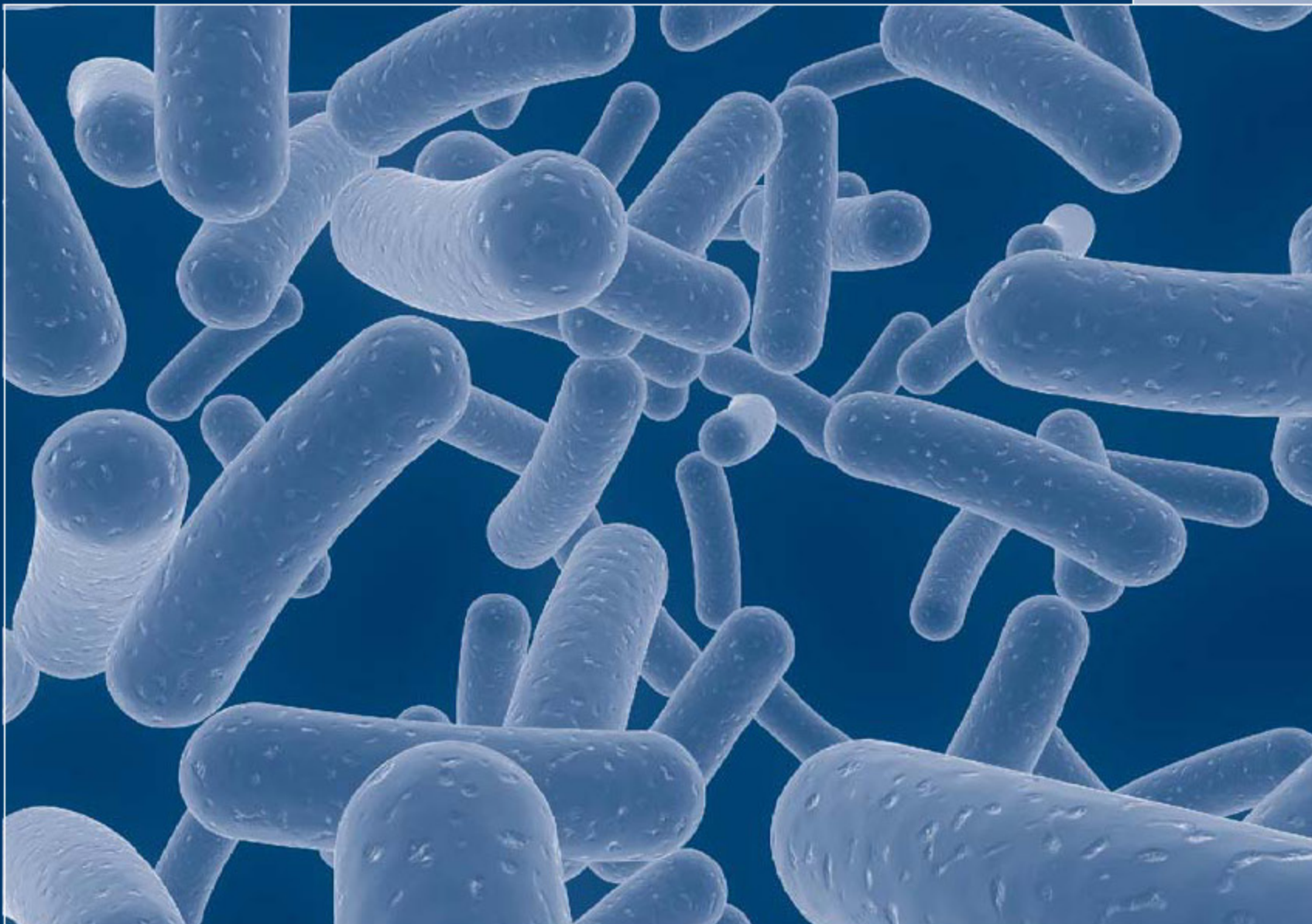


INFECTIOUS DISEASE  
AND THERAPY SERIES

Volume 51

# Infectious Diseases in Critical Care Medicine

*Third Edition*



Edited by  
**Burke A. Cunha**

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healthcare

Infectious  
Diseases in  
Critical Care  
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# Infectious Diseases in Critical Care Medicine

*Third Edition*

Edited by

**Burke A. Cunha**

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*for  
Marie*

*Peerless wife and mother,  
Provider of domestic peace and tranquility,  
Paragon of truth and beauty,  
Paradigm of earthly perfection . . .*

*With gratitude for her love and constant support.*





# Foreword

In the United States during the 1950s, the development of mechanical ventilation led to the organization of special units in hospitals, where health care personnel with specific expertise could efficiently focus on patients with highly technical or complex needs. Over the ensuing years the sickest patients as well as those needing mechanical ventilation were grouped into special care units. In 1958, Baltimore City Hospital developed the first multidisciplinary intensive care unit. The concept of physician coverage 24 hours a day, seven days a week became a logical approach to providing optimal care to the sickest, most complex patients.

