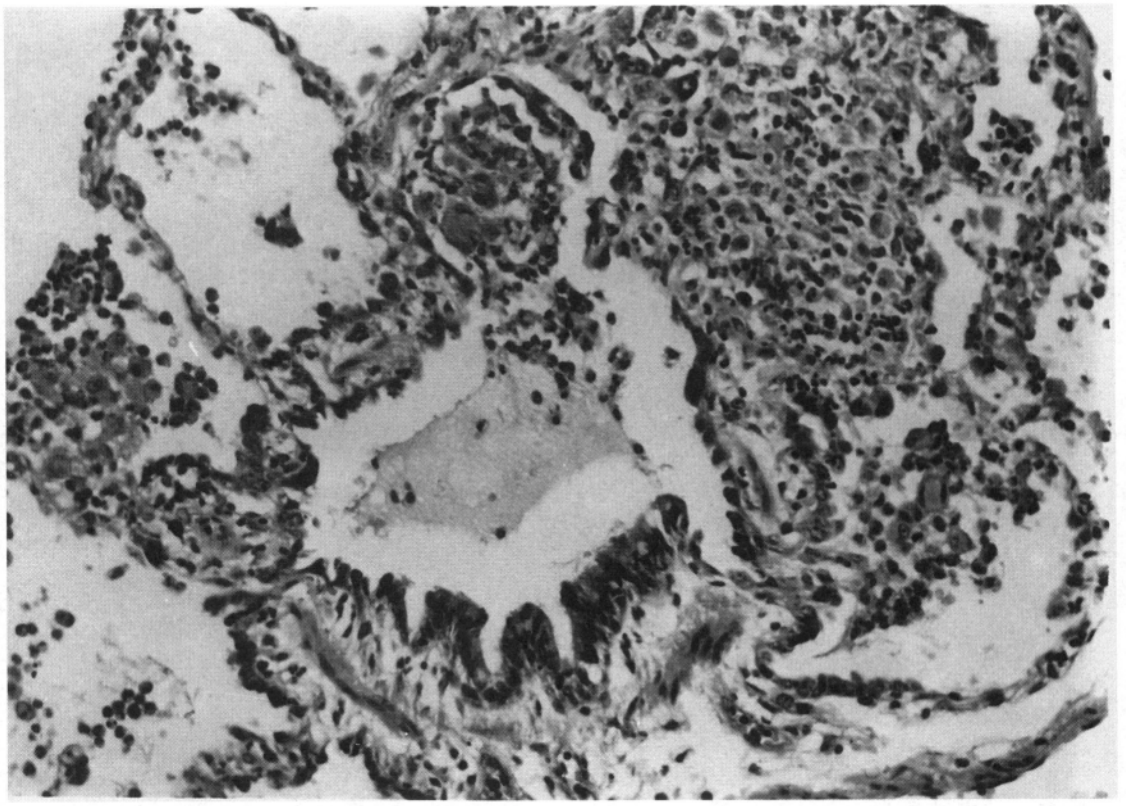

FIGURE 5. Photomicrograph of open-lung biopsy specimen from a patient with *Coxiella burnetii* pneumonia. Note the exudate in an airway and the hyperplasia of the cells lining the airway. Magnification × 480.

olfactory. Six patients described symptoms compatible with an expressive dysphasia. Three had hemifacial pain suggestive of trigeminal neuralgia. Diplopia and dysarthria were described in one patient each, and one patient had a visual field disturbance. These deficits lasted for only a few days. The rate of neurological involvement in these two studies is so much higher than that reported from any other country that it raises the possibility that a neurotropic strain of *C, burnetii* is currently circulating in the United Kingdom.

Rarely Q fever meningoencephalitis may be accompanied by seizures and coma (Reilly et al., 1990). Other neurological manifestations of Q fever include behavioral disturbances, cerebellar signs and symptoms, cranial nerve palsies, extrapyramidal disease, and the Miller-Fisher syndrome. Demyelinating polyradiculoneuritis has been reported in a 71-year-old man 10 weeks after the onset of *C. burnetii* pneumonia (Bonetti et al., 1991).

Miscellaneous Manifestations

Miscellaneous manifestations include Q fever in infancy (Richardus et al., 1985), hemophagocytosis (Estrov et al., 1984), hemolytic anemia (Cardellach et al., 1983), lymphadenopathy mimicking lymphoma (Ramos et al., 1957), splenic rupture (Baumbach et al., 1992), and erythema nodosum (Conget et al., 1987).

Acute Q Fever Treatment

Acute Q fever usually resolves without treatment within 15 days. Clinical evaluation of efficacy

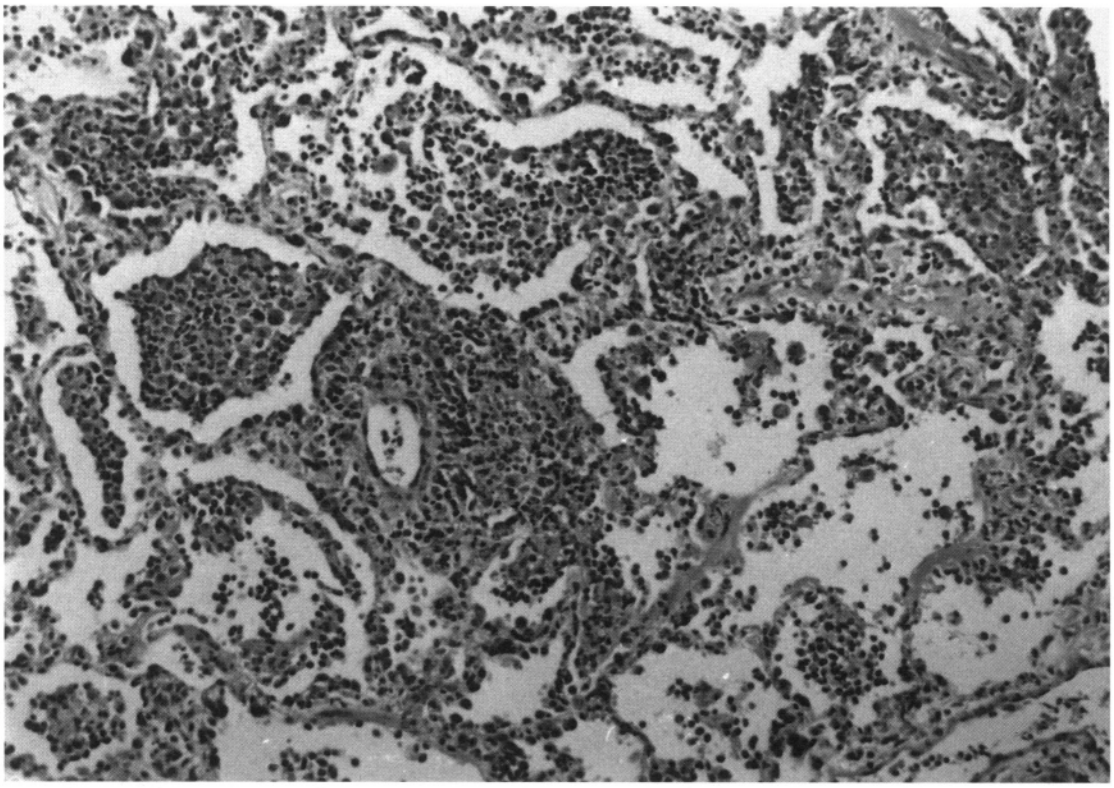

FIGURE 6. Photomicrograph of lung tissue from a patient with *Coxiella burnetii* pneumonia. Note the dense inflammatory infiltrate filling the alveoli.

of antibiotic regimens is difficult because of the short duration of the disease as well as the late confirmation of the serological diagnosis. According to these considerations, uncontrolled studies are of little value. A randomized study has been carried out with tetracycline only, which reduced the duration of fever by 50% (Powell et al., 1962). However, treatment had to have been started within the first 3 days of illness to be effective. Thus, blind therapy appears to be justified in severely ill patients as serological diagnosis is not available at that time.

In a randomized comparison of two regimens of acute Q fever treatment, doxycycline was superior to tetracycline, which was superior to placebo. Ofloxacin (600 mg/day) and pefloxacin (800 mg/day) were reported to be effective in Q fever pneumonia, producing apyrexia and clinical improvement 2 to 4 days after establishment of chemotherapy (Bertrand et al., 1988). However, antibiotic treatment lasted 16 days with ofloxacin and 21 days with pefloxacin. Erythromycin has been used to treat pneumonia caused by *C. burnetii* (Perez-del-Molino et al., 1991). Those with acute Q fever pneumonia who received erythromycin had a rapid clinical improvement, with apyrexia. However, erythromycin was reported by Marrie to be ineffective in severe cases of Q fever pneumonia despite using a daily dosage of 4 g (Marrie, 1990a). Whether erythromycin is an adequate treatment for atypical pneumonia when Q fever is a possible diagnosis has to be confirmed. Other antibiotics such as chloramphenicol, cotrimoxazole, and ceftriaxone were reported to be effective in acute Q fever.

However, tetracycline compounds and especially doxycycline are still the drugs currently recommended to treat acute Q fever illnesses. A regimen of doxycycline at 200 mg daily (100 mg bid) for 15 to 21 days is commonly prescribed. Quino-

lone compounds should be considered in Q fever meningoencephalitis as they penetrate the cerebrospinal fluid.

Laboratory Diagnosis of *Coxiella burnetii* Infections

In most instances the laboratory diagnosis of *C. burnetii* is serological. The microagglutination (Fiset et al., 1969), complement fixation (Murphy & Field, 1970), and indirect immunofluorescence antibody tests are available (Field et al., 1983; Peter et al., 1985). The last of these is best. The choice of a negative cut-off titer depends on the source and purity of the antigen and the amount of background antigen stimulation in the population to be studied. We use a 1:8 dilution as our first positive dilution in Nova Scotia. In Marseille, Tissot-Dupont et al. (1994) used a 1:50 dilution. A 4-fold rise in antibody titer is diagnostic of acute Q fever.

In acute Q fever, the phase II antibody titer is higher than the phase I antibody titer. In chronic Q fever the reverse occurs. Here, extremely high phase I antibody titers (>1:256,000) are often found.

Isolation of *Coxiella burnetii*

C. burnetii can be isolated in embryonated eggs or in tissue culture. Most laboratories are not able to work with C. *burnetii* because of its extreme infectiousness. The shell vial technique is useful for isolating *C. burnetii* and for determining antibiotic susceptibility (La Scola & Raoult, 1996). C. *burnetii* is isolated from the blood of 15% of patients with Q fever pneumonia sampled prior to antibiotic therapy in the first few days of disease and in 50% of patients with Q fever endocarditis (Musso & Raoult, 1995).

DNA Amplification Techniques

Polymerase chain reaction can be used to amplify *C. burnetii* DNA from tissue (Stein & Raoult, 1992b; Mallavia et al., 1990). This technique can be modified so that the amount of *C. burnetii* in tissue can be quantified (Fritz et al., 1995).

ACKNOWLEDGMENT

Portions of this chapter were published in *International Journal of Antimicrobial Agents,* 1997; 8: 145–167, and are reproduced here with permission of Elsevier Science B.V.

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Viral Pneumonia Due to Influenza and Parainfluenza Viruses and Adenoviruses

THOMAS R. CATE

Influenza Viruses

Introduction

Outbreaks of infection with influenza virus types A and B occur annually, usually during the cool months in temperate climates. These viruses have two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), against which protective antibodies are directed. Major factors determining the severity of the outbreaks of infection are the degree of antigenic change in the HA and NA, and the degree of immunity in the population. Influenza viruses can be spread by aerosol or contact. Propagation of an epidemic in a community often involves early spread of the virus among school children, who then take it home and to other activities. Increases in school and industrial absenteeism, emergency room visits for respiratory illness, hospital admissions for pneumonia, and pneumonia-influenza mortality generally become noticeable when influenza attack rates exceed 10%. More severe epidemics with attack rates exceeding 20%, or even 50% with a new pandemic strain, can severely strain the healthcare system and work force.

THOMAS R. CATE • Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030-3498.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

Virology

Classification, Physiochemical Characteristics, and Replication

Influenza virus types A and B constitute one genus in the family Orthomyxoviridae (Lamb & Krug, 1996; Hayden & Palese, 1997). A second genus in this family consists of type C influenza viruses that also infect humans, while two additional genera consist of viruses that do not. Influenza viruses have a lipid envelope derived from the host cell and a negative-sense, single-stranded RNA genome in segments that code for different viral proteins. The virions are somewhat pleomorphic spherules about 80 to 120 nm in diameter and have several hundred surface spikes 10 to 14 nm long. Influenza virus types can be distinguished by the antigenic specificity of two internal components, the nucleoprotein (NP), which together with three different polymerases and the RNA segments forms ribonucleoprotein (RNP) complexes, and the major component of matrix protein (M1), which underlies the lipid membrane. Type C influenza viruses differ from types A and B physiochemically (e.g., they have only a single surface glycoprotein that mediates binding to a different receptor than the HA of types A and B, as well as esterase receptor destroying and fusion activities), and they are an infrequent cause of respiratory disease (Moriuchi et al., 1991; Greenbaum et al., 1998). This chapter focuses on influenza virus types A and B.

For influenza viruses A and B, the surface spikes consist of rod-shaped HA and mushroom-shaped NA glycoproteins in a ratio of 4:1 and 5:1, respectively. The receptor for the HA on cells or in mucus is a terminal sialic acid with an α-ketosidic linkage to D-galactose or D-galactosamine. Following attachment and then endocytosis of an influenza virus by a potential target cell, HA also mediates fusion of the virus membrane with the endosome wall, which allows viral RNP to gain access to the cellular cytoplasm, a necessary step for infectivity. One requirement for fusion is prior proteolytic cleavage of HA, either within the parent cell or extracellularly. This cleavage yields two disulfide-linked chains, HA1 and HA2, the latter of which contains the fusion site at its N-terminus. A second requirement for fusion is a conformational change in HA that occurs within the acidic endosome of the target cell and activates the fusion site. Also critical for release of RNPs through the fused virus-endosome walls into the cytoplasm for influenza A viruses is pH-activated, ion channel activity of a second component of matrix protein, M2, which is an integral membrane protein represented in small amounts on the virus surface. The antiviral activity of amantadine and rimantadine depends on blocking M2's ion channel activity. Influenza B viruses lack a direct M2 counterpart but have a transmembrane protein, NB, that is derived from the NA gene segment and may serve a similar function.

Once RNPs reach the cytoplasm, they are transported into the nucleus, where they are transcribed into messenger RNAs (mRNAs) and template RNAs that serve as patterns for synthesis of new viral RNAs. A nonstructural protein (NS1) coded for by the virus regulates export of mRNAs to the cytoplasm for translation into viral proteins. Newly formed NP and polymerases are transported back to the nucleus, where new RNPs are formed, whereas HA, NA, and M2 or NB are transported to and inserted into the cell membrane from which new virions will bud. Ml protein mediates transport of newly formed RNP to the virus-modified membrane and forms the framework for budding virions. An important function of the NA is removal of sialic acids from glycoproteins on the cell, other virions, and mucus, thus preventing aggregation of the virions as they are released and facilitating their spread.

Antigenic Shift and Drift

The primary characteristics of influenza viruses are the frequent changes in antigenicity of their HA and/or NA (Lamb & Krug, 1996; Hayden & Palese, 1997; Cox & Fukuda, 1998). Minor changes ("drift") due to point mutations occur commonly. The frequency of mutations during replication of influenza virus RNA genomes is 1000-fold or more than that of mammalian DNA genomes, and the resulting minor changes in the HA or NA that give the virus a growth advantage in the face of immune pressure will be selected. This continuing antigenic drift results in emergence of variants of the circulating influenza A and B viruses that gradually become predominant at 2 to 5 year intervals.

Influenza A viruses, but not type B, can also exhibit a sudden, major antigenic change ("shift") in HA, with or without one in NA. One part of the explanation for these shifts is the occurrence of infections of various mammals and avian species with many different influenza A viruses, a genetic pool that is lacking for influenza B viruses. Avian influenza A viruses include strains with surface glycoproteins (termed H or N, followed by a number to indicate related groups) like those known to have caused human infections, plus others that are completely distinct antigenically. Avian viruses can transfer to lower mammals (Webster, 1997) and can occasionally cause human respiratory disease, as seen in the severe H5N1 influenza virus infections that were acquired from chickens in Hong Kong during 1997, which were fortunately poorly transmissible person to person (Claas et al., 1998; Shortridge et al., 1998). Receptor specificity of the HA is an important factor determining species selectivity of an influenza A virus (Ito et al., 1998). However, both avian and human influenza A strains can cause productive infections in hosts such as swine. If dual infection of respiratory epithelial cells with such viruses occurs in swine, a phenomenon known as reassortment can yield progeny viruses with various combinations of parental virus RNA segments. Reassortment of "internal" genes can affect replication and virulence of derivative viruses, and reassortment of those coding for the surface glycoproteins may render antibodies induced by prior infections of humans ineffective. If the derivative virus can

replicate well in humans and has novel, avian-derived surface glycoproteins, a new pandemic virus may emerge if that strain is transmitted to a human. The close proximity of people, swine, and water fowl in the Far East may explain the increased likelihood for new influenza strains to arise in that part of the world.

Such antigenic shifts occurred at intervals of one to four decades during the 20th century, with the influenza A subtype H1N1 in 1918, H2N2 in 1957, and H3N2 in 1968. Each of these viruses caused progressive worldwide epidemics (a pandemic) due to lack of protective immunity in the population, and each displaced the preceding subtype. The return of influenza A (H1N1) in 1977 after only a two-decade absence differed in that the epidemics it caused were milder, involved mostly children and young adults not previously exposed to an A(H1N1) virus, and did not displace the A(H3N2) subtype; A(H1N1) and A(H3N2) have co-circulated for more than two decades. Formal nomenclature of influenza viruses includes the virus type, the place where the virus was isolated, a serial or specimen number, the year of isolation, and, for influenza A viruses, the subtype designation in parenthesis. Examples are influenza B/Beijing/184/93, and A/Sydney/5/97 (H3N2).

Immunity

Antibodies directed against the HA and exhibiting hemagglutination-inhibiting (HAI) and neutralizing activities against the virus are the primary means of protection against infection by influenza A and B viruses (Couch & Kasel, 1983; Murphy & Clements, 1989). A serum HAI titer of 1:40 or greater is generally associated with resistance to infection by the test virus, but locally produced and/or serum-derived antibodies on mucus membranes of the respiratory tract have first contact with these viruses and thus an important role in preventing infection. Anti-HA antibodies that are insufficient in amount to prevent infection may, nevertheless, help reduce virus spread and facilitate recovery (Palladino et al., 1995).

Antibodies to the other surface glycoprotein, NA, are "infection permissive," that is, they do not prevent infection but can reduce cell-to-cell spread of virus and disease severity (Johansson et al., 1993). Similarly, antibody to the influenza A M2 protein is infection permissive but can reduce virus replication and disease severity in a murine model (Treanor et al., 1990). Cytotoxic T-lymphocyte responses to a variety of both type- and subtype-specific influenza virus antigens develop after one or more weeks in humans in response to influenza virus infection (Jameson et al., 1998), and these cells can play a role in reducing the severity of subsequent, crossreactive influenza virus infections (McMichael et al., 1983). However, despite the clear demonstration in infection models of these immune mechanisms that can provide road protection across influenza A virus subtypes and type B variants (but not crossing between types A and B), the clearest corollary of protection is the titer of functional antibody directed against the HA.

Antibodies to the first influenza virus with which an individual was infected as a young child tend to persist with age, presumably as a result of boosting by infections or vaccinations with related viruses (McElhaney et al., 1993). This phenomenon, known as "original antigenic sin," has been useful for deciphering influenza A viruses that circulated prior to development of the ability to cultivate the viruses.

Epidemiology

Influenza virus infections occur annually, usually over a period of 6 to 10 weeks during the cool months of the year in temperate climates, or at any time in the tropics with some accentuation during the rainy season (Hayden & Palese, 1997; Cox & Fukuda, 1998). They can be transmitted by aerosols generated by sneezing and coughing (Moser et al., 1979). One influenza virus strain may predominate, or two or three may cause overlapping or sequential waves of infection. Influenza A strains predominate most frequently, but type B strains do so at intervals of 2 to 4 years. Sporadic influenza cases have been reported throughout the year, even in temperate areas, perhaps aided by increases in international travel, and influenza should be considered in an outbreak of febrile respiratory disease at any time of year (Centers for Disease Control and Prevention [CDC], 1998b).

Within a community, increased absences of children from school for respiratory illness are fre-

quently the first sign of an influenza outbreak, and this absenteeism generally peaks during the first half of the outbreak (Glezen & Couch, 1978). Crowding together of susceptible persons in poorly ventilated areas facilitates transmission of these infections, just as when influenza A (H3N2) infected 49% of 81 healthy adolescents at a crowded ski hostel over a few days and led to the death of one in early 1997 (Lyytikainen et al., 1998). Although school children appear to be important disseminators of influenza virus in the community (Fox et al., 1982), spread among adults is also important (Foy et al., 1979b). Peak increases in industrial absenteeism and hospitalizations for pneumonia tend to occur in the second half of the epidemic, as do pneumonia-influenza deaths which are used to track influenza epidemics (Glezen & Couch, 1978).

Rates of respiratory illness, hospitalization, and death follow different age-related patterns during influenza epidemics (Glezen, 1982). Acute respiratory illness for which medical attention is sought has its highest rates in children and young adults. In contrast, rates of hospitalization peak at opposite ends of the age spectrum in young children and older adults, while deaths exhibit a third pattern with over 90% occurring in older adults (CDC, 2000). It should be noted that, while overall pneumonia rates for adults rise 2- or 3-fold during influenza epidemics, they do not do so in young children since influenza-associated pneumonia in the latter occupies a niche usually filled by respiratory syncytial virus and, to a lesser extent, parainfluenza and adenoviruses (Foy et al., 1973b, 1979a). Conditions increasing the risk for hospitalization for acute cardiopulmonary illness or death during influenza epidemics include infection with HIV; chronic heart, lung, and/or renal disease; malignancy, and diabetes (Neuzil et al., 1999), as well as the later stages of pregnancy (Neuzil et al., 1998). Chronic cardiovascular and/or pulmonary disease are particularly important for increasing the risk of death with pneumonia-influenza during epidemics (Barker & Mullooly, 1982). During influenza epidemics from 1969–1970 through 1993–1994, influenza-associated hospitalizations averaged between 130,000 and 170,000 per epidemic, and tended to be higher, between 160,000 and 200,000, for influenza A(H3N2) epidemics (CDC, 2000). More than 20,000 influenza-associated deaths occurred during 11 epidemics from 1972–1973 through 1994–1995, and more than 40,000 deaths during six of them.

Clinical Manifestations

Non-Pneumonic Influenzal Illness

Symptoms and complications of influenza virus infection can vary according to immune status, age, and underlying conditions or diseases, but it is useful to first consider the typical influenza syndrome. Although the primary target cells for influenza viruses in humans are those of the respiratory mucosa, systemic symptoms are often prominent, perhaps related to the release of inflammatory cytokines (Hayden et al., 1998; Kurokawa et al., 1996). The influenza syndrome often begins rather suddenly after an incubation period of 1 to 5 days with symptoms that can include fever, chills, headache, malaise, myalgias, lethargy or prostration, nasal obstruction, pharyngeal irritation, and nonproductive cough that may be associated with rasping substernal discomfort. Peripheral white blood cell counts are usually in the normal range (Douglas et al., 1966). The uncomplicated acute illness lasts 3 to 5 days, but there may be residual cough for several days and lassitude can persist for weeks. Part of the explanation for the latter may be bronchial hyperreactivity and small airways dysfunction that are common accompaniments of influenza virus infection, even without roentgenographic evidence of pulmonary involvement, and can take weeks to clear (Little et al., 1976, 1978). Significant decreases in forced expiratory volume have been noted following influenza virus infection of persons with chronic obstructive pulmonary disease (Smith et al., 1980) and cystic fibrosis (Pribble et al., 1990). Antiviral treatment of acute influenza A virus infection can speed recovery from the small airways dysfunction but not the hyperreactivity (Little et al., 1978), and influenza can play a significant role in precipitating exacerbations of asthma (Teichtahl et al., 1997; Atmar et al., 1998).

In contrast to the typical syndrome, influenza virus infection may cause few symptoms or only coryza in partly immune individuals, and symptoms in elderly persons can include lethargy, confusion, anorexia, and unexplained fever with or without respiratory complaints. Infected young children

may present with fever alone or with irritability, cough, and/or rhinorrhea; abdominal pain can be prominent, especially with influenza B virus infections (Kerr et al., 1975), although the pathogenesis is uncertain. Illnesses leading to hospitalization of young children infected with influenza virus include fever of unknown origin, pneumonia, encephalopathy other than Reye's syndrome, and seizures (Glezen et al., 1980; Caul et al., 1976; Brocklebank et al., 1972). Influenza virus infection can also cause laryngotracheobronchitis (croup) in young children, a disease more commonly associated with parainfluenza virus type 1, but bronchiolitis is unusual with influenza and much more suggestive of respiratory syncytial virus infection. The importance of influenza in precipitating febrile otitis media in young children is indicated by the significant reduction in this complication following administration of live, attenuated influenza vaccine (Belshe et al., 1998); influenza viruses can also contribute to acute sinusitis (Hamory et al., 1979). Rare nonpneumonic complications of influenza include encephalitis (Fujimoto et al., 1998), post-influenzal encephalitis (Hayase & Tobita, 1997), myocarditis with or without pericarditis (Proby et al., 1986; Ray et al., 1989), myositis, and rhabdomyolysis (Gamboa et al., 1979). Reye's syndrome (fulminant hepato-encephalopathy, fatty liver) has become uncommon with the recognition of the importance of avoiding salicylates for the treatment of children with influenza (or varicella) (Ward, 1997).

Pneumonia and Influenza Virus Infection

Pneumonia accounts for the majority of the severe morbidity and mortality that accompany influenza epidemics. It may occur as a continuum of the acute influenza syndrome when caused by the virus alone or by a virus plus bacteria, or after a delay of a few days when caused by secondary bacterial infection. Many clinical and pathological descriptions of these influenza-associated pneumonias followed the 1957–1958 A(H2N2) and 1968–1969 A(H3N2) pandemics, and the following summary is a compilation of several of them (Louria et al., 1959; Martin et al., 1959; Oseasohn et al., 1959; Oswald et al., 1958; Petersdorf et al., 1959; Lindsay et al., 1970; Bisno et al., 1971; Schwarzmann et al., 1971).

As noted, small airways dysfunction is a common component of the uncomplicated influenza syndrome, and patients with the acute influenza syndrome may have increased peribronchial markings interpreted as "interstitial pneumonia" even though no definite alveolar infiltrate is present. In a febrile, acutely ill patient who has nonexudative pharyngitis, a cough productive of only small amounts of nonpurulent sputum, and a few rales, rhonchi, and/or wheezes on chest exam without signs of consolidation, the increased bronchial markings may more appropriately be interpreted as evidence of acute bronchitis or tracheobronchitis (Petersdorf et al., 1959). However, some of these patients can have indistinct patches of alveolar infiltrate involving a portion of one of two lobes, but lack the severe hypoxia that accompanies the fulminant pneumonia described later in this chapter. This bronchitis/interstitial pneumonia occurring as a component of the acute influenza syndrome is the form of influenza pneumonia commonly seen in children; it is often due to the virus alone, but evaluation of the patient for secondary bacterial infection is appropriate. The course of the illness is usually like that of the uncomplicated influenza syndrome.

A vastly more ominous circumstance is the patient who presents during the acute phase (first 1 to 4 days) of influenza virus illness with acute respiratory distress and unequivocal alveolar opacification involving two or more lobes. A typical history is 1 to 2 days of the influenza syndrome with progressively increasing dyspnea and development of cyanosis and severe obtundation. Sputum is thin, often bloody, and sometimes frothy, with few cells and a few mixed bacteria on smear. Chest roentgenograms can be difficult to distinguish from pulmonary edema with hazy opacification in at least the lower lobes and perihilar congestion; pleural effusions may also be present. This fulminant pneumonia carries a mortality rate in excess of 50% and is uncommon except during severe epidemics or pandemics when immunity to the virus is minimal or absent. It most often occurs in persons with preexisting pulmonary vascular congestion due to atherosclerotic, valvular, or congenital heart disease, or during the second half of pregnancy. While it can be due to infection with influenza virus alone, combined acute bacterial and viral infections also

occur. Findings that would suggest bacteria include the occurrence of pleuritic pain and the presence of increased numbers of polymorphonuclear cells on smears of the bloody sputum, which may occur even if the peripheral white blood cell count remains in the normal or low range. *Staphylococcus aureus* is present in many of the fulminant, combined viral-bacterial pneumonias, sometimes in previously healthy young people, perhaps because this bacterium can facilitate proteolytic cleavage of influenza HA, which may speed up spread of infective virions from cell to cell (Scheiblauer et al.. 1992). Pneumococci are the other bacteria commonly present in combined viral–bacterial pneumonia. Chest roentgenograms of patients with combined viral-bacterial pneumonia may have areas of focal consolidation, but differentiation of rapidly progressive pneumonia due to virus alone from that due to virus plus bacteria is very uncertain unless one or more abscesses or pneumatoceles suggestive of *S. aureus* is present. Ventilatory support is required for managing these patients, and secondary infections with *Pseudomonas aeruginosa* and other resistant organisms are common. Patients who survive may develop pulmonary fibrosis with permanent reduction in pulmonary function, even though it may not be severe enough to interfere with normal activities (Winterbauer et al., 1977).

Most pneumonias occurring during influenza epidemics are not the fulminant form just described, but are due to delayed secondary bacterial infection. A typical history is one of an influenza syndrome that seems to be easing after a few days, but then shows recurrence of fever, increase in cough, and production of purulent sputum that may become blood-tinged or rusty in appearance. Shaking chills, pleuritic pain, and increases in peripheral blood polymorphonuclear cells with immature forms may occur. Chest roentgenograms usually reveal localized or patchy consolidation in one or more lobes rather than the diffuse, hazy opacification more typical of early fulminant pneumonia; a pleural effusion may be present. Pneumococci are the bacteria most frequently involved, but in a somewhat lower proportion than in nonepidemic periods, whereas the frequency of secondary *S. aureus* pneumonia increases disproportionately during influenza epidemics. For example, in one series of patients with bacterial pneumonia during the 1968–1969 influenza A(H3N2) epidemic, a pneumococcus was the organism found in 48% and *S. aureus* alone or with other bacteria in 26%, while the percentages during a nonepidemic period in the same institution were 62% and 10%, respectively (Schwarzmann et al., 1971). Toxic shock syndrome due to secondary infection with a toxigenic strain of *S. aureus* has been described (MacDonald et al., 1987). Mortality rates for secondary bacterial pneumonias during influenza epidemics are similar to the overall rate for hospitalized patients with community-acquired pneumonia, 10% to 25% (Bartlett & Mundy, 1995); increased age and underlying disease are important cofactors. However, patients with secondary *S. aureus* pneumonia tend to be younger than patients having secondary infections with other bacteria, and, despite this, their mortality rate is at the upper end of the range (Oswald et al., 1958; Schwarzmann et al., 1971).

Diagnosis

Although other respiratory viruses can cause the influenza syndrome, influenza viruses will largely displace them in the midst of an epidemic so a clinical diagnosis is often sufficient, and public health authorities will be knowledgeable about which influenza virus is circulating. However, specific viral diagnosis is often desirable in other settings for defining the epidemiology of the infection, guiding therapeutic decisions, or confirming the cause of a severe or unusual illness presentation. Influenza viruses are present in respiratory secretions in high titer during the first 1 or 2 days of illness, and then progressively decline; recovery of virus 5 or 6 days after onset of illness is unusual in adults, but virus shedding can persist a few days longer in children, and several days longer in immunosuppressed patients (Hayden & Palese, 1997). Nasal washes and aspirates, sputa, and nose and throat swabs are appropriate specimens for virus culture. Placing the specimen in a protein-containing medium such as veal infusion broth wilh 0.5% bovine serum albumin and maintaining it at 4°C can preserve infectivity for up to 5 days (Baxter et al., 1977).

Influenza viruses can be grown in cell cultures or embryonated eggs and can be detected by hemadsorption, hemagglutination, immunofluorescence, or enzyme immunoassay (EIA), a process that requires 2 to 5 days. Common cell lines employed are

Madin-Darby canine kidney (MDCK) and rhesus monkey kidney derived LLC-MK2, each with trypsin but no serum in the culture medium. More rapid culture results can be obtained in 1 to 2 days using centrifugation of the specimen on to shell vial cell cultures, followed by immunofluorescent antibody detection after incubation for 24 hours (Johnston & Siegel, 1991). Even quicker but somewhat less sensitive means for demonstrating the presence of virus are tests for direct detection of viral antigens in the specimen rather than in culture. A dot-blot EIA that detects influenza A-specific antigen (Directigen FluA, Becton-Dickinson) is 75% to 85% as sensitive as culture, and direct fluorescent antibody staining of cells from the specimen can also be used (Atmar et al., 1996; Reina et al., 1996). Reverse transcription-polymerase chain reaction (RT-PCR) detection of influenza nucleic acid in the respiratory specimens appears to be at least as sensitive as culture for diagnosis (Atmar et al., 1996; Pregliasco et al., 1998). Among these means for detecting the virus in respiratory secretions, the EIA for influenza A virus is available commercially in a format easily and quickly performed in the office setting. New rapid tests suitable for office use are an EIA that can detect NP antigens of both influenza A and B viruses and uses a unique optical detection system (AB Flu OIA, Biostar, Boulder, CO), and an assay that detects enzymatic activity of the NA of both influenza A and B viruses (ZstatFlu, ZymeTx, Oklahoma City, Oklahoma).

The other means for diagnosing influenza virus infection is demonstration of a significant increase in the amount of antibody to the virus in the interval between collection of acute and convalescent (2 to 3 week) sera. Common assays detect complement-fixing (CF) antibodies against type-specific influenza virus antigens; hemagglutination-inhibiting (HAI) antibodies that are directed against the specific influenza virus strain, but may exhibit some cross-reactivity to related strains; and neutralizing antibodies that are also primarily strain-specific. Enzyme-linked immunosorbent assays (ELISA) can also be used to measure antibody class and subclass responses to HA or other antigens. Estimates of the relative ability of these assays to detect significant increases in infection-induced antibody can differ widely in different studies (Madore et al., 1983; Foy et al., 1987), perhaps because of differences in epidemic viruses, test antigens, laboratory techniques, and/or other factors. When detection of all influenza virus infections is desired, use of at least two different antibody assays and two different, sensitive methods for detecting virus may be appropriate.

Treatment

Therapy of acute, uncomplicated influenza virus infection is aimed primarily at alleviating troublesome symptoms and minimizing the risk of complications. Extra fluid intake is necessary to compensate for losses due to fever and to maintain the flow of secretions. A decongestant may be needed to help clear secretions. Antihistamines may inspissate secretions so that they are less effectively cleared, and sedative effects of first-generation antihistamines can amplify central nervous system side effects of amantadine if the latter is also being administered therapeutically (Millet et al., 1982). If reduction of excess secretions is needed for comfort of an allergic individual with influenza, a nonsedating antihistamine may be preferred. Analgesics and antipyretics provide some relief and facilitate rest, but aspirin should be avoided in children because of the risk of Reye's syndrome.

Antiviral treatment of acute influenza A virus infection with amantadine, if begun within 48 hours of illness onset and continued for 3 to 5 days (24–48 hours after major symptoms abate), can shorten the duration of fever and symptoms (Douglas, 1990); rimantadine is also approved for this purpose in adults, but not children. This antiviral treatment can also shorten the duration of the small airways dysfunction associated with acute influenza (Little et al., 1976), but reduction in other complications of influenza has never been clearly demonstrated. Side effects of these antiviral agents include dizziness, drowsiness, insomnia, nausea, and vomiting and tend to be more prominent with amantadine than rimantadine, but they are not often a problem during brief use of the medications for treatment (Millet et al., 1982). Cross-resistance of the influenza A virus to these antivirals often develops during therapy with either of them in three of the groups of persons most prone to complications of influenza—young children (Hall et al., 1987), the elderly (Mast et al., 1991), and immunosuppressed individuals (Englund et al., 1998). Shedding of resistant viruses by immunosuppressed persons can be prolonged

(Klimov et al., 1995), and resistant viruses can spread to others in close proximity if they lack protection or are dependent on one of these antiviral agents for prophylaxis (Mast et al., 1991). Isolation procedures should be used in institutions such as nursing homes and hospitals for persons with influenza A virus infection until their symptoms have ceased, whether or not the person is or has been treated with amantadine or rimantadine. Resistant viruses have not thus far spread widely in the community (Belshe et al., 1989; Prud'homme et al., 1997; Valette et al., 1993); however, the possibility exists that more recent isolates may have some decreased sensitivity (Pemberton et al., 1986), and an influenza A strain with a resistance mutation in M2 RNA has been recovered from a nursing home patient prior to administration of amantadine or rimantadine in the institution that season (Houck et al., 1995). Two new anti-influenza medications active against both type A and B influenza viruses by means of NA inhibition (Calfee & Hayden, 1998) have recently become available for treatment of infections with these viruses, zanamivir administered by inhalation and oseltamivir taken orally (CDC, 2000).

Treatment of delayed, secondary bacterial pneumonia requires an antibiotic regimen active against known or presumptive pathogens, most commonly a pneumococcus or *S. aureus.* The amount of virus present in respiratory secretions from these patients will usually have decreased to low or undetectable levels, and no benefit could be expected from use of an antiviral agent.

Patients who present with fulminant pneumonia within 2 or 3 days of influenza illness onset are a much greater therapeutic problem. Ventilatory support is often required. They will likely have high liters of virus in respiratory secretions and may have concomitant bacterial infection that can be difficult to diagnose clinically. Death can occur quickly, before bacterial culture results are available. Administration of an antibacterial effective against the most common organisms, pneumococci and .V. *aureus,* is appropriate after cultures are collected. Stopping the antimicrobial therapy or keeping its spectrum as narrow as possible based on culture results may help reduce the frequent nosocomial infections with resistant organisms that occur in these patients. With regard to antiviral therapy, orally administered amantadine or rimantadine will face uncertain adsorption in these critically ill patients and will require at least a few hours to achieve therapeutic levels in the respiratory tract. In murine models of influenza pneumonia, administration of amantadine or ribavirin directly into the respiratory tract via small-particle aerosol provides therapeutic benefit later in the course of the infection than administration by a nonrespiratory route (Wilson et al., 1980). Ribavirin aerosol is approved only for treatment of severe lower respiratory tract infections due to respiratory syncytial virus in infants or young children. However, the medication is active against a wide variety of viruses with either DNA or RNA genomes, including influenza A and B viruses, and it has been shown in small trials and compassionate use protocols to have therapeutic activity against both uncomplicated influenza and influenza pneumonia of adults when administered by aerosol (Knight et al., 1981; Wilson et al., 1984; Gilbert et al., 1985, 19092; Aschan et al., 1989). If a patient receiving assisted ventilation is treated with ribavirin aerosol, careful monitoring is required because drug deposits can cause ventilator malfunction.

Prevention

Influenza Vaccine

The two measures currently available for preventing or reducing the impact of influenza are parenteral vaccination with inactivated (killed virus) vaccine and, for influenza A, oral administration of one of the antivirals, amantadine or rimantadine (CDC, 2000). Policies are presently aimed primarily at preventing influenza in those at greatest risk for severe disease: persons 50 years of age or older; residents of nursing homes or other chronic care facilities for persons with chronic medical conditions; persons of any age with chronic disorders of the cardiovascular or pulmonary systems, including asthma; persons who require regular medical care for chronic metabolic disease including diabetes mellitus, impaired renal function, hemoglobinopaihies, or immunosuppression from any cause; persons 18 years old or younger who are receiving long-term aspirin therapy and might be at risk for Reye's syndrome; and women who will be in the second or third trimester of pregnancy during the influenza season. An annual vaccination should be given to these high-risk individuals, as well as to

persons who care for or are in regular contact with them to reduce the risk of transmitting the infection. Others who are candidates for vaccination are those who perform essential services, members of work groups in which significant illness would disrupt the group's function, and anyone who simply wants to avoid influenza illness.

Inactivated influenza virus vaccines are prepared from virus grown in embryonated chicken eggs and rendered noninfectious. Their virus composition is updated annually as necessary to include strains representative of the most current A(H1N1), A(H3N2), and B viruses identified from worldwide surveillance, but preparation must begin 9 or more months before the usual appearance of annual influenza outbreaks, time enough for antigenic drift to occur in the circulating virus(es). The vaccines are highly purified preparations containing nondisrupted whole virions ("whole virus"), disrupted virions with partial purification of surface glycoproteins ("split virus" or "subvirion"), or "purified surface antigen." Minute amounts of egg protein may remain in the vaccine, and persons with anaphylactic hypersensitivity to eggs should not routinely receive it. Febrile reactions to influenza vaccination are more common in children than in older subjects, and more so with whole than split virus vaccine; therefore, split virus or purified surface antigen vaccine should be given to children 12 years old or younger. Reactions to whole and split virus vaccines are similar in older individuals. Antibody responses to vaccine will generally be at their highest levels 1 to 4 months after vaccination and may decline somewhat thereafter. The optimum time for vaccination so that protection will be at its highest level at the usual time of influenza outbreaks in the northern hemisphere is October to mid-November, but vaccination is more important than its precise timing.

An excess of about 10 cases of Guillain-Barre Syndrome (GBS) per million recipients of the 1976 swine influenza vaccine occurred within a few weeks of the vaccination (CDC, 2000; Safranek et al., 1991). GBS is an ascending paralytic syndrome that usually occurs in 10 to 20 persons per million each year independently of influenza vaccination. Slow, incomplete, or complete recovery is possible, but GBS results in the death of 5% to 10% of patients. Surveillance from 1976 to 1991 revealed very slight increases in the incidence of GBS in the 6 weeks following influenza vaccination that did not reach statistical significance, but combined data for the 1992–1993 and 1993–1994 seasons was statistically significant with an estimated excess of one to two cases of GBS per million vaccinees (Lasky et al., 1998). This incidence of vaccine-induced GBS, even if documented in subsequent studies, is much less than the severe influenza morbidity and mortality that can be prevented by an active vaccination program. However, persons who have developed GBS following influenza vaccine should not as a rule receive further influenza vaccinations.

Protection by influenza vaccine varies in part according to the closeness of fit between the vaccine strain and the virus that spreads in the community, but usually more according to the population being vaccinated. Protection of healthy young to middle-aged adults against influenza illness is usually 70% to 90% effective, but is only half as effective or lower in elderly nursing home residents (CDC, 2000; Patriarca et al., 1985). However, protection of the latter high-risk subjects against the more severe consequences of influenza—hospitalization, pneumonia, and death—are higher and can approach 80%) against death. Factors that increase the level of vaccine protection in institutions such as nursing homes are higher levels of vaccination of the residents to provide a degree of "herd immunity" (Patriarca et al., 1986), and, more importantly, high levels of vaccination of the care providers (Potter et al., 1997).

Live attenuated influenza virus vaccines prepared by controlled, in vitro reassortment to have genes coding for surface glycoproteins from a current wild-type virus and remaining genes from an attenuated cold-adapted "master strain" (Maassab & DeBorde, 1985) have been investigated for more than two decades in both low- and high-risk subjects. These cold-adapted vaccines are administered by nose drops and have been shown to provide effective prophylaxis against influenza in young children (Belshe et al., 1998), apparently more effective in them than standard inactivated vaccine (Clover et al., 1991). Young children will be a major target group for these live attenuated influenza virus vaccines when they are released, but it also appears that their simultaneous use with parenteral inactivated vaccine may offer more effective prophylaxis to elderly, high-risk persons than inactivated vaccine alone (Treanor et al., 1992), perhaps because of

enhanced secretory antibody (Gorse et al., 1996) and/or cell-mediated immune responses (Gorse & Belshe, 1990).

Antiviral Agents

The two available antiviral medications for prevention of influenza, amantadine and rimantadine, have many similarities. They are active only against influenza A viruses, they inhibit growth of these viruses through the same mechanism, and each can induce resistance that crosses to the other. They are administered orally to healthy individuals in similar doses and are each about as effective as vaccine for preventing influenza A virus infection so long as they are taken regularly (Dolin et al., 1982; CDC, 2000; Hayden, 1997; Mahmood & Sacks, 1995). Despite these similarities, important differences exist in how the two medications are metabolized, and in their side effects. Amantadine is excreted unchanged by the kidneys; its dosage must be reduced in proportion to any reduction in creatinine clearance, and in the elderly because of the natural decline in renal function with age. In contrast, about 75% of rimantadine is metabolized in the liver, with metabolites and any remaining rimantadine being excreted by the kidneys (Wintermeyer & Nahata, 1995). Reductions in rimantadine dose are required only for severe hepatic or renal failure, but, as with amantadine, some elevations in rimantadine blood levels occur in the elderly, and reduction in dose in persons 65 years of age or older is recommended to reduce side effects. Both medications are effective prophylactically at a dose of 100 mg once a day in these older individuals (Arden et al., 1988; Drinka et al., 1998; Hayden, 1997; Nicholson, 1996; Monto et al., 1995).

Both amantadine and rimantadine can cause some nausea and vomiting, but amantadine is about twice as likely as rimantadine to cause troublesome central nervous system side effects such as dizziness, drowsiness, and insomnia. In one comparative study, for example, 13% of healthy young adult recipients of amantadine discontinued its prophylactic use because of side effects versus 6% of recipients of rimantadine (Dolin et al., 1982). The incidence and severity of central nervous system side effects are also substantially lower in elderly persons with rimantadine than amantadine even when drugs are given in renally-adjusted reduced doses (CDC, 2000), and amantadine can increase seizure activity in persons with a preexisting seizure disorder (Atkinson et al., 1986). These central nervous system side effects give a preference to rimantadine over amantadine for chemoprophylaxis against influenza. However, amantadine also has useful therapeutic activity against Parkinson's disease that is not shared by rimantadine (Hingtgen & Siemers, 1998).

Either medication must be taken daily for the duration of an epidemic if it is the sole means of prophylaxis, which makes efficacy largely dependent on compliance. Also, the cost of 2 weeks of prophylaxis with one of these medications is approximately that of an influenza vaccination, and so continuing the medication for the 6- to 8-week duration of a community influenza epidemic would be relatively costly. Neither amantadine nor rimantadine interferes with antibody responses to vaccine. When vaccination has been delayed until an influenza A virus epidemic has begun, a cost-effective use of one of these antiviral agents is to administer it only for the 2 weeks required for initiation of an antibody response to the vaccine. Another very important use is for control of influenza A outbreaks within institutions such as nursing homes. Although vaccination of residents and caregivers is the primary means for preventing institutional outbreaks of influenza, brief (1 to 3 weeks) additional use of amantadine or rimantadine can be effective for control of influenza A outbreaks that sometimes occur within such facilities despite the vaccinations (Arden et al., 1988; Patriarca et al., 1987; Drinka et al., 1998). Medications that act as NA inhibitors offer the potential for effective prophylaxis against type B as well as type A influenza virus illness in the future (Calfee & Hayden, 1998).

Parainfluenza Viruses

Introduction

Parainfluenza viruses are the most common cause of laryngotracheobronchitis (croup) in young children and are second only to respiratory syncytial virus as causes of lower respiratory tract illness in children below 6 years of age. In older children and young to middle-aged adults whose general health is good, parainfluenza viruses are usually minor

causes of upper respiratory illnesses. However, they can directly cause severe pneumonia and/or precipitate secondary bacterial pneumonia in immunosuppressed persons and the elderly. No vaccines or preventive medications presently exist; control within institutions depends on effective application of isolation procedures.

Virology

Classification, Physiochemical Characteristics, and Replication

The parainfluenza viruses comprise four types and are members of the Paramyxoviridae family, which includes measles, mumps, and respiratory syncytial viruses, as well as other animal viruses (Lamb & Kolakofsky, 1996). They have a negative-strand, nonsegmented RNA genome encased within a helical nucleocapsid formed by nucleoprotein with attached polymerases, and a lipid envelope derived from the host cell overlying a matrix protein layer. The viruses appear like somewhat pleomorphic droplets 150 to 350 nm in diameter and have two different types of glycoprotein spikes protruding 8 to 12 nm from their surface. One type of spike, "HN," mediates both hemagglutination (attachment) and NA (release) activities. The other spike, "F," which must be proteolytically cleaved to become active, mediates fusion of virus and cell membranes to give the nucleocapsid access to the cell cytoplasm. Virus replication occurs entirely within the cytoplasm of host cells, with budding of new virions from the cell surface. Hemadsorption mediated by HN inserted into the cell membrane at the site from which a new virion will bud is useful for detecting infected cells in cultures. Also, fusion between infected cells can be mediated by protruding F protein, and multinucleated (fused) cells with cytoplasmic inclusions may be seen histopathologically in lung tissue of immunosuppressed patients with progressive parainfluenza pneumonia (Akizuki et al., 1991; Wendt et al., 1992; Apalsch et al., 1995).

Immunity

Antibody responses to both HN and F proteins appear to be required to provide immunity (Kasel et al., 1984; Ray et al., 1988a), which is type-specific (Ray et al., 1990). Presence of these antibodies in secretions may enhance their ability to provide protection (Smith et al., 1966; Ray et al., 1988b). It should be noted, however, that parainfluenza viruses can persist in the respiratory tract for weeks or months (Muchmore et al., 1981) and may do so in the presence of both serum and secretory antibody (Gross et al., 1973). The role of cell-mediated immunity in protection against parainfluenza viruses has not been defined, but the occurrence of progressive, severe infections in immunosuppressed patients implies that it may participate in clearing the infection.

Epidemiology

Most information about the epidemiology of parainfluenza virus infections concerns types 1, 2, and 3 and their important roles in lower respiratory tract disease of young children. Parainfluenza virus type 4 is more difficult to isolate, and reagents to identify it have not in the past been as routinely available as those for the other types. Type 4 viruses have been assumed to cause mostly upper respiratory illnesses on the basis of illnesses from which they were initially recovered (Piedra et al., 1997). However, two groups have identified type 4 viruses as causes of a portion of severe lower respiratory tract disease and occasional aseptic meningitis, predominantly in children less than 2 years of age (Rubin et al., 1993; Lindquist et al., 1997). More work is needed to fully define the epidemiologic niche of parainfluenza virus type 4.

Parainfluenza virus types 1, 2, and 3 each tend to occur in clusters or outbreaks that can change in pattern over the years (Knott et al., 1994). Type 3, usually the most frequently recovered parainfluenza virus, tends to cause outbreaks in the spring, but these outbreaks can occur in or extend to other seasons. Type 1, the next most frequently recovered, causes sharp peaks of infection in the fall of alternating years; these were even-numbered years for a while, but switched to odd-numbered years in the early 1970s. Type 2 parainfluenza virus, the third most frequently recovered of this group, causes sporadic fall outbreaks that may or may not coincide with a type 1 outbreak. The majority of infections are identified during the first 6 years of life, with some sparing during the first 6 months (Foy et al., 1973a; Chapman et al., 1981; Knott et al.,

1994), presumably because of maternally derived antibody. Primary infections and many first reinfections with a parainfluenza virus occur within the first 2 years of life for the majority of children, and the primary infection with a given type is more likely to cause clinically significant lower respiratory tract illness (Glezen et al., 1984). Among children over 6 years of age who are identified as being infected with a parainfluenza virus, upper respiratory illnesses predominate (Knott et al., 1994). These viruses are infrequently identified as a cause of respiratory illness in healthy adults (Nicholson et al., 1997; Makela et al., 1998), although adults frequently exposed to children with respiratory illness are at increased risk (Yang & Rubin, 1995). Also, parainfluenza viruses can occasionally cause upper respiratory illness and pneumonia in otherwise healthy adults under special circumstances; examples are pneumonia among marine recruits (Wenzel et al., 1972) and an outbreak of upper respiratory illness that preceded several cases of bacterial lobar pneumonia among residents of a chronic care facility for older people (Fiore et al., 1998). Immunocompromised persons of any age are also at risk (Wendt & Hertz, 1995). Among recipients of bone marrow or other organ transplants, parainfluenza virus infections have been predominantly due to type 3 and may occur at any time of the year (Wendt et al., 1992, 1995; Apalsch et al., 1995; Lewis et al., 1996).

Clinical Manifestations

Parainfluenza virus infections can cause the full range of respiratory tract illnesses ranging from the common cold to pneumonia, and they may also cause undifferentiated febrile illness (Knott et al., 1994) or, rarely, aseptic meningitis (Rubin et al., 1993; Lindquist et al., 1997). The most distinctive illness caused by parainfluenza viruses is croup in young children (Henrickson et al., 1994; Knott et al., 1994; Marx et al., 1997), with its brassy, barking cough and inspiratory stridor. The incidence of croup notably rises with fall outbreaks of parainfluenza virus type 1 infection (Marx et al., 1997), but it can also be caused by types 2 and 3, as well as by respiratory syncytial, influenza, and other respiratory viruses to a lesser extent (Henrickson et al., 1994; Knott et al., 1994). Secondary bacterial infection of children with croup is uncommon (Korppi et al., 1990).

Parainfluenza viruses are also prominent causes of tracheobronchitis, bronchiolitis, and pneumonia in young children, although they are exceeded by respiratory syncytial virus for the latter two, particularly in early infancy (Chapman et al., 1981; Piedra et al., 1997). However, infants who have preexisting lung disease and become infected with a parainfluenza virus have a higher probability of developing bronchiolitis and/or pneumonia than previously healthy infants with this infection (Heidemann, 1992). Bronchiolitis will cause expiratory wheezing, as well as air trapping with hyperaeration on chest roentgenograms, while parainfluenza virus pneumonia often causes patchy interstitial to interstitial-alveolar type infiltrates, perhaps with some areas of atelectasis. Mixtures of these two roentgenographic patterns can be seen. Bacterial superinfections, particularly with pneumococci, do occur in children with pulmonary disease caused by parainfluenza virus infection (Korppi et al., 1990; Piedra et al., 1997), although they are infrequent with croup or with pulmonary disease caused by respiratory syncytial virus.

Immunodeficient persons, including older children and adults, are at risk for parainfluenza virus infection that can begin with upper respiratory manifestations and progress to pneumonia (Wendt & Hertz, 1995). Concomitant or secondary infections with other agents are common and the mortality rate can be high (Wendt et al., 1992; Apalsch et al., 1995; Lewis et al., 1996).

Diagnosis

Parainfluenza virus can be detected in respiratory secretions by virus culture, or by demonstration of viral antigen or nucleic acid in the specimen. A nasal wash or aspirate is the most useful specimen. While specimens collected within a few days of onset will have the greatest likelihood of yielding a positive culture, shedding of parainfluenza viruses can persist for 3 or 4 weeks (Frank et al., 1981). These viruses are stable for several days under refrigeration in a protein-containing medium (Baxter et al., 1977). A useful and relatively inexpensive cell line for growing the viruses is LLC-MK2 with added trypsin. Five to 14 days of incuba-

tion may be required before virus can be detected in cell cultures by hemadsorption with guinea pig red cells. More rapid culture results can be obtained using the shell vial culture technique and immunofluorescent antibody staining at 48 hours (Brinker & Doern, 1992). Monoclonal antibody panels are available for the latter purpose and/or direct immunofluorescent antibody staining of cells from the original specimen. The newest technique for rapid and sensitive detection of parainfluenza viruses in respiratory specimens is the multiplex RT-PCR that can detect and differentiate nucleic acids of types 1, 2, and 3 in a combined reaction (Echevarria et al., 1998). Demonstration of a significant increase in antibody to the virus in convalescent (2 to 3 week) serum relative to acute serum is another means for diagnosing parainfluenza virus infection. CF, HAI, and neutralization tests can be used for this purpose, although many cross-reactions exist between paramyxoviruses, including mumps (Ito et al., 19987), which may confuse interpretation of CF and HAI results. Neutralization tests are the most specific antibody assay.

Treatment

No approved antiviral agents for parainfluenza viruses exist, although ribavirin has activity against them. Management of most manifestations of parainfluenza virus infection in previously healthy persons is symptomatic, but some special considerations exist concerning treatment of croup that depend on the severity of the airway obstruction (Piedra et al., 1997). Severe disease with signs of hypoxia will require hospitalization in intensive care, oxygen therapy, and possible intubation. Systemic and nebulized corticosteroids can be beneficial and may keep a child with mild to moderate croup from advancing to a more severe stage. Racemic epinephrine can also provide some short-term relief of the airway obstruction, but children given this medication require very close observation for possible deterioration when the effect wears off. Antibiotics are not of use in the management of typical croup. The usual course of the disease is 3 to 4 days.

Development of parainfluenza virus pneumonia in an immunodeficient patient is a potentially lethal complication. Limited experience of one group suggests that ribavirin may be beneficial in treating such patients if it is administered before the onset of severe respiratory failure (three of three patients survived) as opposed to after ventilatory support is required (two of two died) (Lewis et al., 1996). As noted previously, management of ribavirin aerosol therapy for patients requiring ventilatory support can be difficult because drug deposits can interfere with ventilator function.

Prevention

No vaccines or antivirals exist for prevention of parainfluenza virus infections. Recommendations for controlling spread of these viruses in hospitals containing high-risk patients (immunodeficiency, pulmonary abnormality) include quick identification and cohorting of known or possibly infected patients, strict contact isolation of these patients with use of gowns and close attention to handwashing and/or glove use, and exclusion of visitors and staff with respiratory illness from seeing or working with high-risk patients (Piedra et al., 1997). Such measures appear to be capable of controlling spread of both parainfluenza and respiratory syncytial viruses (Singh-Nasz et al., 1990; Leclair et al., 1987).

Adenoviruses

Introduction

Adenoviruses that infect humans can cause a wide variety of illnesses affecting not only the respiratory tract, but also other organs. Adenovirus pneumonia was initially defined in military recruits, but it now is seen largely as a portion of the pneumonia occurring in infants and in immunosuppressed individuals of any age, in outbreaks within closed groups of persons of any age, occasionally in older children, and sporadically in others. In infants and immunosuppressed individuals, the infection can progress to disseminated disease commonly involving lungs, liver, and kidneys with a high mortality rate. An oral live virus vaccine was effective for controlling adenovirus disease in military recruits but is being phased out. No other vaccine or therapy is approved.

Virology

Human adenoviruses are members of the Mastadenovirus genus of the Adenoviridae family along with adenoviruses of several different animal species; the other genus in the family, Aviadenovirus, contains strains that infect only birds (Ruuskanen et al., 1997; Shenk, 1996). All Adenoviridae have a linear, double-stranded DNA genome within a nonenveloped icosahedral protein shell 70 to 100 nm in diameter. The protein shell is composed of 252 subunits, of which 12 are pentons at the vertices of the icosahedron, and the remainder are hexons that form the 20 triangular faces. Protruding from each penton is a fiber that varies in length for different serotypes and has a terminal knob.

A conserved hexon antigen is shared between adenoviruses of humans but does not cross to adenoviruses of other species. Adenovirus serotypes can be distinguished by the specificity of neutralizing antibodies that bind to epitopes on the hexon and on the terminal knob of the fiber, and by the specificity of HAI antibodies that prevent binding of red cells from different animal species to the fiber shaft of different serotypes. At least 49 serotypes have been defined, and multiple genotypes defined with restriction endonucleases can exist within a serotype. Other biologic characteristics are the ability of adenoviruses to transform rodent cells and the ability of certain serotypes to induce tumors in rodents; however, transformation occurs very inefficiently in more permissive human cells in vitro, and no evidence of adenovirus oncogenicity has been found in humans. Human adenoviruses are divided into six subgroups of related viruses, A through F, on the basis of hemagglutination pattern, oncogenic potential, and a variety of properties of the viral DNA and proteins.

Growth of an adenovirus initially involves attachment to an unknown cellular receptor, endocytosis, loss of fibers and pentons from the virion within the acidic endosome, disruption of the endosome releasing the partly dismantled virion, and transport of the latter to the nucleus into which the viral DNA is injected, all of which occurs within 45 minutes of attachment. Viral nonstructural proteins expressed early during the infectious cycle have important functions not only for facilitating and regulating virus reproduction, but also for inhibiting cellular functions that could be useful for controlling the infection. Inhibited functions of infected cells include apoptotic death; transfer of major histocompatibility complex class I antigen to the cell surface, thereby blocking cytotoxic T lymphocytes; cytolysis caused by tumor necrosis factor a; and the antiviral effect of interferons. Such actions likely contribute to the ability of adenoviruses to cause persistent subclinical or latent infection in lymphoid tissue, intestines, lungs, and other sites. After viral DNA replication, late viral protein synthesis includes structural and nonstructural proteins necessary for assembly and maturation of new virions, while cellular protein synthesis is shut down. One of the late regulatory proteins can also interfere with the antiviral activity of interferon. New virions are released by cell lysis after 20 or more hours and can number as many as 100,000 per infected cell.

Epidemiology

Adenoviruses are distributed worldwide. In addition to disease in any portion of the respiratory tract, different adenovirus serotypes can, with varying degrees of selectivity, cause diseases such as conjunctivitis, keratoconjunctivitis, gastroenteritis, hemorrhagic cystitis, central nervous system disease (meningitis, seizures, lethargy), urethritis, and penile and labial ulcers (Hierholzer, 1992; Ruuskanen et al., 1997). Disseminated and often fatal infections commonly involving lungs, liver, and kidneys can occur in immunocompromised persons, and many of these infections are due to higher-numbered adenovirus serotypes than usually encountered in otherwise healthy persons. Recovery from the disease and cessation of easily detectable virus shedding at site(s) of infection in immunocompetent hosts typically occurs within 2 weeks, although intestinal shedding of adenoviruses can persist for months or years (Adrian et al., 1988), even if the initial infection did not cause gastrointestinal symptoms. Shedding of adenovirus from multiple sites of involvement is typically much more persistent in immunocompromised patients (Hierholzer, 1992), and the viruses can also remain infective for prolonged periods in the environment. These factors facilitate multiple modes of transmission of adenoviruses including close contact, self-inoculation with contaminated fingers, fecal–oral route, sexual intercourse, swim-

ming pool water, and small-particle aerosol. Spread of infection within families can be extensive (Ruuskanen et al., 1988), as can spread from infected, immunocompromised patients to hospital personnel unless isolation precautions are carefully applied (Brummitt et al., 1988). Another consideration is the ability of adenoviruses to cause persistent subclinical or latent infection, which contributed to initial isolation of the viruses from surgically removed adenoids (Rowe et al., 1953); reactivation of latent adenovirus from the patient or from donated organs appears to account for some adenovirus infections in immunocompromised hosts (Hierholzer, 1992).

With regard to adenovirus respiratory disease, serotypes belonging to subgroup C (1, 2, 5, and 6) usually cause endemic respiratory infections, serotypes of subgroups B (7, 14, and 21) and E (4) are more likely to cause sporadic outbreaks, and serotype 3 of subgroup B may do either (Ruuskanen et al., 1997). Adenoviruses tend to spare infants during the first 6 months of life (Schmitz et al., 1983; Edwards et al., 1985), but they can occasionally cause very severe neonatal pneumonia (Abzug et al., 1990; Pinto et al., 1992; Kinney et al., 1994; Kim et al., 1997) and may play a role in some cases of sudden infant death (Bajanowski et al., 1996). Between 6 months and 5 years of age, adenoviruses account for 5% to 10% of febrile and/or lower respiratory tract disease, mostly with an endemic serotype (Foy et al., 1973a; Fox et al., 1977). Sporadic infections, more with epidemic serotypes, occur during school years, and sporadic outbreaks of infection with epidemic serotypes occur in closed groups of any age, somewhat more in winter or spring than at other times. The mode of transmission can be important for determining subsequent disease manifestations; experimental administration of adenovirus to volunteers via aerosol was much more likely to cause acute respiratory disease with lower tract manifestations than topical administration in the upper respiratory tract (Couch et al., 1966), and selective infection of the intestine via enteric-coated capsule produced no disease with an adenovirus type 7 that was capable of causing pharyngoconjunctival fever if inoculated on the conjunctiva (Couch et al., 1963). The presence of serum-neutralizing antibody is associated with 80% to 85% protection against re-infection with the same serotype, but antibody to the shared adenovirus antigen does not protect (Fox et al., 1977; Brummitt et al., 1988).

About half of adenovirus serotypes are orphans, that is, they have not been associated with disease (Hierholzer, 1992). Moreover, only about half of adenovirus isolates from virus watch programs can be associated with illness, even serotypes with known disease-producing potential (Fox et al., 1977). Possible reasons for this are persistent shedding after remote adenovirus illness or acquisition of the infection by a route that caused asymptomatic infection.

Clinical Manifestations

Adenovirus infections involving the respiratory tract commonly cause some combination of fever, rhinitis, otitis media, conjunctivitis, pharyngitis, tonsillitis, laryngitis, tracheobronchitis, bronchitis, bronchiolitis, and/or pneumonia. Manifestations of acute infection in these sites can occur in persons of any age with the exception of acute bronchiolitis, which occurs primarily in children below 2 years of age, perhaps because of decreased conductance of these small airways in the first years of life (Hogg et al., 1970).

Among military recruits in whom much of the initial observations of adenovirus disease were made, illness manifestations short of pulmonary disease are usually gathered together under the name “acute respiratory disease” (Dudding et al., 1973). Adenovirus lung infection in the recruits typically causes “atypical pneumonia,” the same illness pattern that is caused by *Mycoplasma pneumoniae* (George et al., 1966). Manifestations of atypical pneumonia include fever, malaise, cough, and often substernal discomfort with cough, and chest exam typically reveals localized rales and or bronchial breath sounds. The chest roentgenogram shows increased peribronchial markings with localized patchy alveolar infiltrate, and the peripheral white blood cell count is typically below 10,000/mm^3. Characteristics that help distinguish adenovirus atypical pneumonia from that due to *M. pneumoniae* are more frequent rhinitis, otitis, pharyngitis, and cervical lymphadenitis with adenovirus than with *M. pneumoniae* (about two thirds versus one third, respectively), and a winter–spring occur-

rence of adenovirus versus mostly fall occurrence for *M. pneumoniae.* Spot assays for cold agglutinins may not be helpful in that they can be elevated in a portion of the recruits with pneumonia due to adenovirus as well as in a majority due to *M. pneumoniae;* although demonstrating a rise in cold agglutinins in paired sera is more specific for *M. pneumoniae,* pathogen-specific diagnostic tests could also be available by then.

Although complications of adenovirus pneumonia in military recruits are typically negligible and recovery usually occurs within 2 weeks (George et al., 1966), occasional occurrence of secondary bacterial pneumonias (Ellenbogen et al., 1974) and deaths (Dudding et al., 1972) have been reported. The latter occurred in young men with no detected underlying disease and were secondary to progressive pneumonia complicated by disseminated intravascular coagulation and multisystem failure. A maculopapular rash can be part of disseminated adenovirus infection, as it was in one of these patients. At autopsy, the lungs revealed bronchial epithelial necrosis, interstitial alveolar thickening and hyaline membranes, and small-vessel thrombi.

Common manifestations of adenovirus infection in children are fever and some combination of upper respiratory symptoms, otitis media, conjunctivitis, pharyngitis, tonsillitis, cervical lymphadenopathy, and gastroenteritis (Ruuskanen et al., 1985, 1988; Putto et al., 1986; Sutton et al., 1976; Edwards et al., 1985; Yamadera et al., 1995). Adenovirus tonsillitis can be exudative and more common than that due to streptococci, from which it is difficult to distinguish clinically (Ruuskanen et al., 1984). Febrile convulsions and meningismus may occur (Ruuskanen et al., 1985; Sutton et al., 1976). Adenoviruses can also cause a pertussis-like syndrome and should be included in the differential diagnosis of pertussis, especially in vaccinated children (Wirsing et al., 1998); these viruses may also co-participate with *Bordetella pertussis* in causing the illness (Nelson et al., 1975; Keller et al., 1980), perhaps by facilitating growth of the bacterium.

Development of adenovirus pneumonia in young children is manifested by increasing dyspnea with diffuse rales and often wheezes heard throughout the lungs, together with or following upper respiratory manifestations by a few days. Chest roentgenograms can show perihilar peribronchial infiltrates with hyperaeration and patchy atelectasis, often with hilar adenopathy, and sometimes lobar collapse (Wildin et al., 1988). Others describe more lobar or segmental pneumonia with homogeneous opacity and air bronchograms, and some mild to moderate pleural effusions (Han et al., 1998). Bacterial superinfection has been reported in about half of the patients (Korppi et al., 1991). Pulmonary function abnormalities often persist following adenovirus pneumonia in infancy (Sly et al., 1984) and may be related to persistence of the infection (Macek et al., 1994). Disseminated adenovirus disease including meningoencephalitis, myocarditis, hepatitis, nephritis, hemorrhagic cystitis, gastroenteritis, conjunctivitis, exanthem, and/or intravascular coagulopathy occurs rarely in immunocompetent young children, but is more likely in immunocompromised children (Munoz et al., 1998). Numerous series describing adenovirus infections in immunocompromised children and adults, many of which were disseminated and fatal, have been gathered by Hierholzer (1992).

Diagnosis

Recovery of an adenovirus from the site of infection is a definitive means of diagnosis. For acute respiratory disease, typical specimens are throat swabs, nasopharyngeal aspirates, and conjunctival swabs. Adenoviruses can often be recovered from rectal swabs, but the long duration of intestinal virus shedding makes the relationship of an isolate from this site to current disease uncertain. Adenoviruses are very stable and require no special handling during transport. Because of host specificity, they are best grown in cells derived from humans. Human embryonic kidney cells are quite sensitive but expensive, and human cell lines such as A-549 derived from lung carcinoma or Hep-2 derived from epidermoid carcinoma are routinely employed (Leonardi et al., 1995; Ruuskanen et al., 1997). Adenoviruses produce a typical cytopathic effect with intranuclear inclusions, but progression of the infection in cell culture is slow, with only about half of eventually positive cultures being detected by 1 week; blind passage after freeze-thawing of the initial culture at 2 weeks and incubation of the passage for an additional 2 weeks are required for maximal sensitivity. Much quicker and equally sensitive culture results can be obtained from centrifugation cultures and use of immunofluorescent anti-

body to common antigen for virus detection after 2 to 5 days of incubation (Mahafzah & Landry, 1989). An adenovirus isolate in regular cell cultures can be confirmed by immunofluorescence (Mahafzah & Landry, 1989), EIA (Player & Westmoreland, 1989), or latex agglutination with antibody-coated particles (Lengyel et al., 1993). The latter assays can also be employed for antigen detection in the original specimen, but this is usually less sensitive for adenoviruses causing respiratory disease than amplification in culture followed by antigen detection. Serotyping can be done by neutralization or HAI with type-specific antisera. Genomic analysis using restriction fragment analysis can reveal the presence of different genotypes within viruses of a given serotype and can be useful for epidemiologic purposes (Kajon & Wadell, 1992; Brummitt et al., 1988).

Another means for demonstrating the presence of an adenovirus in a specimen is detection of its nucleic acid using PCR and/or *in situ* hybridization (Matsuse et al., 1994), or a multiplex RT-PCR assay designed to detect multiple respiratory pathogens (Osiowy, 1998; Grondahl et al., 1999). The diagnosis can also be made retrospectively by demonstrating an increase in antibody to the common hexon antigen using either CF or EIA, but these tests are less sensitive than culture. Serotype-specific neutralization and HAI assays are more sensitive than CF for diagnosis, but the infecting serotype must be known or suspected on epidemiologic grounds.

Treatment

Treatment of adenovirus infections is primarily supportive, and heroic measures such as extracorporeal life support can lead to recovery of some patients such as infants with overwhelming adenovirus pneumonia (Kinney et al., 1994; Meyer & Warner, 1997). Adenovirus respiratory disease can clinically resemble bacterial infection (Ruuskanen et al., 1985), and secondary bacterial infections can occur in cases of adenovirus pneumonia (Ellenbogen et al., 1974; Korppi et al., 1991). Careful work-up is required to avoid unnecessary use of antibiotics, or to guide their appropriate use for secondary infection.

No approved antiviral agents are available for treatment of adenovirus infections, but hemorrhagic cystitis in immunosuppressed patients has been successfully treated with ganciclovir (Chen et al., 1997), vidarabine (Kitabayashi et al., 1994; Kawakami et al., 1997), and intravenous ribavirin (Cassano, 1991; Murphy et al., 1993). Both success (Aebi et al., 1997) and failure (Mann et al., 1998) have been reported with use of intravenous ribavirin for disseminated adenovirus disease, and oral ribavirin therapy successfully suppressed adenovirus pneumonia in a patient with end-stage AIDS (Maslo et al., 1997).

Prevention

Controlling spread of adenovirus infection in the home setting primarily involves careful attention to hygiene; because of the stability of adenoviruses, reuse of towels can serve as a means of transmission and should be avoided. Procedures for avoiding spread of keratoconjunctivitis in ophthalmology offices (D'Angelo et al., 1981) also include attention to cleaning and sterilization of instruments, use of unit-dose medications, and cohorting of patients who possibly have this illness. For patients hospitalized with adenovirus respiratory disease, respiratory and contact isolation are recommended (Brummitt et al., 1988).

Enteric-coated, live adenovirus serotypes 4 and 7 proved to be effective vaccines against adenovirus acute respiratory disease in military recruits (CDC, 1998a; Howell et al., 1998). However, this type of vaccination is not transferable to civilian use because it results in enteric shedding of virus that could cause disease in others, or in the vaccinees if they are immunocompromised. Manufacture of this vaccine has ceased (CDC, 1998a), and no other immunoprophylactic or chemoprophylactic measures are available.

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38

Respiratory Syncytial Virus Pneumonia

ANN R. FALSEY

Introduction

Respiratory syncytial virus (RSV) is a ubiquitous respiratory virus and is well known as the most important cause of lower respiratory tract infection in young children (Hall & McCarthy, 1996). It also causes annual epidemics of respiratory illness in adults including upper respiratory infections, bronchitis, and pneumonia. Although previously considered a significant pathogen only in children, RSV has recently been recognized as a cause of serious disease in immunocompromised and elderly adults as well as persons with underlying heart and lung disease. Additionally, it has been shown to cause pneumonia in previously healthy, young adults, although the incidence is unknown (Dowell et al., 1996).

Organism

RSV was first isolated in 1955 by Morris and colleagues from a chimpanzee with a cold and named "chimpanzee coryza agent" (CCA) (Morris et al., 1956). It was subsequently shown by Chanock to cause respiratory illness in infants and was renamed respiratory syncytial virus to reflect the characteristic syncytia that develop in cell culture (Chanock et al., 1957). RSV is an enveloped RNA virus belonging to the Paramyxoviridae family and the genus Pneumovirus (Walsh & Hall, 1989). Other viruses in the paramyxovirus family include measles, mumps, and the parainfluenza viruses.

By electron microscopy, RSV is seen as a pleomorphic spherical or filamentous virus of variable diameter (80–350 nm) and length ($\leq$10 μm). It has ten genes that encode for ten viral proteins. Eight structural and two nonstructural proteins have been characterized (Walsh & Hall, 1996). The two major transmembrane glycoproteins are the fusion protein (F) and the attachment protein (G). These proteins are integral for infectivity and pathogenesis and are also the primary targets of neutralizing antibody (Collins, 1991). There are two major antigenically distinct groups of RSV, designated A and B, with a number of subgroups (Hendry et al., 1986). The major antigenic differences between strains of both groups A and B reside in the G protein (Melero et al., 1997; Cane et al., 1996). Strains of both groups may circulate simultaneously, but the proportions of A and B generally vary each year, with one group usually dominating. Data from children suggest that infections with group A viruses are more severe than those with group B (Walsh et al., 1997). The mechanism for increased severity of group A is not understood.

RSV grows in many standard tissue culture cell lines including HEp-2, HeLa, Vero, and fibroblasts (Walsh & Hall, 1989). The virus replicates well in primary human nasal and bronchial epithelial cells and to a lesser extent in macrophages (Johnson et al., 1961). The presence of RSV in cell

ANN R. FALSEY • Department of Medicine, Rochester General Hospital, University of Rochester School of Medicine and Dentistry, Rochester, New York 14621.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

cultures is generally detected after 3 to 5 days by the formation of characteristic syncytia, which progress until the monolayer is completely destroyed. RSV is thermolabile, and 99% of infectivity is lost at 37°C in 2 days.

Transmission

Natural infection with RSV is limited to humans. Infection results from direct contact with infectious secretions and transmission is most efficient by large-particle fomites rather than small aerosols, in contrast to influenza (Hall et al., 1981). Thus, outbreaks of RSV in closed populations tend to occur more slowly than the explosive epidemics of the influenza virus (Hart, 1984). Despite its thermolability, RSV is stable on environmental surfaces for several hours, which allows contamination of hands and subsequent inoculation of the eye or nasal mucosa (Hall et al., 1980). The average incubation period is 5 days, with a range of 2 to 8 days (Hall & McCarthy, 1996). Hospitalized infants with primary infection shed virus for approximately 1 week, but may shed for up to 21 days (Hall et al., 1976a). During re-infection, viral shedding is much shorter, typically less than 4 days (Hall et al., 1976b; Hall et al., 1978). Infection with RSV is generally confined to the respiratory tract. Lower respiratory tract involvement occurs by the spread of the virus from the upper respiratory tract rather than viremia (Hall & McCarthy, 1996).

Pathology

The classic manifestation of disease in infants with primary infection is bronchiolitis, which occurs in 20% to 30% of infections. The pathologic findings show a lymphocytic peribronchiolar infiltration with edema of the bronchiolar walls and surrounding tissues (Hall & McCarthy, 1996). Bronchioles become obstructed from sloughed necrotic epithelium and mucus, which leads to impedance of airflow with air trapping and atelectasis. In pneumonia, interstitial infiltration of mononuclear cells accompanied by edema and necrosis leads to alveolar filling (Ahern et al., 1970). Eosinophilic cytoplasmic inclusions and giant cells may be demonstrated on histology (Fig. 1). Little information exists on the pathologic changes found in the lung of the normal adult with RSV pneumonia. Autopsy findings of a previously healthy 72-year-old woman who died of RSV pneumonia showed the lungs to be beefy red and congested. Microscopically, intraalveolar and interstitial fibrosis with mononuclear cell infiltrates and hyaline membranes were observed. Eosinophilic cytoplasmic inclusions similar to fatal childhood cases of RSV were also seen (Levenson & Kantor, 1987). Autopsies from immunocompromised adults with RSV show diffuse alveolar damage with cells sloughed into the alveolar airspaces (Harrington et al., 1992). Multinucleated giant cells and variable amounts of RSV antigen have been seen with 5% to 80% of epithelial cells infected (Whimbey et al., 1995a; Harrington et al., 1992).

Epidemiology

RSV causes annual winter epidemics in temperate climates and rainy season outbreaks in the subtropics (Parrott et al., 1973; Kim et al., 1973). Sporadic summertime infections may also occur in temperate climates but are relatively uncommon (Washburne et al., 1992). In the United States, RSV epidemics usually begin in Florida in November, move through the Southeast in December and January, and reach their peak in the northern states in February (Torok et al., 1996).

Approximately 50% to 70% of infants are infected with RSV during the first year of life and infection is nearly universal by the second birthday (Mufson et al., 1973). Although most illnesses are relatively mild, approximately 1% of infants require hospitalization for pneumonia, bronchiolitis, or croup (Hall & McCarthy, 1996). Immunity to RSV is incomplete and reinfection with RSV occurs throughout life (Hall et al., 1991). Family studies by Hall et al. (1976b) demonstrated that 43% of parents became infected when RSV was introduced into the household by school-age children. Re-infection with RSV is generally mild in normal, healthy adults, with infection limited to the upper respiratory tract (Johnson et al., 1962). Although early studies of RSV using young, healthy military recruits emphasized the mild nature of reinfection

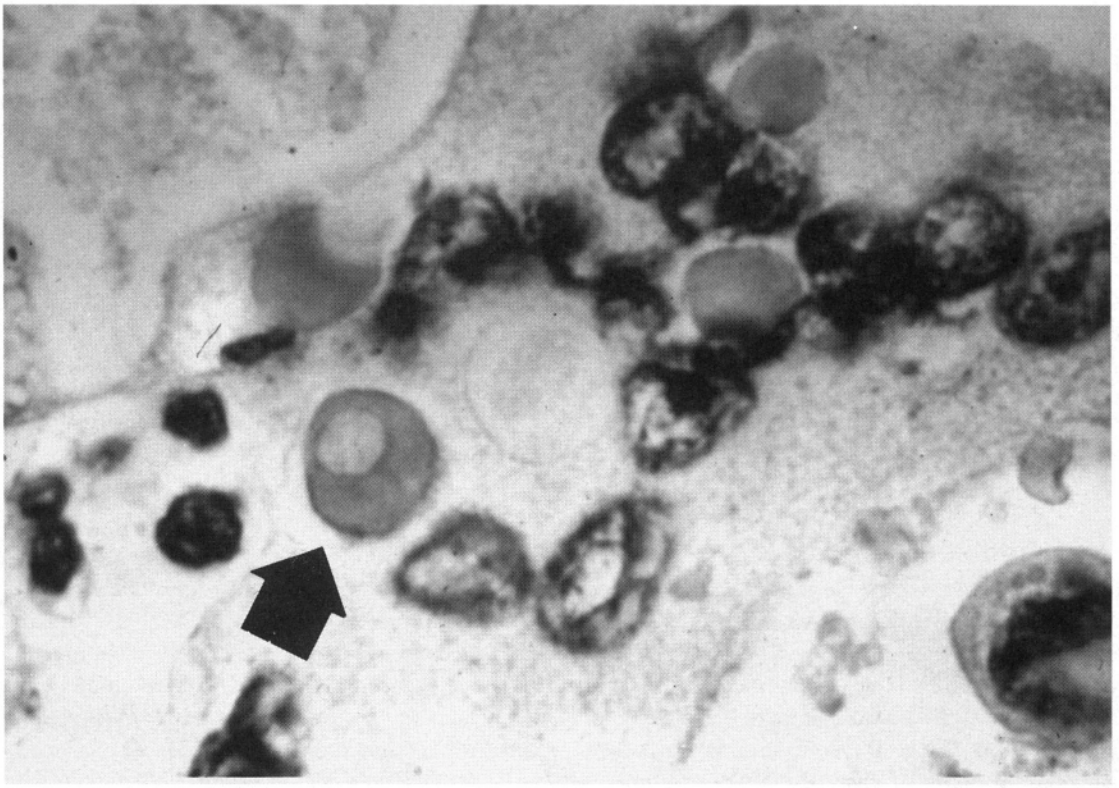

FIGURE 1. Multinucleated giant cell with characteristic eosinophilic cytoplasmic inclusion (arrow) in epithelial cells from RSV-infected lung tissue (Hematoxylin and eosin stain, ×400). Provided by Caroline Breese Hall, MD.

(Kravetz et al., 1961; Johnson et al., 1962), subsequent investigations showed that RSV causes significant symptoms even in healthy adults. Approximately half of nosocomially RSV-infected hospital personnel missed work and a relatively high proportion developed prolonged coughing and signs of tracheobronchitis (Hall et al., 1975). In addition, serial pulmonary function tests of adults following RSV infection revealed airway hyperactivity for up to 8 weeks following illness (Hall & Hall, 1979).

Rates of community-acquired RSV pneumonia in normal adults have likely been underestimated due to the lack of good diagnostic tools. Older studies employing complement fixation and viral culture documented RSV as the cause of community-acquired pneumonia in up to 3% of cases (Greenberg, 1991). More recent studies using more sensitive diagnostic tests have shown that RSV causes 5% to 14% of wintertime community-acquired pneumonias (Falsey et al., 1995a; Dowell et al., 1996; Zaroukian & Leader, 1988). In a recent study of community-acquired pneumonia, Dowell and coworkers demonstrated that the four most commonly identified pathogens in 1195 adults admitted to the hospital for pneumonia during the winter were *Streptococcus pneumoniae* (6.2%), influenza types A and B (5.4%), RSV (4.4%), and *Mycoplasma pneumoniae* (4.1%). A reasonable estimate using data from a number of studies throughout the world over the past 30 years is that RSV accounts for 2% to 5% of pneumonias throughout the year and approximately 5% to 15% during the winter (Table 1).

A high proportion of adults with RSV pneumonia have underlying chronic disorders such as diabetes mellitus, cancer, and collagen vascular disease. Although there are isolated reports of pneumonia in persons infected with HIV, severe RSV disease in HIV-positive adults or children has not been found to be a significant problem (King,

TABLE 1. RSV-Associated Pneumonia in Adults: Representative Studies

Author	Date	Location	Diagnostic tests	No. positive/no. tested (%)
Fransen et al., 1969	1963–1967	Sweden	CF	31/598 (5.2)
Hers et al., 1969	1967–1968	Netherlands	CF	10/207 (4.3)
Vikerfors et al., 1987	1971–1980	Sweden	CF, Ag, IgM	57/2400 (2.0)
Kimball et al., 1983	1980–1981[a]	Washington, United States	Culture, CF	2/100 (2.0)
Stanek et al., 1988	1983–1985	Czechoslovakia	CF, culture	2/74 (2.7)
Zaroukian et al., 1988	1987–1988[a]	Michigan, United States	IAH, Ag, culture	3/55 (5.5)
Melbye et al., 1992	1988–1989[a]	Norway	CF	5/36 (13.9)
Marrie et al., 1996	1991–1994	Canada	CF	0/149 (0)
Falsey et al., 1995	1989–1992[a]	New York, United States	EIA, Ag, culture	69/483 (14.3)
Dowell et al., 1996	1990–1992[a]	Ohio, United States	EIA	53/1195 (4.4)

CF, complement fixation serology, single high or ≥4-fold rise in titer; EIA, enzyme immunoassay serology, ≥4-fold rise in titer; IAH, immune adherence agglutination serology; Ag, antigen detection by IFA or EIA.
[a]Winter only.

1997). Similarly, the use of chronic steroids does not increase the risk for serious RSV disease, although in both these groups viral shedding may be prolonged (Hall et al., 1986; King, 1997). Three groups of adults have been identified as at highest risk of severe RSV disease and will be discussed in greater detail. These include the elderly, persons with chronic lung disease, the severely immunosuppressed host with hematologic malignancy, and transplant recipients.

Elderly

In adults, RSV was first recognized as a significant pathogen among frail elderly persons residing in long-term care facilities. Seventeen reports have been published since the early 1980s describing both outbreaks and prospective surveillance studies in nursing homes (Falsey, 1991). Attack rates of RSV infection ranged from 9% to 89% during outbreaks, and from 1% to 7% during prospective surveillance studies (Agius et al., 1990; Public Health Laboratory Service, 1983; Osterweil & Norman, 1990; Falsey et al., 1992; Wald et al., 1995). Rates of pneumonia ranged from 5% to 55% and mortality from 0% to 53% (Hornsleth et al., 1975; Nicholson et al., 1990; Public Health Laboratory Service, 1983). The marked variability in outcomes in these studies may reflect case selection criteria, different diagnostic methods, and strain variation. A reasonable estimate of the impact of RSV in nursing homes is a 10% annual attack rate with a pneumonia rate of 10% in those infected. RSV infection was also found to be common in frail elderly persons attending senior day care centers (Falsey et al., 1995b). During a 15-month period encompassing two winter seasons, RSV was identified in 16 of 165 subjects, with one participant requiring hospitalization for pneumonia.

The incidence and impact of RSV infection in community-dwelling elderly are less well defined. Data are limited to case reports of RSV pneumonia and studies of elderly persons requiring hospitalization (Levenson & Kantor, 1987; Spelman & Stanley, 1983; Falsey et al., 1995a). Although the precise incidence is unknown, recent studies suggest that RSV may cause excess morbidity and mortality in persons over age 65 at rates similar to nonpandemic influenza (Nicholson, 1996). Fleming and Cross compared rates of respiratory illness and excess deaths with viral activity in the United Kingdom during four winter seasons (Fleming & Cross, 1993). When the peaks of viral activity for influenza and RSV were temporarily separated, two distinct peaks in the number of respiratory illnesses and deaths in persons over age 65 were also noted. In a study of elderly persons admitted during three winters with influenza-like illness or acute cardiopulmonary conditions, RSV was identified in 10% of patients compared with influenza in 13% (Falsey et al., 1995a). Although 44% had a discharge diagnosis of pneumonia, much of the RSV morbidity was associated with other diagnoses, including 19% with exacerbation of chronic obstructive pulmon-

ary disease (COPD) and 20% with congestive heart failure (CHF).

Chronic Obstructive Pulmonary Disease

Persons with chronic lung disease are particularly prone to complications of RSV. Illness with RSV frequently manifests as exacerbations of COPD and bronchitis rather than pneumonia. In published series, the percentage of illnesses due to RSV in persons with COPD ranges widely from 0.8% to 17.4% (Carilli et al., 1964; Gump et al., 1976; Smith et al., 1980; Fagon & Chastre, 1996; Sommerville, 1963; Wiselka et al., 1993; Lamy et al., 1973; Lambert & Stern, 1972). In a recent prospective evaluation of persons with severe COPD and/or CHF, the incidence of RSV was 4.3 per 100 subject winters compared to influenza A at 7.0. The clinical impact was similar, with 3 of 8 RSV-infected patients hospitalized compared to 6 of 13 influenza A-infected subjects (Walsh et al., 1998).

Immunocompromised

Among immunocompromised adults at risk for severe RSV infection are those with chemotherapy-induced myelosuppression, leukemia, lymphoma, and aplastic anemia, and recipients of bone marrow and solid organ transplants (Wendt, 1997; Couch et al., 1997; Englund et al., 1988). Patients with acute leukemia and bone marrow transplant recipients appear to be at highest risk (Fouillard et al, 1992; Whimbey et al., 1995b). The temporal occurrence of these infections in immunosuppressed persons mirrors the occurrence of RSV in the general community (Whimbey et al., 1997). Although RSV can be acquired in the community, nosocomial infection is more common in this population (Whimbey et al., 1995b). Among the common respiratory viruses, RSV appears to be the most frequent, causing 30% to 50% of the viral associated illnesses (Couch et al., 1997; Bowden, 1997). Furthermore, RSV is associated with the most severe disease, with higher pneumonia and death rates than influenza (Whimbey et al., 1996). The pneumonia associated with RSV is usually primarily viral, in contrast to influenza, in which bacterial and fungal superinfection often ensue (Whimbey et al., 1996). After transplantation, patients are at highest risk prior to engraftment, when infection may rapidly spread from the upper airways to pneumonia in 50% of subjects. If pneumonia develops, mortality rates may reach 90% (Whimbey et al., 1996). In 87 adults with leukemia followed through a winter season, nine (10%) developed RSV infection; six of eight who had profound chemotherapy-induced myelosuppression developed pneumonia with a mortality rate of 83% (Whimbey et al., 1997).

Clinical Manifestations

The clinical manifestations of RSV pneumonia may be difficult to distinguish from other forms of viral or bacterial pneumonia since there is significant overlap of signs and symptoms and no pathognomonic findings. However, some helpful clinical clues exist to alert the physician to the possibility of RSV infection (Table 2). The pre-illness characteristics of the RSV-infected patient are somewhat different from those in patients with bacterial or atypical pneumonia. Patients with RSV pneumonia are older, more likely to have underlying heart or lung disease, and more likely to report exposure to someone with a cold in the past month (Dowell et al., 1996).

The typical RSV illness begins with nasal congestion and discharge and these symptoms help to distinguish RSV from bacterial and influenza pneumonia (Mathur et al., 1980; Dowell et al., 1996). The presence of rhinorrhea or sinusitis also distinguishes RSV from other causes of viral pneumonia such as cytomegalovirus in the immunocompromised host (Hertz et al., 1989). Fever is seen in

TABLE 2. Clinical Features of RSV Pneumonia

	RSV	Bacterial
Winter season	++++	++
Older age	+++	++
Underlying disease	+++	++
Exposure to illness	++	+
High fever	+	+++
Rhinorrhea	+++	+
Wheezing	+++	+
White blood cell count > 12,000/mm^3	+	++

approximately 50% of RSV patients compared to 75% with influenza or bacterial infections (Dowell et al., 1996; Falsey et al., 1995a). Fever is typically low-grade, although high temperatures of 39° to 40°C have occasionally been reported (Fransen et al., 1967; Falsey et al., 1995a). Wheezing either by report or on exam is also commonly found in RSV patients and serves to differentiate RSV-related illness from other forms of pneumonia. The high percentage of wheezing patients with RSV pneumonia may in part reflect the larger numbers of persons with underlying lung disease, yet wheezing is also seen in young, healthy adults. In a study by Dowell et al., seven of eight patients between the ages of 18 and 39 with RSV pneumonia presented with wheezing and none had a prior history of asthma or other lung disease (Dowell et al., 1996). Dsypnea is very common (60%–80%), as is cough, which may be dry or productive. Sore throat (8%–42%) and earache (20%) are variable complaints (Dowell et al., 1996; Falsey et al., 1995a). Malaise and myalgias are more frequent in influenza than in RSV and the presence of gastrointestinal symptoms such as nausea, vomiting, and diarrhea is also more suggestive of influenza infection (Wald et al., 1995).

Chest radiographs frequently show patchy bilateral alveolar infiltrates but may also show interstitial changes (Sorvillo et al., 1984; Multz et al., 1992). Radiographic appearance may be confused with CHF, which can be problematic in patients with underlying heart disease (Fig. 2). Overall, chest radiographs are not helpful in distinguishing RSV pneumonia from bacterial infection. In Dowell's study, 40% of patients had consolidation seen on chest films, and in 35%, it was described as "lobar" (Dowell et al., 1996). The white blood cell count is normal in approximately 70% of patients with RSV pneumonia compared to 40% of those with bacterial and 55% with atypical pneumonia. If sputum can be obtained, the gram stain usually

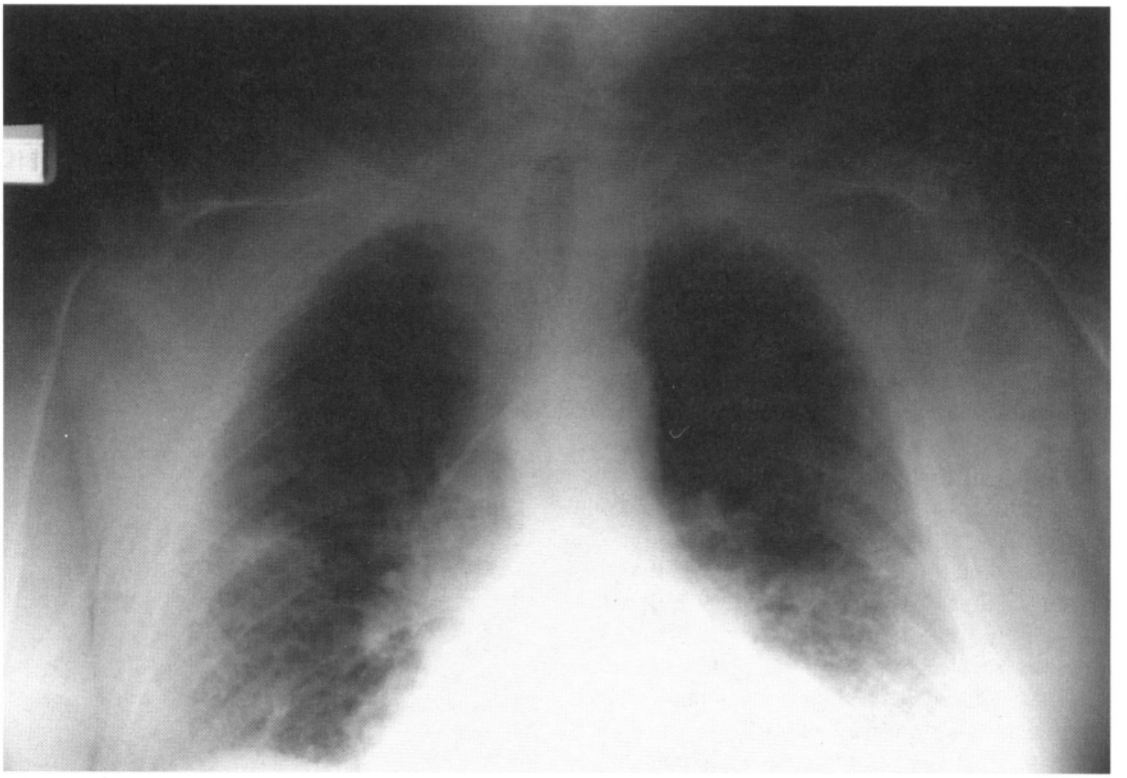

FIGURE 2. Chest radiograph of an elderly man hospitalized with culture-proven RSV pneumonia. Radiograph shows interstitial infiltrates, which may be difficult to distinguish from congestive heart failure. Printed, with permission, from Betts et al., (1996).

reveals white blood cells but no predominant organism. In several studies of elderly patients with RSV pneumonia, bacterial sputum cultures demonstrated potential pathogens such as *S. pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* in up to 30% of cases (Vikerfors et al., 1987; Morales et al., 1983; Falsey et al., 1995a; Zaroukian et al., 1988; Fransen et al., 1967). However, the adequacy of the sputum specimens was not described and therefore the significance of these findings is uncertain. In summary, during the winter months the clinician should suspect RSV as the cause of pneumonia in a patient with coryza, wheezing, low-grade fever, and a normal WBC.

The clinical impact among those infected with RSV is significant. The mean length of stay in the hospital is approximately 2 weeks; 70% require oxygen, 20% are admitted to intensive care, and 7% to 10% require ventilatory support (Falsey et al., 1995a; Dowell et al., 1996). Mortality rates are likely inaccurate owing to dependence on serology for diagnosis but, in one study, the rate was 10% compared to 6% for influenza (Falsey et al., 1995a). The estimated annual cost of RSV pneumonia hospitalizations in the United States using Medicare cost data is $150 million to $680 million dollars (Han et al., 1999).

Diagnosis

Culture, direct antigen detection, or serologic analysis can provide the diagnosis of RSV infection. However, diagnosis of RSV in adults is problematic for two major reasons. First, it is rarely considered in adults and proper specimens are not collected. Second, the amount of virus shed by adults with re-infection, even with severe immunosuppression, is markedly less than the amount shed by infants with primary infection (Englund et al., 1996). The small amount of virus in secretions makes standard viral detection techniques much less sensitive.

Viral culture is the gold standard of diagnosis, but RSV is labile and does not survive changes in temperature or pH or prolonged transit time well (Hall & McCarthy, 1996). Specimens should be placed in viral culture media and transported on ice to the laboratory, where they should be inoculated on cell culture as soon as possible. Nasal washes are the usual sample; however, sputum, bronchoalveolar lavage (BAL) fluid, and lung tissue are acceptable specimens. In elderly or uncooperative patients in whom collection of a nasal wash is difficult, a nasal swab placed in viral culture media can be used, although sensitivity is likely lower. In immunosuppressed patients with pneumonia, sampling of the lower airways is highly desirable. Englund et al. found that the sensitivity of using nasal secretions to detect virus was 15% compared to 89% for BAL in patients with pneumonia (Englund et al., 1996). In cell culture, the characteristic cytopathic effect is usually present within 3 to 7 days and the use of shell vials may hasten identification (Hall & McCarthy, 1996).

Rapid diagnostic tests, such as indirect immunofluorescence (IFA) and enzyme immunoassay (EIA), have been used successfully on nasal wash specimens from children (Kellogg, 1991). Unfortunately, both of these methods are insensitive in elderly adults, likely due to low viral titers and the use of nasal swabs rather than nasal washes to collect specimens (Falsey et al., 1996). In a recent comparative study using three standard methods in the elderly in which seroconversion by EIA was used as the gold standard, the sensitivity of culture, IFA, and EIA was 45%, 9%, and 0%, respectively (Table 3).

Infection with RSV can be demonstrated by serology, although it is only of value retrospectively and may be unreliable in the immunocompromised host The methods used most frequently are complement fixation (CF) and EIA (Walsh &

TABLE 3. Diagnostic Tests for RSV in Adults

	Approximate sensitivity (%)
Serology > 4-fold rise	
Enzyme immunoassay IgG	90
Complement fixation	50
Enzyme immunoassay IgM	10–80
Bedside culture	70
Standard culture	50
Rapid antigen detection	
Immunofluorescence assay	10
Enzyme immunoassay	0
Reverse transcription-polymerase chain reaction	60

Hall, 1989). Since all adults have detectable RSV antibodies at baseline, the use of a single high titer is not felt to be a reliable method of diagnosis (Falsey & Walsh, 1992). Although CF antibody resolves more rapidly than IgG detected by EIA, and therefore a single high CG titer may be suggestive of recent RSV, diagnosis based on this should be considered presumptive at best. EIA may be accomplished using whole virus or purified antigens such as the F or G protein. Serology by EIA using a ≥4-fold increase in RSV-specific IgG as diagnostic is both sensitive and specific (Falsey et al., 1990). Eighty-five percent of frail nursing home residents who were culture-positive for RSV showed a serologic response using these criteria (Falsey et al., 1992). Serology by EIA also appears to be approximately twice as sensitive as CF (personal communication, T. Marrie). Although a ≥4-fold increase in RSV-specific IgG is very sensitive when true baseline sera are available, the sensitivity may be significantly lower in the patient hospitalized with pneumonia (Dowell et al., 1996). Since infection may have been present for a number of days prior to hospitalization, antibody levels may have already risen, obscuring a 4-fold rise on presentation to the hospital. RSV-specific IgM has been detected in 11% to 81% of infected patients (Agius et al., 1990; Dowell et al., 1996; Vikerfors et al., 1988). In a study of community-acquired pneumonia, Dowell et al. found that 58% of those with a ≥4-fold rise in RSV IgG were IgM-positive, as well as an additional 19% of subjects who had high-acute RSV IgG titers without seroconversion (Dowell et al., 1996). Although IgM is rarely positive before the sixth day of illness and the sensitivity and specificity have not been well defined, it may be of value in the immediate diagnosis of RSV pneumonia.

Lastly, the use of new molecular techniques such as RT-PCR holds much promise in adults. The enhanced ability to detect very small quantities of virus has improved diagnosis for other difficult-to-grow respiratory viruses such as rhinovirus (Nicholson et al., 1997). Published reports suggest that PCR for RSV is at least as sensitive as virus culture in infants with primary infection and may be more sensitive in children with re-infection (Freymuth et al., 1995; Henkel et al., 1997; van Milaan et al., 1994). In a small study of elderly adults, RT-PCR was positive in 12 of 13 (92%) culture-positive cases and 7 of 17 (41%) seropositive-only cases, improving the acute diagnosis rate from 43% to 63% (Falsey et al., 1998). At present, PCR for the diagnosis of RSV is not widely available, although it is offered in the form of a mutliplex PCR (Hexaplex, Prodess, Milwaukee) for the diagnosis of multiple common respiratory viruses (Fan et al., 1998a).

Treatment

The treatment of RSV pneumonia in nonimmunocompromised adults is largely supportive. Supplemental oxygen and bronchodilators are frequently required and ventilatory support may be necessary in some hospitalized patients (Falsey et al., 1995). No controlled data exist on the use of corticosteroids for wheezing adults with RSV infection; however, in view of the significant number of patients with underlying COPD, the administration of steroids is reasonable and not likely to be harmful. The incidence of secondary bacterial infection in children with RSV pneumonia is low but it is unknown in adults. Therefore, it seems prudent to administer antibiotics in patients with a sputum gram stain suggesting bacterial infection. Specific antiviral therapy with both aerosolized ribavirin and RSV-specific immunoglobulin has been approved for high-risk infants but has not been tested in adults in a controlled manner (Hall et al., 1983, 1985; Hemming et al., 1987; Groothuis et al., 1993, 1995). Ribavirin is administered as a small-particle aerosol into a tent, mask, or ventilator at a reservoir dose of 20 mg/mL for a period of 12 to 20 hours daily for 2 to 5 days (Hall et al., 1983). High-dose, short-duration therapy (60 mg/mL for 2 hours given three times a day) has been used in children, and anecdotal experience suggests that this method is better tolerated in the nonintubated adult (Englund et al., 1990). The use of ribavirin has only been described in elderly adults with RSV pneumonia in sporadic case reports and, thus, efficacy in impossible to determine (Zaroukian & Leader, 1988). Although data are not placebo-controlled, retrospective analyses suggest that the administration of aerosolized ribavirin and RSV-specific IgG in the treatment of severely immunosuppressed adults with RSV infection may be life-saving if administered prior to the onset of respiratory failure (Whimbey et al., 1995b).

Prevention

Currently, no vaccine is available for the prevention of RSV, although preliminary reports indicate that a subunit vaccine composed of the RSV fusion protein is safe and immunogenic in elderly adults (Falsey & Walsh, 1996, 1997). RSV-specific immunoglobulin has shown benefits when administered prophylactically to high-risk children, but no data exist for adults (Groothuis et al., 1995). Extremely frail elderly persons or those with severe cardiopulmonary disease should avoid contact with persons with acute respiratory infections during the winter, particularly young children with colds. Once hospitalized, the patient with RSV pneumonia does not require respiratory isolation. Since the virus is transmitted by large-particle fomates, hand washing is of prime importance in limiting nosocomial transmission (Graman & Hall, 1989). The use of gown and gloves may also be helpful in outbreak situations.

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Measles and Varicella Pneumonia

B. LYNN JOHNSTON

Measles Pneumonia: Case Presentation

A 20-year-old female presented to the emergency room in Halifax, Nova Scotia, with a 24-hour history of dyspnea and a nonpruritic rash starting on her face and trunk and spreading to her extremities. Six days before this she noted sore throat and fever for which she was treated empirically with penicillin. She had also had headache, a sense of fullness in her right ear, and cough productive of a small amount of clear sputum over the week prior to admission.

As a toddler she had received a single dose of measles, mumps, and rubella vaccine with a rubella booster at age 12. She was attending boarding school in England. About 2 weeks before her illness she had spent a few days with a school friend who was later diagnosed with measles.

On exam she was tachycardic (104 beats per minute) and had a low-grade fever (38°C orally) but no respiratory distress. She had bilateral conjunctival injection, Koplik spots, and a diffuse morbilliform rash. Bibasilar crackles were heard on auscultation. Her oxygen saturation breathing room air was 87%. Chest radiograph was normal.

She was admitted to hospital for supportive management. Serological testing confirmed the diagnosis of measles (IgM positive; IgG negative). Oxygenation normalized within 24 hours and she was discharged without additional complications.

B. LYNN JOHNSTON • Department of Medicine, Dalhousie University, and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, B3H 2Y9 Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Measles

Measles is a highly contagious acute infection caused by the rubeola virus, a single-stranded RNA virus of the Paramyxoviridae family. Although great strides have been made in the control of measles over the last 30 years, it still remains a significant cause of childhood morbidity and mortality, especially in developing countries. Despite measles immunization programs in developed countries, outbreaks continue to occur. Hence, it is likely that cases of measles will continue to occur in the foreseeable future. Respiratory complications are the most common of the serious complications associated with measles and the major cause of death due to measles. This chapter provides an overview of measles followed by more detail about measles pneumonia.

Epidemiology

Most of the complete data regarding the epidemiology of measles comes from the United States. An understanding of the natural history of measles and the response to vaccine programs provides insight into its epidemiology. As noted, it is a highly contagious infection. Outbreaks occur when the pool of susceptibles is large enough (Gellin & Katz, 1994). As levels of maternally acquired antibodies wane, infants become more susceptible. This maternal antibody, however, has a neutralizing effect on live attenuated measles vaccine. Hence the younger the child is at immunization, the less effective is the vaccine (Cutts & Markowitz, 1994). Choosing the age for administering the first dose of vaccine involves a balance between protecting

young children while allowing for longer-lasting immune response.

In the prevaccine era (before 1963), approximately 400,000 cases of measles were reported each year in the United States (Centers for Disease Control and Prevention [CDC], 1998) with an average of 500 measles deaths per year (Barkin, 1975a). The highest age-specific incidence rates were in children aged 5 to 9 years (Atkinson & Orenstein, 1992) and by adolescence virtually all children had acquired measles with subsequent lifelong immunity. Introduction of vaccine, initially given as a single dose to children at least 15 months of age, decreased the reported incidence of measles by >99% within a few years (CDC, 1998). The greatest decrease occurred in children <10 years of age with an attendant shift in highest age-specific incidence to children aged ⩾10 years. To address this, a two-dose vaccine regimen for all children was recommended in 1989, with the second dose to be given before school entry. Despite these efforts, there was a major resurgence of measles in the United States during 1989-1990, with outbreaks involving preschool-age children assuming greater importance. The majority of cases were in nonimmunized children living primarily in poor, urban areas (Hutchins et al., 1996). Outbreaks were also seen in young adults, not surprising given one study showing that 19% of US military recruits were seronegative for measles antibody (Struewing et al., 1993). Enhanced immunization initiatives have led to the lowest ever levels of measles in the United States: 488 cases in 1996 and 135 in 1997 (CDC, 1998). More than half the cases were related to importation from countries where vaccine programs are not as effective.