Now, 50 years after the first multidisciplinary intensive care unit was opened, there are now 5000 to 6000 intensive care units in the United States: Over 4000 hospitals offer one or more critical care units, and there are 87,000 intensive care unit beds. Critical care represents 13.3% of hospital costs, totaling over \$55 billion per year.

Health care providers are well aware of the role that infections play in the intensive care unit. A substantial number of patients are admitted to the intensive care unit because of an infection such as pneumonia, meningitis, or sepsis. A substantial number of patients admitted to intensive care units for noninfectious disorders develop infections during their stay. Thus, intensivists need expertise in the diagnosis, treatment, and prevention of infectious diseases. Management of infections is pivotal to successful outcomes.

In this third edition of *Infectious Diseases in Critical Care Medicine*, Burke Cunha has organized 31 chapters into an exceedingly practical and useful overview. Providers often find it surprisingly difficult to distinguish infectious and noninfectious syndromes, especially when patients have life-threatening processes that evoke similar systemic inflammatory responses. Part I and Part II provide many clinical pearls that help with diagnosis and with developing a strategy for initial patient management. Specific chapters focus on special intensive care unit problems, such as central venous catheter infections, nosocomial pneumonias, endocarditis, and *Clostridium difficile* infection. Particularly useful are chapters on special populations that many clinicians rarely encounter: tropical diseases, cirrhosis, burns, transplants, or tuberculosis. Chapters on therapy also provide practical advice focused on critically ill patients, in whom choice of agent, toxicities, drug interactions, and pharmacokinetics may be substantially different from patients who are less seriously ill.

Critical care medicine is becoming more and more technology based. Genomics and proteomics can predict susceptibility to various diseases and drug metabolic problems. Patients can be assessed by ultrasonography to supplement physical examination. Diagnostic biopsies can be performed on virtually any organ. Invasive arterial and venous monitoring as well as monitoring of central nervous system and cardiac activity is commonplace.

Despite these advances in technology, knowledge of differential diagnosis, natural history, and therapeutic options is still essential. To understand these processes, Burke Cunha has assembled an impressive team of experienced clinicians to provide insight into the infectious challenges of critical care medicine. This edition continues to provide relevant, current information that will enhance clinical practice with this growing segment of hospitalized patients.

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# Preface to the First Edition

Infectious diseases are very important in critical care. In the critical care unit, infectious diseases are seen in the differential diagnoses of the majority of patients, and maybe patients acquire infections in the critical care unit. However, infectious disease is accorded a relatively minor place in most critical care textbooks and does not receive the emphasis it deserves given its presence in the critical care unit.

The infectious diseases encountered in the critical care setting are some of the most severe and often difficult to diagnose. This book was developed for critical care practitioners, the majority of whom are not trained in infectious diseases. It is written by clinicians in infectious diseases in critical care and is meant as a handbook to provide valuable information not included in critical care textbooks.

The text is unique in its emphasis and organization. It comprises four main sections: The first section deals with general concepts of infectious diseases in the critical care unit; the second deals with infectious diseases on the basis of clinical syndromes; the third deals with specific infectious disease problems; and the fourth, with therapeutic considerations in critical care patients.

One of the unique features of this book is its emphasis on differential diagnosis rather than therapy. The main problem in the critical care unit is not therapeutic but diagnostic. If the patient's problem can be clearly delineated diagnostically, treatment is a relatively straightforward matter. Therapy cannot be appropriate unless related to the correct diagnosis. *Infectious Diseases in Critical Care Medicine* emphasizes the importance of differential diagnoses in each chapter and includes chapters on various "mimics" of infectious diseases. In fact, it is with the "mimics" of various infectious disorders that the clinician often faces the most difficult diagnostic challenges. This book should help the critical care unit clinician readily discern between infectious diseases and the noninfectious disorders that mimic infection.

This is the first and only book that deals solely with infectious diseases in critical care medicine. It is not meant to be a comprehensive textbook of infectious diseases. Rather, it focuses on the most common infections likely to present diagnostic or therapeutic difficulties in the critical care setting. The authors have approached their subjects from a clinical perspective and have written in a style useful to clinicians. In addition to its usefulness to critical care intensivists, this book should also be helpful to internists and infectious disease clinicians participating in the care of patients in the critical care unit.

Burke A. Cunha

## Preface to the Second Edition

Infectious diseases continue to represent a major diagnostic and therapeutic challenge in the critical care unit. Infectious diseases maintain their preeminence in the critical care unit setting because of their frequency and importance in the critical unit patient population.

Since the first edition of *Infectious Diseases in Critical Care Medicine*, there have been newly described infectious diseases to be considered in differential diagnosis, and new antimicrobial agents have been added to the therapeutic armamentarium.

The second edition of *Infectious Diseases in Critical Care Medicine* continues the clinical orientation of the first edition. Differential diagnostic considerations in infectious diseases continue to be the central focus of the second edition.

Clinicians caring for acutely ill patients in the CCU are confronted with the common problem of differentiating noninfectious disease mimics from their infectious disease counterparts. For this reason, the differential diagnosis of noninfectious diseases remain an important component of infectious diseases in the second edition. The second edition of *Infectious Diseases in Critical Care Medicine* emphasizes differential clinical features that enable clinicians to sort out complicated diagnostic problems.

Because critical care unit patients often have complicated/interrelated multisystem disorders, subspecialty expertise is essential for optimal patient care. Early utilization of infectious disease consultation is important to assure proper application/interpretation of appropriate laboratory tests and for the selection/optimization of antimicrobial therapy. Selecting the optimal antimicrobial for use in the CCU is vital. As important is the optimization of antimicrobial dosing to take into account the antibiotic's pharmacokinetic and pharmacodynamic attributes. The infectious disease clinician, in addition to optimizing dosing considerations is also able to evaluate potential antimicrobial side effects as well as drug-drug interactions, which may affect therapy. Infectious disease consultations can be helpful in differentiating colonization ordinarily not treated from infection that should be treated. Physicians who are not infectious disease clinicians lack the necessary sophistication in clinical infectious disease training, medical microbiology, pharmacokinetics/pharmacodynamics, and diagnostic experience. Physicians in critical care units should rely on infectious disease clinicians as well as other consultants to optimize care these acutely ill patients.

The second edition of *Infectious Diseases in Critical Care Medicine* has been streamlined, maintaining the clinical focus in a more compact volume. Again, the authors have been selected for their expertise and experience. The contributors to the book are world-class teacher/clinicians who have in their writings imparted wisdom accrued from years of clinical experience for the benefit of the critical care unit physician and their patients. The second edition of *Infectious Diseases in Critical Care Medicine* remains the only book dealing with infections in critical care.

Burke A. Cunha

## Preface to the Third Edition

Infectious disease aspects of critical care have changed much since the first edition was published in 1998. Infectious diseases are ever present and are becoming important in critical care. *Infectious Diseases in Critical Care Medicine* (third edition) remains the only book exclusively dedicated to infectious diseases in critical care.

Importantly, *Infectious Diseases in Critical Care Medicine* (third edition) is written from the infectious disease perspective by clinicians for clinicians who deal with infectious diseases in critical care. The infectious disease perspective is vital in the clinical diagnostic approach to noninfectious and infectious disease problems encountered in critical care. The third edition of this book is not only completely updated but includes new topics that have become important in infectious diseases in critical care since the publication of the second edition.

The hallmark of clinical excellence in infectious disease consultation is the diagnostic experience and expertise of the infectious disease consultant. The clinical approach should not be to arrive at a diagnosis by ordering a bewildering number of clinically irrelevant tests hoping for clues from abnormal findings. The optimal differential diagnostic approach depends on the infectious disease consultant carefully analyzing the history, physical findings, and pertinent nonspecific laboratory tests in critically ill patients to focus diagnostic efforts. Before a definitive diagnosis is made, the infectious disease consultant's role as diagnostician is to correctly interpret and correlate nonspecific laboratory tests in the correct clinical context, which should prompt specific laboratory testing to rule in or rule out the most likely diagnostic possibilities. As subspecialist consultants, infectious disease clinicians are excellent diagnosticians. For this reason, infectious disease consultation is of vital importance for all but the most straightforward infectious disease problems encountered in critical care.