Worldwide, measles control has varied considerably (CDC, 1998). In the western hemisphere, measles transmission occurs only sporadically and some countries have reported no cases in the last 3 years. Canada reported an outbreak in young adults in two provinces in 1997. This again highlights the potential for measles outbreaks in young adults who have missed the second dose of the two-dose schedule. In 1996, Europe had the second highest number of reported cases of measles after the Americas, Eastern Mediterranean, Western Pacific, and Southeast Asian areas. In Africa, measles vaccine coverage is poor in most countries and about one half of the million measles deaths worldwide per year occur there. Hence, the epidemiology of measles in a country will be related to the type of immunization program and its success rate.

In the 1991 U.S. outbreak, medical facilities were reported as the likely site for acquisition of measles in 18.4% of cases, the site for 25.8% of cases occurring in children under 5, and for 27.4% of cases in those over 20 (CDC, 1992). In 1983–1984, 59% of nosocomially acquired cases occurred in those too young to be immunized (Biellik & Clements, 1997). A high index of suspicion for measles must be maintained in healthcare facilities to minimize the risk of transmission to those most at risk from infection and its complications.

Transmission

The virus is expelled from the infectious individual in airborne droplets during coughing. Transmission occurs when a susceptible individual comes into direct contact with these infectious droplets. It stands to reason that transmission is facilitated by close contact, such as may occur in crowded homes or child care facilities. The potential for nosocomial measles, when susceptibles mix in crowded waiting rooms or share hospital rooms with patients with undiagnosed measles, should be kept in mind.

Clinical Manifestations

The incubation period averages 10 to 12 days from exposure to prodrome and 14 days from exposure to rash. The prodrome of high fever, malaise, conjunctivitis, coryza, and cough is typically followed after 2 to 4 days by the classic maculopapular rash, which lasts for several days. The rash usually begins on the face and moves down the body and peripherally. In children, just before the appearance of the rash the pathognomonic Koplik spots appear. In adults, Koplik spots and rash frequently coexist (Mouallem et al., 1987). These bluish-gray specks on a red base most often appear on the mucosa opposite the second molars but may involve the entire oral mucosa (Gershon, 1995).

A few variations should be noted in the typical manifestation of measles. In 1965, a syndrome that came to be known as atypical measles was reported in individuals who had previously received the

killed measles vaccine and were later exposed to wild-type virus. The pathogenesis is proposed to be an abnormal immune reaction in a previously sensitized host (Hall & Breese Hall, 1979). With this syndrome, Koplik spots tend to be absent (Martin et al., 1979). The rash is more variable in appearance with three general patterns: predominantly vesicular (Hall & Breese Hall, 1979; Martin et al., 1979), predominantly petechial with some purpura (Hall & Breese Hall, 1979; Martin et al., 1979), or an erythematous maculopapular rash with smaller lesions than usually seen with typical measles (Hall & Breese Hall, 1979). Some combination of all three rashes may be seen concurrently. The rash tends to start distally and move proximally (Martin et al., 1979). With this syndrome, pulmonary findings on exam and/or chest radiographs are prominent (Hall & Breese Hall, 1979; Martin et al., 1979; Frey & Krugman, 1981). Virus cannot be isolated from these individuals and their serological response is typically an abrupt and very large increase in antibody titer (Hall & Breese Hall, 1979; Frey & Krugman, 1981).

In immunocompromised individuals, measles may have an atypical appearance, not to be confused with atypical measles. In particular, the rash may be mild, atypical, or even absent (Gray et al., 1987; Kernahan et al., 1987; Wong et al., 1993). In a study of measles in 17 children with malignant disease, the presence of Koplik spots and a typical rash was associated with recovery, whereas none of five children who died had the typical rash (Kernahan et al., 1987). Immunocompromised patients are at greater risk for complications from measles. In the absence of a typical (or any) rash, pneumonitis due to measles may not be suspected. Hence, a high index of suspicion must be maintained in these patients if measles cases have been reported in the community or if the individual (or a family contact) has recently been immunized (Kaplan et al., 1992; Angel et al., 1998; Monafo et al., 1994).

Measles Pneumonia

Epidemiology

Although pulmonary complications are the most common and serious ones seen with measles, the reported frequencies and outcomes of measles pneumonitis have been quite variable. Factors likely contributing to this variability include the population studied (children vs. adults, all adults vs. hospitalized adults, immunocompetent vs. immunocompromised hosts, children in developed vs. developing countries), the diagnostic criteria for pneumonia (whether a chest radiograph was done routinely or on the basis of symptoms), and the era studied (early 1900s vs. 1990s). Measles pneumonitis should be distinguished from the secondary bacterial or viral pneumonia that may complicate measles later in its course. With the latter, the picture is one of initial improvement followed by recurrence of fever and pulmonary symptoms (Hockberger & Rothstein, 1986). This chapter focuses on measles pneumonitis and not the superinfections.

In the pre-vaccine era, age-specific mortality rates from measles were highest in those under 1 year of age and, in that age group, higher for blacks than for whites and for children in counties with a higher proportion of the population living below the poverty level (Barkin, 1975b). This was in part related to the greater number of cases in this group as well as the higher mortality rate. Based on estimates of measles incidence and reported measles deaths, the estimated death rate was 1 per 10,000 and 60% of deaths were attributed to respiratory causes (Barkin, 1975a).

A more recent and probably more representative picture of the morbidity and mortality associated with measles comes from a study of measles in the United States in the early 1990s (CDC, 1992). There were 9644 cases and 36 deaths reported during the 1991 resurgence (Table 1). The highest incidence was in children under 1 year of age, especially in those 10 to 12 months old. These data show similar pneumonia rates for those less than 5 years and more than 20 years old and a measles case death ratio that was highest for those aged 20 years or more and those less than a year old. These data support historical impressions that measles is more serious in infants less than 1 year of age and in adults.

Two studies of measles in Israeli soldiers found pneumonia rates of 2% and 15% (Giladi et al., 1987; Mouallem et al., 1987). In the United States, pneumonia rates have varied from 3% in military recruits (Gremillion & Crawford, 1981) to

TABLE 1. Measles Cases, Incidence Rates,[a] Complications, and Deaths, United States, 1991[b]

Age group (years)	No. (%) of total	Rate	No. (%) of cases with pneumonia	No. (%) of cases requiring hospitalization	No. (%) of deaths among cases
<1	1852 (19.2)	46.9	502 (11)	1525 (32)	9 (0.49)
1–4	2904 (30.1)	19.6			4 (0.14)
5–9	991 (10.2)	5.5	97 (3)	343 (11)	12 (0.40)
10–14	905 (9.4)	5.3			
15–19	1102 (11.4)	6.2			
20–24	660 (6.8)	3.5	216 (11)	681 (36)	11 (0.58)
≥25	1230 (12.8)	0.8			
Total	9644 (100.0)	3.9	815 (8)	2549 (26)	36 (0.37)

[a]Cases per 100,000 population.
[b]From CDC, 1992.

12% of adult patients with measles seen in an emergency room (Henneman et al., 1995). There were no deaths in these four studies. There are little data on measles in pregnant women and the risk of pneumonitis is not well defined. Atmar et al. (1992) found that 6 of 13 women (12 pregnant and one immediately postpartum) had clinical evidence of pneumonitis (symptoms and/or signs) but only two (15%) had abnormal chest films.

The risk of pneumonia appears to be higher and associated with a poorer outcome in immunocompromised individuals with measles. Two studies in Great Britain found that approximately 65% of immunocompromised children with measles developed pneumonitis (Gray et al., 1987; Kernahan et al., 1987). In one study the mortality rate was 83% (Gray et al., 1987) and in the other it was 36% (Kernahan et al., 1987). The higher mortality in the first group was attributed to delayed diagnosis but it is not clear how this would have affected the outcome, provided supportive care was given.

Clinical Manifestations

There have been a number of articles describing the clinical, radiographic, and laboratory findings associated with measles pneumonitis. Variations may be seen depending on whether it is typical or atypical measles and whether the host is immunocompetent or immunocompromised. In immunocompetent individuals with typical measles, the usual clinical course seen with measles is evident. Pneumonitis (or pneumonia) is usually diagnosed on the basis of cough, fever, and radiographic abnormalities. Chest radiographs are usually done only if pneumonia is suspected on the basis of symptoms. Thus, by definition, cough is almost always present with pneumonitis. However, cough is not infrequently seen in patients with measles but with normal chest films (Henneman et al., 1995).

Henneman et al. (1995) retrospectively reviewed the presentation and course of 75 patients during a measles outbreak in California from 1989 to 1991. The median age of the group was 25 years. Cough was present in 68 (91%) and dyspnea in 39 (52%). Ten (13%) had abnormalities on auscultation, predominantly crackles and, less often, wheezing. In their study, pneumonitis was defined as a physician's diagnosis of pneumonia, an A–a gradient >30 mm Hg and/or an infiltrate on chest film. Using this definition, 43 (37%) patients had pneumonitis. However, only 9 (21%) of them had an abnormal chest film and 27 (63%) had both a normal physical exam and chest film, the diagnosis of pneumonia being based only on an abnormal A–a gradient. Patients with pneumonitis differed from those without pneumonia only in having a higher heart rate (110 vs. 101 beats per minute) and higher respiratory rate (24 vs. 20 breaths per minute). There were no deaths in this group. Thus, this study would suggest that whereas many patients with measles pneumonitis will have cough, dyspnea, and an abnormal A–a gradient, chest film abnormalities are considerably less common.

In their study of 40 Israeli soldiers with measles, Mouallem et al. (1987) found that eight (20%) patients had an abnormal chest exam but only four had an abnormal chest radiograph. In addition, one

patient with an abnormal film had no signs or symptoms of pneumonia. Again, this suggests that symptoms and/or signs of pulmonary involvement may not be associated with chest radiographic abnormalities.

Wong et al. (1993) followed the course of 33 patients hospitalized for measles during the 1989–1991 California outbreak. Dyspnea was noted in 75% and an abnormal chest exam in 52%. Thirteen (39%) had an abnormal chest film. Six patients, all with pulmonary infiltrates, required mechanical ventilation.

With atypical measles, the important features to remember are the greater variability in appearance of the rash and its predilection to start peripherally rather than centrally. Pulmonary manifestations are felt to be more common with atypical measles (Hall & Breese Hall, 1979; Martin et al., 1979). The specific pulmonary signs and symptoms, however, are not appreciably different between atypical and typical measles. In the immunocompromised host, the rash may be absent or atypical and, hence, the diagnosis of measles pneumonitis may go unsuspected.

Laboratory Findings

In patients with measles pneumonia but without superimposed bacterial pneumonia the white blood count is usually low to normal but with a left shift (Gremillion & Crawford, 1981; Hall & Breese Hall, 1979). Thrombocytopenia was seen in Forni et al.'s (1994) group of six patients and Martin et al.'s (1979) review of seven patients with atypical measles but was not universal. Elevation of transaminases is common (Martin et al., 1979; Gremillion & Crawford, 1981; Atmar et al., 1992; Forni et al., 1994). Elevated creatine kinase (Giladi et al., 1987; Forni et al., 1994; Gubler et al., 1995) and calcium (Mouallem et al., 1987; Forni et al., 1994) have also been reported. As noted previously, abnormal oxygenation was common in two studies (Hall & Breese Hall, 1979; Henneman et al., 1995), even in the absence of chest film abnormalities (Henneman et al., 1995).

Radiographic Findings

Gremillion and Crawford (1981) have the largest series of patients with radiologically confirmed measles pneumonia. Chest films were done only for patients with pulmonary symptoms and/or signs to suggest lung involvement. A fine reticulonodular infiltrate, the most common abnormality, was found in 87% of films. It was commonly multilobar with the lower lobes predominating. Pleural effusions, lobar consolidation, and nodular infiltrates were uncommon. In severely ill patients the pneumonia may progress to include alveolar infiltrates (Forni et al., 1994; Gray et al., 1987) or the picture of adult respiratory distress syndrome (Forni et al., 1994). There are no radiographic findings that are specific for measles pneumonitis. Hilar adenopathy and progression of opacifications to residual nodular lesions are reported more often with the pneumonitis associated with atypical measles (Hall & Breese Hall, 1979; Martin et al., 1979; Frey & Krugman, 1981; Gremillion & Crawford, 1981).

Diagnosis

The diagnosis of measles is often a clinical one based on the characteristic signs and symptoms and a confirmed exposure history. Laboratory diagnosis of measles is done by serologic testing and/or viral culture (Laboratory Centre for Disease Control [LCDC], 1998). Measles-specific IgM serology is the standard test, with a significant rise in IgG titer representing an acceptable alternative. Measles-specific IgM antibodies appear around the time of rash onset and last at least 28 days. Tests done within 3 days of the onset of rash may be negative and should thus be repeated within 28 days before eliminating measles as the diagnosis. Measles virus is present in throat and nasopharyngeal secretions during the acute stage (within 4 days after onset of rash) and excreted in urine for at least 7 days after onset of rash. Virus isolation can take weeks so a serologic diagnosis can generally be more promptly made.

The pathologic hallmark of measles pneumonia is the presence of numerous macrophages within the alveolar spaces, which are often lined by inclusion-bearing giant cells (Archibald et al., 1971). Ultrastructural studies indicate that the giant cells are formed by fusion of alveolar lining cells. Hyperplasia and degeneration of the respiratory epithelium, squamous metaplasia of bronchial and bronchiolar epithelium, and interstitial pneumonia of a predominantly mononuclear type may also be seen.

One study demonstrated severe necrosis in bronchi and bronchioles of children who developed intercurrent adenovirus and herpes virus infection, perhaps contributing to the subsequent development of bronchiectasis, one of the long-term sequelae of measles pneumonitis (Kaschula et al., 1983).

Outcome

In the various studies cited in this chapter, measles pneumonia death rates have varied from 0% to 83%. Most of these studies have focused on hospitalized patients who represent a sicker subgroup. For the most part, however, mortality was very low in healthy young children, adolescents, and adults and full recovery was generally the rule (Hall & Breese Hall, 1979; Martin et al., 1979: Gremillion & Crawford, 1981; Henneman et al., 1995; Mouallem et al., 1987; Giladi et al., 1987; Swift et al., 1993). However, the risk of death from measles pneumonia is clearly higher in immunocompromised persons, ranging from 36% to 83% (Gray et al., 1987; Kernahan et al., 1987). Kaplan et al. (1992), in reviewing the literature and several of their own cases, found a mortality rate of 65% for measles pneumonitis in patients with malignancy and 33% in patients with HIV infection. Survival may be better in immunocompromised children who have a typical rash, detectable immune response, and disappearance of giant cells from their nasopharyngeal secretions, but the condition was uniformly fatal if the child went on to require mechanical ventilation (Kernahan et al., 1987). The death rate was higher (26%) in children admitted to an intensive care unit with measles and respiratory failure (Swift et al., 1993). There are insufficient data to determine a mortality rate for adults requiring ventilation for measles pneumonitis but even here recovery is generally the rule if the adult is not immunocompromised (Wong et al., 1993; Forni et al., 1994; Gubler et al., 1995). In a study of 13 pregnant women with measles, only 1 (8%) died (Atmar et al., 1992).

An immunocompromised state and vitamin A deficiency are risk factors for death from measles (Underwood & Arthur, 1996). The role of malnutrition as an independent risk factor for mortality has not been conclusively determined (Dover et al., 1975; Beckford et al., 1985).

Management

The management of measles pneumonia is primarily supportive. Given that patients may have abnormal oxygenation, even in the presence of a normal chest radiograph, it would be prudent to check oxygen saturation and, if abnormal, an arterial blood gas may be warranted. Such patients should be followed for development of progressive respiratory distress.

The only specific therapy shown to be of benefit in the treatment of measles is vitamin A. Barclay et al. (1987) determined that vitamin A improved survival in Tanzanian children aged less than 2 years. In a second trial, also in African children, vitamin A at a dose of 200,000 iu by mouth daily for 2 days reduced both morbidity and mortality in measles, not just in those less than 2 years (Hussey & Klein, 1990). All children with severe measles should receive vitamin A, regardless of nutritional status. Its benefit in adults has not been demonstrated.

There are a number of articles reporting the use of ribavirin intravenously and/or by aerosol in the treatment of measles. Ribavirin is a guanosine nucleoside analogue with in vitro activity against a broad spectrum of DNA and RNA viruses including the measles virus (Gilbert & Knight, 1986). One of the major side effects noted with ribavirin has been anemia (Forni et al., 1994). Trials demonstrating the benefits of ribavirin in reducing the duration of disease in healthy children are cited in several articles (Kaplan et al., 1992; Forni et al., 1994; Gururangan et al., 1990). There are no other randomized, controlled clinical trials evaluating ribavirin in treatment of measles pneumonia or measles in the immunocompromised host. There are anecdotal reports of its success (Gururangean et al., 1990; Forni et al., 1994; Kaplan et al., 1992; Atmar et al., 1992; Ross et al., 1990) but also of its failure (Forni et al., 1994; Kaplan et al., 1992; Angel et al., 1998). Combining reports from the literature of its use in immunocompromised patients, 6 of 11 who were treated survived (Kaplan et al., 1992). At this time its benefit in treatment of severe measles is unproven.

There are even fewer anecdotal reports on the use and/or potential benefits of interferon and immunoglobulins in the treatment of measles.

Varicella Pneumonia: Case Presentation

A 21-year-old gravida 2 para 2 was admitted to hospital after delivering a healthy baby boy at home at 32 weeks gestation. Four days prior to this she had developed a vesicular skin rash and 2 days prior to admission she developed a cough that later became productive of brownish sputum. On admission she complained of 24 hours of dyspnea and of rib cage pain.

She had a history of hypothyroidism and was on thyroid hormone replacement. She smoked slightly less than one pack of cigarettes per day. Although she had a 3-year-old daughter, she had no known exposure to varicella.

Her physical exam revealed moderate respiratory distress with a respiratory rate of 30 to 50 breaths per minute, pulse rate of 120 beats per minute, and blood pressure 114/70 mm Hg. She was afebrile. There was a diffuse vesicular and pustular eruption with a few crusted lesions. Breath sounds were decreased at both bases and she had scattered inspiratory crackles.

Laboratory investigations showed minimal elevation in white cell count to 10.8×10^9/L (normal $4.5–10.5 \times 10^9$/L) with normal hemoglobin and platelets. She had elevated transaminases, CK, alkaline phosphate, and hypoalbuminemia. Her creatinine was normal. Arterial blood gases on supplemental oxygen (8 L/minute) revealed a mild respiratory alkalosis with pH 7.46, pCO_2 26 mm Hg, and pO_2 106 mm Hg. Chest radiograph showed a diffuse interstitial infiltrate.

She received intravenous acyclovir (5 mg/kg every 8 hours) for 72 hours and was discharged home on oral acyclovir, 800 mg five times a day for another 7 days.

Varicella

Chickenpox (varicella), the primary infection caused by varicella-zoster virus (VZV), is also one of the most contagious of the infectious diseases, although slightly less so than measles. VZV is an enveloped, double-stranded DNA virus. Similar to measles virus, primary varicella produces the greatest morbidity and mortality in the very young (under 1 year of age) and in adults. In addition, it may pose a significant threat to the immunocompromised individual. In keeping with its membership in the herpes virus family, VZV can establish latency in dorsal root and trigeminal ganglia and reactivate as shingles (herpes zoster) some years later. Herpes zoster has the potential to disseminate in immunocompromised patients. However, pneumonitis in association with zoster is uncommon in HIV-infected patients, occurring in only one (0.7%) of 134 episodes (Veenstra et al., 1996). This chapter will focus on varicella pneumonia in the healthy individual.

Epidemiology

Despite being a notifiable disease, reported cases of chickenpox in the United States and Canada significantly underestimate the true numbers of infection. In the United States, infection, complication, and hospitalization rates represent estimates from data compiled by the CDC, Health Interview Surveys (HIS), Commission on Professional Hospital Activities (CPHA), the National Center for Health Statistics (NCHS), local and state health departments, and census data. Similar estimates have not been calculated for Canada but it is anticipated that they would be proportionately similar to those in the United States.

VZV causes 3 to 4 million cases of primary infection in the United States each year (Choo et al., 1995; Preblud & D'Angelo, 1979). Data from the 1970s indicate that 80% of cases occurred in children less than 10 years, with individuals over 15 years accounting for only 3.9% (Preblud & D'Angelo, 1979). There were no observed differences in rates by race or sex. Over the last decade, and even prior to licensing of varicella vaccine in the United States, there were suggestions that the epidemiology was changing with a greater proportion of cases occurring in those 15 or older (Choo et al., 1995; Gray et al., 1990; Fairley & Miller, 1996). In a 1990-1992 study of varicella in a New England health maintenance organization, 16% of cases were in adolescents and adults >15 years (Choo et al., 1995). A study of 1533 US navy and army recruits in 1989 found that 8.2% were susceptible to varicella, with the risk being greater for those from outside the continental United States (Struewing et al., 1993). This is in keeping with the well-recognized observation that varicella typically occurs

among older persons in tropical areas. The reasons for this are not clear (Wharton, 1996).

Natural infection produces lifelong immunity. Maintenance of immunity may be promoted by periodic exposure in varicella. Incidentally, vaccine-induced immune response is also boosted by exposure to natural varicella (White, 1997). There are questions regarding the possibility of a change in epidemiology with widespread use of VZV vaccine, which may not produce lifelong immunity but eliminate the source of "natural boosting." We may see varicella occurring more frequently in adolescents and adults.

Transmission

Humans are the only known reservoir for VZV. Transmission is likely by the respiratory droplet route with secretions of the nasopharynx or upper respiratory tract and uncrusted vesicles representing the source of virus. Patients are generally infectious for 48 hours prior to vesicle formation and for the 4 to 5 days it takes for the lesions to completely crust. Zoster is much less infectious than varicella. As noted, varicella is a highly contagious infection. The secondary attack rate in household susceptibles is >85% (Wharton, 1996).

Clinical Manifestations

Chickenpox is almost always a clinical diagnosis. A prodrome of low-grade fever and malaise may occur 1 to 2 days before the rash. The skin manifestations consist of maculopapules, vesicles, pustules, and crusts in varying stages. They appear on the trunk and face and rapidly spread outward to the extremities. Constitutional symptoms of malaise, pruritus, anorexia, and listlessness gradually resolve as the disease abates. In immunocompromised children studied by Feldman et al. (1975) the incubation period, clinical manifestations at onset, and distribution and extent of lesions were similar to those in healthy children but the duration of rash tended to be longer. Hence, varicella should not be a missed diagnosis, even in the immunocompromised patient.

Nonpulmonary Complications

There are several studies reporting on hospitalization and/or mortality rates for varicella. Between 1979 and 1982 there were an average of 1462 hospitalizations annually for varicella in the United States; the rates varied from 8/10,000 varicella cases in children aged 5 to 9 years to 127/10,000 varicella cases in adults ≥20 years (Guess et al., 1984, 1986). In general, complications involving the central nervous system were second in frequency to cutaneous complications, usually bacterial superinfections (Preblud, 1986), and accounted for only 10% of all chickenpox-associated deaths for all age groups (Preblud & D'Angelo, 1979). More recent data has suggested that encephalitis is rather infrequently seen and that the most common severe complications from varicella are secondary bacterial infections and pneumonia (Choo et al., 1995; CDC, 1998).

During the late 1970s, approximately 100 varicella-related deaths a year were reported in the United States. The number of varicella-related deaths began to drop in the early 1980s, but they began to increase again later in the decade so that approximately 60 to 100 previously healthy individuals die from complications of chickenpox each year in the United States (Wharton, 1996; White, 1997). Varicella is now the leading cause of vaccine-preventable deaths in children in the United States (CDC, 1998). Ninety percent of the children who died between 1990 and 1994 did not have high-risk conditions for severe varicella (CDC, 1998). Although persons ≥20 years account for only 2% of varicella cases, 47.5% of deaths occur in this age group (Preblud, 1986). Estimated age-specific varicella death-to-case ratios for persons without underlying malignancy are 7.2/10,000 for children less than 1 year, 1.3/10,000 for children 1 to 19 years, and 30.9/10,000 for adults ≥20 years. This is similar to 1972-1977 data that found that although adults ≥20 years accounted for 1.8% of cases, they represented 24% of deaths, with death-to-case ratios of 6/10,000 for those under 5 years and 70.6/10,000 for those ≥20 years (Preblud & D'Angelo, 1979).

Varicella Pneumonia

Epidemiology

As previously indicated, most of the information regarding the epidemiology and severity of varicella is based on studies of selected patients,

epidemiologic data from the few jurisdictions that collect and analyze their varicella data, literature reviews, and anecdotal information (Preblud, 1981). Hence, information regarding the rates (0.3%–50%) and outcomes (9%–50% mortality) of varicella pneumonia have been remarkably variable (Nilsson & Ortqvist, 1996). Using various sources of data, Guess et al. (1984, 1986) estimated that 11% of hospitalizations for children less than 5 years (1.3/10,000 varicella cases), 6% for those aged 15 to 19 years (2.4/10,000 varicella cases), and 21% for adults aged >20 years (26.7/10,000 varicella cases) were for pneumonia. More recent data indicated that compared to previous studies, adults were more likely to be hospitalized (62.3/10,000 cases) for varicella pneumonia (Choo et al., 1995) but that only 12% of hospitalizations for varicella in adults were due to pneumonia, with 8% due to encephalitis (Nilsson & Ortqvist, 1996). Another study of varicella in adults found that 4% of hospitalizations were for pneumonia (Pugh et al., 1998). Therefore, varicella pneumonia, although infrequent, is the most common serious complication among adults and more frequently seen in adults than in children and adolescents. Although some literature has suggested that pregnant women are at greater risk for developing varicella pneumonia (Harris & Rhoades, 1965; Triebwasser et al., 1967), Baren et al. (1996) and Nilsson & Ortqvist (1996) were unable to confirm this. A well-described risk factor for the development of varicella pneumonia is cigarette smoking (Ellis et al., 1987). Pneumonia, when it does occur, is more likely to be a bacterial superinfection in children but due directly to varicella in adults (Preblud, 1986).

Clinical Manifestations

The first clue that the pneumonia is due to varicella should be the presence of the typical rash, found in both immunocompetent and immunocompromised individuals (Nilsson & Ortqvist, 1996; Triebwasser et al., 1967; Ruben & Nguyen, 1991). There have been several studies reporting on the clinical manifestations of varicella pneumonia in adults and immunocompromised children. Data on the clinical findings of varicella pneumonia in immunocompetent children are exceedingly sparse, in keeping with its rarity.

The symptoms of pneumonia develop, on average, 2 days (range, 1–6 days) after the onset of rash; prominent symptoms include cough (89%), dyspnea (70%), hemoptysis (38%), and chest pain (21%) (Nilsson & Ortqvist, 1996; Triebwasser et al., 1967). Baren et al. (1996), however, found that the frequency of cough was not different in patients with varicella pneumonia compared with those without pneumonia, whereas dyspnea and chest pain were. A study of adults with varicella in the United Arab Emirates also found dyspnea only in those with pneumonia (Pugh et al., 1998). Although more common with pneumonia, cough was found even in the absence of pneumonia. On the other hand, chest radiographic abnormalities may be present in the absence of symptoms (Mermelstein & Freireich, 1961; Weber & Pellecchia, 1965). This highlights the possibility that there may be many more cases of varicella pneumonia that are asymptomatic or are so mild as to be overlooked clinically. Examination of the chest is often unimpressive and correlates poorly with the severity of pneumonia (Triebwasser et al., 1967; Mermelstein & Freireich, 1961). Clinical improvement usually parallels resolution of the rash with recovery in 7 to 10 days (Hockberger & Rothstein, 1986; Mermelstein & Freireich, 1961). Although recovery in nonfatal cases is usually complete, there has been one case report of usual interstitial pneumonitis occurring several months after varicella pneumonia and attributed to the preceding varicella (Keane et al., 1998).

Laboratory Findings

Laboratory findings are unremarkable. A review of 38 patients hospitalized for varicella (1953–1960), 13 of whom had pneumonia, found that hemogram and blood chemistries were usually normal (Mermelstein & Freireich, 1961). This finding was supported by a later review reporting that the white blood cell count was usually normal or only slightly elevated (Triebwasser et al., 1967). The one patient with an elevated white blood cell count had a secondary bacterial skin infection (Mermelstein & Freireich, 1961).

Radiographic Findings

Although the chest radiographic findings with varicella pneumonia are fairly consistent, they are not specific to this entity. The most frequent abnor-

mality is bilateral peribronchial nodular infiltrates with patchy confluence, more often near the lung bases (Treibwasser et al., 1967; Weber & Pellecchia, 1965; Hockberger & Rothstein, 1986). The nodules are rarely more than 0.5 cm in diameter (Hockberger & Rothstein, 1986). Pleural effusions, dense reticular markings, and hilar adenopathy may be present (Triebwasser et al., 1967; Hockberger & Rothstein, 1986). The radiographic findings seem to correlate best with the peak severity of the skin rash rather than with the physical exam of the lungs (Triebwasser et al., 1967). Pulmonary infiltrate clearing is typically found in 6 to 10 days (Weber & Pellecchia, 1965) with complete clearing in 2 weeks in uncomplicated cases (Mermelstein & Freireich, 1961). After recovery, necrotic foci may calcify and appear as miliary calcifications on chest radiographs many years later (Meyer et al., 1986). In keeping with the distribution of infiltrates during acute varicella pneumonia, these nodules may be more dense at the base than at the apex (Meyer et al., 1986). Thus, a chest film showing miliary calcifications in an asymptomatic individual may reflect previous varicella pneumonia.

Diagnosis

Even more so than with measles, chickenpox is a clinical diagnosis that rarely requires confirmation with virological or serological testing. Confirmation can be accomplished by isolation of the virus from vesicular fluid or by showing seroconversion or serologic rises through antibody testing. Rapid diagnosis can be made by Tzank smear or direct fluorescent antibody staining of smears made by scraping the base of the lesions.

Pathologically, the lungs show focal necrosis and occasionally complete consolidation. Vesicles may be found on pleural surfaces and within the tracheobronchial tree (Triebwasser et al., 1967). Microscopically, the findings of varicella pneumonia include necrotic foci involving alveolar walls, blood vessels, and small bronchioles. In the most recently affected areas there are eosinophilic intranuclear inclusions and syncytical giant cells. The alveoli and bronchioles may be lined with hyaline membranes and the bronchioles filled with exudate (Triebwasser et al., 1967). Herpes virus particles can be seen on electron microscopy of involved tissues (Feldman, 1994).

Outcome

Pneumonia has been considered a serious complication of varicella, with 9% to 50% mortality (Nilsson & Ortqvist, 1996). However, mortality estimates in the literature have suffered from the same biases as estimates of pneumonia rates—incomplete denominator data and preferential reporting of the most severe cases. Mortality has been considered especially high (approximately 41%) for pregnant women, but these determinations were based on reported cases in the literature with incomplete denominator data (Broussard et al., 1991; Harris & Rhoades, 1965; Mendelow & Lewis, 1969).

More recent studies provide a more representative view of varicella pneumonia mortality. Several studies examining outcomes of all individuals seen with varicella pneumonia have reported no deaths in the 67 patients reviewed (Nilsson & Ortqvist, 1996; Weber & Pellecchia, 1965; Mermelstein & Freireich, 1961). Two patients (15%) with varicella pneumonia died in one study (Baren et al., 1996). Both had underlying disease—one had chronic renal failure and the other amyotrophic lateral sclerosis. In a review of varicella in children with malignancy (Feldman et al., 1975), although 4 of 15 with pneumonitis died, in only one was the death attributable to pneumonia. The overall varicella mortality in this pre-acyclovir study was 7%. In bone marrow transplant patients, two of four died from their varicella pneumonia (Han et al., 1994). Two studies in pregnant women reported mortality rates of 14% (Smego & Asperilla, 1991) and 25% (Paryani & Arvin, 1986), with mortality rates of 25% to 50% for those requiring mechanical ventilation (Paryani & Arvin, 1986; Smego & Asperilla, 1991). The four deaths in these two studies occurred in the third trimester of pregnancy. Other studies have noted no deaths in pregnant women although their numbers were very small (Nilsson & Ortqvist, 1996; Baren et al., 1996). Definite proof that varicella is more severe in pregnant women than in nonpregnant women is lacking (Brunell, 1992).

Management

Acyclovir, a specific and selective inhibitor of the replication of herpes viruses, has been used for almost two decades and is recommended for treat-

ing varicella in adolescents, adults, and high-risk patients. A number of studies have demonstrated its efficacy and safety in the treatment of chickenpox in normal children and adults (Wallace et al., 1992; Balfour et al., 1990; Dunkle et al., 1991) but have not been able to demonstrate an impact on the complications of varicella. Compared to historical controls, with the inherent biases of such comparisons, there is a suggestion that outcomes in pregnant women are improved with acyclovir and its use appears safe for the developing fetus (Smego & Asperilla, 1991; Broussard et al., 1991). Another retrospective study of acyclovir in the treatment of varicella pneumonia (historical controls) found that although there was no change in need for mechanical ventilation or mortality, it did result in reductions in duration of fever, tachypnea, temperature, and respiratory rate and an improvement in oxygenation (Haake et al., 1990). Thus, there are no randomized controlled trials or retrospective studies to show that the outcome of varicella pneumonia in the previously healthy individual is modified by acyclovir. The benefit of acyclovir in treating varicella in immunocompromised patients has been demonstrated (Shepp et al., 1986).

A major drawback of acyclovir is its limited oral bioavailability. Two newer agents, famciclovir and valacyclovir (a prodrug of acyclovir) have spectrums of antiviral activity and mechanisms of action similar to acyclovir but enhanced bioavailability and longer half-lives (White, 1997). They currently do not have indications for the treatment of varicella.

Vidarabine, although effective in the treatment of varicella, has more side effects and lower efficacy and therefore has essentially been replaced by acyclovir (Shepp et al., 1986). Foscarnet also has VZV activity, directly inhibiting the viral DNA polymerase. Its use is limited primarily to acyclovir-resistant varicella zoster infections, rarely seen in healthy individuals (Balfour et al., 1994).

The use of corticosteroids for varicella pneumonia, with their potential to modify the intrapulmonary inflammatory response, has been quite controversial. In a small, noncontrolled review of healthy adult patients admitted to the ICU with varicella pneumonia, 4 of 12 (33%) not treated with corticosteroids died compared with 0 of 6 who did receive steroids (Mer & Richards, 1998). Although these findings were not statistically significant, the authors had the impression that clinical responses to the steroids were dramatic and lengths of ICU and hospital stay were both significantly shorter in the steroid-treated group. They suggested that a short course of steroids (48 hours) he considered in addition to antiviral therapy and supportive care in previously well patients with life-threatening varicella pneumonia. There is one reported case where steroids were successfully used to treat usual interstitial pneumonitis occurring several months after varicella pneumonia (Keane et al., 1998). The use of steroids, in combination with antiviral and other supportive therapy, in the treatment of severe varicella pneumonia needs further study.

Several patients with severe varicella pneumonia have been successfully managed with extracorporeal life support (Lee et al., 1997). Its role is purely one of support allowing the lungs to rest and ultimately recover.

Prevention

Varicella vaccine, licensed in the United States in March 1995 and in Canada in December 1998, has been studied extensively worldwide since the late 1970s. It is a live, attenuated vaccine prepared from the Oka strain of VZV first isolated in Japan in the early 1970s (Gardner et al., 1996). It is less immunogenic in adults than in children (78% seroconversion vs. $\geqslant$95% seroconversion after one dose), and the immune response is improved in adults (99% seroconversion) following a second dose (Gardner et al., 1996).

Protection has been demonstrated for several years (Asano, 1996; Watson et al., 1994). Efficacy and safety have also been demonstrated in children immunized when their leukemia was in remission (LaRussa et al., 1996). Safety data in healthy adults and children is also favorable (Asano, 1996; Meurice et al., 1996; Varis & Vesikari, 1996; Ramkissoon et al., 1995). Although questions regarding its long-term efficacy and effect on the epidemiology of varicella and zoster have yet to be answered, the vaccine has been recommended for infants and children as well as susceptible adolescents and adults (CDC, 1998c; Gardner et al., 1996). However, it is anticipated that varicella will not be eradicated for a number of years (CDC, 1993). It will remain important for physicians to be able to recognize and treat varicella pneumonia.

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Hantavirus Pulmonary Syndrome

STEVEN Q. SIMPSON

Introduction

Hantavirus pulmonary syndrome (HPS) was first recognized in May 1993 when two young, healthy adults who lived together in the New Mexican desert near the Four Corners, died within 5 days of one another of rapidly progressive respiratory failure (Duchin et al., 1994; Hjelle et al., 1994b). The precipitous nature of their illnesses, which were clinically identical and which appeared to be infectious, led local physicians to notify health authorities of the two deaths. Within a month, more than a dozen people in the southwestern United States died from similar clinical syndromes that began with nonspecific viral symptoms. Early mortality rates were as high as 76%, and all of the patients were identified because of their need for critical care. By mid-June investigators in the Special Pathogens Branch of the U.S. Centers for Disease Control and Prevention (CDC) determined that sera from the disease victims contained antibodies with reactivity to several species of hantavirus.

Using reverse transcription-polymerase chain reaction (RT-PCR), researchers at the CDC and at the University of New Mexico (UNM) were able to identify and characterize the virus by amplifying viral gene sequences taken from human and animal tissues (Elliott et al., 1994; Feldman et al., 1993; Spiropoulou et al., 1994). Sequencing of major portions of the viral genome demonstrated that the virus was a unique member of the hantavirus genus. The agent responsible for the initial outbreak was eventually named the *Sin nombre* virus, or the "virus without a name," although over a dozen viruses are now known to cause the syndrome throughout North and South America. Before 1993, no hantaviruses were known to cause human disease in the Americas, although hantaviruses were known for causing hemorrhagic fevers accompanied by renal insufficiency in Europe and in Asia. For the most part, victims of HPS have not suffered hemorrhage or renal failure.

HPS is named for its dramatic effects on cardiopulmonary function. In HPS, nonspecific influenza-like symptoms lead to increased pulmonary capillary permeability and pulmonary edema, which can progress over a few hours to a severe state similar to adult respiratory distress syndrome (ARDS), and to shock due to low cardiac output (Hallin et al., 1996). Effective treatment requires supportive care in an intensive care unit and frequently includes mechanical ventilation, intravenous hydration, hemodynamic support, and even extracorporeal membrane oxygenation (Crowley et al., 1998; Hallin et al., 1996).

Hantaviruses

The hantaviruses constitute a genus of negative-sense RNA viruses belonging to the family Bunyaviridae (McCormick, 1991; Peters, 1994, 1995). A number of species of the genus have been identified, including Hantaan virus, Seoul virus, Puumala virus, and Dobrava virus. The Bunyaviridae share a common viral structure. The viral genome, encased within a nucleocapsid shell, typically consists of three segments: the S segment or small segment

STEVEN Q. SIMPSON • Division of Pulmonary and Critical Care Medicine, University of Kansas, Kansas City, Kansas 66160.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

codes for the nucleocapsid protein (N protein), the M or medium segment codes for the viral envelope glycoproteins (two proteins: G_1 and G_2), and the L or large segment codes for a viral transcriptase. The hantaviruses, including those that cause HPS, conform to this basic structural pattern.

The hantaviruses are also similar to other bunyaviruses in that each virus is predominantly associated with a specific rodent reservoir, usually rural field mice, voles, or rats. When a rodent becomes infected the virus disseminates throughout the host's body during a period of viremia that lasts several days. Following the viremic period hantavirus antigens are detectable in lungs, kidneys, and other organs; these tissues appear to remain antigen-positive for the duration of the host's life. The rodents remain apparently healthy but shed virus in urine, feces, and saliva. Unlike other bunyaviruses, infection by hantavirus species is not transmitted via an arthropod vector but appears to be transmitted via aerosols of urine and feces from the infected animal. The hosts harbor and shed live virus in spite of developing neutralizing IgM and IgG antibodies. Sin nombre virus and Black Creek Canal virus appear to follow this pattern in their rodent hosts (Green et al., 1998; Hutchinson et al., 1998).

Hemorrhagic Fever with Renal Syndrome

The prototype virus of the genus is the Hantaan virus, named for the Hantaan river on the Korean peninsula, where it was first encountered by western physicians during the Korean conflict (McKee, 1991). However, both the virus and its host, the rural field mouse *Apodemus agrarius,* are found throughout northeastern Asia. The Hantaan virus causes a life-threatening illness that was originally named Korean hemorrhagic fever but is now known as hemorrhagic fever with renal syndrome (HFRS). The clinical manifestations of HFRS are classically described in five relatively distinct phases. Their description is germane to this discussion because they are strikingly similar to the clinical phases of HPS. During the febrile or prodromal phase, the patient experiences high fevers and myalgias for an average of 4 to 5 days. Just as patients defervesce, they develop severe vascular leak, especially notable in the peritoneum, which leads to ascites and retroperitoneal edema and causes severe back and abdominal pain. This phase may also be accompanied by profound hypotension and shock. The patients then develop a severe oliguria that may be accompanied by severe pulmonary edema, which is exacerbated by volume resuscitation. During the shock and oliguric phases of the illness, disseminated intravascular coagulation results in severe bleeding complications that may include exsanguination or intracranial hemorrhage. One third of deaths from HFRS result from such bleeding complications. Patients who survive these severe phases of the illness develop a pronounced diuresis and tend to recover. Convalescence from this illness requires a number of months for patients with severe disease. The current mortality rate of HFRS is 5% to 15%.

The Dobrava virus of eastern Europe causes a severe form of HFRS with a mortality rate of 5% to 35%. Seoul virus, which is distributed worldwide in its host *Rattus norvegicus,* and Puumala virus, which is found in Scandinavia and eastern Europe, cause mild forms of HFRS with low mortality. The first hantavirus recognized to be indigenous to the western hemisphere, Prospect Hill virus, was discovered in the early 1980s in the meadow vole of the northeastern United States but has not caused known human disease. Nucleotide sequence analysis indicates that Sin nombre virus is a novel hantavirus that is most closely related to the Prospect Hill and Puumala viruses (Hjelle et al., 1994c).

Hantavirus Pulmonary Syndrome

Since the initial outbreak in 1993, Sin nombre virus has been detected in humans and in rodents in nearly every geographical area of the continental United States and in Canada (CDC, 1993, 1994a,b,c; Hjelle et al., 1995a; Morzunov et al., 1995). Several other hantaviruses that are closely related to Sin nombre virus have been identified in California, Louisiana, Texas, and Florida and are associated with HPS. Additionally, outbreaks of HPS have occurred in Uruguay and in the Patagonian Andes of Argentina and Chile (Enria et al., 1996). The Patagonian outbreaks were caused by the Andes virus, a hantavirus isolated from the long-tailed rice rat, *Oligoryzmus longicaudatus,* in 1996 (Lopez et al., 1996). Table 1 shows the New World hantaviruses and their geographic locations.

Genetic linkage analysis demonstrates that Sin

TABLE 1. Hantaviruses in the Americas

Virus	Rodent host	Geographic location	Clinical syndrome	Mortality	Reference
Sin nombre/Muerto Canyon/Convict Creek/Four Corners	Deer mouse *Peromyscus maniculatus*	Western North America, Mexico, Canada	HPS	50%	Li et al., 1995
New York/Shelter Island/Rhode Island	White-footed mouse *Peromyscus leucopus*	Eastern North America, Canada	HPS	1 fatal case	Hjelle et al., 1995a,b
Black Creek Canal	Cotton rat *Sigmodon hispidus*	United States, Venezuela, Peru	HPS with hemorrhage	1 case	Khan et al., 1996
Muleshoe	Cotton rat *Sigmodon hispidus*	West Texas, United States	None known	—	Rawlings et al., 1996
Bayou	Rice rat *Oryzomys palustris*	Louisiana, United States	HPS with hemorrhage	1 fatal case	Khan et al., 1995; Morzunov et al., 1995
Prospect Hill	Meadow vole *Microtus pennsylvanicus*	Eastern North America, Canada	None known	—	Lee et al., 1985
Leakey	Grey mouse *Mus musculus*	Texas	None known		Baek et al., 1988
Bloodland Lake	Prairie vole *Microtus ochrogaster*	Southern Canada, Midwestern United States	None known	—	
Isla Vista	California meadow mouse *Microtus californicus*	California and Oregon, United States; Baja California, Mexico	None known	—	Song et al., 1994
El Moro Canyon	Western harvest mouse *Reithrodontomys megalotis*	Western states of United States, Central Mexico, Canada	None known	—	Torrez-Martinez et al., 1995
Rio Segundo	Mexican harvest mouse *Reithrodontomys mexicanus*	Mexico and Costa Rica, South America	None known	—	Hjelle et al., 1994a
Cano Delgadito	Cotton rat *Sigmodon alstoni*	Venezuela	None known	—	Fulhorst et al., 1997
Rio Mamoré	Pygmy rice rat *Oligoryzomys microtis*	Bolivia	None known	—	Bharadwaj et al., 1997; Hjelle et al., 1996a
Andes	Coli largo *Oligoryzomys longicaudatis*	Argentina, Chile	HPS	70%	Lopez et al., 1996

HPS, Hantavirus pulmonary syndrome.

nombre virus and other, closely related hantaviruses are not recent variants of the genus, but have existed in their present forms for many years (Hjelle et al., 1994c). Because each of these hantaviruses survives in its own unique rodent reservoir, it is possible that they all coevolved with their respective hosts. Cases of HPS as early as 1959 have been retrospectively diagnosed by serum antibody titers, indicating that the disease itself existed unrecognized for years (Hjelle et al., 1994c; Yamada et al., 1995). Furthermore, Native American mythology in the Four Corners area relates that humans should avoid close contact with mice or they risk illness or even death, possibly reflecting a prior experience of these peoples with HPS (Simpson et al., 1995).

Epidemiology

Because the data are more complete and accessible, this discussion of the epidemiology and clinical features of HPS is largely restricted to the syndrome that is caused in North America by the Sin nombre virus and other closely related viruses. Forty-eight cases of HPS were reported in the United States during 1993, the year in which HPS was first recognized; the overall case fatality rate was 56% in that outbreak year. The majority of cases occurred in the region known as the Four Corners area, the boundary common to the states of New Mexico, Arizona, Utah, and Colorado. As of October 30, 1998, 200 cases were identified in 30 states in the United States and additional cases have been found in Canada. The disease seems to have a predilection for affecting healthy adults; the median age of patients confirmed to have HPS is 37 years, with a range of 11 to 69 years. Remarkably, preadolescent children have suffered only mild illnesses and have not required mechanical ventilation. Sixty percent of patients have been male and 40% female. The overall case-fatality rate now stands at 43%, although the mortality among patients diagnosed since January 1, 1994, is slightly lower, at 34%. The initial cluster of HPS cases was unusual for an outbreak of infection in that it occurred in an area of sparse population, and HPS remains a disease that is contracted in the rural setting. The Four Corners area continues to have the highest case rate, and all but 15 of the cases have been identified west of the Mississippi River.

Clinical Features

Clinical Course

In those patients whose exposure to the virus can be identified, the incubation period for HPS induced by Sin nombre virus averages 7 to 10 days. However, incubation periods up to 50 days' duration have been observed. After the onset of symptoms, HPS resulting from Sin nombre virus infection is characterized by four clinical phases: prodrome, pulmonary edema and shock, diuresis, and convalescence. During the initial prodromal phase, symptoms are virtually identical to the febrile phase of HFRS (Duchin et al., 1994). This phase typically lasts 3 to 6 days, at which time the onset of respiratory symptoms and shock is abrupt. Mortality is greatest in the first 24 hours of the pulmonary edema and shock phase of the illness, which also tends to last from 3 to 6 days. Patients who survive the shock phase enter the diuretic phase of the illness. In this phase, they may have urine flow rates ranging from 300 to 500 ml per hour, simultaneous with rapid resolution of respiratory and hemodynamic abnormalities (Hallin et al., 1996). Following diuresis and extubation, patients enter the convalescent phase of the illness, which may last 6 months or longer. During the convalescent phase, they experience gradually resolving malaise and weakness, along with fibromyalgia-like symptoms. Some patients have mild pulmonary function abnormalities that persist as long as a year. Rarely, hearing loss and impaired mental functioning have been reported as long-term sequelae of HPS, though the latter is likely no more frequent than in other forms of acute respiratory failure and shock (Hopkins et al., 1998; Javer et al., 1998).

Symptoms and Physical Signs

Differentiating HPS from other, less severe viral illnesses is difficult during the prodromal phase, because the most common signs and symptoms are identical to those of milder illnesses. Nearly all patients complain of subjective fever or chills upon presentation, and most patients have myalgias or headache. Eighty-nine percent of patients initially have nausea/vomiting, diarrhea, or abdominal pain. In fact, several patients have been admitted for treatment of gastroenteritis before the diagnosis of HPS became clear.

Cough is present in nearly two thirds of patients on presentation. The cough is most often nonproductive, but occasionally a patient produces amber-colored pulmonary secretions that have been confused with purulent sputum. Despite the central role that pulmonary problems play in HPS, dyspnea is not a common early complaint. Dyspnea is associated with advanced disease and often is a sign of impending respiratory failure. Table 2 shows presenting symptoms of HPS, as well as symptoms that are uncommon in the syndrome. These latter symp-

TABLE 2. Presenting Symptoms in Hantavirus Pulmonary Syndrome

Frequent[a]	Common[b]	Uncommon[c]	Essentially absent
Fever	Nausea/ vomiting[d]	Sweats	Sore throart
Chills	Dyspnea	Dizziness	Meningismus
Myalgia	Cough	Arthralgia	Rash
Headache	Diarrhea[d]	Chest pain	Sinusitis
		Back pain	Pleuritic pain
		Abdominal pain[d]	

[a]Frequent, present in >50% of cases.
[b]Common, present in 20%–50% of cases.
[c]Uncommon, present in <20% of cases.
[d]One or another of these abdominal symptoms is present in >85% of cases.

toms have been helpful in distinguishing HPS from other viral syndromes.

The most frequent initial physical findings in HPS are tachypnea, fever, and tachycardia (Duchin et al., 1994; Hallin et al., 1996). Examination of the lungs reveals fine rales. Severe abdominal tenderness is present in approximately 10% of patients and may mimic appendicitis. Hypotension is unusual on presentation but, when it is present, indicates advanced disease and requires aggressive resuscitation. Although most patients are thrombocytopenic, no petechiae are seen. Several findings seen commonly in HFRS, such as conjunctival hemorrhage, flushing, or peripheral edema, are not present in HPS.

Laboratory Findings

Thrombocytopenia, leukocytosis with a left shift, and circulating immunoblasts constitute a triad of findings that is unique to HPS in North America (Duchin et al., 1994; Dull et al., 1994). Thrombocytopenia is present in 79% of patients at presentation and in all patients during their hospital course. Hemoconcentration is common, with hemalocrits as high as 77% (Zaki et al., 1995). While blood cell count is increased, and immature neutrophils such as myelocytes and promyelocytes are frequently present. All patients have a lymphocyte population that includes at least 10% immunoblasts and plasma cells, a finding not seen in similar disorders such as ARDS (Jenison et al., 1995; Nolle el al., 1995). The immunoblasts are characterized by deeply basophilic cytoplasm, enlarged nuclei, and variably prominent nucleoli, and they vary in size, with mature circulating plasma cells at the upper extreme. Most patients have elevated prothrombin times and partial thromboplastin times at some point during their illness. Disseminated intravascular coagulation may develop in patients with severe disease, but it is far less common in HPS than in HFRS.

Liver enzymes, including aspartate aminotransferase and alanine aminotransferase, tend to be increased but not dramatically so. Hypoalbuminemia is a common finding, but bilirubin and alkaline phosphatase typically are normal (Nolte et al., 1995). Serum lactate dehydrogenase (LDH) level is frequently increased with an electrophoretic pattern that indicates lung and liver injury (Hallin et al., 1996). Analysis of pleural fluid can demonstrate either transudative or exudative levels of protein and LDH (Bustamante et al., 1997). The findings likely depend on the degree of intravascular to extravascular fluid shift and the time during disease evolution at which the pleural fluid specimen is obtained.

Serum lactate levels help to establish the severity of the disease. An increased serum lactate level identifies patients in whom poor tissue perfusion is present, and who require immediate resuscitative efforts. In an early series all patients with a serum lactate level of 4.0 mmol/L or higher died in spite of aggressive treatment, with the exception of two patients who were treated with extracorporeal membrane oxygenation (ECMO) (Crowley et al., 1998; Hallin et al., 1996). Arterial blood gases demonstrate a decreased ratio of PaO_2 to FiO_2 in all cases, and frank hypoxemia is frequently present on initial presentation.

Radiographic Findings

Chest radiographic abnormalities are noted on admission in most patients, even when dyspnea is not present. The major findings are those of interstitial edema and include Kerley B lines, hilar indistinctness, and peribronchial cuffing (Ketai et al., 1994, 1998). Many patients progress to develop severe air space disease and progressive hypoxemia. Air space flooding typically begins in dependent areas of the lung and progresses to involve all lung

fields. This progression may be as rapid as 4 to 6 hours from the time of presentation. Cardiac silhouettes are not enlarged, and pleural effusions develop in all patients as the disease progresses. Lobar infiltrates are not seen in HPS, and their presence should strongly suggest another diagnosis.

Diagnosis

Clinical Evaluation and Differential Diagnosis

Diagnosis of HPS is difficult early in the course of disease or in patients with mild disease. Certainly, a high degree of awareness must be maintained in areas of relatively high incidence, such as the Four Corners area, but it is equally important for physicians in other areas to be vigilant, because of the rapidly progressing nature of the illness (Duchin et al., 1994; Dull et al., 1994; Hallin et al, 1996). A history of rodent exposure may be helpful. Typically, the history may be one of cleaning a dusty closet or outbuilding and encountering significant amounts of mouse excreta or mice (Armstrong et al., 1995). Unfortunately, such a history is frequently absent. The minimum requirement for clinical diagnosis should include some elements of the prodrome, since all patients have had the prodrome, and either evidence of pulmonary edema or the typical hematological changes described above. Although thrombocytopenia and interstitial infiltrates on chest radiograph are often found at presentation, in several patients these elements have been absent for up to 2 days (chest radiograph) and 4 days (thrombocytopenia) after admission. The presence of a lobar infiltrate or of symptoms not included in the usual prodrome should prompt the physician to consider etiologies other than Sin nombre virus infection (Moolenaar et al., 1995). If the diagnosis of HPS is suspected after the history and physical examination, initial screening should include a complete blood count, including platelets; a peripheral smear examined for immature neutrophil precursors and immunoblasts; serum LDH, AST, and albumin levels; coagulation studies; a chest radiograph; and either an oxygen saturation or arterial blood gases (Dull et al., 1994).

A differential diagnosis for more severe disease is shown in Table 3. In the Four Corners area *Yersinia pestis* is endemic among rodent species, especially prairie dogs, and pneumonic plague must be considered in any patient with severe respiratory illness, especially in the summer months. Patients with pneumonic plague have disease that mimicks HPS and have been admitted for diagnosis and treatment of potential HPS (Whitten et al., 1997). Tularemia is also endemic in the western United States, including the Four Corners area, and needs to be considered in patients who present with rapidly progressive illness. Infection with *Legionella* species is so rare as to be reportable in the Four Corners area, but it must be considered in the differential diagnosis of severe respiratory illness in many areas of the United States. At this time virtually all of the infections listed in Table 2 are more common than HPS and severe, rapidly progressive respiratory illness in any individual patient is much more likely to be the result of infection with one of these agents than the result of infection with a hantavirus. However, the pan-American distribution of HPS makes it a legitimate consideration when the differential includes others listed diseases.

TABLE 3. Differential Diagnosis of Rapidly Progressive ARDS-Like Illness in the Febrile Patient

Bacterial	Viral
Plague	Influenza
Tularemia	Adenovirus
Anthrax	Parvovirus
Legionella	Coxsackie
Chlamydia	Respiratory syncytial virus
Mycoplasma	
Brucella	Hemorrhagic fevers
Q fever	
Rocky Mountain spotted fever	
Pneumococcus	
Meningococcus	

ARDS, adult respiratory distress syndrome.

Serologic Testing

The diagnosis of HPS is confirmed by identification of antibodies to Sin nombre virus antigens in serum or by detection of Sin nombre genetic material in blood mononuclear cell preparations via

RT-PCR (Hjelle et al., 1994d; Jenison et al., 1994). The diagnosis can also be confirmed at autopsy by RT-PCR analysis of infected tissues or by immunologic staining of these tissues for Sin nombre antigens (Feldmann et al., 1993; Schwarz et al., 1995). During the initial months of the Four Corners outbreak in 1993, RT-PCR assumed a crucial role in the rapid diagnosis of patients with suspected Sin nombre virus infection. However, this form of diagnosis is labor-intensive and therefore expensive. Additionally, false-positive results may result from minor contamination in the laboratory. PCR also lacks the ability to diagnose remote infection, because Sin nombre virus is cleared from the circulation within 2 to 4 weeks after the onset of clinical symptoms (Hjelle et al., 1994d). These drawbacks of PCR analysis limit its usefulness as a mainstay of diagnosis, so immunologic assays were developed very soon after the initial HPS outbreak.

A western blot assay was developed at UNM that is based on recombinant N and G proteins expressed in *E. coli* (Jenison et al., 1994). Patients who are acutely ill have both IgG and IgM antibodies to the viral nucleocapsid protein, as well as IgG antibody to the glycoprotein-1 (G1) protein of the Sin nombre virus. Most patients also have IgM antibody to the G1 protein. The enormous number of specimens tested at the CDC necessitates a simpler serologic test that is more suitable for large-scale screening, so the CDC principally uses enzyme immunoassay for serologic diagnosis. The ELISA uses recombinant Sin nombre nucleocapsid antigens in the solid phase to capture antibodies in patient serum. The most important limitation of the serologic tests is the delay before a result is obtained, owing to the need to send a specimen to UNM or to the CDC.

Not every clinical laboratory, especially in the rural locations where HPS tends to develop, has the equipment and expertise to perform Western blotting or to maintain reagents for an ELISA that would be used only rarely. To deal with this problem a recombinant immunoblot assay in the form of a test strip has been developed that is both accurate and speedy (Hjelle et al., 1997). Unfortunately, initial industry support for the test has waned, and it is not yet available for widespread use.

At present, one may obtain serologic testing in patients with an appropriate clinical syndrome through both the CDC and UNM. Since HPS is a reportable disease, all patients must eventually be tested by the CDC laboratories. The diagnosis of HPS is based on the presence of IgM antibodies in an acute-phase serum or a 4-fold rise in IgG titer from the acute phase to the convalescent. At the CDC specimens are batched and run on a weekly basis. At UNM specimens are assayed as needed and results are reported within 24 hours of receipt of the serum specimen. One may obtain testing from the CDC by contacting one's state health department. HPS testing at UNM is coordinated by the infectious diseases physician on call.

Treatment

Emergency Department and Pre-Intensive Care Unit

Because of the extreme severity of the illness, and because HPS progresses very rapidly, patients with suspected HPS should be transferred immediately to a facility with experience and expertise in managing severe shock (Hallin et al., 1996). Since HPS tends to be acquired in rural areas, air ambulance to a major center is frequently the best mode of transport. Intravenous access with large-bore catheters should be established prior to transfer. Crystalloid or colloid fluids should be administered to hypotensive patients. However, volume administration should be limited if signs of pulmonary edema develop. If pulmonary edema develops, an inotropic agent, such as dobutamine 5 to 20 μg/kg/min or dopamine 4 to 10 μg/kg/min, should be administered, even if a pulmonary artery catheter is not yet available. It is advisable to avoid agents with principally vasoconstrictor effects.

Because other infections that cause severe respiratory failure are more common than HPS, all patients with suspected HPS should be empirically treated with antibiotics to cover agents shown in Table 2. During the initial HPS outbreak in 1993, patients were treated with very broad-spectrum coverage that included erythromycin, an extended-spectrum penicillin or imipenem/cilastatin, and an aminoglycoside. In patients with severe disease that includes respiratory and/or circulatory failure, such a combination still has merits, in that the severity of

the illness dictates that all possible agents are well covered. In patients with early disease or with mild disease, antibiotics are directed to organisms causing atypical pneumonias (Moolenaar et al., 1995). Reasonable agents include intravenous macrolides or one of the newer, extended-spectrum fluoroquinolones. Appropriate specimens should be collected for the diagnosis of an atypical pneumonia. Such specimens should include sputum, if available, for direct immunofluorescence of appropriate agents and serum for measurement of appropriate antibodies and antigens.

Intensive Care Unit Management

HPS poses a dilemma for those who attempt to treat it. As patients develop a severe pulmonary capillary leak, they simultaneously develop myocardial insufficiency and shock that demands increased cardiac filling pressures. As pulmonary capillary pressures increase during volume administration, fluid pours indiscriminately into the alveolar space. This is a similar circumstance to that encountered when treating patients with ARDS, but the consequences are much more dramatic. The situation is best managed via a flow-directed pulmonary artery catheter, which should be placed at the first sign of pulmonary edema or decreasing PaO_2/FiO_2 in patients with suspected Sin nombre infection. Pulmonary artery occlusion pressures higher than 10 to 12 mm Hg lead to severe flooding of the alveolar space with edema fluid, and this knowledge must temper the desire to administer volume to a patient who may be hypotensive. Simultaneously with volume resuscitation, patients should be given an inotropic agent. Since nearly all patients who enter this shock phase of the illness demonstrate decreased cardiac output and increased systemic vascular resistance, dobutamine is the most logical choice for inotropic support.

Patients whose interstitial edema progresses to alveolar disease nearly always require mechanical ventilation (Hallin et al., 1996). For this reason one may consider early, elective intubation of patients whose oxygen requirements are not met by nasal cannula oxygen. As stated above, currently accepted modes of mechanical ventilation, with precautions against alveolar overdistension, repetitive alveolar collapse and reexpansion, and oxygen toxicity are effective in most patients. In a series of 30 patients cared for in New Mexico and in Kansas, only one failed to respond to mechanical ventilation according to these principles; that is, adequate, if not ideal, oxygenation and ventilation were achieved in all but one patient.

Salvage Therapy

Because of the combination of cardiogenic shock and pulmonary capillary leak, which seemed to resolve quickly in recovering patients, it was hypothesized that ECMO might be an appropriate therapy for some patients with HPS, since the modality could address both problems simultaneously (Crowley et al., 1998). Additionally, the rapid recovery of surviving patients led the investigators to believe that the duration of ECMO would be shorter than had been observed in patients with ARDS, and that the risk of nosocomial sepsis would for that reason be reduced. The ECMO protocol was initially designed to treat patients with serum lactate levels greater than 4 mmol/L or a cardiac index less than 2.0 $L/min/m^2$ (normal value, 2.5–3.5 $L/min/m^2$) while on full inotropic support, because, at the time, all such patients had died.

Two patients who met these criteria were treated. The first patient, who was suffering pulseless electrical activity at the time of ECMO institution, died. The second patient, whose cardiac index was 0.8 $L/min/m^2$ at the time of ECMO institution, survived. A third patient, who could not be adequately oxygenated or ventilated using standard mechanical ventilation, also survived. Both survivors required ECMO treatment for less than 96 hours. ECMO appears to be a viable mode of salvage therapy for certain critically ill HPS patients who would otherwise die. One patient with severe HPS has also been successfully treated with inhaled nitric oxide (Rosenberg et al., 1998). The rationale for its use is quite similar to the rationale for ECMO. Both of these intensive therapeutic measures require transport of the HPS patient to a tertiary-level center.

Isolation Precautions

A final issue in the therapy of HPS is the potential for nosocomial transmission to other pa-

tients or to healthcare workers. There is no evidence that Sin nombre infection can be spread person to person; all cases in North America can be adequately explained by rodent exposure. A study of nosocomial transmission during the 1993 Four Corners outbreak involved 266 health care workers with varying degrees of exposure to HPS patients or to their blood and body secretions (Vitek et al., 1996; Wells et al., 1997b). No serologic evidence of infection by Sin nombre virus was found in any of the healthcare workers. Until late in 1996 there was no evidence for human-to-human transmission of any hantavirus. However, during the Patagonian outbreak in October and November 1996, such transmission appears to have occurred. Traditional epidemiological techniques suggest that some patients in this outbreak, including at least three physicians and one nurse, had no rodent exposure and contracted the illness from exposure to other patients (Enria et al., 1996; Wells et al., 1997a). Some of these exposures may have been blood-borne, but others appear to have been respiratory in nature.

The possibility of respiratory transmission from human to human potentially could be refuted by molecular epidemiological techniques. In this approach viral specimens could be obtained from each infected patient and the RNA sequences from each patient's virus would be determined. While the sequences of all viruses within a species are largely identical, viruses from geographic locations separated by more than 100 meters should have minor base substitutions (substitutions that have minimal, if any, effect on protein structure) that distinguish them from one another (Hjelle et al., 1996b). For any pair of patients in whom viral sequences differ, person-to-person transmission has not occurred. If the viral sequences are identical between two patients, human-to-human transmission is not confirmed, but such transmission is likely if classical epidemiology fails to reveal a potential common exposure. Viral sequences obtained from patients during the Patagonian outbreak of 1996 in fact demonstrate identical sequences in both the M segment and noncoding regions of the S segment in 16 patients who were linked by classical epidemiology (Padula et al., 1998). Some of these HPS patients had no potential exposure to the virus other than caring for other hospitalized HPS patients.

It is difficult to say what effect the information from Argentina should have on the isolation of HPS patients in North America. The epidemiological evidence argues against a requirement for respiratory isolation, although universal precautions clearly are prudent. At UNM, where the largest series of patients has been treated, patients with suspected HPS are placed in respiratory isolation only because *Yersinia pestis* is endemic in the area and the pneumonic form of plague can appear similar in many ways to HPS. Routinely, only universal precautions are used, once HPS is confirmed. Personal communications with physicians and health officials in Argentina suggest that universal precautions may not be adequate to prevent nosocomial transmission of the responsible hantavirus. In South America it appears prudent to use respiratory isolation unless further epidemiological studies rule out the possibility of human-to-human transmission.

Summary

The number of known HPS cases in the United States is now >200, and the illness has occurred in all geographic areas of the country. Though the incidence of the disease is low, the mortality rate remains at 50%, owing to the difficulty in treating a simultaneous severe pulmonary capillary leak syndrome and cardiogenic shock. Adequate treatment of severe cases requires experienced critical care physicians and nurses, as well as advanced facilities. Although nosocomial transmission appears unlikely in North America, universal precautions must be used and some consideration may be given to the use of respiratory isolation.

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41

Epstein–Barr Virus Pneumonia

MASIS PERK AND THOMAS J. MARRIE

Introduction

Infection with Epstein–Barr virus (EBV), the etiological agent of infectious mononucleosis, is ubiquitous, such that by adulthood in most populations the seroprevalence rate is 95% (Strauss et al., 1993). Primary EBV infection during childhood is usually asymptomatic; while during adolescence infectious mononucleosis has a wide spectrum, but fever, sore throat, exudate on tonsils, tender cervical lymphadenopathy, and atypical lymphocytosis are most common (Hoagland, 1960). However, most organ systems can be involved and at times involvement of a single organ system may dominate the clinical picture. Thus meningitis or menigoencephalitis occurs in 1% to 2% of patients (Derkay & Bramhall, 1995; Strauss, 1992). The liver is involved in almost all patients with infectious mononucleosis but only about 35% of patients are jaundiced (Strauss, 1992). Rare manifestations are renal impairment, genital ulcers (Sixbey et al., 1986), and fulminant hepatic necrosis (Penman, 1970). While pulmonary involvement is noted radiographically in up to 5% of patients with infectious mononucleosis, pulmonary symptoms are rarely the major manifestation of infectious mononucleosis (Lander & Palayew, 1974). Haller et al. (1995) recently reported the case of a 30-year-old man with severe pneumonia, requiring ventilation, due to EBV infection and summarized the features of 12 previously reported cases. In this chapter we add three more cases of symptomatic pulmonary involvement in EBV infection and summarize the clinical picture of pulmonary involvement due to this virus.

MASIS PERK • Department of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 4H7 Canada. **THOMAS J. MARRIE** • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Case1

A 23-year-old white male was admitted for the investigation of fever and left pleural effusion. One month previously, he was seen at his local hospital because of fever, sore throat, and cervical lymphadenopathy. A throat swab was positive for *Streptococcus pyogenes* on culture. A slide agglutination test (Monospot®) for EBV infection was also positive. There was no improvement in the fever after oral penicillin therapy. Two weeks later, he developed left-sided chest pain and pleural effusion. Blood and pleural fluid cultures were negative. A 9-kg weight loss was noted. On admission, his temperature was 38.5°C. He had cervical lymphadenopathy and a large left pleural effusion (Fig. 1). The white blood cell count (WBC) was 8.1×10^9/L (neutrophils 80%, lymphocytes 14%, monocytes 5%, eosinophils 1%). Hemoglobin was 110 g/L, and platelets 734×10^9/L. Atypical lymphocytes were not seen. The aspartate aminotransferase (AST) was 36 IU, alanine aminotransferase (ALT) 88 IU, alkaline phosphatase 260 IU, and albumin 27 g/L. Computed tomography of his chest showed no mass or lymphadenopathy. The pleural fluid contained 3.7×10^9/L WBCs (neutrophils 86%, lymphocytes 4%, monocytes 10%) and was negative on culture for viruses and bacteria. There was no evidence of malignancy on cytologic examination. A pleural biopsy showed fibroconnective tissue, with poly- and mononuclear cell infiltration. Acute and

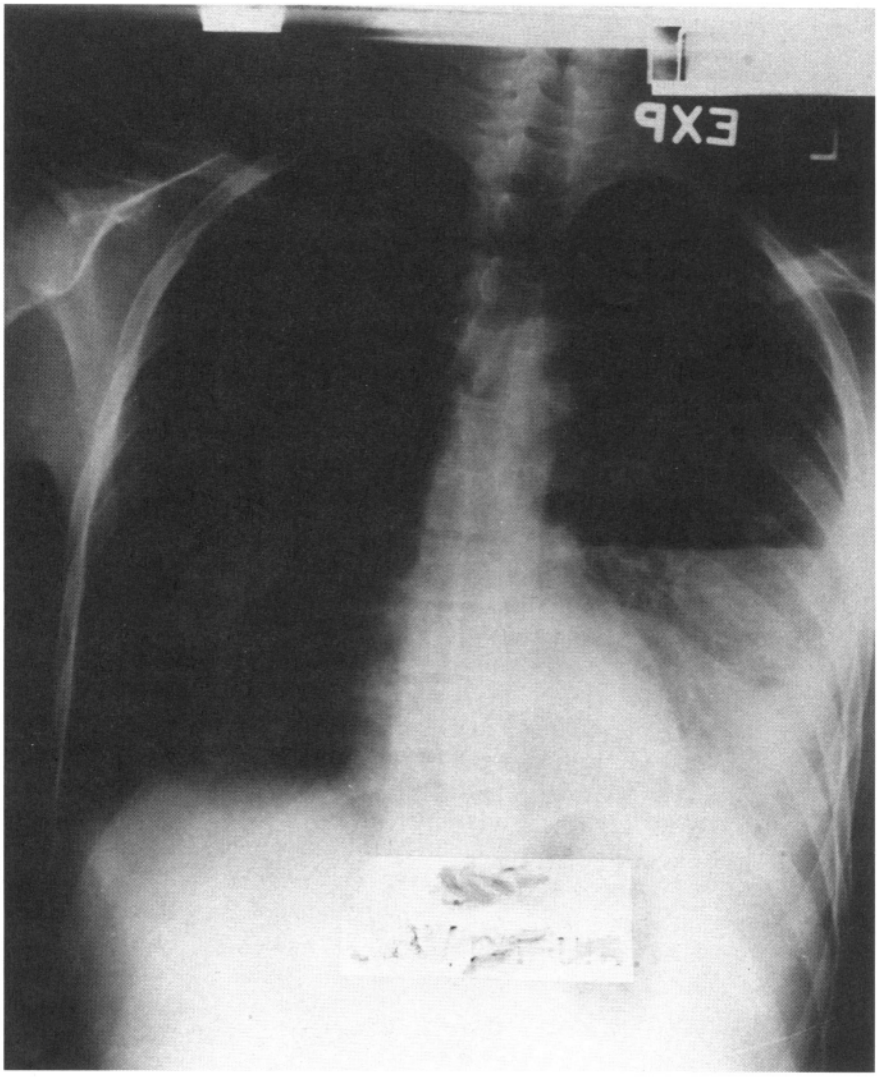


FIGURE 1. Chest radiograph in case 1 showing a a left-sided pleural effusion.

convalescent antibody titers to adenovirus, *Chlamydia* species, cytomegalovirus, influenza viruses A and B, parainfluenza viruses 1, 2, and 3, *Coxiella burnetii,* respiratory syncytial virus, and *Mycoplasma pneumoniae* were all negative or showed no rise. A heterophil antibody titer (Paul-Bunnell test) was positive at 1:40 dilution. On admission, anti-EBV viral capsid antigen (VCA) IgM was <1:5, anti-EBV VCA IgG 1:20, and anti-EBNA >1:5 but <1:80 dilution, consistent with a diagnosis of recent EBV infection. The temperature was elevated from 37.5° to 38.0°C until the fifth hospital day and was normal thereafter. The pleural effusion resolved in 2 weeks and he was well when seen in follow-up.

Case 2

A 45-year-old white female was admitted for the investigation of fever of undetermined origin. She had been receiving azathioprine and prednisone for 1 month because of a relapse of Crohn's disease. Two weeks earlier, she developed fever

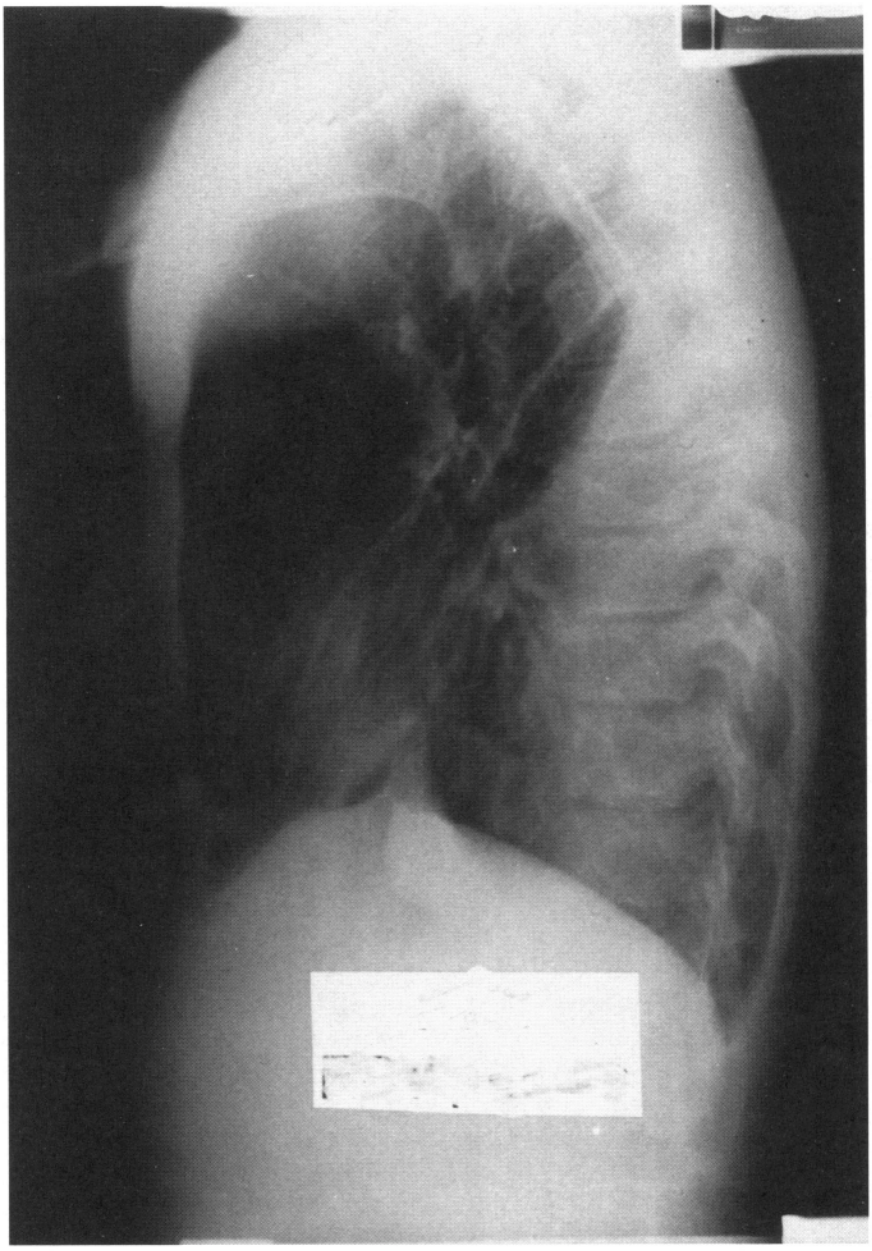
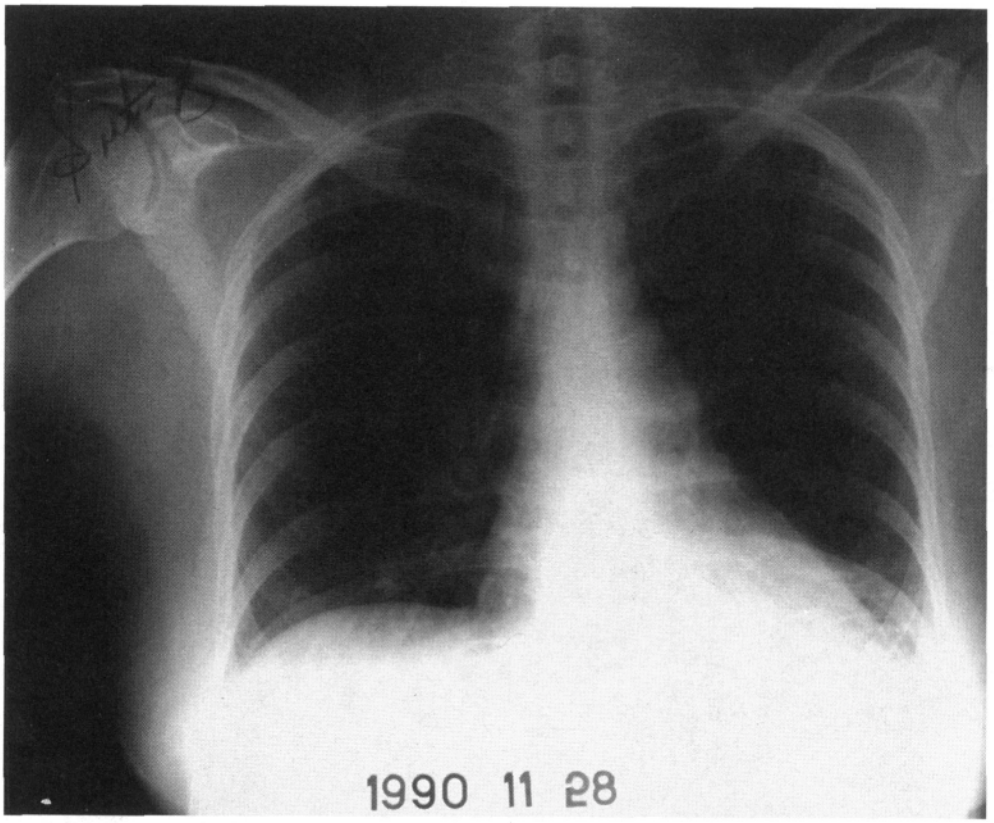


FIGURE 1. (*Continued*)

with chills. The WBC was 1.7×10^9/L and empiric antibiotic treatment with IV ceftazidime and gentamicin was given for 1 week, then vancomycin, imipenem, and amphotericin were administered for a second week, with no improvement in her fever. Blood and urine cultures were negative. Dyspnea with minimal exertion developed and she was transferred to hospital. On admission, the temperature was 38.2°C, blood pressure 94/52 mm Hg, and heart rate 126 bpm. Scleral icterus was evident and there were left basal inspiratory crackles on lung auscultation. A 2-cm node was felt in the left axilla. The WBC count was 1.9×10^9/L (neutrophils 46%, bands 17%, monocytes 3%, atypical lymphocytes



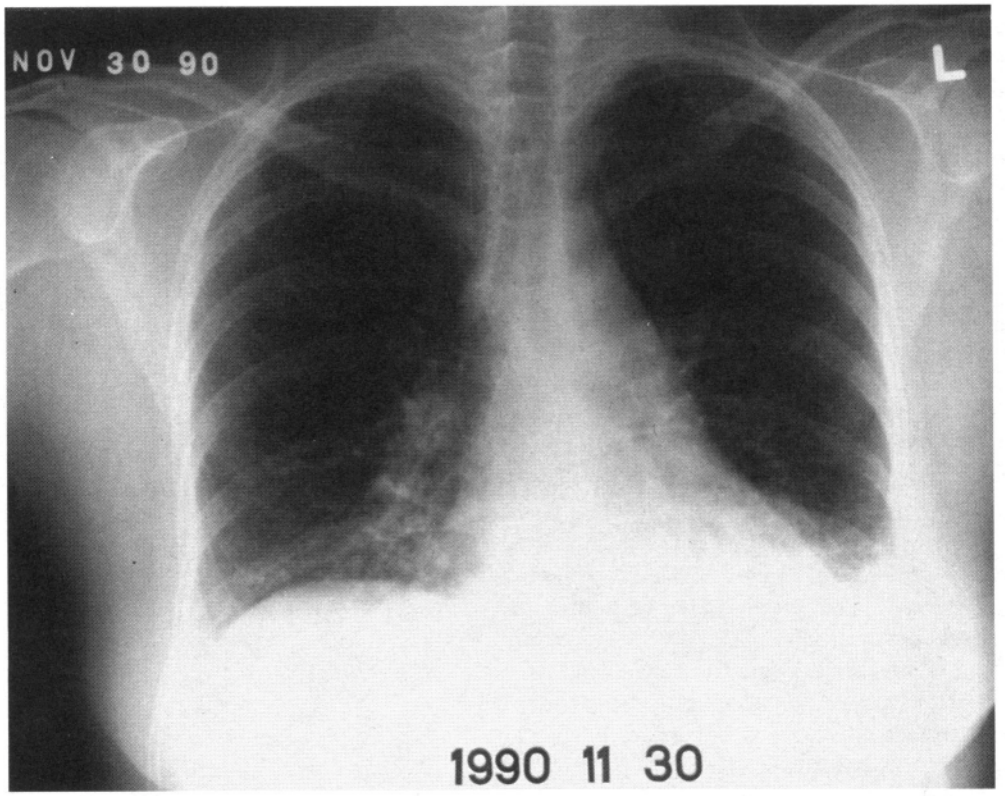
A

FIGURE 2. Serial chest radiographs in case 2. The top radiograph (A) shows a small left lower-lobe opacity. Two days later (B) there is progression of the left basal opacity and (C) bilateral interstitial opacities and an alveolar opacity at the right base. (*Continued*)

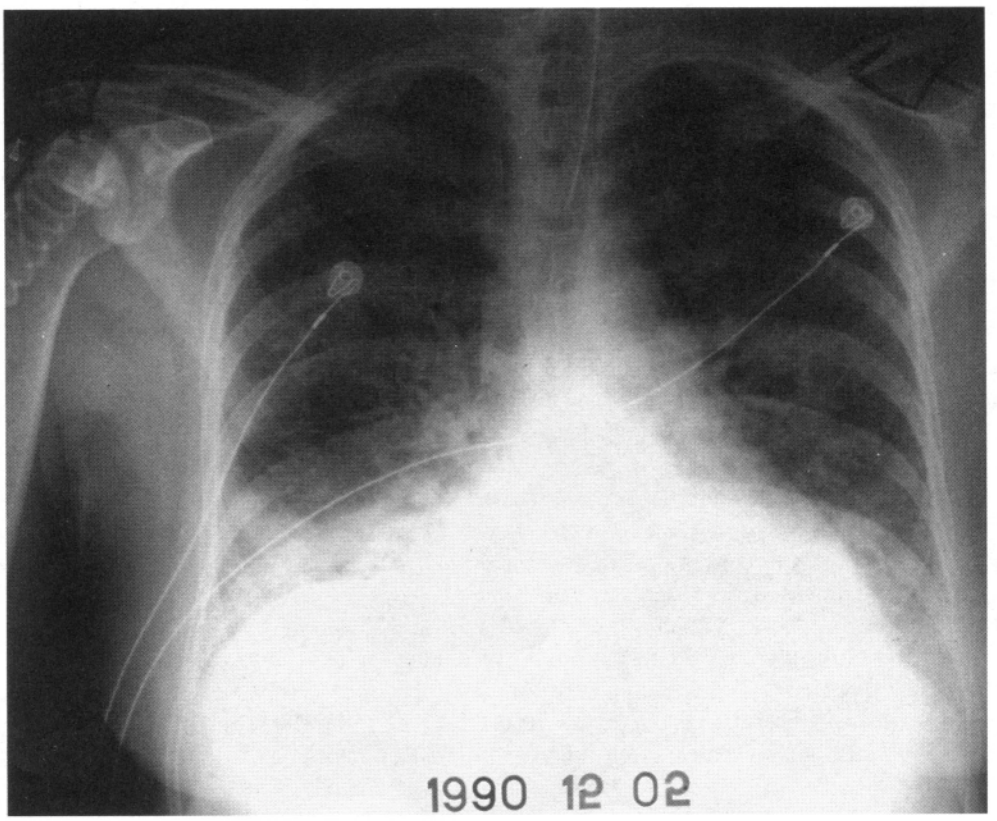
11%), hemoglobin 95 g/L, platelets 47 × 10^9/L Bone marrow examination showed hematophagocytic histiocytosis, likely secondary to viral infection. The serum AST was 136 IU, ALT 84 IU, alkaline phosphatase 565 IU, gammaglutamyltransferase 404 IU, total bilirubin 143 mmol/L. Liver biopsy showed steatosis and cholestasis. Chest radiograph showed a left basal opacity (Fig. 2A). Five days after admission, she was transferred to the intensive care unit because of increasing dyspnea and hypoxemia (pO_2 50 mm Hg, O_2 saturation 87% while inspiring 40% O_2). Mild splenomegaly was noted. A chest radiograph (Fig. 2C) shows bilateral interstitial opacities. Mechanical ventilation was instituted. Examination of a bronchoalveolar lavage specimen was negative for *Pneumocystis carinii* on stain and for fungi, bacteria, and mycobacteria on culture. Ganciclovir therapy was instituted because of a presumptive diagnosis of cytomegalovirus infection. Acute and convalescent serum samples for antibodies to adenovirus, *Chlamydia* species, cytomegalovirus, influenza virus, and *Mycoplasma pneumoniae* were all negative, as was the HIV test. Heterophil antibodies (Paul-Bunnell test) were negative. The anti-EBV VCA IgM was positive at $\geq$1:10 and $<$1:1280. Anti-EBNA remained negative throughout the period of follow-up. She had a slow recovery due to *Staphylococcus aureus* bacteremia and a urinary tract infection. The pneumonia improved gradually, as did the pancytopenia and liver enzyme abnormalities. She was discharged from hospital 1 month after her admission. She remains well 8 years later.

Case 3

A 31-year-old male was admitted to the hospital for the investigation of lower back pain and fever. Two weeks prior to admission, he awoke with



B



C

FIGURE 2. (*Continued*)

an ache in the lower back that was also felt in the buttocks and posterior aspect of his thighs. The onset was rapid and its course progressive. It was worsened by rolling over in bed or standing. The leg pain was aggravated by movement. After 5 days, he was unable to go to work or to get out of bed due to this pain. He felt chilly and warm with increased sweating. At the time of admission, 1 week after the onset of symptoms, back pain was the most prominent symptom but he also had intermittent headache with fever, neck pain, and dysuria. There was muscular tenderness on examination but no neurological abnormality. Ampicillin and gentamicin therapy was begun because of presumed urinary tract infection with secondary discitis. This was discontinued after 3 days when he developed a maculopapular rash. The urine and blood cultures were negative. A bone scan did not show any abnormality. Fever persisted (up to 39.5°C) and he developed a nonproductive cough.

At this point, 1 week after his admission, he was transferred to the hospital. There was no history of recent trauma causing injury. Ten days before his back pain had started, he was seen in the emergency room with right lower quadrant abdominal colic, nausea, and microscopic hematuria. An intravenous pyelogram suggested a right renal mass. Abdominal ultrasound, CT, and retrograde pyelography were all negative. The abdominal pain disappeared abruptly after he vomited violently. It was concluded that he passed a stone. His past illnesses included pneumonia twice (the last episode was in 1994), asthma aggravated by cold air since his childhood, and intermittent low back pain mostly related to heavy lifting. Oral temperature was 39.4°C, BP 120/84 mm Hg, heart rate 102 bpm, and respiratory rate 28 per minute. The pharynx was hyperemic. There was no lymphadenopathy. Basal coarse inspiratory crackles were heard on auscultation. The costovertebral areas were tender to blunt percussion as was his entire lower back, including paraspinal muscles, gluteal muscles, and hamstrings. There was marked tenderness over the spinous process of the fifth lumbar vertebra and there was some limitation to the range of motion in his back and hips mostly due to pain. There was a petechial rash on the lateral aspect of the dorsum of his feet. Pertinent laboratory data are shown in Table 1.

TABLE 1. Laboratory Data, Case 3

	10 days prior	Day 5	Day 8	Day 12
White blood cell ($\times 10^9$/L)	6.2	7.3	14.2	9.2
Hemoglobin (g/L)	155			136
Platelet count ($\times 10^9$/L)	190			97
Differential				
Lymphocytes	34%		62%	28%
Monocytes	13%			
Atypical lymphocytes				43%
Eosinophils	8%			
AST (IU)	35			237
ALT (IU)	38			243
Alkaline phosphatase (IU)	89			243
Gamma GT (IU)	42			217
Lactic dehydrogenase (IU)				1043
Creatine phosphokinase (IU)				1329
Albumin (g/L)	46			28

Urinalysis showed moderate blood by dipstick, 0.3 g/L protein; microscopy indicated 0–1 WBC/hpf, 1–3 RBC/hpf, no bacteria. Throat swab was negative. Urine and blood cultures were negative for bacteria and for cytomegalovirus. The po_2 was 61 mm Hg while inspiring 3 L O_2/min via nasal prongs. A right lower-lobe superior segment pneumonia and left basal atelectasis were evident on chest radiograph (Fig. 3). A lung scan had low probability for pulmonary embolus. The CT scan showed that the spleen was enlarged compared with an examination 3 weeks previously. The spine was normal with no evidence of discitis.

The Monospot® was positive and the EBV VCA IgM antibody titer was negative. Anti-toxoplasma IgM was negative. He gradually improved and was discharged on the sixth hospital day.

Discussion

We report three cases of EBV infection in adults with symptomatic pulmonary involvement. All had serological evidence of acute or recent EBV infection and they had no evidence of any other viral or bacterial pulmonary infection. Recovery was prompt and uneventful in two patients. One

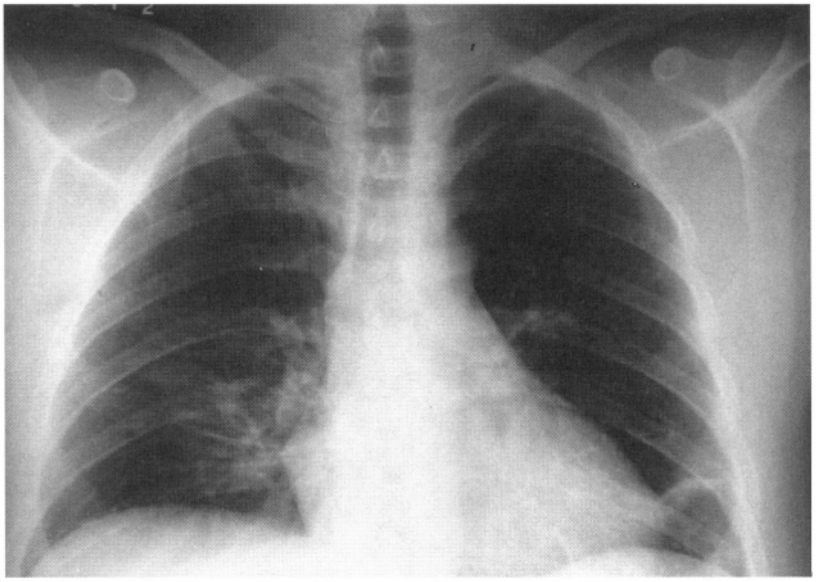


FIGURE 3. Chest radiograph in case 3. Note the right lower-lobe opacity and left basal atelectasis.

patient who was immunosuppressed had a complicated course.

Infectious mononucleosis is uncommon in adults older than 25 years. During various outbreaks, the number of cases in this age group have varied between 4% and 10% (Gunn-Rugg, 1954; Evans et al., 1968; Dunnet, 1963; Mundy, 1972). The diagnosis of the disease in older adults is difficult owing to atypical clinical and laboratory features. Heterophil antibodies can be negative in up to 20% of cases with clinical infectious mononucleosis. There is no uniform hematological picture at the time of presentation. Symptomatic pulmonary involvement is rare and may lead to diagnostic confusion particularly when other manifestations of infectious mononucleosis do not alert the clinician to this diagnosis. Among the 13 previously reported cases of EBV infection with symptomatic pulmonary involvement, 5 required hospital admission. Four of the patients were older than 25 years of age. Patients usually had cough and dyspnea of variable severity at the time of presentation. Only two had bronchial breath sounds while seven had more diffuse crackles on lung auscultation. Six had an interstitial pattern on chest radiograph, with or without consolidation. Five had an alveolar pattern with or without effusion and two had bronchopneumonia. Five had hypoxemia during the course of their illness and all but one recovered from the disease (Lander & Palayew, 1974; Haller et al., 1995; Andiman et al., 1981; Vander, 1954; Eaton et al., 1965; Fermaglich, 1975; Veal et al., 1990; Rodstein, 1948; Offit et al., 1981; O'Donohue et al., 1981;; Myers et al., 1989) (Table 2).

The finding of atypical lymphocytosis can be very helpful diagnostically but it may not be present early in the course of the illness. The Paul-Bunnell test was negative in two of our patients early in the course of the illness. The Monospot® test was positive in the third one. If the titer of heterophil antibodies fails to increase, EBV-specific serodiagnosis, by demonstrating a rise in antibodies to EBV capsid antigen, is necessary. The diagnosis of EBV infection with pulmonary involvement has been usually based on the temporal relationship to EBV infection and the failure to demonstrate any other coexisting viral or bacterial lung infection.

Abnormalities on the chest radiograph, with or without respiratory symptoms, can occur in patients with EBV infection. These abnormalities may be present prior to me development of antibodies that are detected as part of the serological diagnosis of infectious mononucleosis. Hilar adenopathy, pleural effusion, and interstitial pulmonary pattern with or

TABLE 2. Characteristics of Previously and Presently Reported Cases of EBV Infection with Symptomatic Lung Involvement

Reference	Age/sex	Duration of symptoms prior to admission	Immuno-compromised	Symptoms			Other symptoms	Organ enlargement			Auscultation crackles
				Cough	Chest pain	Dyspnea		Liver	Spleen	Lymph nodes	
Lander & Palayew, 1974	29 years/M	6 days	?	+	+	−	Mucoid sputum	?	?	Cervical	Crackles
Mundy, 1972	31 years/F	1 day	−	−	−	+	Hypotension, headache	−	+	Cervical	−
Vander, 1954	9 months	?	?	+	−	+	−	−	−	Cervical	−
Vander, 1954	17 years/F	3 weeks	—	+	—	+	Sore throat	+	−	Cervical	−
Eaton et al., 1965	22 years/M	3 weeks	−	+	−	−	Sore throat	+	+	Generalized	Consolidation
Fermaglich, 1975	18 years/M	6 weeks	—	+	−	+	−	+	+	Generalized	Consolidation
Veal et al., 1990	3.5 years/F	14 weeks	−	+	−	+	−	−	+	−	Crackles
Rodstein, 1948	48 years/M	2 weeks	?	+	−	+	Sore throat, headache, myalgia	−	−	Cervical, axillar	Crackles
Haller et al., 1995	30 years/M	10 days	−	+	−	+	−	+	+		Crackles
Offit et al., 1981	21 years/M	3 weeks	?	+	+	+	Yellow sputum, headache	−	−	Cervical	Crackles
O'Donohue et al., 1981	17 years/M	3 weeks	−	−	−	+	Confusion	+	+	Cervical	Crackles
O'Donohue et al., 1981	22 years/M	4 weeks	+	+	−	+	Sore throat	+	+	Generalized	Crackles
Myers et al., 1989	16 years/F	1 week	?	+	−	+	Myalgia	−	−	Generalized	−
Present series, Case 1	23 years/M	1 month	−	−	+		−	−	−	Cervical	Pleural effusion
Present series, Case 2	45 years/F	2 weeks	+	−	−	+	−	−		Axillar	Crackles
Present series, Case 3	31 years/M	2 weeks	−	−	−		Low back pain	−	−	−	Crackles

without consolidation may present as single or multiple radiographic abnormalities. The overall incidence was found to be 5% or less (Lander & Palayew, 1974).

In two patients with chronic EBV infection transbronchial biopsies showed patchy expansion of alveolar septa by an infiltrate of small, mature lymphocytes associated with peribronchiolar and perivascular lymphocytic infiltrates and occasional alveoli containing fibrin, neutrophils, and histiocytes (Schooley et al., 1986).

Post-mortem histopathology of the lungs of patients dying of infectious mononucleosis has shown patchy lymphoplasmacytic infiltrates and lymphoid aggregates within the pulmonary interstitium and around the blood vessels. In contrast to other herpes virus lung infections, intranuclear viral inclusions are not seen (Hogg & Hegele, 1995).

EBV is now considered to be the etiologic agent of a number of lymphoma-like disorders that involve the lung. These include lymphomatoid granulomatosis and lymphocytic interstitial pneumonia (Hogg & Hegele, 1995).

The role of corticosteroids in the treatment of severe pulmonary infection due to EBV is supported by anecdotal evidence only (Haller et al., 1995). There is no benefit from corticosteroid treatment of uncomplicated infectious mononucleosis.

Conclusions

Symptomatic pulmonary involvement is a rare manifestation of infectious mononucleosis. The diagnosis becomes even more difficult in adults, who often present with atypical features of the disease. A careful analysis of the symptoms and WBC count and differential can yield valuable clues and ultimately lead to the correct diagnosis.

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Community-Acquired Pneumonia Due to Cytomegalovirus, Herpes Simplex Virus-1, and Human Herpes Virus-6

KEVIN FORWARD

Introduction

Cytomegalovirus (CMV), Herpes simplex virus 1 (HSV-1), and human herpes virus-6 (HHV-6) are members of the Herpesviridae family, which has more than 100 other members. Only eight appear to be primarily human pathogens. Human CMV and HHV-6 are members of the Betaherpesviridae subfamily; HSV-1 and HSV-2 belong to the subfamily of Alphaherpesviridae. Other important human herpesviruses include the Epstein-Barr virus, varicella-zoster virus, and human herpesviruses 7 and 8. Except for varicella-zoster, which occasionally causes symptomatic pneumonitis during primary infection, other human herpesviruses infecting humans rarely cause pneumonitis. The viruses discussed in this chapter cause pulmonary infection almost exclusively in patients with altered cell-mediated immunity. Pulmonary infection may occur with primary infection; however, pneumonia occurs most often in patients whose latent infections reactivate as a result of immunosuppressive treatment or underlying disease. Patients developing pneumonia due to these agents may do so while in the community. As a result they should be considered in the differential diagnosis of community-acquired pneumonia in the immunocompromised patient.

KEVIN FORWARD • Department of Medicine, Division of Infectious Diseases, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia B3H 2Y9, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Herpesviridae

Viruses of the Herpesviridae family are enveloped viruses with an icosahedral nucleocapsid comprising 162 capsomeres. The genome is a linear, double-stranded DNA molecule of approximately 170 kb. Members of this family cannot be distinguished by electron microscopy. The nucleocapsid itself is approximately 100 nm in diameter. Between the nucleocapsid and the envelope is a tegument consisting of an amorphous assembly of virus-encoding proteins. The enveloped virus is between 150 and 250 nm in diameter. The envelope is derived primarily from nuclear membrane into which viral glycoproteins have been integrated prior to their release through the cytoplasmic membrane. There glycoproteins are involved in adherence to target cells and to other human proteins such as Fc immunoglobulin receptors.

All human herpesviruses have the ability to establish latent infection. The mechanisms by which latency is established are incompletely un-

derstood. In the case of HSV-1 and HSV-2, central nervous system ganglia appear to be the usual site of latency. After CMV infection, lymphocytes and probably neutrophils and monocytes are latently infected, whereas for HHV-6, CD4 lymphocytes are the principal site of latent infection.

Viral surface glycoproteins mediate attachment and penetration into target cells. After cell entry, the envelope is removed and the capsid is transported through the nuclear pores. The DNA is released in the nucleus. Transcription, DNA synthesis, capsid assembly, and envelopment take place in the nucleus. Viral replication occurs in the nucleus of infected cells. Almost immediately after infection, a small number of "immediate-early" genes encode proteins, regulating their own synthesis and the subsequent synthesis of "early" proteins.

Human Cytomegalovirus Pneumonia

Infection with CMV is very common. In most countries, approximately 40% of adolescents are seropositive (Britt & Alford, 1996). Thereafter, approximately I% of individuals per year seroconvert. Seropositivity rates are generally inversely related to socioeconomic status. The horizontal transfer of CMV usually results from close personal contact with asymptomatic individuals. Infections with CMV may occur in utero, especially when the pregnant mother experiences a primary infection. In such a setting, approximately 40% of infants become infected. The rate of transmission is much lower in women who have antibodies to CMV before pregnancy. Children enrolled in day care programs acquire CMV infection at a particularly rapid rate. There is considerable evidence suggesting that CMV in transmitted through sexual contact. CMV is frequently transmitted in the hospital setting either as a result of transplantation or by blood transfusion (Bowden, 1995).

CMV pneumonia occurs very rarely in the normal host. In one series pulmonary infiltrates developed in only 2 of 33 patients with primary CMV infections (Klemola et al., 1970). In another report pneumonia was associated with CMV mononucleosis in 6% of cases (Cohen & Corey, 1985). Eight cases of CMV pneumonia were found in nonimmunocompromised patients. These patients all had elevated transaminases and usually had bilateral patchy changes on chest x-ray.

Mera et al. (1996) reported 20 cases of CMV pneumonia in patients with cancer. The diagnosis of CMV pneumonia had not been made until autopsy in 19 of the 20 cases. They emphasized that CMV pneumonia was an uncommon cause of death in adults with cancer and that it was usually found in patients with widespread disease. Wallace & Luchi (1996) described fatal CMV pneumonia in a patient on immunosuppressive therapy for mixed connective tissue disease.

Humoral immunity appears to have very little utility in protecting individuals from disseminated CMV infections including pneumonia. CMV pneumonia occurs primarily in patients with severely compromised cell-mediated immunity. Despite this, CMV pneumonia is infrequently seen in patients with AIDS (Drew, 1988). Salomon et al. (1997) described 18 cases over a 5-year period in a large New York hospital. CMV lung infection alone was documented in only 2% of transbronchial lung biopsy specimens examined. They noted that patients with CMV pneumonia usually had CD4 counts less than 75×10^6/L and often had evidence of extrapulmonary CMV infection.

CMV pneumonia has been reported most often in the context of bone marrow transplantation. Risk factors favoring development of CMV disease include the use of total body irradiation, increasing age, and the development of graft-versus-host disease (Ljungman, 1995). The diagnosis of CMV pneumonitis may be strengthened by other evidence of CMV-induced damage involving retina, gastrointestinal tract, bone marrow, and liver. Most published series contain relatively few cases of pneumonia in which CMV is the only identified agent and when the diagnosis has been based on histologic evidence of CMV infection. CMV is often isolated from clinical specimens (sputum and urine) in asymptomatic immunocompromised patients. Diagnosis is further complicated because CMV infection may lead to an increased rate of superinfection due to other respiratory pathogens (Rand et al., 1978).

In the last 10 years, there has been a dramatic reduction in both the incidence of severe CMV infections (including interstitial pneumonia) and the mortality rate from CMV pneumonia. These

changes relate to the avoidance of CMV-containing blood products in susceptible transplant recipients, the use of prophylactic or preemptive ganciclovir therapy, and more effective treatment regimens (Miller et al., 1991). The current incidence of CMV disease in seropositive bone marrow transplant recipients in many centers is less than 10%.

Typically, CMV pneumonitis occurs an average of 50 to 60 days after bone marrow transplant. Onset of CMV interstitial pneumonia may be delayed in patients receiving posttransplant antiviral prophylaxis. Syngeneic and autologous marrow transplant recipients have a much lower incidence of CMV pneumonitis. The risk of CMV pneumonia is greatest in patients who have graft-versus-host disease.

Most patients with CMV pneumonia present with cough, dyspnea, and fever. Symptoms are present on average 2 weeks before presentation and most patients will have symptoms of less 1 month's duration. Physical examination may reveal diffuse or localized crackles but may be normal. A variety of chest radiographic patterns may be seen. Typically, the findings are suggestive of interstitial pneumonia beginning at the bases and progressing to involve the upper lung fields. Patients may have a miliary pattern, localized areas of consolidation, nodular opacities, and pleural effusions (Beschorner et al., 1980). Approximately one third of patients may present with normal chest radiographs. In these patients, 67-gallium citrate lung scans often show a diffuse bilateral lung uptake.

It is important that an appropriately high index of suspicion be maintained if the diagnosis of CMV pneumonia is to be confirmed and treatment initiated. The diagnosis is based primarily on the examination of lung tissue for evidence of an injury pattern consistent with CMV infection and the presence of "owl's eye" intranuclear inclusions (Fig. 1). These are eosinophilic, intranuclear inclusions with a surrounding halo and marginated chromatin. They can be seen with Wright, Giemsa, hematoxylin-eosin, and Papanicolaou stains. Histologic changes include evidence of interstitial pneumonitis and pulmonary vasculitis with alveolar hemorrhage in addition to inclusions alone (Meyers et al., 1975). The diagnosis is also supported by in situ hybridization studies or immunohistological evidence of CMV-infected cells (Myerson et al., 1984; Volpi et al., 1983; Weiss et al., 1990). Cytologic examination of cells retrieved by bronchoalveolar lavage (BAL) may reveal evidence of CMV infection in the form of intranuclear inclusions. Occasionally, cytologic changes are seen, even in asymptomatic patients subjected to bronchoscopy (Solans et al., 1995). Others have found cytology to be specific but insensitive (Paradis et al., 1988; Crawford et al., 1988).

Serologic testing for CMV is sufficiently sensitive that CMV infection almost never occurs in seronegative individuals. The detection of IgM antibodies to CMV is usually not useful for the diagnosis of primary infection as this test is both insensitive and nonspecific (Waner et al., 1973).

Patients at risk frequently have positive blood cultures for CMV, either by conventional culture or by the centrifugation-enhanced shell vial culture method (Ibrahim et al., 1997; Boeckh et al., 1992; Webster et al., 1993). The shell vial method is generally preferred because the result is available more rapidly (Gleaves et al., 1985). In patients with altered cell-mediated immunity, CMV cultures of either induced sputum or BAL are frequently positive (Ibrahim et al., 1997; Uberti-Foppa et al., 1998; Meduri et al., 1991; Miles et al., 1990; Rush et al., 1989). A negative BAL culture does, however, make CMV pneumonitis unlikely (Erice et al., 1988; Uberti-Foppa et al., 1998; Emanuel et al., 1986). The quantitation of CMV in either tissue or BAL fluid does not predict the severity of disease or predict outcome (Forman & Zaia, 1994; Slavin et al., 1992). Indeed, because CMV is found so frequently in the lungs of patients with AIDS, positive tests for its presence are often unassociated with disease (Miles et al., 1990; Millar et al., 1990).

Patients who have high numbers of polymorphonuclear or mononuclear cells in peripheral blood (>50/200,000 cells) expressing CMV antigens have a greater likelihood of CMV disease. Leukocytes separated from heparinized blood are stained with antibodies to the CMV early antigens and examined by either immunofluorescence or immunoperoxidase staining (The et al., 1990, 1992). Patients who go on to develop pneumonia usually have antigen-positive cells in the weeks before disease develops (Egan et al., 1995). Higher numbers of infected cells make disease more likely due to CMV. Use of this test to assess the efficacy of treatment has not been fully developed.