Another distinguishing characteristic of infectious disease clinicians is that they are both diagnostically and therapeutically focused. Many noninfectious disease clinicians often tend to empirically "cover" patients with an excessive number of antibiotics to provide coverage against a wide range of unlikely pathogens. Currently, most of resistance problems in critical care units result from not appreciating the resistance potential of some commonly used antibiotics in many multidrug regimens, such as ciprofloxacin, imipenem, and ceftazidime. Some contend this approach is defensible because with antibiotic "deescalation" the unnecessary antibiotics can be discontinued subsequently. Unfortunately, except for culture results from blood isolates cultures with skin/soft tissue infections, or cerebrospinal fluid with meningitis, usually there are no subsequent microbiologic data upon which to base antibiotic deescalation, such as nosocomial pneumonia, abscesses, and intra-abdominal/pelvic infections. The preferred infectious disease approach is to base initial empiric therapy or covering the most likely pathogens rather than clinically unlikely pathogens. Should diagnostically valid data become available, a change in antimicrobial therapy may or may not be warranted on the basis of new information.

Because infectious disease consultation is so important in the differential diagnostic approach in critical care, this book's emphasis is on differential diagnosis. If the diagnosis is inaccurate/incorrect, empiric therapy will necessarily be incorrect. To assist those taking care of critically ill patients, chapters on physical exam clues and their mimics, ophthalmologic clues and their mimics in infectious disease, and radiologic clues and their mimics in infectious disease have been included in this edition. In addition, several chapters notably, "Clinical Approach to Fever" and "Fever and Rash," also emphasize on physical findings.

Since the last edition, some infectious diseases, such as *Clostridium difficile* diarrhea/colitis, SARS (severe acute respiratory syndrome), HPS (hantavirus pulmonary syndrome), avian influenza (H5N1), and swine influenza (H1N1) have become important in critical care medicine.

Another important topic has been added on infections related to immunomodulating/immunosuppressive agents. The widespread introduction of immune modulation therapy has resulted in a recrudescence of many infections due to intracellular pathogens, which are important to recognize in patients receiving these agents. Because miliary tuberculosis is so important and is not an infrequent complication of steroid/immunosuppressive therapy, a chapter on this topic also has been included in the third edition.

As mentioned, antibiotic resistance in the critical care unit is a continuing problem with short- and long-term clinical consequences. Currently, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci are the most important gram-positive pathogens in critical care, and a chapter has been added on antibiotic therapy of these pathogens. Among the multidrug-resistant aerobic gram-negative bacilli, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* continue to be difficult therapeutic problems, and a chapter has been included on this important topic.

The contributors to the third edition of *Infectious Diseases in Critical Care Medicine* are nationally or internationally acknowledged experts in their respective fields. The authors have been selected for their clinical excellence and experience. They are teacher-clinicians also known for their ability to effectively distill the key points related to their topics.

The third edition is not just a compendium of current guidelines. Guidelines are not definitive and for this reason often change over time. Guideline followers may not agree with this book's clinical approach which is evidence based, but tempered by clinical experience. Especially in critical care, the key determinant of optimal patient care is experienced based clinical judgment which the clinician contributors have provided.

In summary, the this edition is both up-to-date and better than ever. Now in its third edition, *Infectious Diseases in Critical Care Medicine*, written by clinicians for clinicians, remains the only major text exclusively dealing with the major infectious disease syndromes encountered in critical care medicine.

Burke A. Cunha

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# 1 Clinical Approach to Fever in Critical Care

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## INTRODUCTION

Fever is a cardinal sign of disease. It may be caused by a wide variety of infectious and noninfectious disorders. The number of disorders that occur in seriously ill patients in critical care units (CCUs) are more limited than in the non-CCU population. The main clinical problems in the CCU are to differentiate between noninfectious and infectious causes of fever and then to determine the cause of the patient's fever.

The clinical approach to fever in the CCU is based on a careful analysis of the acuteness/chronicity of the fever, the characteristics of the fever pattern, the relationship of the pulse to the fever, the duration of the fever, and the defervescence pattern of the fever. It is the task of the infectious disease consultant to relate aspects of the patient's history, physical, laboratory, and radiological tests with the characteristics of the patient's fever, which together determine differential diagnostic possibilities. After the differential diagnosis has been narrowed by analyzing the fever's characteristics and the patient-related factors mentioned, it is usually relatively straightforward to order tests to arrive at a specific diagnosis.

Most patients in the CCU have some degree of temperature elevation. Trying to determine the cause of fever in CCU patients is the daily task of the patient's physicians. Fever in the CCU can be a perplexing problem because the clinician must determine whether the patient's underlying disorder is responsible for the fever or fever is a superimposed phenomenon on the patient's underlying problem responsible for admission to the CCU. The infectious disease consultant's clinical excellence is best demonstrated by the rapidity and accuracy in arriving at a cause for the patient's fever (Table 1) (1–10).