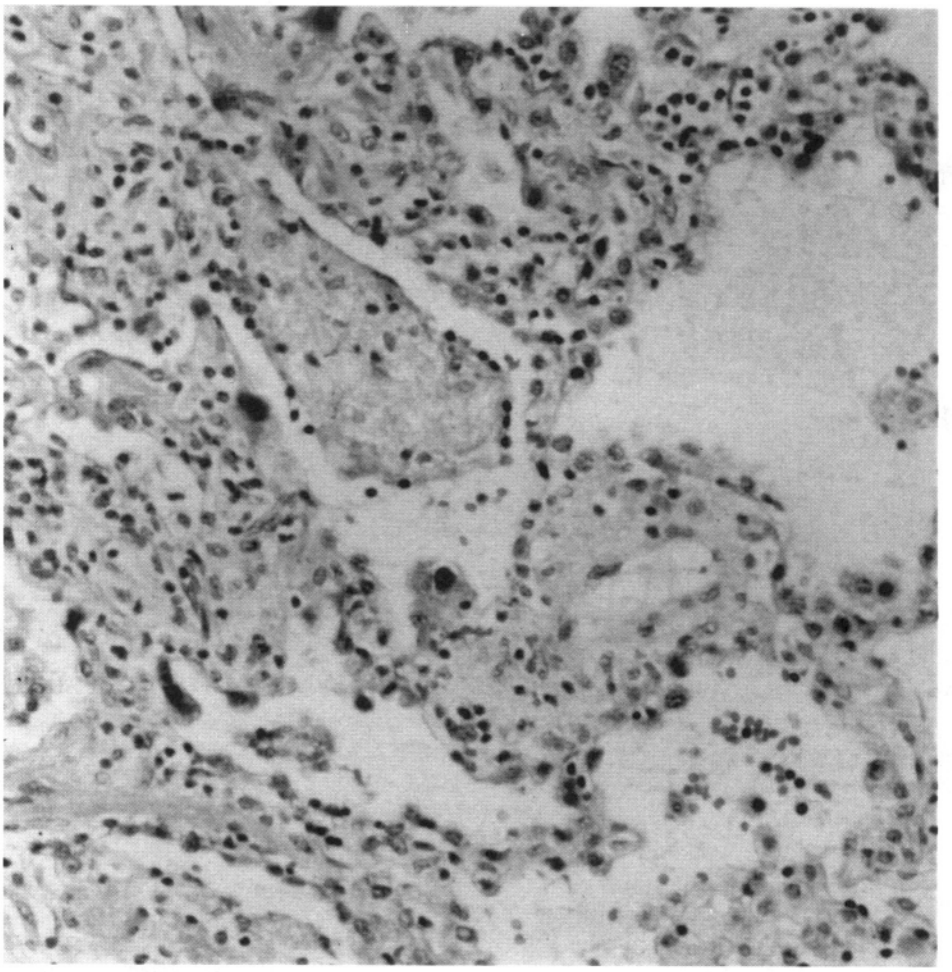

FIGURE 1. Hematoxylin and eosin stain of a lung biopsy in a patient with cytomegalovirus pneumonia. Alveolar walls show interstitial thickening. Large cytomegalovirus intranuclear inclusions are seen in alveolar lining pneumocytes.

As a general rule, the application of PCR to peripheral blood, respiratory tract tissues, or secretions is highly sensitive but has low specificity (Jiwa et al., 1989; Abecassis et al., 1997; Buffone et al., 1993; Myerson et al., 1993). Attempts to improve the specificity by performing reverse transcription PCR, which detects CMV mRNA and theoretically should more accurately reflect active viral replication, may be more useful; however, these approaches need to be validated further.

Quantitative PCR or PCR to detect mRNA may also prove useful in distinguishing between infected and colonized patients (Bitsch et al., 1992; Patel et al., 1995; von Laer et al., 1995). More work needs to be done in order to better determine the performance characteristics of this test in different populations at risk.

Ganciclovir is the preferred treatment for patients with proven CMV pneumonitis. It is a nucleoside analogue of guanosine. It differs from acyclovir only by the presence of a hydroxymethyl group. Ganciclovir is highly active against CMV. Typical inhibitory concentrations are between 0.2 and 3.0 mg/L. There are no comparative studies of ganciclovir for the treatment of CMV pneumonitis in which ganciclovir was compared with either placebo or with foscarnet.

Ganciclovir alone is generally less effective

for the treatment of CMV pneumonia in bone marrow transplant recipients. Two studies suggest that the concurrent use of immunoglobulin increases the efficacy of ganciclovir in patients who have received bone marrow transplants (Emanuel et al., 1988; Reed et al., 1988). Usually, ganciclovir is administered at a dose of 5 mg/kg twice daily for 14 to 21 days. The most common adverse affect associated with intravenous ganciclovir administration is hematologic toxicity. Bone marrow recipients in particular are at high risk for neutropenia. Thrombocytopenia frequently develops, particularly in HIV-infected patients. Nephrotoxicity is frequently seen and occurs more often in patients receiving nephrotoxic immunosuppressive agents such as cyclosporin.

Foscarnet is a pyrophosphate analogue with activity against HSV-1 and HSV-2, CMV, and HHV-6, as well as a number of other herpesviruses. There is little published experience with foscarnet for the treatment of CMV pneumonia. In most cases, it has been used as salvage therapy in patients who have not responded to ganciclovir.

Cidofovir is an acyclic phosphonate nucleotide analogue with activity against CMV. In general, CMV strains resistant to ganciclovir and foscarnet remain susceptible to cidofovir. Although there is some experience with cidofovir for the treatment of CMV retinitis in HIV patients, there is inadequate evidence to recommend the use of cidofovir over either ganciclovir or foscarnet for CMV pneumonia.

Human Herpesvirus-6 Pneumonia

There are two genetic variants of HHV-6, A and B (Aubin et al., 1991). The B variant appears to be primarily responsible for disease, but serologic tests do not distinguish between the two. Co-infections with both variants appear to be common (Cone et al., 1996). Most adults have antibodies to HHV-6. Huang et al. (1992) found that, by the age of 2, most children have been infected with this virus. The highest incidence is seen after the disappearance of maternally derived antibody, between the ages of 6 and 12 months. Almost all adults have antibodies to HHV-6 (Pellet et al., 1996).

The mode of transmission of HHV-6 has not been clearly established. Infection by HHV-6 is most often a result of contact with infected saliva and is probably primarily from mother to child. Primary HHV-6 infection appears to be most often associated with acute febrile illness in infants. Although HHV-6 causes roseola infantum (exanthem subitum), most children do not present with an exanthem. Pruksananonda et al. (1992) observed that only 18% of children had skin rash at the time of presentation and a similar proportion developed rash within a week of presentation. Fewer than 10% of children had a classic roseola-like illness. Of children with primary HHV-6 infection seen in an emergency department, a large proportion had fever and otitis media or an undifferentiated febrile illness. In adults, primary infection due to HHV-6 may rarely cause an infectious mononucleosis-like syndrome in adults (Akashi et al., 1993; Steeper et al., 1990).

Lower respiratory tract infection occurring in the usual setting of primary HHV-6 infection is unusual. In a study of 34 children with primary HHV-6 infections who presented with fever to an emergency department only three had lower respiratory tract illness (Pruksananonda et al., 1992). Hall et al. (1994) studied 160 children with acute febrile illness associated with HHV-6 infection. Although 41 had upper respiratory tract signs, only two were hospitalized with lower respiratory tract disease. One patient was co-infected with respiratory syncytial virus, which may have caused the respiratory symptoms. There have been no descriptions of the histopathology of HHV-6-associated pneumonitis in immunocompetent patients.

Pneumonitis associated with HHV-6 has been described in immunocompetent adults. Russler et al. (1991) reported a case of a 37-year-old immunocompetent man who developed both *Legionella pneumophila* and pneumonia attributed to HHV-6. Evidence supporting the role of HHV-6 included a 64-fold rise in the IgG antibody titer, the recovery of HHV-6 from a sample of peripheral blood, and immunohistochemical staining of lung tissue for HHV-6 antigens.

Interstitial pneumonitis associated with HHV-6 was first reported by Carrigan et al. (1991). They reported two cases, each in patients undergoing bone marrow transplantation. In the first case, inter-

stitial pneumonitis developed 1 month after transplantation. HHV-6 was isolated from samples of blood and bone marrow. At autopsy, there was evidence of pneumonitis and pulmonary hemorrhage with edema. Immunohistochemical staining showed widespread HHV-6 infection of the lung. In the second case, pneumonitis developed 2 weeks after transplantation. HHV-6 was isolated from BAL fluids and two sputum specimens. Immunohistochemical staining of the lung tissue revealed clusters of HHV-6-infected cells.

Cone et al. (1993a) used PCR to detect HHV-6 DNA in lung tissue from patients with pneumonitis after bone marrow transplantation. Symptoms of pneumonitis developed an average of 48 days after transplantation but occurred as early as 9 and as late as 4 years later. Eight of the 15 patients had no other etiologic agent identified, and seven had other causes. Histopathologic examination revealed evidence of bronchiolitis, interstitial pneumonitis, and diffuse alveolar damage. There may be an association between the development of graft-versus-host disease and the development of HHV-6 pneumonitis, since patients with the highest number of DNA copies were also more likely to have severe graft-versus-host disease (Cone, 1993a).

Fatal pneumonitis attributed to HHV-6 has been described in an infant with thymic atrophy and T lymphocytopenia (Knox et al., 1995). Disease appeared to be the result of reactivation of latent virus. At autopsy there was evidence of nonspecific pneumonitis, diffuse alveolar damage, and atelectasis. Knox and Carrigan (1994a) reported on the use of an immunohistochemical stain for HHV-6 in nine patients dying with AIDS. Lung, lymph node, spleen, liver, and kidney specimens were all positive for HHV-6 antigen. Although all patients had significant lung disease at the time of death, three of nine patients had *P. carinii* pneumonia, and one had CMV pneumonitis. The ubiquity of HHV-6 has led to skepticism that it is anything other than a commensal organism in such a setting (Griffiths et al., 1994). It has also been suggested that since there are no features unique to HHV-6 pneumonia, the diagnosis cannot be made without quantitative measures of viral load (Knox & Carrigan, 1994b).

Interstitial pneumonitis associated with HHV-6 has been described in the setting of liver transplantation. Singh et al. (1997) described four cases of interstitial pneumonitis developing a median of 50 days after liver transplantation. No other viral cause of pneumonia was identified and immunohistochemical staining of lung tissue revealed HHV-6-infected cells in three of four cases. In one case, the diagnosis was based primarily on the recovery of HHV-6 from peripheral blood mononuclear cells and may not have warranted inclusion in the reported series.

The diagnosis of HHV-6-associated pneumonia remains problematic. When HHV-6 is suspected, it is invariably in the setting of interstitial pneumonitis in a patient with severely compromised cell-mediated immunity. Virtually all older children and adults have preexisting antibodies and increases in antibody titers are poorly predictive of disease. Occasionally there is cross-reactivity between CMV and HHV-6 antibodies (Irving, 1990). IgM antibodies to HHV-6 are not useful in the setting of reactivated HHV-6 (Fox et al., 1990).

The isolation of HHV-6 from lung tissue, BAL fluid, or peripheral blood is generally performed only in large academic centers. Cultures of peripheral blood mononuclear cells are usually negative in convalescenl immunocompetent children. Positive blood cultures are common in seropositive healthy adults and after organ transplantation (Jarrett et al., 1990). PCR has been widely used to detect HHV-6 DNA in peripheral blood. When performed on children without HHV-6 antibody, PCR tests are almost always negative (Cone et al., 1993b). When PCR tests were performed on children convalescing from primary HHV-6 infection, 68% of children remained PCR-positive 1 to 3 months after primary infection. In studies of healthy adults, PCR performed on blood and saliva is usually positive (Jarrett et al., 1990; Cone et al., 1993b). In bone marrow recipients and in patients with AIDS, PCR performed on serum or plasma may be positive, even in the absence of symptoms (Kadakia et al., 1996). Secchiero et al. (1995a) found HHV-6 DNA in the plasma of 23% and 22% of patients with bone marrow transplants and asymptomatic patients with AIDS, respectively. In the three bone marrow transplant patients with transiently positive PCR there was a temporal association with the onset of fever and respiratory symptoms. PCR has also been applied to respiratory secretions. However, because otherwise healthy individuals may have HHV-6

DNA in their saliva, results must be interpreted with caution (Hartnett et al., 1990; Kelley & McClain, 1994). It is not yet clear whether quantitative PCR for HHV-6 will prove useful in identifying patients who have disease (Secchiero et al., 1995b).

Several antiviral compounds have demonstrated in vitro activity against HHV-6. Ganciclovir and foscarnet are the most active (Russler et al., 1989; Agut et al., 1989; Burns & Sandford, 1990). Ganciclovir is much more active that acyclovir. It is difficult to compare the results of susceptibilities performed in different laboratories because of differences in the methodologies used. The treatment of HHV-6 pneumonia has not been evaluated in clinical trials and the results of small series and individual case reports are difficult to evaluate. This is especially difficult in the absence of an agreed-upon case definition. Drobyski et al. (1993) treated six bone marrow transplant patients with HHV-6 viremia. Follow-up blood cultures demonstrated resolution of viremia in all six patients.

Herpes Simplex Pneumonia

HSV-1 infection occurs at a very early age in developing countries and among the socially disadvantaged. Where socioeconomic standards are high, approximately one quarter of children are seropositive by the age of 5. By age 25, approximately half of individuals are seropositive. The most important reservoir for HSV-1 infections is likely among individuals who have been previously infected and who periodically excrete the virus in saliva. At any given time as many as 15% of seropositive individuals may be excreting HSV-1 in their saliva.

Almost always, adults with HSV-1 pneumonia have underlying diseases, including malignancies, renal failure, alcoholism, and organ transplantation (Nash, 1972; Cheever et al., 1965; Caldwell & Porter, 1971; Jordan et al., 1975; Douglas et al., 1969; Moore, 1973; Breyer et al., 1983; Camazine et al., 1995). HSV pneumonia is seldom recognized during life. Ramsey et al. (1982) reported 20 cases, all of which were initially recognized at autopsy. They described two patterns of lung involvement and suggested that different pathogenic mechanisms might be responsible. In one form, there were focal areas or necrosis in the lung and evidence of extension of oral mucocutaneous herpes down the tracheal bronchial tree into the lung. The second pattern is that of diffuse pneumonia, which has been postulated to be due to hematogenous dissemination from either mucocutaneous oral or genital lesions to the lung and other visceral organs. HSV pneumonia is most frequently recognized in bone marrow transplant patients. Pneumonia usually develops within 2 months of transplantation. In a study of 525 consecutive allogeneic bone marrow transplant recipients, Herpes simplex viruses were isolated in 9 of 183 patients with nonbacterial pneumonia (Meyers et al., 1982). In the same study, 46% of patients had CMV pneumonia and 34% had idiopathic interstitial pneumonia. Herpes simplex pneumonia has also been described in post-thoracotomy patients, especially where patients have required endotracheal intubation and ventilation (Breyer et al., 1983). Diagnosis in this setting may be difficult since culture results themselves may be misleading. Porteous et al. (1984) have shown that oral shedding of HSV-1 occurs frequently in critically ill patients. Eighteen of 42 severely ill surgical patients had evidence of reactivation of HSV in the postoperative period. Tuxen et al. (1982) found HSV-1 in the lower respiratory tract of 30% of patients with adult respiratory distress syndrome.

Herpes simplex viruses are easily grown in the clinical virology laboratory. A number of cell lines including foreskin fibroblasts are highly susceptible, and conventional cultures are usually positive within 4 days. The application of the shell vial assay may shorten the time to recovery to 24 hours (Pruneda & Almanza, 1987). Serologic diagnosis of HSV pneumonia is of little value since infection is often the result of reactivated rather than primary infection. Most commercially available assays are unable to distinguish between HSV types 1 and 2 antibodies; pre-existing IgG antibodies are often present, and the liter of antibody may fluctuate. Because a large proportion of asymptomatic immunocompromised patients will have reactivated HSV, PCR of respiratory sections is unnecessarily sensitive and not specific for the diagnosis of respiratory infections.

Alternatives to virus culture include direct antigen detection by either immunoperoxidase or immunofluorescence in lung tissue (Fig. 2). Neither of

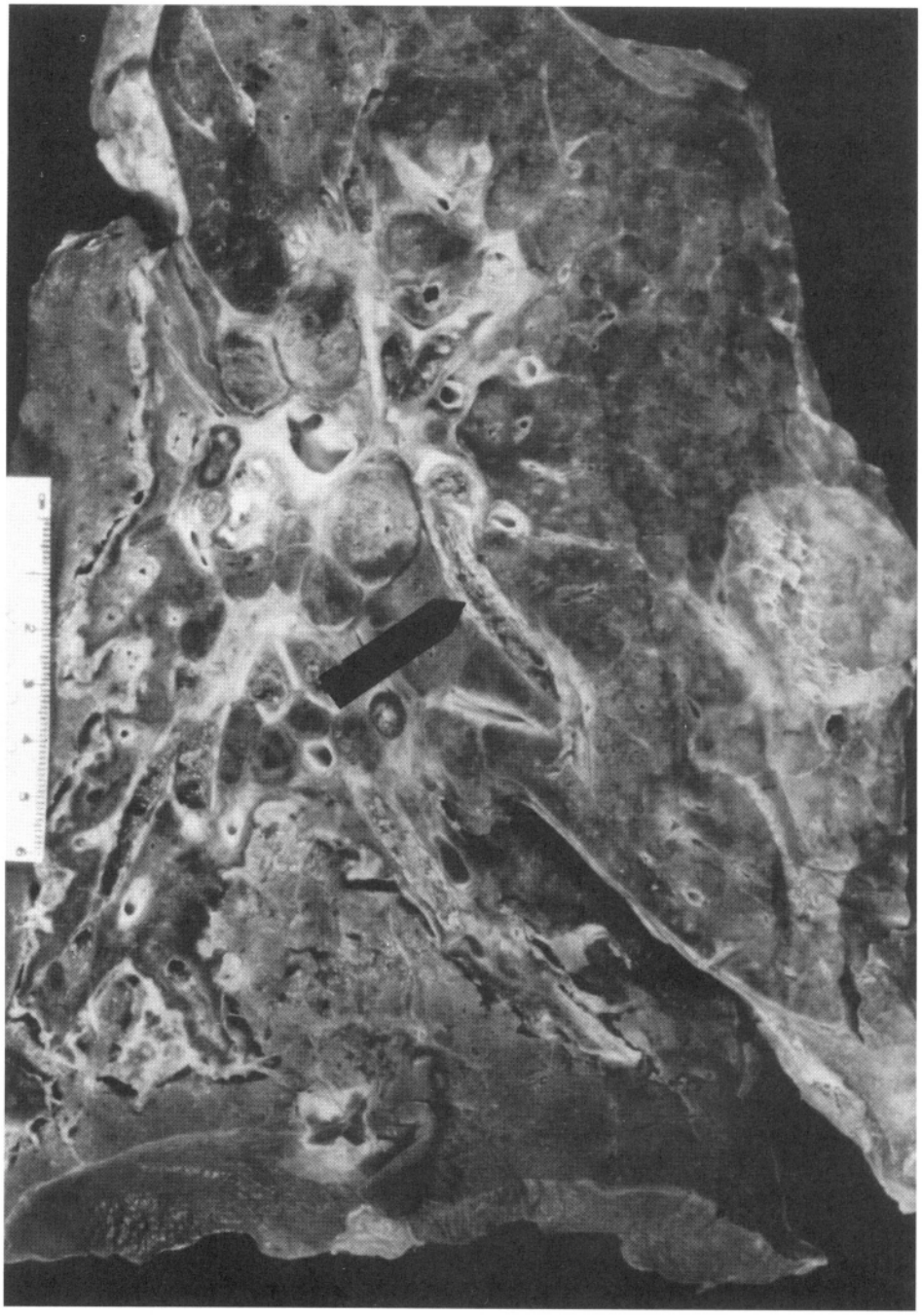

FIGURE 2. Autopsy specimen of left lung from a patient dying from *Herpes simplex* 1 pneumonia. The airways that have been cut longitudinally show extensive mucosal damage (arrow). Confluent necrosis is seen in the lower lobe and lingula. The background lung is consolidated and hemorrhagic.

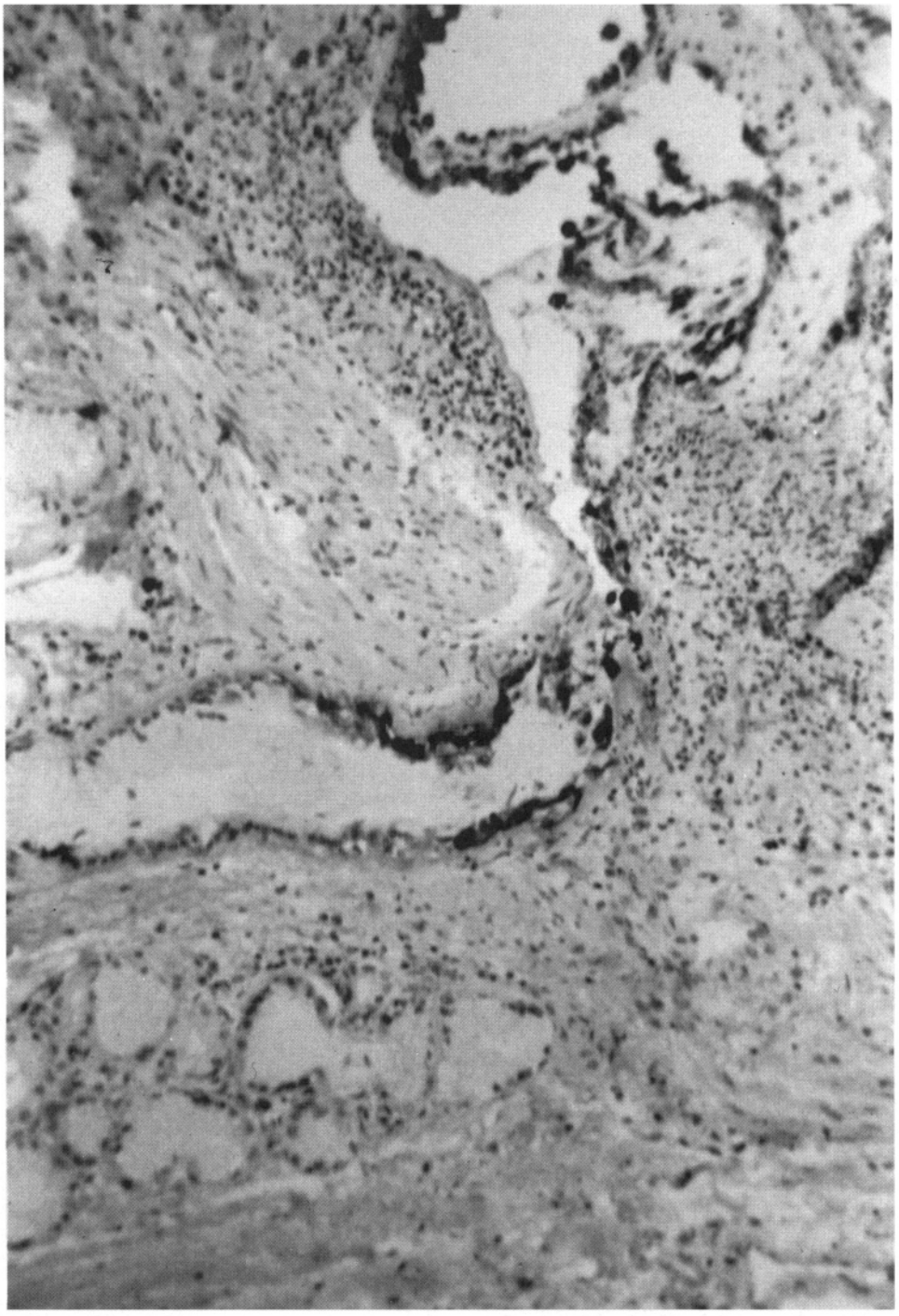

FIGURE 3. Immunoperoxidase stain using antibody detected against *Herpes simplex* type 1. The section is through a bronchus and shows compression and distortion of the bronchial lumen. Most of the lining epithelium is intact. The darkly staining cells are those expressing *Herpes simplex* type 1 antigens on their surface.

these methods has been adequately evaluated in the setting of suspect HSV pneumonia to draw conclusions relating to either the sensitivity or specificity of these tests.

As with CMV pneumonia, the diagnosis usually depends on primary histologic findings. There is an inflammatory infiltrate, parenchymal necrosis, and hemorrhage (Fig. 3). Typically, there is ballooning degradation of cells, ground-glass nuclei with large basophilic inclusions, and marginated chromatin. Eosinophilic intranuclear inclusions and multinucleated giant cells are often seen. Changes may be in a patchy distribution or may be more diffuse. The tracheo-bronchial tree often has evidence of necrotizing herpetic tracheitis; patients often have concurrent herpetic esophagitis. Mucocutaneous herpes infections are usually present and often precede the development of pneumonia.

There are no clinical trials to evaluate the use of currently available antivirals for the treatment of HSV-1 pneumonia. Acyclovir is generally considered the treatment of choice. In the highly immunocompromised population in which HSV pneumonia occurs, patients should probably receive intravenous acyclovir 5 mg/kg every 8 hours for 14 to 21 days. Acyclovir resistance does occur, especially in HIV-infected patients who have previously received acyclovir for mucocutaneous HSV infections. Although studies suggest thymidine kinase-deficient mutants have diminished virulence, these strains may cause progressive infections.

Since foscarnet directly inhibits viral DNA polymerase, it remains active against thymidine kinase-deficient HSV strains. At least one randomized multicenter study has shown that foscarnet is superior to vidarabine for the treatment of mucocutaneous infections due to acyclovir-resistant strains (Safrin et al., 1991). Because HSV pneumonia occurs rarely and is seldom diagnosed antemortem, it is unlikely that clinical trials will ever be performed to evaluate different modalities.

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Community-Acquired Fungal Diseases

GEORGE A. SAROSI AND SCOTT F. DAVIES

The causative organisms of the endemic mycoses *(Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis)* and *Cryptococcus neoformans* share certain characteristics. All these fungi reside in soil, require organic nitrogen for optimum growth, and have distinctive reproductive cycles. The reproductive cycle depends a great deal on environmental conditions including moisture and temperature. *H. capsulatum, B. dermatitidis,* and *C. immitis* grow in nature as molds, and the spores produced by the mycelia are the infective agents. The yeasts of *C. neoformans* also grow in soil rich in bird excreta. In the case of *C. neoformans,* however, there is no saprophytic form, and it is thought that small desiccated yeasts, lacking a capsule, are the infectious particles.

When a nidus containing any of these fungi is disturbed, an infecting aerosol is formed and may be inhaled. Following inhalation into the mammalian host, the organisms reach the alveolar spaces, where they begin propagation. *H. capsulatum, B. dermatitidis,* and *C. immitis* are dimorphic fungi, meaning that their tissue-invasive forms are different from their infective particles. *C. neoformans,* on the other hand, does not change its form following inhalation, but it begins to grow a large polysaccharide capsule. *H. capsulatum* and *B. dermatitidis* are thermal dimorphic fungi. At 37°C. whether in the alveolar spaces of a mammalian host or on a culture plate, they convert to their tissue-invasive form. *C. immitis* is a tissue-dimorphic fungus; the organism changes into its pathogenic form only in tissue.

Once the infecting particles lodge in the alveoli, roving neutrophils and resident alveolar macrophages attack them (Schaffner et al., 1986). To avoid phagocytosis and destruction, conversion to the tissue-infective form occurs. The organisms are ingested by alveolar macrophages and other cells of the reticuloendothelial system, which initially lack ability to kill the fungi. The yeasts of *C. neoformans* following lodgment develop their large polysaccharide capsule, which is antiphagocytic, thus allowing propagation of the yeast without danger of engulfment and eventual destruction (Diamond et al., 1972).

Following inhalation and propagation, symptoms may develop. The severity of these symptoms largely depends on the size of the inhaled inoculum as well as on the immune competence of the host. Infection that is acquired in open spaces usually leads to inhalation of small numbers of infecting particles, and in the immunocompetent host either produces no symptoms or at most a mild illness, which is almost invariably self-limited (Goodwin et al., 1981; Sarosi et al., 1974). It is important to realize that exposures to these fungi result on no symptoms at all, and the only evidence of illness is the conversion of a previously negative skin test to a positive skin test (Goodwin & DesPrez, 1978; Sarosi & Davies, 1979; Drutz & Catanzaro, 1978a). While this is well documented for the dimorphic

GEORGE A. SAROSI • Indiana University School of Medicine, and Roudebush VA Medical Center, Indianapolis, Indiana 46202. **SCOTT F. DAVIES** • University of Minnesota, School of Medicine and Pulmonary Service, Hennepin County Medical Center, Minneapolis, Minnesota 55415.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

fungi, it can only be inferred for *C. neoformans,* owing to lack of reliable information (Sarosi, 1997). On the other hand, when the infecting aerosol is large, such as can occur in a closed space (e.g., a chicken coop, a bat cave, or storm cellar), the inhalation and lodgment of a large number of infecting particles may produce a symptomatic and occasionally severe illness even in immunocompetent individuals (Goodwin & DesPrez, 1978; Sarosi & Davies, 1979; Drutz & Catanzaro, 1978a).

Physicians caring for patients with acute respiratory symptoms must be aware that diagnosis of the acute respiratory infection caused by these fungi is difficult. Their clinical manifestations are not sufficiently characteristic to allow a syndromic diagnosis, and diagnostic tests during the acute illness are often ineffective. While serologic tests exist for the diagnosis of *H. capsulatum* and *C. immitis,* there is usually a delay of several weeks before the results can be obtained. In addition, the tests are usually performed in remote reference laboratories (Davies & Sarosi, 1987). Although all fungal organisms can be readily cultured from expectorated sputum or other respiratory specimens, their cultural identification is time-consuming and tedious; the results frequently become available after the symptoms have already disappeared. Adding further to diagnostic difficulty, the results of skin testing are difficult to interpret. For example, a positive histoplasmin skin test in a patient with an acute respiratory illness most likely represents previously established skin test positively and a totally unrelated lower respiratory infection.

Histoplasma capsulatum

The Organism

Histoplasma capsulatum is a soil-dwelling thermal-dimorphic fungus. It exists in nature as a mycelium (mass of branching hyphae). The infecting particles are microconidia (small spores) that become airborne when the site is disturbed.

Epidemiology

Infection and skin test conversion to *H. capsulatum* are extremely frequent in the endemic area. The histoplasma-endemic area is very large, and it is estimated to include over 20% of the U.S. population. The endemic area for histoplasmosis includes the Ohio and Mississippi River valleys, but it also extends into the neighboring areas to include most of Texas, Oklahoma, Kansas, western Pennsylvania, Maryland, and Virginia. In Canada, the St. Lawrence Valley is also in the endemic area (Goodwin & DesPrez, 1978). In heavily endemic areas, the frequency of a positive histoplasmin skin test in lifelong residents may be as high as 98% by age 18. Careful histories from some of these histoplasmin-positive individuals reveal that less than 10% of them remember a significant lower respiratory infection. Newcomers from nonendemic areas are also susceptible to histoplasmosis; in the endemic area histoplasmosis should be included in the differential diagnosis of any respiratory infection.

The endemic area should not be viewed as being uniform in the intensity of infectious risk. *H. capsulatum* grows in microfoci, usually in well-treed areas, where large flacks of black birds roost. Bird droppings servo as the source of organic nitrogen for the propagation of the fungus (Sarosi et al., 1971). In addition to soil under bird roosts, bat caves and other closed spaces where birds roost, such as belfries, often contain the organism.

When an individual with suspected histoplasmosis is evaluated, a careful epidemiologic history must be obtained, since it will frequently reveal exposures to areas such as construction work, cleaning of storm cellars, spelunking, or cutting of fallen trees. This is especially true when the clinical illness is severe (i.e., diffuse micronodular infiltrate), implying heavy exposure. In these patients a specific exposure to a high-risk activity can often be elicited, approximately 2 weeks prior to the onset of the acute febrile illness.

Pathogenesis

Following inhalation into the mammalian lung, the infecting particles (microconidia), which are 1 to 2 μm in diameter, reach the alveoli and lodge in them. These spores rapidly convert to the tissue-invasive yeast form, and propagation of the yeast by binary fission begins immediately.

The original inflammatory exudate in the alveoli consists predominantly of polymorphonuclear

cells but this is followed rapidly by ingress of monocytes and macrophages with phagocytosis of the organisms. The organism grows unchecked within these mononuclear cells and reaches the lymphatics and then the systemic circulation, spreading throughout the body. Cells of the fixed reticuloendothelial (RE) system remove organisms from the blood and propagation continues in these fixed tissue macrophages. Intracellular growth continues during the entire preimmune phase of the illness; large numbers of organisms are produced (Goodwin et al., 1981).

Once T-cell-mediated immunity develops, the now armed macrophages can destroy or at least wall off the invading organisms, leading to the development of granulomas. Frequently these granulomas undergo central necrosis; especially in younger individuals these necrotic areas frequently calcify, leaving behind multiple calcified lesions in the lung, in hilar and mediastinal lymph nodes, and in the liver and spleen. These lesions are common in endemic areas and strongly suggest healed primary histoplasmosis, especially in tuberculin-negative individuals (Christi & Peterson, 1945; Palmer, 1945).

Incubation of the infection is approximately 14 days. In a small outbreak in one of the western suburbs of Minneapolis, where the actual time of exposure was pinpointed to within 2 hours, symptomatic disease appeared exactly at 14 days (Davies, 1986). This 2-week incubation period is possibly much shorter in patients whose initial exposure was the result of the inhalation of a large aerosol.

It is important to recall that the vast majority of infected individuals, while they undergo the various stages of propagation and eventual destruction of the organism, have minimal or no symptoms (Goodwin et al., 1981). This containment of the organism, leading to eventual destruction of the fungus, is the norm in healthy, normal hosts. In individuals whose immune system is abnormal, either because of an underlying immunocompromising condition (especially advanced HIV infection) or because of the administration of glucocorticoids or immunosuppressing drugs, adequate T-cell-mediated immunity cannot develop. In these patients unchecked propagation of the fungus continues, leading to a progressive, potentially lethal illness. In most immunocompetent patients the infection is self-limited and permanently controlled,3 leaving only occasional viable fungi behind. However, when previously existing, well-developed T-cell-mediated immunity is destroyed because of illness or the administration of various drugs, reactivation of latent fungal infection may occasionally occur (Davies et al., 1978).

It is important to remember that dissemination of the organism throughout the body occurs in every patient with *H. capsulatum* infection (Goodwin et al., 1981). Therefore, by definition every histoplasma infection is "disseminated." however, only in immunocompromised hosts does benign fungemia become progressive and life-threatening.

Progressive disseminated histoplasmosis usually occurs at the extremes of age, or among patients whose T-cell-mediated immunity is abnormal, such as patients with Hodgkin's disease or HIV infection (Davies et al., 1978; Wheat et al., 1982). With increased use of glucocorticoids, cytotoxic agents, and anti-rejection drugs in transplantation, the number of individuals with compromised immunity is very large. In these individuals, even a small infecting dose may cause a primary lung infection that rapidly disseminates, leading to progressive disseminated histoplasmosis.

There are certain individuals whose reaction to the infecting organism is unusual. These individuals produce an extraordinarily exuberant inflammatory response. Marked enlargement of hilar and mediastinal nodes occurs. Proliferation of fibrous tissues around these nodes can have serious consequences. A dense fibrotic reaction may occasionally entrap various structures within the mediastinum, leading to narrowing or occlusion of pulmonary arteries and veins, the superior vena cava, the bronchi, or the esophagus. The most challenging form of this exuberant fibrosis is mediastinal fibrosis, which can cause pulmonary hypertension and early death. In the United States histoplasmosis is the single most common cause of mediastinal fibrosis (Goodwin et al., 1972).

Healed histoplasmosis frequently lead to calcifications on the chest radiograph, but they rarely cause ill effects, only occasionally, calcifications in strategic areas may over years erode into vital structures, such as the bronchi, producing a broncholith that can cause lithoptysis, hemoptysis, and post-obstructive infection. Primary infection occurring in older individuals is less likely to produce calcification. This lack of calcification produces a di-

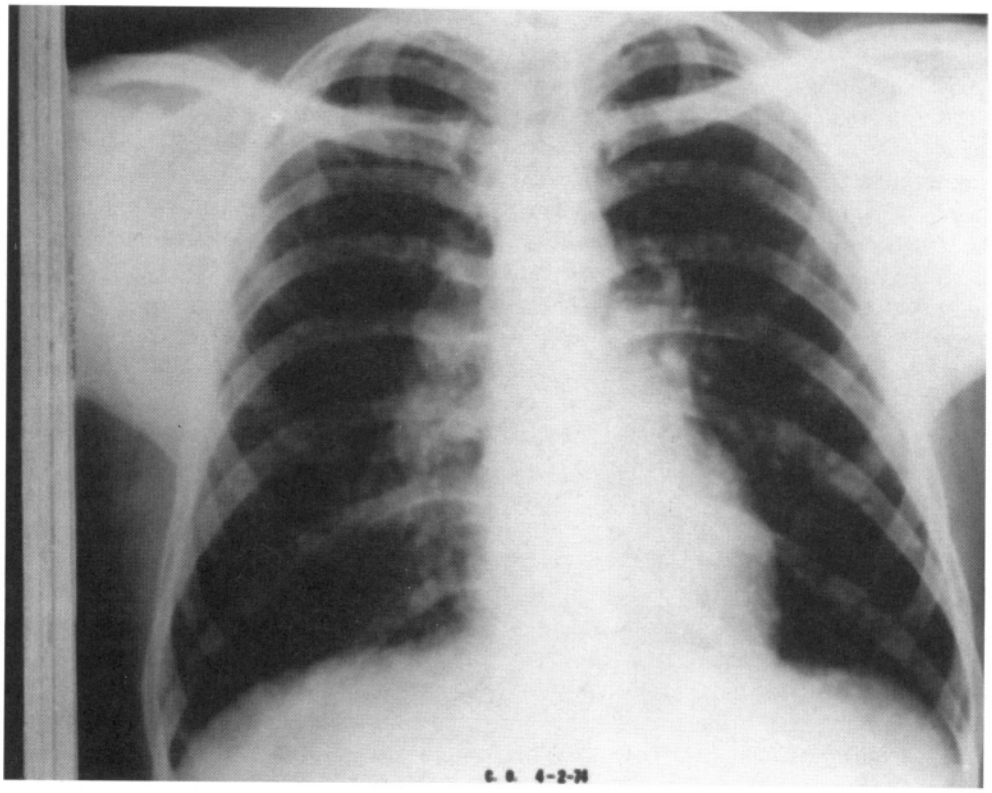

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FIGURE 1. (A) Sixteen-year-old student with symptomatic acute histoplasmosis. Note multiple small peripheral nodules and marked hilar adenopathy. (B) Same patient 8 months later. The parenchymal lesions have resolved and the hilar nodes are smaller. Patient was symptom-free.

agnostic dilemma where peripheral lesions due to histoplasma may develop and mimic either primary or metastatic carcinoma as seen in chest radiography.

The Clinical Illness

Acute symptomatic pulmonary histoplasmosis is an influenza-like illness. The patient develops fever and chills, and a dry, nonproductive cough follows. During the early part of the infection patients frequently complain of arthralgias and myalgias and severe headache is common (Goodwin & DesPrez, 1978). In a small minority of patients, erythema nodosum or erythema multiforme may develop, which frequently draws attention, leading to further evaluation and eventual diagnosis of histoplasmosis (Medeiros et al., 1966). These cutaneous manifestations of acute histoplasmosis are most common in Caucasian women (Sarosi et al., 1971). Occasionally patients may also have acute pericarditis (Wheat et al., 1983). Physical examination during the acute infection is usually negative, unless the patient manifests the skin lesions described above. Chest radiographs obtained during the acute phase of infection show one or more peripheral, patchy infiltrates within the parenchyma of the lung. Ipsilateral mediastinal and hilar adenopathy may be present (Wheat, 1997) (Fig. 1). The laboratory evaluation is seldom helpful during the acute infection, since the white blood count is seldom abnormal. In patients whose infecting aerosol was unusually large, a rapidly progressive respiratory illness may develop, with diffuse micronodular infiltrates and severe hypoxemia, occasionally this may progress to the adult respiratory distress syndrome (ARDS), and all its attendant complications.

When the fungus infects individuals with abnormal lungs, such as smokers who have developed

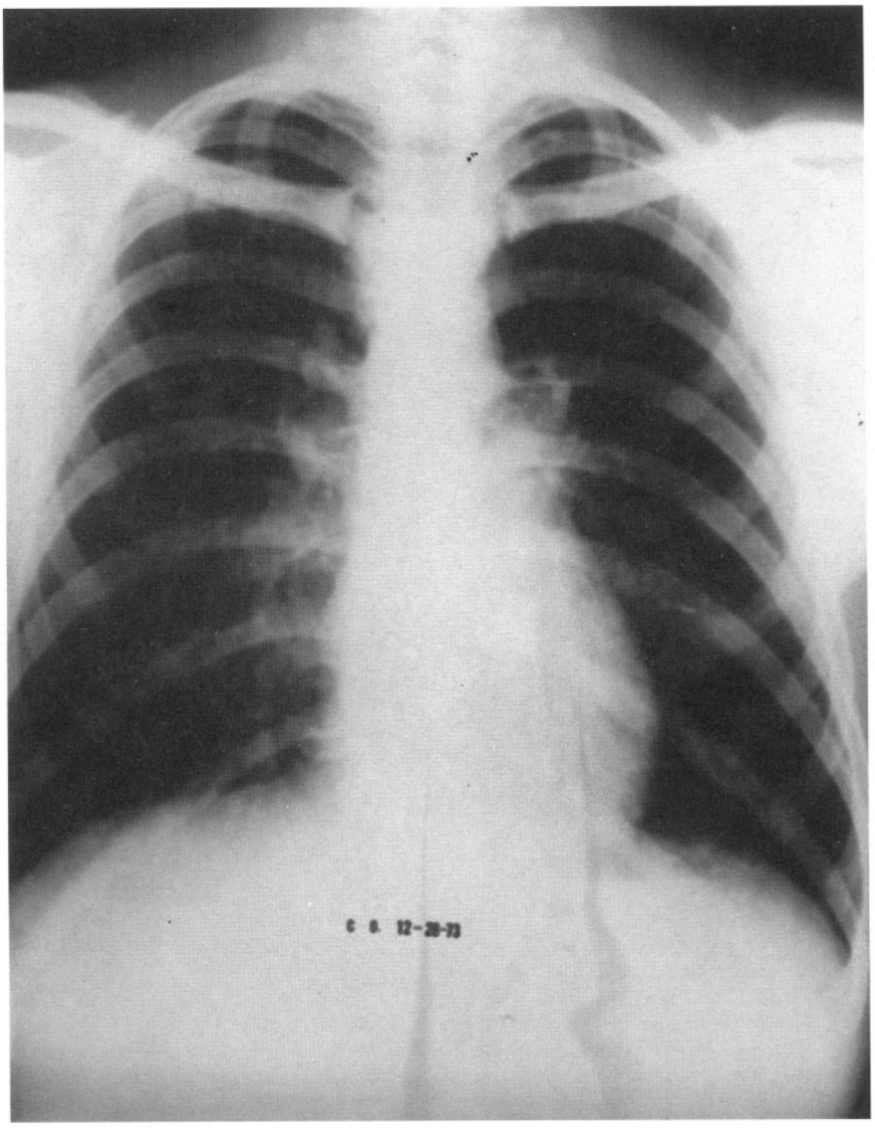

FIGURE 1. (*Continued*)

centrilobular emphysema, the initial infection may involve the upper zones. Chest radiography mimics re-infection tuberculosis, because the infiltrates frequently outline abnormal air spaces. Approximately 20% of such individuals may develop a progressive, destructive pulmonary process, again quite similar to re-infection tuberculosis (Fig. 2). It is important to remember, however, that many patients even with this form of potentially chronic histoplasmosis still clear the infection without any residual findings (Davies & Sarosi, 1978; Sarosi & Davies, 1992). It is unpredictable which patients will undergo progression and which patients will heal uneventfully; thus careful follow-up is mandatory (Goodwin et al., 1976).

Extrapulmonary benign fungemia occurs routinely following infection with *H. capsulatum.* Once T-cell-mediated immunity has developed, however, the infection is contained and cleared in most patients. If the patient has a T-cell abnor-

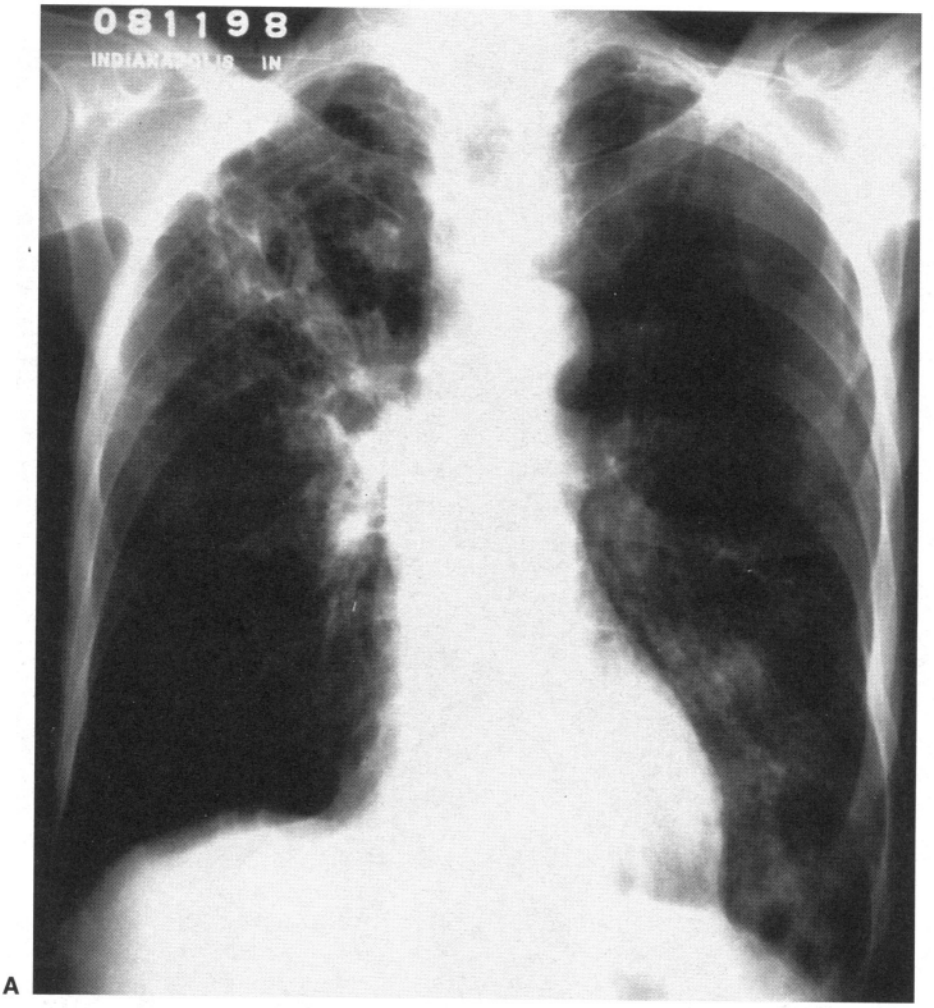

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FIGURE 2. (A) Sixty-nine-year-old man with bilateral (right left) fibrocavitary disease due to histoplasmosis. He has a 150 pack year smoking history. (B) After 14 months of itraconazole therapy, patient is without symptoms, and sputum is now negative for *H. capsulatum*. (C) One year after completion of therapy the radiograph is stable.

mality, however, the disease usually progresses, often at a rapid pace. Untreated it may be fatal in a short time. This form of the illness is referred to as progressive disseminated histoplasmosis (PDH) (Goodwin & DesPrez, 1978). PDH may also develop in patients whose initial infection was controlled by adequate T-cell-mediated immunity, but reactivates later with waning of T-cell-mediated immunity (either from HIV infection or from treatment with glucocorticoids, cytotoxic agents, or antirejection drugs) (Witty et al., 1992).

PDH, whether the result of a primary infection or reactivation, is a disease of the RE system. Clinically, patients have a severe febrile illness with weight loss, lassitude, and, when extensive pulmonary involvement is present, gas exchange abnormalities. Physical examination usually shows hepatosplenomegaly and occasionally lymphadenopathy. Laboratory examination uniformly shows significant pancytopenia and evidence of hepatic involvement, usually with the elevation of the alkaline phosphatase (Goodwin et al., 1980).

Chest radiographs in patients with PDH may be normal or may show multiple nodules (small,

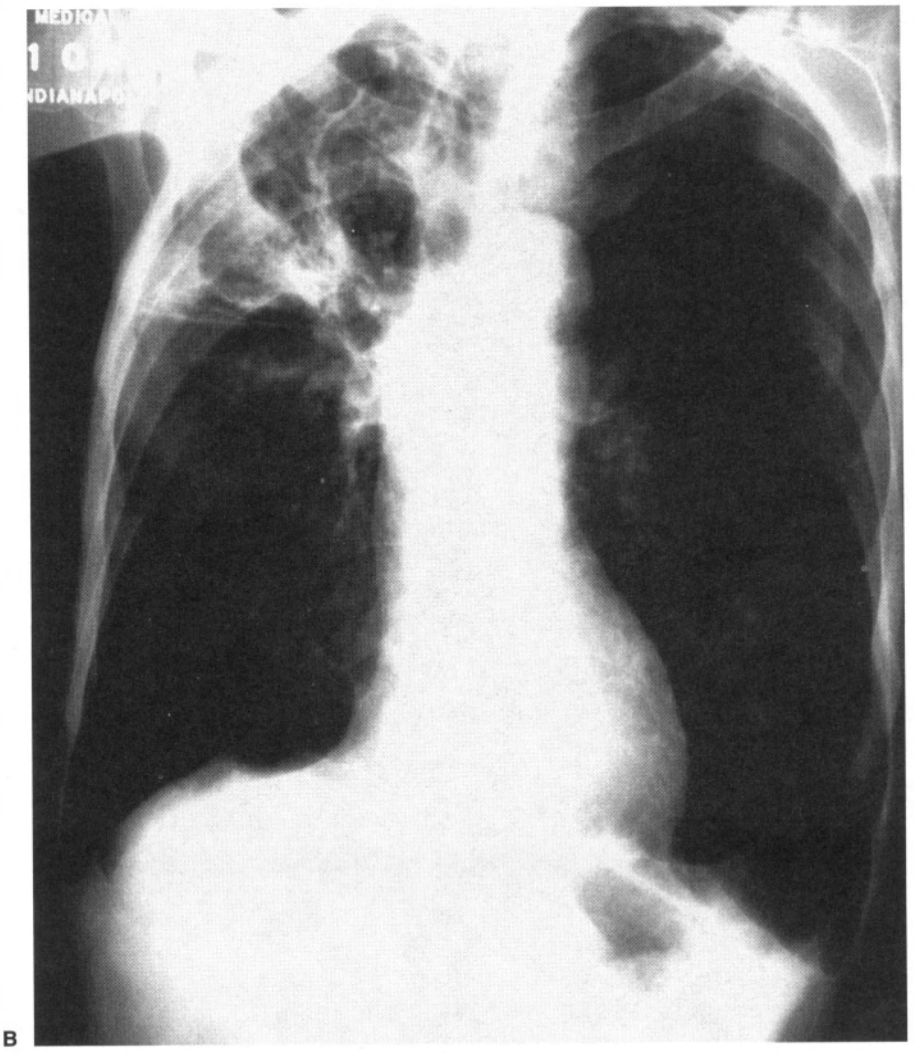

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FIGURE 2. (*Continued*)

2–4 mm in diameter) throughout both lungs, which will enlarge rapidly and, if untreated, will lead to ARDS (Witty et al., 1992; Goodwin et al., 1980). Especially in individuals whose PDH is the result of reactivation (most frequently seen in patients with remote uncomplicated primary histoplasmosis who develop HIV infection later in life), PDH may manifest without any chest radiography abnormality at its onset (Sarosi & Johnson, 1992). Unless the disease is quickly diagnosed and treated, it progresses and diffuse micronodular infiltrate uniformly develops.

Diagnosis

The most important factor in establishing the diagnosis in community-acquired histoplasma infection is a high degree of suspicion. An influenza-like illness that follows a possible exposure by 2 weeks should prompt consideration of the diagnosis. During a mild acute infection invasive diagnostic procedures are seldom indicated; in the rare individual whose illness is rapidly progressive and leads to gas exchange abnormality, invasive procedures may be necessary. The diagnosis is seldom

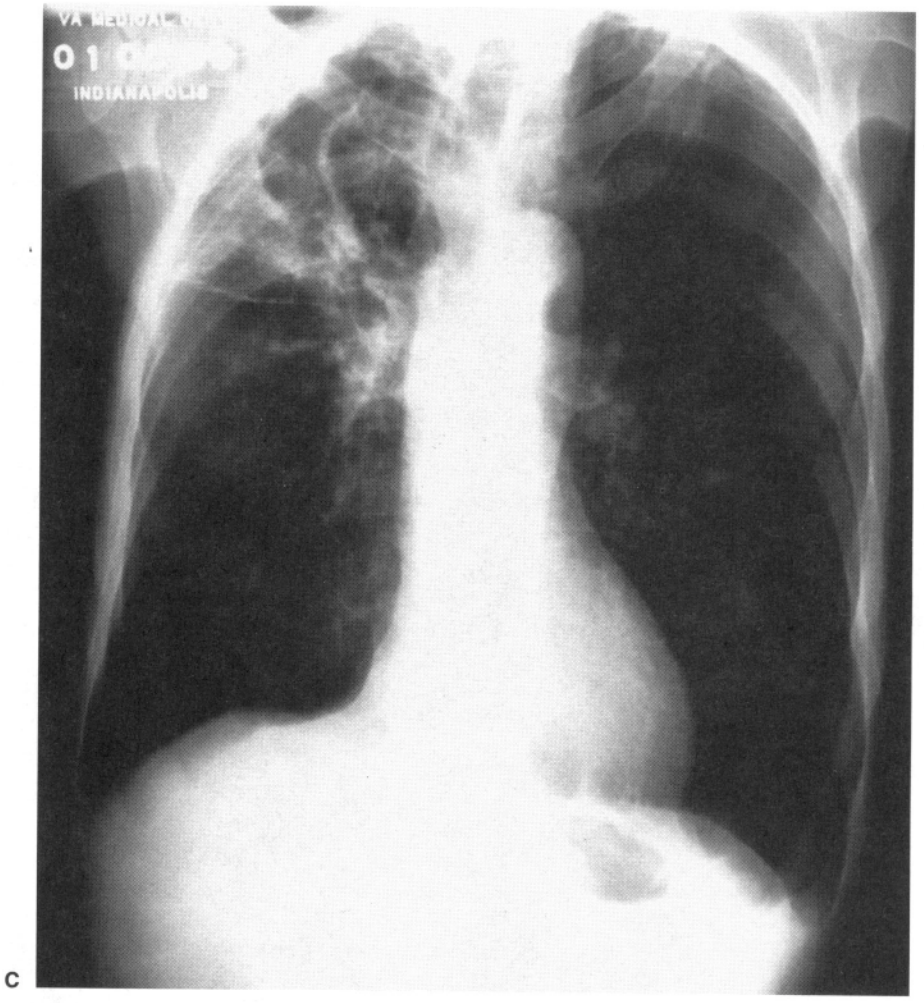

FIGURE 2. (*Continued*)

made by transbronchial biopsy, but it may still be attempted. Frequently these individuals must undergo open lung biopsy to reach a diagnosis.

The gold standard for the diagnosis of histoplasmosis is recovery of the fungus in culture. During acute histoplasmosis there is seldom an opportunity to recover the organism, although occasionally blood cultures (especially using the lysis-centrifugation system) may be positive (Paya et al., 1987). In patients with upper-lobe cavitary histoplasmosis or in patients with PDH, the organism can often be recovered in culture from respiratory specimens. While the organism is quite hardy and survives transportation to reference laboratories, it may take several weeks to isolate and identify it. Thus cultures are seldom timely. Exoantigen testing has accelerated the final identification step. In patients with PDH, blood cultures with the lysis-centrifugation system can be positive in just 5 days, because of the high density of the organisms. Thus they are extremely useful for diagnosis. Since the organism involves the RE system, sampling of the RE system should be considered early. Bone marrow cultures are frequently positive and direct smears often give an immediate answer (Davies et al., 1979).

The organism is readily identified in histopathologic sections, provided appropriate staining techniques are used. Most pathology laboratories

use one of the many modifications of the silver stain, which stains the fungal cell wall black. This is a highly effective method but it frequently loses morphologic detail. The periodic acid-Schiff (PAS) stain stains the fungus a brilliant red while maintaining morphologic detail. In PDH direct smears of bone marrow aspirates often show the characteristic 1–2-μm intracellular organisms within macrophages. In AIDS the density of the organism is so high that direct smears of the Buffy coat of the peripheral blood are positive up to half of the time (Nightingale et al., 1990).

Since the majority of individuals with acute histoplasmosis do not have productive sputum, attempts to culture respiratory secretions are seldom fruitful. In addition, cultural identification of the organism is tedious and time-consuming and may take up to 30 days. Direct smears of respiratory secretions are not very useful. Therefore, most acute infections that are not life threatening are diagnosed by serologic testing. The time-honored complement fixation (CF) test is quite helpful, but it takes several weeks before diagnostic titers are reached. In the outbreak mentioned above, CF tests became positive between 4 and 6 weeks after the infection (Davies, 1986). Lack of timeliness makes them less than ideal. Sensitivity is only about 75%; thus the lack of a diagnostic titer does not rule out the possibility of histoplasmosis. Frequently, by the time diagnostic titer rises have occurred, the patient has fully recovered and neither the patient nor the physician is motivated to get a late follow-up blood test. The available immunodiffusion (ID) test is easier to perform. It has reasonable specificity but poor sensitivity (Davies & Sarosi, 1987; Davies, 1986). In outbreak situations, less man half of the affected individuals show diagnostic bands of identity. The hisloplasma polysaccharide antigen (HPA) lest, as described by Wheat el al. (1986), is an excellent test in AIDS patients with PDH where the burden of organisms is very high. It is frequently positive both in serum and in urine (70/72 positives in one series of PDH in AIDS) (Wheat et al., 1991). Unfortunately, it is seldom positive in patients with acute histoplasmosis, chronic cavitary histoplasmosis, or even mild PDH with lesser degrees of immunosuppression. The amount of antigen in serum and urine is not large enough to reach the threshold of a positive test (Wheat, 1997). HPA has proven value in AIDS (in both diagnosis and follow-up) and is useful in other patient groups with severe PDH. The test is now available in a kit form, which is increasingly available.

To establish serologic diagnosis of histoplasmosis, a 4-fold rise in eilher the mycelial or the yeast phase is required. A single titer of $\geqslant$ 1:32 to the yeast phase antigen is highly suggestive of the diagnosis if the clinical illness is consistent with histoplasmosis. When the pretest probabilily is high (focal infiltrate with ipsilateral hilar node enlargement or diffuse micronodular infiltrate), then even lower liters have considerable diagnostic specificity.

While there is a commercially available histoplasmin skin test, the use of the skin test for diagnosis of individual patients with histoplasmosis is not recommended. A positive histoplasmin skin test in the acute phase of a nonspecific respiratory illness usually reflects a preexisting positive skin test positivity and has nothing to do with the acute respiratory problem (Sarosi et al., 1988). Thus, skin testing should not be used for the diagnosis of individual cases, but should be reserved for epidemiologic studies of populations.

Treatment

The vast majority of patients with acute histoplasmosis not only do not have an illness warranting treatment, but usually have no symptoms at all. Mild illness, even if accompanied by influenza-like symptoms, usually does not require treatment, since the illness is self-limited. Even a mild decrease in oxygen saturation is not an indication for treatment.

On the other hand when symptoms are severe and debilitating and gas exchange is severely impaired or progressively deteriorating, treatment is mandatory. Intravenous amphotericin B (AMB) is the treatment of choice because it produces the fastest clinical improvement. The amount of AMB required and the duration of therapy is not known. Anecdotal experience suggests that a total cumulative dose of 500 to 1500 mg AMB administered over 3 to 10 weeks is usually adequate (Naylor, 1977).

The availability of highly active oral azoles has revolutionized treatment of histoplasmosis. Ketoconazole, the first available azole, is still effective, in doses of 400 to 800 mg daily. Serious gastrointestinal distress frequently results from the use

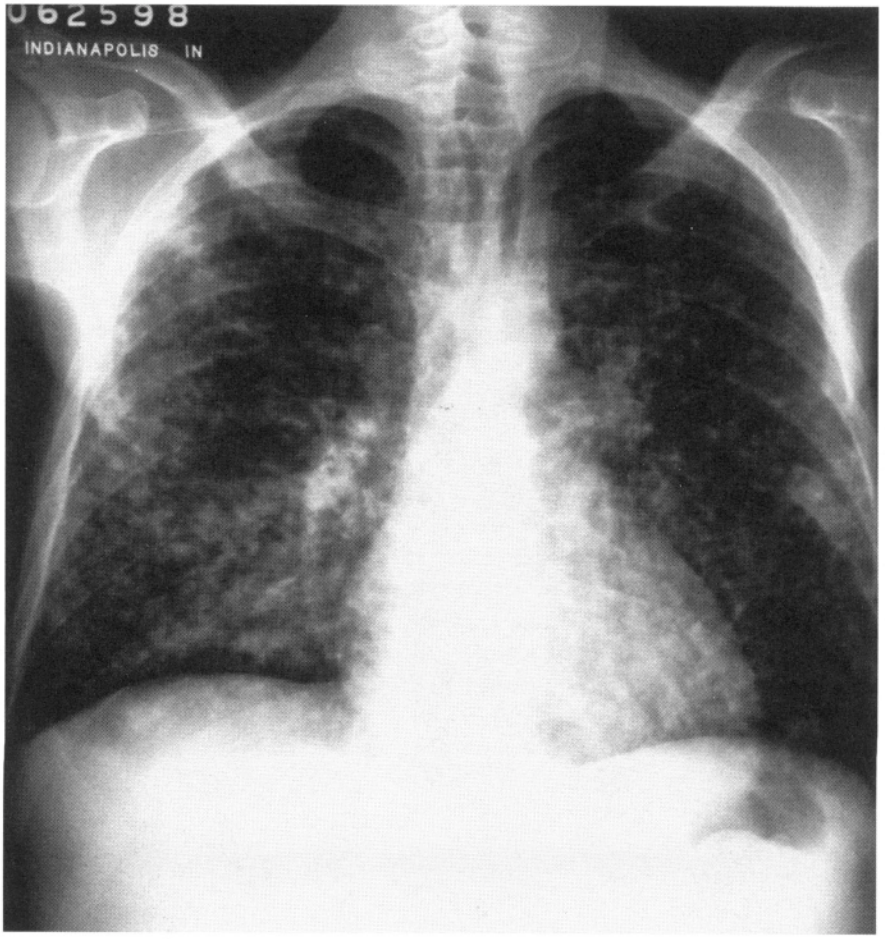

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FIGURE 3. (A) Forty-year-old HIV-positive man with progressive disseminated histoplasmosis. He has an excellent response to amphotericin B, followed by itraconazole suppressive therapy. (B) One year later patient stopped all treatment, resulting in relapse.

of higher doses (Dismukes et al., 1985). In addition, the antitestosterone effect of large doses of ketoconazole makes it a less attractive choice. Itraconazole, on the other hand, is highly effective and in doses of 200 mg twice daily is the currently recommended treatment of choice for illness caused by histoplasmosis that is not life threatening (Dismukes et al., 1992). The duration of treatment in acute histoplasmosis is unknown, and most authorities use the drug as long as symptoms persist. In the treatment of progressive upper-lobe histoplasmosis the recommended treatment is a minimum of 6, but occasionally 12 months to eradicate the infection. Amphotericin B can also be used in patients with upper-lobe disease, especially when there are gas exchange abnormalities. The total dose recommended is 35 mg/kg, administered over 10 to 16 weeks (Parker et al., 1970).

For progressive disseminated histoplasmosis in non-AIDS patients, itraconazole 200 mg twice daily can be used from the onset (total course 6–12 months) unless the patient is critically ill (Goodwin et al., 1976). In critically ill patients initial treatment with 500 to 1000 mg of AMB should be given until the patient is stabilized; then the patient can be switched to itraconazole for 6 to 12 months. In HIV-positive patients with PDH initial therapy with AMB should be used to induce a clinical remission, followed by lifelong maintenance therapy with itraconazole (Wheat et al., 1993, 1995) (Fig. 3).

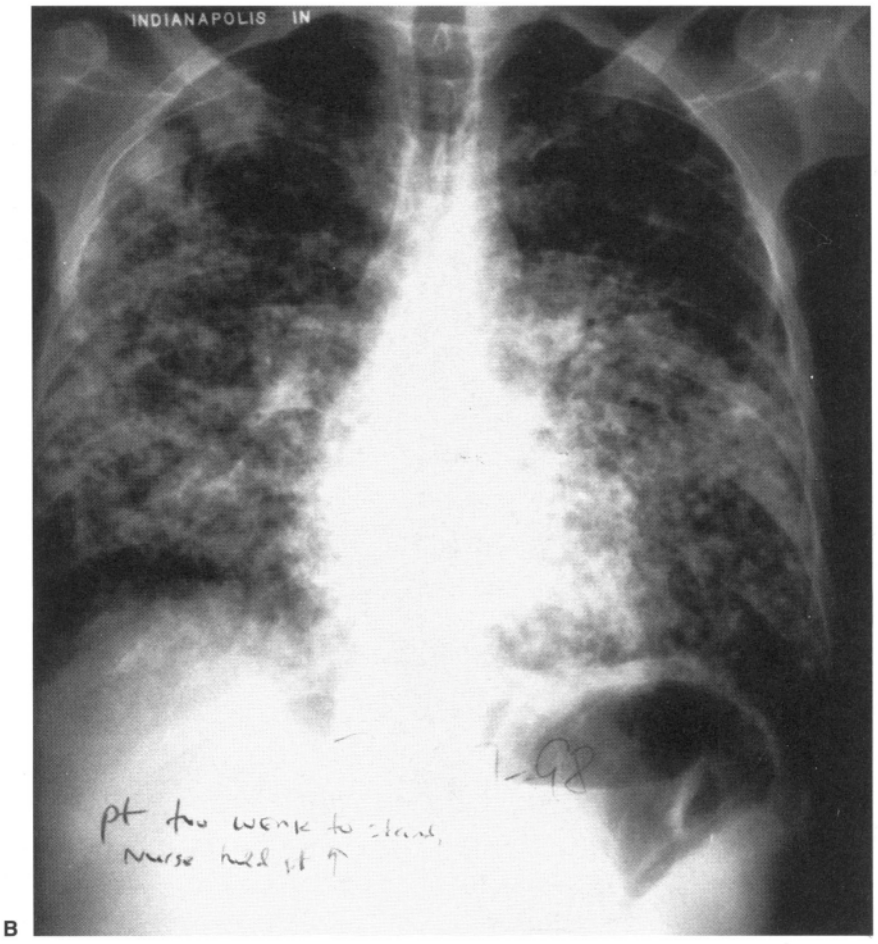

FIGURE 3. (*Continued*)

Selected patients with mild to moderate illness can be treated with itraconazole from the onset. Again, lifelong itraconazole therapy is necessary to prevent relapse. The dose for active treatment is 200 mg twice daily. For maintenance therapy, 100 mg twice daily is sufficient.

Blastomycosis

The Organism

Blastomyces dermatitidis is a soil-dwelling thermal-dimorphic organism. Its ecologic niche is not as well defined as that of *H. capsulatum.* The endemic area is equally poorly defined because there is no sensitive and specific skin test antigen, in contrast to histoplasmosis, where large-scale skin test surveys have precisely mapped the endemic area (Goodwin et al., 1981).

The putative endemic area for blastomycosis overlaps with that of histoplasmosis, encompassing most of the southeastern and south central United States. However, it extends much further north, including the states bordering the Great Lakes, predominantly Wisconsin and Minnesota, as well as the Canadian provinces of Ontario and Manitoba. This endemic area has been defined by reports of clinical cases rather than by skin test surveys (Sarosi & Davies, 1979).

Investigation of small outbreaks has extended our understanding of the ecological niche of *B. dermatitidis*. Apparently the organism grows in highly specific but sharply circumscribed areas. Many outbreaks of human and canine illness have been associated with recreational waterways (Klein et al., 1986a, b). Soil enriched by organic nitrogen through the excrement of various animals and birds favors fungal growth (Sarosi & Serstock, 1976).

Pathogenesis

Following disturbance of a site, the small spores of *B. dermatitidis* form an aerosol and are then inhaled. It appears that close contact with epidemic sites is needed. Besides humans many other mammals may be infected. The most frequently involved animal is the dog, and in some areas canine blastomycosis is far more common than the human equivalent (Sarosi et al., 1979). Following exposure to the infectious site, the median incubation period is about 6 weeks with a broad range of 3 to 15 weeks. These estimates are derived from the large outbreak in Eagle River, Wisconsin, where the time of exposure was brief and well defined (Klein et al., 1986a).

The clinical illness that occurs during an outbreak often has acute onset (Sarosi et al., 1974). It mimics influenza, with arthralgias and myalgias, headache, and fever. It can also mimic bacterial pneumonia, with cough, purulent sputum, and even lobar infiltrates. Rarely, erythema nodosum has been associated with the acute onset of blastomycosis, as with other fungal illnesses (Miller et al., 1982).

After the spores are inhaled, they reach the alveoli, where the organism converts to its pathogenic yeast form, which is a large single-budding yeast measuring up to 20 μm in diameter. Conversion to the yeast form is temperature-dependent and may enhance resistance to nonimmune phagocytosis. The appearance of the yeast is characteristic, allowing rapid diagnosis from the sputum. The yeast has a broad neck of attachment between parent and daughter cells. Multiple nuclei are visible, as well as a doubly refractile wall (Sarosi & Davies, 1979). Unlike *H. capsulatum, B. dermatitidis* is not predominantly an infection of the RE system.

The initial inflammatory response to the budding yeast of blastomycosis is predominantly neutrophilic. Only later do macrophages move in to a greater or lesser extent. Unlike in histoplasmosis, the initial polymorphonuclear tissue response never completely disappears, even after the appearance of giant cells and granulomas. A mixed pyogenic and granulomatous histopathology is quite characteristic for blastomycosis (and also for coccidioidomycosis).

Following development of a local area of pneumonitis, the organism may spread to the hilar lymph nodes and then to distant sites, usually skin and bone. It is unclear whether this systemic spread occurs only occasionally, or whether, as seen in histoplasmosis, there is a benign fungemic spread of the fungus that occurs routinely as part of the primary infection. This uncertainty remains one of the major deficits in understanding of the pathogenesis of blastomycosis. Following the development of cell-mediated immunity, the organism is contained and healing occurs. When T-cell-mediated immunity is impaired the infection progresses rapidly and often widely disseminates.

The Clinical Illness

Acute pulmonary blastomycosis as seen in outbreak situations is usually a self-limited, acute illness. Most patients who are seen in such epidemic settings without specific therapy resolve their illness (Sarosi et al., 1974; Klein et al., 1986a). However, not all cases of acute pulmonary blastomycosis resolve spontaneously (Fig. 4). Careful evaluation and close follow-up are needed to identify worsening or subsequent dissemination of the illness.

Some patients with pulmonary blastomycosis are highly toxic, with lobar infiltrates or even with diffuse alveolar infiltrates. Blastomycosis is one of the infectious causes of ARDS (Fig. 5). All such patients require urgent therapy. Some have severe gas exchange abnormalities and require ventilator support (Meyer et al., 1993).

Patients presenting with sporadic blastomycosis usually follow a different clinical course. Most are identified because of symptomatic disease, and virtually all of them will require treatment, even if there is no significant gas exchange abnormality present. All patients with chronic or subacute symptoms resembling tuberculosis or lung cancer should

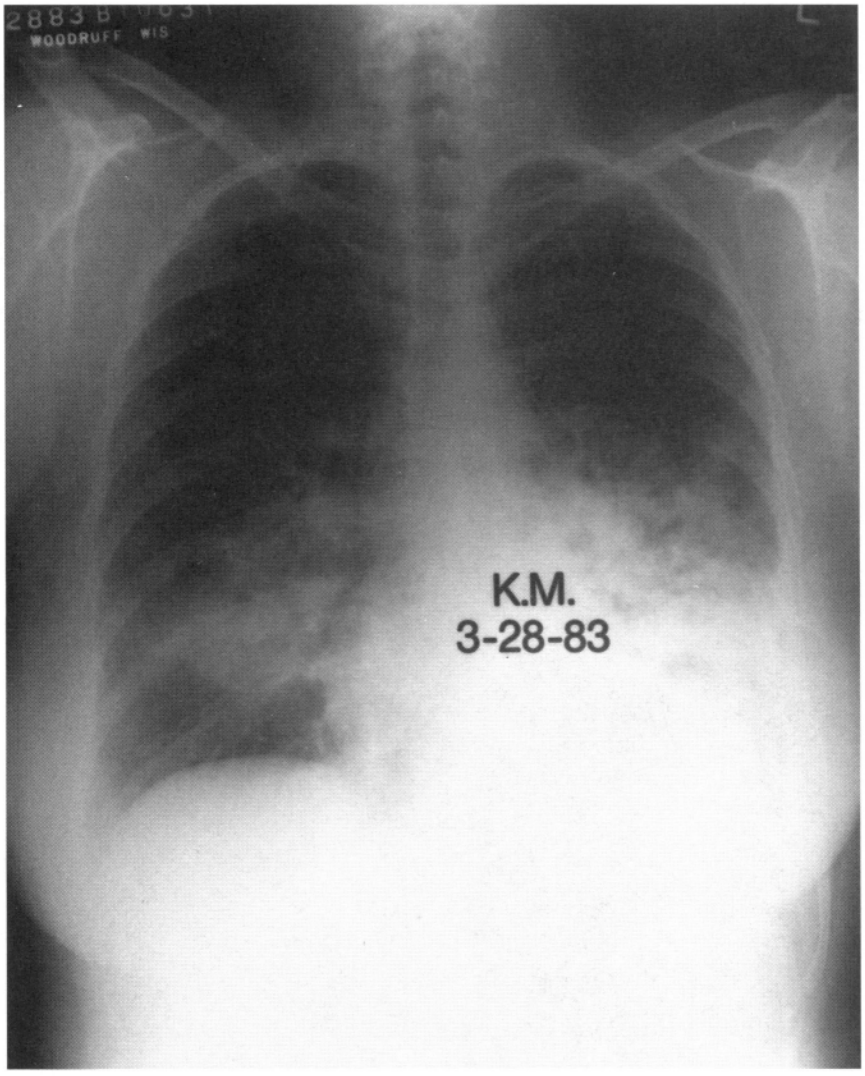

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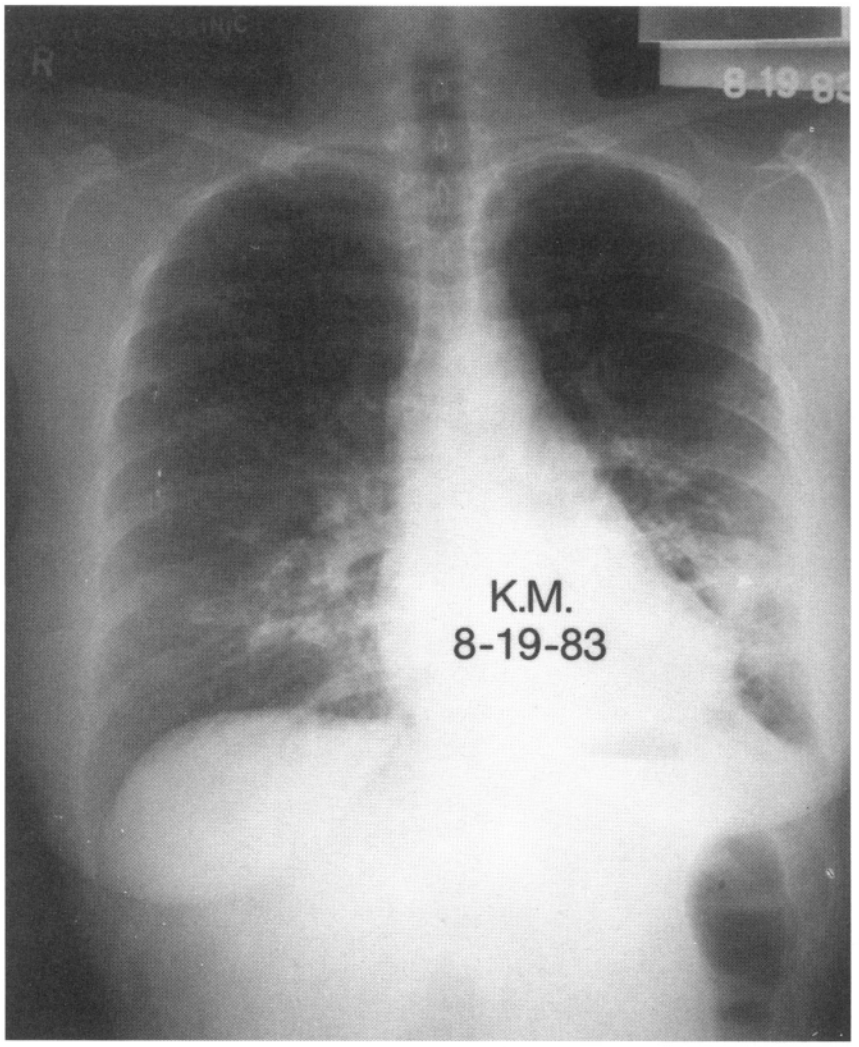
FIGURE 4. (A) Acute onset of severe blastomycosis in a young woman. Sputum shows the fungus. (B) After 6 months' treatment with ketoconazole, she is asymptomatic and sputum culture is negative. She received a total of 12 months' treatment. (*Continued*)

be treated (Fig. 6). Patients with acute onset resembling bacterial pneumonia can sometimes be observed for a period of 2 to 4 weeks to establish the direction and tempo of the illness. This is particularly appropriate if the illness is mild and already improving by the time the diagnosis is established (Sarosi et al., 1986). Some of these patients will still have self-limited disease, while others will worsen and require antifungal therapy.

Blastomycosis frequently involves extrapulmonary sites. The organs most frequently involved are the skin and bones, while the prostate gland and the meninges are involved far less frequently. In the early literature, involvement of multiple other organs was reported, usually in very advanced cases. Since the advent of effective antifungal therapy these other organ involvements are rare. Once the disease is beyond the confines of the lung, spontaneous improvement is highly unlikely and therapy is mandatory (Sarosi el al., 1974).



B

FIGURE 4. (*Continued*)

Diagnosis

Because of the low incidence of the disease, the first step toward successful diagnosis is a high index of diagnostic suspicion. If epidemiologic features suggest exposure to recreational waterways or other potential sources of the fungus, careful evaluation will usually yield an answer. Many such patients are treated once with an antibacterial agent. Diagnostic efforts are escalated when treatment is unsuccessful. Patients should never receive a series of multiple different antibacterial agents for a nonresolving, undiagnosed pneumonia. There is no commercially available skin test. Currently work is ongoing to identify skin test antigens that are specific and sensitive.

Unlike histoplasmosis, where serodiagnosis is extremely well established, serodiagnosis of blastomycosis remains difficult and elusive. The standard CF serologic test is not specific or sensitive and thus cannot be relied on. The ID test has better specificity but is not highly sensitive. Work is ongoing to identify more specific and sensitive serologic tests (Bradsher & Pappas, 1995). The currently available

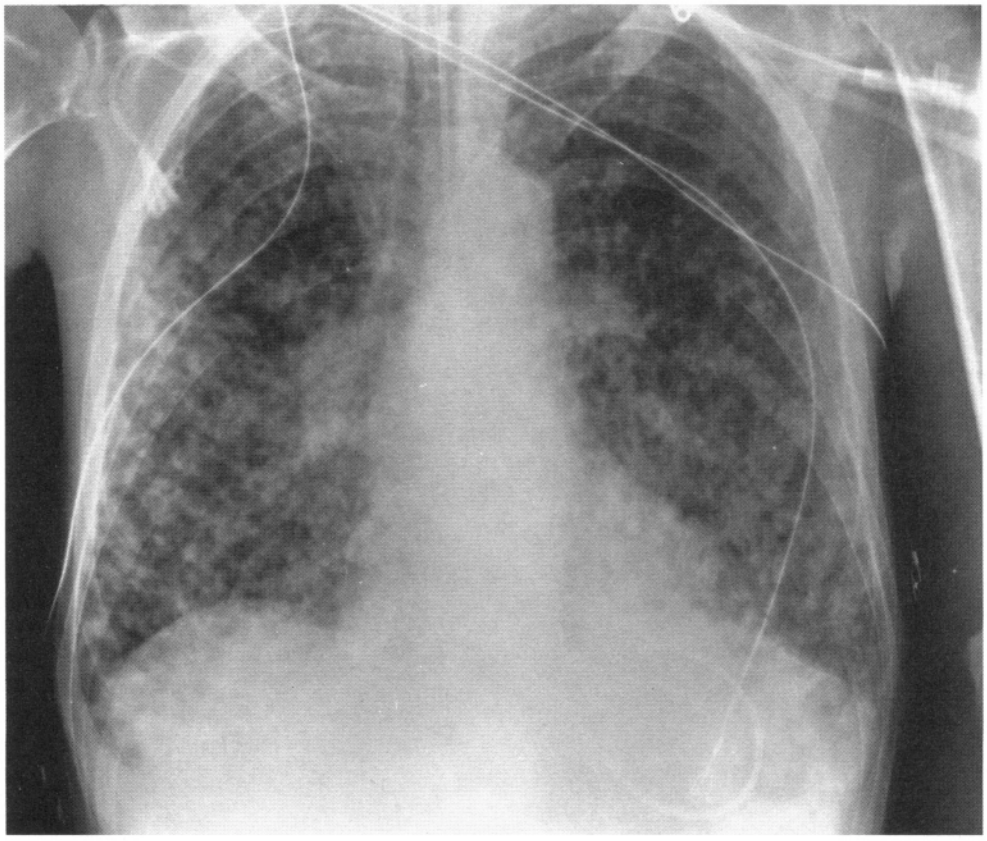


FIGURE 5. Admission radiograph of a 50-year-old Native American man with dialysis-dependent chronic renal failure. Initial suspicion of tuberculosis led to open lung biopsy, showing blastomycosis. Patient recovered following a course of amphotericin B.

ultrasensitive assays, such as enzyme immunoassay, have increased sensitivity but markedly decreased specificity. At the present time most patients with blastomycosis are not diagnosed by serology. A negative serodiagnostic test does not exclude the diagnosis. A positive result in one of the many serodiagnostic tests in a patient with a compatible clinical illness does have value and should prompt aggressive diagnostic testing to confirm the diagnosis of direct smear, culture, or histopathology.

The gold standard for the diagnosis of the infection is either direct visualization of the organism (from respiratory secretions, from pus from other sites, or by histopathological examination of biopsies) or cultural recovery of the organism. The simplest and most direct method to identify the fungus is examination of respiratory secretions or other biologic material suspected of harboring the fungus, after digestion by 10% potassium hydroxide (KOH) (Sarosi et al., 1974). One drop of material is mixed with one drop of 10% **KOH**, covered with a slip, and examined after 30 minutes. The strong alkali destroys other extraneous material, allowing identification of the large yeasts of blastomycosis (with the characteristic broad-necked single bud). Visualization of the infecting organism in histopathologic sections is also easy, as long as appropriate special stains are used. Most laboratories rely on the standard methenamine-silver stain, which is fairly accurate but loses a great deal of morphologic detail. The PAS stain better preserves morphologic detail. The Papanicolaou stain is also helpful (Sanders et al., 1977).

Cultural identification of the organism is not difficult but is often slow. The rapidity of cultural

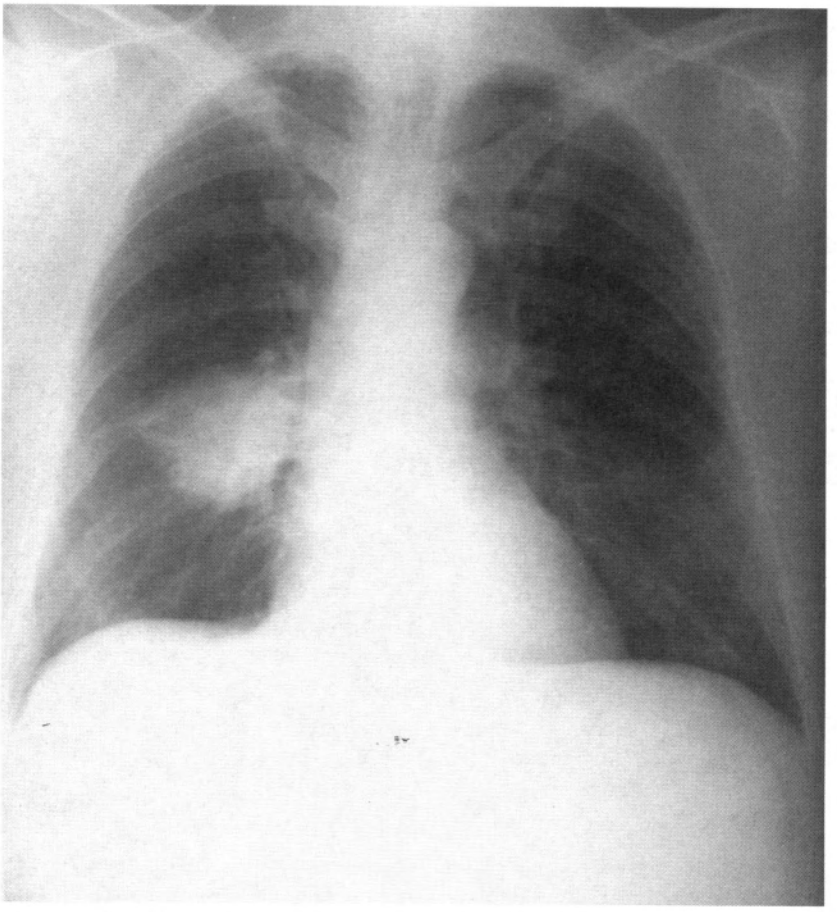


FIGURE 6. Initial chest radiograph of a 61-year-old man with an extensive smoking history. Bronchoscopy showed no endobronchial lesions, but washings were positive for the fungus on culture.

recovery is directly proportional to inoculum size. Formerly identification of the organism required recovery in the mycelial phase, conversion to the yeast phase, and eventual reconversion to the mycelial phase, resulting in a delay of up to 30 days. Currently exoantigen testing is used and can provide a positive identification as soon as good mycelial growth is established, in 5 to 7 days. The laboratory should always be alerted when blastomycosis is clinically suspected.

Treatment

As noted previously, acute pulmonary infection due to blastomycosis can sometimes be self-limited. In the past, cases with acute onset that were already improving by the time of diagnosis were often followed carefully without treatment, because the only treatment option was intravenous AMB. Since the availability of highly effective oral therapy, some authorities question the wisdom of ever observing patients with pulmonary blastomycosis, because of fear of local progression and/or dissemination.

Our practice has been to observe selected patients for 2 to 4 weeks. These are patients with acute onset of illness who are already improving by the time of diagnosis. Using this approach, we have followed many patients whose disease has resolved without antifungal treatment (Sarosi et al., 1986). All patients who present with chronic or subacute symptoms, all patients with acute onset whose

symptoms persist or progress, and all patients with extrapulmonary disease should be treated immediately upon diagnosis.

For most cases of pulmonary, cutaneous, osseous, and prostatic blastomycosis, the treatment of choice is itraconazole 200 mg twice daily for 6 to 12 months (Dismukes et al., 1992). The agent is highly effective and has relatively few side effects. Ketoconazole is also effective and is less expensive. However, it is not as effective as itraconazole and is associated with more toxicity (Dismukes et al., 1985).

Patients with rapidly progressive pulmonary blastomycosis with gas exchange abnormalities, patients who are co-infected with HIV, and patients with meningitis should all be treated with AMB. AMB in a total dose of 2 g delivered over 10 to 14 weeks produces a very high cure rate with few relapses (Parker et al., 1969). For patients with nonmeningeal disease, AMB can be used until clinical improvement occurs (usually 500–1000 mg cumulative dose), followed by 6 months of itraconazole. Patients with meningitis should received at least 2000 mi AMB (Gonyea, 1978; Kravitz et al., 1981). HIV-infected patients should be treated with AMB until they are stabilized, followed by lifelong administration of itraconazole (Pappas et al., 1992).

Coccidioidomycosis

The Organism

Coccidioides immitis is a soil-dwelling and tissue-dimorphic organism. Conversion to the spherule (pathogenic form) occurs only in the infected human or animal and it is not dependent solely on changes in temperature but rather on complex factors.

Epidemiology

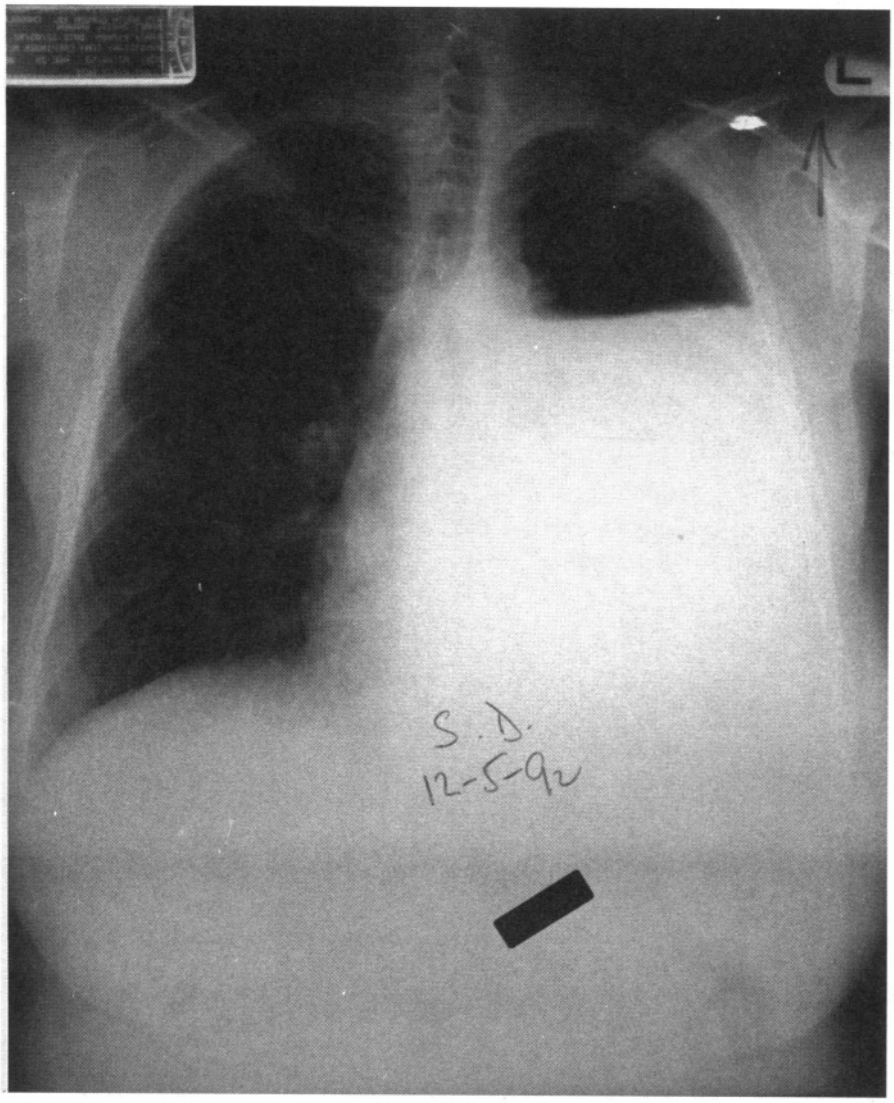
Within the United States, the endemic area for coccidioidomycosis extends from across the southern border from west Texas to the coast of California. The northward extension of the endemic area is the southern tip of Utah. The San Joaquin Valley in central California and the lower desert valley of Arizona (including Phoenix and Tucson) are areas of intensive disease activity. The areas of northern Mexico abutting on Arizona and New Mexico are also highly endemic (Galgiani, 1993; Stevens, 1995). The endemic area coincides with the so-called lower Sonoran Life Zone and covers the Sonoran desert area of the southwest United States. Characteristic climatic conditions in the endemic area are intensely hot summers with very low rainfall. The rainfall tends to occur in intense, short bursts, which, along with rapidly rising soil temperatures, leads to germination of the fungus. The organism survives the hot, dry periods beneath the surface of the desert in structures such as rodent burrows. Because of the adverse climatic conditions there is relatively little competition from other microbes. Droppings of birds and rodents provide a ready source of nitrogen.

Following a burst of growth activity, an aerial mycelium forms. The fragile arthroconidia break off and become airborne, giving rise to the infecting aerosol. Outbreaks of coccidioidomycosis occur when archeological excavations or even ordinary agricultural activities disturb areas heavily infected with the fungus.

Pathogenesis

Following inhalation of the arthroconidia, which are, to 4 μm in size, lodgment in the alveoli occurs. In the alveoli, there is an influx of neutrophils that fail to contain the organism. It rapidly converts to its tissue-invasive form, with development of spherules. These structures rapidly enlarge and may reach 100 μm in diameter. Once mature, septations become evident and the entire interior of the giant spherule becomes packed with small endospores. Eventually the spherule ruptures, the endospores are released, and the infection spreads. Each released endospore can give rise to a new spherule.

Following inhalation, areas of alveolitis develop and the initial neutrophilic exudate is rapidly augmented by influx of macrophages and monocytes. As with blastomycosis, however, the neutrophilic component never fully disappears and the characteristic histopathology of the infection is a pyogranulomatous inflammatory exudate (Drutz & Catanzaro, 1978a). The disease usually remains localized to the lungs, but in a small number of patients the infecting organisms gain access to the systemic circulation and cause widespread disease.



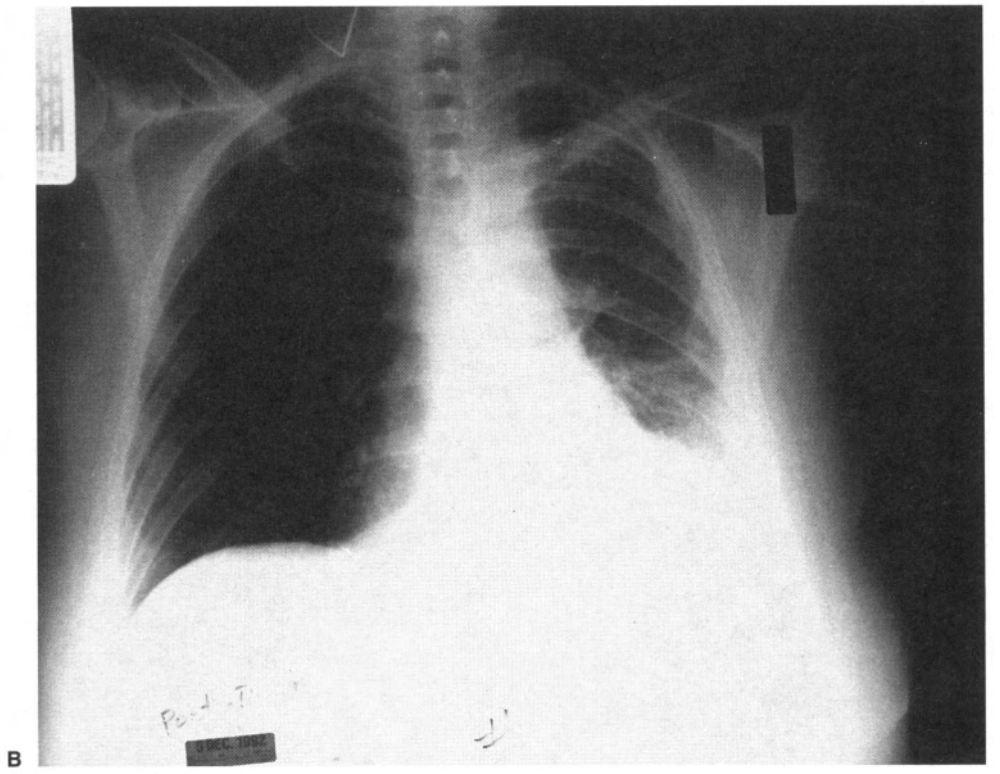
A

FIGURE 7. (A) Admission radiograph of a young woman with a sudden onset of dyspnea and pleuritic chest pain. (B) Post-thoracenthesis radiograph. The pleural fluid showed an exudate. Pleural biopsy showed *Coccidioides immitis*. (C) Complete clearing, while taking fluconazole.

The most common distant sites of involvement are the skin, bones, and meninges. Spread to other sites is possible but much less frequent (Drutz & Catanzaro, 1978a).

The Clinical Illness

The acute infection is similar to acute blastomycosis, but tends to be more severe. Fever, cough productive of mucoid sputum, arthralgias, and myalgias are frequently seen. A characteristic feature of acute coccidioidomycosis is the development of intense pleuritic chest pain, even though frank pleural effusions are relatively uncommon (Fig. 7). The incubation time is approximately 1 to 3 weeks after exposure. The clinical illness is of variable severity, ranging from a mild inconvenience to a severe bilateral pneumonia (Fig. 8) that causes se-



B

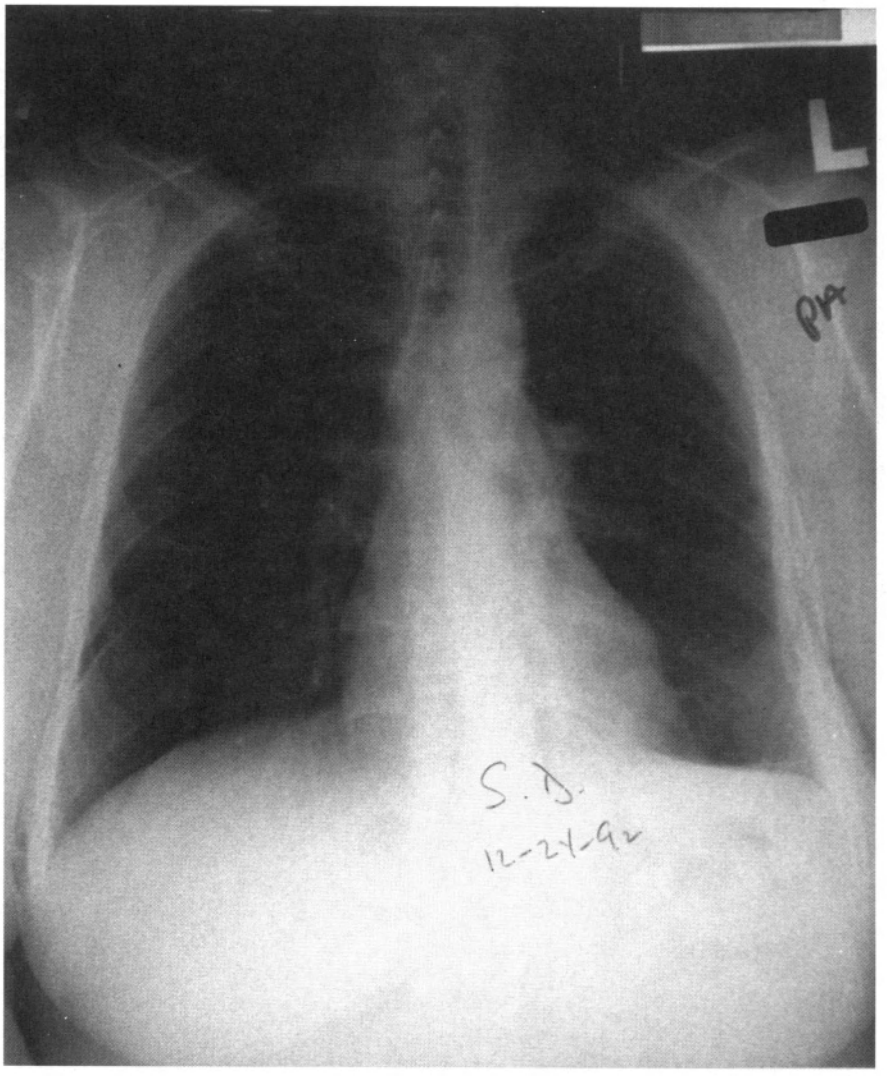
FIGURE 7. (*Continued*)

vere hypoxemia and progresses to ARDS (Drutz & Catanzaro, 1978b).

In addition to productive cough, pleuritic pain, and influenza-like systemic symptoms, a surprisingly large number of patients, especially Caucasian females, develop the "bumps," which is erythema nodosum. The presence of erythema nodosum leads to rapid clinical diagnosis. Physicians practicing in the endemic area recognize that the development of erythema nodosum has high specificity for "valley fever" or coccidioidomycosis (Dickson & Gifford, 1938). In addition, an evanescent, salmon-colored, "toxic" rash may develop during the acute infection. In sporadic cases this rash is seldom described, but in one outbreak approximately half the involved individuals had it (Werner et al., 1972). The rash usually resolves quickly, although occasionally it may persist for weeks.

Routine laboratory tests are seldom helpful for diagnosis of coccidioidomycosis. A small number of patients develop significant eosinophilia, but the presence of eosinophilia is not sufficient to diagnose coccidioidomycosis. Atopic individuals may run high eosinophil counts even during the epidemic season tor coccidioidomycosis.

Radiographic manifestations of the primary infection are variable. The most common abnormality is a small peripheral infiltrate. Hilar lymph node enlargement is relatively uncommon. As the infection evolves, the peripheral infiltrate may round up and become a coccidioidomycotic abscess. One of the more characteristic radiographic manifestations of the disease is the cavitation of these round lesions, leading first to the formation of a thick-walled cavity and then a thin-walled cavity, highly characteristic of coccidioidomycosis (Winn, 1968; Hyde, 1968; Bayer, 1981). Rupture of these cavities during the acute infection is a well-recognized complication (Cunningham & Einstein, 1982). Patients may first present for medical attention when they develop an intensely painful pneumothorax. Caused by the rupture of a subpleural



C

FIGURE 7. (*Continued*)

cavity. With the pneumothorax, there is often a sizeable pleural effusion. The diagnosis can frequently be established by smear and/or culture of pleural fluid or by direct visualization of spherules in pleural biopsy specimens.

In the majority of instances the primary infection is a quickly resolving self-limited illness. In a small number of patients symptomatic pulmonary infection persists for 6 weeks or longer. The arbitrary dividing point of 6 weeks moves the patient from the category of primary infection to that of persistent pulmonary coccidioidomycosis (Galgiani, 1993). Clinically these patients have a subacute or chronic illness, with persistent low-grade temperature, anorexia, cough, weight loss, and chest pain. Occasionally, hemoptysis may complicate the course of the illness. Radiographic examination shows persistence of previously noted pulmonary lesions with little tendency for either progression or resolution.

In the endemic area the characteristic thin-walled cavity is frequently discovered during routine radiographic examination (Fig. 9). Most cavities are small, about 2 cm in diameter, and located

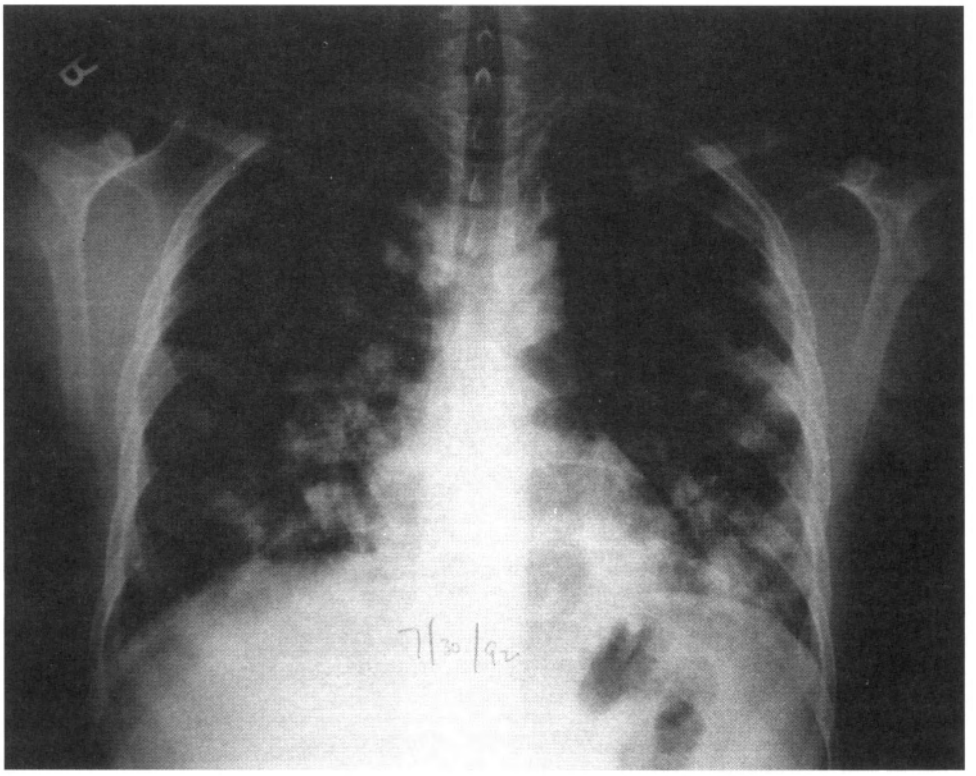


FIGURE 8. Eighteen-year-old agricultural worker with extensive acute coccidioidomycosis.

in the upper lung zones. Most cavities show progression; as they enlarge they may abut the pleura. Because these cavities may rupture, various authorities recommend either antifungal therapy or surgical resection. No randomized, controlled studies have been done to evaluate these options. In an occasional patient a slowly progressive illness develops, reminiscent of tuberculosis (Fig. 10). Chest radiograph shows bilateral apical fibrocavitary involvement, which progresses slowly (Sarosi et al., 1970).

A much more severe illness can occur in immunocompromised patients, especially in those who are co-infected with HIV. In these individuals, the first manifestation of coccidioidomycosis may be a rapidly progressive pneumonia, radiographically showing diffuse macronodular (2-5 mm or larger) infiltrates. When this form of the illness is seen, there is a great deal of urgency to establish the diagnosis and initiate treatment because the prognosis is poor. Untreated, the illness progresses rapidly to death (Tutala & Smith, 1978; Bronniman et al., 1987; Singh et al., 1996).

Diagnosis

More than for the other endemic fungal diseases, **CF** tilers are highly useful for initial diagnosis for prognosis and for sequential follow-up. Largely through extensive work done by Smith and coworkers at the California Department of Public Health in the 1940s and 1950s, the role of serodiagnostic testing is extremely well documented (Smith et al., 1950). Acute infection leads to the development of IgM antibodies, which classically were determined by the tube precipitin technique. Because this test is technically difficult it has been replaced by ID test for IgM, which is easier to perform, and gives the same information. IgM antibodies appear by the second or third week of the infection, peak at about 4 weeks and are usually gone by 6 weeks. The presence of IgM antibodies

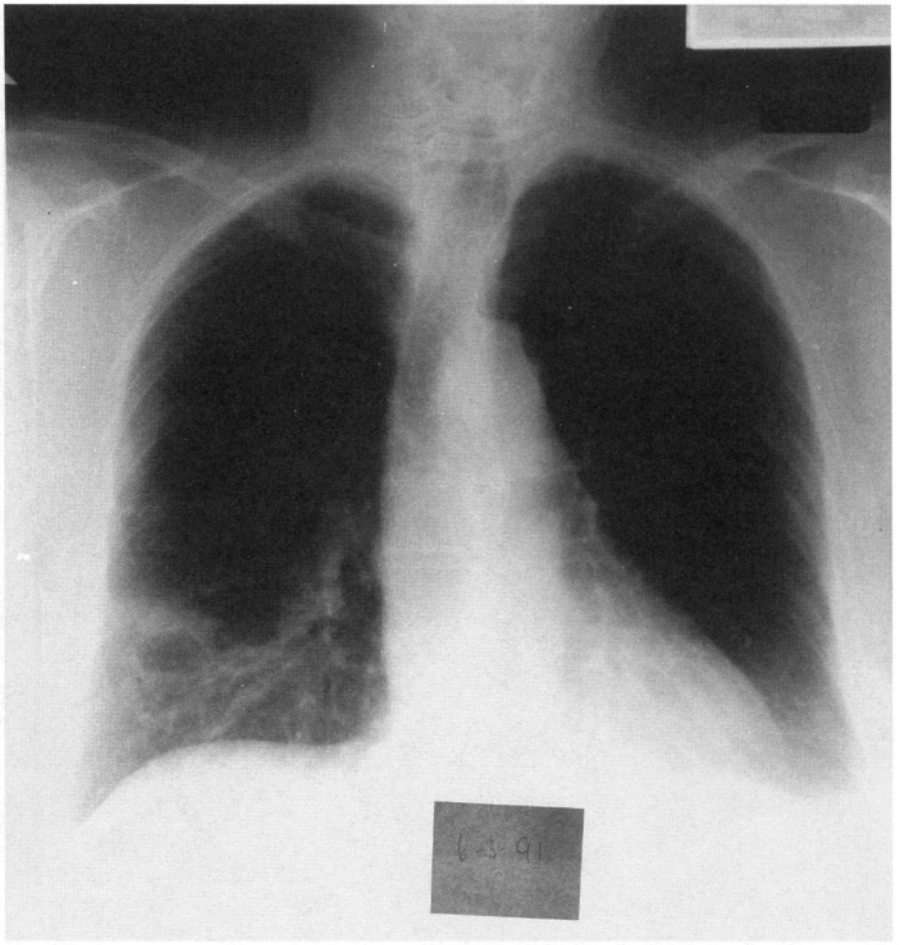


FIGURE 9. Incidental finding of a small coccidioidomycotic cavity in an asymptomatic 61-year-old woman. Note air-fluid level.

(any titre) isl highly specific and should be accepted as diagnostic of acute coccidioidomycosis. The CF test, measuring IgG anlibodies (any titer) is highly specific and should be accepted as diagnostic of acute coccidioidomycosis. The CF test, measuring IgG antibodies, is well characterized and highly useful. Unfortunately, there is much variation in technique, which has led to confusion. The only laboratory that still uses Smith's original antigen and technique is the microbiology laboratory at the University of California, Davis. Tilers obtained from this reference laboratory can be interpreted with confidence and can be matched against the vast published experience. Many other laboratories can vary a great deal and must be interpreted with some caution.

On the basis of nearly 40,000 determinations, Smith et al. showed that patients with titers $\geq$1:16 frequently had disseminated disease (Smith et al., 1950). They did not establish that lower titers are not compatible with dissemination or that a given high titer proves dissemination in a given patient. Clinicians should be aware that no liter is diagnostic of disseminated disease. However, a titer in excess of 1:16 should prompt a diligent search for the presence of disseminated disease.

Currently a similar ID for IgG antibodies is available. Many laboratories use it instead of the CF test, which is more cumbersome and more difficult tocontrol.Interpretationrequiresclinicaljudgment and experience (Galgiani, 1993).

The gold standard for the diagnosis of coccidi-

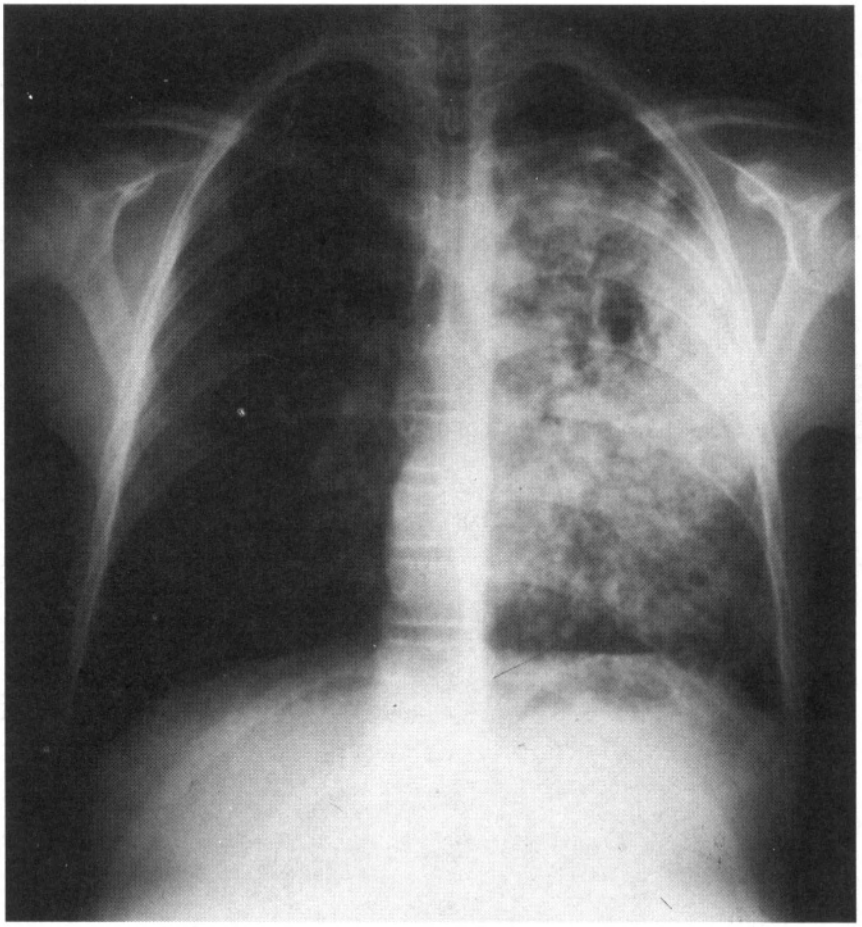


FIGURE 10. Thirty-year-old man with a 6-month history of fever, cough, and productive sputum. Initial diagnosis was tuberculosis, but sputum culture yielded *Coccidioides immitis*. Patient refused treatment.

oidomycosis is culture from biological material of the fungus. The fungus grows readily under standard laboratory conditions and recovery is seldom difficult. However, there is an extreme biohazard risk. the laboratory should be informed whenever coccidioidomycosis is suspected. The aerial mycelium is extremely fragile, and the least bit of air current may aerosolize the infectious particles, causing laboratory outbreaks. To prevent such an occurrence, most laboratories do not culture suspected coccidioidomycosis in petri dishes, but rather on slants where the likelihood of creating an aerosol is lower.

Skin testing in coccidioidomycosis is also well studied. There are two skin test antigens currently available; one is the time-honored coccidioidin skin test, and the second is the more recently developed spherulin skin test, made from the tissue phase of the organism. Both antigens are highly effective in documenting previous infections (Levine et al., 1975). Their use is limited for diagnosis of acute infection because considerable time is required to develop sufficient T-cell-mediated immunity to make the skin test positive (Galgiani, 1993; Stevens, 1995). As with the other fungal diseases, the presence of a positive skin test in a patient with a concurrent respiratory illness most likely represents remote infection unrelated to the acute illness under investigation (Sarosi et al., 1988). On the other hand, conversion of a previously known negative

skin sent to positive in the context of a compatible clinical illness is diagnostic or acute infection. The skin test has also been used to monitor response to therapy. Fading of a previously positive skin test in the context of disseminated coccidioidomycosis is a poor prognostic sign.

Direct smears and histopathology are frequently used to confirm the diagnosis. Respiratory secretions are best stained with the Papanicolaou technique, which is considerably more sensitive than direct examination of fresh unstained secretions after KOH digestion (Warlick et al., 1983). Diagnosis of coccidioidomycosis may also be established by histopathology using special stains. Intact giant spherules may sometimes be seen on routine hematoxylin-eosin stained sections. Silver stains are more sensitive and are used routinely when coccidioidomycosis is suspected.

Treatment

Most immunocompetent patients with primary pulmonary coccidioidomycosis have a self-limited illness. Unless they are severely ill, have a pneumothorax, or have impaired gas exchange, it is reasonable to monitor them closely without treatment. Recently, however, especially in heavily endemic metropolitan areas, most patients with suspected or proven acute pulmonary coccidioidomycosis are given treatment with fluconazole in doses of 400 mg/day. While there are positive anecdotal reports, to date no controlled study has ever shown that treatment of primary coccidioidomycosis hastens resolution or decreases the risk of progression to more serious forms of the disease (Stevens, 1995).

On the other hand, persistent pulmonary disease with symptoms continuing beyond 6 weeks should always be treated. Early, uncontrolled experience showed efficacy for AMB, usually to a total dose of approximately 1500 mg (Drutz & Catanzaro, 1978b). More recently, ketoconazole has been used with good initial response, but with substantial incidence of recrudescence after discontinuation of therapy (Ross et al., 1982). Currently, fluconazole in doses of 400–800 mg/day is recommended, the agent is well tolerated and appears to be effective (Stevens, 1995). Itraconazole is also useful, but more clinical experience has been accumulated with fluconazole.

Extrapulmonary dissemination always requires prompt and aggressive therapy. Because of the high frequency of meningeal involvement whenever there is suspicion of disseminated coccidioidomycosis, a lumbar puncture should be done to obtain cerebrospinal fluid for culture and for determination of CF titers. Nonmeningeal disseminated disease may be treated either with AMB or with fluconazole, most authorities recommend the use of AMB if the patient is very ill, and especially if there are gas exchange abnormalities (Singh et al., 1996).

Meningeal involvement must always be treated. Fluconazole is highly effective (Galgiani et al., 1993); excellent results were obtained during the large outbreak in central California during the early 1990s. Patients with established coccidioidal meningitis must continue fluconazole for their lifetime, since relapse of the infection following discontinuation of treatment is common (Dewsnup et al., 1996). HIV co-infected patients represent a special group. HIV-infected patients with well-preserved immunity (with CD^4 count of 500 or greater) frequently develop coccidioidomycosis that is seen in immunocompetent hosts (Ampel et al., 1993). However, primary pulmonary coccidioidomycosis in these patients should never be simply observed. Treatment should always be started immediately because of the extremely high risk for progression. More severely immunocompromised patients frequently present with diffuse nodular pulmonary infiltrates and severe gas exchange abnormalities (Fish et al., 1990; Ampel et al., 1991; Singh et al., 1996). Treatment of these patients must be initiated with AMB (Singh et al., 1996). Following stabilization, they may switch to oral fluconazole. There is no advantage of using fluconazole intravenously, although it is available in that form. Following control of the symptomatic illness, all HIV-positive individuals must continue lifelong maintenance therapy to prevent relapse.

Cryptococcal Pneumonia

The Organism

Cryptococcosis is an infection caused by the encapsulated yeast *Cryptococcus neoformans.* This fungus occurs in two major varieties: *C. neofor-*

mans var. *neoformans* and *C. neoformans* var. *gattii.* In North America, *C.* var. *neoformans* is the organism usually encountered.

Epidemiology

Unlike the other endemic fungal diseases, cryptococcal disease is endemic in all continents. Despite intense efforts, the ecological niche of the fungus is still not fully defined. Since the original isolation of cryptococci from pigeon nests and droppings, droppings from pigeons and other birds have been considered an important substrate for growth of this fungus. Fresh pigeon droppings do not contain the fungus, but dry specimens frequently are teeming with the fungus. Pigeons likely have nothing to do with the propagation of the infection, except that their accumulated droppings serve as a ready source of organic nitrogen for the growth of the fungus (Sarosi, 1997).

C. neoformans occurs in nature as a yeast and the infectious particle is a desiccated, unencapsulated yeast. The yeast without its capsule is 2 to 3 μm in size; when aerosolized, it can reach the alveoli.

To complicate the ecological story further, a sexual state exists for *C. neoformans. Filobasidiella neoformans* produces spores that range from 1.5 to 3 μm in diameter (Kwon-Chung, 1975). There is speculation that the spores of the sexual state can also cause human infection. This has been demonstrated in experimental animals, but it is only conjectured in human illness.

Pathophysiology

As in other fungal infections, the lung is the portal of entry. Following inhalation, some of the spores lodge in the alveoli and begin to multiply. Once inside the human host, the yeast rapidly develop a very large polysaccharide capsule, which is antiphagocytic (Diamond et al., 1972). Because of the presence of this antiphagocytic capsule, tissue reaction in normal hosts is limited, and it is not unusual to find large areas of cryptococcal pneumonia without any neutrophilic or monocytic infiltrate. In fact, at gross inspection of a resected mass, cryptococcal infection can be inferred when the mass is gelatinous, consisting only of yeasts and capsular material. Histopathology, however, can vary a great deal; in some cases well-developed granulomas form after the development of T cell-mediated immunity. During the pre-immune phase of the illness, widespread dissemination may occur throughout the entire body, as in other fungal infections.

The organism exhibits an unusual tropism for involvement of the central nervous system and in clinical medicine cryptococcal meningitis is far more common than symptomatic cryptococcal pulmonary disease. Other tissues may also be involved, including the skin, bone, and prostate gland.

Localization and eventual control of the infection depends solely on adequate T cell-mediated specific immunity. This feature of the illness was recognized long before T cell-mediated immune defenses were understood. Cryptococcal meningitis frequently occurred in patients with Hodgkin's disease, now known to have severe deficiency of T cell-mediated cellular immunity (Collins 51). Because control of the infection depends on T cells, cryptococcal disease became extremely widespread with the development of the **HIV** pandemic. It was estimated that approximately 300 cases of cryptococcal meningitis were seen annually in the United States prior to 1980, while in the early 1980s, as a result of the **HIV** outbreak more than 5000 cases were seen each year (Larsen, 1993). This number has been reduced lately, likely because of the widespread use of fluconazole for prophylaxis and treatment of oropharyngeal candidiasis (Hajjeh et al., 1999).

Clinical Manifestation

Clinically diagnosed isolated cryptococcal pulmonary disease is fairly uncommon, representing probably less than 10% of the total burden of cryptococcal disease. Perhaps less than 20% of immunocompetent patients with cryptococcal meningitis have a concomitant cryptococcal pulmonary infection, usually just an incidental focal infiltrate seen on chest radiograph.

However, recovery of the cryptococcus from respiratory secretion does not prove that cryptococcal disease is responsible for the pulmonary process. Cryptococci are frequently seen as commensals in sputum, especially in patients with chronic

obstructive pulmonary disease in normal hosts is most likely related to the low virulence of the organism, since exposure appears to be quite common. Even when cryptococcal pulmonary disease is established, symptoms may be minimal (Baker, 1976). The infiltrates may be small or large, single or multiple, solid or cavitary, with or without involvement of the hilar nodes. Because of the great variation in radiographic appearance, no single radiographic picture is characteristic of cryptococcal pneumonia (Campbell, 1966). While a few patients have fever, chills, and productive cough, the majority of patients with cryptococcal pneumonia have few symptoms. Many are asymptomatic, with an infiltrate discovered incidentally on a routine chest radiograph. One radiographic pattern is a large, round pneumonia 5 to 10 cm in diameter, which can be easily confused with bronchogenic carcinoma.

Patients with AIDS generally have widely disseminated infection when they present with meningitis. Headache, stiff neck, and decreased level of consciousness may be the dominant symptoms, or the patient may just have a systemic febrile illness without localizing features (Chuck & Sande, 1989). Blood cultures (and serum cryptococcal antigen) are frequently positive. The chest radiograph may be normal initially but, as the disease progresses, often shows diffuse interstitial infiltrates. These infiltrates may evolve further to diffuse alveolar involvement, similar to ARDS of any cause (Cameron et al., 1991). patients at this stage are critically ill with severe hypoxemia.

No discussion concerning cryptococcal disease is complete without a brief discussion of the major clinical manifestations of cryptococcosis, namely cryptococcal meningitis. The inordinate tropism of the fungus for the central nervous system is still not fully understood. The meninges are involved most commonly, but the brain itself can also be infected. Clinically, cryptococcal meningitis may range from an acute, fulminant illness, indistinguishable from bacterial meningitis to a minimally symptomatic illness, with mild headache but no fever or meningeal signs (Chuck & Sande, 1989; Larsen, 1993). In a recent paper a surprisingly large number of patients had no complaints beyond headache yet cerebrospinal fluid (CSF) examination yielded the fungus (Chuck & Sande, 1989). In chronic slowly progressive infections, especially in immunocompetent hosts, cranial nerve abnormalities are frequently seen; the sixth nerve is the nerve most frequently involved (Sarosi et al., 1969). The development of hydrocephalus is a frequent complication of the infection. Serial CT scans should be done whenever there is progressive decrease in the level of consciousness or even stepwise escalation in the severity of headache (Mangham et al., 1983).

Diagnosis

There has been limited experience with serodiagnostic tests measuring anti-cryptococcal antibodies. The availability of cryptococcal antigen (CRAG) determination, however, revolutionized the diagnosis of cryptococcal disease. CRAG in CSF is a sensitive and specific test for cryptococcal meningitis. In non-AIDS patients serum (CRAG is usually negative. In AIDS concomitant serum CRAG is nearly always positive, usually in higher titer than in CSF. Immunocompetent patients with isolated cryptococcal pneumonia usually have negative serum CRAG. On the other hand serum CRAG is usually positive in immunosuppressed patients with isolated cryptococcal pneumonia and is almost always positive in patients with systemic cryptococcal infections (Chuck & Sande, 1989). Determination of blood and CSF CRAG is mandatory in all patients suspected of having the disease, because it is the most rapid and specific way to establish the diagnosis. There is no readily available skin test for cryptococcus.

Culture identification of the fungus is readily accomplished on most media. The organism grows rapidly and within 3 to 5 days specific diagnoses can be established. Prior to the routine availability of CRAG determination, India ink preparations of the CSF were in frequent use. While some laboratories still use the technique (and in expert hands it is an excellent way to establish the diagnosis), in most laboratories, the more readily standardized CRAG has replaced the India ink test.

Treatment

Pulmonary cryptococcal disease is quite uncommon. When colonization is excluded and only established pulmonary infections are considered, the number of cases in immunocompetent hosts is

quite small (Sarosi, 1999). Since the landmark paper by Kerkering in 1981, it has been customary to offer no specific antifungal treatment to immunocompetent patients with cryptococcal pulmonary disease (Kerkering et al., 1981). When the data are carefully examined, however, a different argument can be made. When Kerkering studied his patients (the paper was originally presented in abstract form in 1979), the only effective therapies for cryptococcal disease were AMB and/or 5-fluorocytosine (5-FC). 5-FC monotherapy was not useful, because resistance rapidly developed when this agent was used as monotherapy. Thus the only real treatment option was AMB. Given this choice, it was sensible to observe patients who were not critically ill and who did not have meningeal disease to see if the disease would resolve. In a recent editorial, Sarosi (1999) identified only 11 patients with cryptococcal pulmonary disease who were observed without treatment; two of these patients had progressed under observation. Given the fact that fluconazole is nontoxic and highly effective for the treatment of cryptococcal disease, it seems more reasonable today to treat all patients who have documented cryptococcal pulmonary disease with fluconazole. Moreover, it is essential that all such patients have a lumbar puncture to rule out meningeal involvement (Sarosi, 1999).

There are no randomized, controlled studies of fluconazole for the treatment of pulmonary cryptococcal disease. However, there is a large experience with fluconazole in cryptococcal meningitis, where it is virtually as effective as AMB (Saag et al., 1992; Dromer et al., 1996). The dose of fluconazole is 400 mg/day. Treatment should be continued to clinical and radiological resolution. In severely ill patients, when gas exchange abnormalities are present, treatment should begin with AMB; once the patient is stabilized, treatment may be changed to oral fluconazole.

All immunocompromised patients with pulmonary cryptococcal disease should be treated. Again, the recommended treatment is fluconazole 400 mg/day. If the patient is seriously ill, AMB is the drug of choice for initial treatment (De Lalla et al., 1995). We recommend 0.7 mg/kg/day of AMB until stabilization and follow-up with fluconazole 400 mg/day. 5-FC may be added to AMB, but care should be exercised to prevent bone marrow suppression. The dose of 5-FC must be kept low to maintain blood levels less than 100 μg/mL. Duration of therapy in immunocompromised patients should be very long. In solid organ transplant recipients treatment should be continued for 6 to 12 months with careful serial follow-up after treatment is stopped to detect relapses. In **AIDS** patients, treatment is changed to fluconazole at a maintenance dose of 200 mg/day and continued for the life of the patient.

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Penicillium and Other Miscellaneous Fungi as Causal Agents in Community-Acquired Pneumonia

TODD F. HATCHETTE

Introduction

Once considered the realm of dermatologists and infectious disease specialists, fungal infections seem to be increasing in frequency. Of the 100,000 to 200,000 known species of fungi, approximately 240 species cause disease in humans (Perfect & Schell, 1996). A wide variety of unusual fungi are capable of causing respiratory infections. Usually these infections occur in immunosuppressed patients often during prolonged bouts of neutropenia and can at times include more than one fungal agent. Tissue is often necessary for diagnosis, which unfortunately is too often made at autopsy. Management must include appropriate antifungal therapy, and surgical debridement and resection when necessary (such as localized cavitary lung lesions, osteomyelitis, infection of the great vessels, progressive sinusitis, and endophthalmitis). Enhancement of the immune system in immunosuppressed individuals with colony-stimulating factors or granulocyte transfusions and discontinuation of potential iatrogenic immune suppressants may be potential adjunctive therapy (Kiwan & Anaissie, 1999).

TODD F. HATCHETTE • Department of Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic / Plenum Publishers, New York, 2001.

Phaeohyphomycosis

Phaeohyphomycosis refers to infection with dematiaceous (darkly pigmented) fungi. These ubiquitous fungi are becoming increasingly prevalent opportunistic infections in immunocompromised hosts. Routine staining of histological specimens may show hyphae that are indistinguishable from *Aspergillus* species. Melanin, which has antioxidation properties that may enhance the virulence of these microorganisms, can be demonstrated with Fontana-Masson stain, a finding specific to dematiaceous fungi (Fothergill, 1996; Perfect & Schell, 1996). Most human infections are caused by *Alternaria* species, *Bipolaris* species, *Curvularia* species, *Cladosporium* species, *Xylohypha* species, and *Exophiala* species (Koneman et al., 1997). *Fonseceae pedrosi* and *Wangiella dermatitidis* are two other species of dematiaceous fungi that have rarely been implicated as causes of pulmonary infections (Morris et al., 1995).

Exophiala Species

Exophiala species are polymorphic and typically start as black yeast-like colonies that become velvety as hyphae develop. The yeast stage multiplies via annellides. Annellides are flask-shaped cells from which conidiophores are produced by extending from the inner layer through the outer layer, causing them to get narrower as they grow (Dixon & Fromtling, 1995). Annellides can be iden-

tified and used to differentiate *Exophiala* from *Candida* species, which develop blastoconidia (Fothergill, 1996). *Exophiala* species are commonly isolated from cutaneous nodules but have been implicated as causing pulmonary disease. Manian and Brischetto (1993) reported a case of *Exophiala jeanselmei* pneumonia in an elderly patient with type 2 diabetes who presented with a 6-week history of worsening cough, hemoptysis, fever, anorexia, and weakness. Percutaneous aspiration of a lung mass and bronchial washing revealed *E. jeanselmei.* He was successfully treated with ketoconazole for 5 months.

Bipolaris Species

Members of the *Bipolaris* genus can be distinguished from other dematiaceous fungi by their conidia. Conidia belonging to *Bipolaris* species are straight, oblong to ellipsoidal, and rounded at both edges. They germinate from each end of the conidium at a 180° angle. Growing the fungus on agar containing 15% V-8 juice can potentiate the formation of conidia (McGinnis et al., 1986). *Bipolaris* species are commonly implicated in sinusitis, have been reported to cause pulmonary infections in immunosuppressed and immunocompetent patients, and have been implicated in causing a syndrome similar to allergic bronchopulmonary aspergillosis (Adam et al., 1986; Karim et al., 1993; Fothergill, 1996; Flanagan & Bryceson, 1997). Karim et al. (1993) reported a case of *Bipolaris spicifera* pleuropulmonary infection in an asthmatic who was taking oral prednisone for several months prior to infection.

Allergic bronchopulmonary disease has been treated effectively with surgical resection of diseased lung and steroids (Adam et al., 1986). Clinical experience from the literature suggests that amphotericin B alone or in combination with the imidazoles is the treatment of choice for invasive disease due to *Bipolaris* species (Flanagan & Bryceson, 1997; Kiwan & Anaissie, 1999).

Xylohypha Species

Xylohypha, a dematiaceous fungus found in soil, has been implicated as a cause of central nervous system infections in humans. Twenty of 26 patients in one series of community-acquired *Xylohypha* infection did not have any recognizable physiologic factors that would predispose them to infection; however, 9 of 12 patients had documented exposure to soil (Dixon et al., 1989). Although *Xylohypha* species have not been identified in the lung specimens of patients with infection, infection is thought to occur through the respiratory tract by inhalation (Dixon et al., 1989; Fothergill, 1996). Other dematiaceous fungi such as *Zygosporium* species have rarely been isolated from sputum (Fothergill, 1996).

Zygomycetes

Zygomycetes are a class of fungi that are commonly distributed throughout nature and cause infections in humans though inhalation of spores. These fungi have been described as "lid lifters" because their growth is so rapid that they tend to lift the lid off the petri dish. Macroscopically the colonies are gray, white, or brown with a cottony or woolly appearance. Microscopically they produce sporangia and have broad aseptate, ribbon-like hyphae. Distinguishing characteristics of this group of fungi include sporangia, which arise from sporangiophores that terminate in a swelling called the columella, and the presence of rhizoids that appear as root-like structures. The position of rhizoids can facilitate genus identification (Koneman et al., 1997).

Cunninghamella Species

The genus *Cunninghamella* belongs to the class Zygomycetes in the order Mucorales. These fungi are capable of both sexual and asexual reproduction. Sexual reproduction occurs by fusion of specialized cells called "gametangia" that give rise to zygospores. Homothallic species can produce spores by themselves, whereas heterothallic species require a compatible strain in order for sexual reproduction to occur (Schell et al., 1982). Asexual reproduction consists of the release of sporangiospores from a terminal structure called a sporangiophore. The inhalation of the sporangiospores is thought to be the mechanism behind initiation of *Cunninghamella* infection (Zeilender et al., 1990).

The morphology of the sporangiophore and the fungi's characteristic branching, nonseptate hyphae characterize this genus (cited in Ventura et al., 1986). The main human pathogen is *Cunninghamella bertholletiae*, which can be differentiated from other *Cunninghamella* species by its ability to grow at 42°C (Cohen-Abbo et al., 1993). *C. bertholletiae* can produce an angioinvasive infection similar to other mucormycosis (McGinnis et al., 1982; Rex et al., 1988).

Cohen-Abbo et al. (1993) reviewed the literature describing the characteristics of *Cunninghamella* infection. Of the 17 cases described, 16 had underlying causes of immunosuppression including steroid use (56%), malignancy (44%) (the majority had received chemotherapy within 6 months of infection), splenectomy (2/16), organ transplantation (2/16), and AIDS (1/16). Seventy-one percent of patients (12/17) had pulmonary involvement. The clinical and radiographic presentations were nonspecific, with fever being the most consistent finding. As in other fungal infections neutropenia appears to be an important risk factor for development of this infection. There is some suggestion that states of iron excess may predispose to infection with the Mucorales group of fungi (mucormycosis). Rex et al. (1988) reported a patient who developed *C. bertholletiae* infection while receiving deferoxamine therapy for iron overload and suggest that both the deferoxamine and the underlying iron overload may have increased her risk of infection.

As with other fungal infections, isolation of *Cunninghamella* species in clinical specimens from immunosuppressed individuals in the right clinical setting should raise suspicion that the isolate is a pathogen rather than a contaminant. A patient with underlying hematopoietic dysplasia had cultures positive for *C. bertholletiae* on three occasions prior to his death from disseminated *Cunninghamella* infection (McGinnis et al., 1982). Definitive diagnosis can be made with a lung biopsy and should be considered in anyone with immune suppression, particularly neutropenia, who has pneumonia that is not improving on appropriate antibiotic therapy. There was an 82% mortality rate with *Cunninghamella* infection. The only patient in this series who did not have any underlying immunosuppression initially had a sputum isolate of *C. bertholletiae* that was dismissed as a contaminant because he lacked any underlying risk factors. Failure to realize this isolate as a true pathogen delayed treatment and likely contributed to his death despite antifungal treatment (Zeilender et al., 1990). Amphotericin B (1.0–1.5 mg/kg/day) is currently the treatment of choice plus surgical debridement if necessary. If possible, discontinuation of immunosuppressive therapy is an appropriate adjunct to antifungal therapy (Cohen-Abbo et al., 1993).

Yeasts

Yeasts are part of the flora of the oropharynx, vagina, and gastrointestinal tract and can often be found in a number of clinical specimens, where they are dismissed as "normal flora." Different species of yeast can produce various infections in humans and should be considered the causal agent when they are isolated in specimens from normally sterile sites. *Candida* species are the most common isolates in clinical specimens, but a number of other organisms are capable of causing disease in humans (Koneman et al., 1997).

Blastoschizomyces capitatus

Blastoschizomyces capitatus is a yeast-like fungus that was previously classified as *Trichosporon capitatum* and *Geotrichum capitatum.* Macroscopically these yeast produce white or cream-colored shiny glabrous colonies with radiating edges. Microscopically they can produce true hyphae, pseudohyphae, and annelloconidia. The annelloconidia may resemble arthroconidia, making the distinction between *Trichosporon* species and *B. capitatus* difficult.

Martino et al. (1990b) presented 20 cases of *B. capitatus* infection that occurred in hematology patients over a 2-year period. Of the 20 cases, 12 (60%) were proven infections with documented positive blood cultures, 4 (20%) were presumed infections, and 4 (20%) were considered to be cases of colonization. All of the patients had an underlying hematological malignancy including acute leukemia (15/20), chronic myeloid leukemia in blast crisis (3/20), multiple myeloma (1/20), and non-Hodgkin's lymphoma (1/20). All but one patient had undergone chemotherapy and 90% of the

patients had received corticosteroids. Seven of the 12 infected patients (58%) had pulmonary infiltrates, with four of these patients presenting typical radiographic features of a mycetoma. *B. capitatus* infection manifesting as a mycetoma has been associated with spontaneous pneumothorax in patients with acute leukemia (Martino et al., 1990). Five of the patients with documented *B. capitatus* infection went on to have an autopsy. All five patients had histological evidence of *B. capitatus* pneumonia, and one patient was co-infected with *Aspergillus fumigatus.* Disseminated infection was present in many of these patients. The clinical presentation was nonspecific and similar to other fungal infections and ultrasound studies of the liver in three patients demonstrated a similar "bull's-eye" pattern that is seen in patients with hepatosplenic candidiasis. All four patients with "presumed" infection presented with pulmonary infiltrates, fever, and positive sputum cultures. However, because patients lacked histological evidence of pulmonary involvement or *B. capitatus* fungemia, lung as the primary site of infection could only be "presumed." There was an 87.5% mortality rate seen in the previous eight cases of *B. capitatus* reported in the literature (Martino et al., 1990). Overall, 13 of the 16 patients in this series died. The most important aspect of treatment is clinical response to the underlying malignancy and reconstitution of the immune system. Eleven of these patients did not achieve remission from their underlying disease and many had evidence of disseminated infection at the time of death. Of the five patients who were able to achieve remission from their underlying hematological malignancy, two died from disseminated *B. capitatus* infection, while infection in the three others was cured with a combination of amphotericin B and 5-fluorocytosine. Combination therapy with amphotericin B and 5-fluorocytosine has controlled the extent of infection until recovery of the immune system in some patients (Martino et al., 1990b). The authors did not indicate if these were nosocomially or community-acquired cases. However, given the fact that a majority of the patients had underlying hematological malignancies and had recently been given chemotherapy, it is likely that the infections were nosocomial rather than community-acquired. No community-acquired cases could be found in the literature.

Malassezia furfur

Malassezia furfur is a yeast that requires long chain fatty acids for optimal growth. They frequently colonize the skin, are a common cause of tinea versicolor, and have been documented in central venous catheter-associated line sepsis usually in immunosuppressed patients (Johnson, 1997). Although there have been cases of nosocomial pneumonia (Richet et al., 1989), there are no documented cases of community-acquired pneumonia due to *M. furfur.*

Hyalohyphomycosis

Hyalohyphomycosis (infection with nondematiaceous fungi) follows inhalation of spores or occurs by progression of previously localized cutaneous lesions. These fungi are differentiated on the basis of macroscopic colony morphology and the microscopic appearance of the hyphal elements, conidia and conidiophores. *Fusarium* species, *Pseudallescheria* species, *Scedosporium* species, and *Scopulariopsis* species are all documented human pathogens (Koneman et al., 1997). Several members of this group, including *Acremonium strictum, Paecilomyces lilacinus*, and *Scedosporium prolificans*, are able to produce adventitious unicellular forms called "propagules." These propagules are still capable of propagating the microorganism and their size and lack of hyphae facilitate entry and circulation of the organisms within the bloodstream. Misdiagnosis can be a problem as these adventitious forms may also be misidentified as yeast species such as *Candida* (Perfect & Schell, 1996). Although *Scedosporium* species can appear dematiaceous in culture, the clinical spectrum of disease that they produce as well as their appearance in tissue specimens lead them to be classified with the hyalohyphomycosis group (Kennedy & Sigler, 1995).

Scedosporium Species

Scedosporium apiospermum (also referred to as *Pseudallescheria boydii* when the fungus is in its sexual or telomorphic form) has been isolated from soil, sewage, birds, and animal waste (cited in

Wood et al., 1992). It has been reported as the cause of pneumonia in patients with chronic granulomatous disease and in immunocompromised hosts usually in the setting of neutropenia (Nomdedeu et al., 1993; Jabado et al., 1998). *S. apiospermum* has been associated with pneumonia in patients who suffered a near-drowning episode in polluted, stagnant, or muddy water (Ender & Dolan, 1997). Ender and Dolan (1997) reviewed the literature on *S. apiospermum* pneumonia after near-drowning episodes and found that pneumonia can be an acute manifestation, appearing within a week of submersion, or it may present up to 6 months later. Most of the patients had disseminated disease, often with central nervous system involvement. The majority of the patients died from their infection.

Scedosporium prolificans, another soil species, was previously referred to as *S. inflatum* but genomic homology studies have confirmed the previously identified species *Lomentospora prolificans* and *S. inflatum* were "conspecific" and therefore they were reclassified as *Scedosporium prolificans.* Rabodonirina et al. (1994) reported a fatal case of disseminated *S. prolificans* infection in a lung transplant recipient. Upon reviewing the 30 published cases in the literature where *S. prolificans* has been isolated from clinical specimens, the majority of these patients have had osteoarticular infections that were generally managed with surgery. Six of the cases were in immunosuppressed individuals, five of whom had hematological malignancies or neutropenia. The case reported by Rabodonirina et al. (1994) was the only one with predominant pulmonary infection. There have been four cases where *S. prolificans* has been isolated from the sputum and bronchial washings in patients who had no histological evidence of infection. Therefore, the authors are uncertain if this represented true infection or colonization (Wilson et al., 1990; Wood et al., 1992).

Prognosis in *Scedosporium* infections correlates with the immunocompetence of the host (Wood et al., 1992). *S. apiospermum* is usually resistant to fluconazole and often resistant to amphotericin B but generally remains susceptible to itraconazole, ketoconazole, and miconazole. Therapy should consist of attempts at reversing immunosuppression, surgical resection of any possible lesions, and intravenous miconazole (1.2–3.6 g/day) or itraconazole (400–600 mg/day). *S. prolificans* is resistant to all the currently available antifungals; therefore surgical resection and debridement is the mainstay of treatment (Wood et al., 1992; Rabodonirina et al., 1994; Kiwan & Anaissie, 1999). Disseminated disease is invariably fatal. Of the seven immunosuppressed patients who had developed disseminated infection only one survived. This patient had received granulocyte-macrophage colony-stimulating factor (GM-CSF) in addition to his antifungal medications, which likely contributed to his recovery (Rabodonirina et al., 1994).

Penicillium

Introduction

Although there are hundreds of *Penicillium* species, this blue-green soil fungus has been rarely described as a human pathogen and is often thought to be an environmental contaminant in the laboratory setting. Its low pathogenicity is due to growth inhibitionat 37°C (Kennedy & Sigler, 1995). There have been a variety of documented pulmonary syndromes secondary to the inhalation of *Penicillium* spores. Huang and Harris (1963) presented a case of disseminated *P. commune.* They found reports of bronchopulmonary penicilliosis dating back to 1918. The most common cause was *P. crustaceum;* however, *P. bicolor*, *P. berati*, *P. glaucum*, *P. spinulosum,* and *P. commune* have all been documented as causing infections in humans. There have been a number of syndromes described that resemble those associated with the more common *Aspergillus* species. *P. citrinum* and *P. chrysogenum* cause pneumonia (Mok et al., 1997; D'Antonio et al., 1997), *P. decumbens* has been documented in a pulmonary fungus ball (Yoshida et al., 1992), and *P. lilacinum* has been isolated from a pleural effusion (Fenech & Mallia, 1972). There have also been documented cases of allergic bronchopulmonary penicilliosis (Sahn et al., 1973) and hypersensitivity pneumonitis ("cheese washer's disease") secondary to *Penicillium* species (Schlueter, 1973). Most of these cases have been associated with immunosuppression, usually as a result of hematologic malignancy. *P. brevicompactum* and *P. olivicolor* have been implicated as a cause of farmer's lung (Nakagawa-Yoshida et al., 1997). Bronchiolitis obliterans or-

ganizing pneumonia has been reportedly caused by inhalation of *P. janthinellum* spores (Bates et al., 1997). *P. italicum* was isolated from a postmortem lung specimen in an HIV-infected patient in Zimbabwe (McLeod et al., 1989). Kagen et al. (1983) suggest that marijuana may contain pathogenic species of fungi including *Penicillium* species. Patients with certain malignancies and AIDS have used marijuana as a therapeutic adjunct, which may put them at increased risk for fungal infections. Under these circumstances, isolation of a *Penicillium* species may represent infection.

Penicillium marneffei

Mycology The most important *Penicillium* species is *P. marneffei,* which is becoming increasingly prevalent as an opportunistic infection in patients with HIV. *Penicillium marneffei* is unique in that it is the only dimorphic fungus in the *Penicillium* genus. At room temperature (25°C) it grows as a mold, whereas at 37°C it grows as yeast. The mold is characteristically described as grayish-white and woolly. Another unique feature of this species is the development of a reddish pigment, which diffuses into the agar as it grows. Microscopically it has typical *Penicillium* features with hyphae that are short, hyaline, septate, and branched. They have lateral and terminally located conidiophores, which have terminal verticils of three to five penicilli that bear the phialides. These phialides give rise to long, basipetal, unbranched chains of conidia (DiSalvo et al., 1973; Paulter et al., 1984).

After 2 days of incubation at 37°C, *P. marneffei* will grow as a yeast producing soft white-tan colonies with a convoluted surface without the diffusible red pigment. A unique feature of this yeast form is that division occurs by fission and not budding, producing easily seen septa, which help distinguish it from *Histoplasma capsulatum* (Deng & Connor, 1985).

Epidemiology This organism, named after Marneffe (Director, Institut Pasteur in Indochina and later in Paris) (DiSalvo et al., 1973), is the third most common opportunistic infection in patients with HIV infection who live in certain parts of Southeast Asia (Duong, 1996; Supparatpinyo et al., 1994; Wong et al., 1998). The increasing incidence of *P. marneffei* infection is a reflection of the increasing prevalence of HIV (Supparatpinyo et al., 1994; Chariyalertsak et al., 1996). Of the 33 cases of *P. marneffei* reported from 1973 to 1990, only 8 were associated with HIV infection. Seven percent of all of the HIV-infected patients reported in Hong Kong up to 1991 (4/54) were diagnosed as having an infection with *P. marneffei* (Tsui et al., 1992). Of the first 400 patients diagnosed with AIDS at the Chiang Mai University Hospital in Thailand, 140 cases of *P. marneffei* were identified (Duong, 1996). Supparatpinyo et al. (1994) reviewed all confirmed cases of *P. marneffei* diagnosed at Chiang Mai University Hospital during a 5-year period between 1987 and 1992. Eighty-six of the 92 patients with this infection had HIV, and for many of them this was their first opportunistic infection. Due to the prominence of fungal infections, it has become routine to search for this organism in any HIV-infected, febrile patient who is admitted to this hospital. Its prevalence and presentation suggest that this infection should be considered an AIDS-defining illness (Supparatpinyo et al., 1992; Hilmarsdottir et al., 1993). Although it is not considered an AIDS-defining illness in the United States, Hong Kong has broadened its case definition of AIDS to include *P. marneffei* infection (Wong et al., 1998).

This facultative intracellular organism was first isolated in 1956 by Capponi et al. from the liver of a bamboo rat (*Rhizomys sinensis*) and has subsequently been isolated from other species of bamboo rats (*Rhizomys pruinous senex* and *Cannomys badius*) (Deng et al., 1988; Chariyalertsak et al., 1996). It is endemic in many parts of Southeast Asia including Vietnam, Thailand (Jayanetra et al., 1984), the Guangxi province of the People's Republic of China (Deng & Connor, 1985), and certain parts of Hong Kong and Taiwan (Pautler et al., 1984; Duong, 1996; Hung et al., 1998). In fact more than 90% of the bamboo rats in the Guangxi province are infected with this fungus (Duong, 1996).

The first human infection documented in 1959 was an accidental inoculation into the finger of a mycologist studying this fungus (Segretain, 1959). It was not until 1973 that the first case of a naturally acquired infection was documented by DiSalvo et al. (1973). In this case *P. marneffei* was isolated from the spleen of an American minister with Hodgkin's disease. Prior to his diagnosis he had

spent time in Southeast Asia. Subsequently a case series documenting *P. marneffei* infection in both immunocompetent and immunodeficient patients living in Thailand was published (Jayanetra et al., 1984).

During the HIV era, *P. marneffei* has become an increasingly significant pathogen. Duong (1996) reviewed the 155 cases of *P. marneffei* infection reported in the English literature up to 1996. The patients were typically male (90%), with 80% having underlying immunosuppression, most commonly HIV. Those with HIV infection had advanced disease with CD4 counts ranging from 1 to 44/μL (Supparatpinyo et al., 1994). The route of infection is not clear but is likely either oral or respiratory. The natural reservoir of *P. marneffei* has not been established. Chariyalertsak et al. (1996) found that there was an increase in the incidence of *P. marneffei* infections during the rainy season, which corresponds to the bamboo rats' breeding season (Phillips, 1996). Apart from the bamboo rat, the fungus has been isolated from the soil in rat burrows. There is some indication that the fungus is "freely present" in the environment (Tsui et al., 1992) and attempts have been made to isolate it from food staples for rats and humans within the endemic area. No fungus could be isolated on sugar cane or bamboo shoots, and exposure to bamboo was not identified as a risk factor for acquisition of the organism (Chariyalertsak et al., 1997). However, growth was easily manifested when these plants were inoculated with *P. marneffei* from an infected patient (Deng et al., 1988). A case–control study was performed to try and identify risk factors for this infection. Chariyalertsak et al. (1997) compared a cohort of 80 cases of HIV-infected patients with *P. marneffei* infections with similar HIV-infected controls who were admitted to the Chaing Mai Hospital between December 1993 and October 1995. They found that the cases were younger than the controls (age 16–30 years vs. >30 years; odds ratio [OR], 2.22), and that they were more likely to have an occupation involving exposure to plants or animals. Interestingly there was no significant difference in exposure to bamboo rats (>50% of cases and controls had seen these rats near their homes) or ingestion of cooked rat between the two groups. The authors of the study suggest infection may be due to exposure to the fungus in soil and that the rats are not the reservoir of human infection, but rather are also susceptible to infection.

Clinical Features The clinical presentation of penicillosis may represent an acute infection, reactivation, or re-infection. Jones and See (1992) reported an HIV patient with *P. marneffei* infection whose only exposure was travel to an endemic area 11 years previously. The disseminated form typically presents with fever, weight loss, and anemia. Many patients have a painful nonproductive cough and typical disseminated papular lesions resembling molluscum contagiosum. Pulmonary infiltrates occur. These may be diffuse or localized alveolar infiltrates, diffuse reticular nodular opacities, and localized interstitial disease. Pleural effusions, cavitation, or abscess formation, and mass lesions may also be seen (McShane et al., 1998; Duong, 1996; Supparatpinyo et al., 1994). *P. marneffei* has been diagnosed in patients from the United States, Canada, and European countries. However, these patients all had traveled to the endemic areas prior to the onset of their disease (Duong, 1996; Pautler et al., 1984; DiSalvo et al., 1973).

The manifestations of *P. marneffei* infection can be nonspecific and may resemble other opportunistic infections. It is not uncommon that overt infections have been misdiagnosed as "resistant tuberculosis" (Tsang et al., 1988). Timely diagnosis is essential. Supparatpinyo et al. (1994) found that early diagnosis and treatment resulted in improved survival rates. The mortality rate in patients in whom diagnosis was delayed or who refused treatment was 75% (9/12).

Diagnosis The organism has been isolated from sputum, bronchial washings, and aspiration of pulmonary abscesses. The highest diagnostic yield is from cultures of bone marrow aspirates, skin scrapings, and lymph node aspirates (Deng et al., 1988; Chan et al., 1989; Duong, 1996; Ma et al., 1991).

Histologically *P. marneffei* produces three distinct reactions. The suppurative and granulomatous reactions take place in a variety of organs, particularly the reticuloendothelial system. The other reaction is "anergy with necrosis" that is more commonly seen in the lung, skin, and subcutaneous tissue (Deng et al., 1988).

Although culture remains the gold standard for

diagnosis, various staining techniques have been used to identify the organism in tissue, including Grocott–Gomori methenamine–silver nitrate and periodic acid–Schiff (Deng et al., 1988), Giemsa (Hilmarsdottir et al., 1993), Wright's (Sapparatpinyo et al., 1994), hematoxylin and eosin (Duong, 1996), and indirect fluorescent antibody stains (Kaufman et al., 1995). *P. marneffei* can be confused with *Histoplasma capsulatum* both clinically and histologically. The distinguishing features of *P. marneffei* including intracellular septa and lack of budding are most evident when the organisms are seen outside the histiocytes.

Antibodies can be detected in the serum of infected patients by various methods including immunodiffusion and indirect immunofluorescence (Yuen et al., 1994). A potential problem with these methods is the possible cross-reactivity with certain *Histoplasma* and *Aspergillus* antigens. The diagnostic utility of serologic diagnosis remains unproven. There are some studies to suggest that the sensitivity of this method is low in HIV-infected subjects (Kaufman et al., 1996).

A study by Kaufman et al. (1996) showed that detection of *P. marneffei* antigen in serum and urine was possible by immunodiffusion or latex agglutination using rabbit antisera raised against *P. marneffei* filtrates. Both methods were highly specific (100%) with sensitivities of 76.5% and 58.8% for latex agglutination and immunodiffusion, respectively. Latex agglutination has the added advantage of allowing quantification of the antibody response. These findings could not be reproduced by Chongtrakool et al. (1997), who described the isolation of a protein that is highly immunogenic and appears to be specific to *P. marneffei.* Cao et al. (1998) have identified a *Penicillium*-specific protein (Mplp) and its gene, *MP1.* Using this information they were able to generate a purified recombinant protein that has been used in an ELISA test for the diagnosis of *P. marneffei* infection in HIV patients. This test has a sensitivity of approximately 80% and is highly specific. None of the patients with tuberculosis or other fungal infections had positive reactions.

LoBuglio and Taylor (1995) have developed polymerase chain reaction primers, which they have used to investigate the pylogenetic relationship of *P. marneffei* with other *Penicillium* species. Unfortunately there have been no studies of the use of this test as a diagnostic method.

Treatment There are no trials to date that compare treatment response for this disease. The suggested therapy comes from case series and anecdotal reports. The first case reported in 1959 was reportedly cured using 20 million units of nystatin orally for 30 days. Oral nystatin for treatment of a disseminated infection is controversial as its bioavailabilty is poor and there has been documented treatment failure (Deng et al., 1988). The most common treatment has been with initially intravenous amphotericin B for 2 to 8 weeks followed by maintenance itraconazole, ketoconazole, or fluconazole, which may need to be lifelong (Hilmarsdottir et al., 1993; Phillips, 1996; Supparatpinyo et al., 1998). In vitro data suggest that *P. marneffei* isolates are highly susceptible to ketoconazole, itraconazole, and miconazole with minimum inhibiting concentrations (MICs) ranging from less than 0.195 μg/mL to 0.39 μg/mL (Supparatpinyo et al., 1993). The organism has intermediate sensitivity to amphotericin B with MICs ranging from less than 0.195 μg/mL to 1.56 μg/mL (mean 0.976 μg/mL) (Supparatpinyo et al., 1993). Seventy-three percent of the isolates tested by Supparatpinyo et al. (1993) showed borderline susceptibility or resistance to fluconazole with MICs ranging from 0.195 μg/mL to 100 μg/mL (mean 7.937 μg/mL). Although there are inherent problems with in vitro susceptibility testing of dimorphic fungi, both animal models and clinical data demonstrate similar findings (Dupont, 1999). In the case series reported by Supparatpinyo et al. (1993, 1994), the infection resolved in 77% (27/39) of patients treated with amphotericin B compared with 75% (9/12) of treated with itraconazole and 36% (4/11) of patients treated with fluconazole. With completion of their antifungal treatments, relapse occurred in 12 patients within 6 months. Four of the 27 (15%) patients successfully treated with amphotericin B relapsed compared with 5 of 9 (55%) in those treated with itraconazole and 3 of 4 (75%) in the fluconazole group. 5-Fluorocytosine has been given in addition to amphotericin B in some patients, with variable results (Jayanetra et al., 1984). Reversal of the immune suppression if possible is also of benefit.

Using a randomized placebo-controlled trial Supparatpinyo et al. (1998) confirmed that itraconazole is an effective and well-tolerated medication to prevent relapse of *P. marneffei* infections in patients with HIV. Seventy-two HIV-infected patients

with *P. marneffei* infection were successfully treated with amphotericin B (0.6 mg/kg/day) for 2 weeks followed by a 10-week course of oral itraconazole (200 mg twice daily). These patients were then randomized to receive maintenance therapy with itraconazole (200 mg once daily) or a placebo. The study was prematurely terminated after an interim analysis revealed that the treatment arm was highly effective. Twenty of the 35 patients (57%) randomized to the placebo arm of the study relapsed in a median time of 24 weeks (relapse rate, 2.6 per 100 person-weeks). None of the 36 patients receiving itraconazole prophylaxis developed a relapse of their infection. Although no significant difference was seen in overall mortality, three of the patients in the placebo group died from *P. marneffei* infection. The remainder of the 26 patients (11 itraconazole, 15 placebo) died from other infectious and noninfectious causes that may reflect the advanced degree of immunosuppression associated with the development of *P. marneffei* infection (CD4 count: 71.3 $\mu L/mm^3$ in the treatment arm, 64.8 $\mu L/mm^3$ in the placebo arm). Ketoconazole has in vitro activity against *P. marneffei* but clinical results are less impressive than those obtained with itraconazole. A trial comparing itraconazole and ketoconazole as secondary prophylactic agents is currently under way (Supparatpinyo et al., 1998).

The current treatment recommendation for AIDS patients in Thailand with *P. marneffei* infections is 2 weeks of intravenous amphotericin B (0.6 mg/kg/day), followed by oral itraconazole (400 mg/day divided into two doses) for 10 weeks. This regimen should produce resolution of symptoms within 2 weeks and has an 80% survival rate. Due to the high degree of relapse, once the initial treatment has been completed patients should be placed on long-term suppressive therapy with itraconazole (200 mg/day) (Supparatpinyo et al., 1998; Dupont, 1999).

It is recommended that patients with HIV infection or other forms of immunosuppression should avoid travel to endemic areas. However, the use of itraconazole as prophylaxis against *P. marneffei* infection in endemic areas remains controversial (Dupont, 1999).

Pulmonary manifestations are common in patients with systemic *P. marneffei* and it is likely that a primary pulmonary infection may in fact precede dissemination, making this an emerging pathogen in community-acquired pulmonary infections for those at risk. This includes immunocompromised patients traveling to an endemic area, including HIV-infected patients, particularly those with CD4 count $<50/\mu L$. However, because this fungus can infect immunocompetent individuals, a high index of suspicion should be held when immigrants or others who have traveled to endemic areas present with a clinical picture of penicillosis. In these patients, particularly those who are immunosuppressed, the isolation of *Penicillium* species should be viewed with concern.

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45

Aspergillus Species as Agents of Community-Acquired Pneumonia

THOMAS J. MARRIE

Introduction

Aspergillus is not usually thought of as a cause of community-acquired pneumonia. However, invasive pulmonary aspergillosis is now emerging as a small but significant entity in both immunocompetent and immunocompromised patients in the community.

The Organism

In 1729 the Italian priest and botanist Michel described the microscopic appearance of this fungus. He noted that the swollen vesicle with its radiating chains of conidia resembled the aspergillum (Fig. 1) he used to sprinkle holy water (Rinaldi, 1983). There are more than 300 species of aspergillus, 20 of which are pathogenic for humans (Ellis, 1998). *Aspergillus fumigatus* accounts for most cases of invasive pulmonary aspergillosis (Rinaldi, 1983). A. *flavus*, *A. niger*, *A. sydowi, A. terreus*, *A. ustus*, *A. versicolor*, *A. amstelodami, A. oryzae*, *A. restrictus*, *A. candidus*, *A. nidulans, A. carneus*, *A. caesiellus*, *A. avenaceus*, and A. *clavatus* have all been reported as causing invasive infection in humans (Bennett, 1995).

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Aspergillus species are ubiquitous molds, found in soil, dust, water, decaying organic material, flowers, tobacco, and food. Everyone is familiar with the black mold (*A. niger*) on bread that has been left uncovered at room temperature for a few days (Fig. 2).

Aspergillus sp. grow as fluffy powdery or velvety colonies of different colors (Figs. 3, 4) that darken with sporulation. Mycelia consist of conidiophores, which bear conidia. Hyphae are seen in tissue. The hyphae are thick and septate and branch at 45° angles (Fig. 5). Conidia are not seen in tissue.

Pathogenesis

The respiratory tract is the usual portal of entry, although the skin can occasionally serve as the portal of entry. The small <3-μm conidia spores are inhaled and deposited in the airway, down to the alveoli. Neutrophils are the main effector cells in protection against the mycelial form, while macrophages rapidly kill conidia (Rinaldi, 1983). Phthioic acid in *A. fumigatus* is said to be responsible for granuloma formation (Rinaldi, 1983). *Aspergillus* tends to invade blood vessels with resulting tissue infarction and dissemination throughout the body. There are several forms of pulmonary disease that result from *Aspergillus* infection. These include allergic bronchopulmonary aspergillosis, aspergilloma, chronic necrotizing aspergillosis, invasive pulmonary aspergillosis, and acute tracheobronchitis. Only the pneumonic form (invasive pulmonary aspergillosis) will be discussed here.

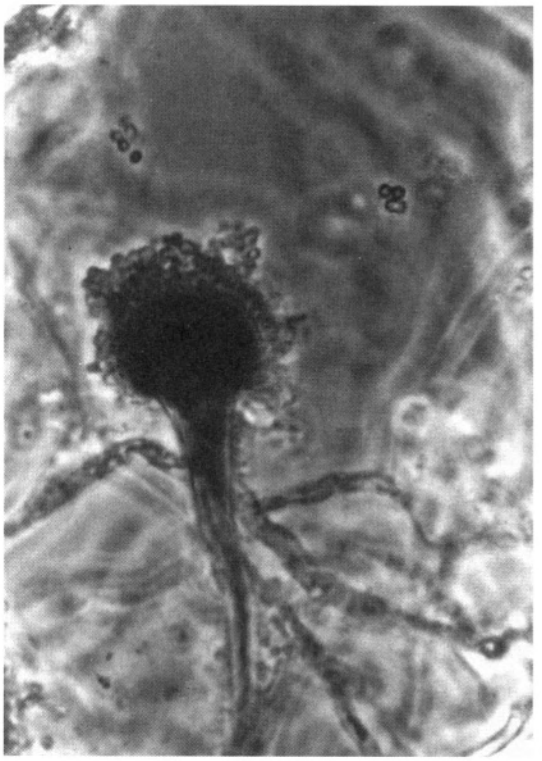

FIGURE 1. Photomicrograph of Aspergillus species showing "the swollen vesicle with its radiating chains of conidia resembling the aspergillum."

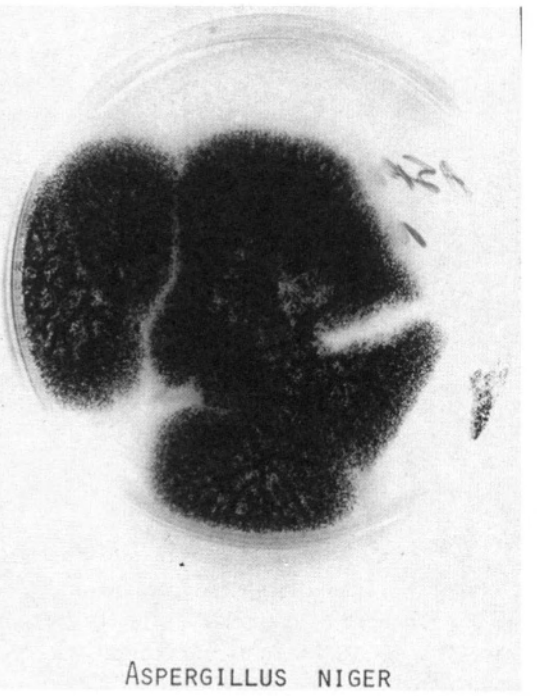

FIGURE 2. *Aspergillus niger* growing on a plate, demonstrating the characteristic black pigment.

Definition of Invasive Aspergillosis

Aspergillus species are second only to *Candida* species as the fungi most commonly isolated from clinical specimens (Kennedy et al., 1995). To help distinguish between colonization and infection, Greub and Bille (1998) devised a scoring system by assigning points to various parameters, summing these points present in an individual patient and then dividing by the maximum possible points. Using this system they could divide patients into three categories: colonization (ratio ≤ 0.3; isolate of undetermined significance) (ratio >0.3 and <0.5); and proven or probable pulmonary aspergillosis (ratio ≥ 0.5). The scoring system included the following: 1 point if more than 50% of the following assessable symptoms or signs were present—fever, cough, sputum, dyspnea, pleuritic chest pain, abnormal auscultation, respiratory rate ≥ 20 per minute; 1 point if a lung infiltrate was present on chest x-ray, CT, or MRI; 2 points if a halo sign, air crescent, or pleural location was present on radiographic examination; 1 point for antifungal treatment effective against *Aspergillus*; 1 point if no improvement after 5 or more days of antibiotic therapy; 1 point if no other etiology was found for the pulmonary symptomatology; 1 point if mild immunosuppression (corticosteroids, cyclosporin, and/or neutropenia) was present; and 2 points if severe immunosuppression (OKT3, high-dose steroids, and or severe neutropenia [<100 PMN/mm^3] was present. The maximum number of points possible is 8. They assessed 73 patients (with 76 isolates of *Aspergillus* species) and for the 7 patients with proven aspergillosis the case definition ratio was >0.3. In this study the sensitivity and specificity of *Aspergillus* spp. detection by culture of lower respiratory tract secretions for proven or probable pulmonary aspergillosis was 35.7% and 70.4%.

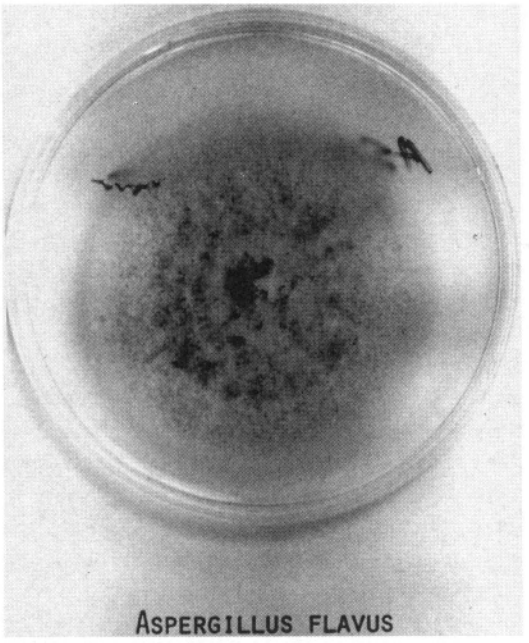

FIGURE 3. *Aspergillus flavus* growing on a culture plate.

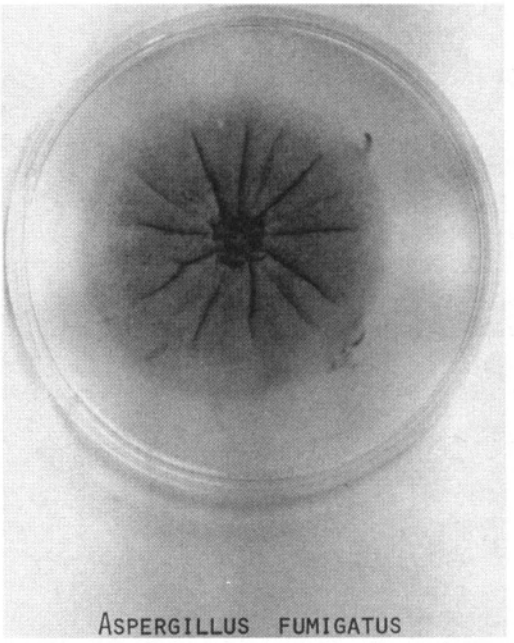

FIGURE 4. *Aspergillus fumigatus* growing on a culture plate.

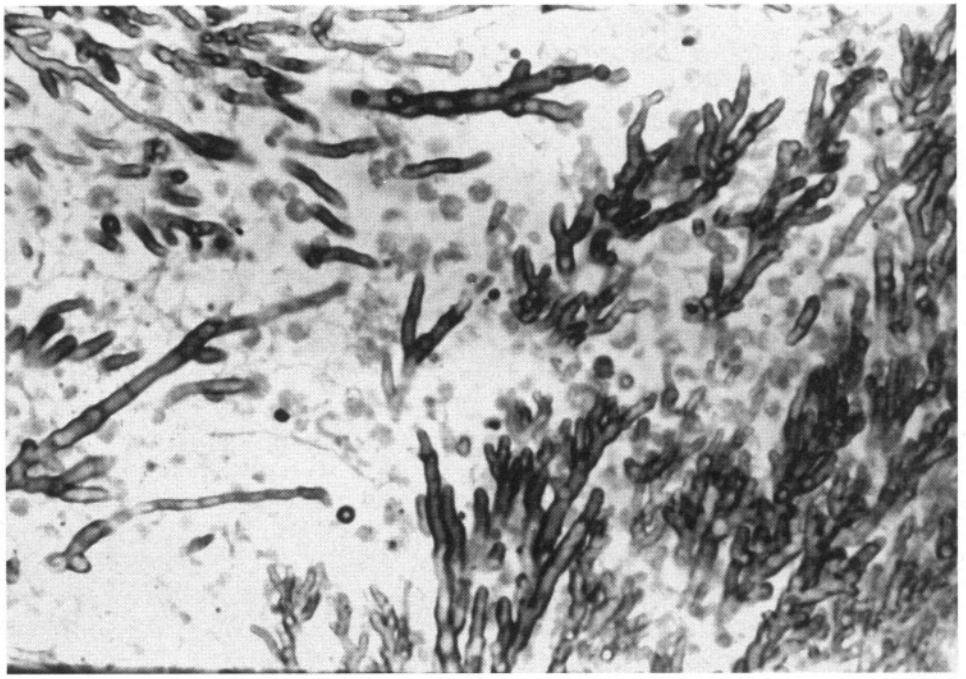

FIGURE 5. Photomicrograph of *Aspergillus* hyphae in lung tissue of a patient with invasive pulmonary aspergillosis. Note the septate nature of the hyphae and their branching at 45°.

Acute Community-Acquired Pneumonia Due to *Aspergillus* in Immunocompetent Hosts

Acute community-acquired pneumonia due to aspergillus in immunocompetent hosts is uncommon but 12 cases were reported until 1998 (Clancy & Nguyen, 1998). All of these patients were infected with *A. fumigatus.* Nine patients were previously healthy, one had chronic obstructive pulmonary disease, one had cirrhosis, and one had hypertension. One patient was exposed to hay and two sisters were exposed to artificial manure as sources of *Aspergillus.* Three were heavy smokers and three had a history of heavy alcohol consumption. Three patients had antecedent or concurrent influenza A infection. The diagnosis was delayed in all patients. The median time from onset of symptoms to definitive or presumptive diagnosis was 15 days. All 12 patients died. The presenting symptoms were fever, cough, and shortness of breath. Ten patients had bilateral pulmonary infiltrates. Cavitation was noted in three cases. Two patients had nodular infiltrates. Five of the ten patients who had an autopsy done had disseminated disease. Pulmonary necrosis and infarction was present in three and one had pulmonary abscesses (Clancy & Nguyen, 1998). Karam and Griffin (1986) also reviewed pulmonary aspergillosis in nonimmunocompromised non-neutropenic hosts. They found 22 patients in addition to the three that they reported. Twenty-two of the 25 had the diagnosis made post-mortem. Eight had no underlying disease, four were alcoholics, three had influenza A, and one had cystic fibrosis. Jiva et al. (1993) reported the case of a 71-year-old man with asthma and left lung infiltrates. He was admitted to intensive care and treated with methylprednisolone 40 mg every 6 hours as well as with antibiotics. Five days later he was worse and sputum as well as bronchoalveolar lavage grew *A. fumigatus.* He improved and was discharged on prednisone 20 mg twice daily. One week later he was readmitted with bilateral lower-lobe opacities and a right pleural effusion, which was aspirated and on culture yielded *Legionella pneumophila.* On day 11 he had hemoptysis and a fatal respiratory arrest. Autopsy showed invasive aspergillosis. His physicians felt that allergic bronchopulmonary aspergillosis evolved into invasive aspergillosis.

Invasive Pulmonary Aspergillosis in Patients with Chronic Obstructive Pulmonary Disease

Rello et al. (1998) reported eight cases of invasive aspergillosis in patients with chronic obstructive pulmonary disease and reviewed the 16 other cases that had been reported from 1966 through 1997. All patients died despite early and aggressive treatment in many of them. Eighteen cases were due to *A. fumigatus*; two each to *A. flavus* and *A. niger.* In four instances the *Aspergillus* isolate was not speciated. Twenty-one of the patients had received therapy with corticosteroids. Eighteen required mechanical ventilation. The authors felt that in most instances the aspergillosis was nosocomially acquired. In the two cases reported by Pittet et al. (1996) an air filter had been replaced 30 hours before the first patient was admitted to the room in which he was hospitalized.

Invasive Aspergillosis in Patients with HIV Infection

Five patients (0.16%) among 3170 patients with AIDS reported to the Centers for Disease Control and Prevention between May 1983 and June 1984 had invasive pulmonary aspergillosis. From then until 1993, 33 patients with this infection were reported (Lortholary et al., 1993). Lortholary et al. reported 33 patients with invasive aspergillosis from 37 French centers from July to December 1991. The mean age was 35 years and there were 30 men and 3 women. *Aspergillus* was cultured from bronchoalveolar lavage specimens in all 28 patients in whom it was performed. The mean time between diagnosis of invasive aspergillosis and death was 8 weeks, with a range of 3 days to 13 months. All patients were febrile, with a median temperature of 39°C; cough was present in 97%, dyspnea in 80%, chest pain in 20%, and hemoptysis in 17%. Fourteen had cavitation on chest radiographic examination and seven had bilateral diffuse nodular opacities; eight had bilateral diffuse opacities and two had mediastinal lymphadenopathy. Minamoto et al. (1992) presented 18 cases of invasive aspergillosis in patients with AIDS identified by reviewing autopsies at St. Luke's–Roosevelt hospital center in

New York from 1981 to 1989. They identified 19 other patients through a computer search of the literature. Twenty-eight of the 37 patients had pulmonary involvement. The lung was the sole site of aspergillosis in 18 patients. The average length of time from diagnosis of AIDS until diagnosis of aspergillosis was 10 months, with a range of 0 to 45 months. *Aspergillus* played a role in the death of 28 of the 37 patients; indeed only one of the patients survived aspergillus infection. This patient died later with a lymphoma. All but one patient had concomitant infection.

In the same year Pursell et al. (1992) reported five patients with invasive aspergillosis and AIDS. They found that 45 of their 972 patients with AIDS had *Aspergillus* spp. isolated from the respiratory tract before death. Thirty-nine of the 45 (87%) had a history of pneumonia prior to recovery of *Aspergillus* from a respiratory specimen. Chest radiographs obtained at the time of isolation of the *Aspergillus* revealed abnormalities in 43 (96%). Forty-one patients died and 26 had an autopsy performed. In four of the 26, invasive pulmonary aspergillosis was found. Miller et al. (1994) found that the major risk factors for the development of pulmonary aspergillosis in patients with AIDS were steroid administration and neutropenia. They also found that one third of 36 patients presented with cavitary upper-lobe disease resembling noninvasive or chronic necrotizing aspergillosis. Fatal hemoptysis occurred in 42% of these 13 patients. In 22% of the patients there were nondescript focal alveolar opacities. In several patients the focal infiltrate remained stable for several months. Bilateral disease seemed to be a marker for disseminated infection and was associated with a high mortality rate. All these patients had advanced HIV disease.

These reports serve as a reminder that patients with advanced HIV disease can develop invasive aspergillosis. However, current antiretroviral therapy has resulted in a substantial decrease in the incidence of AIDS-defining illness but the spectrum of infections is said to remain unchanged (Forrest et al., 1998). Thus, it is likely that we will continue to see invasive aspergillosis in HIV patients but the absolute number of cases may be much less. A study from Germany seems to contradict this assumption (Woitas et al., 1998). These workers observed 10 cases of invasive aspergillosis in a cohort of 140 (7%) patients with AIDS studied from December 1993 to January 1996. They also noted that no cases of invasive aspergillosis were diagnosed in a cohort of 278 cases of patients with AIDS at their center from 1986 until 1993. Woitas et al. (1998) went on to carry out a case–control study in which each of their ten patients with invasive aspergillosis was matched with a control patient with respect to age, gender, risk factor, duration, and onset of HIV infection. They found that patients with aspergillosis had more AIDS-defining events (3.5 vs. 2 in the control group) and a longer median survival time with full-blown AIDS (31.5 months vs. 20.5 months). The patients with invasive aspergillosis tended to have lower white blood cell counts and lower median CD4 counts (7 vs. 27/mm^3). Woitas et al. (1998) also found that *Aspergillus* antigens could not be demonstrated in blood or urine specimens.

Invasive Aspergillosis in the Immunocompromised Host

Often *Aspergillus* infection in the immunocompromised host is acquired nosocomially. However, some of these patients who are neutropenic because of their disease may have invasive aspergillosis as the presenting manifestation of their immunocompromised state, usually a hematological malignancy. Invasive aspergillosis occurs seven times more frequently in patients with leukemia than in patients with Hodgkin's disease or other lymphomas (Meyer et al., 1973). Young et al. (1970) described the spectrum of invasive aspergillosis in 98 immunocompromised patients. Thirty patients had necrotizing bronchopneumonia: 29 had hemorrhagic pulmonary infarcts, 9 had miliary microabscesses, 3 had focal lung abscess, 8 had lobar pneumonia, 8 had aspergillary bronchitis, 1 had aspergilloma, and 1 had a solitary granuloma. The central nervous system was involved in 13 patients and the gastrointestinal tract in 10.

Invasive aspergillosis is the most important cause of life-threatening fungal infection in the organ transplant recipient (Denning & Stevens, 1990). Heart and renal transplant patients have the best prognosis when infected with this pathogen, while liver and bone marrow transplant patients have the

worst prognosis (Denning, 1996). Overall, however, 80% of immunocompromised patients with invasive aspergillosis die (Denning, 1996).

Invasive aspergillosis may also be precipitated by corticosteroid therapy of patients with an aspergilloma. Figures 6 through 8 show such a patient. This patient had sarcoidosis and was treated with corticosteroids. He then developed progressive pneumonia secondary to invasive aspergillosis.

Chronic Necrotizing Pulmonary Aspergillosis

Chronic necrotizing pulmonary aspergillosis is a slowly progressive form of aspergillosis occurring in patients with diabetes, alcoholism, poor nutritional state, inactive tuberculosis, and sarcoidosis and in patients who are receiving corticosteroid therapy. Patients are chronically ill with fever, weight loss, productive cough, and hemoptysis. Slowly evolving opacities are evident on chest radiographs (Fig. 9). Aspergillomas frequently develop.

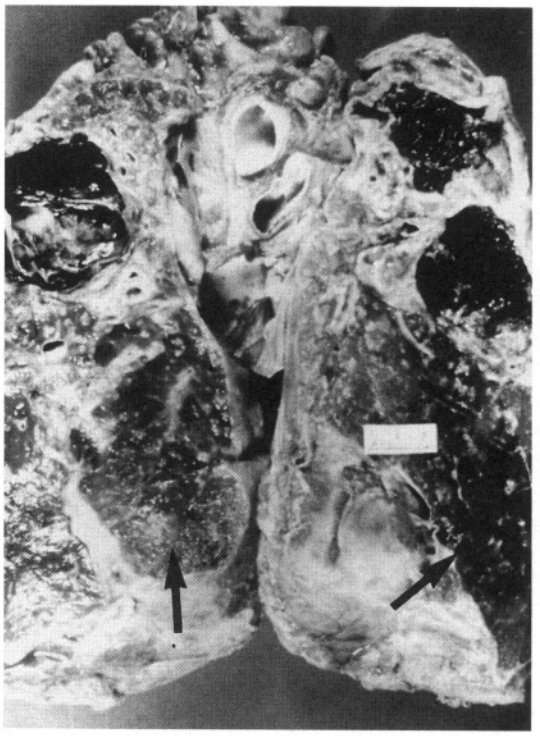

FIGURE 7. Photograph of right lung of patient. The black material in the cavity is the aspergilloma. *Aspergillus niger* was isolated. The consolidated areas of lung (arrows) represent pneumonia due to invasive aspergillosis.

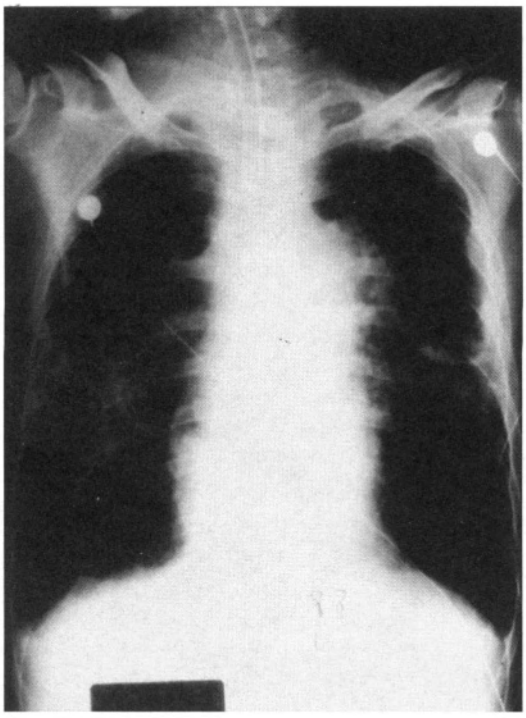

FIGURE 6. Chest radiograph of patient with sarcoidosis and severe asthma. Patient was given corticosteroid therapy for asthma and developed invasive aspergillosis secondary to aspergilloma in a right lung cavity, which is not well seen on this radiograph. A right midzone opacity is evident.

Diagnosis

The diagnosis of invasive aspergillosis requires a high index of suspicion. In a hospital setting where an outbreak is suspected nose cultures of patients who are at risk are useful (Aisner et al., 1979). In this setting if an immunocompromised patient has pulmonary infiltrates and a positive nose culture for *Aspergillus*, the likelihood of invasive *Aspergillus* infection is high (Aisner et al., 1979). Sputum is insensitive for the diagnosis of invasive pulmonary aspergillosis: 15% to 69% of patients with this diagnosis had positive cultures before death (Horvath & Dummer, 1996). Bronchoalveolar

FIGURE 8. Pleural surface of lung shown in Figure 7. Note the small abscesses (arrows) due to *Aspergillus* infection.

lavage and bronchial brushings are positive in <50% of patients with invasive pulmonary aspergillosis (Horvath & Dummer, 1996). Various assays have been devised to detect *Aspergillus* antigens in serum or in respiratory secretions. Verweij et al. (1995) used a sandwich ELISA, which detects *Aspergillus galactomannan*, and PCR with two *Aspergillus*-specific primers on serum and bronchoalveolar lavage fluid. Of seven patients with probable aspergillosis, five were PCR-positive and five were ELISA-positive.

Treatment

Amphotericin B is the treatment of choice for invasive aspergillosis. Its effectiveness is dose-related. In neutropenic rabbits infected with *A. fumigatus* amphotericin B at a dose of 1.5 mg/kg could eradicate the infection, while at 0.5 mg/kg it could not (George et al., 1996). High doses of amphotericin B are necessary to treat invasive pulmonary aspergillosis, usually 1 to 1.5 mg/kg/day. These patients are very ill and often have impaired renal function, which is made worse by high doses of amphotericin B. A number of lipid preparations of amphotericin B are now available. These preparations greatly reduce the nephrotoxicity of amphotericin B. Amphotericin B liposomal preparation (AmBisome) is given in a dose of 4 to 5 mg/kg/day; amphotericin B colloidal dispersion (Amphocil, Amphotec) and amphotericin B lipid complex (Abelcet) are other preparations that are also given in doses of 4 to 5 mg/kg/day. The total dose of amphotericin B to treat invasive aspergillosis is 30 to 40 mg/kg; for the amphotericin B lipid preparations the total dose is 150 to 200 mg/kg. There is a suggestion that combination therapy is better than monotherapy. Flucytosine is synergistic with amphotericin B in vitro and in animal experiments (Arroyo et al., 1977; Polak et al., 1982). Many authorities recommend adding flucytosine 100 mg/kg/day to amphotericin B to treat invasive aspergillosis. Itraconazole, a triazole antifungal agent that is only available for oral administration, has activity against *Aspergillus* spp. It has poor absorption and is useful as follow-up therapy once a good response to amphotericin B therapy has occurred.

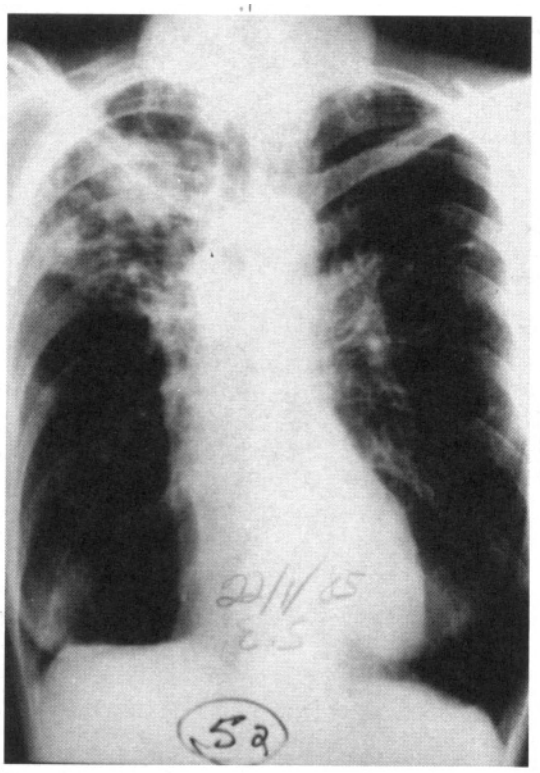

FIGURE 9. Chest radiograph of patient with chronic necrotizing aspergillosis. Note the right upper-lobe opacity. In the center of this is a rounded opacity which developed into an aspergilloma.

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Pneumocystis carinii Pneumonia

VALENTINA CARLA MONTESSORI AND JULIO S. G. MONTANER

Introduction

A number of factors have been shown to favor the development *Pneumocystis carinii* pneumonia (PCP), including malnutrition, chemotherapy, corticosteroid therapy, and, more recently, HIV infection. All have in common the presence of cellular immunodeficiency (Arend et al., 1995). Over the past 15 years, however, most of the attention has been focused on PCP developing in the context of HIV infection. Initially PCP was, together with Kaposi's sarcoma, the index disease that facilitated the recognition of AIDS as a new disease. PCP rapidly became the most frequent serious opportunistic infection among HIV-infected patients in the developed world. Today, PCP is the first major AIDS-related opportunistic infection for which therapeutic developments over the last decade have raised the possibility of complete control (Centers for Disease Control and Prevention, 1992; Jones et al., 1998). Extrapulmonary infection with *Pneumocystis carinii* has been described in several organ systems (Phair et al., 1990). However, this discussion will be primarily limited to PCP.

P. carinii remains a difficult organism to grow in cell-free media. Recently, with the aid of molecular biology, this organism has been characterized as a fungus, largely on the basis of its genomic characteristics. A number of questions, however, remain unanswered regarding its biological properties (Stringer, 1993; Edman & Sogin, 1994; The Pneumocystis Workshop, 1994), and the debate as to its taxonomy continues.

P. carinii infection is usually, but not exclusively, confined to the lungs. The characteristic pathological picture, as seen with hematoxylin and eosin (H & E) staining, is a mild-to-moderate interstitial inflammatory reaction with a predominance of lymphocytes and alveolar macrophages and the presence of a foamy alveolar exudate (Kimetal, 1987). The foamy appearance of the alveolar exudate is a result of the presence of *P. carinii* cysts, which are not readily stained with H & E but can be easily recognized with special stains such as silver or methylene-O-blue (The Pneumocystis Workshop, 1994). Bronchoalveolar lavage studies have shown that this is an inflammatory exudate rich in immunoglobulins, macrophages, and suppressor/cytotoxic lymphocytes (Escamilla et al., 1992).

Epidemiology

P. carinii is a ubiquitous organism, recognized to produce human disease throughout the world. Serological studies provide evidence that asymptomatic primary *P. carinii* infection generally occurs early in life. Rarely, organisms can be incidentally found at autopsy in the absence of symptoms. It is not clear, however, whether this represents latent infection or early disease not yet clinically manifested. PCP usually represents reactivation of earlier infection. However, airborne transmission of the organism is possible and has been demonstrated in animal models. Whether airborne transmission

VALENTINA CARLA MONTESSORI AND JULIO S. G. MONTANER • British Columbia Centre for Excellence in HIV/A1DS and Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

plays a significant role in clinical practice remains unclear.

In the first decade of the AIDS epidemic it was estimated that in North America PCP represented the AIDS index disease in 65% of cases and eventually developed in over 85% of patients during their lifetime (Murray et al., 1984; Stover et al., 1985). The prevalence of PCP declined slightly with the introduction of PCP prophylaxis (with trimethoprim–sulfamethoxazole [TMP-SMX], dapsone, or aerosolized pentamidine) in the late 1980's (Forrest et al., 1998). The incidence of PCP, as well as that of every other AIDS-related complication, has declined sharply with the introduction of potent triple-drug antiretroviral therapy regimens (Jones et al., 1998; Forrest et al., 1998).

The development of PCP remains, generally, a late event in the evolution of HIV infection. The risk of developing this complication increases rapidly as the CD4 or helper T-cell count decreases, particularly below 200/mm^3 or 15% of the absolute lymphocyte count (Polk et al., 1987). The risk of developing PCP is also particularly high among HIV-infected individuals who have had previous episodes of oral candidiasis, or systemic symptoms, such as unexplained fevers or weight loss or those who have had other AIDS-defining conditions (CDC, 1992). Prophylaxis failures have been associated with declining CD4 cell counts and the use of prophylaxis regimens other than TMP-SMX (Saah et al., 1995).

Clinical Features

Shortness of breath, nonproductive cough, and fever are the typical features of PCP. The chest x-ray usually demonstrates a bilateral interstitial pattern of varying severity. Less commonly, pneumothoraces, cavities, nodular densities, consolidation, or diffuse air space filling can be seen. As awareness increases, more cases are recognized at an earlier stage when there are no obvious radiological abnormalities. On clinical examination, the chest is generally clear, which can be in sharp contrast to the degree of radiological involvement.

A number of laboratory markers have been found to be useful in assessing the severity of a PCP episode. Among them are an elevated level of lactate dehydrogenase (LDH), a decreased lung diffusion (DLco), an increased uptake of radiolabeled gallium, an enhanced lung clearance of Tc-DTPA aerosol and oxygen desaturation at rest or with exercise. Although these markers may be used in the initial evaluation or follow-up of individual patients, they cannot be used to confirm the etiological diagnosis. Earlier suggestions regarding the diagnostic value of an elevated LDH level have recently been refuted (Kagawa et al., 1988; Garay & Greene, 1989; Quist & Hill, 1995; Boldt & Bari, 1997).

Microbiological Diagnosis

P. carinii cannot be readily cultured in the laboratory; thus, the diagnosis of PCP relies heavily on the microscopic demonstration of the characteristic organisms in respiratory specimens. A variety of approaches have been proposed to obtain suitable specimens for microbiological assessment. Induced sputum and/or brochoalveolar lavage (BAL) are the most commonly used means to obtain suitable samples for microbiological confirmation of a suspected diagnosis of PCP (Leigh et al., 1989; Torrington & Finelli, 1995; Hopewell, 1988a, b). Expectorated sputum is unsuitable for this purpose. Transbronchial biopsies are generally not recommended in this context as they can significantly increase morbidity without enhancing the diagnostic yield of the procedure (Broaddus et al., 1985).

A typical algorithm for obtaining respiratory specimens would suggest that induced sputum be used as a screening tool (Bigby et al., 1986). If the sputum examination fails to confirm the diagnosis of PCP, a BAL should be performed. Where sputum induction is not routinely available, BAL is preferred. A negative induced sputum is not sufficient evidence to rule out the diagnosis of PCP.

Sputum induction has been shown to be rapid and cost-effective, particularly in centers handling large numbers of PCP cases. The reported sensitivity of induced sputum combined with immunofluorescent techniques involving monoclonal antibodies against *P. carinii* ranges from 55% to 75% with a negative predictive value of approximately 60% (Kovacs et al., 1988). It should be emphasized that the diagnostic yield of sputum induction varies greatly between institutions, as a function of ex-

perience and case load. In addition, the value of sputum induction is diminished in patients who present with early or mild PCP or those who experience break through episodes while receiving aerosol pentamidine prophylaxis or while receiving therapy (Leigh et al., 1989; Hopewell et al., 1988 a, b; Bigby et al., 1986).

Torrington and Finelli (1995) reported on the usefulness of small-volume BAL, which consists of three to four 60-mL aliquots of room-temperature, sterile, saline solution, in the diagnosis of AIDS-related PCP. Each syringe of BAL effluent was numbered and its volume measured. Immunofluorescent stains were performed on 8-mL aliquots of the initial, final, and aggregate specimens. A modified Giemsa stain was also performed on a 0.4-mL aliquot of the aggregate specimen. Both staining methods were 100% specific (95% confidence interval [CI], 83%–100%) and 100% sensitive (95% CI, 72%–100%). The volume of lavage effluent in the initial specimens positive for *P. carinii* ranged from 15 to 25 mL. The authors concluded that a single 60-mL BAL specimen stained with immunofluorescent methods may suffice to confirm the diagnosis of PCP (Torrington & Finelli, 1995).

A number of staining techniques can be used to identify *P. carinii* in appropriate specimens. The Papanicolaou or Wright Giemsa stains are commonly used to recognize the trophozoites in patients with large numbers of organisms (Hopewell, 1988a, b). Both stains are widely available and inexpensive and can be performed rapidly.

P. carinii DNA fragments have been sequenced from the lung tissue of rats with experimentally induced PCP as well as from infected humans (Wakefield et al., 1990a). Since then, PCR-mediated amplification of *P. carinii* genes from respiratory samples has become possible (Wakefield et al., 1990b; Evans et al., 1995). PCR from induced sputum has been reported to have a sensitivity and specificity approaching 100%. A recent analysis of the cost-effectiveness of this technique, however, supports the ongoing use of BAL to diagnose PCP (Chouard et al., 1995).

Other Laboratory Tools

Although the definitive diagnosis of *P. carinii* requires identification of the organism as described previously, a number of laboratory procedures have been shown to contribute to the overall management of the disease. Among them, the serum LDH level, the arterial blood gases, oxygen saturation with exercise, and nuclear medicine techniques such as gallium scan and TC-DTPA clearance scan have proven of value in the initial assessment, prognostic stratification, and monitoring of individuals with PCP (Hopewell, 1988a, b). In addition, the CD4 cell count is important in assessing individual patient risk for PCP.

CD4 Lymphocyte Counts

CD4 lymphocyte counts have long been regarded as a valuable laboratory tool in the staging of HIV disease. Both the absolute and relative number of CD4 lymphocytes have been shown to correlate inversely with the risk of developing PCP in several retrospective and prospective studies. Some investigators prefer to use CD4 percentages because this measurement is less variable than the absolute count and is measured directly by the flow cytometer. However, there is no definitive evidence that one marker is superior to the other in its ability to predict the degree of immunosuppression or, more importantly for the purpose of this discussion, the risk for developing PCP. Data from the Multicenter AIDS Cohort Study (MACS) demonstrate that the cumulative incidence of PCP rises significantly once the absolute CD4 count is below 200 or the CD4 fraction is below 11% (Saah et al., 1995). In general, the risk of developing PCP is regarded as negligible as long as the CD4 count remains above $200/mm^3$ or 15%. In the absence of a CD4 count, lymphopenia or the presence of constitutional symptoms or even minor opportunistic infections, such as oral candidiasis, carry a similar prognostic value.

Saah et al. (1995) studied the predictors for failure of PCP prophylaxis within the MACS. CD4 lymphocyte count was found to be the main predictor for failure of PCP prophylaxis. In this study, 86% of failures occurred after the CD4 count decreased to $<75/mm^3$, and 76% occurred after counts decreased to $<50/mm^3$. In multivariate time-dependent analysis, the risk ratio for failure with counts $<50/mm^3$ was 2.90 ($P < 0.001$) compared with counts between $100/mm^3$ and $200/mm^3$.

Arterial Blood Gases

Arterial blood gases generally show increase in the A–a gradient of varying degrees during a PCP episode. Partial oxygen pressure in arterial blood, however, can vary widely depending on the severity of the process. Up to 25% of patients may have a Pao_2 >80 mm Hg while breathing room air. Pao_2 and the A–a gradient have been shown to correlate with disease severity and prognosis of the PCP episode. Additionally, most AIDS patients with PCP will show worsening hypoxemia within 24 to 72 hours of starting therapy. The mechanism of this early hypoxemia has not been fully elucidated. It is generally felt that initiation of therapy exacerbates the inflammatory process characteristically present in the lungs among patients with PCP (Montaner et al., 1990; Guillemi et al., 1995). Corticosteroids have been shown to prevent this early deterioration when given as adjuncts to the specific antimicrobial therapy (Montaner et al., 1990; Guillemi et al., 1995; Bozzette et al., 1990).

Arterial blood gases on room air are used to classify the PCP episode as mild (Pao_2, >90 mm Hg or PA–ao_2, <35), moderate (Pao_2 >60 mm Hg or PA–ao_2, 36–45 mm Hg), or severe (Pao_2 <60 mm Hg or PA–ao_2, >45 mm Hg). This classification has prognostic and therapeutic implications (NIH, 1990). The risk of death from AIDS-related PCP has been shown to rise sharply once the partial pressure of oxygen decreases below 75 mm Hg. Also, as discussed later in this chapter, adjunctive corticosteroids are currently recommended for patients with moderate and severe PCP.

As many as 36% of patients with PCP can have a normal A–a gradient at rest. Stover et al. (1989) have shown that the A–a gradient with exercise is more sensitive than the resting value in this context. They studied a total of 57 HIV-infected patients who had arterial blood gases performed at rest and during exercise. A total of 22 patients had PCP, 15 had pulmonary Kaposi's sarcoma, 7 had cytomegalovirus pneumonia, and 13 had nonspecific pulmonary disease. The exercise protocol consisted of 1.5 minutes of exercise using a Masters two-step staircase. Blood gases were monitored using an indwelling catheter into the radial artery. While only 64% of PCP patients had an A–a gradient >20 mm Hg at rest, 91% had an abnormal exercise test as defined by an increase in the A–a gradient with exercise >10 mm Hg. The exercise test, therefore, had a 91% sensitivity and a 77% specificity for PCP in this group of patients. Similar findings were reported by Smith et al. (1988), who found that exercise hypoxemia was present in 80% of patients with PCP who had a normal oxygen pressure at rest, whereas only 10% of HIV-infected patients with other chest disorders showed significant desaturation during exercise.

Pulse oximetry has been successfully used as a noninvasive alternative to the arterial blood gases. This has proved a valuable tool in identifying patients with mild AIDS-related PCP as they will have a resting oxygen saturation >90% while breathing room air. Pulse oximetry has also been successfully used to identify exercise-related hypoxemia.

Pulmonary Function Tests

Abnormalities in lung volumes, spirometry, and diffusing capacity have been reported with varying frequency in patients with AIDS-related PCP. Although a low diffusing capacity for carbon monoxide (DLco) and lung volumes, such as vital capacity (VC), are relatively frequent in PCP, these findings lack specificity. Mitchell et al. (1993) conducted serial pulmonary function tests in patients with HIV infection. A total of 118 patients who developed respiratory illness were prospectively followed with measurements of lung function. In 36 patients in whom PCP was diagnosed, monthly lung function tests showed a decrease in DLco from 68 ± 3% of predicted 8 weeks prior to diagnosis to 44 ± 3% of predicted at the time of diagnosis. The pulmonary function test in 22 patients who did not have PCP demonstrated a decrease in DLco from 71 ± 5% to 57 ± 3%. Although a decrease in DLco was present in all HIV-infected patients, the reduction in this parameter was significantly ($P < 0.05$) greater among those who developed PCP. A decrease in DLco of 5% from initial values had a sensitivity of 75% and a specificity of 28% with a positive predictive value of 56% and a negative predictive value of 48% as a diagnostic marker of PCP in this study. In a second group of patients undergoing a single lung function test, the

DLco was <70% of the predicted value in 72 of 78 patients with PCP. The sensitivity was therefore estimated at 92% and specificity at 71% with a positive predictive value of 34% and a negative predictive value of 98%.

The changes in DLco have been associated with changes in other parameters such as the forced vital capacity (FVC). A marked decline in FVC was documented in the month prior to the diagnosis of PCP. This decline was found to be less marked in patients who had non-PCP respiratory disease. Similarly, the nadir FVC was significantly lower in the PCP group than in the acute non-PCP respiratory disease group ($P < 0.05$). Changes in pulmonary function tests are not specific enough to contribute to a positive diagnosis of AIDS-related PCP. However, the high negative predictive value of a single DLco measurement can be of value in that a normal DLco can virtually exclude a diagnosis of PCP in an HIV-infected individual.

Spirometric changes, particularly airways obstruction and hyperactive airways disease, have been reported to occur with increased frequency among HIV-infected individuals. Spirometric changes, however, are not specific in patients with AIDS-related PCP. Aerosol pentamidine, which is often used for PCP prophylaxis, has been shown to be frequently associated with cough and bronchospasm. Forced expiratory volume in the first minute (FEV^1) changed following the first dose of aerosol pentamidine at a mean of −7% (range, +1.82% to −47%) in 53 consecutive patients starting aerosol pentamidine at St. Paul's Hospital (Quieffin et al., 1991). Methacholine challenge was performed in 51 of these, confirming a statistically significant relationship between nonspecific bronchial hyperresponsiveness and aerosol pentamidine-associated bronchoconstriction. Despite this association, the positive and negative predictive values for the PC20 (provocative concentration required to produce a 20% fall in FEV [forced expiratory volume in the 1st second]) with methacholine, even at the optimal threshold of 32 mg/mL, were not sufficiently high to warrant the use of methacholine challenge as a clinical predictor of aerosol pentamidine-induced bronchospasm. Furthermore, given the demonstrated ability of salbutamol to prevent the aerosol pentamidine-induced bronchospasm, liberal use of premedication with salbutamol is anticipated to be a more cost-effective approach.

Imaging Techniques

There is no specific radiological presentation of AIDS-related PCP. A diffuse or perihilar interstitial infiltration has been described as the most distinctive radiological feature of PCP (Hopewell, 1988a, b). Despite standard treatment, this pattern can evolve to a diffuse air space consolidation with acinar infiltrates and air bronchograms or the radiographic pattern of adult respiratory distress syndrome (ARDS). Up to one third of patients can present with asymmetric or predominantly upper lobe infiltrates, especially among those who have received aerosol pentamidine prophylaxis (Baughman et al., 1993; Moe & Hardy, 1994). A normal chest x-ray can be found in approximately 20% of PCP patients (Golden & Sollitto, 1988). Less frequent presentations include bullae and cystic changes, pneumothorax, nodular or mass-like densities, cavitary lesions, hilar or mediastinal adenopathy, and pleural effusions. These atypical features can be the result of infection by *P. carinii* itself or concomitant infections or tumors (Moe & Hardy, 1994).

The extent of radiological involvement at presentation has been shown to parallel indicators of clinical outcome (Opravil et al., 1994). Normal chest radiographs have been associated with mild symptoms and low serum LDH but images of air space consolidation were more likely observed in the chest x-rays of patients with severe PCP.

On follow-up, most of the patients who respond to therapy demonstrate a progressive clearing of radiographic infiltrates within 2 months (Federle, 1988; De Lorenzo et al., 1987). A protracted course of PCP with persistent focal lesions has been suggested to represent chronic forms of the disease (Wasserman et al., 1993). Although linear opacities can be observed on chest x-rays after successful treatment, residual parenchymal damage is better assessed by imaging techniques of higher resolution. Standard and high-resolution computed tomography (HRCT) provide more information regarding lung interstitial processes than those provided by plain films. Not surprisingly, CT and HRCT provide better definition of PCP lesions.

Unsuspected changes in those cases with normal chest radiographs have been described such as regional consolidation, cystic air spaces, and subpleural sparing (Moskovic et al., 1990; Bergin et al., 1990; Guillemi et al., 1996).

Since gallium lung scan is more sensitive than the chest radiograph in detecting parenchymal lung disease, it has been extensively used to assess patients with a clinical suspicion of PCP and normal or equivocal chest roentgenograms (Golden & Sollitto, 1988). In fact, a positive gallium scan can precede the chest radiographic changes by weeks in this setting (Bekerman & Bitran, 1988). In addition, resolution of abnormal lung uptake can be observed promptly after initiation of successful treatment. An intense and diffuse pulmonary uptake of ^{67}Ga has been reported as highly specific for PCP in the context of HIV disease (Golden & Sollitto, 1988). It has been reported, however, that the characteristic pattern described in PCP may not be present if the patient has received aerosol pentamidine. From a practical standpoint, however, it should be noted that ^{67}Ga scanning may require up to 3 days to perform (Hopewell, 1988). The best sensitivity of ^{67}Ga scanning is achieved 48 to 72 hours after the administration of the radionuclide. Also, the sensitivity of ^{67}Ga scanning is substantially increased when it is combined with pulmonary function tests.

Alveolar clearance of the inhaled radioaerosol, technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), provides an index of pulmonary epithelial permeability to solutes. Patients with early PCP generally present with an increased clearance of ^{99m}Tc-DPTA. Of note, this may precede abnormalities of arterial blood gases, chest x-ray, and abnormal uptake of ^{67}Ga (Picard et al.. 1987). Unfortunately, this test is also rather nonspecific.

Prognosis

Untreated AIDS-related PCP is universally fatal. With the use of appropriate antimicrobial therapy the mortality has been dramatically improved. The overall mortality of AIDS-related PCP was approximately 20% before the introduction of triple-drug antiretroviral therapy. This clearly varies with the severity of the episode, and to a lesser extent with the number of prior PCP episodes. The mortality of a mild first episode of PCP, therefore, is usually negligible. In contrast, $Pao^2 < 50$ mm Hg while breathing room air is associated with a mortality > 30%. Furthermore, patients with respiratory failure requiring mechanical ventilation have been reported to have a mortality of up to 100% in some series. In general, young age, early diagnosis, aggressive antimicrobial therapy, and early initiation of adjunctive corticosteroids have been shown to correlate with improved survival.

Treatment

Antimicrobials

TMP-SMX, systemic pentamidine, and dapsone are the most commonly used drugs for the treatment of PCP. Although these agents appear to have comparable effectiveness, at least one study has suggested that, for those patients who are able to tolerate it, TMP-SMX may be superior to other treatment options such as systemic pentamidine (Wharton et al., 1986; Settler et al., 1988).

TMP-SMX is an antibacterial agent effective against many gram-negative and gram-positive organisms. For the treatment of PCP, it is administered intravenously or orally at doses of 20 and 100 mg/kg/day, respectively, in four divided doses for not less than 14 days. Adverse reactions have been reported to occur in 60 to 100% of treated patients. These include rash, fever, liver dysfunction, renal dysfunction, leukopenia, thrombocytopenia, hyponatremia, anemia, and GI upset, which often interferes with oral administration. Less common, but at times severe, are mucocutaneous reactions, pancreatitis, mental status changes, and hypocalcemia. Approximately 50% of patients will eventually require discontinuation of therapy due to the development of adverse reactions, occurring generally at the end of the first week of treatment. A number of reports have documented successful desensitization using progressively larger doses of the drug. Hypersensitivity type reactions such as fever or rash can also be successfully treated with diphenhydramine or corticosteroids.

Pentamidine isothionate was initially used for the treatment of trypanosomiasis. Since 1958, it has

been known to be effective against PCP. Although initially used intramuscularly, this practice has been discontinued because of local complications. Pentamidine, therefore, is usually administered intravenously once daily at a dose of 4 mg/kg diluted in 250 cc D5W for not less than 14 and preferably for 21 days. Adverse reactions, including renal or liver dysfunction, neutropenia, thrombocytopenia, hyponatremia, rash, fever, and GI upset, are common. Occasionally severe and long-lasting hypotension or carbohydrate metabolism abnormalities may develop. In some instances, the latter result in the development of insulin-dependent diabetes. Less commonly, ventricular arrhythmias or pancreatitis have been reported. Because adverse reactions to pentamidine are related to the systemic level of the drug and because it is poorly absorbed through the alveolar surface, attention has turned to the potential value of aerosol therapy. Unfortunately, the success rate of treatment with aerosol pentamidine has been disappointing and therefore this practice has been abandoned (Soo Hoo et al., 1990; Conte et al., 1990).

Dapsone, a sulfone used for the treatment of leprosy and dermatitis herpetiformis, has been shown to be effective in PCP. This is particularly the case when oral dapsone 100 mg/day is combined with oral TMP 20 mg/kg/day in four divided doses. Adverse reactions include dose-dependent hemolytic anemia with methemoglobinemia, thrombocytopenia, neutropenia, liver dysfunction, rash, and GI upset that can interfere with oral administration. The hemolytic anemia with methemoglobinemia is particularly severe among individuals with glucose-6-dehydrogenase deficiency. Possible treatment alternatives include clindamycin (300 to 450 mg every 6 hours) and daily primaquine (15 mg base) or atovaquone 750 mg orally three times a day (Toma et al., 1989; Dohn et al., 1994; Hughes et al., 1993).

Corticosteroids

Adjunctive corticosteroids have been repeatedly shown to improve the outcome of AIDS-related PCP. Prospective, placebo-controlled studies have demonstrated decreased mortality, faster and steadier resolution of hypoxemia, as well as a sustained increase in exercise tolerance up to a month after the diagnosis of PCP (Montaner et al., 1990; Guillemi et al., 1995; Bozzette et al., 1990; NIH, 1990). An added benefit of steroid therapy is the prevention of antimicrobial-related adverse events.

Consensus statement guidelines recommend the use of adjunctive corticosteroids in patients with PCP and moderate or severe pulmonary dysfunction, as defined by an arterial oxygen pressure of less than 70 mm Hg or an arterial-alveolar gradient of more than 35 mm Hg. The recommended regimen is 40 mg of oral prednisone given twice a day on days 1 through 5, 40 mg daily on days 6 through 10, and 20 mg daily on days 11 through 21 (NIH, 1990). Although patients with milder hypoxemia may benefit from corticosteroids, the ultimate benefit of this intervention has not yet been proven in randomized controlled trails.

Selecting a Therapeutic Regimen

From a practical standpoint, PCP patients can be divided into those with mild, moderate, or severe disease on the basis of their degree of respiratory distress and laboratory parameters. Mild disease can usually be treated in an outpatient setting with oral dapsone (100 mg per day) with trimethoprim (800 mg per day divided in four doses). Alternative oral regimens include TMP-SMX (two double-strength tablets four times daily), or possibly clindamycin-primaquine or atovaquone.

Moderate to severe disease will often require hospitalization. These patients are best started on treatment with intravenous TMP-SMX or pentamidine. Patients presenting with severe disease should be offered mechanical ventilation, if warranted. Patients with moderate to severe PCP should be given adjunctive corticosteroid therapy.

Drug choice may also be dictated by a number of special circumstances. TMP-SMX, given its broad antibacterial spectrum, should be preferentially used in the presence of a concomitant bacterial pneumonia. This agent is also preferred (in reduced doses) if there is evidence of renal impairment. On the other hand, pentamidine is favored in the presence of sulfa-drug allergy, when fluid restriction is necessary, or when preexisting bone marrow dysfunction is present. Finally, a lack of response to one of these agents, after not less than 5 days of continued therapy, would dictate a change

to one of the alternative agents. It must be emphasized that there is no evidence that combining TMP-SMX with pentamidine enhances therapeutic success; in fact, this combination gives rise to increased toxicity.

PCP in the Intensive Care Unit

Acute respiratory failure in the setting of AIDS-related PCP has been associated with high in-hospital mortality (Hawley et al., 1994; Rosen & De Palo, 1993; Wachter & Luce, 1994). However, this has been variable through the AIDS epidemic (Wachter & Luce, 1994). In the early years of the epidemic (1981–1985), outcomes were reported as universally poor with survival to discharge of less than 10%. This was followed by a second era (1986–1988) characterized by an improved survival to hospital discharge of approximately 40%, mostly attributed to the increased use of adjuvant corticosteroids. More recently (1989 to date) there has been a decrease in survival to hospital discharge to 25% or less (Hawley et al., 1994; Wachter & Luce, 1994; Montaner et al., 1992; Staikowsky et al., 1993). In this context, Staikowsky et al. (1993) have shown that mortality among patients who develop respiratory failure after at least 5 days of combined therapy with anti-PCP drugs and adjuvant corticosteroids was 95%, compared with only 50% among patients treated with fewer than 5 days of combined therapy. Also, a study by Forrest et al. (1998) examined prognostic variables in patients with respiratory failure and PCP. In this study the duration of maximal therapy (including combined anti-PCP and corticosteroids prior to the development of respiratory failure) and the multi-system organ failure (MSOF) score were highly predictive of in-hospital mortality. Patients who had been maximally treated for fewer than 5 days prior to the onset of respiratory failure had a mortality rate of 47%, while those who were treated for at least 5 days prior to the onset of respiratory failure had a mortality rate in hospital of 89%. This confirms the findings of Staikowsky et al. (1993), who identified a mortality rate of 95% among patients who had received at least 5 days of combined therapy prior to the onset of respiratory failure. An increment in the MSOF score was also predictive of poor outcome, each increment increasing the odds of dying approximately 3.9 times. Patients who had an MSOF score of 3 or more had a mortality of 100% (Forrest et al., 1994). This validates earlier work demonstrating the predictive value of the modified MSOF score (Montaner et al., 1992). The outcome of patients who had a combination of a high MSOF score (>1) and who have received more prolonged maximal therapy ($\geq$5 days) had an extremely poor prognosis, and a mortality in this cohort of 100% (Montaner et al., 1992).

Prophylaxis

Early experience with chemotherapy-induced immunosuppression demonstrated that PCP can be successfully prevented using TMP-SMX. One single- and one double-strength tablet daily have comparable effectiveness. In other words, what can be gained in efficacy with a higher dose is compromised because of increased adverse effects (Schneider et al., 1995). A simple practical solution is to offer one double-strength tablet daily to reserve the single tablet daily for those who cannot tolerate the full regimen. Treatment guidelines support dapsone 100 mg daily as second-line prophylaxis (Masur, 1992). A number of studies have also demonstrated the short-term safety and efficacy of intermittent aerosolized pentamidine in the prevention of PCP (Montaner et al., 1991). A regimen of 300 mg monthly via a continuous flow-driven nebulizer has been shown to be effective (Montaner et al., 1991; Leoung et al., 1990). Common to either schedule is the approximately 10% of patients who may experience mild cough and bronchospasm which responds to an inhaled beta ^{2}-agonist bronchodilator (Quieffin et al., 1991).

In addition, recent work has compared atovaquone suspension to dapsone or aerosol pentamidine for the prevention of PCP (El-Sader et al., 1998; Chan et al., 1999). Among those patients unable to tolerate prophylaxis with TMP-SMX, atovaquone (1500 mg suspension daily) and dapsone were similarly effective for the prevention of PCP.

Conclusion

PCP is a life-threatening complication in patients with AIDS and other forms of cellular immunodeficiency. Despite the availability of effective

prophylaxis, PCP remains one of the most common respiratory infections related to HIV disease. In this population, susceptible to a variety of opportunistic lung pathogens, clinical manifestations, radiological features, and blood chemistry due to PCP are often nonspecific. Clinical suspicion and diagnostic investigations are of great importance in the diagnosis and successful treatment of PCP.

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Group B Streptococcal and Other Non-Pneumococcal Streptococcal Pneumonia

JAMES W. MYERS AND STEVEN L. BERK

Introduction

Group A and B streptococci rarely cause pneumonia. Other streptococci from groups C and G and enterococci are also uncommon causes of pneumonia. Although not as prevalent as *Streptococus pneumoniae* (Fang et al., 1990), these organisms can still be the cause of significant morbidity and mortality in susceptible hosts. This chapter reviews the pertinent features of each of these nonpneumococcal causes of pneumonia.

Group B Beta-Hemolytic Streptococcal Pneumonia

Microbiology

When cultured on sheep blood agar, group B streptococci (GBS) form a zone of beta-hemolysis. The colonies of GBS are somewhat larger, but form a more narrow zone of hemolysis, than those of group A streptococci. They are facultative diplococci. Presumptive identification of GBS may be made by the hydrolysis of sodium hippurate and bile esculin. More than 90% of strains are resistant to bacitracin. More than 98% of GBS produce an extracellular protein called CAMP factor than can be used in their identification. This extracellular protein produces synergistic hemolysis on blood agar with the beta-lysin of *Staphylococcus aureus.* Definitive identification of GBS is usually made serologically using antiserum.

The common group B antigen is a complex polysaccharide of rhamnose, *N*-acetyglucosamine, and glycerol phosphate. Strains of GBS can also be divided into serotypes based on the antigenic differences in a carbohydrate antigen, distinct from the group B carbohydrate, called the type-specific antigen. There are five subtypes based on this second carbohydrate antigen. These are Ia, Ib, Ic, II, and III. Additional types IV, V, VI, VII, and VIII were subsequently identified. Recent data (Blumberg et al., 1994) suggest that type V is common in infections among infants and may be a predominant serotype in adult disease. Type III strains of GBS have been isolated from most newborns who have early-onset infection, usually meningitis. This serotype also accounts for the majority of late-onset infections, either meningitis or pneumonia (Baker & Barrett, 1974).

Predisposing Factors for Infections in Adults

Adults with group B bacteremia include the elderly, but the age distribution ranges from 18 to 99 years (Verghese et al., 1986). Schwartz and col-

JAMES W. MYERS AND STEVEN L. BERK • James H . Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee 37614.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

leagues (1991) studied the incidence of invasive group B streptococcal disease in adults. This was a population-based study in metropolitan Atlanta between the years of 1982 and 1983. Fifty-six nonpregnant adults were identified with infection. There was an incidence of GBS infection of 2.4 cases per 100,000. The incidence was higher in blacks than in whites, and in males than females, and it increased with age. The case-fatality rate was noted to be 32%. The GBS was most often isolated from blood and soft tissue. Pneumonia accounted for 11% of the total. Compared with the general population, the risk of infection for a person with diabetes was increased to 10.5-fold. In those patients who had cancer, it was increased 16-fold. In a 1-year study at our 500-bed Veterans Administration hospital, GBS were isolated from the sputum of 35 patients, 10 of whom had definite evidence of pneumonia (Ekenna et al., 1988). Neurological conditions and alcohol have also been cited as risk factors for group B streptococcal disease.

Jackson and colleagues (1995) have also investigated risk factors for group B streptococcal disease in adults. They performed a case–control study that involved three metropolitan areas in the United States with an aggregate population of 6.6 million persons. Two hundred and nineteen nonpregnant adults with invasive group B streptococcal infection were identified between 1981 and 1992. Conditions noted with a significant odds ratio included diabetes, stroke, breast cancer, decubitus ulcers, and neurogenic bladder. Nosocomial infection was independently associated with placement of a central venous line, diabetes, congestive heart failure, and a seizure disorder. Pneumonia was found to account for 12% of cases in this series.

Clinical Features

GBS pneumonia has been described in bacteremic patients, and in patients who were diagnosed by transtracheal aspiration. Patients are usually described as being tachycardiac and tachypneic. The average temperature is 39°C, and leukocyte counts are often elevated above 15,000/mm^3. The mortality rate has ranged from 50% to 100%, but the severity of underlying disease plays a significant role in outcome. It may be found with other copathogens, particularly *S. aureus* (Bayer et al., 1976). Necrotizing pneumonia has been reported, but unlike pneumonia caused by group A beta-hemolytic streptococci, this organism rarely causes empyema (George & Savage, 1987). In one series (Verghese et al., 1982), the most common roentgenographic finding was bilateral infiltrates, although one patient had left lower-lobe consolidation with effusion, another patient had a left lower-lobe infiltrate with a pneumothorax, and one patient had a consolidated right lower-lob infiltrate.

Antibiotic Therapy

Penicillin G is the drug of choice when the diagnosis is established in adults. The organisms are also susceptible to ampicillin, vancomycin, and cephalosporins. Among the quinolones, ciprofloxacin would be expected to have less activity than the newer fluoroquinolones. Resistance to erythromycin, clindamycin, and clarithromycin occurs in 1% to 3% of isolates (Edwards & Baker, 1990). Higher doses of penicillin G (10–12 million units/day) may be needed because the minimum inhibitory concentrations (MICs) of penicillin are 4-fold to 10-fold greater for group B than for group A organisms. For serious infections including bacteremia pneumonia, treatment for at least 10 to 14 days appears to be adequate, although there are few data to make firm recommendations. Mixed infections may require broader antibiotic coverage.

Group C Streptococci

Microbiology and Epidemiology

Most group C beta-hemolytic streptococci produce beta-hemolysins on sheep blood agar, although other forms of hemolysis have been noted (Plummer, 1941). Group C streptococci generally are large colony-size ($\geq$0.5 mm in diameter) beta-hemolytic streptococci. Usually they are resistant to bacitracin, although this varies according to the literature. They are common pathogens in domestic animals and birds. Group C organisms may test sensitive to a trimethoprim–sulfamethoxazole disk but group A organisms will be resistant (Salata et

al., 1989). There are four species of group C streptococci. *Streptococci dysgalactiae* is a common cause of mastitides in cows and arthrilis in lambs, but it is an uncommon human pathogen. *Streptococcus equisimilis* is the most common cause of infections in humans. It produces streptolysin O. It may produce elevated antistreptolysin (ASO) liters because of the presence of streptolysin O. Domestic animals may also be infected (Johnson & Tunker, 1995). *Streptococcus zooepidemicus* may cause human infections (Bradley et al., 1991). It does not produce streptolysin O or S. Usually it is associated with consumption of homemade cheeses or unpasteurized cow's milk (Centers for Disease Control, 1983). *Streptococcus equi* is primarily a pathogen of horses and does not produce streptolysin O or S.

Clinical Findings

Group C beta-hemolytic streptococci have been identified in nasal pharynx, skin, and the genital tract of humans. Underlying conditions have been noted in most patients with group C streptococcal infection. These conditions include cardiopulmonary disease, diabetes, chronic dermatologic conditions, malignancy, immunosuppression, alcohol abuse, renal or hepatic failure, and injection drug use. Exposure to animals has been documented in up to 24% of cases (Salata et al., 1989; Johnson & Tunker, 1995; Bradley et al., 1991). Group C streptococcus is an uncommon cause of pneumonia but may be associated with significant morbidity and mortality. It is often preceded by a viral upper respiratory tract infection. The pneumonia is typically lobar and is often preceded by fever, chills, shortness of breath, and pleuritic chest pain. Bacteremia has been documented in 75% of cases in one series. All the patients in this series had pleural effusions (Dolinski et al., 1990). These cases were complicated by metastatic infection, cavitation, and empyema. Group C streptococcus causes similar manifestations to group A streptococcus (Stamm & Cobbs, 1980; Rose et al., 1980; Noble & McGowan, 1983; Rivest et al., 1985; Siefkin et al., 1984; Vartian, 1991). Penicillin is the drug of choice for group C beta-hemolylic streptococci. Other potential agents include vancomycin and erythromycin and the cephalosporins. Tolerance has been reported with group C streptococci with minimum bactericidal concentration, MBC, ranging from 32- to 512-fold greater than the MIC. Gentamicin may produce synergistic results. Combinalion therapy with gentamicin and rifampin would probably be indicated for cases complicated by sepsis or endocarditis (Portnoy et al., 1981).

Group G Streptococci

Microbiology

Most strains of group G streptococci show beta-hemolysis. Although most strains show resistance to bacitracin, a significant majorirty can be sensitive. Group G streptococci produce a streptolysin that is similar to streptolysin O. Patients with group G streptococcal pharyngitis may have significant increase in serum ASO titers (Johnson & Tunker, 1995).

Epidemiology

Investigators have found that up to 65% of patients with group G streptococci may have an underlying malignancy. Other studies have found lower incidences of malignancy and have found that alcohol abusers and patients with diabetes mellitus appear to be at increased risk for infection with group G streptococcus (Auckenthaler et al., 1983).

Clinical Features

Pneumonia caused by group G streptococcus is rare. In a literature review (Armstrong et al., 1970; Vracin et al., 1982) of eight cases of group G streptococcal pneumonia and empyema, seven occurred in adults with malignancy. Most group G streptococci are susceptible to penicillin, cephalosporins, vancomycin, and erythromycin. Clindamycin, erythromycin, and chlorophenol have relatively poor bactericidal activity against group G streptococci (Lam & Bayer, 1983). Combinations of gentamicin with cell-wall active agents are synergislic against the majority of strains. Unlike with

group C streptococci, penicillin tolerance is not a major feature of group G streptococci.

Enterococcal Pneumonia

Microbiology

Enterococci are facultative anaerobes that can grow in 6.5% NaCl at pH 9.6, and at temperatures ranging from 10 to 45°C. They will grow in the presence of bile salts and hydrolyze esculin and L-pyrrolidonyl-β-naphthylamide (PYR) (Murray, 1990; Facklam & Collins, 1989).

Clinical Features and Epidemiology

The enterococcus has been a well-appreciated pathogen in endocarditis, urinary tract infection, intra-abdominal processes, and septemia. However, it has not been as common a cause of pneumonia. Berk and colleagues (1983) describe two patients with enterococcal pneumonia documented by transtracheal aspiration. Both of these patients were veterans who had received enteral hyperalimentation and broad-spectrum antibiotic therapy. There have been several cases of patients with enterococcal bacteremia that have revealed the lower respiratory tract to be a source of infection. Table 1 summarizes the studies. A total of 27 cases of bacteremic enterococcal pneumonia have been reported. These patients generally tend to be elderly with nosocomial pneumonia. Many were receiving broad-spectrum antibiotics, especially cephalosporins. Antimicrobial treatment of enterococcal infections has become increasingly complicated because of drug resistance. Specifically, vancomycin-resistant enterococci have emerged during the last decade (Huyke et al., 1998). Ampicillin is usually the drug of choice if the organism is susceptible.

Streptococcus pyogenes

Microbiology

Group A streptococci, when grown in broth media, frequently produce long chains. The organisms are nonmotile, do not form spores, are catalase-negative, and are facultatively anaerobic. When cultured on blood agar plates they appear as white to gray colonies, 1 to 2 mm in diameter, and surrounded by zones of complete hemolysis.

Clinical Manifestations and Therapy

Respiratory infections caused by group A streptococci may occur in previously healthy individuals and are often preceded by a viral illness. Historically, they have caused numerous epidemics in military recruit populations (Basiliere et al., 1968; Gamba et al., 1997; Brundage et al., 1996; Schugk et al., 1997; Kalima et al., 1998; Davies et al., 1996).

The onset may be gradual but is typically abrupt. Pleuritic chest pain, fever, chills, and dyspnea are common symptoms. Approximately one half of patients have an associated pleural effusion. Unlike in other forms of streptococcal pneumonia, these effusions are often infected. Empyema develops in 30% to 40% of cases. These often require early drainage to prevent loculation and other com-

TABLE 1. Enterococcal Pneumonia in Series of Enterococcal Bacteremia

Investigation	Cases of pneumonia	Cases of bacteremia	Comments
Garrison et al., 1982	4	114	All four patients died
Bryan et al., 1983	9	190	67% mortality rate in Veterans Administration and community hospitals
Barrall et al., 1985	1	73	Surgical series
Maki & Agger, 1988	1	153	
Malone et al., 1981	4	55	Three or four pneumonias were nosocomial; 50% mortality rate
Rimailho et al., 1988	3	35	Protected brush used
Gullberg et al., 1989	5	75	Four of five patients were using mechanical ventilators

plications. Bacteremia occurs in 10% to 15% of cases. Other potential complications include mediastinitis, pericarditis, pneumothorax, and bronchiectasis. Therapy consists of penicillin G (Bisno, 1995).

Streptococcus intermedius Group

Microbiology

The *streptococcus intermedius* group often require CO_2 for growth, and may be alpha-, beta-, or gamma-hemolytic. The colonies are often tiny, even under microaerophilic conditions, in comparison to other streptococci (Kambal, 1987). The organisms may produce a caramel-like odor that may be of value (Chew & Smith, 1992). The characteristics that allow presumptive identification of members of the *S. intermedius* group have been described by Whiley et al. (1990) and Straton (1995).

Clinical Features

S. intermedius has been associated with a variety of infections including oral, bacteremic, and central nervous system infections, abdominal abscess, and cellulitis (Murray et al., 1978; Shlaes et al., 1981). Aspiration pneumonia, lung abscess, and empyema have also been reported to be caused by this group of organisms (Murray et al., 1978; Shlaes et al., 1981; Molina et al., 1991; Miller et al., 1983; Brook et al., 1988).

Therapy

Resistance to penicillin G and other β-lactams has been reported (Farber et al., 1983). Potgieter and colleagues (1992) found that overall, 29% of the Viridans group, including members of the *Streptococcus milleri* group, were resistant to intermediate concentrations of penicillin (MICs >4 μg/mL) (Stratton, 1995; Murray et al., 1978; Shlaes et al., 1981; Molina et al., 1991; Miller et al., 1983; Brook et al., 1988; Farber et al., 1983; Potgieter et al., 1992). Bantar and colleagues (1996) studied the antimicrobial susceptibility of the *S. milleri* group as well.

They found a penicillin resistance rate of 12.5% (intermediately resistant, 9.4%; resistant, 3.1%) for the *S. milleri* group as a whole. No vancomycin resistance was observed. Combination therapy with gentamicin might be prudent for serious infections. Clindamycin and newer fluoroquinolones are alternatives.

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Mycobacterium tuberculosis as a Cause of Community-Acquired Pneumonia

DICK MENZIES

Introduction

On a global scale, *Mycobacterium tuberculosis* is a very important pulmonary pathogen. In industrialized countries, tuberculosis (TB) is a relatively rare disease in the general population and is concentrated in a few high-risk subpopulations. In these subpopulations, TB remains an important infectious cause of pulmonary infiltrates. It is often misdiagnosed as pneumonia, resulting in delayed treatment and increased morbidity and mortality. Because TB is one of the few causes of pneumonia that can be transmitted to healthcare workers and other patients, it is important to consider *M. tuberculosis* in the differential diagnosis, particularly if certain features are present.

This chapter reviews first the bacteriology, transmission, pathogenesis, reactivation, and epidemiology of TB. The clinical features, methods for diagnosis, and treatment are also reviewed.

DICK MENZIES • Montreal Chest Institute, McGill University, Montreal, Quebec H3A 1A3, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Bacteriology of Tuberculosis

The TB complex comprises three closely related organisms that cause disease in humans: *Mycobacterium tuberculosis, Mycobacterium africanum,* and *Mycobacterium bovis.* Of these, *M. bovis* is an important pathogen in animals—predominantly ungulates such as cattle—while *M. africanum* is considered by many microbiologists to be a subspecies of *M. tuberculosis.*

M. tuberculosis is a thin rod 2–5 μm in length that is nonmotile, does not have a capsule, does not sporulate, and does not produce branching. In addition, it does not produce a toxin. The cell wall of *M. tuberculosis* is thick with a high lipid content as it is composed chiefly of lipopolysaccharides with arabinogalactan, the primary polysaccharide. The cell wall also contains complex waxes, as well as peptides and proteins that have tuberculin activity. Unlike gram-negative bacteria but similar to gram-positive bacteria, it does not have an outer cell membrane.

The thick waxy coat protects the bacteria from acid environments (such as those that occur within macrophages) and also accounts for the characteristic "acid-fast test." These organisms are difficult to stain but can be stained with carbol fuchsin and then resist decolorization with strong mineral acids and alcohol.

M. tuberculosis is a strict aerobe and grows more rapidly under higher oxygen tension. How-

ever, even under optimal in vitro conditions, the average doubling time is 17 to 18 hours.

Transmission

TB is transmitted almost exclusively by the airborne route. For transmission to occur, a source case with active TB must produce aerosols of bacteria-laden droplets, the smallest of which become droplet nuclei. If inhaled, these droplet nuclei can reach the alveolus of a susceptible host. Likelihood of transmission is affected by three major factors: the contagiousness of the source case, the environment and proximity of contact, and the susceptibility of the exposed individual.

Contagiousness of the source or index case is determined by the site, extent of disease, treatment, and behavior of the individual. For someone with active tuberculosis to be contagious, the site must almost always involve the respiratory tract. Occasionally, it may involve the larynx—this is a highly infectious form of tuberculosis demonstrated to be as contagious as measles (Riley et al., 1959). Laryngeal TB may occur as the only site of disease but more commonly occurs in patients with extensive pulmonary disease from upward spread along the airways. By far the most common and important site of disease resulting in transmission is pulmonary. Individuals with pulmonary TB are more contagious if cavitation is present, particularly if there are multiple cavities with more extensive infiltrates. The best indicator of contagiousness of pulmonary TB is the direct microscopic examination of a freshly stained smear of respiratory secretions. Individuals in whom bacteria can be seen, that is, those who are smear-positive, are approximately four times more contagious than those who are smear-negative (Menzies, 1997a,b; Grzybowsky et al., 1975). Effective treatment will rapidly reduce contagiousness (Rouillon et al., 1976). A smear-negative but culture-positive individual should be rendered noncontagious within 2 weeks of starting effective therapy (Menzies, 1997b). The time period in which smear-positive patients become noncontagious is less well defined. Most patients will become smear-negative within 4 weeks, at which time they can be considered no longer contagious (Menzies, 1997b). However, the patient must be compliant with therapy, and therapy must be effective (i.e., the tubercle bacilli should not be drug-resistant). In several well-documented hospital outbreaks of TB, a frequent mistake was that respiratory isolation was discontinued without ensuring that the patients were actually taking the therapy, and that the therapy was effective. As a result, patients who were noncompliant or had multidrug-resistant organisms were transferred out of respiratory isolation and subsequently transmitted infection to other patients and workers (Menzies et al., 1995). Patient behavior is important, particularly compliance with therapy. In addition, cough frequency and severity is a determinant of contagiousness, as is younger age perhaps because of more forceful cough or more social contacts (Lincoln, 1965).

The environment in which contact occurs and closeness of contact also affects transmission. Epidemiologic studies have demonstrated that the highest risk of transmission is from mothers to nursing infants or between individuals who share the same room, followed by other household contacts, then nonhousehold contacts (Grzybowski et al., 1975; Van Geuns et al., 1975). Risk of transmission is roughly proportional to the duration of exposure (Rose et al., 1979), but there is no threshold or absolute cut-off. A nonhousehold contact with exposure of several hours' duration daily may have greater exposure than a person who lives in the same household, but is rarely home (e.g., a teenager).

The environment is an important determinant because airborne tubercle bacilli are susceptible to light, particularly ultraviolet light, and drying (Riley et al., 1962, 1976). Outdoors, the aerosolized tubercle bacilli are rapidly dispersed and diluted so that the chance of inhaling a viable airborne tubercle bacillus is infinitesimally small. Therefore, transmission occurs almost exclusively indoors. Risk of transmission in the indoor environment increases it the room is small and/or the rate of exchange of air is low (i.e., poor ventilation) (Riley and O'Grady, 1961). Both of these factors act to increase the concentration of airborne tubercle bacilli and therefore the likelihood of inhaling them. In addition, dark and damp conditions will increase the survival of airborne tubercule bacilli and therefore increase risk of transmission.

Susceptibility of the exposed individual is a

less well-understood determinant. It is clear that individuals with prior TB infection are much less likely to become re-infected than immunologically naive individuals (Menzies, 1997a; Stead, 1995; Stead et al., 1968). Otherwise, there is no clear evidence of increased susceptibility to infection. It has been stated that HIV-infected individuals and the very young have an increased risk for infection. But it is unclear whether they simply have increased risk for disease if infected or a truly increased risk for infection. On theoretical grounds, individuals with increased minute ventilation should have greater likelihood of infection simply because they inhale more air. This may explain why men have slightly higher incidence than women, HIV-infected patients are more likely to be infected than healthcare workers in nosocomial outbreaks (Menzies et al., 1995) and South African gold miners have high rates of infection and disease (Cowie, 1994).

Pathogenesis

Infection with *M. tuberculosis* by a single droplet nucleus containing as few as one to three viable bacteria can result in infections that eventually result in disease (Wells, 1934). Larger droplets containing viable tubercle bacilli, if inhaled, will usually affect upper airway mucosa and be cleared by upper airway mechanisms. Therefore, only inhalation of droplet nuclei small enough to reach the alveolus results in infection (Wells, 1934). Development of disease following infection can be divided into four stages as described by Dannenburg (1989). The interested reader should also read the excellent, albeit older, text by Youmans (1979).

Stage 1: First Week

After the droplet nuclei containing viable tubercle bacilli are inhaled and deposited into an alveolus, the tubercle bacilli are engulfed by alveolar macrophages. In an immunocompetent host with previous TB infection, activated macrophages capable of killing the tubercle bacilli will rapidly accumulate and the infectious focus is usually cleared within a week. In immunologically naive (i.e., previously uninfected) hosts, tubercle bacilli will replicate unimpeded within the alveolar macrophage, causing it to rupture. By the end of the first week, a localized alveolar infiltrate with neutrophils and macrophages develops.

Stage 2: Weeks 2 and 3

There is a repeated cycle of unimpeded growth of M. *tuberculosis* within the macrophages that rupture, after which the tubercle bacilli are rephagocytosed by other immature alveolar macrophages. During this time, the tubercle bacilli will pass to the regional hilar and mediastinal nodes. From there, bacilli enter the bloodstream with the result that, even in immunocompetent hosts, bloodborne dissemination will occur within 3 weeks of primary infection.

Stage 3: Week 4 and Onward

In stage 3, the tubercle bacillary population stabilizes and there is progressive development of cell-mediated immunity largely mediated by CD4 lymphocytes. Delayed type hypersensitivity also develops, mediated largely by CD8 lymphocytes. This is associated with development of a positive tuberculin test, within a minimum of 3 and a maximum of 8 weeks from the date of primary infection.

Granulomas form around each focus of tubercle bacilli. Mature macrophages accumulate around the periphery of the granuloma and form the characteristic epithelioid cells. Within granuloma, central caseating necrosis will occur where the tubercle bacilli can be found. These tubercle bacilli remain dormant yet alive for years. They do not multiply because of the unfavorable circumstances for growth within the necrotic caseum.

In more than 95% of immunocompetent hosts, the tubercle bacilli will then enter the latent phase. This phase can last for many years.

Stage 4: Development of Disease

Disease may develop in four ways. Which manifestation occurs depends largely on host immune factors, the best defined of which are age and HIV infection.

1. Early disseminated disease: If the development of cell-mediated immunity is inadequate after the third week, then hematogenous dissemination

will result in foci of tubercle bacilli in all organs, where logarithmic growth will continue. By the third month, clinical disease appears. This form, known as miliary tuberculosis, is seen in the very young (less than 5 years old), very old, and individuals with advanced HIV infection (i.e., CD4 counts less than 200).

2. Progressive primary: Despite the development of apparently effective cell-mediated immunity and delayed type hypersensitivity, the tubercle bacilli never enter the latent or dormant phase, but rather progress steadily to clinically apparent active disease. This occurs frequently in adolescents and young adults. Disease may affect the lower lobes or produce the classic upper lobe disease with cavitation.

3. Reactivation of latent or dormant infection: In industrialized countries, it is believed that the great majority of TB cases develop from this mechanism.

4. Re-infection: In most industrialized countries, risk of TB infection is very low and the majority of cases result from reactivation in individuals infected elsewhere (i.e., the foreign-born) or long ago (i.e., the elderly). However, in developing countries, risk of infection is high. When an individual with previous primary TB infection is reexposed, the risk of re-infection and development of disease is 80% lower than for individuals not previously infected. However, re-infection can occur and result in active disease (Stead, 1995; Nardell et al., 1986; D'Elia et al., 1982). This re-infection will have radiographic manifestations indistinguishable from reactivation. Reactivation cannot be distinguished from re-infection on clinical or radiographic grounds (Nardell et al., 1986; Stead et al., 1985) but can be distinguished with the technique of restriction fragment length polymorphism (RFLP) or DNA fingerprinting.

Reactivation

Reactivation TB occurs at a variable interval after primary infection, as shown in Figure 1 (adapted from Walgren, 1948). Pulmonary TB accounts for 80% of all reactivation forms of TB in non HIV-infected populations. Incidence is highest 1 to 2 years following primary infection but can occur as much as 40 to 50 years later. Factors resulting in reactivation include HIV infection, other conditions resulting in immunocompromise, particularly T-cell lymphomas, immunosuppressant medications including corticosteroids and cancer chemotherapy, diabetes mellitus, renal failure particularly if severe enough to require dialysis, malnutrition and weight loss, and silicosis for the pulmonary forms of tuberculosis. The most common factor worldwide is now HIV infection. The other common factor in industrialized countries is advanced age. In these countries, incidence among the elderly is high because cell-mediated immunity is reduced with aging, and because of the high prevalence of latent TB infection related to exposure in the pre-antibiotic era.

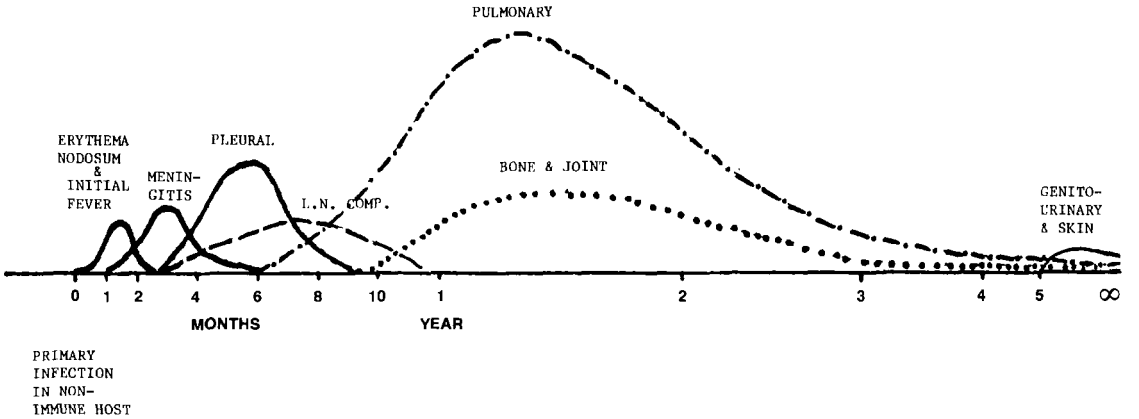

FIGURE 1. Time table of tuberculosis: usual interval from primary infection to appearance of tuberculosis complications including pulmonary and extrapulmonary forms.

Epidemiology

Global

Globally, TB is the single most important infectious agent causing death in adults aged 15 to 49 years. The World Health Organization has estimated that one third of the world's population is infected with *M. tuberculosis,* that there are approximately 20 million prevalent active cases at any time, and that 8 to 9 million new active cases occur each year resulting in 2 to 3 million deaths annually (Kochi, 1991; Dolin et al., 1994). In most developing countries, TB has very high incidence and prevalence, making it the most important adult pathogen. The HIV endemic has exacerbated this problem dramatically. In some sub-Saharan countries, incidence of TB has doubled and even tripled since the beginning of the HIV epidemic (Harries et al., 1999). This is because when HIV infection occurs in an individual with preexisting latent TB infection, active TB is highly likely to develop (Selwyn et al., 1989). In persons with latent infection, the most common presenting illness is TB, as *M. tuberculosis* is the most pathogenic of the common opportunistic infections to arise in HIV-infected individuals. The prevalence of HIV among individuals newly diagnosed with active TB now exceeds 70% in many sub-Saharan countries (Sudre et al., 1992).

Industrialized Countries

In industrialized countries, the incidence of TB peaked in the 19th century and steadily declined throughout the 20th century until the 1980s. In many European countries and the United States, incidence increased between 1985 and 1990, primarily in large urban centers as a result of deteriorating social conditions, the HIV epidemic, and inadequate public health programs (Brudney & Dobkin, 1991). In Canada, TB incidence failed to decline between 1985 and 1993 (Long et al., 1999). Since 1993, in most industrialized countries, TB incidence has again begun to decline, largely because of dramatically increased investment in TB control (Long et al., 1999; Frieden et al., 1995).

The rate of disease in the general population has declined markedly. For example, in Canada, incidence of TB was less than 3 per 100,000 among the nonaboriginal Canadian-born population in 1996 (Long et al., 1999). However, in industrialized countries, the incidence remains much higher in certain subgroups (Long et al., 1999).

Foreign-Bom Persons

Incidence of tuberculosis among the foreign-born tends to parallel rates in their country of origin (Enarson et al., 1979). Incidence of disease is highest in immigrants from sub-Saharan Africa, Southeast Asia, and the Indian subcontinent. TB rates are intermediate in immigrants from countries in Latin America or Eastern Europe, and are low in immigrants from Western Europe and other industrialized countries (Long et al., 1999; Nolan et al., 1989; Rivest et al., 1998). Incidence of disease is highest in the first 5 years following arrival (Rivest et al., 1998; McKenna et al., 1995). This is believed to reflect higher incidence following recent infection or re-infection. Incidence, however, remains substantially higher than in the native-born population for up to 20 years following immigration. As in the countries of origin, incidence is highest in young adults, although there is a second peak in the elderly. Because the incidence in the native-born population has fallen and because of large numbers of immigrants arriving in Canada, TB among the foreign-born now accounts for more than 60% of all cases compared to 30% in 1980 (Long et al., 1999). In the United States, TB among the foreign-born also accounts for an increasing proportion of all cases and in 1996 accounted for close to 40% (Centers for Disease Control and Prevention, 1996).

An important clinical aspect of TB among the foreign-born is the greater likelihood of drug resistance. This is because primary and secondary drug resistance is common in many developing countries where access to anti-tuberculous drugs is uncontrolled, drugs may be of substandard quality, and the TB control programs to ensure full compliance with therapy are often inadequate. As a result, there are high rates of drug resistance (Pablos-Mendez et al., 1998). Particular hot spots for multidrug-resistant TB are certain countries in Eastern Europe, Latin America, and Southeast Asia (Pablos-Mendez et al., 1998). On the other hand, most countries in sub-Saharan Africa have relatively low rates of drug resistance, primarily a re-

(lection of lack of access to any form of therapy for the majority of the population.

Minorities

In the United States, minorities include Blacks, Hispanics, and, in some areas, aborigines. Prevalence of infection is often four to six times higher among these minorities than in Whites living in the same areas. Incidence of disease is also many times higher and affects primarily young adolescents and young adults. In Canada, the aborigines are disproportionally affected and account for approximately 20% of all cases in Canada (Long et al., 1999). Rates are particularly high among aborigines from the western plains and the far north. This may reflect lower innate resistance because these populations have been exposed to TB only within the past century (Enarson & Grzybowski, 1986).

Elderly

A common phenomenon in all industrialized countries is that the incidence of TB among the native-born general population is highest in the elderly. In this age group, incidence in males is double that in females, a difference that has not been explained. The increased occurrence among the elderly is a reflection of waning immunity in old age and the high prevalence of latent TB infection due to exposure in the pre-antibiotic era.

Urban Poor

A difficult subpopulation that is increasingly affected with TB are the disenfranchised or marginalized populations that include the homeless and IV drug users in many large cities in North America and Europe (Brudney & Dobkin, 1991). These populations often have high prevalence of HIV infection and may be in and out of prison and homeless shelters or other environments where TB can be transmitted. Further contributing to transmission among this group is the lack of access and/or use of healthcare resources resulting in delayed diagnosis, as well as noncompliance with treatment (Brudney & Dobkin, 1991; Frieden et al., 1993). As a result, outbreaks of disease are common in this group although often not recognized (Nardell et al., 1986).

Clinical Features

History

The most important and common symptom of pulmonary TB is cough. More than 90% of patients with smear-positive pulmonary disease will have chronic cough (i.e., of more than 2 weeks' duration). The International Union against Tuberculosis (Enarson et al., 1994) has recommended that TB should be suspected if an individual presents with cough of more than 2 weeks' duration, and appropriate diagnostic tests should be performed if the cough is of more than 3 weeks' duration. In patients diagnosed to have active tuberculosis in North America, the typical history is a cough of 1 to 2 months' duration, for which they have already seen other health professionals on one or two occasions and been given antibiotics without improvement.

The cough is initially nonproductive but will eventually become productive of purulent sputum as the disease becomes more advanced. Hemoptysis is uncommon. Slight or scanty hemoptysis can be seen as with any pulmonary infectious disease. Massive hemoptysis is fortunately rare and tends to be associated with late-stage or advanced disease because it occurs when large cavities erode into pulmonary arteries (Rasmussen's aneurysm).

Fever is often low-grade and typically occurs in the late afternoon and early evening. The classic symptom of night sweats results from spontaneous defervescence of the fever overnight and is a fairly common early sign. Chills and rigors are generally not seen. Chest pain is a sign of relatively advanced disease or a complication such as pleural effusion or pneumothorax. Anorexia and weight loss are also generally seen with advanced disease.

If laryngeal involvement is present, the patient may have noticed hoarseness and pain in the throat.

Physical Examination

In pulmonary TB, it is essential to remember that physical examination of the chest is usually normal. Even when there are extensive radiographic abnormalities including cavities, the exam will be surprisingly normal. In more advanced disease, there may be signs of volume loss of the affected lobe (tracheal or mediastinal shift) and dullness to

percussion over the apex, as well as rales, bronchial breathing, and even amphoric breathing if there are extensive cavities. Post-tussive rales, that is rales, that appear after coughing, are a classic sign of TB.

It is important to examine for signs of HIV infection, such as oral candidiasis, Kaposi's sarcoma, lymphadenopathy, or hepatosplenomegaly. It is also important to examine for coexistent extrapulmonary tuberculosis which can be found in 50% of HIV-TB cases, and 10% to 25% of non-HIV-associated active TB. This includes lymphadenopathy, pleural effusion, abdominal involvement, or signs of osteoarticular involvement.

Clubbing is not usually seen and may be a sign of other pulmonary diseases such as lung cancer or bronchiectasis that may appear concomitantly with TB. Cyanosis is also rare.

Laboratory Diagnosis

Chest X-Ray

In most circumstances, the first test ordered for diagnosis of community-acquired pneumonia is the chest x-ray.

Classic Triad of features

1. Apical posterior position: In 90% of non-HIV-infected individuals, pulmonary TB originates in the apical posterior section of the upper lobes or the apical segment of the lower lobes.
2. Volume loss of affected lobe: This is an important differential diagnostic clue as most other community-acquired pneumonias do not result in volume loss.
3. Cavitation: Cavities can be single or multiple and of variable size. There is usually surrounding air space disease, but the cavities themselves are not necessarily thick-walled. Air-fluid levels are rare.

Radiographic Variants

Lower lobe air space disease without upper lobe cavitary disease can be seen in adolescents or young adults with progressive primary tuberculosis or in immunocompromised individuals such as HIV-infected persons or diabetics. This is indistinguishable from typical lobar pneumonia except for the more chronic history, resulting in delayed diagnosis.

Endobronchial Spread

A common radiographic feature is endobronchial spread of tuberculosis. The pathogenesis of this finding is the spread of bacilli along the airways and development of multiple scattered foci of disease in the adjacent and contralateral lungs. On chest x-ray, this phenomenon is seen as multiple ill-defined nodules 5 to 10 mm in diameter in the ipsilateral and contralateral lower lobes. When this is seen, the patient almost always has smear-positive disease.

Tuberculosis Pneumonia

When multiple acinar foci coalesce, diffuse air space disease results. Radiographically this will appear to be a lobar pneumonia in the ipsilateral and/or contralateral lower lobes. Patients will be severely ill and toxic, may be hypoxemic, and without treatment will have a rapid downhill course. This form was classically known as "galloping consumption."

Effusion

Pleural effusion can occur from spread of bacilli from the affected lung to the pleura, or concomitant reactivation of a dormant pleural focus. With either of these two etiologies, the effusion will be free-flowing and straw-colored. Rarely, a caseous focus will erode and rupture into the pleura rather than into the bronchus. When this occurs, TB empyema results. Radiographically, one cannot distinguish TB empyema from the more common effusion.

Miliary Tuberculosis

Generally, miliary TB is not seen in conjunction with classic reactivation pulmonary TB because the immunologic response that gives rise to classic reactivation pulmonary TB with cavitation

will prevent the development of miliary disease. Conversely, miliary disease occurs when there is insufficient immunologic response, so cavitation is not seen.

The radiographic appearance of miliary TB is that of interstitial micronodular disease. The nodules are evenly distributed throughout both lungs and are of uniform size, generally 3 to 5 mm. They tend to be sharply defined on x-ray because they are interstitial rather than alveolar in location.

Pnenmothorax

This is a rare complication that occurs when a caseous focus erodes into both the pleura and a bronchus, establishing a bronchopleural fistula. It is a very serious complication with a high mortality rate.

Differential Diagnosis

If the chest x-ray shows upper lobe cavitary disease and there is a more chronic or indolent history, the following should be considered:

1. Nontuberculous mycobacteria (NTM): In elderly individuals with chronic obstructive pulmonary disease (COPD) or other preexisting pulmonary conditions, disease caused by NTM will present with upper lobe cavitation. The most common causative organisms belong to the *Mycobacterium avium* complex (this includes *M. avium, M. intracellulare,* and *M. scrofulaceum,* although the last does not cause pulmonary disease). In some parts of North America, *M. kansasii* is an important cause of this pattern, whereas it other parts of the world, particularly Britain and Europe, *M. xenopi* and *M. malmoense* are common NTM pathogens producing this pattern. Since acid fast bacilli (AFB) will be seen on smear microscopy, NTM will often be considered and treated as TB initially until the specific organism is identified.

2. Chronic cavitary histoplasmosis: In certain areas of the world where histoplasmosis is endemic, such as the midwestern United States and Mississippi floodplain, chronic cavitary histoplasmosis must be considered in the differential diagnosis. It typically affects older males with preexisting chronic obstructive lung disease.

3. Semi-invasive *Aspergillus:* This is an ill-defined entity that is difficult to diagnose. It is an important consideration because *Aspergillus* may secondarily infect old cavities or bronchiectases, initially forming a fungus ball or aspergilloma. Over time, this may become semi-invasive, producing cough, progressive dyspnea, productive sputum, and hemoptysis.

4. Actinomycosis: This is a rare condition but can cause upper lobe chronic cavitary disease. It is usually distinguished with appropriate respiratory cultures but biopsies may be needed.

5. Melioidosis: In Southeast Asia, melioidosis is an important pathogen causing upper lobe cavitary disease and hemoptysis. Therefore, this diagnosis should be considered in recent immigrants or travelers returning from this area.

6. Coccidioidomycosis: This is endemic in the southwestern United States and can cause multiple upper-lobe thin-walled cavities. It should be considered in individuals residing in or travelers returning from this area.

7. Noninfectious causes: Upper lobe fibrosis with progressive massive fibrosis due to sarcoidosis and silicosis can sometimes be confused with tuberculosis. Given that both of these conditions may be complicated by TB or NTM, it is important in individuals with typical chest x-ray findings and a compatible work exposure history to obtain multiple sputa for mycobacterial smear and culture. Individuals with ankylosing spondylitis can develop bilateral upper lobe fibrosis with volume loss that can be confused with noncavitary active pulmonary TB.

Accuracy and Reliability of the Chest X-ray

A major problem of the chest x-ray is that it is not highly accurate or reliable for the diagnosis of pulmonary TB. This is not altogether surprising given the broad differential diagnosis and numerous potential complications or radiographic variants described above. Despite this, many clinicians place great faith in the chest x-ray because it is readily accessible, results are immediately available, and they can verify the radiographic findings themselves. Therefore, it is worth reviewing the accuracy and reliability of the chest x-ray in the diagnosis of TB. (Interested readers should refer to Toman, 1979.)

TABLE 1. Sensitivity and Specificity of Chest X-Ray Compared to Sputum Cultures[a]

		Cultures		
		Positive	Negative	Total
Chest x-ray reading	Active TB	142	85	227
	Not active TB	20	1982	2002
Sensitivity		88%		
Specificity		97%		
Positive predictive value		63%		

TB, tuberculosis.
[a]Modified from Toman, 1979.

As seen in Table 1, the chest x-ray can be highly sensitive for detection of active TB. In this study, however, of 227 individuals in whom active TB was diagnosed radiographically, only 142 (63%) actually had TB. High sensitivity is accompanied by a high false-positive rate.

As shown in Table 2, the agreement between expert readers on rereading the same films was poor, even though they were asked only a simple question as to whether a pair of x-rays were better, worse, or unchanged. The same readers disagreed with themselves on approximately every fifth occasion.

In a study organized by the International Union against Tuberculosis, 1100 chest x-rays were selected: 200 from patients with confirmed smear-positive and culture-positive TB, 400 individuals who had received a full course of therapy and were now culture-negative, 100 from patients with minimal stable abnormalities, 300 with x-rays considered normal, and 100 from patients with confirmed other lung diseases. Each film was read by 90 reviewers and an index of inter-observer agreement, equivalent to a kappa statistic, was calculated.

In total, only one third of patients with smear-positive active TB were considered to have cavitary disease by more than half of all readers. In about one quarter of these smear-positive patients, they were considered to have a normal x-ray or only minimal non-TB-related abnormalities by the majority of readers. Furthermore, four to five times as many nontuberculous patients would have received therapy based on the readings as the number of confirmed active cases. Disagreement over x-ray findings was greater for certain abnormalities than others, as shown in Table 3 (Toman, 1979).

These findings suggest that the chest x-ray is useful to raise the suspicion of active TB but should not be relied on to confirm diagnosis.

Computerized Tomography

Computerized tomography (CT) scan of the chest is now widely used for diagnosis of many pulmonary conditions in industrialized countries. The CT is helpful in detecting small lesions, because the limit of resolution is approximately 1 mm for CT compared to 3 to 5 mm for standard chest x-rays. CT is also helpful in better defining the extent of disease, presence of cavities, bronchiectasis, or interstitial fibrosis. However, to date, no study has compared the yield, accuracy, and inter- or intra-reader agreement using CT scan for diag-

TABLE 2. Reliability of X-Ray Readings[a]

	Disagreement (%)	
Study	Between readers	Within readers
Radiologists and respirologists		
Group 1	29	19
Group 2	27	24
Expert readers from mass chest x-ray screening programs	30	21

[a]9000 pairs of x-rays judged "better," "worse," or "unchanged." Modified from Toman, 1979.

TABLE 3. Reliability of X-Ray Readings[a]

Question (readers answered yes or no)	Disagreement (%)
Film abnormal?	34
Noncalcified abnormality, probably tuberculous?	37
Cavity present?	28[b]
Abnormality in lung—probably not tuberculous?	45
Abnormality in lymph nodes?	60
Calcification present?	42
Need for medical action?	31

[a]IUAT trial, 99,000 readings. Modified from Toman, 1979.
[b]Lowest level of disagreement for all questions asked.

nosis of TB. Until studies are performed of similar design and quality as were used to evaluate the chest x-ray in the 1960s, the role of CT scan in diagnosis of TB remains undefined. It is the author's opinion that CT scan is unlikely to be substantially better than chest x-ray, and microbiology will remain the gold standard.

Microbiologic Tests

When TB is suspected, it is essential to obtain specimens for mycobacterial smear and culture. Microbiologic tests are important for confirming the diagnosis, measuring drug susceptibility of the causative organisms, as well as assessing extent of disease and contagiousness of the patient. During follow-up, microbiology can be used to confirm response to therapy as there are well-defined benchmarks to indicate whether response to therapy is adequate or suboptimal.

Specimen Collection

Obtaining a spontaneous sputum collection is usually first attempted. Early morning specimens are best because they will be most concentrated. Patients should be instructed to cough deeply and expectorate directly into a sterile or clean container. They should be instructed not to eat before producing the sputum specimen because food particles can result in false-positive AFB smears. If the specimen is not processed immediately, it should be kept in the dark and refrigerated, although not frozen. This is because heat and light will kill *M. tuberculosis* and because refrigeration prevents overgrowth by other bacteria that contaminate sputum specimens.

The optimum number of sputum samples to diagnose pulmonary TB has been established in older studies summarized by Toman (1979). In patients with confirmed smear-positive disease, the smear of the first specimen obtained was positive in 78% to 83%. If the first smear was negative, the second was positive in another 12% to 15% and if the first two were negative, the third was positive in 4% to 6% (Toman, 1979; Ipuge et al., 1996). In other words, 99% of all those with a positive smear were detected with the first three specimens examined (Toman, 1979). Similarly, among all those with confirmed positive cultures, in 80% of patients the first specimen obtained will be positive, if the first is negative the second will be positive in another 8%, and if the first two are negative the third will be positive in 3%. If the first three are negative, three additional specimens will be positive in another 9% (Toman, 1979). This means that 91% of patients will be positive with the first three specimens obtained (Toman, 1979). For this reason, three specimens for AFB smear and culture are recommended as the most efficient method.

Handling the Specimens

In the microbiology laboratory, the specimen is digested with N-acetylcysteine (NALC) and decontaminated with sodium hydroxide (NaOH) to eliminate other bacteria. This will often reduce the viability of some of the *M. tuberculosis* present as well. The specimen is then centrifuged at high speed, to increase yield for smear and culture (Ratnam & March, 1986).

Smear

Most laboratories in industrialized countries will screen the smear by first staining with a fluorochrome stain such as auramine. This technique has greater sensitivity because a greater area of the slide can be screened more rapidly. If the fluorescent screening is positive, then a confirmatory stain must be done using the traditional Ziehl-Neelsen, which employs initial carbol-fuchsin staining, acid alcohol decolorization, and then counterstaining with methylene blue. Tubercle bacilli and NTM will appear as reddish rods. The likelihood that a smear will be positive depends on the concentration of bacteria in the sputum (Table 5). This in turn depends on the number of bacteria in the lesion, which has been quantified in careful experiments by Canetti (1955) (Table 4).

As with chest radiography, the accuracy of smear microscopy was evaluated in a series of international studies. In reference centers, the sensitivity of smear microscopy was 80% compared to cultures, while the specificity was 99.3% and the positive predictive value was 90%, that is, there was a much lower false-positive rate (Toman, 1979).

Compared to culture, the sensitivity of AFB

TABLE 4. Number of Viable Tuberculosis Bacilli in Different Lesions

Lesion	No. of bacteria
Granuloma	10^3
Fibronodular scarring	10^4
Infiltrate (no cavity)	10^6
Single cavity	10^9–10^{10}
Multicavity	10^{11}–10^{13}
Death	10^{14}

smear varies considerably between centers, from as little as 20% to more than 80% (Gordin & Slutkin, 1990; Boyd & Marr, 1975; Kim et al., 1984). However, as shown above, the sensitivity of AFB smears is highly dependent on the extent of disease (Kim et al., 1984) and therefore on the patient population and methods of case finding. In our center, patients are diagnosed both passively (i.e., symptomatic patients come to the physician) and actively, through screening programs. Among patients diagnosed from screening, 14% were smear-positive compared to more than 70% among passively diagnosed cases.

The repeatability of AFB smears has also been compared. In one study, 250 sputum smears were performed using the Ziehl-Neelsen technique in one reference laboratory. They were then sent for reading by technicians in ten peripheral laboratories. Disagreement as to whether the smears were positive or negative occurred in less than 10% of readings if there were eight or more bacilli per slide (i.e., still in the 1+ range). Disagreement was 10% if there were three or more bacilli per slide, which is considered the threshold to consider a test positive or negative. A similar study compared readings prepared from patients known to be smear- and culture-positive or culture-negative. The false-positive rate of readings was 1.3% in the reference laboratory and 2.6% in eight peripheral clinics, while the false-negative rate (compared to culture) was 29% in the reference laboratory and 38% in the peripheral clinics (Toman, 1979).

These findings demonstrate that AFB smear is much more reliable and reproducible than the chest x-ray, although the smear is not as sensitive as culture.

Culture

Mycobacterial cultures were traditionally performed on solid media—Lowenstein-Jensen or Middlebrook agar. Growth on solid media was slow and required an average of 3 to 4 weeks for appearance of visible colonies and up to 8 weeks to be sure that the cultures were negative. More recently, liquid radiometric media have been developed such as the Bactec systems, which are much more rapid. Growth can be detected within 2 weeks on average. Detection is more rapid if the patient has a heavy bacillary load and slower if the patient has minimal disease, such as patients who are smear-negative but culture-positive.

It is currently recommended that both media be used, as sensitivity is improved by combining methods.

When growth is detected, the specific mycobacterial species must be identified. Traditionally, this was done using biochemical methods such as growth and niacin, which inhibited most mycobacteria except *M. tuberculosis*. These tests were time-consuming and often required another 1 to 2 weeks. However, new molecular biology techniques of amplification of segments of RNA or DNA specific to

TABLE 5. Probability of Positive-Smear Microscopy and Laboratory Interpretation

No. of tuberculosis bacilli (per mL of sputum)	Probability of positive smear (%)	Number of bacilli seen (per 100 fields under high power)	Laboratory reading
<1000 (<10^3)	<10	0–1	Indeterminant
5000–10,000	50	1–2	Indeterminant
20,000–30,000	80	5–10	1^+
40,000–50,000	90	10–100	2^+
100,000	96	100–900	3^+

M. tuberculosis, followed by assay with DNA probes specific to the same sequences, have been developed. These can rapidly distinguish bacilli belonging to the *M. tuberculosis* complex (*M. tuberculosis, M. africanum, M. bovus*) from all others. In individuals who are culture-positive, this test has excellent discriminatory ability with very high sensitivity and specificity.

False-positive cultures can occur because of cross-contamination of instruments such as bronchoscopes, or in the laboratory (Dunlap et al., 1995). Using DNA fingerprinting techniques, it has been recognized that 2% to 4% of all positive cultures are the result of such cross-contamination (Burman et al., 1997). Occasionally, it may happen that a few colonies of *M. tuberculosis* are isolated from sputum yet there is no evidence of disease activity, as with patients who have stable fibronodular disease. Among 7000 subjects given placebo in the IUAT Eastern European trial of preventive therapy for fibrotic lesions, 67 had a single positive culture yet were asymptomatic, had no evidence of disease, and so were not treated. A high proportion developed clinically apparent active tuberculosis within 5 years (Krebs, 1983). Therefore, once the possibility of laboratory contamination has been excluded, a positive culture should be considered evidence of active disease and treated appropriately.

Reproducibility of Cultures

Since cultures are considered the gold standard, it is difficult to compare the sensitivity and specificity of cultures against another technique. However, studies have been performed in which repeated cultures were done in the same patient. As shown in Table 6, the major reason for false-negative cultures is the extent of disease. In this study, patients with confirmed active TB had sputum cultures performed on 8 consecutive days before therapy was begun.

These results emphasize that multiple cultures are needed for diagnosis of patients with minimal active disease.

TABLE 6. Consistency of Cultures

Smear status	No. of patients	No. of cultures	No. (%) of cultures positive	No. (%) of cultures negative
Positive	46	368	347 (94)	21 (6)
Negative	22	176	62 (35)	114 (65)

Drug Sensitivity Testing

Generally conducted in reference laboratories, drug sensitivity tests were initially performed on solid media, therefore requiring at least 4 weeks for results. Today most reference laboratories use the liquid media for the first-line anti-tuberculosis drugs, such as isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin, so that results are usually available within 2 to 3 weeks.

Sensitivity testing to second-line drugs generally is performed if there is resistance to any of the first-line drugs, or at the request of the treating physician. These are performed on solid media and therefore 4 to 6 weeks are required for results.

Other Tests

Other diagnostic tests are needed primarily for diagnosis of smear-negative cases. This is because smear-positive cases are readily identified with polymerase chain reaction (PCR) techniques, *M. tuberculosis* can be confirmed within 48 hours. However, early diagnosis of TB while still smear-negative is important because patients who are smear-negative are less contagious, and they have lower morbidity and mortality than patients with more advanced disease.

Bronchoscopy

Bronchoscopy has been recommended to confirm the diagnosis of TB when spontaneous sputum is unavailable or is smear-negative. Bronchoscopy is of considerable utility if other pulmonary diseases such as lung cancer are also suspected, but it entails risk and discomfort for the patient, is expensive, and can contribute to nosocomial spread of TB. As summarized in Table 7, in nine prospective

TABLE 7. Yield of Bronchoscopy in Smear-Negative and Culture-Positive Patients in Nine Series with 431 Patients in Total[a]

Procedure	Yield (%)	Range (%)	No. of studies
Post-bronchoscopy sputum	45	10–68	7
Bronchial aspirate	49	17–83	8
Bronchoalveolar lavage	75	61–88	2
Transbronchial biopsy	34	18–58	4
Brush	25	2–63	4
Overall yield	77	26–95	9

[a]Chawla et al., 1988; So et al., 1982; Wallace et al., 1981; Chan et al., 1990; Uddenfeldt & Lundgren, 1981; Fujii et al., 1993; de Gracia et al., 1988; Khoo & Meadway, 1989; Al-Kassimi et al., 1991.

TABLE 8. Prospective Comparison of Mycobacterial Culture of Induced Sputum versus Gastric Aspirate[a]

		Gastric aspirate	
		Positive	Negative
Induced sputum			
Positive		166	56
Negative		28	2265
Sensitivity			
Gastric aspirate	77%		
Induced sputum	90%		

series of patients with smear-negative culture-confirmed TB, the yield of bronchoscopy averaged 77% (Chawla et al., 1988; So et al., 1982; Wallace et al., 1981;Chan et al., 1990; Uddenfeldt & Lundgren, 1981; Fujii, 1993; de Gracia et al., 1988; Khoo & Meadway, 1989; Al-Kassimi et al., 1991). In these series, bronchoscopy was the only method to confirm the diagnosis in 8% to 16% of all patients with culture-confirmed disease. However, it is important to note that the overall yield of bronchoscopy was only 77% and that post-bronchoscopy sputum was of equal yield compared to bronchial aspirate. Bronchoalveolar lavage (BAL) appeared to have higher yield but was used in only two series.

Gastric Aspirate

The gastric aspirate technique was introduced more than 70 years ago and is still used in some centers (Bahammam et al., 1999). The primary indications are investigation of possible TB in children who are not able to expectorate sputum. It may be considered, for the same reasons, in elderly demented patients.

The technique is relatively simple. When the subject first wakes, a nasogastric tube is introduced to the stomach. Small quantities of normal saline are instilled and aspirated. A problem with this technique is that it must be done immediately upon awakening, which means the patient often must be kept overnight in hospital. Moreover, it is uncomfortable and unpleasant for patients.

Induced Sputum

The induced sputum technique was used for the diagnosis of TB and compared to gastric aspirate more than 35 years ago. As shown in Table 8, in three studies that compared the yield in patients who were smear-negative on spontaneous sputum, induced sputum had sensitivity of 90% compared to 77% for gastric aspirate (Carr et al., 1967; Elliott & Reichel, 1963; Hensler et al., 1961). In addition, Carr et al. (1967) noted that patient discomfort was greater with gastric aspirate and that patients expressed a preference for sputum induction.

Despite this, with the advent of fiber-optic bronchoscopy, induced sputum fell into disuse. However, because of issues of cost containment and infection control, interest in induced sputum has revived. To date, induced sputum has been compared to bronchoscopy in only one prospective study. As shown in Table 9, the yield of a single sputum induction was slightly, although not significantly, better than that of bronchoscopy (Anderson et al., 1995). In that study, no adverse effects were experienced among patients undergoing induced sputum, which required only half an hour of patient time compared to half a day for bronchoscopy. In addition, bronchoscopy was nine times more expensive than sputum induction (Anderson et al., 1995).

In this same study, when 3 to 5 mL of 3% hypertonic saline was administered with a Venturi mask (commonly used to administer bronchodilator

TABLE 9. Prospective Comparison of Induced Sputum versus Bronchoscopy[a]

		Bronchoscopy	
		Positive	Negative
AFB smear			
Induced sputum	Positive	5	2
	Negative	0	85
Mycobacterial culture			
Induced sputum	Positive	17	7
	Negative	4	64
Sensitivity of TB culture			
Bronchoscopy	75%		
Induced sputum	86%		

[a]All patients were spontaneous smear-negative and untreated and underwent each procedure once. From Anderson et al., 1995.

therapy), sputum was produced by only one of six patients. Of the five who did not produce sputum, two were confirmed to have active TB by bronchoscopy. When 30mL of 3% hypertonic saline was used, 88% of patients produced an adequate sputum specimen, whereas 96% of patients produced adequate sputum when 80 to 90 mL were administered over 15 minutes (Anderson et al., 1995).

Of the three techniques, sputum induction has several distinct advantages. It is by far the least unpleasant and least invasive, has equivalent or better yield, is much less expensive, and poses less risk for nosocomial transmission. At present, sputum induction is grossly underused for the diagnosis of pulmonary TB in North America.

Amplification Techniques

A remarkable development in the diagnosis of TB has been the development of DNA probes, which can identify segments of DNA or RNA that are specific to organisms of the *M. tuberculosis* complex. When these probes were first developed, they could only be used for identification of *M. tuberculosis* in cultures because they required significant concentrations of DNA or RNA. However, subsequent molecular biologic discoveries permitted 10,000- to 100,000-fold amplification of these specific DNA or RNA sequences. If amplification techniques are used, then the DNA probes are sensitive enough to detect *M. tuberculosis* nucleic acid sequences in clinical specimens such as sputum. These clinical specimens must be prepared in the same way as for culture, that is, they must be decontaminated unless the specimen is obtained from a normally sterile site such as pleural fluid, cerebrospinal fluid, or tissue biopsy.

The specificity of PCR used in clinical specimens is excellent, as shown in Table 10, as is the sensitivity of PCR in sputum from smear-positive patients. However, in patients with smear-negative but culture-positive sputum, as well as in extrapulmonary samples, the sensitivity of PCR averages 50% to 60%.

Newer amplification techniques, particularly second-generation tests such as the MTD assay (Genprobe, San Diego, California) which amplify RNA, have reported sensitivity of 70% to 80% in sputum samples taken from patients who are smear-

TABLE 10. Results of Polymerase Chain Reaction (PCR) in Sputum Specimens

Reference	Total no. of patients	TB: S+ C+[a]		TB: S− C+[b]		Control (no TB)	
		No.	PCR+ (%)	No.	PCR+ (%)	No.	PCR+ (%)
Abe et al., 1993[c]	135	22	21 (95)	10	5 (50)	82	5 (6)
Claridge et al., 1993[c]	1127	127	121 (95)	52	33 (63)	948	11 (1.2)
Nolte et al., 1993[d]	297	110	105 (85)	14	8 (57)	173	1 (0.5)
Forbes & Hicks, 1991[d]	727	59	52 (88)	21	15 (71)	647	23 (4)
Eisenach et al., 1991[d]	115	42	42 (100)	2	1 (50)	71	2 (3)
Jonas et al., 1993[d]	119	49	48 (98)	70	47 (67)	—	—
Total	2499	409	389 (95)	169	109 (64)	1921	42 (2.2)

[a]S+ C+: Smear AFB-positive, culture-positive with *M. tuberculosis*.
[b]S− C+: Smear AFB-negative, culture-positive with *M. tuberculosis*.
[c]PCR: Amplification with IS 986.
[d]PCT: Amplification with IS 6110.

negative but culture-positive (Pfyffer et al., 1996; Bradley et al., 1996).

Serology

The first serologic test designed to diagnose TB was described in 1898. However, after a century of effort an accurate serologic test for the diagnosis of active TB remains one of the holy grails of medicine. This is partly because the humoral response in TB is not the primary immunologic response. In addition, the antigens used have never been standardized and in early years were quite crude, resulting in poor sensitivity and specificity as shown in Table 11 (Daniel & Debanne, 1987). Newer antigens using ELISA (enzyme-linked immunosorbent assay) to detect monoclonal antibodies have better specificity, as shown in Table 12 (Daniel & Debanne, 1987). The sensitivity was high in smear-positive patients, particularly those with symptoms of long duration, but lower in smear-negative or extrapulmonary disease. In addition, in these studies, specificity was excellent among healthy controls, but if patients had other pulmonary diseases (as is more likely to be the case in clinical practice), specificity was lower.

A further problem in the development of an accurate serologic test for TB is that the antibody response in TB patients is highly heterogeneous. In a recent report, 52 of 59 patients with active TB responded to at least one of ten different tuberculosis antigens (Lyashchenko et al., 1998). However, no patient reacted to all ten, and, as shown in Table 13, less than half of patients reacted to any single antigen. This heterogeneity of response is best demonstrated in graphic form, as shown in Figure 2. The heterogeneity of response may be hereditary, because humoral response to these ten TB antigens is different in TB patients from Africa versus TB patients in New York City (M. Gennaro, personal communication). The heterogeneity of response may also reflect changes in humoral response as the disease progresses. Patients with minimal disease have a different antibody profile from those with more advanced disease. This may explain differences between studies using different antigens and/or patients at different stages of disease.

This evidence has led to the development of serologic tests that include a cocktail of different antigens. The only problem with this approach is that as the number of antigens in the ELISA increases, the sensitivity for any one of them decreases. Nevertheless, assuming that these technical problems can be overcome, the approach of testing for multiple antibodies seems rational and promising. It can be hoped that in the next century, a valid and accurate serologic test may be available. The advantages of such a test would be speed, ability to detect both pulmonary and extrapulmonary forms of disease, and the relatively low technology required, which means that a serologic test should be inexpensive and easily applied throughout the world.

Restriction Fragment Length Polymorphism

Another exciting contribution of molecular biology to TB has been the development of restriction fragment length polymorphism (RFLP), or DNA fingerprinting, as it is commonly know. This technique allows one to identify individual strains of *M. tuberculosis* and thereby trace the transmission of these strains from individual to individual (van Soolingen et al., 1991; Daley et al., 1992; Hermans et al., 1990). As shown in Figure 3, the pattern is

TABLE 11. Summary of Older Studies of Serodiagnosis of Tuberculosis (TB)

	Patients with tuberculosis			Control subjects[a] (no TB)		
Antigens	No. of patients	Sensitivity of serology[b] (% positive)	Range (% positive)	No. of patients	False-positive serology (%)	Range (% positive)
PPD	496	70	31–72	661	10	0–17
Purified extracts	653	75	48–94	1053	3	0–9

[a]When normal controls were used, false-positive rates were much lower than for other pulmonary diseases.
[b]Sensitivity higher if disease chronic, that is, >3 months' duration.

TABLE 12. Sensitivity and Specificity of Monoclonal Antibodies for Serodiagnosis

Reference	Country	Antigen	Active TB			Controls	
			Type of TB	No.	True positive ELISA	No.	False-positive ELISA
Sada et al., 1990	Mexico	30 kDa	Pulmonary	59	70%	25	0
			Miliary	18	22%	37	0
			Pleural	14	14%	63	0
Charpin et al., 1990	France	A-60	Pulmonary	25	68%	32	0
Bothamley et al., 1992	England	38 kDa	Pulm: S+ C+	52	80%	39	0%
		19 kDa	Pulm: S− C+	27	58%	39	3%
		38 kDa	Pulm: S− C+	27	46%	39	0%
		3 antigens	Pulm: S− C+	27	72%	39	5%
Verbon et al., 1993	Netherlands	10 kDa	Pulmonary	44	50%		
		24 kDa	E-Pulm	32	50%		
		38 kDa	HIV TB	15	46%		
Verbon et al., 1990	Netherlands	5T	Pulmonary	26	54%	21	0
		12T		26	61%	21	0
		Both		26	77%	21	0
Wilkins and Ivanyi, 1990	Britain	39 kDa	Pulm: S+ C+	46	54%		
			E-Pulm	64	73%		
Chan et al., 1990	Hong Kong	Ag5	Pulm: S+ C+	88	45%	140[a]	2%
			Pulm: S− C+	37	40%	217	9%

Pulm: S+ C+, pulmonary TB: smear-positive and culture-positive for *M. tuberculosis*; Pulm: S− C+, pulmonary TB: smear-negative and culture-positive for *M. tuberculosis*; E-Pulm, Extrapulmonary TB.
[a]In Hong Kong study controls were: 140 normal healthy volunteers and 217 with inactive TB.

TABLE 13. Presence of IgG Antibodies to Specific Tuberculosis Antigens in Patients wth Active Tuberculosis[a]

Antigen	No. (%) of responders		% of high-level responders among total responders
	Total[b]	High level[c]	
ESAT-6	12 (20)	9 (15)	75
14 kDa	26 (44)	20 (34)	73
MPT63	9 (15)	7 (12)	78
19 kDa	23 (39)	10 (17)	50
MPT64	7 (12)	4 (7)	57
MPT51	5 (8)	0 (0)	0
MTC28	16 (27)	7 (12)	38
Ag85B	10 (17)	2 (3)	20
38 kDa	15 (25)	8 (14)	53
KatG	8 (14)	2 (3)	25

[a]Lyashchenko et al., 1998.
[b]TB patients having antibody levels greater than or equal to the mean OD_{450} plus 3 SD, obtained with negative control sera.
[c]TB patients having antibody levels greater than or equal to the mean OD_{450} plus 6 SD, obtained with negative control sera.

identical in epidemiologically linked cases in outbreaks and totally different in unrelated cases (Hermans et al., 1990). This technique promises to contribute to our understanding of TB transmission and development of disease, to the same extent that tuberculin testing did during the 20th century.

However, the technique is of very limited utility clinically. It is of no help in diagnosis or management of individual cases. In public health settings, RFLP can be used to confirm an outbreak among several individuals with TB who appeared to be linked epidemiologically (Daley et al., 1992). Such applications might include investigation of nosocomial transmission or outbreaks in prisons, homeless shelters, or other settings where arresting transmission is an important objective.

Tuberculin Skin Testing

No treatise on TB would be complete without some reference to tuberculin skin testing, partic-

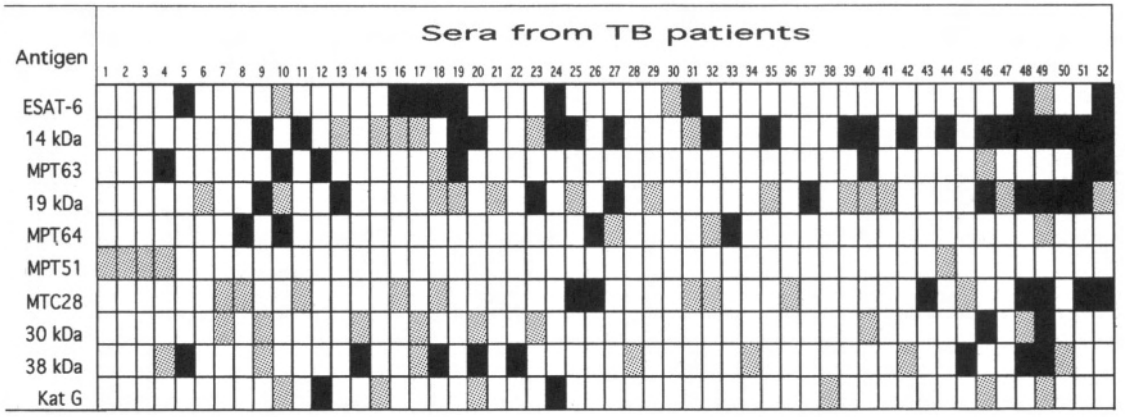

FIGURE 2. Demonstration of heterogeneous antigen recognition by serum IgG antibodies in patients with active tuberculosis (TB). Each lane represents one serum sample tested by an ELISA. Data for 52 antibody reactors are shown. Sera 1 to 22 are sputum smear-positive for TB. Sera 23 to 46 are sputum smear-negative for TB. Sera 47 to 52 are culture-positive for TB but sputum smear information was not available. Dark gray indicates high titer of antibodies, light gray indicates low titer of antibodies, and white indicates no antibodies detectable. Reproduced, with permission, from Lyashencko et al., 1998.)

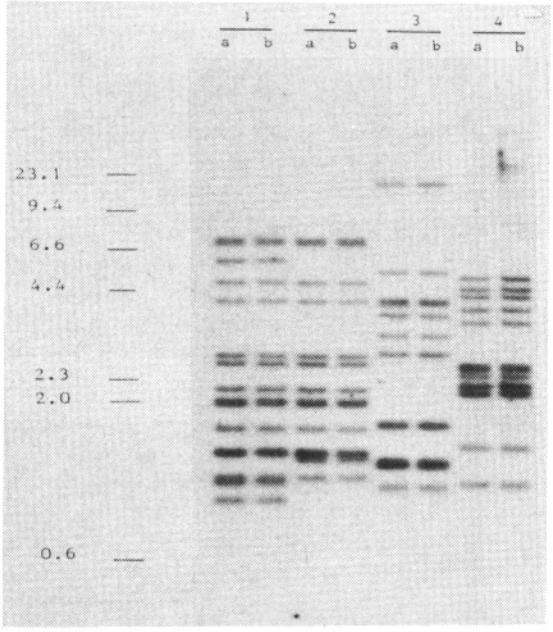

FIGURE 3. Restriction fragment length polymorphism analysis of nine strains from *M. tuberculosis* outbreak (lanes 1 to 9) and two nonrelated strains (lanes 10 and 11). Numbers in the left indicate sizes of standard DNA fragments in kilobase pairs. Reproduced, with permission, from Hermans et al., 1990.

ularly since a positive tuberculin reactor is the most commonly encountered TB-related situation in North American clinical practice. Unfortunately, the tuberculin skin test is not useful in the diagnosis of active TB because it has poor sensitivity and very poor specificity. At the time of diagnosis, 20% to 30% of patients with active TB will be tuberculin-negative (Pesanti, 1994; Holden et al., 1971), although, if tested after several months of therapy, almost all will be tuberculin-positive (WHO, 1955). This anergy can be specific to tuberculin antigens (i.e., testing with other antigens such as mumps, trichophyton, Candida, or tetanus will result in normal delayed type hypersensitivity reactions), or it can be nonspecific, that is, testing with these other antigens fails to provoke any response and the patient is considered anergic. The anergy, whether specific or generalized, is temporary.

In addition, the tuberculin test has a very high false-positive rate, so the value of a positive test in predicting disease is less than 5%. This is because virtually all individuals with TB infection will have a positive tuberculin test. Only 0.1% to 0.5% of those with latent TB infection will develop active disease in a given year. This means that the vast majority of tuberculin reactors do not have active disease. This situation is particularly problematic

because the population groups most at risk of developing active TB are the elderly, foreign-born, and minorities, who also have high prevalence of latent TB infection.

There is a common misconception that the size of the tuberculin reaction is useful in distinguishing disease from infection. However, the mean, mode, and distribution of tuberculin reactions are identical in patients with active TB and individuals with latent TB infection (WHO, 1955).

Tuberculosis Treatment

Principles of Treatment

Treatment in Two Phases

The initial intensive, or induction, phase usually lasts for the first 2 months. During this time, at least three effective bactericidal drugs are given, usually daily and under close supervision. The objective of this phase of treatment is to ensure rapid killing of the bacillary population to improve clinical status, prevent further morbidity and mortality, and render the patient noncontagious.

The maintenance or continuation phase follows and usually lasts 4 months. The duration of this phase is longer if there is drug resistance or the standard therapy must be altered because of drug intolerance. During this phase, two effective drugs are given daily or intermittently, either self-administered or directly observed. The objective of this phase is to ensure cure and to prevent relapse.

Multiple Effective Drugs

When streptomycin was introduced in 1946, it was the only drug available for TB. Within a few years, it had been observed that approximately one third of patients, particularly those who were heavily smear-positive initially, would improve over the first 3 to 4 months of therapy with streptomycin, but then relapse after 6 to 7 months. At the time of relapse, the bacilli were uniformly resistant to streptomycin, when they had initially been sensitive (Toman, 1979). Since this phenomenon was observed in many centers and in at least one third of patients, it was obviously not a rare event. The phenomenon was later observed with monotherapy with other drugs, or if a single drug was added to treatment of a patient who had relapsed with streptomycin-resistant isolates.

It is now realized that in any large population of tubercle bacilli, such as are present in active, particularly cavitary, pulmonary disease, a small proportion will have resistance to any one anti-TB drug as a result of spontaneous mutation. The frequency of these random mutations has been estimated from in vitro studies. The mutations for resistance to each drug are independent so the likelihood of spontaneous mutation to two drugs by the same bacillus is exceedingly rare. As shown in Table 14, the likelihood of emergence of resistance can be predicted from the number of drugs used and the total bacillary load of the lesion.

As a result, it is currently recommended that at all times, at least two drugs must be given for the treatment of active TB. Monotherapy is only effective in individuals with latent TB infection because the number of tubercle bacilli is so low. If the bacillary load is very heavy, then at least three drugs should be given.

Likelihood of Preexistent Drug Resistance

Even in the best circumstances, approximately 4 weeks are required between receipt of a clinical specimen in laboratory to determination of drug susceptibility. Therefore, initial drug therapy is usually given without knowledge of the drug susceptibility pattern of the bacillary population. It is important to adjust initial therapy on the basis of likelihood of drug resistance.

TABLE 14. Probability of Development of Resistance by Number of Bacilli and Number of Effective Drugs[a]

	Number of bacilli in lesion			
No. of drugs	10^4	10^6	10^8	10^{10}
One	1%	63%	100%	100%
Two	0	0	.01%	1%
Three	0	0	0	0

[a]From Toman, 1979

The likelihood of drug resistance is greater if:

- the patient is failing therapy, that is, still smear- and/or culture-positive after 5 months while on therapy (very high likelihood of resistance) (Goble et al., 1993)
- there is relapse after completion of therapy (Frieden et al., 1993; Goble et al., 1993)
- there is an undocumented history of prior drug therapy (Frieden et al., 1993)
- there is contact with a known drug-resistant case, such as in a setting of multi-drug resistant (MDR) outbreak (Edlin et al., 1992)
- the patient comes from a country where primary drug resistance rates are high (Pablos-Mendez et al., 1998; Aitken et al., 1984).

The last situation is common among foreign-born patients because in many developing countries supervision of therapy, availability of drugs, and even drug quality has been suboptimal for the past 30 years or more. Resistance to isoniazid among individuals never before treated exceeds 20% in many countries, while rifampin resistance has rapidly increased in the past decade (Pablos-Mendez et al., 1998).

Drugs Used in Tuberculosis Therapy

Rifampin

Rifampin is the most important medication for treatment of active TB disease (Fox, 1978) (Table 15). Inclusion of this drug allows the total duration of therapy to be shortest, as little as 6 months. Rifampin is bactericidal for bacilli that are intracellular (within macrophages) and extracellular. It is also important in eradicating the bacillary population with minimal metabolic activity (Dickinson and Mitchison, 1981), as are present in caseous necrotic foci.

Although rifampin is mainly used for treatment of TB disease, it can be used as monotherapy for treatment of latent TB infection. It has been recommended for treatment of contacts of isoniazid-resistant cases, but also may be used when isoniazid (INH) is not tolerated. There is limited experience with rifampin, but it appears that 4 months of rifampin is at least as efficacious as 6 months of INH in treatment of latent TB infection (Hong Kong Chest Service, 1992).

Toxicity When rifampin is given alone, it does not appear to cause hepatotoxic reactions. However, when rifampin and isoniazid are given together, then the rate of hepatotoxic reactions is higher than if INH is given alone. The major side effect of rifampin therapy is the frequent occurrence of drug interactions because rifampin activates the cytochrome p450 enzymes, thereby augmenting the metabolism of many medications, including oral contraceptives, warfarin, and others. As a result, before rifampin is given, patients must be carefully questioned about other medications they are taking. Rash is fairly common with rifampin. In addition, if rifampin is taken irregularly, it may result in a flu-like syndrome with thrombocytopenia.

Isoniazid

Isoniazid is the second most important drug used in therapy of active disease and is the most

TABLE 15. Common Antituberculosis Agents[a]

Drug	Clearance	Major side effect	Considered safe for use in:		
			Pregnancy	Breastfeeding	Pediatrics
Rifampin	Hepatic	Rash, drug interactions, ?hepatitis	Yes	Yes	Yes
Isoniazid	Hepatic	Hepatitis, rash, drug fever, peripheral neuritis	Yes	Yes	Yes
Pyrazinamide	Hepatic	Hepatitis, arthralgia, rash	No	Yes[b]	Yes
Ethambutol	Renal	Optic neuritis, rash	Yes	Yes	Yes[b]
Streptomycin	Renal	8th nerve damage, deafness, rash	No	Yes	?

[a]From American Thoracic Society, 1994; Canadian Thoracic Society, 2000.
[b]Available data is minimal, so some controversy remains. Use with caution.

commonly used drug for treatment of latent TB infection. This drug is also bactericidal for intracellular and extracellular bacilli.

Toxicity The most important and well-known side effect of isoniazid is drug-induced hepatitis. The major risk factors for drug-induced hepatitis are daily alcohol use; coexistence of other active hepatitides, such as hepatitis B or hepatitis C; and older age (Kopanoff et al., 1978; Snider et al., 1992). Under the age of 20, drug-induced hepatitis is rare except in the presence of other risk factors. Between the ages of 20 and 35, approximately 1% of recipients may develop hepatitis. Between the ages of 35 and 50, as many as 2.5% may develop hepatitis (Kopanoff et al., 1978), and over the age of 50 the frequency increases so that 5% of recipients aged over 65 will develop hepatitis (Stead et al., 1985). In one surveillance study, none of those under 35 with hepatitis died, but deaths occurred in those over the age of 35 for a total mortality of 55 per 100,000 treated (Kopanoff et al., 1978). Two reports later documented a much lower rate of mortality, ranging from no deaths among 11,141 individuals treated (Nolan et al., 1999) to 2 per 100,000 (Salpeter, 1993). The authors attributed the lower mortality to better selection of patients and more careful monitoring during therapy (Nolan et al., 1999; Salpeter, 1993).

Isoniazid can cause rash and drug fever. It can also cause a peripheral neuritis due to pyridoxine deficiency, which presents as burning paresthesias on the soles of the feet and palms of the hands. Neuritis is seen in individuals with vitamin B^6 deficiency because of malnutrition or alcoholism, may also be seen in pregnant women, and can be seen in individuals at risk for other neuropathies such as those with uremia or diabetes.

Pyrazinamide

Pyrazinamide is the third most important anti-TB agent and is bactericidal. It has the unique feature of being bactericidal at low pH, which is hypothesized to be the mechanism by which pyrazinamide is especially active in individuals with cavitary disease. In randomized clinical trials, the addition of pyrazinamide results in more rapid microbiologic conversion of sputum and allows the total duration of therapy to be reduced from 9 months to 6 months.

Toxicity However, pyrazinamide is likely to be the most toxic of the three main bactericidal drugs. In one series, it was the most common cause of drug-induced hepatitis and rash in patients treated with all three drugs. In addition, it causes severe arthralgia in approximately 11% of patients. This affects large joints without clinical signs of arthritis, but can become debilitating to the point of preventing individuals from walking. In addition, pyrazinamide will interfere with uric acid clearance, causing an elevation in the uric acid concentration in almost all recipients. In patients with a history of preexisting gout, this may precipitate an acute gout attack.

Ethambutol

Ethambutol is the least effective of the standard first-line drugs. It is considered to be bacteriostatic, not bactericidal. In randomized controlled trials, the addition of ethambutol resulted in no difference in the rate of microbiologic conversion compared with placebo. However, the presence of ethambutol in the drug regimen does prevent the emergence of drug resistant strains.

Toxicity Ethambutol is not cleared by the liver but rather is excreted by the kidneys. Therefore, there is no hepatotoxicity. However, rash and other allergic manifestations can occur. The main serious toxicity is optic neuritis, which is more common at higher dosages, such as 25 mg/kg. This optic neuritis can present as red/green color blindness, but in literate patients, a more sensitive indicator is loss of visual acuity such as when reading fine print. For patients who are placed on ethambutol for the long term, periodic ophthalmologic examination is strongly recommended.

Streptomycin

Streptomycin is bactericidal but is less commonly used than the other first-line drugs because it must be given by injection. In addition, there are significant problems of eighth nerve toxicity since this is an aminoglycoside. This drug is cleared by

TABLE 16. Standard Regimens for Drug-Sensitive Tuberculous Organisms[a]

Daily self-administered regimen
H/R/Z/E for 2 months → H/R for 4 months
H/R/E for 2 months → H/R for 7 months
Intermittent, directly observed regimen
H/R/Z/E daily for 2–8 weeks → H/R/Z/E/ 2 or 3 times weekly for remainder of first 8 weeks → H/R 2 or 3 times weekly for another 4 months

H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol.
[a]From American Thoracic Society, 1994; Canadian Thoracic Society, 2000.

the kidneys, so dosages must be adjusted if there is renal insufficiency.

Toxicity Toxic effects present as tinnitus, vertigo, and hearing loss. These may be irreversible, particularly the hearing loss. See Tables 16 and 17 for standard regiments for pan-sensitive organisms.

Other Considerations for Therapy

The same therapy is equally effective for extrapulmonary and pulmonary TB. The only exceptions are for osteoarticular, meningeal, and miliary forms where treatment up to 1 year is recommended. Tuberculous lymphadenitis may require 9 months of therapy, particularly since it is common during therapy for lymph nodes to regress and then reappear or new lymph nodes to appear and have significant residual disease at the end of therapy.

In elderly patients where hepatotoxicity is a major concern, initial therapy with INH, rifampin and ethambutol is recommended. Four-drug initial therapy should be given whenever drug resistance is suspected, including for individuals without a history of prior therapy from populations where the incidence of drug resistance exceeds 4%.

It is often recommended that TB drugs be taken on an empty stomach. However, pharmacokinetic studies have shown that meals have very little effect on drug absorption. The only exception is that isoniazid absorption is reduced by approximately 25% following a pure carbohydrate meal. All other anti-TB drugs are unaffected by food, and even isoniazid was unaffected if the meal included the usual mixture of protein, fat, and carbohydrate. Since patients frequently experience gastrointestinal upset when taking TB medicines on an empty stomach, patients should be asked to take the medication regularly with food rather than on an empty stomach. The latter may have substantial adverse effects that may lead patients to not take the pills at all.

INH, rifampin and ethambutol are considered safe in pregnancy (Hamadeh & Glassroth, 1992). These drugs are much more safe than suboptimal or

TABLE 17. Dosage Recommendation for the Initial Treatment of Tuberculosis in Children[a] and Adults[b]

	Daily dose (mg/kg)		Thrice-weekly dose (mg/kg)		Twice-weekly dose (mg/kg)	
Drugs	Children	Adults	Children	Adults	Children	Adults
Izoniazid	10–20 Max 300 mg	5 Max 300 mg	20–40 Max 900 mg	15 max Max 600 mg	20–40 Max 900 mg	15 max Max 900 mg
Rifampin	10–20 Max 600 mg	10 Max 600 mg	10–20 Max 600 mg	10 Max 600 mg	10–20 Max 600 mg	10 Max 600 mg
Pyrazinamide	15–30 Max 2 g	15–30 Max 2 g	50–70 Max 34 g	50–70 Max 34 g	50–70 Max 4 g	50–70 Max 4 g
Ethambutol[c]	15–25	15–25	25–30	25–30	50	50
Streptomycin	20–40 Max 1.0 g	15 Max 1.0 g	25–30 Max 1.5 g	25–30 Max 1.5 g	25–30 Max 1.5 g	25–30 Max 1.5 g

[a]Children <12 years of age.
[b]From American Thoracic Society, 1994; Canadian Thoracic Society, 2000.
[c]Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<8 years of age). However, it should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely.

no therapy because active untreated TB will result in high rates of miscarriage and stillbirths (Hamadeh & Glassroth, 1992). Streptomycin is known to cause fetal ototoxicity and the safety of pyrazinamide is unknown in pregnancy and therefore should be avoided. The management of pregnant patients with drug-resistant forms of TB is very complicated, and consultation with a TB expert is recommended.

In women who are breastfeeding, approximately 2% to 3% of the total daily dose of most anti-TB drugs will be excreted in breast milk (Snider & Powell, 1984). Even in newborn infants, this means that they would receive less than the recommended daily dose, so toxicity should not be seen, However, if the newborn is also receiving TB therapy, then the dosage it receives directly should be reduced by the amount it is likely to be receiving in breast milk (Snider & Powell, 1984).

In patients with renal insufficiency, the dosage of ethambutol may have to be adjusted and streptomycin or other injectable aminoglycosides should be avoided if possible.

Drug Resistance and Intolerance

The discussion of management of active tuberculosis in patients with drug-resistant strains or in patients who are not able to tolerate one of the first-line drugs is beyond the scope of this text. In such instances, a TB expert should be consulted. However, certain general guidelines are summarized in Table 18. It is important to emphasize that all randomized controlled trials of short course anti-TB therapy, as well as all trials involving intermittent therapy, included *only* patients with fully drug-sensitive organisms who tolerated all drugs given. Therefore, none of the recommendations summarized in Table 18 are supported by evidence from randomized trials; they are rather derived from the consensus of experts (Goble et al., 1993; Park et al., 1996).

The most common error noted in retrospective surveys of TB management of patients with drug resistance is the failure to prolong therapy beyond the customary 6 months and to ensure that at least two drugs are given to which the organisms are sensitive (Goble et al., 1993). Inadequate duration such as 6 months increases the risk of relapse with resultant risk of selection for new drug-resistant strains.

Compliance with Therapy

By far the most common cause of failure of anti-TB therapy worldwide is that patients do not take a full course of therapy as prescribed (Sumartojo, 1993). The most commonly given reason is that they simply feel much better. Indeed, resolution of all symptoms usually occurs by 2 to 3 months of therapy except in the sickest patients. Naturally, it is difficult to convince patients to continue taking pills that may make them feel worse when they are completely asymptomatic. A course of therapy of 2 to 3 months is sufficient to render almost all patients smear-negative, but there will still be a considerable population of viable bacilli remaining. These bacilli are relatively resistant, since the most susceptible portion of the bacillary population has already been killed (Toman, 1979). When therapy is stopped prematurely, this bacillary population recovers within 2 to 3 months, so that the patient becomes smear-positive and symptomatic again. However, the bacillary population will now be more resistant, either fully or partly, to the therapy first given. For this reason, noncompliance is the most significant factor contributing to the

TABLE 18. Regimens for Patients with Drug-Resistant Organisms or Who Are Intolerant of First Line Anti-Tuberculous Drugs[a]

Resistant/intolerant to:	Regimen		Total duration
Isoniazid	R/Z/E/ 3 months	→ R/E 10 months	12 months
Rifampin	H/Z/E/ ∓ 2 months	→ H/E 16 months	18 months
Pyrazinamide	H/R/E 2 months	→ H/R 7 months	9 months
Ethambutol	H/R/Z 2 months	→ H/R 4 months	6 months
Isoniazid + rifampin	Z/E/S + Q 2 months	→ Z/E/Q 16–22 months	18–24 months

development of drug resistance, and since patients become contagious again, these resistant organisms can be transmitted.

Human behavior is difficult to predict, and compliance with therapy is no different. Numerous articles have eloquently discussed this problem. However, certain factors indicate a high risk for noncompliance (Sumartojo, 1993). These include (1) Homelessness or unstable housing, (2) major psychiatric disorder, (3) history of substance or alcohol abuse, (4) prior noncompliant behavior, (5) failure of therapy or relapse shortly after the end of therapy (generally an indicator of suboptimal compliance). In patients without such risk factors, almost half will fail to complete a full course of anti-TB therapy if left entirely to their own devices. This noncompliant behavior is not associated with age, gender, socioeconomic status, educational level, or ethnic origin, contrary to the firmly held beliefs on the part of many providers.

As a result, directly observed therapy (DOT) was developed and widely promoted as an essential component of therapy of TB disease. However, even its most passionate supporters will admit that DOT alone is not enough. Part of the success of DOT lies in the regular human contact with patients. The most successful programs are ones where the workers administering DOT also assist patients by resolving many other problems in their lives. Moreover, more dispassionate observers have noted that introduction of DOT has had little impact in well-functioning TB control programs where compliance rates were already high.

The essential principle of treatment of active TB is that every patient must complete therapy as prescribed and every dose must be taken. Whatever method of monitoring of therapy is adopted, the program must ensure that the therapy is flexible so that it can be adapted to patient needs, that drug supplies are accessible and completely free, that staff who follow the patients take a close interest in all aspects of the patient's care, and that if suboptimal compliance is noted there is an immediate response on the part of the caregivers to intensify supervision. It is not considered acceptable medical practice to simply prescribe anti-TB medication and assume that the patient will take the therapy as prescribed. This practice is a recipe for disaster, both for the patient and for those around him.

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Pneumonia Caused by *Yersinia pestis:* Plague Pneumonia

DENNIS JAMES CLERI, RANDY MARTON,
MOHAMMED RABBAT, AND JOHN VERNALEO

Introduction

After millennia of epidemics that have changed the course of human history, plague is still considered among the "emerging bacterial zoonotic and vector-borne diseases" and a special risk to modern man (Franz et al., 1997; Walker et al., 1996). We are in the midst of the Third Pandemic, which began in 1896 (Walker et al., 1996). In 1994, the first reported cases of plague in India in 28 years resulted in local panic. This prompted the Centers for Disease Control and Prevention (CDC) to issue special surveillance guidelines for the isolation of imported pneumonic plague (Fritz et al., 1996).

Risk Factors

The risk of human disease is directly related to urbanization, wars, social and political upheavals, and natural disasters (Ell, 1994; Goldstein, 1992; Tuchman, 1978). In North America, humans most often become infected when they come in contact with sylvatic sources of the disease and are bitten by infected fleas. Typically, cases are first reported in the early spring and peak in the summer, and occasional cases are reported through the fall.

In the United States, all cases are either reported from the western states, or were imported from the western half of the country; two thirds of the infections occurred in males; two thirds were the results of flea bites (fleas from ground squirrels, rock squirrels, prairie dogs, and a domestic cat); 15% were the result of contact with an infected animal, most often a rabbit, and in the remainder of the cases the source of the infection could not be identified. About one half of the cases occur in Native Americans. Eight percent had pure septicemic plague, 10% had bubonic plague with secondary pneumonia, and the remainder had bubonic disease, with most disease being either axillary or cervical (Barnes & Poland, 1984). Primary plague pneumonia is a rare event and has occurred after contact with an infected domestic cat (Barnes & Poland, 1983, 1984).

Risk activities put the individual in contact with either the vector or reservoir. Individuals at risk include those who engage in outdoor work, camping, or hunting in endemic areas; the poor (who are in close contact with the rat-flea population in endemic areas); veterinarians and assistants; and pet owners in enzootic areas (especially cat owners) (Cleri et al., 1997).

Plague Pneumonia: Introduction to Pathogenesis and Risks

Pneumonia caused by *Yersinia pestis* results from hematogenous spread from bubonic or rapidly

DENNIS JAMES CLERI Internal Medicine Residency, St. Francis Medical Center, Trenton, New Jersey 08629. **RANDY MARTON AND MOHAMMED RABBAT** • St. Joseph's Hospital and Medical Center, Paterson, New Jersey 07501. **JOHN VERNALEO** • Western Queens Community Hospital, Astoria, New York 11102.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

developing septicemic plague, or from direct inhalation of aerosolized bacteria after coming in contact with a person or animal with plague pneumonia (Butler, 1983, 1990; CDC, 1984, 1992b, 1993; Cleri et al., 1997; Doll et al., 1994). Pneumonic plague is one of the seven or possibly nine recognized clinical forms of human disease caused by *Y. pestis* (if cutaneous and gastrointestinal presentations are considered separate entities) (Butler, 1990; Cleri et al., 1997; Hirota & Wake, 1995).

Plague and plague pneumonia are both endemic and epidemic diseases. A high index of clinical suspicion and immediate therapy prior to the definitive diagnosis of plague pneumonia are essential for successful treatment of patients with the most severe and contagious forms of the disease (Welty, 1986). These goals may only be achieved by the complete understanding of its epidemiology, ecology, bacteriology, pathogenesis, and most importantly the ability to recognize all forms of the disease in order to link one case with another.

History

Early texts suggest that plague was first recognized as a disease in the Himalayas (Mollaret, 1995). Epidemic plague is suspected to have occurred among the Philistines in 1320 B.C. "The Great Dying/the Great Pestilence" was described by Samuel as involving pelvic boils, rash, high mortality, and an association with mice (Blaser, 1998; Cleri et al., 1997; Ell, 1994; Ganem, 1986; Goldstein, 1992; Palmer, 1998; Tuchman, 1978).

The Old Testament dictates involving the 7-day Jewish holiday of Passover (Pesah) beginning on the 14th day of the month of Nisan in the Hebrew calendar (Exodus 12:18) in the early spring, just prior to the annual warm weather increases in rat and flea populations in the summer months, could decrease the risk of epidemic plague. The religious obligation of cleaning all grain from households, precluding long-term grain storage, and permitting only the keeping of perishable foods would reduce the opportunity for rodent infestation (Blaser, 1998). Conversely, there is no evidence that attack rates among Jews during the Black Death was lower. The importance of person-to-person spread from pneumonic or human-flea transmission; the practice of symbolically selling the "chametz" (leaven) to non-Jews, thus permitting the storage of grain; the fact that in Europe plague epidemics began in the fall and not the spring; and the free movement of rats and their fleas in and out of religious enclaves are all factors cited for the inefficacy of this biblical protection (Blaser, 1998).

Plague in China is described in writings from 281 to 341 A.D. (Mollaret, 1995). Thucydides (406–400 B.C.) described the epidemic of Athens (430–426 B.C.) at the outbreak of the Peloponnesian War (431–404 B.C.) that many believed was the classic description of plague. Others have suggested that the epidemic may have been actually viral influenzae, epidemic typhus, smallpox, or arboviral disease (e.g., Rift Valley fever) (Langmuir et al., 1985; Relief & Cilliers, 1998). Rebuttals still make a strong case for the "Thucydides syndrome" being classical plague (Holladay, 1986; Langmuir et al., 1986). Still others have suggested that mycotoxins may have played a role in making the populations of Athens and Attica more susceptible to microbial pathogens (Schoental, 1995).

The First Great Pandemic

More definitively described by Procopius was Justinian's plague (the First Great Pandemic, 541–767 A.D.), believed to have started in central or eastern Africa and spread along the Nile River to Pelusium and Alexandria, the rest of Egypt, Palestine, and all the Mediterranean coastal areas. Its spread inland was limited (Mollaret, 1995). Deaths were estimated at between 40 and 100 million (Ell, 1994; Gage, 1998; Goldstein, 1992; Guiyoule et al., 1994; Mollaret, 1995; Tuchman, 1978). World population at that time has been estimated at about 260 million (Gage, 1998). Epidemic disease disappeared from western civilization for more than seven centuries, probably because of a scarcity of rodents (Mollaret, 1995).

Plague with famine may have been responsible for 63 million deaths in China (population estimated at 123 million in 1193–1195 A.D. to 60 million in 1381 A.D.) (Mollaret, 1995).

The Second Great Pandemic—The Black Death

It is believed that plague persisted in the rodents in the steppes of Central Asia and among the

nomadic tribes of the area (Mollaret, 1995). The disease was reintroduced into Europe with the arrival of Genoese trading ships from the besieged city of Caffa on the Black Sea, landing in Messina, Sicily, with dead and dying sailors on October 1, 1347 (Tuchman, 1978). By 1351, the plague had spread across Europe and killed 25 million people (Mollaret, 1995). This was termed "demic plague" with direct person-to-person transmission (Mollaret, 1995). Again, other interpretations of historical writings have suggested multiple diseases operating at the same time. One reason is that epidemic spread of plague has been described as "faltering" or diffusing very slowly ..." rather than the explosive outbreaks of historical writings (Twigg, 1995).

This Second Great Pandemic, also known as the "Black Death," killed one third of the human population from Iceland to India during the next 200 years. Susceptibility to disease varied in local populations with mortality rates as low as 20% and as high as 90% (Barnes & Quan, 1992; Guiyoule et al., 1994). Periodic outbreaks of plague occurred until 1839, when the disease finally disappeared from Constantinople (Mollaret, 1995).

Yersinia pseudotuberculosis, prior to the two world wars of this century, was isolated exclusively in Europe. In 1953, Devignat postulated that *Y. pseudotuberculosis* appeared in Europe as a mutant of *Y. pestis,* slowly spreading among rodents and enabling them to develop cross-immunity against *Y. pestis* (Mollaret, 1995). Experiments with the rodent *Meriones* species have demonstrated that peroral feedings of *Yersinia enterocolitica* will also confer immunity against *Y. pestis,* and the fecal shedding of the *Yersinia enterocolitica* spreads the organism to other noninfected rodents, also conferring immunity (Mollaret, 1995).

The Third Great Pandemic

The Third Great Pandemic (the Modern Pandemic) began in China, spreading from Yunan province to the southern Chinese city of Kun-ming in 1866; to the port of Pei-hai in 1882; to Hong Kong in 1894; to Bombay in 1896; to Suez in 1897; to Madagascar and Mauritius in 1898; to Alexandria, Japan, and the port cities of East Africa and Portugal in 1899; and to Manila, Sydney, Glasgow, and San Francisco in 1900 (Gage, 1998; Mollaret, 1995). Plague was imported into Honolulu in 1908; into Java in 1911; into Ceylon in 1914; and into France in 1920 (Mollaret, 1995). Although many of the harbor cities became transiently infested (New York City, Galveston, and New Orleans), plague established itself inland in the rodent population in western North America from above the Canadian border through Mexico, in the highlands of Madagascar, and in South America (Boisier et al., 1997; Cleri et al., 1997; Gage, 1998; Mollaret, 1995; Palmer, 1998).

The first case of plague in the United States was imported from China and identified in San Francisco on March 6, 1900. By 1914, mini-epidemics were reported in Texas, Louisiana, and Florida (Butler, 1983; Gilespi & Timoney, 1981; Risse, 1992). During the first 50 years of the 20th century, there were 523 cases of plague in the United States, with a 65% mortality (Gilespi & Timoney, 1981). The number of cases doubled by 1980 (Kaufmann et al., 1980). Between 1970 and 1983, the United States experienced between 1 and 40 cases per year (Palmer, 1998). Four cases were reported in 1997 and 6 cases were reported in the first 8 months of 1998 (CDC, 1998). Table 1 describes the history of the plague (Barnes & Quan, 1992; Cook, 1995; Kilwein, 1995; Langer et al., 1952; Perry & Fetherston, 1997; Mills, 1995; Risse, 1992; Sutphen, 1997).

The Discovery of the Plague Bacillus

The story of the identification of the causative agent of plague is as dramatic as the history of the epidemics. In Paris, Alexandre Yersin was introduced to Louis Pasteur and Emile Roux while seeking a vaccine after he cut himself while performing an autopsy on a rabies patient (Butler, 1983, 1994; Cleri et al., 1997). He subsequently worked with Emile Roux on *Corynebacterium diptheriae* and its toxin. Their publication in 1888 described the "poison tres active" and its effect on the entire body. They were able to isolate the toxin from patients' urine and proposed the development of an attenuated toxin as a vaccine in 1889 (Solomon, 1995).

Yersin interrupted his career to join the merchant navy shipping to French Indochina in 1887. He made several expeditions into the Indochinese interior during the subsequent years, until 1894, when he was sent to Hong Kong by the French Colonial Medical Corps during the plague epi-

TABLE 1. History of the Plague

Year	Event	Mortality	Comment
1320 B.C.	"The Great Dying/The Great Pestilence" affecting the Philistines		Described in Samuel as being associated with mice and victims suffering with boils and a rash.
430–426 B.C.	The epidemic of Athens described by Thucydides at the outbreak of the Peloponnesian War. Pericles dies of plague in 429 B.C.		Others have suggested that the epidemic was caused by viral influenzae, epidemic typhus, smallpox or an arboviral disease such as Rift Valley Fever.
162–165 A.D.	Returning from campaigns in Parthia, Antioch, Artaxata, Seleucia, Ctesiphon, Armenia, and other parts of Mesopotamia troops of the Roman general Verus introduce the plague to the western Empire.		
281–341 A.D.	Plague first described in China		
451 A.D.	Attila the Hun must withdraw his forces from battle with the Romans after plague breaks out among his troops		
541–767 A.D.	Justinian's plague, also known as the "First Great Pandemic," described by Procopius	40–100 million (world population was believed to be less than 500 million). Local death rates are estimated between 15% and 40% with an overall population loss of 50% to 60%.	Believed to have started in central Africa and first recorded in Pelusium, Egypt.
1193–1195 A.D.	Plague and famine in China	Reduced the population from 123 million to 60 million.	
8th to 14th centuries	Europe experiences no epidemic plague.		Europe has 300% increase in population from the 10th to 14th centuries.
October 1, 1347	Plague introduced into Europe through the port of Messina, Sicily, from a Genoese trading ship from Caffa on the Black Sea.	Over the next 200 years one third to one half of the human population was killed by plague from Iceland to India.	Believed to be the beginning of the Second Great Pandemic, also known as the "Black Death." The plague reached England in 1348, Germany in 1349, and Russia in 1350.
1347–1350		One quarter to one third of the European population (17–28 million) dies in the first 3 years of the outbreak.	
1433–1438	Celebrating the disastrous reign of Edward (Duarte) I, an epidemic of plague hits all of Portugal.		
1664–1665	The Great Plague of London	60–65,000 deaths	Inspiration for Daniel Defoe's *Journal of the Plague Year* (1722). The Great Fire of London of 1666 may have been instrumental in stopping the epidemic.

TABLE 1. *(Continued)*

Year	Event	Mortality	Comment
1720	Plague erupts throughout Europe; Marseilles epidemic		Europe experienced smaller outbreaks of plague during the 15th through 17th centuries.
1834	Egyptian epidemic		
1839	Plague disappears from Constantinople.		Believed to be the end of the Second Great Pandemic.
1894	Epidemic in Canton	100,000 deaths	Beginning of the Third Great Pandemic.
1894	Hong Kong epidemic. Yersin identifies etiologic agent within 1 week of arrival. James Cantilie associates plague with disease in rats.		Kitasato and Yersin are both credited with the discovery by contemporaries.
1895	Epidmeic in India	1,300,000 deaths	Reaches Bombay in 1896 and Calcutta in 1898.
1897	Plague reaches Suez.		
1898	Plague introduced to Madagascar from ships in the Tamatave harbor, and Mauritius.		
1897–1898	Rat-flea theory proposed by Paul Louis Simond, and independently by Masanori Ogata during the Indian epidemic.		
1899	Plague reaches Alexandria, Japan, East Africa, and Portugal.		
1898–1918	India experiences over 10 million deaths.		
March 6, 1900	Plague introduced into San Francisco and North America	Only by 1914 did science and political will enable San Francisco to rid itself of plague.	
1908	Plague invades Honolulu.		
1911	Plague invades Java.		
1914	Plague breaks out in Ceylon.		
1914	Rat-flea transmission proven by Bacot and Marton.		
1920	Outbreak of plague in Marseilles.		
1924–1925	Last urban epidemic of plague in the U.S. (Los Angeles)		Last known cases of person-to-person spread of pneumonic plague in the U.S.
1958–1975	Vietnam War results in plague being reported in that country at 10,000 cases/year		In 1990, Vietnam was still reporting the highest number of cases, 32% of 1250.
August 1994	Outbreak of bubonic plague in Beed district of Maharashtra in western India.		
September 1994	Reports of pneumonic plague in the city of Surat in Gujarat, neighboring Beed. 400,000 to 500,000 leave Surat		By the end of October 1994, 6300 suspected cases reported from 12 Indian states, but few with laboratory confirmation.
July 1995–March 1996	Plague outbreak in Majunga, Madagascar	24 deaths (case–fatality rate: 8.7%)	617 suspected cases, of which 394 underwent laboratory tests; only 60 (15.2%) could be confirmed.

demic. On June 15, 1894, Yersin landed in Hong Kong and promptly had all his money stolen. He and his assistant were left with a microscope and an autoclave. Three days earlier, the better equipped colleague of Robert Koch, Shibasaburo Kitasato, had arrived and was already seeking the etiologic agent for the plague (Butler, 1994; Solomon, 1995; Yule, 1995).

Yersin was introduced to Kitasato at Kennedy Town Hospital while Kitasato's team was performing an autopsy on a plague victim. Yersin noticed that, although the blood and all organs were carefully examined, the buboes and skin lesions were ignored. Yersin was denied access to corpses and hospital facilities reserved for Kitasato (Butler, 1995; Solomon, 1995).

Yersin had a bamboo hut built for his laboratory. His guide, an Italian missionary, bribed the British sailors who were disposing of bodies to allow Yersin time in the cellar where the cadavers were stored before burial (Solomon, 1995, 1997a). He removed buboes, and in his laboratory, although the Gram's stain was negative, identified the causative organism by its bipolar staining with Loeffler's blue stain. Pure cultures of the organism killed guinea pigs, and gram-negative bacilli were isolated from the animals' lymph nodes (Solomon, 1995). James Alfred Lowson, Port Medical Officer of the (British) Colonial Medical Service of Hong Kong, noted in his diary, "23rd June. Got microscopes out again. Frenchman Yersin got his bacillus" (Yule, 1995). Legend has it that Yersin may have succeeded because of ambient temperatures in his bamboo hut and his lack of an incubator, as the organism grows better at 28–30°C rather than at 37°C (Perry & Fetherston, 1997).

On August 4, 1894, *The Lancet* reported Kitasato's discovery, In a rush to publication, believed to be spurred by Lowson, slides sent to both *The Lancet* and the *British Medical Journal* on August 11 were described in print as being polymorphic but predominantly an encapsulated diplococcus (Solomon, 1997b; Yule, 1995). August 18 saw reports of Yersin's letter to the French Academic de Sciences. Kitasato's paper in the August 25, 1894, issue of *The Lancet* failed to identify the organism as either gram-positive or gram-negative (Solomon, 1995, 1997a,b; Yule, 1995).

Controversy raged for years. By 1900, Aoyama and Ogata, Japanese colleagues of Kitasato, published papers stating that the causative agent of plague was the bacillus described by Yersin (Yule, 1995). Kitasato admitted he was mistaken at a medical conference in 1925. In 1953, L. Fabian Hirst published *The Conquest of Plague,* in which he states that Kitasato was the first to see the bacillus, but Yersin described it better, because of technical superiority. Most recent authorities give the entire credit to Yersin and, since 1970, the organism has been known as *Y. pestis* (Butler, 1995; Yule, 1995). We believe it is still possible that Kitasato was observing the plague bacillus, as, when grown above 33°C, the organism forms a carbohydrate-protein envelope, while others believe Kitasato was describing a contaminating pneumococcus (Perry & Fetherston, 1997).

Microbiology

Yersinia Species and *Yersinia pestis*

Yersinia species are facultative anaerobic members of the Enterobacteriaceae family (Barnes & Quan, 1992; Bercovier & Mollaret, 1984; Corbel, 1990; Goldstein, 1992; Perry & Fetherston, 1997; Wanger, 1998). They ferment glucose without the production of gas. The staining and biochemical properties of these organisms are shown in Table 2 (Bercovier & Mollaret, 1984; Gage, 1998; Quan, 1988; Reddin et al., 1995; Wanger, 1998; Worsham et al., 1995). *Y. pestis* is one of the three human pathogens (with *Y. pseudotuberculosis* and *Yersinia enterocolitica)* of the 11 species of the genus *Yersinia* (Bercovier & Mollaret, 1984; Butler, 1995; Perry & Fetherston, 1997). It is a gram-negative rod or coccobacillus (0.5–0.8 mm diameter and 1–3 mm length) (Bercovier & Mollaret, 1984; Perry & Fetherston, 1997). Organisms grown in liquid media may appear as short chains of four to rive bacteria (Bercovier & Mollaret, 1984). It is the only species of this genus that is nonmotile at 25°C (although *Yersinia ruckeri* is only weakly motile at 25°C and all are nonmotile at 37°C). Motile species exhibit a peritrichous flagellum when grown below 30°C (Bercovier & Mollaret, 1984). *Y. pestis* has no true polysaccharide capsule, but forms a carbohydrate-protein envelope termed capsular antigen or fraction

TABLE 2. Microbiological and Biochemical Properties of *Yersinia* Species

Gram stain	Gram-negative rods or coccobacilli 0.5–0.8 μm wide by 1.0–2.0 μm long.
Other staining characteristics	*Y. pestis* stains in a bipolar fashion ("safety pin") with Giemsa, Wright's, or Wayson's stains, *not* with the Gram's stain. The organism is *not* acid-fast.
Metabolism	Facultative anaerobes.
Fermentation	Ferments glucose without gas production, also ferments fructose, galactose, maltose, mannitol, mannose, N-acetylglucosamin, and trehalose.
	Y. pestis is non-lactose fermenting.
Biochemistry	Oxidase-negative; catalase-positive; reduces nitrates; positive isocitrate lyase test.
	Y. enterocolitica, *Y. frederiksenii*, and *Y. intermedia* produce acetoin at 28°C, but not at 37°C.
Growth characteristics	Grows on nutrient agar but colonies are smaller than 1 mm at 24 hours' incubation at 28–37°C. At 48 hours, the colonies are 1–2 mm in diameter with a "hammered metal surface" appearance. Growth in broth results in pellicle or stalactite that is not uniformly turbid.
	Y. pestis requires more than 48 hours to produce nonmucoid, pitted gray colonies 1 to 2 mm in diameter. *Y. pestis* will grow between 4 and 37°C with an optimum growth temperature of 28°C. The organism cannot survive for long periods above 40°C.
	The organism may survive and multiply in soil, especially rodent burrows, and is inactivated by heating to 56°C, 3–4 hours of sunlight, gamma radiation, or exposure to phenol for 15 minutes. It survives if dried on threads for several days, in dried blood for 3 weeks, in flea feces for 5 weeks, and in rodent burrows for up to 11 months.
Other tests	Positive slide or tube agglutination with antiplague antiserum and formalin-killed suspension of the organisms.
	Positive specific fluorescent staining with fraction 1 antiserum with culture material or tissue samples from inoculated laboratory animals. The antigen is expressed at 37°C and may be falsely negative in cultures grown below 35°C, in fleas, and in samples refrigerated for prolonged periods of time.
	Lysis by specific *Y. pestis* bacteriophages at 25 and 37°C will confirm the diagnosis (used by the Centers for Disease Control and Prevention).
Motility	Motile at 22–30°C, nonmotile at 37°C, except *Y. pestis*, which is always nonmotile.
Serology	Paired serum samples for anti-F1 IgG processed by passive hemagglutination although pathogenic strains not expressing F1 have been reported. A 4-fold rise in titer or a single titer greater than 10 in an unvaccinated patient is considered a positive test. Although it is highly immunogenic, recent studies have found that F1 is not essential for mouse pathogenicity and researchers have suggested that future diagnostic tests and vaccine development should not center exclusively on F1.
	ELISA, PCR, and DNA hybridization methods have also been used but are still considered experimental.

1 when grown above 33°C (Bercovier & Mollaret, 1984; Perry & Fetherston, 1997). It does not form spores and exhibits its classical bipolar ("safety-pin") staining with Wright's, Giemsa, or Wayson stains (Cleri et al., 1997; Perry & Fetherston, 1997).

Based upon DNA–DNA pairing, *Y. pseudotuberculosis* and *Y. pestis* represent two biovars of the same species (Barnes & Quan, 1992; Corbel, 1990; Goldstein, 1992; Perry & Fetherston, 1997). To avoid confusion, *Y. pestis* and *not Y. pseudotuberculosis pestis* is the most accepted designation for the plague bacillus (Corbel, 1990).

Yersinia pseudotuberculosis and Yersinia enterocolitica

Y. pseudotuberculosis is a human and animal pathogen causing sepsis in debilitated patients (patients with cirrhosis, hemochromatosis, and diabetes), diarrhea, and most commonly mesenteric lymphadenitis (resulting in symptomatology resembling acute appendicitis) (Bercovier & Mollaret, 1984; Butler, 1995). Rarely, erythema nodosum and polyarthritis have also been associated with this infection (Butler, 1995).

Y. pseudotuberculosis infection must be differentiated from another zoonosis, *Corynebacterium pseudotuberculosis,* which has been associated with abscesses, ulcers, bacteremia, abortion, and pneumonia in sheep, goats, and horses and usually infects the lymph nodes, skin and solid organs. In humans, it has caused pneumonia, and caseous lymphadenitis in persons exposed to infected animals, drinking raw milk, or handling hides (Clarridge et al., 1997; Quan, 1997).

Yersinia enterocolitica causes enterocolitis,

reactive polyarthritis lasting up to a year, persistent back pain, and sacroiliitis lasting more than 1 year, especially in patients who are positive for HLA-B27-positive. Less commonly, patients develop erythema nodosum and, rarely, exudative pharyngitis. Sepsis is seen in debilitated patients (those with diabetes, severe anemia, hemochromatosis, cirrhosis, and malignancy) and the elderly (Butler, 1995). Pneumonia, empyema, and lung abscesses are rare. Sepsis has resulted in endocarditis, mycotic aneurysms, abscesses of the liver and spleen, osteomyelitis, meningitis, and would infections (Butler, 1995; Bercovier & Mollaret, 1984).

Table 3 describes other members of the genus *Yersinia* (Bercovier & Mollaret, 1984; Butler, 1995; Cleri et al., 1997; Perry & Fetherston, 1997; Quan, 1998; Wanger, 1998). *Y. intermedia, Y. fredriksenii, Y. kristensenii, Y. aldovae, Y. mollaretti, Y. bercovieri,* and *Y. rohdei are* all considered opportunistic infections, while *Y. ruckeri* is a fish pathogen (Quan, 1997).

TABLE 3. *Yersinia* Species

Organism	Ecologic niche	Pathogenicity
Yersinia pestis	Zoonotic infection of rodents (especially *Rattus rattus* and *R. norvegicus* with flea vectors (most importantly *Xenopsylla cheopsis*, *Cheratophyllus fasciatus*, *Ctenocephalus canis*, and *Ctenocephalus felis*. Also infects camels, goats, monkeys, and rarely wild carnivores. Survives in the soil in animal burrows.	Causes bubonic plague, pneumonic plague, plague sepsis, meningitis, pharyngitis, subclinical disease (seroconverters) and abortive bubonic plague (pestis minor).
Yersinia pseudotuberculosis	Infects rodents and wild birds but most common mode of transmission is through contaminated water or food.	Mesenteric lymphadenitis, diarrhea, sepsis, reactive arthritis, erythema nodosum.
Yersinia enterocolitica	Wild and domesticated animals (including healthy pigs) may be infected. The organism is also transmitted by contaminated food and water.	Enterocolitis, erythema nodosum, reactive arthritis, Reiter's syndrome, pharyngitis, sepsis, hepatic and splenic abscesses, osteomyelitis, wound infections, meningitis, pneumonia, empyema, lung abscesses, endocarditis, mycotic aneurysms, wound infections.
Yersinia frederiksenii	Water, soil, fish, food, animals.	Considered a commensal, it has been found to colonize the human gastrointestinal tract.
Yersinia mollaretti	Humans, water, food.	Possible cause of diarrhea.
Yersinia bercovieri	Humans, vegetables, soil.	Possible cause of diarrhea.
Yersinia rohdei	Surface water and stools from healthy dogs, human, rodents.	Cultured from 2 cases of human diarrhea.
Yersinia ruckeri (may soon be reclassified out of the *Yersinia* genus)	Infects trout and salmon, causing inflammation around the head of the fish. Also found in humans, food and water. The organism has been isolated only in North America.	Fish pathogen, one of the causes of "enteric redmouth disease" of trout and salmon.
Yersinia intermedia	Fresh water, fish, food, and healthy humans	Has been isolated from the stools of humans with diarrhea.
Yersinia kristensenii	Soil, fresh water, food, healthy animals, and humans	Isolated from stools of humans with enterocolitis.
Yersinia aldovae	Considered a *Y. enterocolitica*-like organism along with *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*. Found in water, fish, and humans.	
Yersinia philomiragia now reclassified as *Francisella philomiragia*	Muskrat pathogen associated with contact with salt water.	Rare human pathogen in both normal and compromised hosts.

Francisella philomiragia: The Other Nonmotile *Yersinia*

Y. philomiragia would have been the only other nonmotile *Yersinia* species other than *Y. pestis.* It was first isolated from a dead muskrat in 1959 and from water sources at the Bear River Migratory Bird Refuge in Utah. In 1969, Jensen, Owen, and Jellison proposed it be classified as a *Yersinia* species because it morphologically resembled *Y. pestis* and had some DNA–DNA relatedness (Bercovier & Mollaret, 1984). In 1980, the organism was reclassified as *Francisella philomiragia.* Human infection has been reported in immunocompetent and -compromised hosts in association with exposure to salt water (Nano, 1998; Wanger, 1998).

Yersinia pestis Biovars

Y. pestis exists as three biovars based on distribution and biochemistry. They are *antiqua, medievalis,* and *orientalis* (also known as *oceanic)* (Bercovier & Mollaret, 1984). rRNA gene restriction patterns (ribotypes) have also been used to classify the organisms. Table 4 describes these differences (Bercovier & Mollaret, 1984; Corbel, 1990; Guiyoule et al., 1994).

Isolation and Microbiological Identification of *Yersinia pestis*

In the past, methods of diagnosis have included splenic puncture in Java and skin testing with emulsions from plague-infected guinea pig lymph glands (Wilcocks & Manson-Bahr 1972). We recommend a more conservative and contemporary approach.

Y. pestis should be isolated only in laboratories equipped with biosafety isolation hoods and equipment (Wanger, 1998). Blood, bubo aspirates, swabs or scrapings from skin lesions, sputum, and, when indicated, cerebrospinal fluid should be obtained for culture. Biopsy or necropsy specimens of lymph nodes, liver, spleen, lung, and bone marrow should also be cultured. Urine and stool cultures have not been of diagnostic value (Quan, 1988). *Y. pestis* may be identified after isolating typical colonies from solid media (pinpoint colonies on blood agar in 24 hours and 1–2 mm colonies with a "hammered metal surface" at 48 hours at 28–37°C) (Quan, 1988). The morphology of the gram-negative organism has been described above.

Specimens should be streaked on 5% blood agar, MacConkey agar, and cystine heart agar with 8% sheep blood in order to recover *Francisella tularensis,* which may present acutely in a manner similar to plague. Media should be incubated for at least 10 days, although growth is usually appreciated within 48 to 72 hours (Quan, 1988).

Flourescent-antibody testing against purified Fl capsular antigen will presumptively identify the organism. But this test may be falsely negative if applied to specimens refrigerated for more than 30 hours, from cultures incubated at less than 35°C, or from fleas (Perry & Fetherston, 1997). Additionally, Fl capsular antigen-negative organisms have been found to be pathogenic in mice, and relying on this antigenic stimulant as the sole serologic screen may be a mistake (Worsham et al., 1995).

(Automated) rapid commercial identification

TABLE 4. Biovars of *Yersinia pestis*

Biovar	Distribution	Biochemistry		
		Produces acid aerobically from glycerol	Reduces nitrate to nitrite	Produces acid aerobically from melibiose
Y. pestis biovar *antiqua* (ribotypes F to O)	Central Asia and Central Africa	Yes	Yes	No
Y. pestis biovar *medievalis* (ribotypes O and P)	Iran, Russia, and countries making up the former USSR	Yes	No	Yes
Y. pestis biovar *orientalis* (*oceanus*) (ribotypes A to G)	Worldwide	No	Yes	No

systems often misidentify *Y. pestis* as *Y. pseudotuberculosis* or other Enterobacteriaceae because of its slow growth and paucity of positive diagnostic biochemical tests. Older Analytical Profile Index (API) systems tend to misidentify less reactive bacteria (CDC, 1997). The recently tested BBL Crystal/Nonfermenter System appeared superior to the API 20NE system, although API updated its system in 1996 (version 10.1) (Wilmoth et al., 1996). Plague laboratory researchers still believe that no automated system can be relied upon for the identification of *Y. pestis,* and classical bacteriologic methods are still necessary to confirm or rule out the diagnosis. Although systems such as the API 20NE have been used to identify organisms, results should be confirmed at a reference laboratory (Lyamuya et al., 1992).

Serodiagnosis of *Yersinia pestis*

Serodiagnostic surveys have been conducted using passive hemagglutination and passive hemagglutination inhibition in humans and animals (De Almeida & Ferreira, 1992; Kilonzo et al., 1993). Enzyme-linked immunosorbent assay (ELISA) and dot-ELISA have been used to detect IgG antibodies to Fl plague antigen (de Almeida & Ferreira, 1992). Polymerase chain reaction technique (using *Y. pestis* plasminogen activator gene primers) and a DNA probe based on a 9.5 kb plasmid have been used to detect the organism in infected fleas and may prove to be a way to monitor plague in wild animals (Hinnebusch & Schwan, 1993; McDonough et al., 1988).

Pathogenesis

Bubonic Plague

Only one quarter of the patients develop a lesion after an infected flea's bite. These may be macular, papular, vesicular, or pustular or may develop into an eschar (Smith & Reisner, 1997). Bacteria rapidly multiply to as many as 10^{10} organisms per gram of tissue (Butler, 1983). Inflammation with effusion assists the organism into the lymphatic system. Lymph nodes initially become congested. Organisms accumulate at the junction of the nodal sinuses and the periphery of the follicles. Special metachromatic stains, tissue Gram's stain, or electron microscopy are necessary to demonstrate that the ground-glass appearance in this area of the infected nodes is due to bacteria. Lymphocytes, vascular cells, and all cell structures are destroyed and bleeding occurs in and around the node. Lymphadenitis and the formation of buboes occur along the lymphatics with resultant serosanguinous effusion, bleeding, and confluent necrosis. Patients develop sepsis, disseminated intravascular coagulation, and septic shock (Smith & Reisner, 1997).

Pneumonic Plague

Secondary pneumonic plague occurs in most untreated patients with bubonic plague (Smith & Reisner, 1997). It begins as a peribronchial, perivascular interstitial inflammation that rapidly evolves into a necrotizing hemorrhagic bronchopneumonia (Smith & Reisner, 1997).

Primary pneumonic plague from inhalation of droplets containing the plague bacillus begins as a lobular pneumonia with bacteria and proteinaceous effusions filling the alveoli (Smith & Reisner, 1997). Necrosis and hemorrhage follow. Grossly, there may be multiple necrotic nodules with hyperemia with areas of grossly normal lung tissue (Smith & Reisner, 1997). Some postmortem lung specimens show confluent patches of lobular pneumonia involving scattered areas in the upper and lower lobes with intervening compensatory emphysema (Reeder & Palmer, 1981). Microscopically, postmortem specimens will reveal organisms and macrophages filling alveoli with large necrotic cavities or masses of plague bacilli surrounding necrotic tissue with excess exudate and inflammatory cell reaction (Reeder & Palmer, 1981).

Septicemic Plague

Primary septicemic plague results from oral, tonsillar, or pharyngeal infections (especially where fleas are crushed in the teeth during grooming). Cervical nodes are enlarged, red, and boggy. Histologically there is edema and congestion with small ground-glass aggregates (which are the accumulated bacilli) (Smith & Reisner, 1997).

Virulence Factors

Table 5 reviews the virulence factors of *Y. pestis* (Bercovier & Mollaret, 1984; Butler, 1983, 1991; Corbel, 1990; Easterbrook et al., 1995; Guan & Dixon, 1990; Lantz, 1997; Leung et al., 1990; Perry & Fetherston, 1997; Reisner & Straley, 1990; Rosquist et al., 1988, 1990, 1991; Smith & Reisner, 1997; Straley, 1988; Une & Brubaker, 1984; Welkos et al., 1998). V antigen inhibits neutrophil chemotaxis and is a virulence factor for *Y. pestis, Y. enterocolitica,* and *Y. pseudotuberculosis.* It has a role in the regulation of secretion of the low Ca^{++} induced pLcr gene products (Yops proteins) and directly inhibits the human inflammatory response. V antigen elicits highly protective antibodies and is a component of candidate vaccines (Leary et al., 1995; Welkos et al., 1998).

Epidemiology

Animal Reservoirs

Plague is a zoonosis transmitted among animals, principally rodents (over 200 species worldwide), although it also affects bobcats, cats, and rabbits, through flea bites (Barnes & Quan, 1992; Butler, 1995; Cleri et al., 1997; Perry & Fetherston, 1997). The domestic rats, *Ratus rattus* (the black rat) and all its races *(R.r. frugivorus* (Mediterranean), *R.r. kijabius* (Uganda), *R.r. rufescens* (Indian gray rat), *R.r. alexandrinus* (Geoff), and *R.r. rattus* (black with gray underpants—domestic rat from cold temperature countries) and *R. norvegicus* (common sewer rat), are important reservoirs for *Y. pestis* (Butler, 1990, 1991, 1995; Corbel, 1990; Manson-Bahr & Apted, 1982). In Mongolia and

TABLE 5. *Yersinia pestis* Virulence Factors

Pathogenic factor	Function
Low calcium response genes on the 75-kb plasmid	Regulates bacterial (Yops) surface and released proteins in the presence of <1 mmol Ca^{++}.
Yop H	Antiphagocytic and phosphotyrosine phosphatase activity.
Yop B and Yop D	Delivers Yop H into the host target cell to block phagocytosis and the oxidative burst.
Yop E	Cytotoxic activity mediated by disrupting cell microfilaments.
Yop M	Binds human thrombin and prevents thrombin-platelet aggregation.
Bacterial capsule fraction 1	Inhibits phagocytosis by neutrophils and monocytes. (*Y. pestis* can survive in macrophages but is killed by neutrophils.) Fraction 1 is contained in the capsular envelope and is produced at 37°C, but not at 28°C.
pH 6 antigen	Helps organism survive in necrotic tissue and aids in adherence.
Pigmentation	Colonies become pigmented on Congo red and hemin agar. Nonpigmented strains are avirulent.
Coagulase/fibrinolysin protein	Acts as a coagulase in the flea at room temperature, and acts as a fibrinolysin in mammals in addition to splitting complement C_3 at 37°C.
V antigen	Inhibits neutrophil chemotaxis and has a regulatory role in gene expression.
Pla antigen or protease	Plasminogen activator. It is believed to cleave fibrin products that might trap the organism, produces excess plasmin, degrades basement membrane and extracellular proteins, reduces chemoattractants at site of infection by inhibiting interleukin-8, and has a temperature-dependent coagulase activity that may be important in flea pathogenesis.
Yad A (formerly Yop A)	Adherence protein for enteropathogenic *Yersinia* but not functional in *Y. pestis.*
Yersiniabactin	A siderophore that assists the organism in absorbing iron.
Murine toxin	Two proteins toxic for mice and rats but not toxic for guinea pigs, rabbits, dogs, monkeys, and chimpanzees.
Catalase activity	This may be a pathogenic determinant, although experimental results are mixed.
Pesticin	A bacterocin linked to coagulase and fibrinolytic activity, pesticin-producing strains are highly invasive and lethal. Pesticin-negative strains, although not invasive, remain lethal when injected intravenously.
Endotoxin including Lipid A as found in other gram-negative organisms	One of the causes of the septic shock syndrome (as with other gram-bacilli causing sepsis) and disseminated intravascular coagulation.

Yop, Yersinal outermembrane protein.

Manchuria, the marmot is the principal plague reservoir and the disease is seen in marmot trappers (Reeder & Palmer, 1981). In Kurdistan and central Asia, mice sisels, gerbils (Meriones), and jerboas are important reservoirs. In South America, the cuis or wild guinea pig is a reservoir. In North America, ground squirrels, rock squirrels, prairie dogs, chipmunks, bats, and rabbits are infected, all west of the 100° meridian (Butler, 1991; Manson-Bahr & Bell, 1987; Reeder & Palmer, 1981).

Except for felines, wild carnivores rarely show signs of disease. Camels and goats may become infected by flea bites, mechanical transmission from piercing of the animals' mouth parts, or after grazing in areas contaminated by plague-infected rodent feces (Butler, 1990, 1995; Manson-Bahr & Bell, 1987; Quan, 1991; Reeder & Palmer, 1981; Wilson & Miles, 1975). Carnivores including domestic cats, dogs, coyotes, badgers, bobcats, raccoons, and mongoose have become naturally infected, while the kangaroo rat is resistant to infection (Hopkins & Gresbrink, 1982; Manson-Bahr & Bell, 1987; Quan, 1991). Domestic dogs have been implicated in one outbreak (Kilonzo et al., 1993).

Dogs, cats, pigs, sheep, goats, and horses are difficult to infect experimentally. Birds (except for sparrows) are resistant to infection; monkeys develop plague pneumonia when infection is attempted by aerosol; and in rats, oral, nasal, conjunctival, and subcutaneous injection of the plague bacillus causes death in 2 to 8 days (Hopkins & Gresbrink, 1982; Wilson & Miles, 1975).

Although ingestion and direct contact may spread the disease, they play no role in the natural cycle of infection (Perry & Fetherston, 1997). Humans are infected by infected flea bite, handling infected carcases, or ingesting infected food (Barnes & Quan, 1992; Butler, 1995). In endemic areas, plague has been transmitted by infected cat bites (Boyce, 1995). Airborne transmission from human pneumonic plague was rare until 1994, when numerous cases were reported from Surat, India (Barnes & Poland, 1984; CDC, 1983, 1984, 1994b).

Arthropod Vectors

Y. pestis may be transmitted among animal reservoirs or to humans by the bite of any one of the 57 genera and 85 species of fleas or the *Hyalomma detritium* tick (the vector for Q fever and Congo hemorrhagic fever—Congo virus) (Butler, 1983; James & Harwood, 1969; Sheals, 1973; Smith, 1973). The most important flea vectors are the *Xenopsylla cheopsis* (rat flea of the tropics, the most frequent carrier of *Y. pestis), Ceratophyllus fasciatus* (rat flea of the temperate zones), *Ctenocephalus canis, C. felis* (which bites humans, dogs, and cats), and the human flea, *Pulex irritans* (James & Harwood, 1969; Mason-Bahr & Bell, 1987).

Fleas are efficient vectors for the following reasons: They will leave a dead rat as it cools and attach themselves to the closest warm animal (or human) in close proximity. The flea's stomach is not large enough to become infected ($0.5\ mm^3$) unless it feeds on animals in the terminal stages of disease. Fleas may mechanically transmit the plague bacillus with contaminated mouth parts if they feed on another host soon after the initial meal, but in most cases, transmission occurs after the organism multiplies inside the flea. *Y. pestis* is excreted with the flea's feces, contaminating bite sites; because the bite site is pruritic, scratching may inoculate the contaminated feces into the bite wound (Butler, 1983; James & Harwood, 1969; Manson-Bahr & Bell, 1987; Quan, 1991).

Y. pestis produces a coagulase as it multiplies inside the flea, causing the flea to be blocked with clotted blood. The infected blocked flea is not satiated, so it continues to feed, regurgitating plague bacillus from its obstructed proventricularis (Butler, 1983).

Clinical Presentations

Subclinical Plague

In endemic areas, hemagglutination assays were positive in 4.7% of the population tested during periods of disease inactivity and in 46.8% of asymptomatic individuals during times of increased disease activity. Antibody tests remained positive for at least 4 years (Manson-Bahr & Bell, 1987).

Plague Pharyngitis

Inhalation or ingestion of *Y. pestis* may result in disease resembling acute tonsillitis accompanied by inflamed anterior cervical nodes. The plague

bacillus may be grown from lymph node aspirates or throat swabs. The organism has been isolated from throat swabs of asymptomatic persons, but long-term carriage has not been documented (Butler, 1983, 1990; Manson-Bahr & Apted, 1982).

Pestis Minor

Patients present with a mild febrile illness and localized lymphadenopathy. They recover without therapy after the lymph node spontaneously drains. Pestis minor is usually seen as part of a larger outbreak and must be differentiated from lymphogranuloma venereum (Manson-Bahr & Apted, 1982). Pestis minor may be mediated by less virulent organisms or the interactions of cytokines, particularly on the macrophage phagolysosomes (Hirota & Wake, 1995).

Cutaneous Manifestations of *Yersinia pestis* Infection

Skin lesions are not a noticeable sign in early bubonic plague, but a study of Vietnamese patients found that 25% developed distinctive skin lesions near the bubo or flea bite. These included pustules, vesicles, eschars, and papules. Cellulitis, abscesses, ulcerations, and rarely ecthyma gangrenosum have been reported. A few patients, sometimes early or late in bubonic plague, develop moist gangrenous skin that resembles carbuncles. These become larger and slough off. Purpura with sepsis may progress to gangrene especially of the distal extremities from endotoxemia. This occurs late in the disease, often near death (from which the term "Black Death" was derived) (Barnes & Quan, 1992; Butler, 1972, 1983, 1990; Manson-Bahr & Apted, 1982; Westrom, 1996). Some untreated patients develop a generalized papular rash of the hands, feet, and pectoral areas. If the patient survives, the rash evolves from papules to vesicles, to pustules resembling smallpox (referred to as "blains") (Manson-Bahr & Apted, 1982).

Bubonic Plague

Clinical Presentation

Bubonic plague is the most common form of infection, representing 75% of all reported cases worldwide. The disease is most often acquired from the bite of an infected flea, although exposure of cut or injured skin to contaminated animal tissues or fluids may also suffice (Butler, 1983, 1990). The incubation period is from 10 hours to 10 to 14 days (average 3–6 days) (Barnes & Quan, 1992; Butler, 1983; Goldstein, 1992; Wilson, 1991). Immunization increases the incubation period (Wilson, 1991).

Symptoms begin with a sudden onset of fever (38.5–40°C) accompanied by rigors, malaise, headache, and weakness (Goldstein, 1992; Butler, 1995). Painless localized lymphadenopathy develops simultaneously with the fever, or no later than the following day. The nodes rapidly become tender and enlarge in size from 1 to 10 cm, are oval, and elevate the skin (Butler, 1983). Groin nodes are most frequently enlarged (52%–86% with femoral nodes more frequently enlarged than inguinal nodes). Axillary (9%–16%) and cervical nodes (5%–33%) are less frequently involved, and abdominal node involvement may be mistaken for a surgical abdomen. Epitrochlear and popliteal nodes are least frequently involved (Butler, 1983; Goldstein, 1992; Spagnuolo, 1986).

During recovery, smaller nodes may continue to enlarge and rupture, draining foul-smelling pus if not incised and drained when fluctuant. All fluctuant nodes should be incised and drained (Butler, 1983, 1990). Other complications include limb edema, especially of the leg because of damage to the lymphatics, and staphylococcal, *pseudomonal,* or other bacterial superinfection of the draining nodes (Butler, 1983, 1990; Manson-Bahr & Apted, 1982).

Bacteremia with the clinical sepsis syndrome is common (Butler, 1983, 1990, 1995; CDC, 1992b; Goldstein, 1992). All patients exhibit fever and chills (Butler, 1983). When patients become septicemic, most will have tachycardia (110–140/minute), tachypnea, and hypotension (blood pressures below 100/60 mm Hg). Older patients may have lower levels of tachycardia or normal pulses (Butler, 1990; Goldstein, 1992). Electrocardiograms usually reveal sinus tachycardia with few patients developing ST-T wave changes (i.e., ST depression) (Butler, 1983).

Patients appear toxic and are fretful. At this stage, the enlarged nodes are so exquisitely tender that patients will resist any attempts at examination (Butler, 1983; Goldstein, 1992).

Neurological signs and symptoms (insomnia, delirium, stupor, weakness, staggering gait, vertigo, slurring of speech, and memory loss) in the non-meningitis patient are believed to be caused by one or more of the plague toxins (Goldstein, 1992). Gastrointestinal symptoms are found in more than 70% of septicemic patients and secondary plague pneumonia is twice as likely to occur in the septicemic patient (Butler, 1983, 1995; Goldstein, 1992; Wilson, 1991).

Laboratory Findings

Leukocytosis is common (peripheral white blood cell [WBC] counts between 10,000 and 20,000 cells/mm^3). The rare patient may develop a leukemoid reaction (peripheral WBC >100,000 cells/mm^3). Disseminated intravascular coagulopathy (DIC) and fibrin split products are present even in the presence of low platelet counts (Butler, 1983, 1990).

Many patients have enlarged livers and elevated liver enzymes and bilirubin are mildly elevated (Butler, 1983, 1990). Some patients may be hypoglycemic and the combination of low blood glucose, coma, and abnormal liver function studies may be mistaken for Reye's syndrome (Butler, 1983; CDC, 1993; Spagnuolo, 1986).

Kidneys are not usually directly invaded, but the fever (and dehydration in untreated or poorly treated patients) results in concentrated urine and sometimes proteinuria. One study reported fibrin thrombi in the glomerular capillaries mimicking the renal lesions of the Schwartzman reaction (Butler, 1983).

Differential Diagnosis

Tularemia In North America, tularemia is the most important zoonosis that may be confused with plague. Tularemia is caused by *Francisella tularensis* and is a widespread disease, while plague is a sylvatic disease found naturally west of the 100° meridian in North America, including Hawaii (Butler, 1983). *F. tularensis* infects squirrels, rabbits, woodchucks, muskrats, and beavers and is spread to humans by ticks, deerflies, horseflies, and ingestion of contaminated water or poorly cooked or uncooked meats from infected animals. The diseases have similar incubation periods (tularemia: 2–10 days), and both have the skin, lungs, oral, and gastrointestinal mucosa as portals of entry, although the last two are much less common with *Y. pestis.* With *F. tularensis,* at the skin entry point, an ulcer or pustule forms, which is much less common in plague (Butler, 1983).

Adenopathy is common in both diseases. Femoral and inguinal adenopathy is more common in plague, while axillary and epitrochlear nodes are most often involved in tularemia.

Tularemia does not result in elevated peripheral WBCs, the organism is rarely cultured, and in general the disease may be indolent or self-limited (Butler, 1983). Untreated, there is a 5% to 33% mortality rate, while treated disease has a 0% to 8% mortality rate. Tularemia and plague are commonly complicated by pneumonia and meningitis. Tularemia causes more pericarditis, while plague is more frequently complicated by shock (Butler, 1983; Cleri et al., 1997).

Reye's Syndrome Reye's syndrome is an acute postinfectious encephalopathy (usually occurring during the recovery phase of an often mild viral illness). The use of aspirin in young children for fever in viral illnesses has been associated with Reye's disease. With the decrease in aspirin use, the median age of onset has increased, although the disease is rarely seen over the age of 18 years.

The illness usually begins with vomiting 4 to 5 days after the onset of the viral illness, but may begin during the first day of illness. As the vomiting subsides, patients become more encephalopathic with confusion, fear, perseveration, outbreaks of profanity, screaming (stage I), delirium (stage II usually lasting 24 hours), deep coma and decorticate rigidity (stage III), decerebrate rigidity (stage IV), and loss of brain stem reflexes (stage V) (Keating, 1998).

The disease is rare (0.42 cases/100,000 urban population to 1.8 cases/100,000 rural or suburban population; 1/20,000 cases of children infected with influenza B) but has an increased incidence in siblings, although cases are almost never seen simultaneously and often occur years apart (Keating, 1998).

Clinical similarities with plague are present early in the disease. Hypoglycemia, once thought to be the hallmark of Reye's syndrome, actually occurs infrequently. Patients with either Reye's syn-

drome or plague will exhibit elevated liver enzymes and both diseases exhibit abnormalities in prothrombin time (Keating, 1998; Cleri et al., 1997).

Differential Diagnosis of Lymphadenopathy of Plague Table 6 lists the differential diagnosis of lymphadenopathy and plague (Cleri et al., 1997; Thin, 1990).

Of special note are *Pasteurella* species infections. Human infection is associated with animal bites or scratches, nonbite animal contacts, and lack of animal exposure. The organism is found in the nose, mouth, throat, or gastrointestinal tracts of dogs, cats, other mammals, and birds and may colonize the nasopharynx of humans exposed to animals *(Pasteurella multocida).* Signs of infection develop between 12 and 72 hours after a bite or scratch wound; 20% of individuals have local lymphadenitis and 10% develop regional lymphadenitis. Nonbite animal exposure infections involve pharyngitis, intra-abdominal infections, arthritis, prosthetic joint infections, or meningitis. Infections involving no animal exposure usually involve the upper respiratory tract or the abdomen (Boyce, 1995). Like *Y. pestis, Pasteurella* species are nonspore-forming, gram-negative, non-acid-fast, and facultatively anaerobic organisms; colonies are small after 24 hour's growth (0.3 to 1 mm diameter on nutrient agar) (Holmes, 1998; Mannheim, 1984). *Pasteurella,* especially from infected animal sources, exhibits bipolar staining with the Gram's stain, whereas *Y. pestis* requires staining with Giemsa, Wright's, or Wayson's stains in order to exhibit bipolar characteristics (Bercovier & Mollaret, 1984; Carter, 1984; Gage, 1998; Quan, 1988; Reddin et al., 1995; Wanger 1998; Worsham et al., 1995).

TABLE 6. Differential Diagnosis of Lymphadenopathy of Plague

Acute lymphadenitis
Staphylococcus aureus infection of node or region draining involved node
Streptococcal infection of node or region draining involved node
Pasteurella species
Primary or secondary syphilis (regional or generalized lymphadenopathy with moderately enlarged nodes that are rubbery, discrete, and not tender)
Acute cervical lymphadenitis
Group A streptococcal pharyngitis—plague pharyngitis resembles acute bacterial tonillitis
Botulism
Diphtheria
Viral upper respiratory infections
Neisseria gonorrhea pharyngitis
Primary syphilis
Inguinal lymphadenitis
Lymphogranuloma venereum
Chancroid
Granuloma inguinale

Gastrointestinal Disease or Acute Abdomen The differential diagnosis of abdominal pain, nausea, and vomiting of plague, sometimes accompanied by DIC, includes the acute surgical abdomen, and *Capnocytophaga canimorsus* sepsis (Cleri et al., 1997; CDC, 1993; Hull et al., 1986). In one study, *all* patients with gastrointestinal (or urinary tract) signs had *Y. pestis* sepsis (Crook & Tempest, 1992).

Other Febrile Illnesses Early stages of plague not only may be confused with tularemia but may mimic typhus, relapsing fever, dengue, and malaria (Reeder & Palmer, 1981).

Septicemic Plague

Sepsis occurs in 26% of patients with bubonic plague (Butler, 1990, 1995) and the disease is referred to as bubonic/septicemic plague, secondary septicemic plague, or pestissiderans (Butler, 1990, 1995; Wilcocks & Manson-Bahr, 1972). In the United States, 10% of plague patients reported from 1947 to 1977 had *Y. pestis* sepsis. In New Mexico, 25% of the patients were reported as septicemic in the 1980s (Perry & Fetherston, 1997). Quantitative blood cultures were found to have 10^2 or more bacteria/mL and these patients were more hypotensive and had a 27% (treated) mortality rate.

Others have defined septicemic plague as the sepsis syndrome with *Y. pestis* bacteremia (Butler, 1990, 1995; Manson-Bahr & Apted, 1982). Most patients are over 60 years of age, have rapidly developing symptoms with rapid clinical deterioration, have less fever when compared to patients with bubonic plague, and have such an intense bacteremia that organisms may be seen on the peripheral smear. This group experiences a 33% mortality in spite of treatment. Postmortem examinations reveal diffusely congested nodes, but the disease progresses so rapidly that peripheral nodes do not have

time to become noticeably enlarged (Butler, 1990, 1995; CDC, 1994a; Lenski, 1988; Spagnuolo, 1986).

Plague Meningitis

Plague meningitis (meningitis caused by *Y. pestis)* most commonly occurs as a result of septicemic spread of the organism during an episode of sometimes inadequately treated bubonic plague from the 9th to the 17th day of disease (Butler, 1983, 1990; Wilcocks & Manson-Bahr, 1972). Patients with axillary buboes are at increased risk for plague meningitis and one third of patients with plague meningitis have axillary buboes (Butler, 1990). Worldwide, flea bites are the most common mode of *Y. pestis* infection and usually result in enlarged femoral and/or inguinal nodes (Butler, 1990). Plague with axillary buboes is usually acquired by handling infected animals (by hunters and veterinarians, for example) (Butler, 1983). Plague bacilli in animal tissue (usually growing at 37°C develop and maintain an antiphagocytic capsule and appear to be more virulent than the organisms growing inside the infected flea at lower temperatures (Butler, 1983).

Plague meningitis has presented without lymphadenopathy (Butler, 1983, 1995). Patients present with fever, headache, and meningismus (Butler, 1983, 1995). Kernig's sign is present and patients may have seizures, vestibulocerebellar symptoms, and coma (Wilcocks & Manson-Bahr, 1972). The cerebrospinal fluid is yellow and pleocytotic and displays abnormal chemistry. The Gram's stain is often positive for organisms consistent with *Y. pestis* (Butler, 1983, 1990; Wilcocks & Manson-Bahr, 1972). Intravenous chloramphenicol rather than streptomycin is the treatment of choice (with a maximum adult dose of 1 g intravenously every 6 hours) (Butler, 1990, 1995; Cleri et al., 1997; Poland, 1989). Postmortem examinations show a congested brain with flattening of sulci and covered with a thick membranous exudate (Wilcocks & Manson-Bahr, 1972).

Pediatric Plague

Pediatric plague closely resembles the adult disease (CDC, 1992a, b). Mann and colleagues (1982) described the average pediatric patient as between 8 and 10 years of age and reported a slight male predominance and a 15.8% mortality rate in the cases from New Mexico, with the majority of cases presenting a bubonic disease (Mann et al., 1982). Sixteen percent of the cases from New Mexico developed pneumonia, 11% developed meningitis, and 18% developed sepsis (Mann et al., 1982).

Plague Pneumonia—Primary/Inhalation and Secondary/Hematogenous Spread

Epidemiology

Y. pestis pneumonia is the result of hematogenous spread from septic bubonic or pure septicemic plague, or the result of inhaling infected droplets from another person or animal (most often a cat) with pneumonic plague (Butler, 1983, 1990; CDC, 1992b, 1993; Doll et al., 1994). Plague-infected cats may develop one or more of the following complications: pneumonia, pharyngitis, lymphadenopathy (cervical), oral lesions, and submandibular abscesses. Primary plague pneumonia represented about 2% of the cases reported in the United States from 1970 to 1993. Plague pneumonia secondary to bubonic or septicemic plague represented 12% of cases during that same period (Kaufmann et al., 1980; Perry & Fetherston, 1997; CDC, 1992b,c; Doll et al., 1994).

Clinical Presentation

Hematogenous Plague Pneumonia Hematogenous plague pneumonia presents acutely with fever, cough, hemoptysis, and chest pain. Less than one half the patients have lymphadenopathy (Butler, 1995; Doll et al., 1994; Reeder & Palmer, 1981). Patients initially have symptoms of sore throat and a swollen neck (Reeder & Palmer, 1981). In an unusual case, a patient presented with abdominal cramps beginning 3 days after direct respiratory exposure from an infected cat. One day later, the patient's temperature increased to 39.6°C accompanied by nausea and vomiting. On day 3, the patient's temperature increased to 40°C and he developed bilateral multilobe pneumonia. The next day the patient went into shock and died (7 days after the initial exposure) (CDC, 1992c).

Another case of untreated bubonic plague progressed to septicemia and pneumonia 3 days after the onset of symptoms, and 1 day after clinical evaluation diagnosed him as having groin muscle strain (CDC, 1997).

Inhalation Plague Pneumonia Inhalation plague is highly contagious and rapidly fatal (Butler, 1990). Person-to-person transmission rates vary greatly (Cambell & Hughes, 1995). High transmission rates are associated with poverty and overcrowded living conditions (Cambell & Hughes, 1995; Perry & Fetherston, 1997). From 1910 to 1911, pneumonic plague is believed to have killed 60,000 people in Manchuria and North China; 16,000 in South Mongolia and China in 1917–1918; and 9000 in Transbaikalia (Wilson & Miles, 1975). Transmission is believed to occur within 2 feet to 2 meters of a coughing patient (Cambell & Hughes 1995; Perry & Fetherston, 1997). In the United States, the risk of person-to-person spread appears to be very small, with no nosocomial cases reported and the last epidemic case occurring during the Los Angeles outbreak in 1924–1925 (Cambell & Hughes, 1995; Perry & Fetherston, 1997).

In a recent case of fatal plague pneumonia, the patient presented with pain and numbness in the left arm with left axillary pain. The patient did not develop classical signs of infection (fever, chills, and vomiting) until a day later. Initially, she was diagnosed as brachial plexus injury, but 2 days later she collapsed and was returned to the hospital. Her chest x-ray showed bilateral pulmonary edema and she was diagnosed as having sepsis, adult respiratory distress, and DIC. She died 5 days after the onset of her original symptoms. *Y. pestis* was identified in cultures and her disease was traced to a prairie dog die-off near her residence. Four of the five family dogs were seropositive, as were one of the family's three cats. The seropositive cat was ill with a submandibular abscess and cared for by the patient (CDC, 1997).

X-Ray Findings Roentgenograms display patchy bronchopneumonia, segmental or lobar pneumonia, sometimes with cavities, mimicking pneumococcal or *Klebsiella* pneumonia (Butler, 1995; Doll et al., 1994; Poland, 1989; Reeder & Palmer, 1981). The affected lungs display consolidation within hours or days, or there are multilobe progressive unilateral or bilateral infiltrates (Reeder & Palmer, 1981). Lobes may swell from edema or hemorrhage, with bowing of the fissures resembling classical *Klebsiella* pneumonia (Reeder & Palmer, 1981). Patients may display a totally normal x-ray followed by widening of the superior mediastinum from enlarged nodes. Pleural effusions and air bronchograms are seen (Reeder & Palmer, 1981).

Clinical Course Incubation periods depend on the inoculum, and onset of disease may occur within hours of exposure but typical incubation periods are from 24 to 60 hours. Incubation periods for hematogenous plague pneumonia and plague pneumonia from bubonic disease are about the same (Butler, 1990; Reeder & Palmer, 1981).

Plague pneumonia has a sudden onset with fever and chills and can be fatal during the first day. Even in cases that result in early fatalities, the initial signs and symptoms may not be alarming, commonly beginning with a painless cough and shortness of breath. Sputum is thin, watery, and blood-tinged. *Y. pestis* is easily seen as a gram-negative organism on the sputum Gram's stain (Reeder & Palmer, 1981), but identification may be difficult as typical bipolar staining is demonstrated with Wright's Giemsa, or Wayson stains (Perry & Fetherston, 1997).

Differential Diagnosis Plague pneumonia must be differentiated from the usual bacterial pneumonias, tularemia, Q fever, psittacosis, mycoplasma, Legionnaires' disease (especially in the presence of diarrhea), tuberculosis, fungal infections, and viral pneumonias (Butler, 1983, 1990, 1995; Cleri et al., 1997).

Treatment

Untreated, 40% to 95% of those infected with plague will die (Butler, 1983, 1990, 1995; CDC, 1992c; Spagnuolo, 1986; Wilcocks & Manson-Bahr, 1972). Early treatments included Haffkine's antiserums and Felix d'Herelle's plague bacillus bacteriophages (Perry & Fetherston, 1997; Summers, 1993; Wilson & Miles, 1975). Sulfonamides, trimethoprim–sulfamethoxazole, kanamycin, and ampicillin have all exhibited some success, but

streptomycin treatment reduced the mortality rate to 5% to 10% and is considered the drug of choice for plague (Butler, 1990, 1994; Spagnuolo, 1986).

Plague meningitis is treated with intravenous chloramphenicol (25 mg/kg loading dose and 60 mg/kg/day in four divided doses with a maximum of 4 g/day). Treatment should last for at least 10 days (Butler, 1990; Poland, 1989). Some authorities recommend oral chloramphenicol at a reduced dose of 30 mg/kg/day in four divided doses for plague meningitis. We recommend completion of the course of therapy with intravenous chloramphenicol, as it is our belief that the intravenous drug presents less of a risk of aplastic anemia than the oral route of administration.

Patients should receive general supportive measures (fluid support, hemodynamic monitoring) and frequent chest radiographs (at least every 8 hours) during the first few days of illness. All patients should be maintained on strict isolation in negative pressure rooms with proper anterooms for at least 48 hours into appropriate treatment to be sure they do not develop plague pneumonia (Butler, 1983, 1990).

Contacts of persons with pneumonic plague or possible plague pulmonary complications should receive prophylaxis of tetracycline 500 mg, four times daily by mouth if over the age of 8 years or streptomycin 20 mg/kg/day intramuscularly in two divided doses (Goldstein, 1992). Doxycycline 100 mg by mouth twice daily may be an adequate substitute for tetracycline. Household contacts should all be given prophylactics because of their increased risk for disease.

Plague vaccine (Cutter Laboratories, Berkeley, California) is the only commercially available human vaccine (Butler, 1983). The vaccine is a killed strain of Indian *Y. pestis.* The vaccine is only partly effective and may prolong the incubation period, requiring exposed or vaccinated individuals to remain under close observation for longer periods. All exposed individuals, including those recently vaccinated, should be given chemoprophylaxis (Goldstein, 1992).

Several treatment regimens are available (Cleri et al., 1997). Streptomycin 30 mg/kg/day intramuscularly (in two divided doses, up to Ig every 12 hours) for 5 days with doses of an alternative drug to complete a 10-day course should be given for *Y. pestis* infections (except meningitis). This is the drug of choice. It has reduced mortality to 5%, and patients respond within 3 days of starting therapy. The risk of eighth nerve damage is small but it is contraindicated during pregnancy and should be limited to 3 days' therapy after the pregnant patient becomes afebrile. It is not the drug of choice for plague meningitis.

Doxycycline 100 mg orally or intravenously twice daily may be adequate in milder cases. Tetracycline orally 2 to 4 g/day in divided doses for 10 to 15 days is alternative therapy for mildly ill patients. Tetracycline is contraindicated in children under 7 or 8 years of age, in renal failure.

Chloramphenicol *intravenously only,* at 25 mg/kg loading dose followed by 60 mg/kg/day, in four divided doses up to 1 g intravenously every 6 hours, is the drug of choice in patients with meningitis or septic shock, or patients who cannot absorb intramuscular medications.

Gentamicin intravenously beginning with a 2.0 mg/kg loading dose followed by 1.7 mg/kg every 8 hours is effective (Sanford, 1997).

Ampicillin, sulfonamides, trimethoprim-sulfamethoxazole, and kanamycin are all less effective (although there was one case of human plague meningitis treated successfully with ampicillin [Cleri et al., 1997]). Amoxicillin, ceftriaxone, and cefotaxime are as efficacious in the mouse model as streptomycin (Bonacorsi et al., 1994; Cleri et al., 1997).

Newborns delivered during the bacteremic phase of the disease should be treated with intravenous gentamicin (5–6 mg/kg/day in four divided doses, following serum levels), *or* intramuscular streptomycin (10–20 mg/kg/day in four divided doses) (Craven, 1994).

The duration of therapy should be determined by the length and severity of the patient's infection, but the minimum therapy should be 10 days (Cleri et al., 1997).

Ofloxacin appears to be an effective antibacterial and is as effective as streptomycin in animal models.

In vitro, ceftriaxone, ciprofloxacin, and ampicillin were more active against *Y. pestis* than streptomycin, tetracycline, or chloramphenicol.

Azithromycin was poorly active (Smith et al., 1995).

For prophylaxis, tetracyclines (including doxycycline), sulfonamides, and chloramphenicol may be used (Dennis & Hughes, 1997), although we do not recommend the use of oral chloramphenicol under any circumstances. Prophylaxis should be administered to those at risk (especially those exposed to pneumonic plague) within 7 days (CDC, 1997).

All contacts of patients with lung disease, either primary or secondary, should be quarantined or kept under strict surveillance. These individuals should be given a prophylaxis with a 10-day course of either oral tetracycline 30 mg/kg/day in four divided doses (every 6 hours) or triple sulfas (60–75 mg/kg/day in four divided doses) (Craven, 1994). Doxycycline (100 mg orally every 12 hours) may be substituted for tetracycline, and trimethoprim–sulfamethoxazole may be substituted for triple sulfas.

Multidrug-resistant *Y. pestis* has recently been reported from a patient in Ambalavao district, Madagascar (Galimand et al., 1997). The organism's resistance gene was carried on a transferable plasmid and succeeded in making it resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, sulfonamides, tetracycline, and minocycline. Ampicillin resistance is the result of production of a β-lactamase; chloramphenicol resistance is caused by production of chloramphenicol acetyltransferase; kanamycin resistance is caused by type I 3'-aminoglycoside phosphotransferase. High-level resistance to streptomycin-spectinomycin is caused by the production of 3-9-aminoglycoside adenylyltransferase. The organism was susceptible to trimethoprim but resistant to sulfonamides and without any synergism at any serum achievable concentrations (Galimand et al., 1997).

Galimand and coworkers (1997) ponder whether the genetic transfer of multidrug-resistance plasmid took place in the peripheral circulation or in deep tissue by chance meeting of *Y. pestis* with invading gastrointestinal Enterobacteria, or in the blood meal in the gut of the flea vector. Whatever the mechanism, this represents a major threat, and at this time no one knows how widespread this resistance might be among rodent carriers and vectors (Dennis & Hughes, 1997).

Summary and Conclusions

The number of plague cases reported to the World Health Organization is increasing every year. Plague epidemics have appeared in Malawi, Mozambique, and India, where they have not been seen in decades, andenzootic foci are increasing, including the increasing number of states in the United States reporting human disease (Galimand et al., 1997). Early diagnosis, isolation, rapid antimicrobial treatment and prophylaxis, and vector and animal reservoir control are the foundations for epidemic control. With the first reported case of multidrug-resistant *Y. pestis* from an epidemic area, the future of treatment and prophylaxis regimens may be problematic, although quinolones and third-generation cephalosporins may hold some promise.

Plague, and especially plague pneumonia, in their early presentations are difficult to diagnose. One must maintain a high index of suspicion and be sure to accurately assess a patient's travel and vector or animal exposure when choosing presumptive therapy for a presumed bacterial pneumonia. A disease that may present itself as a pneumonia, adult respiratory distress syndrome, a surgical abdomen, undifferentiated sepsis with or without DIC, Reye's syndrome, or any form of lymphadenopathy with or without the above presentations is a diagnostic and treatment challenge. This is especially true in patients with plague pneumonia, where often there will be no second chance at therapy if empiric therapy fails.

Untreated, the disease is fatal in 90% to 95% of cases. Appropriate treatment reduces mortality to 5% to 18% (Cleri et al., 1997).

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Nontuberculous Mycobacteria

STEPHEN D. SHAFRAN

Introduction

Mycobacteria differ from conventional bacteria in several important respects. First, mycobacteria grow considerably slower, with a doubling time in culture of about 24 hours compared with 30 to 60 minutes for conventional bacteria, resulting in the inability to detect growth before 1 to 2 weeks at the earliest. Second, mycobacteria have large quantities of lipid in their cell wall, which accounts for their acid-fast staining properties and their inability to react with a gram stain. Third, mycobacteria have different nutritional requirements and require special media for growth. Mycobacteria do not grow on conventional media, such as blood agar or brain-heart infusion, but most grow readily on Middlebrook media and Lowenstein–Jensen medium.

The most important mycobacterial species in human health is *Mycobacterium tuberculosis,* which is perhaps the leading infectious cause of death worldwide. Tuberculosis is discussed in detail in this volume. The next most frequent mycobacterial cause of human disease is *Mycobacterium leprae,* the causative organism of leprosy. This organism does not cause pulmonary disease and will not be discussed here. All other mycobacteria are referred to as nontuberculous mycobacteria (NTM). NTM have also been referred to as mycobacteria other than tuberculosis (MOTT), environmental mycobacteria, saprophytic mycobacteria, and atypical mycobacteria, but the term NTM is preferred.

STEPHEN D. SHAFRAN • Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, Alberta T5A 1B0, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Several dozen species of NTM are now recognized, with a number of new species being described in recent years. It is expected that additional species will be described in the future. Not all NTM organisms have been associated with human disease. Unlike *M. tuberculosis,* which is an obligate human pathogen with no environmental reservoir and no natural animal hosts, NTM are commonly isolated from environmental sources such as water and soil, and many NTM are natural animal pathogens. The traditional Runyon classification of NTM (Timpe & Runyon, 1954) divides them into four groups based on the time to detect growth. Groups I, II and III are considered slow growers, requiring a similar time to grow in culture as does *M. tuberculosis,* and Group IV organisms are considered rapid growers. The slow growers are further differentiated by their ability to produce yellow (carotenoid) pigment. Group I NTM are called *photochromogens,* as they produce pigment upon exposure to light. Group II NTM are *scotochromogens* and produce pigment even when shielded from light. Group III NTM produce no pigment and are called *nonchromogens.*

The Runyon classification has become less relevant in recent years due to advances in mycobacteriology, including more rapid culturing techniques, DNA probes for speciating common species, and ribosomal RNA typing for resolving speciation in difficult cases.

Once mycobacterial growth is detected in culture, speciation is essential. In the past, speciation was accomplished using biochemical tests, which often required >1 week to complete. Presently, DNA probes are commercially available for *M. tuberculosis, Mycobacterium avium* complex, *Mycobacterium kansasii,* and *Mycobacterium gordonae,* so that the majority of clinical mycobac-

terial isolates can be speciated within 1 to 3 days after isolation in culture. Biochemical testing is still necessary for other NTM species. Ribosomal RNA sequencing can be done in research laboratories to resolve speciation in difficult cases. This technique has led to the recognition of several new NTM species over the past decade.

Human disease due to NTM is classified into four types: pulmonary disease, cutaneous disease, lymphadenitis, and disseminated disease. Only pulmonary disease will be discussed in this chapter.

Pulmonary Disease

The most common NTM species to cause pulmonary disease are organisms of the *M. avium* complex (MAC). Following MAC, the organisms next most likely to cause pulmonary disease are *M. kansasii, Mycobacterium xenopi,* Mycobacterium abscessus, and *Mycobacterium malmoense,* the relative frequency of which varies substantially depending on the geographic area of the world. Disease due to each of these organisms will be discussed in turn. Other NTM cause pulmonary disease only rarely.

Before discussing each pathogen individually, it is appropriate to review the diagnostic criteria for pulmonary NTM disease, as these criteria are independent of the NTM species.

Criteria for Nontuberculous Mycobacterial Pulmonary Disease

Unlike *M. tuberculosis,* NTM are not obligate pathogens and are commonly found in environmental sources, such as water and soil. Accordingly, the isolation of a NTM species from a respiratory sample is not sufficient evidence for the presence of NTM lung disease. The diagnosis of NTM lung disease requires clinical, radiographic, and bacteriologic criteria (Wallace et al., 1997). These diagnostic criteria have been derived largely from series of patients with MAC, *M. kansasii,* and *M. abscessuti* pulmonary disease and have not been validated with NTM pulmonary disease due to other NTM species. Nevertheless, they are the best guidelines available and it is reasonable to use them for all NTM species.

The clinical criterion required is the presence of compatible symptoms and signs, such as cough, fatigue, fever, weight loss, hemoptysis, and dyspnea with the reasonable exclusion of other etiologies of pulmonary disease. Radiographic criteria consist of infiltrates, cavitation, or multiple nodules on plain radiography and/or the presence of multiple small nodules or multifocal bronchiectasis on high-resolution computed tomography (CT) of the lungs. The bacteriologic criteria depend on the specific specimens examined in the laboratory. A single positive culture is sufficient in the case of a lung biopsy. If only sputum is examined, there should be at least three positive cultures for the same NTM species or two positive cultures with at least one sample positive for acid-fast bacilli on direct smear. If neither biopsy tissue nor sputum is available, a bronchial wash culture positive for NTM is sufficient for diagnosis, except that a single positive culture with only 1+ growth (light growth on a scale of 4; ATS guidelinesis not considered diagnostic unless the patient is immunocompromised.

Individual NTM species differ in both their virulence and prevalence in the environment. Consequently, the probability that a particular NTM isolate is associated with disease varies. In a U. S. series of approximately 10,000 NTM isolates, 75% of *M. kansasii,* 47% of MAC, and 25% of *M. xenopi* were associated with clinical disease (O'Brien et al, 1987).

Disease Due to Specific Nontuberculous Mycobacteria Species

Mycobacterium avium Complex

The Microorganism

The MAC comprises Runyon Group III NTMs that consist of three specific species: *M. avium, Mycobacterium intracellulare,* and *Mycobacterium lepraemurium,* the last of which is not a human pathogen (Wayne & Sramek, 1991). *M. avium* has three subspecies, of which only *M. avium* subspecies *avium* is a human pathogen (Thorel et al., 1990). Both *M. avium* subspecies *avium* and *M. intracellulare* cause human pulmonary disease and appear to do so in relatively similar proportions,

whereas nearly all disseminated MAC disease in HIV-infected individuals is due to *M. avium* subspecies *avium* (Guthertz et al., 1989). As the name suggests, *M. avium* is also a pathogen of birds, and it has also been found to affect a number of mammals. Nevertheless, there is little or no evidence of transmission of MAC from animals to humans. MAC organisms are ubiquitous in nature, especially in water and soil (Inderlied et al., 1993; Falkinham, 1996). Pulmonary MAC disease most likely is acquired through the inhalation of infectious aerosols. Person-to-person spread of MAC or any other NTM has not been documented and, consequently, respiratory isolation is not required once a diagnosis of tuberculosis is excluded.

Epidemiology

Pulmonary MAC disease is not a notifiable disease, so that estimates regarding its incidence are imprecise. Based on a laboratory-based study conducted by the Centers for Disease Control and Prevention (CDC) prior to the HIV/AIDS era, it was estimated that the incidence of MAC disease in the United States was 1.3 cases per 100,000 population (O'Brien et al., 1987). There is evidence to suggest that the incidence of MAC pulmonary disease is increasing. Some of this increase may be related to improved laboratory diagnosis, but it is most likely that there is a "real" increase in the incidence of MAC pulmonary disease.

Clinical Features

There appear to be two distinct subtypes of MAC pulmonary disease (Wallace, 1994). Both present with productive cough and pulmonary infiltrates. The first form is cavitary pulmonary disease with a predilection for the upper lobes. This form of MAC pulmonary disease is more common in men and clinically resembles tuberculosis, except that it is not more prevalent in individuals born in highly tuberculosis-endemic regions.

The second form of pulmonary MAC disease most commonly occurs in middle-aged to elderly women, and is associated with multiple small pulmonary nodules and focal bronchiectasis on CT scans (Wallace, 1994, Huang et al., 1999). Many of these patients are nonsmokers. Pulmonary cavitation is distinctly uncommon and this clinical presentation is seldom confused with tuberculosis.

Diagnosis

The criteria for diagnosis are summarized above. The diagnosis requires the appropriate clinical suspicion to pursue mycobacterial smears and cultures of respiratory secretions. As noted above, the growth of MAC in a single sputum culture is not conclusive evidence of pulmonary MAC disease.

Treatment

In vitro susceptibility testing is essential in the management of tuberculosis, for which there are NCCLS (National Clinical Committee on Laboratory Standards) susceptibility guidelines. In contrast, there are no NCCLS guidelines for in vitro susceptibility testing of NTM. Nevertheless, there is some role for such testing, depending on the particular NTM species and the specific drug(s) tested.

In the case of MAC, there is considerable evidence that in vitro susceptibility to clarithromycin or azithromycin is clinically important. Primary resistance of MAC isolates to these two macrolides is rare, but acquired resistance during therapy is an important cause of treatment failure (Chaisson et al., 1994). Accordingly, macrolide susceptibility testing is not currently recommended for baseline isolates, but is recommended on isolates from individuals with prior macrolide exposure (Wallace et al., 1997). In vitro, MAC isolates demonstrate some degree of susceptibility to ethambutol, rifamycins (rifabutin is more active than rifampin), some fluoroquinolones, amikacin, and clofazimine. MAC isolates are uniformly resistant to isoniazid and pyrazinamide. Most studies have been unable to demonstrate any correlation between in vitro susceptibility testing and clinical outcome of treatment of MAC infection for drugs other than clarithromycin or azithromycin (Wallace et al., 1997; Shafran et al., 1998). Consequently, such testing is not recommended (Wallace et al., 1997).

Several clinical trials comparing specific regimens for the treatment of MAC infection have been carried out in AIDS patients with MAC bacteremia. These studies have clearly demonstrated superior

outcomes with macrolide-containing regimens (Shafran et al., 1996). Furthermore, these studies have demonstrated that the addition of ethambutol to clarithromycin or azithromycin significantly reduces the risk of the development of secondary macrolide resistance and treatment failure. The role of additional antimycobacterial agents for treating MAC infections is less well defined. Two randomized trials in AIDS patients examined the role of adding rifabutin to a combination of clarithromycin and ethambutol, and these studies yielded discordant results (Gordin et al., 1999; Benson et al., 1999). In another study in AIDS patients, the addition of clofazimine to clarithromycin and ethambutol was deleterious (Chaisson et al., 1997). The specific role of fluoroquinolones in the treatment of MAC infection has not been clearly established in randomized trials, although these agents are occasionally included in multidrug regimens. Amikacin did not add to the efficacy of the four-drug regimen of rifampin, ethambutol, clofazimine, and ciprofloxacin (Parenti et al., 1998).

The essential elements of a regimen for MAC infection are either clarithromycin or azithromycin plus ethambutol. The addition of other antimycobacterial agents should be considered optional at this time. Treatment should be given until sputum cultures are negative after therapy for 12 months. The optimal management of infections due to macrolide-resistant MAC is unknown. A regimen consisting of rifabutin, ethambutol, and fluoroquinolone with or without amikacin should be considered for these rare cases. For refractory cases, the addition of interferon-γ, given either subcutaneously (Holland et al., 1994) or via aerosol (Chatte et al., 1995), has been reported to result in sputum conversion in a few cases. Unfortunately, the multidrug regimens for MAC are often poorly tolerated by elderly patients with pulmonary MAC (Huang et al., 1999) compared with younger patients with AIDS-associated disseminated MAC infections.

Mycobacterium kansasii

The Microorganism

M. kansasii is a photochromogenic NTM that was first isolated in 1953 from the sputum of a patient in Kansas City, Missouri (Buhler & Pollak, 1953). *M. kansasii* has been recovered from water samples in many parts of the world, and less frequently from soil samples. Pulmonary infection is presumed to result from inhalation of infectious aerosols.

Epidemiology

M. kansasii infections have been reported from North America, Europe, Japan, and Australia (Falkinham, 1996). In Europe, *M. kansasii* has been particularly prevalent in Wales and Southeast England. In the United States, Texas and Louisiana have reported significant numbers of *M. kansasii* cases. In most of these regions, *M. kansasii* is the second or third most prevalent NTM species causing pulmonary disease, with MAC nearly always the leading cause. However, in Europe, *M. kansasii* infection may be the most common cause of pulmonary NTM infection (Banks et al., 1983). The CDC estimates an annual incidence of 0.33 cases per 100,000 population in the United States. *M. kansasii* appears to be more pathogenic for the lung than most NTM, with a majority of respiratory isolates (approximately 75%) being associated with clinical disease (O'Brien et al., 1987). Approximately 75% to 80% of cases occur in men.

Clinical Features

Pulmonary disease due to *M. kansasii* typically presents with unilateral cavitary disease in males over the age of 50 with underlying chronic obstructive pulmonary disease (Banks et al., 1983; Contreras et al., 1988; Pang, 1991; Jenkins et al., 1994). The clinical and radiographic appearance is quite similar to cavitary tuberculosis, except for differences in demography. In the United States, Canada, and the United Kingdom a large portion of cases of tuberculosis occur in the foreign-born. In contrast, nearly all cases of pulmonary *M. kansasii* disease occur in nonimmigrant Caucasians. The features of *M. kansasii* pulmonary disease are summarized in Table 1.

Treatment

There are no NCCLS guidelines for *M. kansasii* susceptibility testing. Nevertheless, most *M. kansa-*

TABLE 1. *Mycobacterium kansasii* Pulmonary Disease: Clinical Features

Reference	Country	No.	% male	Median age (years)	% underlying pulmonary disease	Chest x-ray cavity (%)
Banks et al., 1983	Wales	35	88	52	66	90
Ahn et al., 1983	United States	40	83	49	NS	98
Schraufnagel et al., 1984	Canada	36	94	53	58	80
Pang et al., 1991	Australia	36	78	53	NS	88
Jenkins et al., 1994	Great Britain	173	73	56	59	88

NS, not stated.

sii isolates are susceptible to rifampin, ethambutol, and clarithromycin and are usually resistant to isoniazid and pyrazinamide.

There have been no randomized comparative trials of specific drug regimens for *M. kansasii* disease. However, a large body of experience indicates that the two essential components of a regimen to treat *M. kansasii* are rifampin and ethambutol, and such a regimen is curative in the vast majority of treated individuals (Pezzia et al., 1981; Banks et al., 1983; Pang, 1991; Jenkins et al., 1994). The British Thoracic Society (BTS) conducted a prospective study in which 173 patients with pulmonary *M. kansasii* infection were treated with a combination of rifampin and ethambutol for 9 months (Jenkins et al., 1994). Nine of these patients died during treatment of unrelated causes. There was only one treatment failure observed, but there were 15 patients (9.7%) who relapsed 6 to 15 months after completion of therapy, four of whom were felt to have been noncompliant with therapy. The American Thoracic Society (ATS) continues to recommend including isoniazid in the treatment of *M. kansasii* disease (Wallace et al., 1997), presumably because isoniazid has been included in combination with rifampin and ethambutol in a number of series with successful outcomes. However, the need to include isoniazid in such a regimen is questionable. The precise duration of therapy is also somewhat controversial. The BTS study had favorable results with a 9-month regimen, whereas the ATS presently recommends treating for 18 months with at least 12 months beyond the last positive culture.

Rare cases of *M. kansasii* disease due to rifampin-resistant strains have been reported (Wallace et al., 1994). The management of these cases has historically been difficult, but as nearly all of these isolates are susceptible to clarithromycin (Biehl & Cavalieri, 1992), a clarithromycin-containing regimen is recommended for the management of rifampin-resistant cases, provided that these isolates are susceptible to clarithromycin in vitro.

Mycobacterium xenopi

The Microorganism

M. xenopi was first isolated in 1959 from a cutaneous lesion of a South African toad, *Xenopus laevis* (Schwabacher, 1959). The organism is nonchromogenic NTM that has been isolated from a number of water sources (Falkinham, 1996). An important laboratory property is its ability to grow at 45°C but not at 28°C. As commercially available DNA probes for *M. xenopi* are not available, laboratory identification usually relies on biochemical testing.

Epidemiology

The CDC estimates that the incidence of *M. xenopi* disease in the United States is approximately one case per 10,000,000 population per year, and that only 25% of *M. xenopi* laboratory isolates are associated with clinical disease (O'Brien et al., 1987; Smith & Citron, 1983; Banks et al., 1984; Contreras et al., 1988). However, *M. xenopi* is of greater relative importance among NTM in Wales, Southern England, and Ontario, Canada. *M. xenopi* pulmonary disease has also been reported from a number of European countries, as well as occasionally in Australia and Japan. Although most cases occur sporadically in the community, nosocomial

infection related to contaminated hospital water has been described. Person-to-person transmission has not been documented.

Clinical Features

Most patients with pulmonary *M. xenopi* disease are males over the age of 50 with chronic obstructive pulmonary disease due to many years of smoking (Smith & Citron, 1983; Banks et al., 1984; Contreras et al., 1988). The clinical features consist of productive cough, weight loss, weakness, and dyspnea. Fever is uncommon. The usual chest radiographic findings are bilateral cavities, particularly in the upper lobes. The radiographic pattern is similar to advanced pulmonary tuberculosis. These clinical features are summarized in Table 2.

Diagnosis

The diagnosis requires the presence of symptoms, radiographic findings, and bacteriologic features as noted above.

Treatment

There are no NCCLS standards for *M. xenopi* susceptibility testing. In vitro susceptibility testing has been reported for a relatively small number of isolates, with inconsistent results. In most series, only a minority of isolates were susceptible to isoniazid, rifampin, ethambutol, and pyrazinamide. However, there is considerate variability among individual isolates and in between series. Virtually all strains of *M. xenopi* are susceptible to clarithromycin in vitro.

No clinical trials have been undertaken comparing regimens for *M. xenopi* disease. Prior to the availability of clarithromycin, the reported cure rates in *M. xenopi* pulmonary infection were low using regimens similar to those used to treat tuberculosis. For this reason, surgical excision has long been considered an important adjunct, when there is adequate pulmonary reserve to withstand such surgery (Parrot & Grosset, 1988). A regimen of clarithromycin plus ciprofloxacin and ethambutol was evaluated in a pilot study of 11 patients with *M. xenopi* pulmonary disease (Dautzenberg et al., 1993). All 11 patients experienced sputum and culture conversion, with one subsequent relapse.

The optimal regimens for *M. xenopi* pulmonary disease is unknown. Given the lack of urgency of immediate treatment, one strategy to be considered is to await the results of a full susceptibility testing panel, including clarithromycin, fluoroquinolones, and traditional antituberculous agents, and then selecting a multidrug regimen based on the in vitro susceptibility profile. A minimum of three antimycobacterial agents is suggested and therapy should be continued for 12 months after the last positive sputum culture. Surgical excision of focal disease should be considered.

Mycobacterium malmoense

The Organism

M. malmoense is a nonchromogenic NTM named for the Swedish city of Malmö where this organism was isolated from four patients with pulmonary disease in 1977 (Schröder & Juhlin, 1977). Subsequently, it was demonstrated that the first

TABLE 2. *Mycobacterium xenopi* Pulmonary Disease: Clinical Features

Reference	Country	No.	% male	Median age (years)	% underlying pulmonary disease	Chest x-ray cavity (%)	Cures (%)
Banks et al., 1983	Wales	47	82	62	75	96	23
Smith & Citron, 1983	England	15	87	62	NS	73	73
Simor et al., 1984	Canada	9	88	59	100	75	13
Contreras et al.,[a] 1988	Canada	34	79	63	100	91	29
Parrot & Grosset, 1988	France	57	89	49	NS	NS	0[b]

NS, not stated.
[a]All hospitalized.
[b]All underwent surgery.

documented isolate of *M. malmoense* was obtained in 1954 from the United Kingdom (Jenkins & Tsukamura, 1979). *M. malmoense* grows unusually slowly, generally requiring at least 6 weeks for primary isolation. For this reason, it can be readily missed in laboratories that discard cultures after 6 weeks' incubation. Although *M. malmoense* can grow in conventional mycobacterial media, it grows more readily in low pH, pyruvate-containing medium, particularly when incubated at 30-33°C.

Epidemiology

In Sweden, *M. malmoense* is the second most frequent cause of NTM pulmonary disease following MAC. *M. malmoense* pulmonary infections have also been reported in other parts of Scandinavia as well as England, Waltes, Scotland, Switzerland, and occasionally the United States. *M. malmoense* has also been isolated from a soil sample in Japan and found to naturally infect armadillos in Louisiana. Among 171 respiratory isolates in Sweden, all but one came from adults with a mean age of 62 years.

Clinical Features

Pulmonary disease due to *M. malmoense* is a disease of older adults (Henrique et al., 1994; Banks et al., 1985). Pulmonary cavities and/or infiltrates are virtually always present and a majority have underlying pulmonary disease, with previous tuberculosis being a particularly common underlying factor. The clinical presentation is similar to that of tuberculosis.

Diagnosis

Diagnosis requires clinical, radiographic, and bacteriologic evidence of disease, as with other NTM. The diagnosis of *M. malmoense* infection is likely frequently missed due to the prolonged time this organisms takes to grow in culture.

Treatment

There are no clinical trials available evaluating therapy for *M. malmoense* infection. Limited in vitro susceptibility data are available and these suggest that *M. malmoense* is virtually always resistant to isoniazid, with a majority of strains also resistant to rifampin and streptomycin (Banks et al., 1985). Most strains appear to be susceptible to ethambutol, cycloserine, and ethionamide (Banks et al., 1985). Data regarding the activity of clarithromycin and rifabutin are not available. In a relatively small series, favorable results were obtained with an 18-month course of isoniazid, rifampin, and ethambutol. It is suggested that in vitro susceptibility testing be performed with traditional antituberculous drugs plus rifabutin, clarithromycin, and fluoroquinolones and then a regimen can be selected that includes two or three drugs active against the isolate in vitro. Given the limited data available, ethambutol and rifamycin should be included where possible. The duration of treatment is not known, but 18 months appears to be reasonable on the basis of the limited information available.

Mycobacterium abscessus and Other Rapidly Growing Mycobacteria

The Microorganisms

Among rapidly growing (Runyon Group IV) mycobacteria (RGM), more than 90% of cases of human disease are attributable to three species: *M. fortuitum, M. chelonae,* and *M. abscessus. M. fortuitum* and *M. chelonae* are most commonly associated with cutaneous disease (Wallace et al., 1983). In contrast, *M. abscessus* is responsible for approximately 80% of the pulmonary disease due to RGM (Griffith et al., 1993). Differentiation among RGM species is important, as there are significant differences in antimicrobial susceptibility. As there are no commercially available DNA probes for speciation of RGM, biochemical and cultural characteristics are typically used to differentiate the RGM.

Epidemiology

RGM are widely distributed in water and soil samples from many parts of the world (Falkinham, 1996). Some RGM have been found to contaminate hospital supplies including gentian violet solution, water baths, bronchoscopes, and prosthetic heart valves.

Pulmonary infection is believed to arise from

inhalation of infectious aerosols. Most clinical disease is sporadic and community-acquired, but occasional nosocomial outbreaks have been reported. RGM lung disease has been reported from many parts of the world, but a disproportionate number of cases appear to occur in the southeastern United States. The patients most commonly affected are Caucasian, nonsmoking women over the age of 60 without underlying pulmonary disease or known immunodeficiency (Griffith et al., 1993). When RGM lung disease occurs in individuals with underlying pulmonary disease, such as prior mycobacterial infection, it tends to occur at a younger age.

Clinical Features

The most common symptom is productive cough with hemoptysis in as many as one/third of patients. With progression, many individuals develop fever and occasionally weight loss and dyspnea. The most frequent chest radiographic patterns are interstitial disease, interstitial/alveolar disease, and reticulonodular patterns, each of which is seen in similar frequencies. Cavitation is uncommon, seen in 16% of 154 patients in the largest series reported (Griffith et al., 1993). The disease involves both lungs in approximately three quarters of cases.

Diagnosis

As with other NTM, the diagnosis requires clinical, radiographic, and bacteriologic criteria.

Treatment

Antimicrobial susceptibility is critically important in the treatment of RGM disease (Wallace et al., 1985). RGM are predictably resistant to isoniazid, rifampin, ethambutol, and pyrazinamide. The antibiotics that should be tested for activity against individual RGM isolates are clarithromycin, ciprofloxacin (or ofloxacin), doxycycline, sultonamide, imipenem, cefoxitin, and amikacin. Among the three most important RGM species, *M. abscessus,* which causes most cases of pulmonary disease, is the most resistant to antibiotics (Griffith et al., 1993).

Comparative clinical trials evaluating the treatment of RGM lung disease have not been performed. Treatment should be initiated with at least two and possibly three antibiotics to which the patient's strain is susceptible in vitro. It is usually possible to successfully treat infections due to *M. fortuitum* and *M. chelonae* medically. In contrast, it is seldom possible to successfully treat *M. abscessus* pulmonary disease with medical therapy alone (Griffith et al., 1993). Surgical excision is extremely important in *M. abscessus* pulmonary disease, and for this reason it is advantageous to identify cases of *M. abscessus* pulmonary disease at the earliest opportunity, when resection may still be feasible. Adjunctive antibiotics should be given whenever resection is undertaken. The duration of therapy for RGM lung disease is not established. A total treatment duration of 12 months is suggested. As has been reported for refractory MAC infection, adjunctive administration of interferon-γ may be useful in refractory cases of *M. abscessus* disease (Colsky, et al., 1999).

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Melioidosis

STEPHEN A. BERGER

Introduction

Melioidosis, an infectious disease that affects a wide variety of mammals, was first identified in Burma in 1911 by Whitmore and Krishnaswami (1912). The etiological agent is *Burkholderia pseudomallei,* a nonfermentative gram-negative bacillus acquired from soil and water. Although widespread in Southeast Asia and other tropical areas, melioidosis has also appeared in temperate zones. The clinical presentation ranges from inapparent infection to pneumonia, acute septicemia, and abscesses involving almost any tissue. Most patients present with fever, productive cough, weight loss, and pneumonia, often with reactivation of upper lobe infiltrates, suggestive of tuberculosis. Case–fatality rates may exceed 40%. Diagnosis is based on a careful epidemiological history, physical examination, bacteriological culture, and serologic tests. Ceftazidime is the treatment of choice.

Epidemiology

Melioidosis is usually acquired through inhalation of contaminated soil and is the most common cause of community-acquired pneumonia in areas of high endemicity (Boonsawat et al., 1990). The chance of disease acquisition appears to be related to inoculum size from soil aerosols (Smith et al., 1995a); indeed, the first reported cases of "nosocomial" melioidosis represented acquisition of bacteria from contaminated soil in proximity to a hospital (Ashdown, 1979). Additional sources include the surfaces of rice paddies, newly planted palm fields, monsoon drains, gardens, and playground soil (Leelarasamee & Bovornkitti, 1989). Survival of the organism is favored by shaded moist soil and still rather than flowing water.

In one unusual case, a woman was infected during an explosion (Wang et al., 1993). Rarely, infection is acquired from contaminated water, as in victims of near drowning (Lee et al., 1985). Traumatic inoculation of an anophthalmic orbit has been described in the United States (Nussbaum et al., 1980).

Although a variety of mammals are susceptible to melioidosis, transmission to humans is uncommon. Nonetheless, epizootics occur; and imported animals could theoretically contaminate the environment, indirectly endangering the local population (Dance et al., 1992). Person-to-person transmission is exceedingly rare. The first reported case was that of a soldier who acquired prostatic melioidosis in Vietnam and transmitted the disease venereally to four women (McCormick et al., 1975).

Although melioidosis has been reported from every continent, most cases originate in Southeast Asia. In Thailand, the highest rates are reported from the northeast, notably in the provinces of Ubon Ratchathani, Nakhon Ratchasima, Buri Ram, Khon Kaen, and Udon Thani (Leelarasamee et al., 1997). Seroprevalence in this region increases at a conversion rate of 24% per year, from 12% at age 1 to 6 months, to a plateau of approximately 80% after age 4 years (Kanaphun et al., 1993). Regional differences in Thailand have been ascribed to dif-

STEPHEN A. BERGER • Departments of Geographic Medicine and Clinical Microbiology, Tel Aviv Medical Center, Tel Aviv, Israel.

Community-Acquired Pneumonia, edited by Marrie Kluwer Academic / Plenum Publishers, New York, 2001.

ferences in the concentration of bacteria in local soils (Smith et al., 1995a).

Melioidosis is often encountered in northern Australia (Popoff et al., 1997), where infection appears to be more common among aboriginal peoples (Thompson, 1997). In northern Queensland 5.7% of the population is seropositive (Ashdown & Guard, 1984). Sporadic and even fatal cases have also been reported in southeastern Queensland (Scott et al., 1997). Recently, 33 cases of acute melioidosis occurred in the Northern Territory during an 8-month period, 25 of these in the capital city, Darwin (Merianos et al., 1993).

Melioidosis was first reported in China in 1990 and is largely limited to South China (Hainan, Guangdong, and Guangxi provinces [Li & He, 1992]. As much as 0.2% of the population of Singapore was seropositive during the 1980s (Lim et al., 1997), with evidence of increasing incidence in that country since 1990 (Lim, 1997); and 29% of Malaysian blood donors were seropositive (Norazah et al., 1996).

Rare autochthonous cases have been described in Puerto Rico (Donnan et al., 1998), Mexico (Barnes et al., 1986), India (John et al., 1996), Taiwan (Lee et al., 1996), Bangladesh (Kibbler et al., 1991), Papua New Guinea (Lee & Naraqi, 1980), and more than 20 other countries; however, it is no longer unusual for a returning traveler to present in any other country with this disease (Riecke et al., 1997; Silbermann et al., 1997; Wilks et al., 1994; Bremmelgaard et al., 1982; Mays & Ricketts, 1975).

Pathogenesis

B. pseudomallei is a facultative intracellular pathogen capable of invading eukaryotic cells (Jones et al., 1997). Virulence factors include a heat-stable extracellular glycolipid exotoxin, which is both cytotoxic and hemolytic (Haussler et al., 1998), and an extracellular protease (Sexton et al., 1994). The pathogen has also been found to reduce the numbers and function of host T lymphocytes (Kalachev et al., 1997).

Variation in virulence among genetically and phenotypically diverse strains may explain the discrepancy between the incidence of melioidosis in specific regions and the occurrence of *B. pseudomallei* in contiguous soil ecosystems (Anuntagool et al., 1998; Norton et al., 1998; Smith et al., 1997; Trakulsomboon et al., 1997; Wuthiekanun et al., 1996).

Although *B. pseudomallei* is readily opsonized and phagocytized, intracellular killing may not necessarily occur (Egan & Gordon, 1996). Intracellular killing of the organism is mediated to a large extent by interferon-induced reactive nitrogen mechanisms (Miyagi et al., 1997). Antibodies to the O-antigenic component of bacterial lipopolysaccharides have been shown to promote complement-enhanced phagocytic killing (Ho et al., 1997). Exopolysaccharide glycocalyces are produced by the organism both in vitro and within the host cell and may serve to protect it from cytoplasmic killing mechanisms (Vorachit et al., 1995). Indeed, it has been found that relapse represents infection by the initial bacterial strain, rather than acquisition of new bacteria from the environment (Desmarchelier et al., 1993; Vadivelu et al., 1998).

Disease rates are highest in certain groups of immunosuppressed patients, notably diabetics (Merianos et al., 1993; Puthucheary et al., 1992). Woods et al. (1993) have suggested that insulin may exert a direct inhibitory effect on the organism. Other predisposing conditions include collagen vascular disorders, alcoholism, malnutrition, chronic renal or hepatic disease, splenectomy, chronic granulomatous disease, corticosteroid therapy, pregnancy, leukemia-lymphoma, and other hematologic malignancies (Ashdown et al., 1980; Tanphaichitra, 1989; Leelarasamee & Bovornkitti, 1989; Dorman et al., 1998). To date, no predilection has been demonstrated among AIDS patients in endemic areas (Kanai et al., 1992).

In autopsy material, the bacteria are concentrated primarily in central necrotic areas within granulomata (Wong et al., 1996). Bacteria within macrophages and "giant cells" are often so numerous as to resemble globi (Wong et al., 1995).

Clinical Presentation

Acute melioidosis can be divided into five distinct clinical forms (Table 1): septicemia without abscess formation, septicemia with disseminated foci, localized infection, transitory bacteremia, and "pyrexia of unknown origin" (Leelarasamee & Bovornkitti, 1989). Forty-five percent of cases pre-

TABLE 1. Clinical Classification of Melioidosis[a]

Acute infection
Disseminated disease with septicemia
Septicemia without dissemination
Local infection
Pulmonary infiltrates and coalescent nodules
Transitory bacteremia
Fever of unknown origin
Subacute infection
Recrudescent infection resembling pulmonary tuberculosis
Pulmonary cavities may be present
Chronic infection
Wasting illness with abscesses of multiple organs
Subclinical infection

[a]Modified from Ip et al., 1995; Leelarasamee & Bovornkitti, 1989.

sent as septicemia with infection of multiple organs. Pericarditis may complicate the pulmonary infection and necessitate surgical drainage for tamponade (Majid, 1990). Visceral abscesses may involve the spleen, liver, kidneys, prostate, or other organs (Dhiensiri & Eua-Ananta, 1995).

Osteomyelitis is not unusual (Popoff et al., 1997). There are reports of instances of nasopharyngitis (Tan & Sethi, 1997), brain abscess (Kasantikul et al., 1992; Pelekanos & Appleton, 1989), septic arthritis (Morgan et al., 1996), orbital cellulitis (Wong & Ng, 1996), meningitis (Chotmongkol & Sukeepaisarncharoen, 1996), epididymo-orchitis (Koh, 1995), suppurative parotitis (Lumbiganon & Viengnondha, 1995), parapharyngeal abscess (Elango & Sivakumaran, 1991), corneal ulcers (Siripanthong et al., 1991), and psoas and other muscular abscesses (Yee et al., 1988).

Renal failure occurs in as many as one third of hospitalized patients with melioidosis and caries a poor prognosis (Susaengrat et al., 1987). In many cases this phenomenon represents exacerbation of preexisting renal disease through the actions of endotoxins, shock, and renal ischemia. Affected kidneys exhibit tubular necrosis, microabscesses, and interstitial nephritis (Susaengrat et al., 1987).

Roentgenographic Findings

Most patients with clinically apparent infection present with pneumonia. Chong and Fan (1996) have stressed the nonspecific nature of roentgenographic findings, which may include pulmonary nodules, consolidation, necrotizing lesions, pleural effusion, pleural thickening, and mediastinal abscesses. Occasionally, the only lesion may be a pleural mass (Girard et al., 1976).

In one series, multiple pulmonary nodular lesions were seen in 84% of patients with pulmonary disease associated with septicemia (Dhiensiri et al., 1988). Alveolar infiltrates were noted in 46% of patients with acute pneumonia, and mixed infiltrates with cavities in 55% of those with chronic disease. Although confluent upper-lobe infiltrates were common, the apices were generally spared in nonsepticemic cases. Rapid progression and early cavitation were common. Pleural effusion was noted in 21% of those with acute disease, and 13% of patients with chronic melioidosis. Pericarditis developed in 6% to 10% of all patients.

Computerized tomographic (CT) findings in pulmonary melioidosis include infiltration with thin-walled cavities, consolidation, pleural nodules or effusion, and hydropneumothorax or end-stage fibrothorax resulting from chronic empyema thoracis (Singcharoen, 1989).

Differential Diagnosis

Melioidosis has been called "the great imitator," since the clinical presentation is protean and can involve virtually any organ (Leelarasamee & Bovornkitti, 1989). The differential diagnosis of pulmonary infection acquired in the tropics must include a variety of common diseases such as tuberculosis, anaerobic lung abscess, and pneumococcal pneumonia. The lesser-known indigenous conditions include paragonimiasis, amoebiasis, leptospirosis, gnathostomiasis, and tropical eosinophilia (Charoenratanakul, 1997).

In nonendemic regions, patients with melioidosis typically present with reactivated disease occurring months to years after initial exposure to the organism. Typical symptoms include fever, productive cough, and weight loss (Everett & Nelson, 1975). These features, and the fact that pulmonary disease most commonly involves the apices (Fig. 1), may result in a misdiagnosis of tuberculosis in such patients (Ip et al., 1995). Indeed, evidence for prior melioidosis is often present among tuberculosis patients in endemic areas, and the two diseases may coexist in a given individual (So et al., 1987).

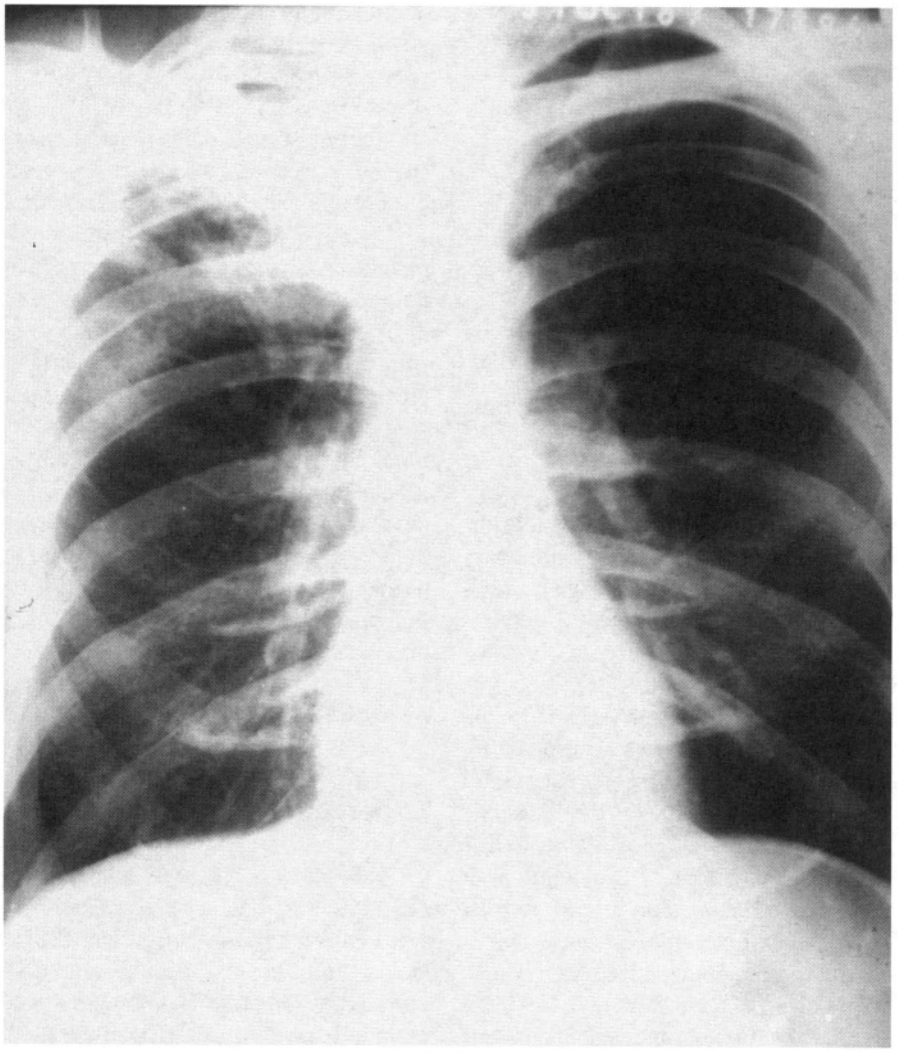

FIGURE 1. Pulmonary melioidosis. Extensive right upper-lobe changes reminiscent of reactivation tuberculosis.

Chromobacterium violaceum should also be considered in patients who present with a septicemic illness, skin lesions, or visceral abscesses after exposure to soil during the wet season in Asia and Oceania (Huffam et al., 1998; Ti et al., 1993). In fact, *C. violaceum* may even be misidentified as *B. pseudomallei* using standard laboratory systems (Inglis et al., 1998). Another opportunistic organism, *Penicillium marneffei,* is increasingly encountered as an agent of pneumonia and visceral abscesses, primarily among AIDS patients in the Far East.

Bacteriology and Laboratory Diagnosis

B. pseudomallei (formerly *Pseudomonas pseudomallei, Flavobacterium pseudomallei, Malleomyces pseudomallei, Bacillus whitmori,* and *Bacterium whitmori)* is an aerobic, motile, oxidase-positive bacillus that demonstrates bipolar staining and fails to ferment glucose. Bacterial colonies may be yellow to orange in color and exhibit an early putrid odor. After a few days, the colonies adopt a wrinkled appearance and earthy odor. Additional

characteristics include nitrate reduction and agglutination using specific antisera.

Although *B. pseudomallei* grows quite well in most bacteriological media, standard automated and semiautomated systems may be insufficient for identification of this taxon (Inglis et al., 1998). More than 60% of blood cultures in bacteremic patients will be positive within 24 hours, and more than 90% within 48 hours (Tiangpitayakorn et al., 1997). Culture of bone marrow may be useful for patients with low-grade bacteremia (Dance et al., 1990).

Selective media that incorporate gentamicin, crystal violet, and neutral red (Ashdown's agar and selective broth) are recommended for respiratory tract specimens in which the pathogen is masked by normal flora (Walsh & Wuthiekanun, 1996). Similar media have been developed for selective culture of soil (Withiekanun et al., 1995).

A variety of serological tests have been used to detect both IgG and IgM antibody, including indirect hemagglutination (IHA), gold blot (Kunakorn et al., 1991), indirect immunofluorescence (Khuulsup & Petchclai, 1986), dot immunoassay (Wongratanacheewin et al., 1995), and enzyme-linked immunosorbent assay (ELISA) (Dharakul et al., 1997b). An IHA titer of 1:40 is suggestive of disease in nonendemic areas, while titers of at least 1:80 are preferred in Thailand (Leelarsamee, 1985).

Bacterial antigen may be detected in clinical specimens using direct immunofluorescence microscopy, ELISA (Anuntagool et al., 1996), or urine latex agglutination techniques (Smith et al., 1995b). Immunohistochemical staining is a highly sensitive technique for identifying *B. pseudomallei* in tissue specimens (Wong et al., 1996). Polymerase chain reaction (PCR) is a sensitive and specific technique for the detection of this organism in clinical specimens (Haase et al., 1998; Dharakul et al., 1997a) and soil (Brook et al., 1997).

Therapy

An extensive review of the in vitro susceptibility of *B. pseudomallei* suggests that the organism is generally resistant to amoxicillin, oxacillin, penicillin, ticarcillin, first- and second-generation cephalosporins, fluoroquinolones, aztreonam, cefsulodin, aminogylcosides, macrolides, polymyxins, and glycopeptides (Wiedemann & Grimm, 1996). Most strains are susceptible in vitro to carbenicillin, azlocillin, novobiocin, piperacillin, amoxicillin–clavulanate, ceftazidime, imipenem, tetracyclines, and chloramphenicol.

Ceftazidime at a recommended dosage of 120 mg/kg daily remains the drug of choice for severe disease. Cotrimoxazole (trimethoprim–sulfamethoxazole) is considered a second-line alternative (White et al., 1989; Suputtamongkol et al., 1994), useful for protracted therapy in the patient with chronic infection. Some authors have advocated a combination of the two drugs (Sookpranee et al., 1992). Preliminary experience with imipenem is encouraging. Recent data suggest that short dosage intervals or even continuous administration should be given, in view of the lack of a postantibiotic effect among clinical isolates (Walsh et al., 1995b). Aminoglycosides combined with penicillin, ampicillin, or second-generation cephalosporins are ineffective in the treatment of septicemia (Chaowagul, 1996).

In vitro resistance to virtually all antimicrobials has been documented, but this has not proven a major problem to date. Resistance mechanisms include chromosomally encoded β-lactamases and highly efficient antimicrobial efflux systems. Dance et al. (1989a, b) have encountered emergence of resistance during therapy and have cautioned against the combined use of bacteriostatic and bactericidal antimicrobials. Chromosomally mediated resistance to β-lactam antibiotics, including ceftazidime, has been identified in clinical isolates of *B. pseudomallei* (Godfrey et al., 1991).

Rajchanuvong et al. (1995) recommend that oral therapy be continued for as long as 20 weeks and note that poor patient compliance is the most important factor in relapse. The response to appropriate therapy is slow, and most patients require at least 2 weeks of initial high-dose parenteral treatment.

Chaowagul et al. (1997) found that ciprofloxacin or ofloxacin given as maintenance treatment for a median of 15 weeks was inferior to amoxicillin–clavulanic acid or the combination of chloramphenicol, doxycycline, and trimethoprim–sulfamethoxazole. They suggest that the fluoroquinolones should be reserved as third-line agents for this disease.

Tanphaichitra (1989) has successfully treated recurrent melioidosis in immunocompromised patients using a combination of antibiotics and transfer factor or levamisole, a cellular immunopotentiating agent. Abscesses should be drained if possible. When pulmonary tissue is to be resected, lobectomy is preferred to segmentectomy, in view of the risk of relapse from retained tissue (Everett & Nelson, 1975).

Prognosis

The case–fatality rate for melioidosis associated with pneumonia and visceral abscesses is 87%, while that for septicemia without localized disease is only 17% (Leelarasamee & Bovornkitti, 1989).

Paradoxically, mortality is highest when bacteremia is detected in blood culture within 24 hours of incubation, perhaps reflecting the higher bacterial concentration in such patients (Tiangpitayakorn et al., 1997). In fact, Walsh et al. (1995a) have demonstrated a relationship between bacterial counts and mortality in bacteremic patients. Similarly, the presence of detectable tumor necrosis factor in serum carries a poor prognosis (Suputtamongkol et al., 1992). Renal failure is also associated with a poor prognosis (Yee et al., 1988; Susaengrat et al., 1987).

Recurrence is common, even following prolonged therapy in some cases (Silbermann et al., 1997). Since relapse may occur several decades following initial infection, patients with pneumonia, visceral abscesses, or other suggestive signs of the disease must be asked whether they had *ever* traveled or lived in the Far East (Morrison et al., 1988; Mays & Ricketts, 1975). This point is well illustrated by a number of recent cases of relapse among Vietnam veterans in the United States (Barrett-Connor, 1978; Mackowiak & Smith, 1978; Beck et al., 1984; Everett & Nelson, 1975). Indeed, 1% to 2% of American military personnel serving in Vietnam became seropositive, equivalent to more than 200,000 former soldiers presently residing in the United States (Sanford, 1985).

The relapse rate following 8 weeks of treatment is approximately 28%; this decreases to 9% with 20 weeks of treatment (Chaowagul, 1996). Relapse rates appear to be unrelated to underlying predisposing conditions and are determined by the extent of initial infection, abbreviated courses of therapy, and use of antibiotics other than ceftazidime (Chaowagul et al., 1993; Chaowagul, 1996). In a study of relapse among 602 patients, the overall relapse rate was 23% (15% per year), and 27% died of the recurrent infection (Chaowagul et al., 1993).

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Pneumonia Due to *Nocardia* Species

THOMAS J. MARRIE

Introduction

Nocardiosis is usually a subacute process caused by several species of *Nocardia* (Filice, 1993) but mainly by *Nocardia asteroides* (Rolfe et al., 1992). Since infection with *Nocardia* is usually acquired by inhalation (Wilson et al., 1989) it is not surprising that pulmonary infection dominates all other manifestations (Filice, 1993). The following three case histories are intended to illustrate the diverse manifestations of this disease.

Case1

A 75-year-old male with a past history of carcinoma of the colon had myasthenia gravis diagnosed in November 1990. Treatment with prednisone 30 mg once daily, pyridostigmine and azathioprine 50 mg twice daily controlled his symptoms of myasthenia. In June 1991 he developed diabetes mellitus and *Klebsiella* bacteremia. The latter was successfully treated with intravenous antibiotics. However, 3 days after this discharge he returned because of severe pain in both calves. Nontender subcutaneous nodules were noted and a left upper-lobe opacity was present. Over the next month he lost 30 pounds and had fever and night sweats. On September 5, 1991, he was transferred to the hospital. Just prior to transfer he had a generalized seizure. On admission he was afebrile and confused and had a left third cranial nerve palsy as well as palsies of the right seventh and twelfth cranial nerves. Multiple nontender, subcutaneous nodules were present, 2 to 3 cm in diameter. The white blood cell count was 9.4×10^9/L, hemoglobin 88 g/L, platelet count 452 $\times 10^9$/L, creatinine 81 mmol/L. There were no HIV antibodies.

A chest radiograph showed air space disease in the left upper and left lower lobes. A computed tomographic (CT) scan of his chest showed bilateral pleural effusions and nodular air space disease in upper and lower lobes. A CT scan of his head showed multiple nonenhancing hypodense lesions in the left cerebellum and the left basal ganglia area.

A lumbar puncture yielded clear cerebrospinal fluid with a white blood cell count of 57/mm^3, of which 97% were mononuclear and 3% were polymorphonuclear leukocytes. The protein concentration was 275 mg/dL and the glucose 4.7 mmol/L. *N. asteroides* was isolated from the blood, cerebrospinal fluid, and bronchial washings. A biopsy of one of the subcutaneous nodules showed necrotizing inflammatory changes and granulation tissue. Filamentous acid-fast bacilli were seen on Ziehl–Neelsen stain.

Therapy was begun with intravenous trimethoprim–sulfamethoxazole and imipenem. The patient's hospital course was complicated by a massive gastrointestinal hemorrhage and right hemiparesis. He was transferred back to his local hospital, where he died 1 month later. An autopsy showed a left upper-lobe lung abscess, right lower-lobe pneumonia, three abscesses in the left parietal lobe, one in the left basal ganglia, and two in the cerebellum. The largest brain abscess was 1 cm in diameter.

This patient manifested a classic evolution of nocardiosis, from pulmonary infection to dissemi-

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

nated disease. Indeed, the triad of pneumonia, central nervous system disease, and subcutaneous nodules should always raise the possibility of disseminated nocardial infection. His nocardial infection occurred following a prolonged hospitalization, raising the possibility of nosocomial acquisition of the infection.

Case 2

A 62-year-old male was admitted May 17,1993, for evaluation of progressive liver disease. He was known to have chronic persistent hepatitis complicated by cirrhosis and esophageal varices. Three months prior to admission a chest radiograph showed a left upper-lobe nodule. His medications included oral prednisone 20 mg once daily and oral azathioprine 50 mg twice daily. He had worked as a coal miner and had mild pneumoconiosis. His chest radiograph and CT scan revealed a left upper-lobe nodule that had not changed in size over 3 months. He was febrile but had no pulmonary symptoms. Initial laboratory data included a white blood cell count of 7.34×10^9/L. While in hospital he developed a fluctuating mass in his left calf. Aspiration of this mass yielded pus which on gram stain showed filamentous gram-positive rods and on culture yielded *N. asteroides.* He became afebrile within 5 days of initiation of therapy with trimethoprim-sulfamethoxazole. This therapy was continued for 6 months. A repeat radiograph 10 weeks after onset of therapy showed complete resolution of the left upper-lobe nodule.

This patient had an asymptomatic pulmonary infection with *Nocardia* that manifested as a pulmonary nodule from which dissemination to one cutaneous site occurred.

Case 3

A 74-year-old male was admitted to his local hospital tor prostatic surgery. The night prior to surgery he fell out of bed and sustained a right pneumothorax. He remained hypoxemic after insertion of a chest tube and was transferred to the hospital on March 16, 1993. At this point bilateral pneumothoraces were evident. He had smoked an unknown quantity of cigarettes for 60 years. The features of chronic obstructive lung disease were present clinically and radiographically. On hospital day 2 he was intubated and ventilated. Bronchoscopy revealed a purulent exudate from the right lower lobe, a culture of which grew *Streptococcus pneumoniae.* Therapy was begun with cefazolin. On day 6 (March 21, 1993) *Staphylococcus aureus* was isolated from his endotracheal secretions and cloxacillin was substituted for cefazolin. A chest radiograph figure showed hyperinflated lungs and flattened diaphragms but no focal opacity. On day 10 (March 25, 1993) his white blood cell count was 15.2×10^9/L and he was afebrile. Three days later a right lower-lobe pleural-based opacity was evident and ceftriaxone therapy was begun. Despite this, there was progression of the pulmonary opacification. On April 1, an infectious disease consultant suspected Legionnaires' disease and recommended treatment with erythromycin and rifampin. This consultant sent specimens to the laboratory for a variety of cultures and *Nocardia farcinica* was isolated. On April 16, therapy with trimethoprim–sulfamethoxazole was begun. A second culture obtained prior to instituting trimethoprim–sulfamethoxazole also grew *N. farcinica.*

This patient meets the definition for nosocomial pneumonia. The major question is whether or not his nocardia was acquired in the community or in the hospital. The clinical presentation was that of rapidly progressive and cavitating pneumonia. The institution of erythromycin for presumed Legionnaires' disease resulted in improvement of the nocardial infection. Some strains of *Nocardia* are very susceptible to erythromycin.

The Organism

Nocardia is a genus in the family Nocardiaceae, order Actinomycetales. There are nine species. *N. asteroides* accounts for 80% to 90% of all cases of nocardiosis; 3% to 9% are due to *Nocardia brasiliensis,* and 0.5% to 3% are due to *Nocardia caviae* (Rolfe et al., 1992). *N. caviae* is now known as *N. otitidiscaviarum. N. farcinica, Nocardia nova,* and *Nocardia transvalensis* have also caused disease in humans (Tsukamura & Ohta, 1989; Wallace et al., 1990, 1991; McNeil et al., 1992).

Nocardia is a gram-positive filamentous branching rod that is weakly acid-fast, a feature that is useful in distinguishing it from *Actinomyces.* It has been isolated from soil and decaying organic material worldwide (Filice, 1993); however, infections due to *N. asteroides* are more common in cold climates while *N. brasiliensis* is more commonly associated with infections in warm climates (Filice, 1993).

Epidemiology

Nocardia was first described by the French veterinarian Edmund Nocard in 1888. Infections due to *Nocardia* have been reported worldwide, and while it is still considered uncommon the number of cases increased from 179 reported up to 1961 to 243 from 1961 to 1971 (Wilson et al., 1989). A survey of members of the Infectious Disease Society of America indicated there were 500 to 1000 new cases of this infection per year in the United States (Beaman et al., 1976).

About half the patients with nocardiosis are immunocompetent (Palmer et al., 1974). The other half include those receiving corticosteroids or other immunosuppressive therapy, recipients of various organ transplants, and those with diabetes mellitus, trauma, or pulmonary alveolar proteinosis (Palmer et al., 1974). Alveolar proteinosis was first described in 1958 by Rosen, Castleman, and Liebow and, by 1964, 7 of 75 reported cases had been complicated by nocardiosis (Andriole, et al., 1964). AIDS is the largest disorder to be complicated by nocardiosis (Telzak et al., 1989; Kim et al., 1991; Simpson et al., 1981). Kim et al. reported 6 cases among more than 2000 patients with AIDS (1991). They added 8 cases from the literature to their review. Seven of the 14 had a pulmonary infiltrate, 3 had pleural effusions. Seven died from nocardiosis. Eleven of the 12 culture-positive cases were due to *N. asteroides* and 1 to *N. brasiliensis.*

Simpson et al. (1991) found that 21 of 160 (13%) cardiac transplant patients developed nocardiosis. The rate of nocardiosis among renal transplant patients treated with cyclosporin was 0.7% (9/1, 255) in one study (Arduino et al., 1993).

Nocardiosis has complicated a variety of neoplastic diseases including carcinoma of the colon, breast, lung, and ovaries (Berkey & Bodey, 1989). Leukemia, lymphoma, and melanoma patients have also been reported to develop this infection. Berkey and Bodey (1989) reported 14 cases of nocardiosis in cancer patients at the M. D. Anderson Hospital in Texas from 1974 to 1986. There is a suggestion that cases of nosocomial nocardiosis do occur (Simpson et al., 1981; Cox & Hughes, 1975; Baddour et al., 1986; Lovett et al., 1981).

Clinical Manifestations

The three cases reported here exemplify the spectrum of disease and the varied clinical manifestations of nocardiosis. The pneumonia is usually subacute, manifesting with a productive cough, fever, weight loss, and malaise. One third of patients develop empyema (Filice, 1993). Fifty percent of patients with pulmonary nocardiaosis develop disseminated disease, 20% of whom present with only extrapulmonary disease.

The central nervous system is involved in 25% of all cases of pulmonary nocardiosis. Headache, nausea, vomiting, and decreased level of consciousness are the usual manifestations of CNS nocardiosis. However, a variety of focal deficits frequently occur. ACT scan will often reveal one or more brain abscesses.

While dissemination to nearly every organ (Phillips et al., 1972; Clenney et al., 1993; Koll et al., 1992; Laurin et al., 1991) has occurred, the skin and subcutaneous tissues are commonly involved. These subcutaneous abscesses produce very little inflammation of the overlying skin.

Local infections of the skin also occur and present in one of three ways: cellulitis, a lymphangitic form (which can mimic sporotrichosis, hence the name sporotrichoid), and mycetoma (Satterwhite & Wallace, 1979). *N. brasiliensis* predominates as a cause of primary cutaneous infection.

The radiographic manifestations of pulmonary nocardiosis include solitary and multiple nodules, consolidation, an interstitial reticular pattern, pleural effusion, enlarged hilar and or mediastinal nodes, cavitation, and diffuse pulmonary opacities (Balikian et al., 1978; Feigin, 1986; Schulman & Enson, 1987).

Presant et al. (1973) reviewed 147 case reports

of nocardiosis to determine the factors that affect survival. They found that patients who had symptoms for longer than 3 weeks before diagnosis were more likely to survive. There was an 81% mortality rate for those with dissemination. This rose to 90% if the central nervous system was involved. The mortality rate was 38% if there was no dissemination.

Treatment

Wallace et al. (1988) found that 95% of 78 clinical isolates of *N. asteroides* fell into one of five susceptibility patterns:

1. 17% exhibited resistance to broad-spectrum cephalosporins.
2. 18% were susceptible to both ampicillin and erythromycin.
3. 17% were susceptible to ampicillin and carbenicillin but intermediate in susceptibility to imipenem.
4. 35% were resistant to ampicillin but sensitive to broad-spectrum cephalosporins and imipenem.
5. 5% were resistant to all aminoglycosides including amikacin but susceptible to ciprofloxacin.

These same investigators found that 19% of 200 clinical isolates of *Nocardia* were resistant to cefotaxime and cefamandole. This feature can be used to distinguish *N. farcinica* from *N. asteroides* (Wallace et al., 1990) in that *N. farcinica* is resistant to those two cephalosporins. The β-lactamases of *N. farcinica* are different from those of *N. asteroides* (Steingrube et al., 1993). The β-lactamases *of N. farcinica* are penicillinases that exhibit low-level hydrolysis of cephalosporins including cefotaxime (Steingrube et al., 1993). *Nocardia nova* isolates were susceptible to ampicillin and erythromycin (Wallace et al., 1991). All isolates were susceptible to sulfa drugs (Wallace et al., 1988).

Sulfonamides are the usual drugs of choice for treating nocardiosis. The combination of sulfamethoxazole and trimethoprim has been used successfully. Large doses are necessary: 4 to 12 g/day of the sulfa component in divided doses. Non-immunosuppressed patients should be treated for 6 months. Relapses are not uncommon (Stropes et al., 1980). Patients with central nervous system disease and immunosuppressed patients should be treated for one year (Filice, 1993). If nocardiosis is recognized early and treated promptly mortality rates are as low as 5% (Simpson et al., 1981).

A variety of other antimicrobial agents may be used to treat nocardiosis—susceptibility testing should be available to guide therapy. Such antibiotics include imipenem, amikacin, minocycline, and a combination of ampicillin and erythromycin (Filice, 1993). Most pathogenic *Nocardia* spp. are resistant to rifampin (Yazawa et al., 1993).

In summary *Nocardia* is an uncommon cause of community-acquired pneumonia. In a prospective study of more than 1100 cases of community-acquired pneumonia no cases of nocardiosis were diagnosed. These three cases were seen over a 2-year period and two of the three may have been nosocomially acquired. The manifestations of nocardiosis are diverse but the triad of pneumonia, central nervous system disease, and subcutaneous nodules should always suggest this diagnosis.

ACKNOWLEDGMENT

Portions of this chapter were published in *Seminars in Respiratory Infections, 9,* 207–212,1994, and are reproduced with the permission of W. B. Saunders, Philadelphia.

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Actinomycosis

DAVID J. M. HALDANE

Introduction

Actinomycosis is now an uncommon cause of community-acquired pneumonia. Although it was once a common and ultimately fatal disease, the number of cases has declined since the introduction of antimicrobial agents, and the outlook for patients suffering from this infection has improved remarkably. Few physicians see many cases and as patients no longer commonly present with advanced disease, actinomycosis has become a more difficult diagnostic challenge.

Bollinger first reported the presence of yellow granules in sarcoma-like masses in the jaws of cattle in 1877. In 1879, Hartz, observing the microscopic appearance of granules from a case of *Actinomyces* infection in cattle, called the organism "strahlenpilz," which means "ray fungus" (in Greek: "actinos mykes"), giving the genus name *Actinomyces.* In 1878, Israel described the first human case and in 1885 he reported an additional 37 patients. Israel and Wolff were successful in culturing *Actinomyces israelli* using anaerobic methods in 1891. Boestrom isolated an aerobic actinomycete in the same year from straw. His findings caused some confusion. Actinomycosis was thought to be a risk of rural exposure, particularly to straw, for some years, until it was demonstrated that the organism was part of the endogenous oral flora and not isolated from the environment (Peabody & Seabury, 1957). Although Wright provided a detailed description of *Actinomyces* and distinguished it from the aerobic actinomycetes in 1905, there was continued confusion between the aerobic and anaerobic actinomycetes until the 1940s. The microscopic appearance of *Actinomyces* with branching filaments led early workers to believe that it was fungal in nature, and it was not until the 1950s that it was clearly established as bacterial (Weese & Smith, 1976).

The classification of *Actinomyces* species has recently changed with transfer of some species to other genera and the addition of new species (Jousimies-Somer, 1997). The species of clinical significance remain unchanged. They are pleomorphic gram-positive rods that may form long, branching filaments with true branching in some species. They do not form spores, are nonmotile, and are not acid fast. They are facultative anaerobes, although some species are more demanding of anaerobic conditions, and some species grow aerobically with CO_2. They grow well on basic nutrient agars and are stimulated by addition of blood or serum. *Actinomyces* spp. are part of the oral flora (Tanner et al., 1998; Moore et al., 1982; Zambon & Kasprzak, 1995) and have not been isolated from the environment. The most common species causing human infection is *A. israelii. Actinomyces gerencseriae* (formally *A. israelii* serotype II), *Propionibacterium propionicus, Actinomyces naeslundii, Actinomyces odontolyticus, Actinomyces viscosus,* and *Actinomyces meyeri* have been report occasionally as causes of disease (Brocket et al., 1972; Kuijper et al., 1992; Dontfraid et al., 1994; Rose et al., 1982). The characteristics of disease are the same for each species. although the freuuencv of

DAVID J. M. HALDANE • Department of Pathology and Laboratory Medicine, Queen Elizabeth II Health Sciences Centre; and Departments of Microbiology and Immunology and Pathology and Medicine, Dalhousie University, Halifax, Nova Scotia B3H 4H7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

infection differs. *Actinomyces bovis* causes infection in cattle but has not, as currently described, been associated with human infection (Peabody & Seabury, 1960).

Epidemiology

Actinomycosis affects all age groups and all occupations. It is distributed throughout the world. Although rates of infection are not readily available in published form, most series have been collected over extended periods of time, suggesting a frequency of not more than one case of thoracic disease a year in a large referral center (Jensen et al., 1989; Kinnear & MacFarlane, 1990; Hsieh et al., 1993; Eastridge et al., 1972). The association with rural exposure has long been discredited (Garrod, 1952). The male–female ratio is approximately 4:1 in most series (Kinnear & MacFarlane, 1990; Brown, 1973; Weese & Smith, 1976). The reason for this male preponderance is not clear. The majority of cases are cervicofacial, but thoracic disease accounts for 15% to 20% of cases of actinomycosis (Warren, 1996) and may be increasing in proportion (Bennhoff, 1984).

A discussion of the other types of actinomycotic infection is beyond the scope of this paper. Carious teeth and poor oral hygiene are predisposing conditions, although cases have occurred in edentulous individuals (Slade et al., 1972). Many patients with actinomycosis have a history of excessive alcohol intake and smoking. The number of cases of actinomycosis has declined since the introduction of antimicrobials (Bennhoff, 1984). Whether this decline is a result of early incidental treatment or a result of the improvement in dental hygiene over the same period is unknown. There is no association with immunosuppression including long-term cancer chemotherapy, prolonged use of corticosteroids for autoimmune disease, or HIV infection (Bennhoff, 1984; Poles et al., 1994). There are case reports of infection in immunocompromised individuals, including patients with lung transplants (Bassiri et al., 1996) and non-Hodgkin's lymphoma (Batt et al., 1996), but it is not clear to what extent their immunosuppression increased their risk of infection. Treatment of these patients in the same manner as nonimmunocompromised patients has generally been effective in the small number of cases reported.

Pulmonary actinomycosis results from aspiration. Rarely it may result from extension of cervicofacial disease of abdominal actinomycosis. Cecal disease can spread through the portal system to the liver and by direct spread involve the lung (Flynn & Felson, 1970). Hematogenous spread from other sites of infection can result in a disease that mimics miliary tuberculosis (Fisher, 1980).

Clinical Features

The presenting symptoms of actinomycosis are often imprecise (Balikian et al., 1978; Ossorio et al., 1997). Cough, which is frequently productive of sputum, is a common symptom and frequently accompanied by dyspnea and pleuritic chest pain. Fever and hemoptysis are less commonly seen. Occasionally, night sweats, malaise, anorexia, weight loss, and, if the disease has been of long duration, a fluctuant chest mass may be seen as well. Draining sinuses are no longer commonly seen. The clinical appearance of actinomycosis prior to the availability of antimicrobial therapy was described by Bates and Cruickshank (1957). The clinical features of thoracic actinomycosis, as described in selected recent references, are summarized in Table 1.

The series reported by Jensen et al. (1989) from Denmark differed from other series by an increased frequency of upper lobe disease. On bronchoscopy, masses were seen that resembled carcinoma. The authors suggested that an intrathoracic process that showed the features of malignant behavior, for example crossing tissue planes, despite benign histology, should raise the suspicion for actinomycosis.

Hsieh et al. (1993) reviewed the experience in Taipei. Patients presented with chronic cough, fever, and chest pain, particularly if the pleura were involved. Disease was confined to the lung in ten patients and involved the chest wall in the remaining seven. Two patients also had pericardial involvement. The chest radiographic findings were abscess in four and pneumonia in three; eight patients had mass lesions resembling carcinoma.

In the series reviewed by Kinnear and MacFarlane (1990), there was a provisional diagnosis of

TABLE 1. Clinical Features of Thoracic Actinomycosis

	Reference			
	Jensen et al., 1989	Hsieh et al., 1993	Kinnear & MacFarlane, 1990	Bennhoff, 1984
Years reviewed	1966–1987	1984–1990	1974–1989	—
No.	9	17	19	13
Age range (mean), years	15–76 (46)	7–76 (40)	9–66 (42)	12–78 (44)
M:F	6:3	13:4	15:4	6:7
Cough (sputum)	5 (3)	>9	16 (14)	11 (3)
Dyspnea	4	—	9	4
Hemoptysis	2	9	6	5
Chest pain	4	>9	13	—
Emphysema	3	2	0	1
Sinus formation	—	2	0	1
Chest mass	6	8	9	5
Diagnosis				
Culture	1	1	1	10
Histology	8	16	18	3

malignancy in 9 out of 19 patients. The median number of weeks between presentation and diagnosis was 3.5, with a range of 1 to 24. Diagnosis was made by resection of the affected lung in seven cases, pleural aspiration or biopsy in four, aspiration or biopsy of skin lesion in four, diagnostic needle aspiration in two, and lymph node biopsy in one. In this series, bronchoscopy was not diagnostic in any of the 11 cases in which it was used.

Brown (1973) reviewed 191 cases of actinomycosis and described the clinical features at a time when advanced disease was seen more frequently than in recent years. This case series was developed from a review of all the cases on file at the Armed Forces Institute of Pathology prior to 1972. Forty-eight of these cases had thoracic disease and presented with productive cough, fever, dyspnea, and an infiltrate on the chest radiograph. Eight had pulmonary disease with dissemination. Fourteen of the cases were diagnosed initially as carcinoma and five were diagnosed as tuberculosis. There was underlying lung disease in 32; 10 had chronic bronchitis and emphysema, 12 had chronic pneumonitis, and 10 had bronchiectasis.

Weese and Smith (1976) reviewed 57 cases with an age range of 2.5 to 85 and a mean of 45 years. There were 43 males and 14 females. Ten of the cases had thoracic infection: the lung was involved in six, the ribs in two, and the mediastinum in two. In this series, prominent symptoms were cough with sputum production, pain, fever, and weight loss.

Eastridge et al. (1972) reviewed 24 patients with *Actinomyces* seen between 1946 and 1971, of whom 15 had thoracic disease. There were three principal presentations. In the first group, patients presented with a pulmonary infiltrate with provisional diagnosis of pneumonia. Symptoms were commonly cough, hemoptysis, and weight loss. Patients presenting with empyema often had chest pain, productive cough, chills, and fever. In the third group, patients had chest wall and mediastinal involvement and presented with chest pain, chest wall mass, sinuses with drainage, and neck swelling from superior vena cava obstruction.

Bennhoff's (1984) series described the experience in the Cleveland and western Cuyahoga County areas during the previous 10 years. This series includes 13 patients with thoracic disease and differs from other series in having a majority of female patients (six males to seven females), and a high proportion of cases diagnosed using culture. It is not clear whether these findings are a result of a case-finding bias, as there were many difficulties in identifying appropriate records.

In children actinomycosis is uncommon, but all series have included children. In the series reported by Bates & Cruickshank (1957), 27% of the

cases of thoracic actinomycosis occurred in children between the ages of 3 and 20 years. Typically they presented with productive cough, fever, weight loss, and pleuritic chest pain. Infection in children and presentations with pulmonary infiltrates and draining sinuses, indicating advanced disease, both become uncommon after antimicrobials became widely used (Varkey et al., 1974; Slade et al., 1972). More recently, Spinola et al. (1981) described two presentations in children in whom the initial diagnosis was malignancy. The first was an asymptomatic 11-year-old boy, who presented with a thoracic mass, which enlarged despite antituberculous treatment. The second was a 17-year-old girl who presented with fever, anorexia, weight loss, lymphadenopathy, and a pleural friction rub. A posterior mediastinal mass and bilateral upper-lobe infiltrates were found on chest radiograph. In both patients, biopsy and histology were required for diagnosis, and culture was positive in the second. Both were successfully treated; the girl with intravenous penicillin for 4 weeks followed by 1 year of oral penicillin V, and the boy with 6 weeks intravenous penicillin followed by 3 months of oral penicillin V.

Endobronchial Actinomycosis

Endobronchial actinomycosis most commonly results from extension of a pulmonary focus of infection to involve the bronchi. Lee et al. (1982) reported a case in a 16-year-old with a 6-year history of probable bronchiectasis who developed multiple cavities with pleural thickening in the left upper lobe. On bronchoscopy, the mucosa was intact but a small, pale endobronchial mass was seen. Biopsy resulted in the release of purulent material that contained granules showing gram-positive filamentous rods. The patient recovered following treatment using high-dose penicillin for 3 months.

Endobronchial actinomycosis can also result from aspiration of a foreign body. There is no pulmonary focus associated with this disease. Dicpinigaitis et al. (1992) reported a case of a 66-year-old man who aspirated a chicken bone and subsequently developed a postobstructive pneumonia. On bronchoscopy, a pearly-gray, slightly friable, polypoid mass was seen obstructing 90% of the lumen and, on histology, bone and plant matter with an inflammatory response and sulfur granules were present. Subsequently, a chicken bone was removed from the bronchus. Interestingly, a chicken bone was also implicated in an aspiration episode reported by Julia et al. (1991). A 58-year-old man developed a right lower-lobe infiltrate and, on CT scan, cylindrical bronchiectasis was seen. On bronchoscopy, a "pinkish, polypoid mass" with intact mucosa, and a distal "yellowish, firm mass" that occluded the bronchus were seen. Gram-positive filamentous rods were seen histologically and *Actinomyces israelii* was cultured. The patient recovered after treatment with high-dose penicillin. Later, the yellow lesion was identified as a chicken bone. Chicken bones are likely a hazard because of their small size. In both of these cases, the presence of poor dental hygiene was noted. In the first, two carious teeth had been removed just days prior to the aspiration event. In a series of 43 consecutive patients with aspiration of foreign bodies in Taipei, Chen et al. (1997) reported a case of actinomycosis that developed after aspirating a fish bone. The occurrence of this case in a series of 43 consecutive cases suggests that endobronchial actinomycosis may be more common than a survey of the literature would suggest. The pathogenesis of the infection may be a result of contamination of the damaged mucosa either at the time of the aspiration or by material subsequently aspirated.

Actinomycosis and HIV

Pulmonary actinomycosis has been reported infrequently in cases of HIV. It does not appear that HIV increases the risk of infection, although it has been suggested that early infection may be undiagnosed and treated empirically, resulting in resolution. Reported cases have been similar to cases in patients who are not infected with HIV, often presenting with imprecise constitutional symptoms. Diagnosis may be delayed because of the resemblance of the clinical presentation to other causes of infection, for example, tuberculosis (Wasser et al., 1988), resulting in delays in implementation of appropriate treatment. Clinical suspicion should be increased when there is a subacute presentation,

poor response to short-course oral antibiotics, and the development of a new infiltrate while receiving intravenous antibiotics.

Cendan et al. (1993) reported a case of a patient who presented with 3 weeks' history of dyspnea, dry cough, and fever with no infiltrates seen on chest x-ray. Despite empiric treatment with erythromycin, the patient did not improve. After 5 days of treatment with pentamidine and erythromycin, the patient's condition improved and he was discharged. However, 2 days later, he was febrile and when *Haemophilus influenzae* was isolated from sputum he was treated with cefuroxime. Ten days after presentation, an infiltrate was seen on chest x-ray. Bronchoscopy revealed a mass in the left main-stem bronchus, which was whitish-yellow and surrounded by erythema and edema. Biopsy of the mass showed necrosis and a gram stain showed gram-positive filamentous rods. The patient was treated with penicillin G 12 million units a day for 4 weeks but deteriorated and developed cryptococcal meningitis and died 4 weeks later.

Ossorio et al. (1997) reported a patient who was HIV-positive and had been treated with zidovudine for 3 years. The patient had low-grade fever, and poor dentition was noted on the initial exam. Chest x-ray showed bilateral infiltrates in the middle lung zones and, on CT scan, numerous nodular densities less than 2 mm in diameter were seen. Bronchoscopy was performed and, in the right middle lobe, sulfur granules were found that, on gram stain, had branching gram-positive rods. The patient was treated with 3 weeks of intravenous penicillin and then ampicillin 500 mg 4 times a day orally for 6 months. Six months later, there was no relapse.

Treatment of patients with HIV and actinomycosis using the same regimens used for non-HIV-infected patients has been effective in most case reports (Poles et al., 1994; Yeager et al., 1986).

Disseminated Actinomycosis

If actinomycotic infection is allowed to progress, it may spread to other areas including the chest wall, the mediastinum, the vertebrae, and more distantly. Occasionally, it is these peripheral lesions that allow a diagnosis to be made (Liaudet et al., 1996; Legum et al., 1978). Pulmonary actinomycosis is the most common source of dissemination (Bennhoff, 1984). The frequency of dissemination has varied in different case series; 18 of 101 cases were disseminated in Brown's series (1973), and 2 of 85 in the series described by Bates and Cruickshank (1957).

In advanced disease, actinomycosis can progress to *empyema necessitatis,* chronic sinus tract formation, supra vena cava syndrome, and pericardial effusions. Fife et al. (1991) reviewed a series of 19 cases of cardiac actinomycosis over 40 years. The age range of the cases was 24 to 57 years, with a mean of 43; 84% of the cases were male. None had preexisting malignancy of immunosuppression and none had an intra uterine device. A third of the patients were ethanol abusers and five had periodontal disease. In 15, there was a primary thoracic focus; the source was unknown in the remaining four. Fever was present in 13, pericardial friction rub in 6, and cardiac tamponade in 10. Seven developed constrictive pericarditis and two were noted to have atrial fibrillation. On aspiration, there was purulent pericardial fluid in ten and *A. israelii* was cultured from the fluid in two. Culture of the biopsy gave rise to the diagnosis in four. Four had cultures positive from the sinus tract and two from chest wall lesions. Although the infection was predominantly restricted to the pericardium, occasionally it spread to the myocardium and even to the endocardium. The cardiac symptoms may cause the patient to present, and pneumonia may be an incidental finding. Vertebral osteomyelitis may also develop as a result of direct extension of pulmonary disease. Like malignancy, actinomycosis may have vertebral involvement while the disk spaces remain normal (Spinola et al., 1981). Chest wall spread was a common development in the pre-antibiotic era and is still occasionally seen. Perez-Castrillon et al. (1997) described a patient who developed *empyema necessitatis* that was caused by *A. odontolyticus.* This condition is usually secondary to tuberculosis. Culture of pleural fluid yielded the organism; no granules were present. Distant dissemination may also occur. There may be painful swelling in the extremities, and chest x-ray may reveal the pulmonary source. Apotheloz and Regamey (1996) de-

scribed a case of dissemination of *A. meyeri* and reviewed an additional 25 patients. They noted that there was poor dentition of recent dental extraction in 18 of the 26 patients and in 11 there was ethanol abuse. Thirteen of the 26 cases involved the lung. The patient they described presented with fever and an effusion of the left knee and then red, firm, painless subcutaneous nodules on the trunk and extremities. Chest x-ray showed a right middle-lobe infiltrate, which was confirmed by CT scan. A biopsy of the knee lesion showed osteomyelitis of the tibia and was culture positive for *A. meyeri.*

The differential diagnosis of actinomycotic pulmonary disease includes a number of causes of chronic chest pathology. The infectious causes include unresolved or poorly responsive pneumonia, botryomycosis caused by *Staphylococcus aureus,* tuberculosis, *Mycobacterium avium-intracellulare* infection, and *Nocardia* infection. Fungal causes include cryptococcosis, geotrichosis, and other opportunistic fungal infections and if there is exposure in endemic geographical areas, histoplasmosis, blastomycosis, and coccidiodomycosis. The relatively indolent course of actinomycosis may help in differentiating these conditions, but histology or culture may be required. Actinomycosis can occur simultaneously with tuberculosis. The present rarity of actinomycosis may result in an alternate initial diagnosis and the true diagnosis may become evident in the course of investigation. Noninfectious causes include malignancy, for example bronchogenic carcinomas and alveolar cell carcinomas, and pulmonary infarction (Legum et al., 1978; Hsieh et al., 1993). The "open bronchus sign," the appearance of an air bronchogram within a mass lesion seen on a chest radiogram, may be helpful as evidence in favor of actinomycosis. Surgical resection is often the means by which the diagnosis is reached.

Pathology

Macroscopically, actinomycosis appears as single or multiple abscesses or indurated masses with hard fibrous walls and soft central loculations with white or yellow pus. These masses may be dense and ill-defined and may be accompanied by multiple draining sinuses. Microscopically, an outer zone of granulation is seen with cellular fibrous tissue with lymphocytes present in moderate numbers. There may be giant cell or epithelioid cell reaction. The loculations, which tend to be round or oval, are crowded with polymorphonuclear leukocytes and "sulfur" granules may be present. Focal liquefaction is seen occasionally. Plasma cells may be seen in the lesion and 15% of the abscesses have eosinophils. In lung tissue, multinucleated giant cells may be seen. In the sinus tracts, there may be macrophages, particularly in acute lesions. The so-called "sulfur granules" are oval or round microcolonies that may be off-white, yellow, or brownish. Their size varies and some granules are microscopic. On microscopy, they consist of mesh-work or gram-positive filaments that are arranged radially and at the edge often have bulbous ends or clubs. The center tends to be basophilic, contrasting with the clubs, which are often eosinophilic; this represents the Splendore-Hoeppli phenomenon (Binford & Dooley, 1976). Larger granules may appear to be loosely aggregated. Granules are easily seen using hematoxylin and eosin (H & E) Giemsa, and methenamine–silver. They may be positive on periodic acid–Schiff stain, but they are not acid-fast. The best stain is the tissue gram stain (Binford & Dooley, 1976).

Diagnosis

The radiological appearance of actinomycosis is influenced by the duration of infection. Acute infection is a nonsegmental-based disease with predominance in the periphery and lower lobes. As the disease proceeds, abscesses form with fibrosis and destruction of lung tissue, with extension to pleura and eventually to chest wall (see Figs. 1–3). In many cases, the appearance may not be specific. One clue may be an unresolved pneumonia that persists despite antibiotic therapy. Flynn and Felson (1970) observed that any chronic indolent pulmonary infiltrate is suspicious for actinomycosis and periosteal reaction of several adjacent ribs in the absence of empyema is pathognomonic. In chronic disease, the radiological appearance may be chronic, bilateral, patchy pneumonia. In some cases, there may be cavitary disease that may simulate tuberculosis, particularly if the cavities are apical and, in

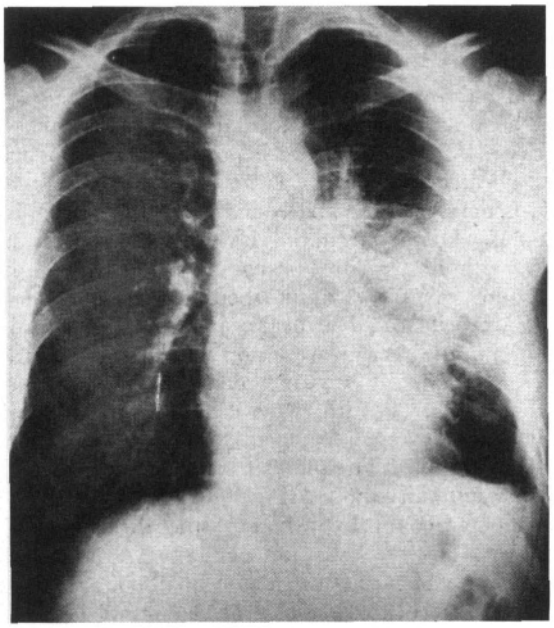

FIGURE 1. A radiograph of the chest of a patient with actinomycosis showing consolidation in the lingula and left upper lobe with pleural thickening along the left lateral chest wall. Reproduced, with permission, from Scully et al., 1983.

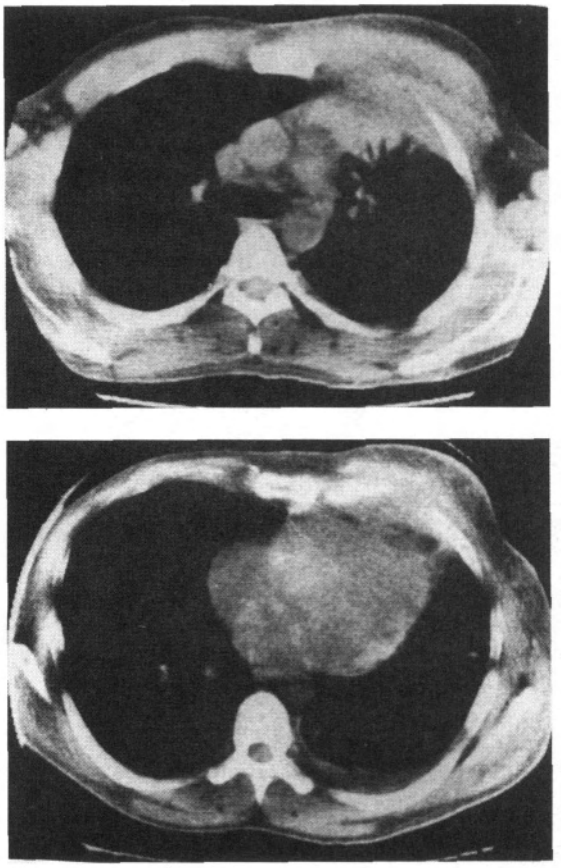

FIGURE 2. A CT scan of the chest with a section (top) taken below the level of the aortic arch revealing a density in the left upper lobe containing air bronchograms, and showing that the soft tissues of the anterior left chest wall are thickened. A section at the level of the heart (bottom) shows the costal cartilage partly destroyed and thickening of the anterior left chest wall. Pleural fluid or thickening is visible posteriorly. Reproduced, with permission, from Scully et al., 1983.

many cases, mass lesions are observed that may mimic carcinoma. The "open bronchus sign" may be seen; this describes the appearance of an air bronchogram within a mass lesion and is more characteristic of actinomycosis than neoplasm (Flynn & Felson, 1970). Commonly, an initial diagnosis of neoplasm is made. Ariel et al. (1991) reviewed five cases in which the initial diagnosis was malignancy. Bronchosopy allowed the diagnosis of actinomycosis to be made in four of the five and lobectomy was performed in the fifth case. In two patients biopsy was not diagnostic and the diagnosis was made by culture of washings, although in one a lobectomy was performed that showed typical histology before the culture result was available. The remainder were diagnosed histologically.

Disseminated disease can present with a miliary appearance on chest radiograph. Fisher (1980) described a case of pelvic actinomycosis that disseminated and resulted in "innumerable small, irregular pulmonary densities." Because of the miliary appearance, treatment with antituberculous agents was attempted and the diagnosis was only made at autopsy.

The value of computerized tomography of the chest was demonstrated by Kwong et al. (1992). In his series, eight patients had airspace consolidation on chest x-ray and by CT scan. In seven patients there was lower lobe involvement, most often the left lower lobe, and only three had upper lobe involvement; the disease was multifocal in three patients by chest x-ray and four using CT scan. In two patients, the appearance was nodular. Three patients were shown to have cavitation, but this was

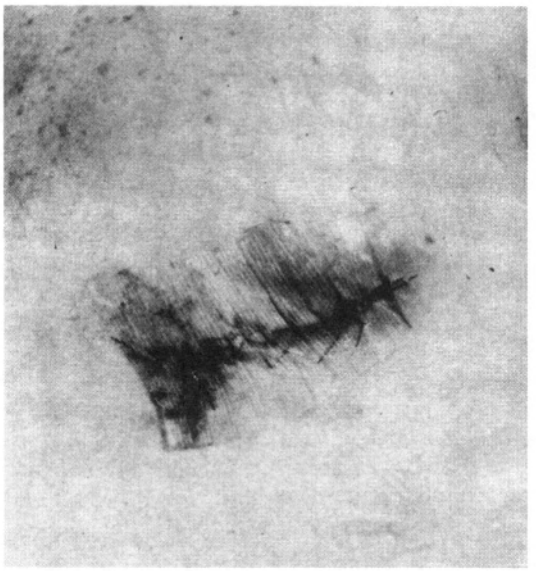

FIGURE 3. A left chest wall lesion after a biopsy with extensive induration and erythema surrounding the incision. Reproduced, with permission, from Scully et al., 1983.

only apparent on CT scan. Lesions crossing pulmonary fissures were seen in three patients by CT scan and two by chest x-ray. Pleural thickening was seen in four patients by chest x-ray, but in all eight using CT scan; the thickening was smooth and localized to the area of infection. Pleural effusions were seen in three on chest x-ray, but in five patients with CT scan. In two of these patients, an empyema was present. Hilar and mediastinal lymphadenopathy was detected in six patients on CT scan but in three on chest x-ray. There was involvement of the chest wall in one patient seen only by CT scan; however, there was no rib destruction or periosteal reaction. These results were in contrast to the earlier series of Flynn and Felson where chest wall involvement was seen in 9 of 15 patients and there was soft tissue swelling in 4. Four patients had periostitis, two had rib destruction, and one had vertebral destruction. Five out of the 15 patients had developed draining sinuses. This difference may reflect earlier treatment, even in the absence of a diagnosis, or earlier investigation for possible neoplasm, for example.

To establish a diagnosis of pulmonary actinomycosis, it is necessary to obtain specimens for histology and for culture. In most series, histology has been more useful than culture. The insensitivity of culture may be a result of inadequate specimen collection, loss of organism viability between the times of specimen collection and plating, failure to culture specimens anaerobically, overgrowth by accompanying organisms, or failure to identify the organism appropriately. Physicians should ensure that these potential defects are avoided and should inform laboratory personnel of their clinical suspicions to ensure appropriate laboratory handling.

A variety of specimens may be sent for culture, including tissue, pus, bronchial washing or brush specimens, or sulfur granules retrieved from draining sinuses or sputum, and autopsy material. If granules are present these may be removed for staining and used for culture. A variety of media can be used successfully, including blood agar (using 5% sheep blood or rabbit blood) supplemented with hemin and vitamin K, brain-heart infusion agar, brucella agar, or phenylethyl alcohol blood agar. Media containing vancomycin should be avoided. Broth media, for example thioglycolate, can also be used. Specimens should be inoculated to prereduced media and incubated anaerobically for at least 5 to 7 days, and incubation of 2—4 weeks may be necessary. Dehydration of plates can be difficult with extended incubation, which may be avoided by sealing the plates. The colonies are variable in their appearance. Classically the colony has a multilobed appearance (Fig. 4), said to resemble a molar tooth or a mulberry, but it may also appear smooth. In broth, aggregations of growth are formed that resemble breadcrumbs suspended in the medium (see Fig. 5). Identification is made using biochemical reactions, growth requirements, and acid end products of carbohydrate metabolism (Hillier & Moncla, 1995). The predictability of antimicrobial susceptibility makes routine testing unnecessary, but if agents other than penicillin are used for treatment, testing may be helpful. Antimicrobial susceptibility testing should be carried out in laboratories with experience in anaerobic susceptibility testing and the results should be carefully interpreted with close monitoring of the clinical response.

Although sulfur granules are the hallmark of actinomycosis, they may not be detected easily. In aspirated pus, they may be seen more easily if the

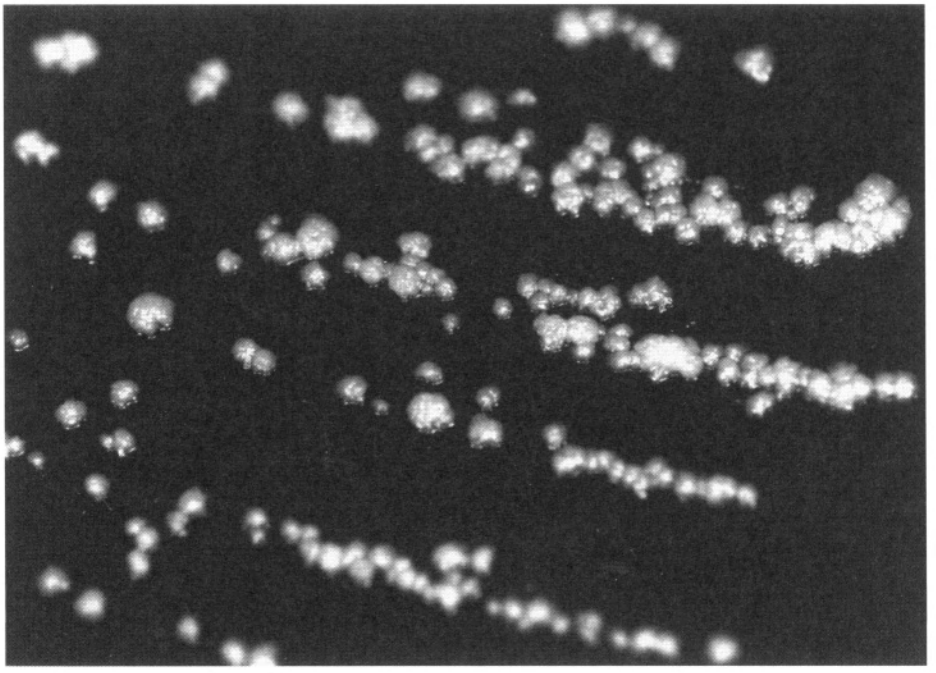

FIGURE 4. Colonial appearance of *Actinomyces israelii* cultured anaerobically on blood agar for 72 hours

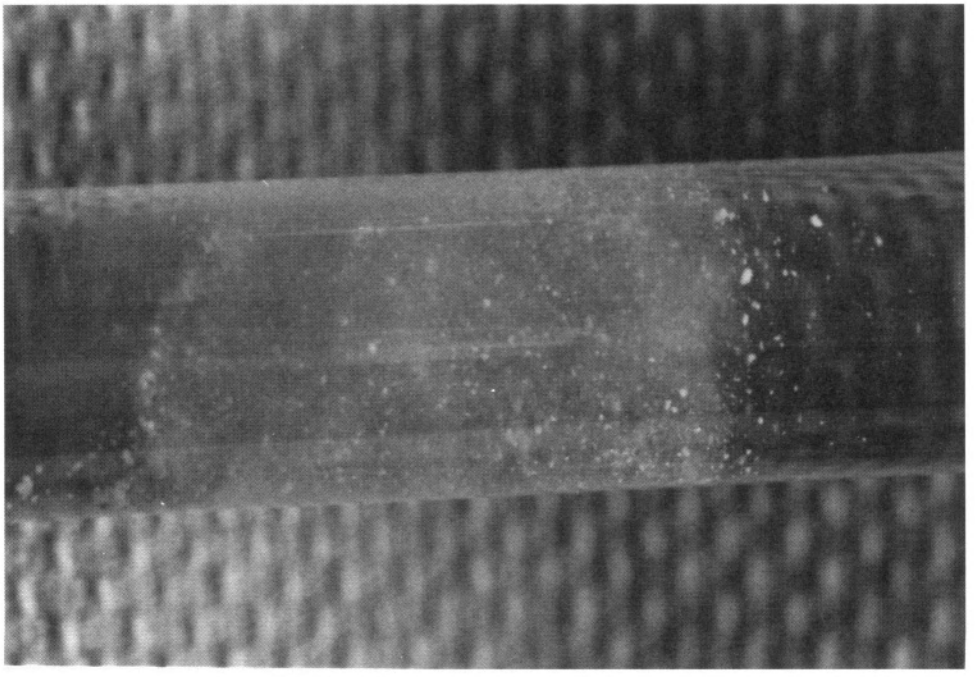

FIGURE 5. Typical "breadcrumb" appearance of *Actinomyces israelii* grown in thioglycolate broth.

pus is diluted five times with sterile water. The granules tend to settle to the bottom of the tube. Alternatively, if pus is swirled in a tube to form a thin layer on the inside of the glass, the granules may be seen in the thin layer (Garrod, 1952). Granules discharged from lesions may be trapped in gauze dressings overlying the sinus tracts. Individual granules may be crushed beneath another slide and gram-stained. Filaments are seen infrequently in pus, which differs from what is seen in nocardiosis (Binford & Dooley, 1976). In Brown's (1973) series, one to three granules were seen in 56% of cases and only one was seen in 26%. They were numerous in only 15%. In the series described by Weese and Smith (1976), sulfur granules were found in 31 of 57 cases. In that series, 34 of the cases were diagnosed by a positive culture, 19 by biopsy histology, and 4 using positive wet smear. The latter four cases were all diagnosed in the 1930s, when a wet mount was considered adequate for diagnosis.

Other organisms are usually isolated in addition to *Actinomyces* from actinomycotic lesions. These organisms include *Actinobacillus actinomycetemcomitans, Eikenella cormdens, Bacteroides* spp., and *Fusobacterium* spp. There is animal evidence that at least *A. actinomycetemcomitans* and *E. cormdens* can augment the development of disease (Jordan et al., 1984). These organisms may increase the virulence *of Actinomyces* spp. by creating anaerobic conditions (Bennhoff, 1984). Isolation of *Actinomyces* can be made more difficult because of overgrowth of cultures with these organisms. As they do not persist in its absence, treatment of *Actinomyces* spp. is sufficient to achieve cure.

Treatment

Prior to the antibiotic era, a variety of approaches were used to treat actinomycosis. These included radiotherapy, which was ineffective for pulmonary disease; iodine, because of the similarity between human actinomycosis and bovine actinobacillosis (Peabody & Seabury 1960); vaccines; antiserum; and thymol. These treatments were used both alone and in combination with surgery. The mortality, however, remained very high and approached 100%. Bates and Cruickshank, who reported in 1957 that a 90% cure rate was expected, demonstrated the dramatic benefit of antibiotic therapy. The earliest antimicrobials to be used for actinomycosis were the sulfonamides, which gave some success. In 1943, Florey and Florey treated two cases unsuccessfully with penicillin administered via duodenal tube, and for the first few years success was limited by the small doses and the short courses used. The importance of sufficient dosing with a sufficiently long course of penicillin was learned after clinical experience of the failure of short courses to prevent relapse of infection (Peabody & Seabury 1960). A recommendation was made that 2 to 6 million units of penicillin should be used per day for 6 to 18 months (Peabody & Seabury, 1960, Utz et al., 1971).

The chronic nature of actinomycosis and the need for antimicrobials to penetrate fibrotic tissue masses, granulomas, and microcolonies of the organism have been proposed as reasons for the necessity for prolonged treatment for actinomycosis (Garrod, 1952). Penicillin has remained the mainstay of treatment. Alternatives to penicillin have been sought in case of penicillin allergy, for example, but there is a dearth of clinical trials demonstrating efficacy. Baron et al. (1979) reported the case of a patient with allergy to penicillin, who was treated with tetracycline, erythromycin, and clindamycin. Desensitization to penicillin was required for cure because of an inability to tolerate the side effects of the alternate therapies. Seligman (1954) reported success with tetracycline in a single case and reviewed 11 others.

Clindamycin has been used with success at a dose of 600 mg every 6 hours for 5 weeks intravenously followed by 600 mg orally four times a day for a further 12 months (Rose & Rytel, 1972). Both chloramphenicol and isoniazid have been used with success in isolated cases (Peabody & Seabury, 1960), and a response to antituberculous therapy has led to diagnostic confusion (Bennhoff, 1984). More recently, there have been attempts to use other β-lactam agents and ceftriaxone has been reported to be effective in two reports (Skoutelis et al., 1994). In one patient, 2 g was given in a single dose every 24 hours for 21 days, followed by ampicillin orally. A CT scan showed almost complete resolution within 3 weeks on this therapy and it was convenient for outpatient administration. Skoutelis

et al. (1994) used ceftriaxone for 4 weeks after initial use of penicillin for 2 weeks with success in one case. Yew et al. (1994) reported a series of patients treated with imipenem; four patients were treated for 6 to 14 weeks with 42 to 105 g of imipenem. Three of the four responded without relapse; however, one patient who received 42 g over 10 weeks did relapse. The authors commented that the therapy was well tolerated. They suggested that advantages of the therapy were coverage of *Nocardia* and the possibility of using shorter courses than with the use of penicillin.

The *in vitro* techniques used in different laboratories vary, reflecting the lack of standardization of susceptibility testing methods for these organisms. The results of such testing, however, are broadly consistent (see Table 2). A change in the pattern of susceptibility has not been detected and the spectrum of effective agents does not vary substantially among strains or species within the genus *Actinomyces.*

Tanaka-Bandoh et al. (1997) used broth microdilution to determine the activity of a range of antibiotics against eight strains of *Actinomyces* and five *of Propionibacterium propionicus.* All were highly susceptible to β-lactams except for aztreonam and ceftazidime, which were less active. The minimum inhibitory concentrations (MICs) to the quinolones tended to be close to the breakpoint. Vancomycin and amikacin had mixed results. Lerner (1974) tested 64 clinical isolates of which 32 were A. *israelii,* seven were *P. propionicus,* and the rest were a variety of other *Actinomyces* species. He used a modified agar dilution method with whole colony immersion in semisolid agar, and used inhibition of colonial enlargement as the endpoint. Erythromycin and rifampin were found to be the most active agents. Penicillin G, minocycline, clindamycin, and cephaloridine were also found to be highly active. Metronidazole was active against A. *israelii* only. Oxacillin and cephalexin were less active, and aminoglycosides were inactive. Although detailed interpretation and comparison of these results is difficult because of methodological differences and the need for clinical validation, the overall results are in keeping with clinical experience.

Holmberg et al. (1997) used an agar dilution method to test 46 strains of A. *israelii* and eight of *P. propionicus,* most of which were clinical isolates. They found that A. *israelii* was highly susceptible to penicillin with an MIC of less than 0.064 mg/L for 44 of 46 strains. All but one of the *P. propionicus* isolates was sensitive to penicillin. The remaining isolate had an MIC of 4 mg/L. Erythromycin was active against all of the isolates. Clindamycin was active against all of the A. *israelii* strains and all but one of the *P. propionicus* strains, which had an MIC of 1 mg/L. Of the A. *israelii* strains, 84% were resistant to metronidazole and 81% resistant to tinidazole. All of the strains of *P. propionicus* were resistant to both agents. Of the A. *israelii,* 82% were susceptible to tetracycline but only three of eight *P. propionicus* strains were. These data are consistent with the results reviewed by Schaal (1986). MICs were low for almost all β-lactams agents. For tetracyclines, macrolides, chloramphenicol, clindamycin, rifampin, fusidic acid, and vancomycin, there was moderate to high inhibitory activity. The aminoglycosides, the nitroimidazole compounds, and colistin were inactive.

The rarity of this disease in recent years may explain the lack of clinical trials using recently developed antimicrobial agents. Further clinical trials are needed to confirm the effectiveness of ceftriaxone and imipenem and to evaluate the utility of alternative agents to penicillin. At this time, there is wide clinical experience and success using high-dose penicillin intravenously, 10 to 20 million units per day for 2 to 6 weeks, followed by penicillin V 2 to 4 g/day orally for 3 to 12 months.

Surgery remains important for removal of devitalized tissue, residual foci of infection, and drainage of abscesses and empyemas. In advanced disease, resection of sinus tracts may be necessary. It is often performed based on an incorrect preoperative diagnosis of malignancy. Surgery should be used in combination with effective antimicrobial therapy (Smego & Foglia, 1998).

Hyperbaric oxygen has been reported to complement therapy in a nonpulmonary case. Manheim et al. (1969) reported the case of a 63-year-old woman with ischiorectal actinomycosis who was treated with penicillin, a sulfonamide, and total excision of the inflammatory mass. She continued to suffer severe pain and so underwent hyperbaric therapy. The pain resolved rapidly and she improved clinically. In this case, hyperbaric therapy may have provided additional benefit to the other

TABLE 2. In Vitro Susceptibility Data for *Actinomyces* spp. and *Propionibacterium propionicus* from Selected References

	Species (No.)													Species (No. not specified)				
	Holmberg et al., 1997[a]		Lerner et al., 1974[a]							Tanaka Bandoh et al., 1997[b]				Schaal, 1986[c]				
Antimicrobial agent[d]	Ai (46)	Pp (8)	Ai (32)	Ae (6)	Av (15)	Pp (7)	An (6)	Ao (5)	Ab (4)	Ai (2)	Ag (2)	An/Av (4)	Pp (5)	Ai	Av	An	Ao	Ab
Penicillin G	0.064	4	0.25	0.5	0.5	0.5	1	0.5	1	—				0.39	0.39	0.2	0.2	1.56
Ampicillin	—	—	1	2	1	1	2	2	2	≤2 (13 strains)				0.78	0.2	0.39	0.1	0.2
Cephalothin	—	—	0.25	2	0.25	1	2	0.25	2	—				0.78	0.78	0.78	0.2	1.56
Cefazolin	—	—	—	—	—	—	—	—	—	≤4 (13)				0.78	0.38	0.78	0.39	3.12
Cefotaxime	—	—	—	—	—	—	—	—	—	—				0.39	0.78	0.39	0.2	0.78
Ceftazidime	—	—	—	—	—	—	—	—	—	≤4 (10), ≥16 (3)				—	—	—	—	—
Gentamicin	—	—	—	—	—	—	—	—	—	—				25	12.5	25	25	25
Amikacin	—	—	—	—	—	—	—	—	—	≤8 (2), 16 (4), ≥32 (7)				100	50	25	50	50
Tetracycline	2	≥2	—	—	—	—	—	—	—	—				3.12	3.12	3.12	1.56	3.12
Doxycycline	—	—	1	4	1	4	4	1	2	—				0.78	1.56	0.78	0.78	0.2
Minocycline	—	—	0.5	0.5	1	0.5	1	0.5	0.5	≤4 (13)				1.56	0.78	0.78	0.39	0.39
Erythromycin	0.25	0.25	0.12	0.06	0.12	0.12	0.12	0.06	0.06	<0.25 (11), 0.5 (1), ≥1 (1)				0.78	0.78	0.78	0.78	1.56
Clindamycin	0.125	2	—	—	—	—	—	—	—	≤2 (13)				1.56	1.56	3.12	1.56	3.12
Metronidazole	>64	>4	125	>125	>125	>125	>125	>125	>125	—				>100	>100	>100	>100	>100
Rifampin	—	—	0.3	>5	.12	>5	>5	0.3	0.6	—				0.39	0.39	0.39	0.39	0.2
Chloramphenicol	—	—	8	4	8	8	8	4	32	—				12.5	3.12	6.25	3.12	1.56
Vancomycin	—	—	10	20	10	10	10	10	10	≤2 (5), 4 (5), ≥8 (3)				1.56	1.56	0.78	0.78	0.39
Ofloxacin	—	—	—	—	—	—	—	—	—	≥4 (13)				—	—	—	—	—

Ai, *Actinomyces israelii*, Pp, *Propionibacterium propionicus*, Ae, *A. eriksonii*, Av, *A. viscosus*, An, *A naeslundti*, Ao, *A. odontolyticus*, Ab, *A. bovis*, Ag, *A. genercseria*.

[a]MIC_{90}

[b]Broth microdulution results (no. of strains for each concentration)

[c]Upper range of MIC results.

[d]All concentrations are in mg/L.

treatments. In pulmonary disease, it might have a theoretical benefit, but it has not been evaluated.

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Tularemia

BURKE A. CUNHA AND DIANE H. JOHNSON

Introduction

Tularemia is a zoonotic illness that was first recognized in the United States in 1911 by McCoy, who described a plague-like illness of ground squirrels in Tulare, California (Avery & Barnett, 1969). The etiologic agent later named *Bacterium tularense* was cultured in 1912, and in 1974 it was renamed *Francisella tularensis* in honor of Edward Francis, who made significant contributions to the study of tularemia (Brooks & Buchanan, 1970). The organism, which is highly infectious, is transmitted to humans via bloodsucking insects, infected animals, and the environment, and it remains an unusual but important pathogen in the United States.

Epidemiology

Tularemia is a disease of the temperate zones of the Northern Hemisphere. It has not been reported from the United Kingdom, Africa, South America, or Australia. In the United States, approximately 200 cases of tularemia are reported each year to the Centers for Disease Control and Prevention, with the majority of those cases originating in Arkansas, Oklahoma, and Missouri. The remaining cases were reported from all states except Hawaii, with the bulk of reports from the southern/central states (Sanford, 1983; Fredricks & Remington, 1996).

F. tularensis has been isolated from mammals, birds, fish, insects, and the environment. Contaminated water is an important environmental reservoir. In the United States, lagomorphs and rodents such as squirrels, muskrats, voles, and beavers are important reservoirs, as are blood-feeding arthropods such as ticks and fleas. Tularemia occurs in all age groups and in both sexes. It is seen with greater frequency in persons with recreational or occupational risk factors such as hunters, trappers, butchers, and veterinarians. The infection rate peaks during the summer months due to the prevalence of biting arthropods in the environment at that time. A second smaller peak occurs during the winter months that can be attributed to hunting-related cases (Brooks & Buchanan, 1970; Jacobs et al., 1985).

The major route of transmission of tularemia is through the skin, although mucous membrane contact may also result in the development of illness. Organisms are injected during the bit of a feeding arthropod or are introduced into the skin from the bite, lick, or scratch of an infected animal or an animal that recently had contact with infected matter. The pathogen can also be inoculated through inapparent skin breaks during the handling of contaminated animal materials, as is often the case with stricken butchers or hunters. Inhalation of the organism is also an important mode of transmission. As with percutaneous exposures, a small inoculum of 10 to 50 organisms is capable of producing severe human illness, so *F. tularensis* poses an important occupational risk for laboratory workers with inadvertent exposure. The ingestion of poorly cooked contaminated meat or water can result in the development of tularemia, although a significantly larger number of organisms (approximately 10^8) is required for illness to occur (Jacobs et al., 1985; Gill & Cunha, 1997).

BURKE A. CUNHA • State University of New York School of Medicine, Stony Brook, New York 11790. **DIANE H. JOHNSON** • Infectious Disease Division, Winthrop-University Hospital, Mineola, New York 11510.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Microbiology

F. tularensis is a small, nonmotile intracellular coccobacillus. It contains a lipopolysaccharide capsule that contains the organism's virulence. *F. tularensis* grows optimally at 37°C and, since it requires cysteine for growth, grows poorly on routine laboratory media. Glucose cysteine blood agar, thioglycolate broth, modified Thayer-Martin medium, and buffered yeast charcoal agar have all been used successfully to recover the organism. Colonies are smooth, round, and blue-green in color and may have a zone of alpha-hemolysis if the medium contains blood. The bacterium is killed easily by heating but can survive freezing for several weeks.

Two main biovars of *F. tularensis* are recognized that differ in their biochemical and growth characteristics and in their virulence. *F. tularensis* biovar *tularensis,* also known as Jellison type A, is the most virulent human pathogen, and is found mainly in North America. It is generally associated with lagomorphs, sheep, and ticks. *F. tularensis* biovar *paleartica* (or Jellison type B) is found in North America, Europe, and Asia; infection with this strain tends to result in less severe human illness and is most often associated with water sources (Stewart, 1995).

Clinical Manifestations

Six classic forms of tularemia are recognized that depend on the portal of entry of the organism and the predominant manifestations of illness: ulceroglandular, glandular, Oculoglandular, oropharyngeal, pneumonic, and typhoidal. There is often overlap between the clinical syndromes. After an incubation period ranging from several days to 3 weeks, there is an abrupt onset of high fever, shaking chills, headache, arthralgias, and myalgias. In one series of patients, approximately 40% had a temperature pulse deficit. Sore throat, nausea, vomiting, and abdominal pain are commonly seen. In tularemia caused by type A strains, illness may be severe, presenting as fulminant septic shock, whereas illness caused by type B strains is milder. Fever, malaise, and lymphadenopathy can persist for weeks if untreated (Jacobs et al., 1985; Jacobs, 1997; Evans et al., 1985).

Ulceroglandular Tularemia/Glandular Tularemia

Ulceroglandular tularemia is the most common form of tularemia in the United States. It occurs after percutaneous inoculation of *F. tularensis,* often following the bite of a tick, fly, or animal. After penetration of the organism through the skin, a red, papular lesion develops. This papule necroses to form a punched-out ulcer with a black base that can persist for several weeks. Tender regional lymphadenopathy ensues; lymphangitis is not present unless the skin ulcer becomes infected. The lymph nodes occasionally suppurate.

Glandular tularemia is similar to ulceroglandular tularemia with tender lymphadenopathy and systemic symptoms; however, the skin lesion is absent or is often missed by the patient or the clinician (Evans et al., 1985; Cox & Everett, 1981).

The differential diagnosis of ulceroglandular and glandular tularemia includes cat scratch disease, sporotrichosis, toxoplasmosis, atypical mycobacterial infections (e.g., *Mycobacterium marinum),* bacterial skin infection, plague, anthrax, and sexually transmitted disease such as lymphogranuloma venereum, chancroid, and syphilis (Penn, 1995; Gill & Cunha, 1997).

Oculoglandular Tularemia

Oculoglandular illness represents only a small percentage (<5%) of cases of tularemia and it is contracted when the organism is inoculated into the eye, either through direct contact or contact with infected aerosols. Patients present with complaints of ocular pain, photophobia, excessive lacrimation, or mucopurulent discharge. On physical examination, there is conjunctival infection with yellowish scleral nodules. The majority of cases are unilateral. Tender preauricular and submaxillary adenopathy may occur and the presence of tender preauricular lymphadenopathy would distinguish Oculoglandular tularemia from cat scratch disease, adenoviral infection, syphilis, and herpes simplex infection. Complications include corneal ulceration or per-

foration and rarely visual loss (Penn, 1985; Cox & Everett, 1981; Halperin et al., 1985).

Oropharyngeal Tularemia

Oropharyngeal tularemia occurs after the ingestion of contaminated food or water. Patients present with a severe sore throat that is often out of proportion to the physical findings. An exudative pharyngitis or tonsillitis is present and ulcers may be present. Some patients have a pharyngeal membrane that may appear similar to the one found in diphtheria (Dienst, 1963). There is associated cervical, preparotid, and retropharyngeal lymphadenopathy. The clinical picture of oropharyngeal tularemia is similar to group A streptococcal pharyngitis, but there is no response to penicillin. Other differential diagnoses include infectious mononucleosis, diphtheria, and adenoviral infection (Penn, 1995).

Typhoidal Tularemia

Typhoidal tularemia is a systemic febrile illness caused by *F. tularensis.* Skin lesions and lymphadenopathy are absent; however, there is generally a history of animal contact, outdoor activity, or another risk factor for exposure. Patients present with fever, chills, headache, myalgias, sore throat, and often gastrointestinal symptoms such as nausea, vomiting, watery diarrhea, and abdominal pain. Central nervous system symptoms such as delirium and stupor may be observed. On physical examination, the patient appears toxic and may be hypotensive. Minimal pharyngitis and/or cervical adenopathy may be present and there is often mild abdominal tenderness and hepatosplenomegaly. There are often significant laboratory abnormalities associated with typhoidal tularemia such as hyponatremia, elevated creatinine phosphokinase, and myoglobin, elevated liver function and kidney function tests. Blood cultures are usually positive for *F. tularensis.* Typhoidal tularemia has a high mortality rate of 30% to 60%, especially in persons with serious underlying medical problems (Cox & Everett, 1981; Ohara et al., 1991; Penn & Kinasewitz, 1987).

Pneumonic Tularemia

Pleuropulmonary involvement in tularemia was first described by Verbryke in 1924. The lungs may be involved in up to one half of cases of typhoidal tularemia and in about 15% of cases of ulceroglandular tularemia (Jacobs, 1997). Pneumonic tularemia occurs as a result of the bacteremic spread of organisms to the lungs or following the inhalation of infectious aerosols. Pneumonic tularemia is seen most commonly in persons with high-risk occupations such as laboratory workers or sheep shearers (Gill & Cunha, 1997). The clinical presentation of pneumonic tularemia is similar to other atypical zoonotic pneumonias with the abrupt onset of high fevers, chills, nonproductive cough, pleuritic chest pain, atthralgias, and myalgias. Sore throat is reported in approximately one fourth of patients, particularly with the pneumonia associated with the Oropharyngeal form. Profuse diaphoresis, anorexia, and fatigue are also common. Physical examination findings are nonspecific and may consist of a relative bradycardia (in approximately 30% of patients), pulmonary rales or dry crackles in varying lung locations, or a pleural rub. Secondary skin rashes may be seen generally with in the first 2 weeks of illness (Avery & Barnett, 1969; Evans et al., 1985; Morgan, 1947; Penn, 1995). Maculopapular vesicular and urticarial lesions have been described, as well as erythema multiforme and erythema nodosum. Radiographic findings vary widely in pneumonic tularemia and may include apical or miliary infiltrates that resemble tuberculosis, single or multiple lobar infiltrates, hilar or mediastinal adenopathy with or without infiltrates, or abscesses with cavitation (Figs. 1, 2). Ovoid densities that were described in the past are rare (Rubin, 1978). Pleural effusions are common, occurring in up to three fourths of patients infected with tularemia. They are generally bilateral and if thoracentesis is performed they are exudative in nature. Lymphocytic, polymorphonuclear, and monocytic cellular predominance have all been reported. The differential diagnosis of pneumonic tularemia includes other atypical pneumonias such as *Legionella, Mycoplasma,* and *Chlamydia pneumoniae,* and other zoonotic illnesses such as psittacosis or Q fever (Table 1). Tularemic pneumonia

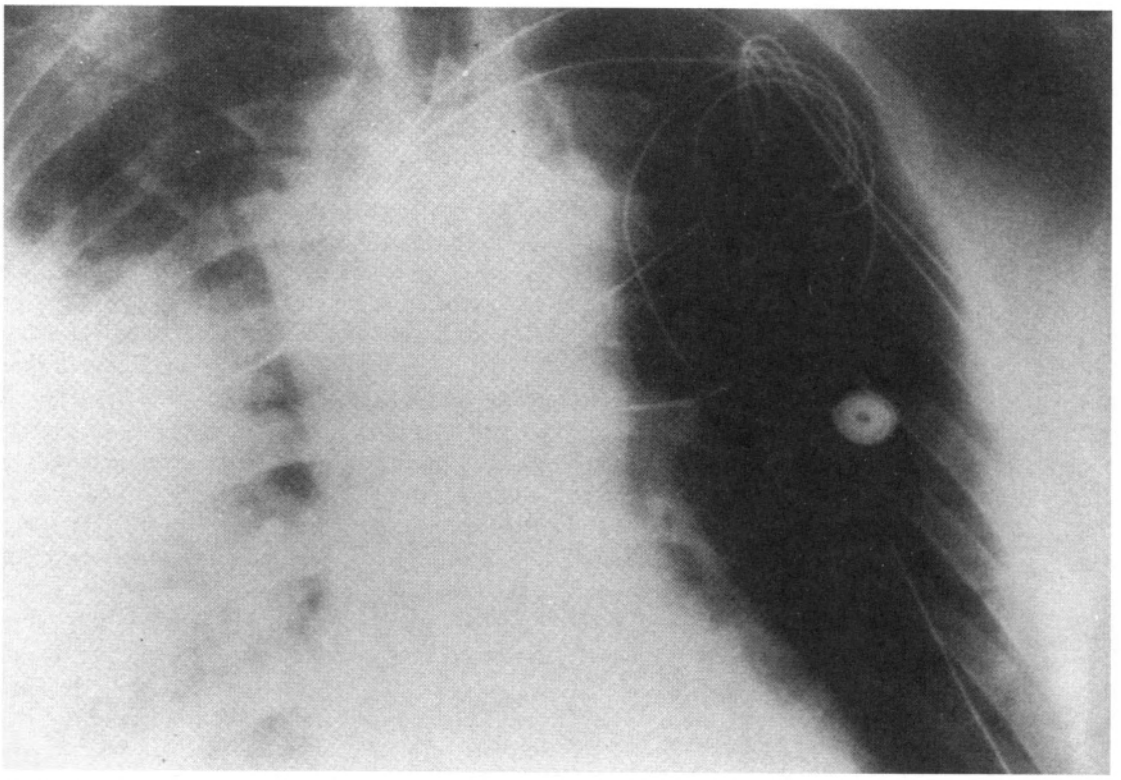

FIGURE 1. Tularemic pneumonia of the RLL and RML (courtesy of Dr. Barney S. Graham, Vanderbilt University School of Medicine, Nashville, Tennessee).

should be suspected when there is an appropriate history of occupational animal or insect exposure, or in cases of community-acquired pneumonias thai do not respond to conventional therapy (Fredricks & Remington, 1996; Roy et al., 1989; Teutsch et al., 1979).

Diagnosis

A high index of clinical suspicion is needed to make a diagnosis of tularemia. Gram-stained specimens of body fluids are nondiagnostic, but the organism can be cultured from blood, sputum, pleural fluid, lymph node, or ulcer tissue when enhanced media is used. Serologic testing demonstrating a 4-fold rise in liters between acute and convalescent sera, or a single acute tiler of 1:160 or greater, is presumplive of tularemia (Stewart, 1995). Antibodies to tularemia may persist for many years, so a single value is of limited use. When agglutination techniques are used, *F. tularensis* displays cross-reaclivily with *Proteus* OX-19 antibodies and *Brucella* and *Yersinia* species; however, in tularemia, titers to *F. tularensis* should be the highest. Enzyme-linked immunosolvent assay is now the preferred serologic method, since it is highly sensitive and specific and there is no cross-reactivity (Gill & Cunha, 1997).

Treatment

Streptomycin (7.5-10 mg/kg/day) for 10 to 14 days remains the drug of choice for the treatment of tularemia in adults. Other aminoglycosides such as genlamicin (3–5 mg/kg/day) and amikacin appear to have comparable efficacy (Enderlin el al., 1994; Stewart, 1995). Doxycycline has been used effec-lively as well. Chloramphenicol therapy has a high

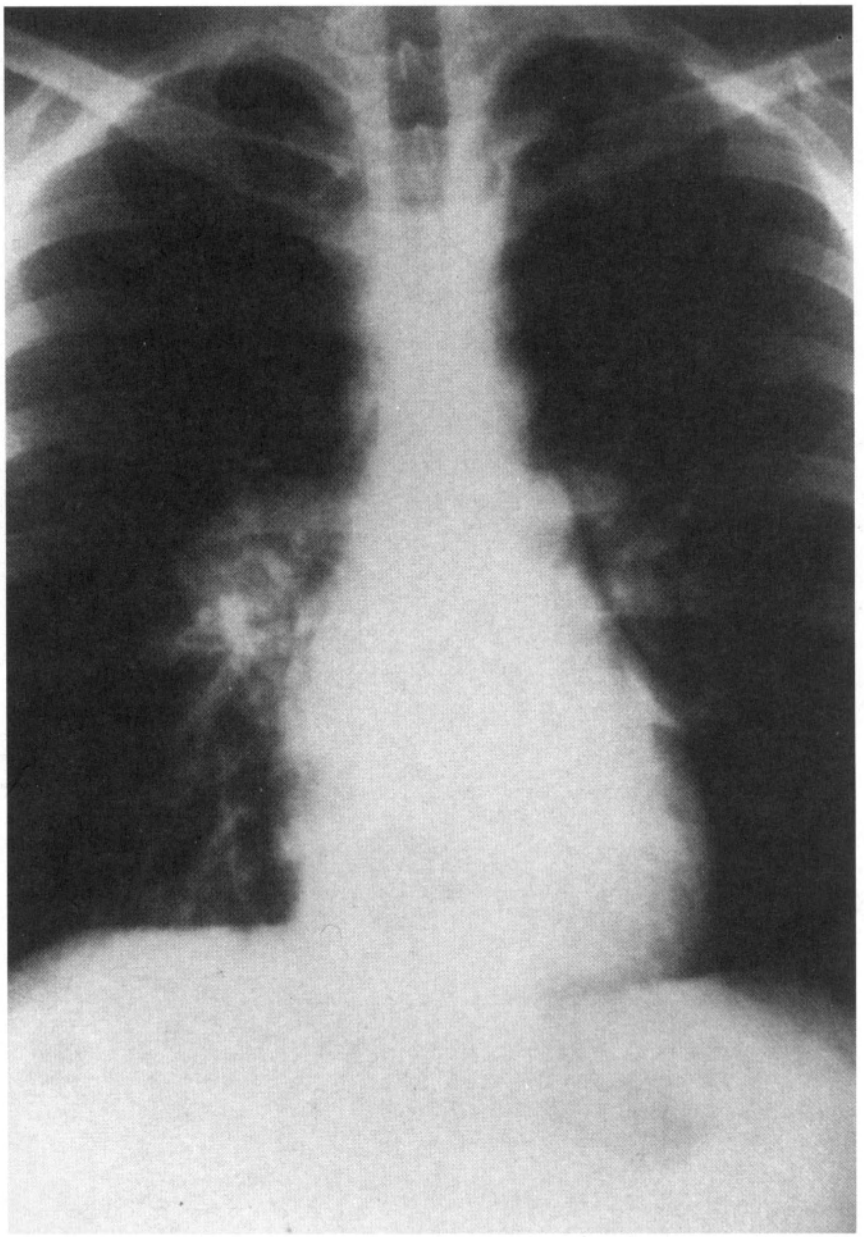

FIGURE 2. Tularemic pneumonia with hilar adenopathy (courtesy of Dr. Barney S. Graham, Vanderbilt University School of Medicine, Nashville, Tennessee).

TABLE 1. Differential Diagnostic Features of the Zoonotic Atypical Pneumonias

Key characteristics	Zoonotic atypical pneumonias		
	Psittacosis	Q fever	Tularemia
Symptoms			
Mental confusion	−	−	−
Prominent headache	+	+	−
Myalgias	+	+	−
Ear pain	−	−	−
Pleuritic pain	−	−	−
Abdominal pain	−	−	−
Loose stools/diarrhea	−	−	−
Signs			
Rash	± (Horder's spots)	−	−
Raynaud's phenomenon	−	−	−
Nonexudative pharyngitis	+	−	±
Hemoptysis	+	−	−
Lobar consolidation	±	±	±
Cardiac involvement	± (Endocarditis)	± (Myocarditis)	−
Splenomegaly	±	+	−
Relative bradycardia	+	+	−
Chest film			
Infiltrate	(Patchy/consolidation)	(Patchy/consolidation)	"Ovoid bodies"
Bilateral hilar adenopathy	−	−	+
Pleural effusion	−	−	+ (Bloody)
Laboratory abnormalities			
White blood cell count	↓	↑/N	↑/N
Hypophosphatemia	−	−	−
Increase in SGOT (AST)/SGPT (ALT)	+	+	−
Cold agglutinin titer (≥1:64)	−	−	−
Microscopic hematuria	−	−	−
Diagnostic tests			
Direct isolation (culture)	±	−	−
Serology (specific)	CF	CF	TA
Psittacosis CF titers	↑	−	−
Legionella IFA titers	−	−	↑

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CF, complement fixation; IFA, immunofluorescence antibodies; TA, tube agglutination.
Adapted, with permission, from Gill & Cunha, 1997.

rate of relapse. Third-generation cephalosporins appear to be effective in vitro, but there have been numerous treatment failures reported with their use (Cross & Jacobs, 1993). The quinolones have good bactericidal activity against *F. tularensis,* but clinical experience is limited (Jacobs, 1997).

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Psittacosis

BURKE A. CUNHA AND NATALIE C. KLEIN

Introduction

Psittacosis is an infection caused by *Chlamydia psittaci,* which is transmitted most often from pet birds to humans. Patients with psittacosis usually develop flu-like illness and/or an atypical pneumonia. The first outbreak of human psittacosis was described in 1879 by A. Ritter, a Swiss physician, among seven patients exposed to sick parrots. Ritter called this disease "pneumotyphus" (Harris & Williams, 1985). In 1895, the term psittacosis was coined from the Greek word for parrots "psittakos." Since then, many outbreaks of psittacosis have occurred, the largest involving 700 to 800 persons from 1929 to 1930 who contracted the illness from infected birds exported from Argentina to the United States and Europe. *C. psittaci* was identified as the causative agent of psittacosis or "parrot fever" in 1930 (Macfarlane & Macrae, 1983). Although primarily associated with parrots and other psittacine birds such as macaws, cockatoos, and parakeets, C. *psittaci* infects other avian species such as turkeys, pigeons, ducks, doves, and mynah birds. Human disease is also referred to as ornithosis, while C. *psittaci* infection in birds is called avian chlamydiosis (AC).

BURKE A. CUNHA • State University of New York School of Medicine, Stony Brook, New York 11790. **NATALIE C. KLEIN** • Infectious Disease Division, Winthrop-University Hospital, Mineola, New York 11510.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Epidemiology

More than 800 cases of psittacosis were reported to the Centers for Disease Control and Prevention (CDC) from 1987 through 1996 (CDC, 1996). In the 1980s, 43% of the cases occurred among bird fanciers and owners of pet birds, while pet shop employees accounted for 10% of cases (CDC, 1998). Other individuals who are at risk of acquiring psittacosis include pigeon fanciers, workers in poultry slaughtering and processing plants, farmers, zoo workers, veterinarians, and laboratory workers (CDC, 1998).

Human cases of psittacosis can occur sporadically as well as in outbreaks. Most patients have had contact with pet birds. Often there is a history of intimate exposure to a sick or dying bird, but some patients have had only transient contact with birds such as visiting a zoo or passing through a room in which a bird was present. Although most birds with avian chlamydiosis appear ill with diarrhea, conjunctivitis, or wasting, birds that look healthy may also transmit infection. In approximately 25% of cases, there is no report of avian exposure (CDC, 1998).

Humans become infected from inhaling *C. psittaci,* which can be found in respiratory secretions or dried feces of the infected birds. Aerosolization of infective discharges from beaks, eyes, feces, urine, contaminated feathers, and cage dust is the usual route of infection (CDC, 1998; Grimes, 1987). Psittacosis can also be spread directly from bird bites, mouth-to-beak contact, and handling of plumage with bird tissues (CDC, 1998). *C. psittaci* transmission to humans from infected sheep, cows, and goats has been reported in ranchers exposed to infected placentas (John et al., 1985; Barnes &

Brainerd, 1964). Transmission of feline strain of *C. psittaci* has occasionally caused human disease (CDC, 1998). Person-to-person transmission is extremely unusual, but there is at least one report of possible nosocomial transmission of psittacosis in a community hospital among seven employees exposed to the index case (Hughes et al., 1997).

Microbiology

C. psittaci is one of three pathogenic *Chlamydia* species. *Chlamydia pneumoniae* causes upper respiratory tract disease and pneumonia, while *Chlamydia trachomatis* causes infant pneumonia, conjunctivitis, urethritis, lymphogranuloma venereum, and trachoma. *C. psittaci* is an obligate intracellular microorganism containing both DNA and RNA but unable to synthesize its own adenosine triphosphate. *Chlamydia* exists intracellularly in two unique forms. The infectious particle called the elementary body is approximately 300 nm in diameter; it attaches to the host respiratory epithelial cell, induces phagocytosis by the host cell, and is transformed into the 800-nm reticulate body, which is responsible for chlamydial replication by binary fission within the cell (Fraiz & Jones, 1998; Cunha, 1994). The reticulate body condenses to form another elementary body in the inclusion body of the host cell cytoplasm (Fraiz & Jones, 1998; Cunha, 1994).

Clinical Manifestations

The incubation period for psittacosis is usually 5 to 14 days but may be as long as 21 days. There are two routes of pathogenesis (Gregory & Schaffner, 1997). Humans inhale *C. psittaci* from infectious aerosols from bird feces or dust, which establishes infection in the lower respiratory tract epithelial cells. In most patients, there is a primary hematogenous dissemination to regional lymph nodes and the reticuloendothelial system followed by a secondary bacteremia that infects the lungs (Gregory & Schaffner, 1997). Occasionally, patients develop invasive lung disease directly after infection of the lower respiratory epithelium. In these patients, pneumonia develops after a shorter incubation period of 1 to 3 days.

Onset of disease may be insidious or abrupt, symptoms are nonspecific, and the severity of disease ranges from mild or inapparent illness to severe, life-threatening pneumonia. Most often, illness begins with abrupt onset of fever, headache, chills, sweats, malaise, and myalgia followed by the development of a nonproductive cough (Crosse, 1990; Yung & Grayson, 1988). Headache is a particularly prominent complaint and may help distinguish psittacosis from other causes of pneumonia. Gastrointestinal complaints, especially diarrhea and vomiting, may occur, but pharyngitis and cervical adenopathy are uncommon (Table 1). Because of the nonspecific presentation, the diagnosis of psittacosis may be initially missed. The initial differential diagnosis is extensive and may include viral syndrome, pneumonia, meningitis, fever of unknown origin, brucellosis, malaria, sepsis, vasculitis, and hepatitis (Crosse, 1990; Yung & Grayson, 1988).

The most common signs are fever and abnormalities on chest exam. The presence of hepatomegaly, splenomegaly, a pulse–temperature disassociation, and an erymematous blanching maculopapular rash are all helpful clues to the diagnosis of psittacosis,

TABLE 1. Clinical Features of Psittacosis

Signs and symptoms	Percentage
Symptoms	
Chills	30–50
Fever	50–100
Cough	50–100
Headache	30–50
Myalgia	30–50
Arthralgia	<10
Diarrhea	~25
Constipation	~25
Sweats	~10
Photophobia	<10
Abdominal pain	<10
Pharyngitis	<10
Hemoptysis	<10
Maculopapular rash	<10
Signs	
Fever >102°F	>90
Relative bradycardia	≥75
Epistaxis	<10
Horder's spots	<10
Hepatomegaly	<10
Splenomegaly	<10

but they are seen in less than 25% of cases. A particular rash called Horder's spots mimics the rose spots of typhoid fever but is seen in less than 10% of patients (Crosse, 1990; Yung & Grayson, 1988). A number of other dermatologic manifestations have also been described in psittacosis including erythema multiforme, erythema nodosum, urticaria, splinter hemorrhages, and acrocyanosis (Green et al., 1990; Semel, 1984). Since psittacosis is a systemic disease, a number of extrapulmonary complications have been described, including hepatitis, hemolytic anemia, disseminated intravascular coagulation, pericarditis, myocarditis, endocarditis, transverse myelitis, cranial nerve palsy, cerebellar involvement, meningitis, glomerulonephritis, interstitial nephritis, and reactive arthritis (Coll & Horner, 1967; Cooper & Ferriss, 1986; Geddes & Skeates, 1997; Hamilton, 1975; Jeffrey et al., 1992; Page et al., 1988; Samra et al., 1991; Shapiro et al., 1992; Shee, 1988; Timmerman & Bieger, 1989; Tsapas et al., 1991; Williams & Sunderland, 1989; Wong et al., 1991; Zumla et al., 1988).

The lung is the organ most commonly involved in psittacosis and abnormal chest films are seen in approximately 75%. Patients typically develop a nonproductive cough accompanied by chest pain and less often shortness of breath. Hemoptysis occurs in less than 10% of patients. A chest radiograph often shows more extensive disease than anticipated from physical exam. There is no characteristic chest film finding in psittacosis. Lobar consolidation or interstitial infiltrates may be seen on radiograph and small pleural effusions may occur in up to 50% (Sahn, 1988).

Laboratory findings are usually nonspecific and not helpful in diagnosis. The white blood cell count is normal or mildly elevated often with a left shift. Hepatic function test abnormalities include a mildly elevated bilirubin in 50% of patients. Renal function is usually normal.

Diagnosis

Since the clinical manifestations, chest radiograph findings, and laboratory data are all nonspecific, the diagnosis of psittacosis has traditionally been made by serologic testing. The CDC defines a confirmed case of psittacosis for surveillance purposes as one in which *C. psittaci* is cultured from respiratory secretions or there is a 4-fold or greater (to a titer $\geq$1:32) increase in antibody against *C. psittaci* between paired acute and convalescent serum samples by complement fixation (CF) or microimmunofluorescence (MIF) or immunoglobulin M antibody (to a titer $\geq$1:16) against *C. psittaci* is detected by MIF (CDC, 1998). A probable case of psittacosis is defined as a case with compatible clinical illness that is linked to an epidemiologically confirmed case of psittacosis or has a single antibody titer 1:$\geq$32 by CF or MIF (CDC, 1998). The CF test has a number of problems asso-

TABLE 2. Diagnostic Approach to Psittacosis

Community-Acquired Pneumonia
↓
No extrapulmoanry features
(typical pulmonary pathogens)
or
Extrapulmonary features
(atypical pulmonary pathogens)

History of bird/animal contact	Zoonotic			Non-zoonotic		
	Birds	Sheep, cats	Insect bites, deer/rabbits			
	Psittacosis	Q fever	Tularemia	*Legionella*	*Chlamydia pneumoniae*	*Mycoplasma pneumoniae*
Relative bradycardia	+	+	−	+	−	−
Epistaxis/Horder's spots	+	−	−	−	−	−
↑ Liver function tests	+	+	−	+	−	−

ciated with it. The CF test for *Chlamydia* is not species-specific and may be positive in cases of infection from *C. pneumoniae* or *C. trachomatis* as well as *C. psittaci* (CDC, 1998). Treatment with tetracycline can delay or decrease antibody response. Some newer techniques for diagnosis such as *Chlamydia*-specific direct immunofluorescence assay staining of sputum and the use of polymerase chain reaction to detect *C. psittaci* in sputum or blood may become the preferred means of diagnosis in the future (Oldach et al., 1993; Tony & Sillis, 1993).

Treatment

The treatment of choice is tetracycline drug (Table 2). Doxycycline 100 mg twice daily is the preferred agent and usually results in resolution of symptoms by 48 to 72 hours. For severely ill patients, intravenous doxycycline is preferred. Therapy should continue for 14 to 21 days or a minimum of 10 to 14 days after fever resolves to prevent relapses (CDC, 1998). In patients with endocarditis, therapy should be prolonged and valve replacement is usually required. Alternate therapy includes erythromycin, azithromycin, and chloramphenicol. Although there is little data on the use of quinolones in the treatment of psittacosis, these agents have excellent activity against other *Chlamydia* spp. and may be a useful alternative in patients unable to tolerate traditional therapy (Bacon et al., 1996).

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Moraxella (Branhamella) catarrhalis

DICK ZOUTMAN

Introduction and Taxonomy

Moraxella (Branhamella) catarrhalis is an aerobic, oxidase-positive, nonmotile gram-negative diplococcus. It was initially named *Neisseria catarrhalis* until Catlin (1970) demonstrated that this organism was distinct from the Neisseriaceae on the basis of DNA hybridization assays and its guanine/cytosine content and suggested its reclassification into the genus *Branhamella.* However, Bøvre (1979) demonstrated *B. catarrhalis* displays significant genetic and physiological similarities to organisms in the genus *Moraxellae* and as a result *B. catarrhalis* was reclassified as a member of the genus *Moraxellae* with the subgenus designation *Branhamella.* In its most proper form the organism is referred to as *Moraxella (Branhamella) catarrhalis. Moraxella catarrhalis*, *M. ovis*, *M. cuniculi*, and *M. caviae* are coccal forms comprising the group 1 subgenus of *Moraxella (Branhamella),* all with ≥95% 16S rRNA similarity, and *M. lacunata, M. nonliquifaciens*, *M. bovis*, *M. osloensis*, *M. phenylpyruvica,* and *M. atlantae* are rod-shaped organisms of the subgenus *Moraxella (Moraxella)* (Bøvre, 1984; Pettersson et al., 1998).

DICK ZOUTMAN • Infection Control Service, Kingston General Hospital, and School of Medicine, Faculty of Health Services, Queen's University, Kingston, Ontario K7L 2V7, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Moraxella catarrhalis Colonization of the Respiratory Tract in Health and Disease

M. catarrhalis, when isolated from saliva, throat swabs, or sputum, has in the past been considered to represent simple colonization of the upper airway with a harmless commensal. Additionally, it is very difficult on the basis of colonial morphology to visually detect *M. catarrhalis* on the inspection of a primary isolation plate of a respiratory sample where other oral flora or pathogens are also present (Hager et al., 1987; Van Hare et al., 1987; Soto-Hernandez et al., 1988). Furthermore it has been shown that the nonpathogenic Neisseriaceae in respiratory samples will inhibit the growth of *M. catarrhalis* on nonselective and semiselective solid media (Vaneechoutte et al., 1988). The current literature suggests that in healthy adults the colonization rate for *M. catarrhalis* is low and ranges from 0.6% to 8.0% (DiGiovanni et al., 1987; Knapp & Hook, 1988; Calder et al., 1986). Ejlertsen et al. (1994a) examined the colonization rate in the throats of 561 women in labor; only 1% were found to carry *M. catarrhalis* in the pharynx and none of the newborns were colonized. Peak colonization rates were found in the children at 1 to 48 months of age, with 54% carrying *M. catarrhalis* in their throats. Older children from 4 to 15 years were colonized 7% of the time. They noted that during episodes of presumed viral respiratory tract infections the colonization rate with *M. catarrhalis* increased and then fell when the respiratory infection abated without antibiotic intervention. In the face of chronic lung disease in adults the colonization rate with *M. catarrhalis* is much higher than in healthy persons. Klingman et al. (1995) found that 24% of

patients with bronchiectasis were chronically colonized with *M. catarrhalis.* They used pulsed field gel electrophoresis to study the dynamics of this colonization and showed that each patient was colonized with up to four different strains, with a mean period of colonization with any given strain of 2.3 months. There was no relationship found between acute exacerbations of the bronchiectasis and the shift to a new strain of *M. catarrhalis.*

In children several systematic studies of the asymptomatic carriage rate of *M. catarrhalis* have been conducted and reveal that the accurate detection of *M. catarrhalis* colonization depends on the use of selective media that suppress the other microorganisms of the respiratory tract and selectively permit the growth and detection of *M. catarrhalis* (Vaneechoutte et al., 1988). A comparative study has shown that the frequency of isolation of *M. catarrhalis* from the respiratory tracts of healthy schoolchildren increases 8-fold when selective agar is used instead of nonselective agar or broth. The carriage rate of *M. catarrhalis* was 56%, which is much higher than recorded rates in adults and children where nonselective methods have been used (Vaneechoutte et al., 1988; Eliasson et al., 1990). Thus *M. catarrhalis* does colonize the respiratory tracts of young children and of older adults with underlying chronic pulmonary disease but is uncommon as a commensal in the respiratory tracts of healthy older children or healthy adults.

The Outer Membrane Proteins and Pili of *Moraxella catarrhalis*

Outer Membrane Proteins

The outer membrane protein (OMP) profile of *M. catarrhalis* has been shown by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) to be very homogenous from strain to strain (Murphy & Bartos, 1989; Murphy, 1989, 1990; Bartos & Murphy, 1988). This is in contrast to the variable OMPs of other pathogenic Neisseriaceae and nontypable *Haemophilus influenzae,* which occupy a similar ecological niche and are associated with a similar spectrum of disease in humans (Murphy & Apicella, 1987). To date nine OMPs have been identified. The OMP of highest molecular weight, known as UspA (for ubiquitous surface protein) comprises two different proteins, UspAl and UspA2, with molecular weights of 88,271 and 62,483 respectively (Aebi et al., 1997). The UspA proteins with their respective genes are found on all clinical isolates of *M. catarrhalis* by western and southern blots. Surface mapping of the UspA protein from *M. catarrhalis* strain 035E with monoclonal antibodies reveals that UspA has highly conserved as well as variable regions. Purified UspA injected into mice or guinea pigs engenders UspA antibodies that demonstrate complement-dependent bactericidal activity against homologous and heterologous strains of *M. catarrhalis.* BALB/c mice immunized with purified UspA that are then subjected to a pulmonary challenge with homologous or heterologous strains of M. *catarrhalis* have much lower numbers of *M. catarrhalis* bacteria isolated from their lungs than nonimmunized control mice (Chen et al., 1996). Patients who have had pneumonia with *M. catarrhalis* develop antibodies to UspA in convalescent serum (Helminen et al., 1994). Thus the UspA surface protein may be a useful vaccine candidate antigen since it is highly conserved, is found on all clinical strains of *M. catarrhalis,* and engenders protective bactericidal antibodies. Isogenic UspA1 minus and UspAl/UspA2 double-minus mutants of M. *catarrhalis* exhibit several times less adherence to Chang conjunctival cells than the UspA wild-type and UspA2 minus mutant. Wild-type and UspAl minus mutants are resistant to the bactericidal effects of serums, while UspA2 and UspAl/UspA2 double-minus mutants are susceptible to serum. These results indicate that UspAl is important for bacterial adherence and UspA2 is important for serum resistance of *M. catarrhalis* (Aebi et al., 1998b).

In a fashion similar to *Neisseria* species, *M. catarrhalis* is able to compete for iron that is bound to transferrin in blood and lactoferrin in secretions. *M. catarrhalis* has transferrin and lactoferrin binding proteins on its cell surface (Schryvers & Lee, 1989). When exposed to conditions of iron deprivation in vitro, *M. catarrhalis* cells express a new set of surface proteins that are likely important for the bacteria to acquire the essential iron it requires for growth (Campagnari et al., 1994). The transferrin-binding proteins of *M. catarrhalis* have been characterized and are designated Tbpl and 2 (Yu &

Schryvers, 1993). Iron-saturated transferrin binds preferentially to Tbp2. Lactoferrin-binding proteins (LbpA and LbpB) have also been purified and their genes have been cloned and sequenced, revealing that the lactoferrin-binding proteins of *M. catarrhalis* are quite conserved (Du et al., 1998; Bonnah et al., 1998). Another transferrin-binding protein called OMP B1 is also expressed under iron-limiting conditions on the surface of M. *catarrhalis* cells and is very homologous to Tbp2 (Campagnari et al., 1996; Mathers et al., 1997). OMP B1 is known to be a target for IgG in human infection with *M. catarrhalis* and possesses heterogeneity across *M. catarrhalis* strains (Sethi et al., 1995).

CopB is an 80-kDa OMP also known as OMP B2. CopB interacts with the immune defenses, as isogenic CopB minus mutants are more sensitive to serum and have poorer survival in lung tissue of mice (Helminen et al., 1993). The gene coding for CopB has been cloned and sequenced, demonstrating that it is a highly conserved protein with discrete regions of heterogeneity (Sethi et al., 1997). Monoclonal antibodies directed against CopB enhance pulmonary clearance of *M. catarrhalis* in mice. Six elderly patients with *M. catarrhalis* pneumonia in Finland demonstrated convalescent antibodies against CopB revealing that this outer membrane protein is immunogenic in vivo (Helminen et al., 1995). The immunogenic epitope of CopB has been mapped with monoclonal antibodies and synthetic peptides of the 26-amino acid epitope have been used to immunize mice (Aebi et al., 1998a). CopB is an iron-repressible surface protein that may also play an important role in iron acquisition in human tissues. CopB minus mutants are still able to bind transferrin and lactoferrin but cannot use the transferrin- or lactoferrin-bound iron (Aebi et al., 1996).

OMP E is a 50 kDa surface protein of *M. catarrhalis* composed of 436 amino acids. The OMP E gene has been cloned and sequenced and OMP E is known to be antigenically as well as structurally conserved. It is postulated that OMP E may be involved in binding and transporting fatty acids (Bhushan et al., 1994). Patients with chronic bronchitis and *M. catarrhalis* infection of their airways demonstrate IgA directed against OMP E in their sputum (Bhushan et al., 1997).

OMP C/D is a 55-kDa heat-sensitive surface protein of *M. catarrhalis* whose structure is very conserved across strains, as is the case for many *M. catarrhalis* surface proteins (Murphy et al., 1993; Yang et al., 1997). Murine antibodies to OMP C/D are bactericidal and bind to the surface of M. *catarrhalis* cells (Yang et al., 1997).

Lipooligosaccharide

Like all gram-negative bacteria, *M. catarrhalis* possesses the lipid A molecule to which are attached a number of carbohydrate molecules. Similarly to many non-Enterobacteriaceae the lipooligosaccharide (LOS) complex of *M. catarrhalis* lacks a long polysaccharide side chain (Johnson et al., 1976; Johnson & Perry, 1976). There are three immunologically distinct LOS types among *M. catarrhalis* strains designated A, B, and C (Rahman et al., 1995). The carbohydrate structure of M. *catarrhalis* LOS has been elucidated in detail (Edebrink et al., 1994, 1995). Chemically detoxified *M. catarrhalis* LOS that has been conjugated to tetanus toxoid or other high-molecular-weight proteins is very immunogenic in mice and rabbits. The resulting antisera have complement-mediated bactericidal activity against *M. catarrhalis* (Gu et al., 1998). Thus it appears that LOS of *M. catarrhalis* is a potentially useful candidate vaccine molecule.

The Pili (Fimbriae) and Other Adhesins of M. *catarrhalis*

The mechanisms by which *M. catarrhalis* adheres to mucosal surfaces has been examined. Rikitomi et al. (1991) described the presence of pili on the surface of *M. catarrhalis* bacteria and showed that there is no correlation between the presence of the pili and hemagglutination. However, others have shown that there is a correlation between bacterial adherence to tracheal epithelial cells and hemagglutination (Kellens et al., 1995). Destruction of the pili by denaturation or with trypsin reduces adherence to epithelial cells as well as hemagglutination (Ahmed, 1992). Treating piliated *M. catarrhalis* cells with anti-pili antibodies likewise interferes with bacterial adherence. Examination of 24 clinical isolates of *M. catarrhalis* revealed that all isolates possessed pili on their surface but that some variability exists in the extent of the piliation

of the bacteria from different patients (Ahmed et al., 1992). On subculturing, the bacteria produce fewer pili. The average length of the pili is 50 to 76 nm (Ahmed et al., 1994). Zoutman et. al. (1991) have demonstrated by transmission electron microscopy two morphologically distinct types of pili. One of the *M. catarrhalis* pili is 4 to 5 nm in diameter and >2 μm in length and tends to be polar in distribution. The other pili are much smaller with a diameter of approximately 1 nm and a length of 10 to 50 nm. The smaller pili are distributed evenly over the entire bacterial cell surface (see Fig. 1). Electron microscopy of a single ATCC strain of *M. catarrhalis* has also revealed the presence of two morphological types of pili (Marrs & Weir, 1990). Within the genus *Moraxellae* the two species *M. bovis* and *M. nonliquifaciens* have been previously shown to produce pili and have had their structure and genetics well characterized (Fulks et al., 1990; Marrs et al., 1985; Beard et al., 1990; Ruehl et al., 1988). The pili of these organisms are of the N-methylphenylalanine (type 4) class of pili, which have also been well described for *Neisseria gonorrhea, Neisseria meningitidis, Bacteroides nodosus,* and *Pseudomonas aeruginosa* (Frost et al., 1978; Paranchych et al., 1990; Paranchych & Frost, 1988; McKern et

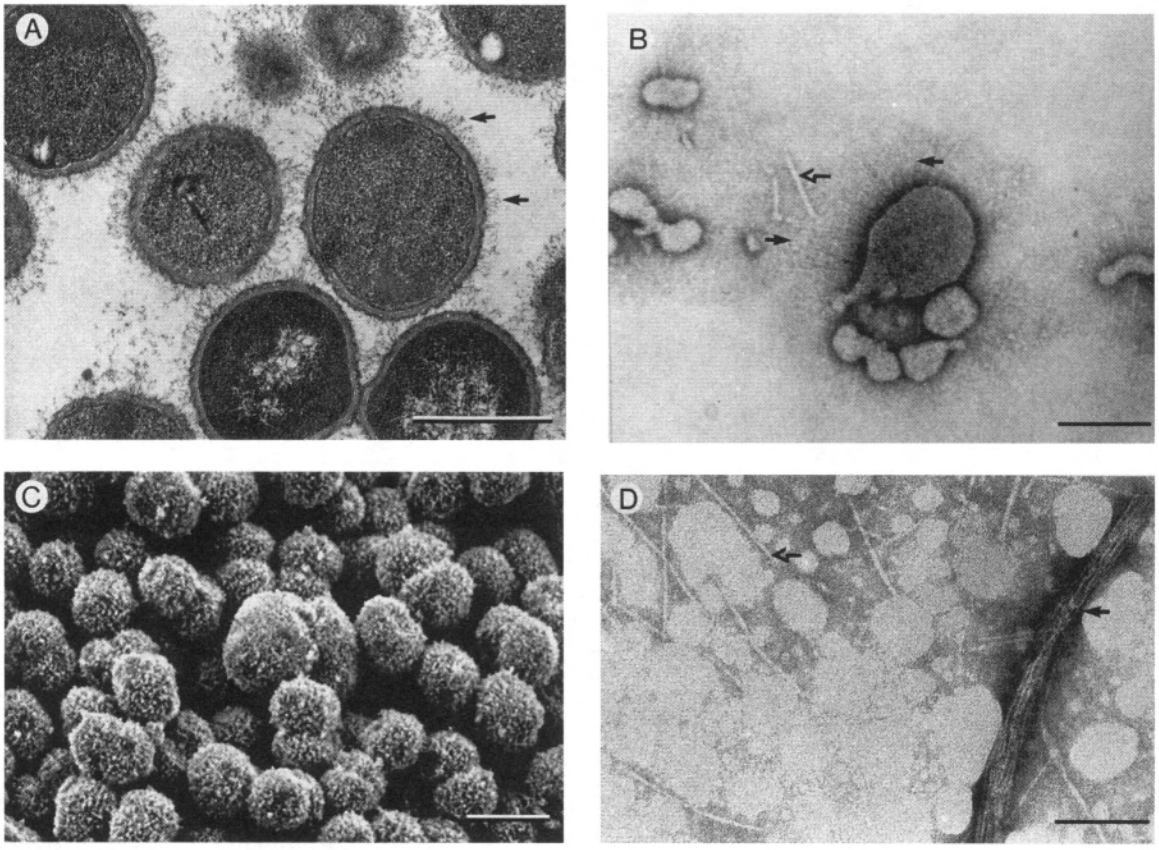

FIGURE 1. (A) Transmission electron micrograph showing a thin section of *Moraxella catarrhalis* cells. Bar = 0.5 μm. Note the peritrichous arrangement of fine pili on the cell surface (arrows). (B) Negatively stained preparation demonstrating an outer membrane bleb of *M. catarrhalis* with pili on their surface (solid arrow). As a size comparison purified pili of *P. aeruginosa* (open arrow) have been added that have an external diameter of 5.2 nm. Bar = 0.1 μm. (C) High resolution scanning electron micrograph demonstrating the irregular surface of a pili-bearing strain of *M. catarrhalis*. Bar = 1.0 μm. (D) Negatively stained preparation of pili of *M. catarrhalis* that have associated into a bundle of parallel fibers (solid arrow). *P. aeruginosa* pili indicated by open arrow. Bar = 0.1 μm.

al., 1988; Froholm & Sletlen, 1977). Allhough not yet proven with certainly, it is likely that the pili of *M. catarrhalis* are homologous to the N-methyl-phenyalanine (type 4) class of pili. Neuraminidase treatment of pharyngeal epithelial cells to remove sialic acid from the cell surface reduces the adherence *of M. catarrhalis* to the pharyngeal cells. This implies that *M. catarrhalis* may use sialic acid as a receptor to mediate adherence. This is further supported by the observation that ganglioside M2 but not asialo-ganglioside Ml inhibits adherence of *M. catarrhalis* in a concentration-dependenl fashion (Ahmed et al., 1996). Adherence *of M. catarrhalis* to bronchial epilhelial cells from persons with chronic obstructive lung disease is increased compared to bronchial cells derived from healthy persons. Piliated strains of *M. catarrhalis* adhere in greater numbers per bronchial cell than do strains that do not express pili (Rikitomi et al., 1997). The N-Me-Phe class of pili are potent immunogens and antibodies raised against them have been demonstrated in vitro and in vivo to prevent bacterial adhesion and clinical disease. The protective effect of pili used as a vaccine has been well documented in the case *of Moraxella bovis* keratitis (Lehr et al., 1985; Ruehl et al., 1988).

Immune Response to Surface Antigens of *Moraxella catarrhalis*

The immunological response to invasive *M. catarrhalis* infections has not yet been extensively evaluated. Brorson et al. (1976) demonstrated complement-fixing antibodies to *M. catarrhalis* in 5% of healthy controls and in 25.7 % of patients with maxillary sinusitis; however, the microbiologic etiology of the sinusitis was not determined, making the significance of these observations unclear. Using an immunofluorescence antibody test directed against whole *M. catarrhalis* cells, Black & Wilson (1988) were able to show at least a 2-fold antibody titer increase in only 20% of patients with respiratory *M. catarrhalis* infections. However, the convalescent sera taken at 14 days may have been drawn too soon to reveal a seroconversion. Eliasson and Chi have reported the immune response to a crude acid extract ("P-protein") of *M. catarrhalis* is an enzyme immunoassay (EIA) format (Chi et al., 1990; Eliasson, 1980). In a small clinical study there appeared to be a low-level immune response in half of the patients to P-protein following lower respiratory infections with *M. catarrhalis.* However, baseline antibody levels to this test antigen occurred in healthy controls and differences in acute and convalescent titers of infected persons were not well predicted. A careful study of the level of IgG and its subclasses of *M. catarrhalis* in 40 healthy uninfected subjects has been conducted (Goldblatt et al., 1990). Using pooled normal human serum as a control and *M. catarrhalis* bacterial cells as the coating antigen a simple E1A was shown to be a sensitive and immunologically specific way to measure IgG and IgG subclass antibodies to *M. catarrhalis* in healthy persons. Intra-test and inter-test variability was low, confirming the validity and accuracy of the assay. Rahman et al. (1997) studied the immune response to *M. catarrhalis* infection and compared the sensitivity of using whole bacterial cells, lipopolysaccharide, or purified OMPs as the coating antigen in the EIA system. The purified OMP gave the best sensitivity especially when examining for increases in IgG3 antibodies. They noted, however, that persons with high antibody levels to *M. catarrhalis* in the acute-phase serum, presumably from prior *M. catarrhalis* infections, tended not to show further increases in their antibody levels. It may be that persons who are chronically colonized with *M. catarrhalis* may not show seroconversion when they suffer an acute invasive infection with *M. catarrhalis.* As many as 16% to 32% of adults without *M. catarrhalis* infection can be found to have elevated titers of IgG or IgM to its OMPs, which limits the diagnostic specificity of serology for *M. catarrhalis* infections (Christensen el al., 1995, 1996). Indeed, Ejlersen et al. (1994b) showed that 100% of 541 women whose maternal cord blood was sampled during labor had high levels of IgG as measured by an EIA based on whole bacterial cell-based EIA. IgG liters increased with age in children and liters peaked by age 10. They could not demonstrate a correlation between IgG levels and *M. catarrhalis* infections in the children. Antibody tilers fall with increasing age > 65 years, and men as well as chronic smokers tend to have higher antibody liters (Kurlli et al., 1997). A more specific immune response can be demonstrated using recombinanl UspA, a high-molecular-

weight OMP of *M. catarrhalis.* In patients with pneumonia due to *M. catarrhalis,* convalescent serum, but not acute serum, contains elevated levels of IgG to UspA in western blot assays (Helminen et al., 1994). Antibodies of the IgA class to OmpE, an OMP of *M. catarrhalis,* are found in the sputum of most patients with chronic bronchitis, and increases do not occur in anti-OmpE antibodies during acute exacerbations where *M. catarrhalis* is cultured (Bhushan et al., 1997). Thus, demonstrating an immune response to *M. catarrhalis* depends on the antigen used in the immune assay system and requires that baseline antibody titers be done prior to the infection. The combination of serological and bacterial colonization data suggests that antibodies to *M. catarrhalis* are produced in response to colonization that occurs in early childhood and that, although colonization with *M. catarrhalis* decreases to very low levels in adulthood, antibodies persist until old age when the reduced antibody levels are again accompanied by increased levels of colonization and invasive disease.

Lower Respiratory Infections Caused by *Moraxella catarrhalis*

A large number of reports have implicated *M. catarrhalis* as an etiological agent of pneumonia and purulent exacerbations of chronic bronchitis in adults (Calder et al., 1986; DiGiovanni et al., 1987; West el al., 1982; Mannion, 1987; Pollard et al., 1986; Nicotra et al., 1986; Davies & Maesen, 1986; Saito et al., 1986; Capewell et al., 1988; Zheng & Cao, 1988). These retrospective reports indicate that *M. catarrhalis* lower respiratory infections occur much more commonly in adults over the age of 60 years, half to three quarters of whom have been or still are smokers (Hager et al., 1987). More than half of affected persons have coexisting chronic obstructive lunch disease, 9.5% asthma, and 5.5% bronchiectasis (Wright et al., 1990; von Graevenitz & Rathbone, 1981; Sarubbi et al., 1990; Hager et al., 1987). As many as 74% of adults with *M. catarrhalis* respiratory infections will have some immunological deficiency as the resull of ongoing treatment or underlying disease. However, 11% of cases have no predisposing factors to account for their *M. catarrhalis* infection.

In a retrospective study of 52 hospitalized adults in Spain in which *M. catarrhalis* was isolated, in almost half of the cases it was isolated in pure culture, and in the remainder it was associated with *H. influenzae* or *Streptococcus pneumoniae.* Twelve patients had pneumonia, 24 had acute exacerbalions of chronic bronchitis, and 7 had acute purulent bronchitis without underlying lung disease. In this cohort of patients, the isolation of *M. catarrhalis* from sputum was considered to represent colonization in only nine cases (17%) (Ferrer Marcelles et al., 1997). Boyle et al. (1991) evaluated the pathogenic significance of *M. catarrhalis* isolates from 118 lower respiratory samples using rigorous clinical criteria over a 3-year period in Australia. Seventy-eight percent of the isolates were from children and two thirds of cases of infection were community-acquired. Half of the cases in which *M. catarrhalis* was isolated satisfied two of their four clinical criteria of pathogenic significance and 35% satisfied all four criteria. The same group of investigators evaluated the pathogenic significance of *M. catarrhalis* from a cohort of patients seen in community general practices and found that half of the isolates were pathogenic. However, while 36% of the isolates were from children less than 5 years of age, only 9% of isolates were considered pathogenic in this age group largely because upper respiratory tract samples were frequently taken in children. Factors associated with pathogenic isolates were the presence of pneumonia, bronchitis, or other lunch disease and a pure culture of *M. catarrhalis* from sputum (Wood et al., 1996). Thus, the isolation of *M. catarrhalis* from sputum or other lower respiratory samples is frequently associated with a pathologic process especially in the elderly with coexisting lung disease or other chronic disease states.

These studies have also shed some light on the microbiology of *M. catarrhalis* respiratory infections. In 60% of cases *M. catarrhalis* is isolated in pure culture and in the remainder it is isolated with other well-known respiratory pathogens: *H. influenzae, S. pneumoniae, Staphylococcus aureus,* and occasionally enteric gram-negative rods. In 10% of cases of pneumonia, bacteremia is also found (Hager et al., 1987; loannidis et al., 1995; Collazos et al., 1992). *M. catarrhalis* in some centers is now the second most common respiratory isolate, exceeded

only by *H. influenzae* (Sarubbi et al., 1990). There is also a striking seasonality in the frequency of isolation of *M. catarrhalis* in most medical microbiology laboratories with the fall and winter months having the highest incidence of *M. catarrhalis*-positive cultures. This seasonal variation was also found to hold true in Australia during its winter months of May to September (DiGiovanni et al., 1987; Wood et al., 1996). It has been speculated that concurrent respiratory viral infections predispose individuals to infections with *M. catarrhalis* but this theory has never been subjected to rigorous study.

M. catarrhalis as the Etiology of Community-Acquired Pneumonia in Adults

Several clinical studies have documented *M. catarrhalis* as the etiologic agent of community-acquired lower respiratory tract infections including pneumonia. Ninane et al. (1978) followed 193 Belgium coal miners with pulmonary silicosis. All of these men had well-documented chronic obstructive lung disease and were followed prospectively for the development of either pneumonia or acute tracheobronchitis. Using transtracheal aspiration as the method to obtain uncontaminated cultures, *M. catarrhalis* was found to be the third most common etiological agent occurring in pure culture in 14.4% of cases. *H. influenzae* and *S. pneumoniae* made up 42% and 21% of the isolates respectively. Clinical cure was confirmed in each case with a repeat transtracheal aspiration. Carr et al. (1991) found *M. catarrhalis* to be the etiologic agent in 10% of cases from a cohort of 127 elderly Irish patients admitted to a geriatric ward from the community with acute lower respiratory tract infections. In a Japanese clinical series 40 cases of lower respiratory tract infection due to *M. catarrhalis* were identified by transtracheal aspirates and 14 of these had pneumonia (Konishi et al., 1992). Six of the patients with pneumonia died and death was associated with underlying nutritional or immune abnormalities. Barreiro et al. (1992) likewise describe 12 cases of pneumonia due to *M. catarrhalis* in patients with underlying chronic lung and heart disease. A large study of 42 cases of pneumonia due to *M. catarrhalis* was published by Wright et al. (1990), who carefully documented the clinical features of this disease. There was a slight preponderance of males over females, a mean age of 64 years, and chronic obstructive disease in 75% of the cases. The clinical features were not fulminant: generally a moderate increase in cough, sputum volume, and fatigue made it difficult or impossible to differentiate an acute exacerbation of chronic obstructive lung disease from pneumonia without a chest roentgenogram in this population of patients. The pattern on chest roentgenograms revealed lobar consolidation in 43%, with the rest of the cases demonstrating interstitial or diffuse infiltrates. In a similar but more recent study of 30 adults with *M. catarrhalis* pneumonia from Singapore, Chin et al. (1993) found similar clinical features as in the study by Wright et al. (1990). In the Singapore study there was an equal male-female ratio and a mean age of 66 years. The majority were smokers and 73% had chronic obstructive lung disease. Shortness of breath and cough were documented in 87%, fever in 60%, leukocytosis in 70%, and chest roentgenographic abnormalities in 78%. The overall mortality was 10%. Bacteremia, which leaves little doubt as to the pathogenicity of *M. catarrhalis,* also occurs in about 10% of cases of pneumonia in adults with underlying lung pathology or immune suppression. Interestingly a purpuric rash resembling that seen with *N. meningitidis* sepsis is described in children with *M. catarrhalis* bacteremic pneumonia (Collazos et al., 1992; Ioannidis et al., 1995). The above studies serve to confirm that *M. catarrhalis* is capable of causing pneumonia, but do not indicate how frequently one can expect *M. catarrhalis* to be found as the etiology of pneumonia in different clinical settings.

Clinical studies attempting to determine the etiology of pneumonia in patient populations from the community, either admitted to hospital or not, or from nursing homes have not yielded uniform results as to the frequency with which *M. catarrhalis* is the etiology of pneumonia. Gabre-Selasie et al. describe isolating *M. catarrhalis* from 68 of 200 sputum samples from patients with community-acquired pneumonia in Ethiopia (Gabre-Selasie, 1998). *M. catarrhalis*-specific IgA and IgM antibodies were detected in 59% and IgG3 antibodies detected in 63% of the pneumonia cases. In control patients without infections only 3% and 0% showed IgA/IgM and IgG3 *M. catarrhalis* antibodies, re-

spectively. Their data suggest that *M. catarrhalis* is etiologic in up to 34% of cases of community-acquired pneumonia in the elderly with underlying chronic diseases, especially those involving the lungs or immune system. Burman et al. (1994) examined 158 adults with pneumonia for evidence of serological responses to *H. influenzae* and *M. catarrhalis.* Six patients (3.8%) had increases in antibody levels to *M. catarrhalis* although two patients with *M. catarrhalis* cultured from a transtracheal aspirate did not have measurable antibody responses. The frequency with which *M. catarrhalis* is the etiology of community-acquired pneumonia appears to range between 1.3% and 3.8% as determined in an overall elderly population of adults whose assessments took place in a hospital (West et al., 1982; Nicotra et al., 1986; DiGiovanni et al., 1987; Capewell et al., 1988; Vaneechoutte et al., 1990; Boyle et al., 1991; Phillips & Branaman-Phillips, 1993; Burman et al., 1994; Drinka et al., 1994; Gabre-Selasie, 1998). The notable exception is that of the very high frequency of M. *catarrhalis* detected in the study by Gabre-Selasie et al. (1998) above. It should be pointed out, however, that several large epidemiological investigations of similar patient groups have failed to detect *M. catarrhalis* in cases of community-acquired pneumonia (Marrie et al., 1989; Torres et al., 1996; Kauppinen et al., 1995; Mundy et al., 1995; Porath et al., 1997; Marston et al., 1997; Bohte et al., 1995).

M. catarrhalis in Community-Acquired Pneumonia in Children

Because of the difficulties involved in obtaining reliable sputum samples from children, defining the precise role of *M. catarrhalis* in lower respiratory tract infections from this age group has been challenging. There is a definite association between respiratory symptoms and the isolation of M *catarrhalis* from respiratory samples in children (Marchant, 1990; Brorson & Malmvall, 1981). There is a well-documented report of 14 cases *of M. catarrhalis* lower respiratory infections in a pediatric intensive care unit where almost one third of the cases were nosocomial in origin (Kasian et al., 1989). Life-threatening community-acquired pneumonia has been described in children as well as in the setting of neonatal intensive care (Fenton et al., 1994; Dyson et al., 1990). Nohynek et al. (1995) found evidence of antibody responses to *M. catarrhalis* antigens in 16.6% of children admitted with acute lower respiratory tract infections in whom an antibody response was measurable. However, only 45% of cases had detectable antibody response to *S. pneumoniae, H. influenzae,* or *M. catarrhalis.* A large study of 284 Swedish children with clinical and radiologically proven community-acquired pneumonia had serological responses to *M. catarrhalis* measured with an EIA directed against whole bacterial cell antigens. Overall, only 9 children (3%) demonstrated an increasing titer in paired serum samples to *M. catarrhalis.* Serological responses to other respiratory tract pathogens were also found concurrently in many of these children, making it difficult to determine the principal pathogen. Thus *M. catarrhalis* pneumonia is uncommon in otherwise healthy children and its exact frequency is not yet precisely defined (Berg & Bartley, 1987; Keren et al., 1989).

Nosocomial Pneumonia Due to *M. catarrhalis*

M. catarrhalis has also been found to cause hospital-acquired pneumonia in several studies (Patterson et al., 1988; Hager et al., 1987). Up to half of all cases of *M. catarrhalis* respiratory infections are acquired during hospitalization in elderly adults. Chromosomal DNA restriction endonuclease analysis has suggested that person-to-person transmission occurs between colonized staff and patients. Colonization among hospital patients and staff has also been documented (Calder et al., 1986). *M. catarrhalis* has been shown to be very resilient and can survive in dried respiratory secretions for 3 weeks or longer (Ahmad et al., 1985). It is thus emerging as an important cause of nosocomial pneumonia, but much more detailed prospective epidemiogical data is needed to determine the scope of *M. catarrhalis* infections in hospitals.

Microbiology Laboratory Identification and Susceptibility Testing of *Moraxella catarrhalis*

In those cases where *M. catarrhalis* causes lower respiratory tract infection, either an exacerbalion of chronic bronchitis or pneumonia, the or-

ganism is typically present in large numbers exceeding 10^7 cfu/mL of sputum (DiGiovanni et al., 1987; Vaneechoutte et al., 1990). On Gram's stain the bacteria generally stain uniformly as gram-negative diplococci in pairs with a slight flattening of the surface where the two cells abut. It has been pointed out that from time to time *M. catarrhalis* will not fully decolorize and appear as a gram-positive coccus, causing possible misidentification with staphylococci or streptococci (Ainsworth et al., 1990; Ferrer Marcelles et al., 1997). In specimens that have a predominance of polymorphonuclear cells seen microscopically the numbers of organisms grown is higher than from sputum specimens that do not have >25 polymorphonuclear cells per 100× field present. *M. catarrhalis* grows in 18 hours on trypicase soy agar with 5% sheep blood in room air. The colonies are 1.5 to 2 mm in diameter, gray to slightly pink, whole, round, and of a characteristic consistency like paste wax. When touched with an inoculating loop the colonies tend to slide on the surface of the agar. The cells are difficult to emulsify into suspension. There is no hemolysis induced on blood agar plates. *M. catarrhalis* is oxidase-positive; it does not produce acid from glucose, maltose, lactose, or sucrose and reduces nitrate, which serves to distinguish *M. catarrhalis* from *N. meningitidis* and *N. gonorrheae.* Definitive identification *of M. catarrhalis* is accomplished by demonstrating the hydrolysis of DNA in an agar medium, and the hydrolysis of tributyrin with a spot disk test (Speeleveld et al., 1994; Catlin, 1990). Other useful tests are the 4-methylumbelliferyl butyrate tube test and the indoxyl acetate strip test. Combination tests prepared commercially can be useful in identifying *M. catarrhalis* when carefully performed and interpreted.

Susceptibility testing need not be performed routinely for *M. catarrhalis.* β-Lactamase testing provides some useful information and is rapidly done with a nitrocefinase disk test or a new chromogenic cephalosporin called S1 in a disk assay (Doern et al., 1995). There are no recognized guidelines for interpretation of minimum inhibitory concentration tests for *M. catarrhalis.* The breakpoints recommended for *H. influenzae* by the National Committee for Clinical Laboratory Standards have been used in several published surveys of *M. catarrhalis* susceptibility as determined by microbroth dilution methods (Berk & Kalbfleisch, 1996; Doern et al., 1996a). *Haemophilus* test medium and Mueller-Hinton medium with lysed horse blood give equivalent results in microbroth dilution susceptibility testing (Barry et al., 1993). Disk diffusion susceptibility testing is also an acceptable method with the one caveat that apparent susceptibility to ampicillin in vitro with a large zone of inhibition among some β-lactamase-positive strains be ignored and that all β-lactamase-positive strains be considered resistant in vivo to ampicillin (Wallace et al., 1990; Fung et al., 1992; Kibsey et al., 1994). Results of susceptibility testing of ampicillin against β-lactamase-positive *M. catarrhalis* are clearly inoculum-dependent, and the use of a higher inoculum of organisms when testing ampicillin has also been recommended (Yeo & Livermore, 1994).

Antimicrobial Susceptibility and Therapy

β-lactamases of M. *catarrhalis*

Prior to the late 1970s virtually all strains of M. *catarrhalis* were β-lactamase-negative and susceptible to penicillin, ampicillin, and all other available antibiotics (Wallace et al., 1989). However, after 1977 there was an extraordinarily rapid increase in the prevalence of β-lactamase-producing strains of *M. catarrhalis* such that 95% or more of all isolates worldwide are now β-lactamase producers (Felmingham et al., 1998; Fung et al., 1998; Preston & Turik, 1998; Richard et al., 1998; Thornsberry et al., 1997; Manninen et al., 1997; Schito et al., 1997; Ejlertsen et al., 1991). The β-lactamases of *M. catarrhalis* are of three types, designated BRO-1, BRO-2, and BRO-3 (for Branhamella and Moraxella). BRO-1 (called Ravasio in the past) is found in approximately 90% of β-lactamase-producing strains of *M. catarrhalis,* while BRO-2 (called 1908 in the past) is seen in the remainder according to a large survey conducted in Taiwan (Fung et al., 1998). BRO-3 is rarely seen in clinical isolates of *M. catarrhalis* (Ikeda et al., 1993; Christensen et al., 1991). It can be demonstrated that BRO-1-producing strains of *M. catarrhalis* possess minimum inhibitory concentrations that are higher than BRO-2-producing strains on the basis of higher enzyme production. This difference in β-lactamase activity accounts for BRO-2 strains often demonstrating

susceptibility to ampicillin or amoxicillin in vitro (Ikeda et al., 1993; Fung et al., 1992). The specific enzyme activity of the BRO β-lactamases are the same (Eliasson et al., 1992). Bootsma et al. (1996) have demonstrated that the genes coding for the BRO β-lactamases of *M. catarrhalis* are chromosomal and highly conserved. Indeed, there is only a single amino acid difference between the predicted sequences of BRO-1 and BRO-2. However, there is a 21-base pair deletion in the promotor region of the BRO-2 gene that may explain the lower production rates of BRO-2. BRO β-lactamase production is constitutive. Insertional inactivation of the BRO gene abolishes all β-lactamase activity,confirming that the BRO molecule is the sole β-lactamase of *M. catarrhalis.* The BRO enzyme has a signal sequence for lipoproteins and this is consistent with the observation that 10% of enzyme activity is membrane-associated (Steingrube et al., 1993). Transfer of the BRO-1 and BRO-2 genes between *M. catarrhalis* strains has been demonstrated to occur by conjugation as opposed to transformation by plasmids (Chaibi et al., 1995). The β-lactamases of *M. catarrhalis* have been postulated to provide a protective effect on other susceptible respiratory tract pathogens such as *S. pneumoniae* in the presence of penicillin or ampicillin. Since the persons most likely to be infected with *M. catarrhalis* are also very likely to be infected with multiple pathogens, the action of *M. catarrhalis* as a co-pathogen could be important. In a mouse model of bacterial pneumonia with penicillin-susceptible *S. pneumoniae,* Hol et al. (1994) demonstrated that β-lactamase-producing *M. catarrhalis* strains co-inoculated into the respiratory tract protected the *S. pneumoniae* from the action of penicillin. Clinical observations suggest that this may occur in humans infected with both a β-lactamase-producing *M. catarrhalis* and a penicillin-susceptible primary pathogen (Stefani et al., 1991). Unfortunately, it is not clear if this happens often enough to be a significant cause of treatment failures.

Antimicrobial Susceptibility of M. *catarrhalis*

Table 1 summarizes recent data on the susceptibility of *M. catarrhalis* to currently available antibiotics. With a few exceptions the cephalosporins and carbapenems are all very active against *M. catarrhalis.* Cefaclor, loracarbef, and cefuroxime are susceptible to hydrolysis by the BRO-1 β-lactamase, but the degree of antibiotic inactivation is not generally sufficient to render the bacteria resistant to these cephalosporins (Doern et al., 1996a; Chaibi et al., 1995). In the survey conducted by Doern et al. (1996a) resistance to cefprozil was noted on 1.6% of 723 *M. catarrhalis* isolates with a minimum inhibitory concentration greater than 32 μg/mL. The Alexander project, an international multicenter surveillance study of antimicrobial susceptibility of respiratory tract pathogens conducted between 1992 and 1995, found that only 3 out of 818 (0.34%) *M. catarrhalis* isolates were intermediate in susceptibility to cefaclor or cefuroxime (Bert & Kalbfleisch, 1996; Schito et al., 1997). Amoxicillin-clavulanic acid has uniformly been active against all strains of *M. catarrhalis* reported from a number of large surveillance studies (Hoogkamp-Korstanje et al., 1997; Traub & Leonhard, 1997). The inhibitor profiles of the BRO β-lactamases of M. *catarrhalis* are the same for clavulanic acid, sulbactam, tazobactam, and BRL 42715 (Steingrube et al., 1993). Piperacillin, ticarcillin, and other ureidopenicillins are also active. A meta-analysis of the Alexander project data concluded that amoxicillin-clavulanic acid and ceftriaxone are the preferred β-lactam antibiotics for empiric treatment of respiratory tract infections due to *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *M. catarrhalis* based on the time the serum concentration of these drugs exceeds the minimum inhibitory concentration during the dosing interval (Drusano & Goldstein, 1996).

The macrolides are uniformly active against *M. catarrhalis* isolates and the new ketolides (HMR 3004 and HMR 3647) are likewise very active (Boswell et al., 1998; Agouridas et al., 1997). The macrolides and ketolides are bacteriostatic; however, the ketolides do demonstrate bactericidal activity at concentrations four to eight times their minimum inhibitory concentration (Biedenbach et al., 1998). Azithromycin has a lower minimum inhibitory concentration than erythromycin and clarithromycin, and the minimum inhibitory concentrations of erythromycin against *M. catarrhalis* were noted to be higher in Europe than in the United States (Doern et al., 1996a; Berk & Kalbfleisch, 1996). Tetracycline resistance has been noted in up to 14% of *M. catarrhalis* strains from Taiwan in 1993–1994 but not reported in other surveys from

TABLE 1. Susceptibilities of *M. catarrhalis*[a]

Antibiotic	MIC range (μg/mL)	Percent susceptible	References
Penicillins			
Penicillin			
β-Lactamase-positive	0.25–>32	0	Doern et al., 1996a; Berk & Kalbfleisch, 1996
β-Lactamase-negative	<0.015–0.12	92–100	
Amoxicillin			
β-Lactamase-positive	0.06–>32	0–20	Doern et al., 1996a; Berk & Kalbfleisch, 1996
β-Lactamase-negative	<0.015–0.25	96	
Amoxicillin/clavulanic acid	<0.015–2	100	Hoogkamp-Korstanje et al., 1997; Doern et al., 1996a
Cephalosporins			
Cefaclor	0.03–16	99.8	Doern et al., 1996a
Cefuroxime	0.06–32	98.5–100	Doern et al., 1996; Traub & Leonhard, 1997
Ceftriaxone	<0.12–2	100	Berk & Kalbfleisch, 1996
Cefixime	<0.015–4	100	Doern et al., 1996a; Berk & Kalbfleisch, 1996, Traub & Leonhard, 1997, Doern 1995
Cefpodoxime	0.06–8	99	Doern et al., 1996a; Doern, 1995
Cefdinir	<1.0	100	Blandino et al., 1996
Cefprozil	0.06–64	94.3	Doern et al., 1996a; Doern & Vautour, 1992
Cefodizime	0.06–0.51	100	Paniara et al., 1994
Cefpirome	0.6–4.0	100	Soussy et al., 1994
Loracarbef	0.06–64	99	Doern et al., 1996a,b; Lees et al., 1993
Faropenem	0.5	100	Cormican & Jones, 1995; Boswell et al., 1997
Sanfetrinem	0.015–0.03	100	Doern et al., 1996b; Wise et al., 1996
Imipenem	0.063	100	Ikemoto et al,. 1996a,b,c
Macrolides and ketolides			
HMR 3004 and 3647	0.06–0.12	100	Biedenbach et al., 1998; Boswell et al., 1998; Agouridas et al., 1997
Erythromycin	0.06–4	100	Doern et al., 1996a; Ikemoto et al., 1996a; Spencer & Wheat, 1992; Berk & Kalbfleisch, 1996
Clarithromycin	0.03–1.0	100	Hoshino et al., 1998; Doern et al., 1996a; Berk & Kalbfleisch, 1996
Azithromycin	0.03–0.12	100	Doern et al., 1996a; Berk & Kalbfleisch, 1996; Manninen et al., 1997
Roxythromycin	<1.56–0.25	100	Hoshino et al., 1998; Spencer & Wheat, 1992; Fung et al., 1995
Tetracyclines and chloramphenicol			
Tetracycline	<0.06–2	86–100	Fung et al., 1995; Doern et al., 1996a; Spencer & Wheat, 1992; Manninen et al., 1997
Minocycline	0.125–0.25	100	Ikemoto et al., 1996a,b,c
Chloramphenicol	0.25–2	100	Doern et al., 1996a
Fluoroquinolones			
Sparfloxacin	0.008–0.5	100	Jones et al., 1998; Richard et al., 1998; Ballow et al., 1997; Hoogkamp-Korstanje et al., 1997; Speciale et al., 1995; Brueggemann et al., 1997
Moxifloxacin	0.03–0.12	100	Souli et al., 1998; Brueggemann et al., 1997
Clinafloxacin	0.008–0.015	100	Brueggemann et al., 1997
Trovafloxacin	<0.002–0.015	100	Brueggermann et al., 1997; Sefton et al., 1996
Ciprofloxacin	<0.002–0.03	100	Hoogkamp-Korstanje et al., 1997; Berk & Kalbfleisch, 1996; Brueggemann et al., 1997
Ofloxacin	0.008–0.125	100	Cormican et al., 1996; Ikemoto et al., 1996a,b,c; Brueggeman et al., 1997
Levofloxacin	0.03–0.06	100	Cormican et al., 1996
Other			
Trimethoprim–sulfamethoxazole	<0.5/9.5	93.5–99.3	Doern et al., 1996a; Spencer & Wheat, 1992; Manninen et al., 1997

the United Slates or Europe (Fung et al., 1995; Doern et al., 1996a; Traub & Leonhard, 1997). The mechanisms of resistance to tetracycline appears to be the chromosomal TetB gene perhaps acquired from *H. influenzae* (Roberts et al., 1990, 1991). Chloramphenicol is uniformly active against *M. catarrhalis.*

The fluoroquinolones have excellent bactericidal antimicrobial activity against all strains of *M. catarrhalis* (Jones et al., 1998; Brueggemann et al., 1997; Souli et al., 1998; Cormican et al., 1996; Sefton et al., 1996). The newer fluoroquinolones such as trovafloxacin and sparfloxacin have low minimum inhibitory concentrations of 0.002 and 0.008 μg/mL, respectively. The activily profiles of the other fluoroquinolones are shown in Table 1. Ciprofloxacin resistance has been reported from a clinical isolate of M. *catarrhalis* and thus continued surveillance for resistance is warranted as fluoroquinolones are used more extensively for respiratory tract infections (Cunliffe et al., 1995).

The activity of trimethoprim-sulfamethoxazole remains high against *M. catarrhalis,* with at least 93.5% of isolates being susceptible (Doern et al., 1996a; Traub & Leonhard, 1997). There is uniform resistance to sulfamethoxazole, and approximately 9% of isolates of *M. catarrhalis* are resistant to trimethoprim (Fung et al., 1995).

Because pneumonia with *M. catarrhalis* is uncommon, randomized controlled trials specifically assessing the best mode of therapy for this clinical syndrome have not been conducted. The observations and review of loannidis et al. (1995) of *M. catarrhalis* bacteremia accompanied by pneumonia discuss significant mortality in cases where there is preexisting respiratory disease, immunoglobulin deficiency, or neutropenia not related to malignancy. Mortality rates for *M. catarrhalis* pneumonia with or without bacteremia are in the range of 10% to 15% (Chin et al., 1993; Barreiro et al., 1992; Collazos et al., 1992; Carr et al., 1991). In all of these observational studies all the patients were treated and thus it is impossible to estimate the effect on mortality of antibiotic therapy for *M. catarrhalis* community-acquired pneumonia. Ejlertsen and Skov (1996) noted that children who received penicillin or ampicillin for lower respiratory tract infection with *M. catarrhalis* did have clinical and bacteriological response despite the 84% β-lactamase production rate. Klugman (1996) in his meta-analysis of the Alexander project susceptibility data for respiratory pathogens expresses the view that there is little evidence that penicillin or ampicillin resistance in *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* is clinically relevant in the setting of community-acquired pneumonia. Studies have documented good responses clinically and bacteriologically to treating *M. catarrhalis* lower respiratory tract infections with second- or third-generation cephalosporins or amoxicillin–clavulanic acid, but most of these cases were acute exacerbations of chronic bronchitis (Perry & Brogden, 1996). The Royal New Zealand College of General Practitioners randomized controlled trial comparing roxithromycin to cefaclor in the treatmenl of acute community-acquired lower respiratory tract infections demonstrated greater than 95% effectiveness of either antibiotic and *M. catarrhalis* was the second most common pathogen isolated (Tilyard & Dovey, 1992). Considering the antimicrobial susceptibility patterns it is recommended that pneumonia due to *M. catarrhalis* be treated with a second- or third-generation cephalosporin, a penicillin plus β-lactamase inhibitor combination such as amoxicillin-clavulanic acid, a macrolide, a fluoroquinolone, or trimethoprim–sulfamethxoazole. Decisions about drug therapy will have to take into account that frequently *M. catarrhalis* is not isolated alone and that *S. pneumoniae* or *H. influenzae,* with their own susceptibility patterns, are present and may be contributing to the pathologic process.

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Pasteurella multocida

THOMAS J. MARRIE

Introduction

Pasteurella multocida is a small gram-negative coccobacillus that is part of the oral flora of many animals including cats, dogs, rats, mice, rabbits, cattle, sheep, swine, reindeer, horses, monkeys, buffaloes, lions, panthers, and lynx (Weber et al., 1984). It is nonmotile and does not form spores. On gram-stained smears the organisms generally appear as single bacilli but they may occur in pairs or chains. They frequently show bipolar staining. The organisms are aerobic, are facultatively anaerobic, and grow well at 37°C on a variety of media including blood, chocolate, and Mueller–Hinton agar but not on MacConkey's agar (Weber et al., 1984).

P. multocida causes hemorrhagic septicemia of cattle, known as "shipping fever," in which it is a secondary invader following myxovirus infection (Weber et al., 1984). Most human infections result from direct inoculation via bites so skin and soft tissue infections predominate. However, infections can occur from contact with animal secretions. Kopita et al. (1993) described the case of a 66-year-old man with chronic obstructive pulmonary disease who was dependent on home oxygen and who developed *P. multocida* bacteremic pneumonia. His wife's pet cats frequently played on and licked his home nebulizer machine. Drabick et al. (1993) suggested that aerosol was the mechanism of infection for a 27-year-old man with HIV infection who had been in the same apartment with a cat while visiting relatives for 2 weeks. The cat regurgitated hairballs throughout the house, giving the apartment a sour smell. The cat had a favorite rug that was completely matted with secretions. The patient did handle the rug, although he avoided the cat during the visit. The patient's and the cat's isolate appeared identical following digestion with Hind III and electrophoresis on an agarose gel. Dendrogram analysis of the fatty acids of these two strains and a library strain also suggested that the isolates from the cat and the patient were more closely related to each other than to the library strain. The organism can remain viable in water for 7 to 25 days and in soil for up to 21 days but is killed by exposure to direct sunlight for 10 minutes (Weber et al., 1984). Human-to-human spread of infection has not been documented.

Pneumonia

Weber et al. (1984) reviewed the literature and found 25 cases of pneumonia due to *P. multocida.* Kopita et al. (1993) in a similar review were able to document 108 cases of pleuropulmonary infection due to this microorganism. Forty-nine of these were pneumonia, 37 tracheobronchitis, 25 empyema, 3 lung abscess, and 1 not specified. They noted antecedent animal exposure in 61% of the cases, including 28 cases in which cats were directly implicated. Exposure to cattle, pigs, poultry, and horses was implicated in other cases. Ninety-three percent of

THOMAS J. MARRIE • Department of Medicine, Walter C. McKenzie Health Sciences Centre, Edmonton, Alberta, T6G 2B7, Canada.

Community-Acquired Pneumonia, edited by Marrie, Kluwer Academic/Plenum Publishers, New York, 2001.

patients had some underlying comorbid condition such as chronic obstructive pulmonary disease, bronchiectasis, malignancy, or other chronic conditions. The mortality rate was 29%.

The clinical features are indistinguishable from those caused by other pathogens. Fever, chills, dyspnea, pleuritic chest pain, and malaise are common. It does appear, however, that empyema is more common following infection with this organism than with other pulmonary pathogens, since 25 of 108 cases of pleuropulmonary infection were empyema.

Occasionally there are unusual manifestations of *Pasteurella* pulmonary infections. One of these is Pancoast's syndrome due to chronic pneumonia (Ribas et al., 1997). In this case a 46-year-old man presented with a 5-month history of nonproductive cough, dyspnea on exertion, anorexia, 8-kg weight loss, and sharp pain in his left scapula radiating down his left arm. There was no abnormality on neurological examination. There was a large opacity in the left upper lobe on chest radiograph, an aspirate of which was negative for malignant cells but grew *P. multocida* on culture. Pain disappeared by the third week of treatment. Another unusual manifestation was hemoptysis as the sole presentation of this infection (Sazon et al., 1998).

Treatment

The most active antibiotics against *P. multocida* are penicillin G, carbenicillin, ticarcillin, piperacillin, second-generation cephalosporins, third-generation cephalosporins, tetracyclines, and chloramphenicol. Less active drugs include first-generation cephalosporins and the semisynthetic penicillins, methicillin, and nafcillin (Weber et al., 1984).

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Rhodococcus equi and Bordetella bronchiseptica

CLAIRE TOUCHIE

Rhodococcus equi

Magnusson first described pyogranulomatous pneumonia of foals due to *Corynebacterium equi* in 1923. The organism has since been reclassified as *Rhodococcus equi* (Prescott, 1991). There are currently 12 established *Rhodococcus* species that are phylogenetically grouped in the mycolate-containing genera including *Corynebacterium, Mycobacterium, Nocardia, Gordona, Tsukamurella,* and *Dietza* species (Bell et al., 1998).

R. equi is a gram-positive pleomorphic coccobacillus that may have rudimentary branching and occasionally stains acid-fast. It is a nonmotile, catalase-positive obligate aerobe with simple growth requirements; thus selective media are not required for isolation. It develops its salmon-pink pigmentation after 3 to 4 days of incubation. Prior to this pigmentation it is often mistaken as a diphtheroid and may be reported as nonpathogenic. Biochemical criteria are best used to identify *R. equi.* It fails to oxidize or ferment carbohydrates or alcohols but reduces nitrate and produces lipase and phosphatase. *R. equi* produces an *equi* factor that interacts with the beta-toxin or *Staphylococcus aureus,* the phospholipase D of *Corynebacterium pseudotuberculosis,* and a hemolysin of *Listeria monocytogenes* to produce an enhanced area of complete hemolysis. This is a very useful test in the identification of *R. equi* (Prescott, 1991).

R. equi is a facultative intracellular bacterium that infects monocyte-macrophage type cells and has the ability to inhibit intracellular killing by phagolysosomes. It can therefore persist within macrophages in an environment that promotes growth. Human disease occurs most frequently in individuals with impaired cell-mediated immunity. Protection by antibodies does not appear to play a significant role in humans. Virulence depends on the presence or absence of an 85-kDa plasmid, especially in immunocompetent individuals (Mosser & Hondalus, 1996).

Epidemiology

R. equi infections have long been recognized as respiratory infections in horses, swine, cattle, and less common species. Human infection was first reported by Golub in 1967 (Golub et al., 1967). Only 12 cases were reported by 1983, 11 of them occurring in immunosuppressed patients with either a hematopoietic malignancy or renal transplantation or in patients receiving immunosuppressive medications (Van Etta et al., 1983). The first case in a patient with HIV infection was reported in 1986 (Sarnies et al., 1986). Since then, more than 100 cases of *R. equi* infection have been documented (Van Etta et al., 1983; Lasky et al., 1991; Harvey & Sunstrum, 1991; Verville et al., 1994; Scott et al., 1995; Arlotti et al., 1996; Donisi et al., 1996). More than half of the cases of *R. equi* are associated with HIV infection and it was the first opportunistic

CLAIRE TOUCHIE • Division of General Internal Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada K1H 8L6.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

infection in up to 50% of these cases. The CD4 lymphocyte count is usually low (mean, 47–50/μL), with only one individual known to be infected with *R. equi* and a CD4 lymphocyte count greater than 200/μL (Arlotti et al., 1996; Donisi et al., 1996).

In individuals who are not infected with HIV, *R. equi* is most commonly associated with cell-mediated immunosuppression due to hematopoietic malignancies, solid organ transplantation (kidney, liver, heart, and lungs), immunosuppressive therapy including prednisone and cyclosporine, and alcoholism (Harvey & Sunstrum, 1991; Prescott, 1991; McNeil & Brown, 1994; Stolk-Engelaar et al., 1995; Muñoz et al., 1998). Cases are also occasionally known to occur in immunocompetent individuals (Verville et al., 1994).

R. equi has been isolated from soil and water but is most often found in grazing areas or soils enriched with horse manure where the organism can find its appropriate growth requirements (Johnson & Cunha, 1997). Infection appears to be transmitted through respiratory droplets, although rare cases of direct inoculation with *R. equi* have been documented (Antinori et al., 1992; Adal et al., 1995).

A history of exposure to farm animals is not always present in patients with *R. equi* infection. Harvey and Sunstrum (1991) found that 9 of 20 (45%) non-HIV-infected individuals had exposure to farm animals compared to 2 of 11 (18%) HIV-infected individuals. Risk of exposure was documented to be as high as 58.3% (14/24) in a study of *R. equi* in HIV-infected individuals by Arlotti et al. (1996). Seven of the patients had contact with horses, five lived on cattle farms, and two shared a room with patients known to have *R. equi* pneumonia. The latter has yet to be identified definitely as a risk exposure but as the infection is spread through respiratory droplets, it appears a reasonable mode of transmission.

R. equi infection is more commonly seen in males (3–5:1) due to the frequency of infection in HIV-infected individuals. Infection has been documented in all age groups (<1–76 years). Mortality from *R. equi* pneumonia and other associated infection is more common in HIV-infected individuals. The overall mortality in all cases averages 25% (Scott et al., 1995; Verville et al., 1994). In HIV-infected individuals mortality has been as high as 90% in one series, but the attributable mortality was only 35% (Arlotti et al., 1996). Mean survival time in patients treated with antibiotics was 11.4 months. In another retrospective study of 12 HIV-infected individuals, overall mortality was 58.3% (42.9% of these directly attributable to *R. equi* infection) and mean survival was 5.75 months (Donisi et al., 1996).

Clinical Features

Infection with *R. equi* most often presents with clinical pneumonia (up to 80% of cases) with or without cavitation. It can disseminate contiguously of hematologically to extrapulmonary sites and can present initially as a variety of clinical entities (Table 1). There have been some cases of direct inoculations reported, including a subcutaneous abscess, septic arthritis from a nail injury, penetrating eye wound, and mycetoma (Antinori et al., 1992; Verville et al., 1994; Adal et al., 1995). Cavitary lung lesions occur in up to two thirds of cases and can easily be confused with infections of *Mycobacterium tuberculosis*, *Nocardia* species, and fungi. In HIV-infected individuals, however, an upper lobe cavitation with a negative work-up for the above infections should raise suspicions of *R. equi* infection. Pleural effusions are also commonly associated with respiratory *R. equi* infections.

Symptoms of fever, cough, dyspnea, chest pain, and occasionally hemoptysis are seen. The onset is insidious over a period of days to weeks, with cavitation occurring at 2 to 4 weeks. Cavitations are characterized by the presence of an air-

TABLE 1. Presentations of Extrapulmonary Infections with *Rhodococcus equi*

Abseceses	Bloody diarrhea
Brain	Endophthalmitis
Liver	Line-related sepsis
Paraspinal	Lymphadenitis
Pelvic	Meningitis
Prostatic	Osteitis/osteomyelitis
Psoas/retroperitoneal	Pericarditis
Renal	Peritonitis
Subcutaneous	Septic arthritis
Bacteremia	Wound infection

fluid level seen within a radiological opacification (Prescott, 1991). Fever alone with bacteremia is not an uncommon presentation. Verville et al. (1994) documented four cases with this presentation, three of whom had a malignancy and underlying neutropenia, and two were found to have infected central venous catheters. Individuals with *R. equi* pneumonia frequently have bacteremia. In four studies, 34 of 66 patients (51.5%) with a radiological diagnosis of pneumonia had positive blood culture (Harvey & Sunstrum, 1991; Scott et al., 1995; Verville et al., 1994; Arlotti et al., 1996).

Diagnosis

Diagnosis is best made by cultures of clinical specimens. *R. equi* has been isolated from sputum, bronchial washings and brushing, blood, abscess aspirate, tissue biopsies, and pleural, peritoneal, joint, and cerebrospinal fluids. Growth occurs on nonselective media and most often can be identified following 2 to 4 days of incubation at 37°C. The organism can be mistaken for diphtheroids early and therefore be reported and interpreted as a contaminant or nonpathogen. As it can be weakly acid-fast, caution must be taken not to misinterpret it as *Nocardia* or *Mycobacterium* species (McNeil & Brown, 1994).

Findings on chest radiographs and computed tomography (CT) scans can suggest the diagnosis. Although the most common findings are those of upper lobe consolidation and cavitary lesions, these are not specific. Nodular opacities and pleural effusions can also be found (Wicky et al., 1996; Johnson & Cuhna, 1997). Air-fluid levels in a cavitary lesion with concomitant effusion should be highly suggestive of *R. equi* in an immunosuppressed or HIV-infected individual (Johnson & Cuhna, 1997).

Findings on histopathology or cytology specimens may be suggestive of the diagnosis. Lung biopsies may show multiple abscesses with a necrotizing granulomatous reaction. Macrophages with eosinophilic granular cytoplasm may contain large numbers of gram-positive coccobacilli. The latter can be identified easily with Brown-Brunn stain and with more difficulty if Giemsa or acid-fast stains are used. Others have found that intracellular organisms can easily be identified using stains such as tissue Gram's stain and Gomori methenamine–silver nitrate (Scott et al., 1995). Chronic granulomatous inflammation has been reported with characteristic Michaelis–Guttman bodies consisting of histocytes containing partly digested intracellular bacteria (Verville et al., 1994; Lachman, 1995).

Treatment

Although in vitro and animal studies of antimicrobial susceptibilities against *R. equi* are reported in the literature, only anecdotal reports exist for treatment of clinical disease (Nordmann & Ronco, 1992; McNeil & Brown, 1992). Long courses of therapy with combinations of antibiotics offer the best chance of cure but relapses are common. In a review of 24 patients with *R. equi* pulmonary disease, Arlotti et al. (1996) reported that 14 out of 17 patients had an average of two or more relapses.

In vitro data demonstrate consistent activity with drugs such as erythromycin, gentamicin, vancomycin, teicoplanin, imipenem, and rifampin (Table 2).

Antibiotics administered orally do not appear as effective as those administered parenterally despite good in vitro activity, as demonstrated by treatment failures. β-Lactams in general, excluding imipenem, have poor activity against *R. equi* (Ar-

TABLE 2. Antimicrobial Susceptibility of *Rhodococcus equi*[a]

Antibiotic	No. susceptible/No. tested (% susceptible)
Amoxicillin–clavulanate	103/103 (100)
Ampicillin	24/116 (21)
Ampicillin/sulbactam	103/103 (100)
Cephalothin	30/108 (28)
Ciprofloxacin	91/117 (78)
Clindamycin	49/98 (50)
Erythromycin	119/122 (98)
Gentamicin	113/113 (100)
Imipenem	115/119 (97)
Penicillin	41/121 (34)
Rifampin	115/119 (97)
Teicoplanin	9/9 (100)
Tetracyclines	100/116 (86)
Trimethoprim–sulfamethoxazole	112/122 (92)
Vancomycin	118/118 (100)

[a]From Mcneil & Brown, 1992; Arlotti et al., 1996.

lotti et al., 1996). Although in vitro data show high susceptibility rates for amoxicillin–clavulanate and ampicillin–sulbactam, little in vivo data exist. Broad-spectrum cephalosporins, tetracyclines, and fluoroquinolones have unpredictable in vitro activity and should be tested against the patient isolate prior to administration to ensure susceptibility.

Antimicrobial agents with good intracellular activity are indicated as *R. equi* overcomes intracellular killing by macrophages. Animal studies have shown synergistic activity with erythromycin and rifampin; thus this combination given over a course of 6 to 12 weeks is recommended (Johnson & Cunha, 1997; Prescott & Nicholson, 1984). Arlotti et al. (1996) recommended intravenous therapy with an agent with extracellular activity (vancomycin, teicoplanin, or imipenem) in combination with an intracellularly active agent, erythromycin being the drug of choice. Length of intravenous therapy is not well defined. To prevent relapses, oral therapy should be administered for weeks following intravenous treatment. Most authors suggest a combination of erythromycin and rifampin as a first choice. Intravenous drugs should be resumed if relapses occur. Therapy should be continued until the patient has clinically improved and repeat cultures are negative. In the HIV-infected individual, as relapses are common, lifelong therapy may be best, although no clinical data exist yet to support this.

Surgical debridement and drainage of abscess cavities should be considered in addition to antimicrobial therapy to eradicate the infection.

Bordetella bronchiseptica

Bordetella bronchiseptica has rarely been implicated in human disease. It is more commonly associated with respiratory infections in both wild and domestic animals. It is thought to be responsible for kennel cough in dogs, sniffles in rabbits, and atrophic rhinitis in pigs. The association of this microorganism with respiratory tract infections in animals was made independently by McGowan in 1911, Ferry in 1912, and Torrey and Rahe in 1912. It was Lopez in 1952 who suggested it should belong to the genus *Bordetella* and it was thus named *B. bronchiseptica* (Woolfrey & Moody, 1991).

B. bronchiseptica is a small gram-negative coccobacillus closely related to *Bordetella pertussis*, the latter being the main etiologic agent of whooping cough. It is an obligate aerobe that has no nutritional requirement for growth, this being one of its differences from *B. pertussis.* It is oxidase- and catalase-positive, is motile, produces urease, and reduces nitrates. It is indole-negative and will not grow in the presence of potassium tellurite.

Virulence factors likely explain the ability of *B. bronchiseptica* to colonize and infect the respiratory tract epithelium. These include adhesins such as filamentous hemagglutinins, pertactin, and fimbriae as well as toxins such as dermonecrotic toxin, adenylate cyclase-hemolysin, and tracheal cytotoxin. *B. bronchiseptica* does not produce the pertussis toxin (Gueirard et al., 1995). The adenylate cyclase-hemolysin may play an important role in diminishing the bactericidal activity of neutrophils and macrophages.

Epidemiology

B. bronchiseptica remains a rare human infection. The first case was described by McGowan in 1911 in an animal caretaker. Woolfrey and Moody (1991) reviewed 25 cases that had been published to date (including two of their own). A few more cases, including five case reports of pneumonia in patients with AIDS, have been reported since (Amador et al., 1991; de la Fuente et al., 1994; Woodward et al., 1995; Decker et al., 1991; Ng et al., 1992). Infections with *B. bronchiseptica* occur more commonly in immunocompromised individuals including those with hematopoietic malignancies, HIV infection, solid organ and bone marrow transplantation, and alcohol abuse, and those requiring dialysis (Woolfrey & Moody, 1991; Borras Sans et al., 1991; Chauncey & Schaberg, 1990; Bauwens et al., 1992; Gomez et al., 1998). Infection with *B. bronchiseptica* has also been reported in immunocompetent hosts without evidence of humoral or cellular defects, the majority of cases presenting with pneumonia (Winters et al., 1992; Gueirard et al., 1995; Tamion et al., 1996).

Animal exposure is the most common source of acquisition. Although it is relatively uncommon for animal caretakers to be carriers of *B. bronchiseptica* (Woolfrey & Moody, 1991) most individuals reported to have infection have had animal

contact (25/35 patients reviewed). Some of the animals were ill at the time of human infection.

Most infections occur in males with no age predilection (2–79 years). Mortality from *B. bronchiseptica* pneumonia is relatively uncommon. Those reported to have infection have been ill enough to warrant admission and an aggressive diagnostic work-up. Three cases have been associated with death attributable to *B. bronchiseptica* pneumonia: a patient with AIDS (Amador et al., 1991), a young girl with Down syndrome (Winters et al., 1992), and a young woman who underwent bone marrow transplantation for acute myelogenous leukemia (Bauwens et al., 1992).

Clinical Features

Of the cases reported in the literature, more than 80% have involved the respiratory tract including tracheobronchitis, sinusitis, whooping cough, and pneumonia. The majority present with community-acquired pneumonia with or without bacteremia. Other presentations have included endocarditis (Sinnott et al., 1989), peritonitis (Byrd et al., 1981), meningitis (Chang et al., 1975), otitis media, and septicemia (Borràs Sans et al., 1991). It is highly likely that more minor infections go undiagnosed especially in immunocompetent hosts.

To date, there have been 15 cases of pneumonia reported in the literature (de la Fuente et al., 1994; Woodward et al., 1995; Gueirard et al., 1995; Tamion et al., 1996; Gomez et al., 1998). Eleven of these have occurred in immunocompromised individuals, including five cases associated with HIV infection, one with leukemia, one following a heart transplantation, one with Crohn's disease, one with alcoholism and malnutrition, and one with Hodgkin's disease. In HIV-associated cases, the CD4 lymphocyte count has varied from 73 to 245/(μL.

There is no clinical feature that characterizes *B. bronchiseptica* pneumonia from other bacterial etiologies. It often presents with shortness of breath, cough, pleuritic chest pain, and purulent sputum. The presentation may be acute or subacute. Many of the individuals are hypoxemic. One patient had a whooping cough-like syndrome along with his pneumonia (Gomez et al., 1998). It is not infrequently associated with bacteremia but does not appear to metastasize through hematogenous spread.

Diagnosis

Diagnosis of *B. bronchiseptica* infection is made on the basis of culture, with proper microbiological identification. A higher level of suspicion must be maintained in immunocompromised patients, especially those with animal contact.

Radiographs are not helpful in establishing a diagnosis, as *B. bronchiseptica* pneumonia can present with lobar pneumonia with or without pneumothorax (Woolfrey & Moody, 1991; Winters et al., 1992), perihilar infiltrates (Gueirard et al., 1995), diffuse alveolar infiltrates (Tamion et al., 1996), and interstitial infiltrates (Amador et al., 1991).

Association of *B. bronchiseptica* infection with animal contact has been confirmed using molecular epidemiological techniques such as pulse-field gel electrophoresis (Gueirard et al., 1995). Ribotyping has also been found to be useful and could be used for epidemiological studies as well (Register et al., 1997).

There are no specific pathological findings suggestive of diagnostic of *B. bronchiseptica* infection. In two cases, postmortem cultures confirmed the presence of *B. bronchiseptica* in lung tissue (Amador et al., 1991; Winters et al., 1992).

Treatment

As *B. bronchiseptica* is a rarely reported infection, antimicrobial susceptibility data are limited to in vitro studies. In general, *B. bronchiseptica* is susceptible to aminoglycosides (gentamicin, tobramycin, and amikacin), antipseudomonal penicillins (ticarcillin and piperacillin), tetracyclines (tetracycline, doxycycline, and minocycline), ciprofloxacin, and chloramphenicol. In one study, all five strains were susceptible to imipenem (Standberg et al., 1983). There is variable susceptibility to cephalothin, ceftazidime, rifampin, and trimethoprim-sulfamethoxazole. The organism is generally resistant to penicillin, ampicillin, most cephalosporins, and erthromycin (Woolfrey & Moody, 1991). Studies have been small and have varied in methodology. Significant differences exist between automated susceptibility testing methods and those that follow the recommendations of the National Committee for Clinical Laboratory Standards (1997) for gram-negative aerobic bacilli.

Clinical cases have been treated with a variety of antimicrobial combinations. Most infected individuals have been successfully treated with 14 to 21 days of therapy. In-vitro susceptibility data have usually guided antimicrobial choices. One individual had persistent infection despite treatment but became free of infection following a prolonged course of antibiotics (>4 weeks) (Gueirard et al., 1995). Prolonged treatment may be prudent in patients who are severely immunocompromised.

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Parasites

KATHRYN N. SUH AND JAY S. KEYSTONE

Introduction

Infections caused by parasites are among the most prevalent diseases affecting humans, yet they are diagnosed relatively infrequently in the developed world. Both the rising popularity of international travel and the continued arrival of immigrants and refugees in developed nations have resulted in an increase in the frequency with which parasitic and other tropical diseases are encountered in these countries. Such infections, if untreated, may have severe consequences, including significant long-term morbidity or death. However, clinical manifestations of these infections are often absent, or may be protean and nonspecific and therefore unrecognized in developed countries. Although pulmonary symptoms are distinctly uncommon, parasitic etiologies of pulmonary disease should be considered in patients with appropriate exposure histories, as early treatment may reduce morbidity and mortality.

This chapter discusses the epidemiologic features of tropical pulmonary disease, and will outline an approach to the patient presenting with this problem. Selected parasitic causes of pulmonary disease are discussed, with emphasis on the epidemiology, clinical manifestations, diagnosis, and treatment of these disorders. One notable exclusion from this chapter is *Pneumocystis carinii,* which is discussed in detail elsewhere in this text.

KATHRYN N. SUH • Infectious Diseases, Department of Medicine, Queen's University, Kingston, Ontario, Canada K7L 3N6. **JAY S. KEYSTONE** • Tropical Disease Unit, Division of Infectious Diseases, The Toronto Hospital, University of Toronto, Toronto, Ontario, Canada.

Community-Acquired Pneumonia, edited by Marrie. Kluwer Academic/Plenum Publishers, New York, 2001.

Tropical Lung Disease

Epidemiology and Etiology

Acute pulmonary disease is common in the tropics. In Thailand, for example, an estimated 25% of both outpatient visits and hospital admissions are due to respiratory disease (Charoenratanakul, 1997), and statistics for African nations are similar (Steinhoff, 1991). Radiographic abnormalities are also common in hospitalized patients in the tropics, occurring in 16% of adults and 36% of children in one study, regardless of the reason for admission (Reeder & Palmer, 1980). In returned travelers evaluated for fever in specialized centers, respiratory infection is an uncommon final diagnosis and accounts for only 2.6% to 11% of febrile illnesses (MacLean et al., 1994; Doherty et al., 1995); however, those with typical upper respiratory tract infections are more likely to be assessed by a primary care physician. Respiratory symptoms may be manifestations of other systemic tropical infections in travelers, such as malaria, typhoid, and Q fever.

Bacteria, particularly *Streptococcus pneumoniae* (and *Haemophilus influenzae* in children), and viruses are responsible for most cases of pneumonia in the developing world. Shann (1986) summarized 13 studies in Africa, Asia, Oceania, and South America that attempted to determine the bacterial etiology of pneumonia in children using lung aspirates. Overall, 62% of bacterial cultures yielded pathogens, of which *S. pneumoniae* and *H. influenzae* were predominant. A small study in Gambia,

which included some adults, showed similar findings (Wall et al., 1986). In a review of nine studies in which viral pathogens were sought, 23% of children with pneumonia had culture or serologic evidence of a viral infection; 60% of these were due to respiratory syncytial, influenza, or parainfluenza viruses (Shann, 1986). With the exception of pneumonia, viruses are responsible for the majority of respiratory infections in the developed world; although studies are lacking, this is presumably also true in developing and tropical nations.

Other less familiar causes of pulmonary disease are endemic in particular geographic regions; these include bacteria such as *Pseudomonas pseudomallei* and *Pseudomonas mallei*, which cause melioidosis and glanders, respectively; fungi such as *Penicillium marneffei* and *Paracoccidioides brasiliensis;* and some viral causes of pulmonary disease such as viral hemorrhagic fevers (Table 1). Although some diseases such as pneumonic plague (*Yersinia pestis*), anthrax, and tuberculosis are widespread, they are more common in developing countries.

While some parasitic infections are restricted to specific geographic areas as a result of favorable climatic, socioeconomic, and ecologic factors, many are surprisingly widespread and may be found in industrialized countries. Parasitic causes of pulmonary disease are often overlooked. A compatible exposure history, and/or the presence of eosinophilia, should raise the possibility of a parasitic infection as the cause of respiratory symptoms or an abnormal chest radiograph, particularly in the absence of a response to conventional antimicrobial therapy.

Eosinophilia and Parasitic Infections

Eosinophilia is defined as an absolute eosinophil count of $\geq 450/mm^3$ in peripheral blood. In the returned traveler or immigrant, eosinophilia is often associated with an underlying parasitic infection, which may or may not be symptomatic but which nonetheless may require treatment. Review of pretravel bloodwork, if available, can be helpful in determining whether eosinophilia is travel-related.

TABLE 1. Geographically Restricted Causes of Pulmonary Infections

	North America	Central/South America	Caribbean	Europe	Middle East	Africa	Asia	Oceania
Bacterial infections								
Glanders		Occ			Occ	Occ		
Melioidosis		Very rare				✓	✓	✓
Plague	Very rare	Occ		Very rare		✓	✓	
Viral infections								
Hemorrhagic fevers				✓		✓	✓	
Fungal infections								
Blastomycosis	✓	Occ			Occ	✓	Occ	
Coccidioidomycosis	✓	✓						
Paracoccidioidomycosis	Mexico	✓						
Penicilliosis							✓	
Helminthic infections								
Echinococcosis	Southwestern U.S.	✓	✓	✓	✓	✓	✓	
Filariasis		✓	Haiti, DR			✓	✓	✓
Paragonimiasis	Mexico	✓		✓		✓	✓	✓
Schistosomiasis		✓	✓		✓	✓	✓	
Strongyloidiasis	Southeastern U.S., PR	✓	✓	South, east		✓	✓	✓
Protozoal infections								
Malaria		✓	Haiti, DR			✓	✓	✓

Occ, occasionally; PR, Puerto Rico; DR, Dominican Republic.

TABLE 2. *Noninfectious Causes of Eosinophilia*

Allergic diseases	Immunodeficiency syndromes
Allergic broncho-pulmonary aspergillosis	Wiskott–Aldrich syndrome
Allergic rhinitis	IgA deficiency
Asthma	Job's syndrome
Drug allergy, including eosinphilia-myalgia syndrome	Skin diseases
Gastrointestinal diseases	Pemphigus
Inflammatory bowel disease	Bullous pemphigoid
Neoplastic diseases	Atopic dermatitis
Lymphoma	Hypereosinophilic syndromes
Leukemia	Eosinophilic pneumonia and gastroenteritis
Adenocarcinomas (solid organ)	Hereditary eosinophilia
Rheumatologic diseases	Loeffler's syndrome
Churg-Strauss vasculitis	Pulmonary infiltrates with eosinophilia
Polyarteritis nodosa	Other causes
Rheumatoid arthritis	Hypoadrenalism
Wegener's granulomatosis	Serum sickness
	Sarcoidosis
	Irradiation
	Kimura's disease
	Idiopathic

While eosinophilia in these settings should prompt investigations for parasitic infection(s), other causes of elevated eosinophil counts should also be kept in mind (Table 2).

With few exceptions, parasitic infections in which eosinophilia occurs are caused by helminths; of the more common helminths are listed in Table 3.

TABLE 3. Helminthic Infections Causing Eosinophilia and Pulmonary Symptoms

Infection	Degree of eosinophilia[a]
Ascariasis	Mild; marked in larval phase
Echinococcosis	None to mild
Filariasis	Variable, usually moderate to marked
Tropical pulmonary eosinophilia	Marked
Gnathostomiasis	Moderate to marked
Hookworm	Mild to moderate
Paragonimiasis	Mild to marked
Schistosomiasis	Marked in early stage
Strongyloidiasis	Mild to marked (usually mild to moderate)
Trichinosis	Moderate to marked
Toxocariasis	Marked

[a]Mild: 450 to 1000 eosinophils/mm^3; moderate: 1000 to 3000 eosinophils/mm^3; marked: >3000 eosinophils/mm^3.

Protozoan infections, on the other hand, are not generally associated with eosinophilia. Since helminths produce eosinophilia during tissue migration and invasion, a specific parasitologic diagnosis is often not possible during this pre-patent period; weeks to months may be required before characteristic ova or microfilariae (larvae) can be detected in clinical specimens. Also, in some infections, eosinophilia may persist for several months after successful antihelminthic therapy (Klion et al., 1994).

The degree of eosinophilia is correlated with the extent of tissue invasion. While the majority of helminths cause mild (450 to 1000/mm^3) or moderate (1000 to 3000/mm^3) eosinophilia, absolute eosinophil counts greater than 3000/mm^3 are typically present in infections caused by *Trichinella spiralis, Toxocara canis,* and some filariae *(Wuchereria bancrofti, Brugia malayi, Loa loa, Onchocerca volvulus).* During the larval stage, *Strongyloides stercoralis, Ascaris lumbricoides,* and hookworm produce maximal eosinophilia that often resolves when migration is complete. However, the absence of eosinophilia does not rule out a helminthic infection. One classical example is disseminated strongyloidiasis in the immunocompromised host, where the eosinophil count is usually low or normal.

Approach to the Patient with Tropical Lung Disease

History and Physical Examination

A complete history and physical examination are essential in assessing the patient with a tropical lung disease. In addition to eliciting any associated symptoms, a detailed geographic history, the duration and dates of travel or residence abroad, the interval to development of symptoms, a thorough exposure history, and assessment of the immune status of the patient are all important factors to consider. Recent and current medications and underlying medical conditions should also be determined.

A careful geographic history can narrow the diagnostic possibilities (Table 1). Regions of travel or residence within each country should be determined since the risk of acquiring a given disease may vary within a country. Wilson's *A World Guide to Infections* (1991) can be very useful in determin-

ing the geographic extent of disease on a country-by-country basis. The dates of travel may define exposures to seasonal pathogens or epidemics, although seasonality may be altered or absent in tropical regions. The duration spent in specific areas affects the likelihood of contracting infection. Bacterial and viral infections and malaria often require only brief exposures, whereas filariasis and most cestode and trematode infections (with the exception of schistosomiasis) usually require prolonged exposure (>3 months). Tuberculosis, melioidosis, fungal infections, echinococcosis, and paragonimiasis may produce chronic symptoms, or may present many years after initial infection. Interestingly, the incidence of tuberculosis reactivation and invasive amoebiasis in immigrants from the developing world is greatest in the first few years after immigration to industrialized countries (Lyche et al., 1990; Centers for Disease Control and Prevention, 1998).

The exposure history is often the most important clue to the diagnosis of a tropical lung infection. Exposures to certain foods and impure water, insect vectors, animals, or other infected persons, in addition to specific environmental exposures, are associated with pathogens that may cause pulmonary disease (Table 4).

Immunocompromised hosts, including individuals who are infected with HIV or who have AIDS, transplant recipients, and those receiving chemotherapy or corticosteroids, are predisposed to pneumonia caused by *Pneumocystis carinii*, opportunistic fungi, *Toxoplasma gondii*, *Cryptosporidium*, and *Microsporidium*. *S. stercoralis* can produce overwhelming infection (hyperinfection syndrome) in these individuals, and in those with human T-cell lymphotropic virus (HTLV)-l infection, with a high mortality rate. Splenectomized and hypogammaglobulinemic individuals are at increased risk for infections due to encapsulated organisms, and in the case of the splenectomized patient, to babesiosis and malaria as well.

TABLE 4. Exposures to Parasites Affecting the Lung

Exposure	Parasitic infection
Untreated drinking water	Amoebiasis, cryptosporidiosis, microsporidiosis
Contaminated soil or food	Ascariasis, toxocariasis
Raw or undercooked fish	Capillariasis, gnathostomiasis, paragonimiasis
Raw or undercooked meat	Trichinosis, toxoplasmosis
Animal contact	Echinococcosis, toxoplasmosis
Vectors—mosquitoes	Dirofilariasis, filariasis, malaria
Freshwater exposure	Schistosomiasis
Barefoot walking	Hookworm, strongyloidosis

Finally, as in all patients, noninfectious causes of pulmonary symptoms such as congestive heart failure, primary lung diseases, and pulmonary manifestations of other systemic diseases must also be considered in patients who have been to the tropics.

Laboratory Investigations

A complete blood count and differential count should be performed, looking particularly for eosinophilia. Other investigations should be guided by the clinical, geographic, and exposure history, and physical findings. Thick and thin blood films should be performed whenever the diagnosis of malaria is considered. Cultures of blood, urine, and stool should be obtained if indicated (e. g., typhoid fever). Sputum samples should be obtained for bacterial, mycobacterial, and fungal cultures, and studies for *P. carinii* if appropriate. Examination of sputum for parasites is indicated in specific circumstances; paragonimiasis and occasionally other helminthic infections such as strongyloidiasis and echinococcosis can be diagnosed by recovery of characteristic larvae in sputum. Stool and/or urine samples are usually free of parasites at the time of pulmonary helminthic disease. However, identification of ova or larvae in stool specimens obtained weeks to months after a respiratory illness may allow a retrospective diagnosis to be made. Additional investigations, including serology (for amoebiasis, filariasis, paragonimiasis, schistosomiasis, strongyloidiasis, trichinosis, and toxocariasis), examination of blood and skin snips for microfilariae, and biopsy of other tissues may also be necessary.

Radiologic Investigations

Chest radiographs in patients with tropical lung diseases may reveal nonspecific pulmonary infiltrates or consolidation. Certain findings are suggestive of an underlying diagnosis, however.

Migratory pulmonary infiltrates of varying sizes that are associated with eosinophilia are characteristic of the larval phase of ascariasis, hookworm, and strongyloidiasis, tropical pulmonary eosinophilia caused by *W. bancrofti* or *B. malayi,* or paragonimiasis. Reticulonodular infiltrates may be seen in tropical pulmonary eosinophilia due to Bancroftian filariasis and schistosomiasis. Cavitary lung lesions are associated with tuberculosis and fungal infections (with the exception of blastomycosis and paracoccidioidomycosis) and may also be present in melioidosis, plague, paragonimiasis, and echinococcosis. Mycobacterial and fungal infections can also produce prominent hilar lymphadenopathy, as can some zoonoses such as tularemia or anthrax. Solitary or multiple pulmonary cysts are suggestive of echinococcosis. Coin lesions are characteristic of dirofilariasis. A pleural effusion may be seen in tuberculosis, paragonimiasis, and, when right-sided, pulmonary amoebiasis. Elevation of the right hemidiaphragm may suggest an underlying amoebic abscess of the liver.

Selected Parasitic Pulmonary Diseases

Helminthic Infections

Overview

Helminths, or parasitic worms, are classified into two major groups: nematodes (roundworms) and platyhelminths (flatworms). The latter comprises cestodes (tapeworms), which are segmented, and trematodes (flukes), which are not.

Helminths may produce pulmonary symptoms by three mechanisms: transgression of alveoli during larval migration in association with eosinophilia and pulmonary infiltration (Loeffler's syndrome) (Table 3); migration through the pulmonary vasculature (e.g., filariasis); or residence in the lung parenchyma as mature adult worms (e.g., paragonimiasis) or larval cysts (e.g., echinococcosis).

Nematode Infections

Ascariasis Ascariasis, caused by the nematode *Ascaris lumbricoides,* is among the most prevalent helminthic infections in the world, affecting more than 1.4 billion people worldwide (Crompton, 1988). Human infection has rarely been caused by the pig roundworm *Ascaris suum* (Phills et al., 1972). Tropical climates, overcrowding, and poor sanitation enhance the transmission of *Ascaris* by the fecal–oral route. Cases occurring in North America and Europe are largely in immigrants from endemic areas.

Eggs produced by mature female worms in the small intestine are excreted in stool. Fertilized eggs embryonate following weeks to months of development in soil, depending on environmental conditions. One to 2 days after ingestion of embryonated eggs, larvae hatch in the small bowel and penetrate the intestinal wall, entering the portal circulation. Within 2 weeks, larvae reach the pulmonary circulation and enter the alveoli, occasionally resulting in clinically apparent pulmonary disease. Larvae then ascend the tracheobronchial tree, are swallowed, and reach the small intestine, where they develop into mature adults and live for 10 to 12 months. Sexual maturation and egg production begin 3 to 4 months after initial infection.

Infection with *A. lumbricoides* is usually asymptomatic. Pulmonary symptoms, due to migration of larvae through the alveoli, are rare even in endemic areas (Spillman, 1975), although the exact incidence is difficult to determine. Clinical disease is more common in children, and with re-infection (Khuroo, 1996). A seasonal variation in pulmonary ascariasis has also been noted in some areas (Gelpi & Mustafa, 1967).

Pulmonary ascariasis is among the most common causes of Loeffler's syndrome (Spillman, 1975; Allen & Davis, 1994). Low-grade fever, chills, dyspnea, wheezing, and dry cough develop 5 to 26 days after ingestion of viable larvae. A productive cough and hemoptysis may occur with a higher parasite burden (Khuroo, 1996). Skin lesions, often urticarial, are present in approximately 15% of patients (Gelpi & Mustafa, 1968). Pulmonary symptoms are a result of hypersensitivity to *Ascaris* larvae, local inflammation, and bronchospasm (Sarinas & Chitkara, 1997). Chest radiographs show bilateral, migratory patchy infiltrates, often perihilar, of varying sizes (Gelpi & Mustafa, 1968). Marked peripheral eosinophilia is the rule. Eosinophils, Charcot–Leyden crystals, *and Ascaris* larvae may be seen in sputum, and larvae can also

be recovered in gastric aspirates. Since lung involvement precedes egg production by 8 to 10 weeks, stool examination for *Ascaris* ova is usually negative.

Ascaris pneumonia is self-limited. Symptoms and radiographic abnormalities improve in 1 to 2 weeks, but eosinophilia may persist for many weeks (Gelpi & Mustafa, 1968). Bronchodilators, antitussives, and rarely steroids may be required to control symptoms. Antihelminthic therapy is not beneficial in the pulmonary stage of disease, but is indicated to eradicate adult worms in the intestine. Mebendazole 100 mg twice daily for 3 days, albendazole 400 mg once, or pyrantel pamoate 11 mg/kg (maximum 1 g) are all effective oral agents.

Filariasis (Tropical Pulmonary Eosinophilia) Tropical pulmonary eosinophilia (TPE), also known as eosinophilic lung, tropical eosinophilia, and Weingarten's syndrome, refers to the pulmonary manifestations of infection with *W. bancrofti* or *B. malayi.*

The World Health Organization (1992) has estimated that almost 80 million people worldwide have filariasis, the majority caused by *W. bancrofti.* Filariasis is endemic in most tropical countries, where it is transmitted by mosquitoes; infection usually requires prolonged exposure in an endemic area. Although infection is common in early childhood, the prevalence of microfilaremia increases with age. Lymphatic filariasis, the most common manifestation, begins in the second decade of life and results in progressive lymphatic obstruction. TPE is a rare consequence of filarial infection, occurring in less than 1% of infected individuals (Marshall et al., 1998: Ong & Doyle, 1998). It is particularly common in India, Sri Lanka, Southeast Asia, Guyana, and South America, although cases have been reported in Africa, China, and the West Indies. TPE appears to be due to hypersensitivity to microfilariae; other factors that may predispose to TPE are unclear. Eighty percent of patients are male, most in their third and fourth decades (Udwadia, 1975).

The life cycles of *W. bancrofti* and *B. malayi* are similar. Infective larvae enter the human circulation at the time of a mosquito bite. Larvae (microfilariae) migrate to the lymphatics, mature to adult worms, and mate. Six to 12 months after infection, and for a duration of up to 10 years, microfilariae are released into the circulation, where they are ingested by night-biting mosquitoes to complete the cycle. In sensitized individuals with antifilarial antibodies, microfilariae are opsonized and carried to the pulmonary vasculature, where an IgE-mediated immune response results in TPE.

The absence of pulmonary symptoms is extremely rare in TPE. Udwadia (1975) found that 90% of patients have cough, typically worse at night, which may be associated with dyspnea or sputum production. Wheezing occurs in one quarter of patients. Constitutional symptoms are common, including fatigue (75%), weight loss (52%), and fever (35%). The illness may be present for weeks to months, remit, and recur (Neva & Ottesen, 1978). Physical findings may be absent in 25% of patients, but wheezing, adventitious breath sounds, or both are generally present on auscultation (Udwadia, 1975). Fluffy reticulonodular infiltrates in the mid- to lower-lung zones, a miliary pattern, or bibasilar vascular prominence are usually seen; in some series, hilar prominence and pleural thickening without effusion have been common (Ball, 1950; Khoo & Danaraj, 1960; Islam & Huque, 1965; Udwadia, 1975). Chest radiographs are normal in as many as 20% to 25% of patients with TPE (Islam & Huque, 1965; Udwadia, 1975). Marked eosinophilia is the rule, sometimes above 50,000/mm^3 (Udwadia, 1975). Total and filaria-specific levels of IgG and IgE are increased, with total IgE levels usually above 1000 U/mL (Neva et al., 1975). Pulmonary function tests initially show airway obstruction, but a restrictive pattern is more common with chronic infection. Eosinophils and Charcot–Leyden crystals may be noted in bronchoalveolar washings (Enzenauer et al., 1990).

The diagnosis of TPE is based on the symptoms, radiologic findings, markedly elevated eosinophil count, and filarial antibody titers in the setting of compatible exposure. In contrast to lymphatic filariasis, microfilariae are notably absent from day and night blood samples, but may be seen in lung biopsy specimens.

Although spontaneous remission can occur, TPE usually worsens without treatment and may progress to chronic pulmonary insufficiency or pulmonary hypertension (Udwadia, 1975; Enzenauer et al., 1990). Diethylcarbamazine (DEC) is the

treatment of choice; 6 mg/kg daily for 21 days kills both microfilariae and adult worms, and is well tolerated. A response to DEC can distinguish TPE from other eosinophilic pneumonias and is sometimes included in the case definition. Clinical improvement and a decrease in eosinophilia are seen after 7 to 10 days of treatment. Twenty percent of patients relapse and will require retreatment with 6 to 12 mg/kg of DEC daily, for 21 to 30 days (World Health Organization, 1992). Higher doses of DEC may produce nausea, vomiting, weakness, and dizziness. An immunologic reaction to microfilarial death may develop, with fever, malaise, anorexia, vomiting, wheezing, and arthralgias. In spite of effective treatment, chronic lung disease may develop in up to 25% of patients (Udwadia, 1975).

Hookworm Infections caused by the human hookworms *Ancylostoma duodenale, Necator americanus,* and rarely *A. ceylonicum* and *A. braziliense,* affect approximately 1 billion people worldwide (Hotez & Pritchard, 1995). Immigrants from endemic areas are frequently infected. Both species are found in varying degrees throughout Asia and Africa. *A. duodenale* is also endemic in South America, North Africa, southern Europe, and the Middle East, while *N. americanus* is found in the southeastern United States. Moist tropical climates, poor sanitation, and lack of footwear perpetuate transmission.

Adult hookworms in the small intestine produce eggs, which are shed in feces. In favorable soil conditions, larvae hatch rapidly and in 5 to 10 days develop into infective filariform larvae that penetrate intact skin, enter the bloodstream, and travel to the lungs, where they ascend the tracheobronchial tree and are swallowed. Once in the small intestines, larvae mature into adult worms. Egg production begins 6 to 8 weeks after infection; adult worms live for several years.

Pulmonary symptoms rarely occur as larvae migrate through the lungs, usually within 2 weeks of infection. Symptoms are not severe and may be preceded by dermatitis at the sites of larval entry. The diagnosis is suggested by a compatible exposure history, dermatitis, and eosinophilia. Chest radiographs are similar to those seen in ascariasis. Identification of larvae in sputum or gastric aspirates is diagnostic. Stool examinations for ova are invariably negative during the pulmonary phase of infection.

Hookworm pneumonitis is mild and self-limited. Treatment is symptomatic. Orally administered mebendazole, albendazole, or pyrantel pamoate are all effective treatments of the adult worm infection (see ascariasis).

Strongyloidiasis Infections with *S. stercoralis* (threadworm), although less prevalent than those caused by *Ascaris* or hookworm, are a more significant cause of morbidity and mortality, particularly in immunocompromised hosts. A unique feature of *Strongyloides* is its ability to replicate within the human host and cause overwhelming infection in susceptible individuals.

S. stercoralis is endemic in Asia, Africa, Central America, southern Europe, and the southeastern United States and Puerto Rico, where warm tropical soil conditions prevail. Immigrants and war veterans who have lived in endemic areas frequently have asymptomatic infection.

The life cycle of *S. stercoralis* is complicated (Fig. 1). It is the only nematode that can complete its life cycle entirely within humans, by internal and external autoinfection, or entirely in the soil (the free-living cycle). Penetration of skin by infective filariform larvae in soil is followed by larval entry into the circulation and migration to the lungs. Over the course of several days, larvae enter the alveoli, ascend the trachea, and are swallowed. Maturation into adult worms in the proximal small intestine leads to mating and egg production within the intestinal submucosa. Rhabditiform larvae that hatch in the small intestine are usually expelled in feces and develop into infective filariform larvae or adult worms in soil. However, rhabditiform larvae may rapidly transform into filariform larvae while still in the intestinal lumen. If this occurs, infective larvae may re-enter the circulation from within the bowel lumen (internal autoinfection) or through the perianal skin (external autoinfection) and reach the lungs. Either route of entry results in ongoing infection in the absence of additional exposure.

Pulmonary symptoms may occur in acute infection as larvae migrate through the lungs. The resulting clinical picture of Loeffler's syndrome is similar to that seen with *Ascaris* and hookworm, but seems to be quite uncommon. Prolonged infection

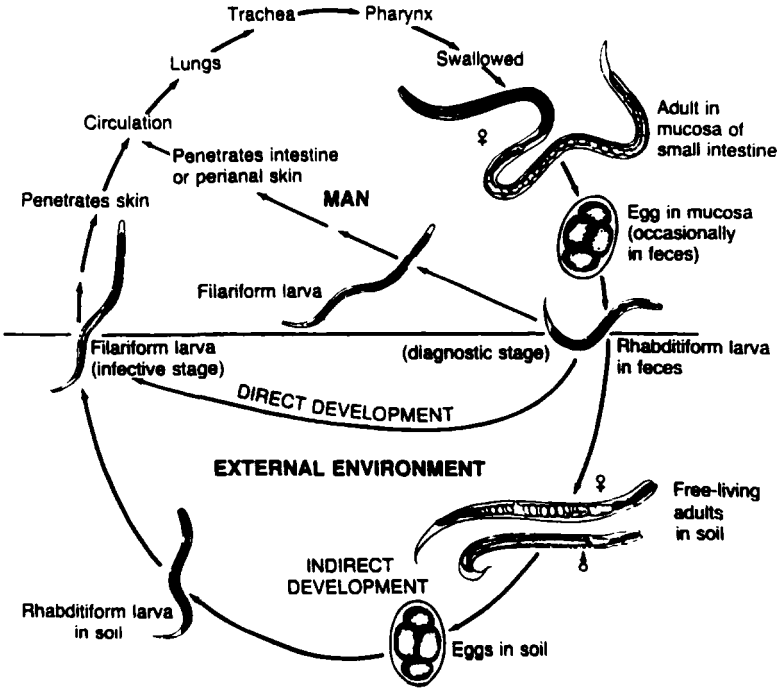

FIGURE 1. The life cycle of *Strongyloides stercoralis*. Reproduced from Melvin et al., 1964.

with *S. stercoralis* can cause wheezing and obstructive symptoms, which may be misdiagnosed as primary asthma (Bruno et al., 1982; Dunlap et al., 1984). Strongyloidiasis has also presented as a primary lung abscess, an eosinophilic pleural effusion, and restrictive lung disease (Ford et al., 1981; Lin et al., 1995; Goyal, 1998).

Clinically apparent pulmonary involvement by *Strongyloides* usually occurs in patients with hyperinfection syndrome, in which an overwhelming parasite burden is present in the lungs. Patients generally have compromised cell-mediated immunity as a result of advanced age, malignancy, or immunosuppression. Systemic corticosteroids, often in the setting of chronic lung disease, are well-documented risk factors. Histamine (H_2) blockers, antacid use, and prior gastric surgery have also been associated with pulmonary strongyloidiasis (Igra-Siegman et al., 1981; Davidson et al., 1984; Berk et al., 1987; Davidson, 1992; Woodring et al., 1996). In addition, hyperinfection has also been described in patients infected with HIV and HTLV-1 (Ferreira et al., 1999; Newton et al., 1992).

The hyperinfection syndrome is a manifestation of remotely acquired, asymptomatic infection. Pulmonary symptoms include productive cough, dyspnea, and wheezing; hemoptysis and chest pain are uncommon (Woodring et al., 1996). Concomitant gastrointestinal symptoms, including epigastric or abdominal pain, gastrointestinal bleeding, nausea, vomiting, or diarrhea, are present in 75% of patients; fever is seen in 25%, and rash or larva currens is rare (Woodring et al., 1996). Adult respiratory distress syndrome (ARDS) and respiratory failure may develop rapidly, necessitating mechanical ventilation. Secondary bacterial infections and sepsis, due to enteric pathogens that exit from the bowel along with migrating larvae, occur in up to 50% of patients and may contribute to respiratory compromise; secondary fungal infections are also common (Igra-Siegman et al., 1981; Woodring et al., 1996). Dissemination of larvae to the central nervous system, heart, thyroid, and other organs has been noted at autopsy (Igra-Siegman et al., 1981).

Pulmonary strongyloidiasis is rarely suspected but should be considered as a cause of respiratory

symptoms in an immunocompromised patient from an endemic area. Chest x-rays are usually abnormal; focal and diffuse pulmonary infiltrates are most common and may progress to ARDS. Pleural effusions are frequently present (in 40% of patients) but cavitary lesions are rare (Woodring et al., 1996). The diagnosis can be confirmed by identifying *Strongyloides* larvae, which are almost always present in stool. Sputum, bronchoalveolar washings, and lung biopsy specimens may also contain characteristic larvae. Eosinophilia is rarely a feature of hyperinfection (Ingra-Siegman et al., 1981; Davidson, 1992) and its absence should not be relied on to exclude the diagnosis.

The outcome of pulmonary strongyloidiasis is variable. With treatment, immunocompetent hosts and those with mild disease do well, but infection is fatal in 30% to 86% of immunocompromised patients (Igra-Siegman et al., 1981; Woodring et al., 1996). Early diagnosis and treatment optimize the chance of survival. Bacterial superinfections also contribute to mortality and must be treated appropriately.

Strongyloidiasis should always be treated, regardless of symptoms. Oral thiabendazole 25 mg/kg twice daily for 2 days, oral albendazole 400 mg twice daily for 7 days, or ivermectin 150 µg/kg once is adequate for uncomplicated infection, but 14 to 28 days of therapy may be required for hyperinfection. Thiabendazole may increase theophylline levels. Relapse rates may be as high as 15%; multiple follow-up stool examinations should be performed and retreatment may be necessary. Patients from endemic areas who are or will be immunosuppressed should be screened for strongyloidiasis and treated if screening is positive, or treated presumptively if screening is not possible. Serology using an enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence has a sensitivity and specificity of 85% to 95% (Liu & Weller, 1993). Serology is much more sensitive and specific than stool examination for screening, but results are often not available soon enough in urgent situations.

Toxocariasis Toxocariasis, infection by the dog roundworm *Toxocara canis* and to a much lesser extent the cat roundworm *Toxocara cati*, is common worldwide. Eighty percent of puppies and 20% of adult dogs in North America harbor *T. canis*, and the prevalence of eggs in soil is high (Shantz & Glickman, 1978). Human infection is most common in children less than 4 years, who place objects contaminated with soil in their mouths. Although rare, infections in adults have been well described (Glickman et al., 1987; Bartelink et al., 1993; Bourée et al., 1997).

Eggs excreted in animal feces embryonate in soil in 2 to 3 weeks. After ingestion of embryonated eggs by humans, larvae hatch in the small intestine, penetrate the mucosa, and travel to the liver. While some larvae remain in the liver, others migrate to the eye (ocular larva migrans) or to other organs including the lungs (visceral larva migrans [VLM]). When larvae are too large to pass through blood vessels, they exit and migrate into local tissues, where they may cause clinical symptoms. Development of adult worms and production of eggs do not occur in humans.

Larval migration through the lungs produces wheezing, dyspnea, or cough in 20% to 86% of symptomatic patients (Snyder, 1961; Huntley et al., 1965; Glickman et al., 1987). Respiratory failure requiring intubation may occur (Beshear & Hendley, 1973; Bartelink et al., 1993). Fever is rare in adults but is present in 55% to 80% of children; rash may also be present (Snyder, 1961; Huntley et al., 1965; Glickman et al., 1987). On examination, 40% have wheezes or crackles (Huntley et al., 1965). Radiologic abnormalities, evident in 40% of cases, include mild pulmonary and peribronchial infiltrates (Snyder, 1961; Huntley et al., 1965). Granulomas may form once acute infection has resolved. Marked eosinophilia is usually present.

Definitive diagnosis of VLM requires demonstration of larvae in tissue biopsies. A presumptive diagnosis is usually based on an appropriate exposure history and the clinical, radiologic, and laboratory findings. Serology (ELISA) is 72% sensitive and 92% specific and is often helpful in confirming the diagnosis (DeSavigny et al., 1979).

Although VLM is self-limited and generally benign, steroids may be required in severe infections (Beshear & Hendley, 1973; Bartelink et al., 1993). The benefit of antihelminthic drugs is unclear; oral diethylcarbamazine (2 mg/kg three times a day for 7 to 10 days) or albendazole (400 mg twice daily) or mebendazole (100 mg twice daily) for 5 days has been recommended.

Trichinosis Trichinosis (trichinellosis) is acquired by ingestion of raw or undercooked meat, usually pork, that contains *Trichinella spiralis* cysts. In the United States, the prevalence of trichinosis has been steadily decreasing and it is now uncommon (Bailey & Schantz, 1990). A simultaneous decline in porcine infection has also occurred. Trichinosis is still common in southern and eastern Europe, Asia, and Latin America, and in other countries where raw or undercooked pork is consumed and where raw garbage is used as pig feed. In developed nations, outbreaks of trichinosis have been associated with pork as well as wild boar, bear, walrus, and horse meat (Clark et al., 1972; Bouree et al., 1979; Margolis et al., 1979; Rodriguez-Osorio et al., 1990). Asymptomatic infection is common.

After consumption of infected meat, the larval cyst wall is digested in the stomach and the released larvae penetrate the small intestinal mucosa, where, within 1 week, they mature into adults, mate, and produce more larvae. Adult worms are expelled in feces within several weeks. The newly formed larvae enter the arterial circulation via the lymphatic system and are distributed to striated muscle, the only tissue in which they can survive. Approximately 3 weeks after infection, larvae encyst in muscle, where they may remain viable for many years.

With a high infectious load, gastrointestinal symptoms develop within 1 week of exposure. Invasion of striated muscle, including respiratory muscles and particularly the diaphragm, begins 7 to 9 days after exposure and lasts for up to 4 weeks. Facial and periorbital edema, myositis, and constitutional symptoms are common; a maculopapular rash, urticaria, or pruritus may be present. Dyspnea and painful respirations result from larval infiltration of respiratory muscles. Severe involvement may occasionally culminate in respiratory failure (Brashear et al., 1971; Compton et al., 1993; Clausen et al., 1996). Myocarditis and heart failure, which develop 4 to 8 weeks into the illness, and neurologic involvement may also contribute to respiratory failure and other pulmonary complications. Direct involvement of the lung parenchyma is rare. In a review of 856 cases of trichinosis in Poland, Januszkiewicz (1967) noted pulmonary involvement in 6.4%; pneumonia, pleural effusion, and spastic bronchitis were most common. Radiographic findings may include increased vascular markings, basilar consolidation or infiltrates, effusions, and rarely a miliary pattern.

Clinical features, a history of recent consumption of poorly cooked meat, and eosinophilia should raise suspicion of trichinosis. Confirmation of the diagnosis requires the demonstration of larvae in muscle biopsy, or may be provided by serologic tests. Serology may be negative early in infection and may need to be repeated.

Although death from trichinosis is rare, morbidity may be significant (Bailey & Schantz, 1986). High-dose steroids, in addition to symptomatic therapy, are recommended for cardiac, pulmonary, or neurologic involvement (Most, 1978). It is unclear whether antihelminthic therapy influences the course of illness and which treatment is most effective, although mebendazole or albendazole are usually recommended.

Trematode Infections

Paragonimiasis Paragonimiasis is a widespread disease caused by several species of the genus *Paragonimus.* The most well known, *P. westermani*, is also the most widely distributed and is endemic in Asia as well as some areas of Africa. In Mexico and Central and South America, *P. mexicanus* is the most common species. Ingestion of raw meat or juices from crabs or crayfish that contain encysted *Paragonimus* larvae is the usual route of infection.

Adult worms reside in the lungs, where they produce eggs that are either expectorated in sputum, or swallowed and excreted in stool. Maturation of eggs to infective larvae in fresh water requires two intermediate hosts—the freshwater snail and subsequently crayfish or crabs. Approximately 3 weeks after ingestion of infected crustaceans by mammalian hosts, immature flukes emerge in the duodenum and penetrate the bowel wall. They migrate through the peritoneum and diaphragm to the pleural space and lungs, causing acute inflammation. Once in the lungs, encapsulation in cystic cavities occurs. Mature adults develop within these cavities and produce eggs after 6 to 10 weeks. When cysts rupture, eggs are discharged in bronchioles, causing cough and hemoptysis. Encapsulated adult

worms may survive and reproduce in the lungs for many years, leading to chronic symptoms.

The spectrum of disease ranges from asymptomatic infection to chronic lung disease, which is often mistaken for bronchiectasis or tuberculosis. Early infection, as flukes enter the thorax, is rarely symptomatic but may cause pleuritic chest pain, cough, pulmonary infiltrates, and eosinophilia. Typically, however, patients present with a chronic cough productive of blood-tinged sputum, often beginning 6 months after initial infection (Shim et al., 1991; Yee et al., 1992). Massive hemoptysis is rare. Frequently associated symptoms include dyspnea (42%), chest pain that is usually pleuritic and intermittent (41%), and rarely fever (11%) (Shim et al., 1991). Most patients appear well despite chronic symptoms, and examination is usually unrevealing. Chest x-rays may be normal in up to 20% (Nana & Bovornkitti, 1991; Shim et al., 1991). Pleural disease, including effusions, hydropneumothorax, and pleural thickening, are found on 70% of x-rays (Kagawa, 1997). Bilateral pleural effusions, rare in tuberculosis, should raise suspicion of paragonimiasis in the appropriate setting. Multiple, low-density patchy infiltrates are present in 60% (Kagawa, 1997). Other parenchymal abnormalities include cystic lesions, cavities, linear densities, or pulmonary nodules that may be calcified (Fig. 2). Peripheral eosinophilia is often but not always present.

Detection of eggs in sputum is diagnostic. Sensitivity is low (30% to 40%) but may be increased with multiple sputum examinations or pooled sputum samples (Coleman & Root, 1981; Kagawa, 1997). Stool examination for ova is even less sensitive (10% to 25%). Pleural fluid is exudative and may be eosinophilic but rarely contains

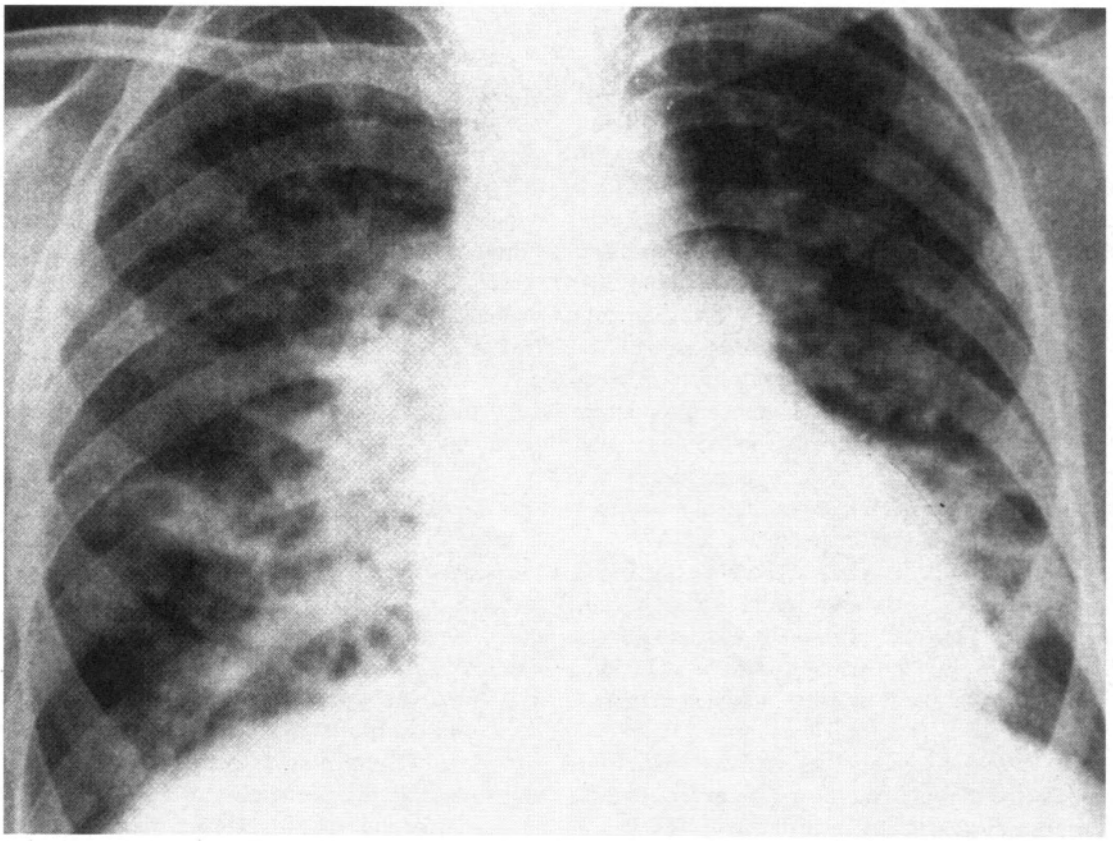

FIGURE 2. Severe paragonimiasis in a Korean male with numerous bilateral cavitary lesions (1–3 cm in size), chiefly in the middle and lower lung fields. Reproduced, with permission, from Reeder and Palmer, 1981.

eggs (Nana & Bovornkitti, 1991). Serologic tests by complement fixation or EL1SA are significantly more sensitive than parasitologic examination of specimens and are recommended when paragonimiasis is suspected.

Paragonimiasis is benign and easily treated with oral praziquantel, 25 mg/kg three times daily for 2 days. Clinical improvement is rapid, with a cure rate of >90% (Kagawa, 1997). Response to therapy can be confirmed by declining serologic titers and stool or sputum examination. Radiologic improvement is gradual, requiring up to 12 months for resolution; calcified granulomas may persist indefinitely. Rarely, surgical treatment may be required.

Schistosomiasis Two hundred million people worldwide are infected with schistosome species, and 200,000 deaths annually are attributable to schistosomiasis (Hopkins, 1992). Most infections are caused by three species of *Schistosoma* that are endemic in many countries. *Schistosoma mansoni* is found in Africa, the Middle East, South America, and the Caribbean; *S. japonicum* in southeast Asia, Japan, and China; and *S. hematobium* in Africa and the Middle East. Transmission of infection is not uniform within each area and is highest in regions with poor sanitation and limited water supply. Infection results from brief exposure to fresh water containing infective cercariae. In endemic areas, infection begins in infancy and peaks in pre-adolescent children. Adults in endemic regions are less commonly infected, in part because of acquired immunity.

After penetration of intact skin, cercariae become schistosomulae and enter the circulation. Within 1 week they reach the heart, lungs, and finally the liver, where they mature into adults within portal vessels. *S. mansoni* and *S. japonicum* migrate to the veins of the intestines, and *S. hematobium* to the vesical plexus, where they reside and mate. Four to 6 weeks after initial infection, eggs are produced, and excreted in stool or urine. Eggs that reach fresh water hatch to release miracidia, which penetrate the freshwater snail and emerge 3 to 5 weeks later as infective cercariae.

A history of cercarial-induced dermatitis may precede the earliest pulmonary symptoms, which occur as schistosomulae enter the lungs. In this rare condition, acute inflammation may produce transient fever dry cough, and dyspnea; wheezes and crackles may be audible on auscultation. Eosinophilia is common, and chest x-rays may reveal pulmonary infiltrates or mottling.

Katayama fever refers to the acute symptoms of schistosomiasis that develop 2 to 8 weeks after infection by *S. mansoni* or *S. japonicum. S. hematobium* rarely causes this syndrome (Lucey & Maguire, 1993). Symptoms are coincident with the onset of egg production and typically occur with heavy infections in nonimmune individuals (such as children and travelers), in whom they are felt to represent a hypersensitivity reaction to egg antigens (Hiatt et al., 1980). Fever malaise, weight loss, arthralgias, myalgias, and abdominal pain are prominent. Respiratory symptoms were present in 19 of 30 patients followed by Rocha et al. (1995). Dry cough, wheezing, dyspnea, and chest pain may be accompanied by pulmonary infiltrates or a miliary pattern on x-ray (Ritchken & Gelfand, 1954; Gelfand, 1966; Rocha et al., 1995). A cavitary lung lesion has also been reported in acute infection (Schaberg et al., 1991). Marked eosinophilia is generally present.

Since acute schistosomiasis occurs prior to excretion of eggs, initial stool (or urine) examinations are unhelpful. Eggs may be detected in subsequent specimens obtained several weeks later. Highly sensitive serologic tests (ELISA, immunoblot) are available but may be negative in early infection. Furthermore, a positive result may not distinguish between recent and remote infection. Therefore, the diagnosis is based on clinical presentation in a patient with recent freshwater exposure in an endemic area. Although not usually necessary, bronchoscopy or lung biopsy specimens may reveal ova (Bethlem et al., 1997).

Acute schistosomiasis is generally benign and self-limited. Treatment should be given, however, to prevent long-term complications. Praziquantel is the treatment of choice; 1 day of treatment (20 mg/kg for two doses for *S. mansoni* and *S. hematobium* and 20 mg/kg for three doses for *S. japonicum)* cures 75% to 100% of infections (Morris & Knauer, 1997). Nausea, vomiting, and abdominal pain may occur transiently after treatment. Steroids should be considered if infection is severe or refractory to antihelminthic therapy (Lucey & Maguire, 1993).

Chronic pulmonary schistosomiasis is a consequence of *S. mansoni* and to a lesser extent *S. japonicum* infection, occurring in 5% of infected individuals from endemic areas, and is rarely caused

by *S. hematobium* (Morris & Knauer, 1997). Eggs lodged in the hepatic venules lead to granulomatous inflammation, presinusoidal obstruction, and periportal fibrosis ("pipestem" or Symmer's fibrosis) in up to 20% of infected patients (Morris & Knauer, 1997). Portosystemic shunting allows eggs to be carried to the pulmonary vasculature, where they cause granulomatous arteritis and may ultimately led to pulmonary hypertension and cor pulmonale. Eggs may also reach the lungs in the absence of hepatic involvement, however. Intersitital lung disease and arteriovenous shunting may also occur with chronic infection (Bethlem et al., 1997). Previously untreated patients should receive praziquantel, although the benefit in chronic pulmonary infection is unknown (Morris & Knauer, 1997).

Cestode Infections

Echinococcosis Human echinococcosis is caused by four species of the dog tapeworm *Echinococcus.* Most cases are due to *E. granulosus* or, less commonly, to *E. multilocularis.* Infection with *E. vogeli* and *E. oligarthus*, a rare occurrence in Central and South America, is beyond the scope of this review.

E. granulosus is widely distributed throughout the world, particularly in sheep-herding regions (temperate regions of South America, Australia, New Zealand, southern Europe, and the former Yugoslavia). Dogs and other canids are definitive hosts, harboring the adult worm, whereas sheep, pigs, cattle, horses, and other mammals act as intermediate hosts containing the cystic larval stage; humans are accidental intermediate hosts. Regional differences in cultural and religious beliefs and farming practices result in a highly variable prevalence of disease: from 3.4 to >200 cases per 100,000 in Algeria and northern Kenya, respectively (Bhatia, 1997). A wild (sylvatic) cycle exists in northern climates (e.g., *E. granulosus var. canadensis),* involving hunting dogs and wolves as definitive hosts and moose, caribou, and reindeer as intermediate hosts.

Adult worms, consisting of two to five proglottids, reside in the small intestine of the dog. The terminal proglottid is shed in feces and releases eggs. Dogs may release over 1 million eggs daily (Kammerer & Schantz, 1993). Eggs ingested by an intermediate host or human hatch in the small intestine and release an onchosphere, which penetrates the intestinal wall and enters the portal circulation to reach the liver; hematogenous spread may occur directly to other organs. Relatively few onchospheres continue past the liver and travel to the lungs, or rarely to other organs. Once deposited in an organ, onchospheres evolve to form larval cysts containing infective protoscolices that grow approximately 0.5 to 1 cm per year and may bud internally to produce daughter cysts. The cycle is completed when viscera containing cysts are consumed by dogs, and protoscolices develop into adult tapeworms.

Most infections with *E. granulosus* are asymptomatic and are discovered incidentally by radiography or ultrasound. Symptomatic disease usually presents many years after infection and results from the mass effect of the cysts.

The lungs are involved in 30% of cases. In a review of 11 case series of pulmonary disease, Bhatia (1997) noted that most cases occurred in the second and third decades, one third of cases involved multiple or bilateral cysts, and 60% of cysts were right-sided. Disease was asymptomatic in 68% of cases, and particularly in the sylvatic form. Cough, hemoptysis, dyspnea, and fever were present in up to 69% of cases. Cysts may rupture into bronchi, sometimes with expectoration of cyst contents and membranes, or into the pleural space with a resultant pleural effusion. Anaphylaxis with intrapulmonary rupture is rare (0.3% to 7.5% of cases) (Bhatia, 1997).

E. granulosus infections, or cystic hydatid disease, should be suspected on the basis of historical, clinical, and radiologic features. Eosinophilia is present in up to 40% of patients. Chest x-rays show a pulmonary mass lesion in 50% to 60% of cases (Bhatia, 1997) (Fig. 3). Other radiographic findings may include evidence of fistula formation, a "crescent" or "meniscus" sign, and fluid-filled cavities; calcification is rare (Ramos et al., 1975; Beggs, 1985; von Sinner, 1991). Computed tomography and MRI imaging may be used to define cyst anatomy and the extent of disease, to detect unsuspected lesions, and to monitor for recurrence after treatment (Gouliamos et al., 1991; von Sinner, 1991; von Sinner et al., 1991). The serologic response to infection is influenced by host factors as well as the number, integrity, viability, and location of cysts (Kammerer & Shantz, 1993; Bhatia, 1997). Anti-

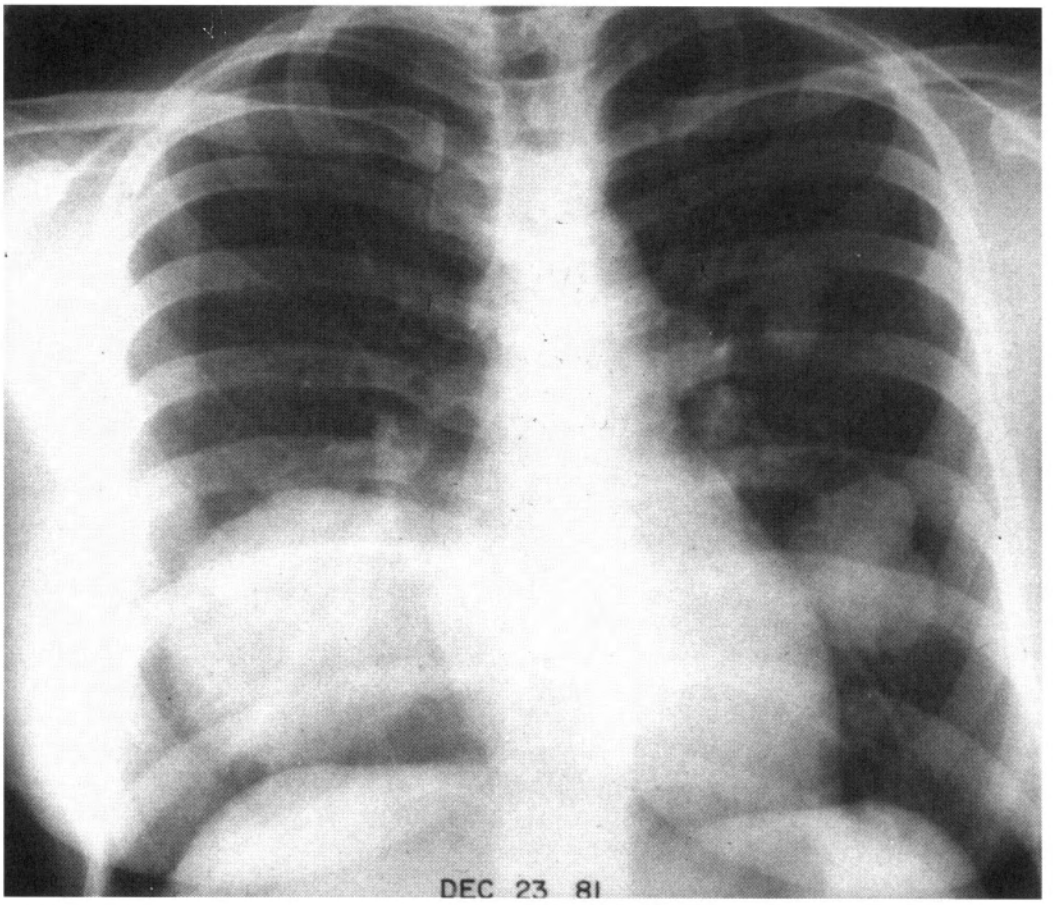

FIGURE 3. Multiple *E. granulosis* cysts found on the routine chest x-ray of a 25-year-old asymptomatic Lebanese woman.

body response is poor in children, with lesions outside of the liver (including the lungs), and with cysts that are solitary, intact, or dead. The suboptimal sensitivity and specificity of these tests warrant caution when interpreting the results. Finally, although therapeutic percutaneous aspiration of liver cysts has become commonplace (von Sonnenberg et al., 1994), pulmonary cyst aspiration is not generally recommended for diagnosis because of the possible risk of anaphylaxis (Kammerer & Shantz, 1993) and spillage of viable protoscolices. However, one small case series found the procedure to be effective, but associated with complications in almost one third of cases (Akhan et al., 1994).

Treatment goals include the elimination of parasites, prevention of cyst rupture, and preservation of involved organs. Surgery, the treatment of choice, leads to few complications and has the best prognosis, with cure rates of up to 90% (Kammerer & Shantz, 1993; Bhatia, 1997; Salih et al., 1998). The recurrence rate is 2% to 10%. Medical therapy is reserved for patients who refuse or are poor candidates for surgery. Albendazole (10 mg/kg per day) or mebendazole (40 to 50 mg/kg daily) for 3 to 6 months has an overall cure rate of 30% and provides symptomatic improvement in 40% to 70% of patients; because of its superior absorption, albendazole is more effective (Davis et al., 1989; Todorov et al., 1992; Nahmias et al., 1994). The optimal duration of antihelminthic therapy is unknown. Regardless of treatment, all patients should be followed clinically, radiologically, and serologically for recurrence, for at least 10 years (Kammerer & Schantz, 1993).

In view of the low risk of complications and the benign nature of the infection, surgical and drug therapy of sylvatic cystic hydatid disease is unnecessary in asymptomatic individuals (Finlay & Speert, 1992).

E. multilocularis infection or alveolar hydatid disease, has been documented in northern Europe, the former Soviet Union, China, Alaska, southwestern Canada, and the northern United States—areas inhabited by the Arctic and red fox. Other definitive hosts include coyotes and wolves. Mice, voles, and other rodents are intermediate hosts.

Disease is most commonly diagnosed in adults >50 years of age who have lived in an endemic area. Symptoms occur years to decades after infection. The liver is always involved; pulmonary disease, usually a result of hematogenous spread, occurs in less than 2% of cases (Bhatia, 1997). Abdominal symptoms are predominant, and respiratory complaints are rare; dyspnea, the most common, is present in less than 10% of patients (Wilson & Rausch, 1980). Chest x-rays may show multiple peripheral, nodular lung lesions consistent with hematogenous dissemination, or involvement of the right lower lobe by contiguous spread (Treugut et al., 1980). Solid lesions with necrosis and calcification are the most frequent CT findings (Didier et al., 1985). Serology is positive in 90% of patients and is specific; titers are usually high.

Without therapy, *E. multilocularis* infection is uniformly fatal. Surgery with wide excision of infective tissue can be curative and is the preferred treatment, but is often not possible because of extensive disease at the time of diagnosis. In such cases, albendazole or mebendazole, used indefinitely, can improve symptoms and prolong survival (Wilson et al., 1992). As in cystic disease, close follow-up for disease progression and recurrence is imperative.

Protozoal Infections

Amoebiasis

Epidemiology *Entamoeba histolytica/dispar* complex infects an estimated 10% of the world's population and is the third most common cause of death due to parasitic infection, preceded only by malaria and schistosomiasis (Guerrant, 1986; Reed, 1992). *E. histolytica,* distributed worldwide, is especially prevalent in tropical areas where poor personal hygiene and sanitation facilitate fecal-oral spread. Humans are the primary reservoir. Males and females are infected at equal rates, although extraintestinal disease has a striking male preponderance and commonly develops in recent immigrants from endemic areas (Ibarra-Perez, 1981; Adeyemo & Aderounmu, 1984; Lyche et al., 1990; Chuah et al., 1992; Reed, 1992). The risk of invasive disease, including colitis, is increased in children, pregnant women, and those receiving steroids (Reed, 1992). In developed countries, the prevalence of asymptomatic infection is high, and it is more common in the institutionalized and in homosexual men. This finding can be ascribed to infection with *E. dispar,* a nonpathogenic species that is morphologically identical to *E. histolytica* and can only be distinguished by serology or DNA and antigen detection methods (Jackson & Ravdin, 1996). It is estimated that, globally, 85% of *E. histolytica* are actually *E. dispar.*

Life Cycle Ingestion of the relatively hardy cysts of *E. histolytica* is followed by excystation in the distal small intestine and leads to development of trophozoites that colonize the large bowel, particularly the cecum. Trophozoites invade the intestinal wall and disseminate to extraintestinal sites, most commonly the liver and rarely to other organs; those that are carried to the rectum evolve into cysts that are subsequently shed in feces.

Clinical Syndromes Ninety percent of amoebic infections are asymptomatic (Reed, 1992). Gastrointestinal manifestations include colitis, bowel perforation, or formation of an intestinal mass (amoeboma) or stricture. Amoebic liver abscesses usually develop in the right lobe of the liver, leading to acute or subacute onset of constitutional symptoms, weight loss, and right upper quadrant pain. Stool specimens are positive for *E. histolytica* in less than one fifth of cases of liver abscess.

Pleuropulmonary Disease Virtually all cases of pleuropulmonary amoebiasis occur in patients with a hepatic abscess, and up to 75% of patients with an abscess will have pleuropulmonary involvement (Adams & MacLeod, 1977; Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche

et al., 1990). Insidious extension or acute rupture of a hepatic abscess into the pleural space or lung often leads to the development of a dry or productive cough, hemoptysis, dyspnea, and pleuritic or right shoulder pain. Acute, tearing pleuritic chest pain or respiratory distress occurs with rupture. "Anchovy-paste" or "chocolate sauce" sputum is pathognomonic of a hepatopulmonary fistula (Adeyemo & Aderounmu, 1984). Evidence of consolidation or pleural effusion, almost always right-sided, is present in over 75% of patients (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990). Fever, hepatomegaly, and hepatic tenderness are also common. Chest radiographs are abnormal in over 50% of patients (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990). Right pleural effusion is the most frequent finding, but right hemidiaphragmatic elevation, or right lower-lobe atelectasis or consolidation may be seen. Left-sided abnormalities and cavitary lesions are rare. Leukocytosis without eosinophilia is the rule.

The diagnosis is made largely on clinical suspicion. Stool, sputum, and pleural fluid rarely contain trophozoites or cysts. Serologic tests are useful for diagnosis and are positive in >90% of patients with amoebic abscess (Reed, 1992).

Metronidazole is highly effective treatment, with cure rates of >95% in hepatic and pulmonary disease (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990; Reed, 1992). A 5-day course (750 mg orally or intravenously every 8 hours) should be followed by iodoquinol 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for 10 days, to eliminate cysts in the intestinal lumen. Recent studies have shown identical cure rates with one to three doses of metronidazole (2 to 2.5 grams daily in a single dose) followed by a lumen-active agent (Irusen et al., 1992). Rarely thoracentesis, chest tube drainage, or other surgical intervention may be indicated for severe or refractory symptoms.

Cryptosporidiosis

Cryptosporidium species are widely distributed intracellular parasites that have a broad host range. They have been increasingly recognized as a cause of acute diarrheal illness in children and travelers. In patients with AIDS and other immune deficiency states, *Cryptosporidium* can cause intractable diarrhea and disseminated disease that may be life-threatening. The prevalence of cryptosporidial infection varies; up to 10% of diarrheal illness in the tropics may be caused by *Cryptosporidium* (Griffiths, 1998), and an estimated 3% to 4% of AIDS patients in North America are infected (Sorvillo et al., 1994). Infection results from ingestion of oocysts, and transmission occurs via person-to-person or water-borne spread.

Respiratory symptoms may be common in the presence of cryptosporidial diarrhea (Griffiths, 1998). In AIDS patients, *Cryptosporidium* has been detected in sputum in the absence of respiratory symptoms (Lopez-Velez et al., 1995) and rarely has been identified as a cause of pneumonia (Lopez-Velez et al., 1995; Mohri et al., 1995; Clavel et al., 1996; Dupont et al., 1996). The pathogenesis of pneumonia is unclear, but it may be a result of aspiration of parasites from the gastrointestinal tract rather than hematogenous dissemination or contiguous spread (Mohri et al., 1996). Pneumonia in immunocompromised hosts usually occurs in association with gastrointestinal disease but may be isolated (Lopez-Velez et al., 1995; Clavel et al., 1996). Diarrhea and cough are present in >75% of patients, and dyspnea, sputum production, and fever are common. Chest x-rays are nonspecific, showing infiltrates or interstitial disease (Lopez-Velez et al., 1995; Dupont et al., 1996).

Cryptosporidial pneumonia may be diagnosed by demonstrating oocysts in sputum or bronchoalveloar lavage specimens in the presence of compatible symptoms. Other pathogens are often identified simultaneously, leading to uncertainty regarding the role of *Cryptosporidium* in these cases. Successful treatment of pneumonia has been reported with inhaled paromomycin and systemic azithromycin (Mohri et al., 1995; Dupont et al., 1996).

Malaria

Epidemiology Malaria is the most important parasitic infection in the world. Each year, 300 to 500 million people are infected, most in Africa, and 1 to 2 million die. Endemic areas include Africa, Asia, Oceania, and Central and South America. Cases in nonmalarious areas are usually imported by travelers and immigrants. Malaria is transmitted by night-biting species of *Anopheles* mosquitoes

and is caused by four species of *Plasmodium. P. falciparum* is the most severe form, responsible for 40% to 60% of infections but >95% of malaria deaths (Hoffman, 1992). *Plasmodium vivax* causes the majority of non-falciparum malaria, with few cases due to *Plasmodium ovale* and *Plasmodium malariae* infection.

Pulmonary Manifestations Symptoms of falciparum malaria usually develop within 6 weeks of departure from an endemic area. Fever, chills, malaise, headache, and myalgia are prominent. Pulmonary symptoms, most often but not exclusively seen in *P. falciparum* infection, are thought to be caused by alterations in pulmonary vascular flow. Fewer than 20% of patients have cough, and less than 5% complain of dyspnea, wheezing, or chest pain on presentation (Froude et al., 1992; Gozal, 1992; Winters & Murray, 1992; Svenson et al., 1995). Chest radiographs may be normal or demonstrate increased vascular markings or variable infiltrates (Cayea et al., 1981; Gozal, 1992). Bilateral pleural effusions have also been described (Cayea et al., 1992). In severe and potentially fatal infections (greater than 5% parasitemia), noncardiogenic pulmonary edema is common and results from increased pulmonary capillary leakage. ARDS associated with severe infections is likely immune-mediated and tends to occur 2 or 3 days after treatment is initiated, when blood parasitemia is decreasing (Feldman & Singer, 1987).

The diagnosis of malaria is confirmed by detection of intraerythrocytic parasites on thick and/or thin smears. Treatment should be administered promptly, specific therapy depending on the species identified. *P. falciparum* malaria should be treated with 5 to 7 days of quinine in combination with 7 days of doxycycline; both can be administered orally or intravenously. Noncardiogenic pulmonary edema is managed no differently from that which occurs with other conditions. Mortality from falciparum malaria is less than 4%, although severe malaria is fatal in 20% or more of cases (Greenberg & Lovel, 1990; Warrell et al., 1990).

Microsporidiosis

Microsporidia are ubiquitous, obligate intracellular parasites that infect a wide variety of hosts through the ingestion of spores. Most infections in humans are caused by *Enterocytozoon bieneusi* and *Encephalitozoon* species. On the basis of seroprevalence surveys, immunocompetent hosts are frequently infected (van Gool et al., 1997); 7% to 50% of AIDS patients are infected (Didier, 1998) and present most commonly with chronic diarrhea.

Pneumonia attributed to microsporidia has been reported mainly in AIDS patients, most of whom also have microsporidial diarrhea (Gunnarsson et al., 1995; Remadi et al., 1995; Georges et al., 1998). Pneumonia without evidence of infection in other sites has also been reported (Scaglia et al., 1997), and disseminated microsporidiosis with lung involvement has occurred following bone marrow transplantation (Kelkar et al., 1997). Symptoms include cough, dyspnea, and fever, sometimes accompanied by interstitial infiltrates on chest x-ray. Diagnosis has been based on identification of spores in sputum or bronchoalveolar lavage specimens, especially in the absence of other pathogens. Treatment with albendazole has not been consistently effective.

Toxoplasmosis

Epidemiology *Toxoplasma gondii* is ubiquitous and causes infection in a variety of mammals, including humans. It is estimated that globally, 50% of people have been infected, although the seroprevalence varies worldwide (Campagna, 1997). In developing nations, infection most often occurs early in childhood due to contact with contaminated soil, while in developed countries seroprevalence rates are lower and infection occurs later in life, as a result of consumption of infected, poorly cooked meat (Frenkel, 1991), or contact with cats.

The Organism *T. gondii* exists in three forms: oocyst, tachyzoite, and bradyzoite. The oocyst, containing sporozoites, is the product of sexual reproduction, which occurs only in the small intestine of the definitive host, the cat. Oocysts are shed in cat feces in large quantity and must mature in soil before they become infective. Intermediate hosts (usually birds and rodents) and humans may acquire infection by ingesting oocysts. Tachyzoites are seen in acute infection and can invade most cell types. Once in tissue, *T. gondii* survives for the lifetime of the host in an encysted form containing bradyzoites. Cysts are found mostly in skeletal

muscle, heart, eye, and brain. Humans are usually infected by ingesting these tissue cysts in raw or poorly cooked meat, but transmission can occur transplacentally, by organ transplantation, or by white blood cell transfusion.

Pulmonary Toxoplasmosis The exact incidence of pulmonary toxoplasmosis is unknown but has increased with the advent of AIDS (Catterall, 1986). Most cases of pulmonary disease develop in immunocompromised hosts, but immunocompetent hosts may also be affected (Pomeroy & Filice, 1992). Patients with AIDS or hematologic malignancy and organ transplant recipients are at highest risk (Israelski & Remington, 1993). Pneumonia is usually due to reactivation of latent infection (Derouin et al., 1992; Campagna, 1997), but it may occur with primary infection in AIDS, or with transplantation of an organ from a seropositive donor to a seronegative recipient (Luft et al., 1983; Renold et al., 1995). Evidence of disseminated infection is frequently present in immunocompromised patients (Derouin et al., 1992).

Transplant patients develop toxoplasmic pneumonia in the first 6 months after transplant (Derouin et al., 1992). The clinical presentation and radiologic findings are nonspecific. The most common symptoms are dyspnea (26% to 83%) and cough (22% to 100%), and fever is almost always present (Oksenhendler et al., 1990; Pomeroy & Filice, 1992; Schnapp et al., 1992). Crackles, wheezes, and other pulmonary findings are uncommon, but patients may be severely hypoxic. Diffuse interstitial infiltrates are the most frequently observed radiographic finding, although lobar consolidation, pleural effusion, nodular densities, and cavitation have all been reported.

The diagnosis is difficult to establish on the basis of clinical and radiologic findings and is often only made at autopsy. A 4-fold rise in *Toxoplasma* IgG titer or detection of new IgM antibodies supports the diagnosis of acute infection, but many immunocompromised patients cannot generate an antibody response, or the titer may be maximal at presentation. Demonstration of *T. gondii* in bronchoalveolar washings, or histology showing both tachyzoites and evidence of acute inflammation, are diagnostic.

Of those with *Toxoplasma* pneumonia, 25% to 50% die (Oksenhendler et al., 1990; Pomeroy & Filice, 1992; Schnapp et al., 1992). Pyrimethamine combined with sulfadiazine is the treatment of choice, with folinic acid supplementation to reduce bone marrow suppression. Clindamycin may be substituted for sulfadiazine in sulfa-intolerant patients. Relapse is inevitable in immunocompromised patients if treatment is stopped, necessitating lifelong suppressive therapy.

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