## CAUSES OF FEVER IN THE CCU

### Noninfectious Causes of Fever in the CCU

A wide variety of disorders are associated with a febrile response. Both infectious and noninfectious disorders may cause acute/chronic fevers that may be low, i.e.,  $\leq 102^{\circ}\text{F}$ , or high grade, i.e.,  $\geq 102^{\circ}\text{F}$ . Of the multiplicity of conditions that may be encountered in the CCU with a few notable exceptions, most noninfectious disorders are associated with fevers of  $\leq 102^{\circ}\text{F}$ . Exceptions to the  $102^{\circ}\text{F}$  fever rule include malignant hyperthermia, adrenal insufficiency, massive intracranial hemorrhage, central fever, drug fever, collagen vascular disease flare, particularly systemic lupus erythematosus (SLE) flare, heat stroke, vasculitis, and certain malignancies particularly lymphomas. The most common noninfectious disorders encountered in the CCU either have no fever, or have low-grade fevers  $\leq 102^{\circ}\text{F}$ , and include acute myocardial infarction, pulmonary embolism/infarct, phlebitis, catheter-associated bacteriuria, acute pancreatitis, viral hepatitis, acute hepatic necrosis, uncomplicated wound infections, subacute bacterial endocarditis, cerebrovascular accidents (CVAs), small/moderate intracerebral bleeds, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), bronchiolitis obliterans organizing pneumonia (BOOP), pleural effusions, atelectasis, cholecystitis, non-infectious diarrheas, *Clostridium difficile* diarrhea, ischemic colitis, splenic infarcts, renal infarcts, pericardial effusion, dry gangrene, gas gangrene, surgical toxic shock syndrome, acute gout, small-bowel obstruction, and cellulitis (1,3,5,11–31).

Extreme hyperpyrexia (temperature  $\geq 106^{\circ}\text{F}$ ) is not a clue to an infectious disease. There are relatively few disorders, all noninfectious, which are associated with extreme hyperpyrexia (Table 2) (1,3,5).

**Table 1** Causes of Fever in the CCU

System/Source	Infectious causes	Noninfectious causes
• Central nervous	Meningitis Encephalitis	Cerebral infarction Cerebral hemorrhage Seizures
• Cardiovascular	Endocarditis Intravascular device infection Central Venous Catheter (CVC)- associated bacteremia Septic thrombophlebitis Pacemaker infection Postperfusion syndrome (CMV)	Myocardial infarction Dressler's syndrome Postpericardiotomy syndrome Thrombophlebitis
• Pulmonary	Pneumonia Empyema Tracheobronchitis Sinusitis	Deep vein thrombosis Atelectasis Chemical pneumonitis Pulmonary emboli/infarction
• Gastrointestinal	Intra-abdominal abscess Cholecystitis/cholangitis Viral hepatitis Peritonitis Diverticulitis <i>C. difficile</i> colitis	Gastrointestinal hemorrhage Acalculous cholecystitis Nonviral hepatitis Pancreatitis Inflammatory bowel disease Ischemic colitis
• Renal	Urinary tract infection (Cystitis) Acute pyelonephritis	
• Rheumatologic	Osteomyelitis Septic arthritis	Gout/pseudogout Collagen vascular disease (SLE) Vasculitis
• Skin/soft tissue	Cellulitis Wound infection	Hematoma Intramuscular injections Burns
• Endocrine/metabolic		Adrenal insufficiency Hyperthyroidism/thyroiditis
• Miscellaneous	Sustained bacteremias Transient bacteremias Parotitis Pharyngitis	Alcohol/drug withdrawal Drug fever Postoperative/postprocedure Blood/blood products transfusion Intravenous contrast reaction Fat emboli syndrome Neoplasms/metastasis

**Table 2** Causes of Extreme Hyperpyrexia (High Fevers  $\geq 106^\circ\text{F}$ )

<ul style="list-style-type: none"> <li>• Hypothalamic disease/dysfunction</li> <li>• Central fevers (hemorrhagic, trauma, infection, malignancy)</li> <li>• Malignant neuroleptic syndrome</li> <li>• Malignant hyperthermia</li> <li>• Drug fever (typically <math>102^\circ\text{F}</math>–<math>106^\circ\text{F}</math>)</li> <li>• Tetanus</li> </ul>
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The clinical approach to the noninfectious disorders with fever is usually relatively straightforward because they are readily diagnosable by history, physical, or routine laboratory or radiology tests. By knowing that noninfectious disorders are not associated with fevers  $>102^\circ\text{F}$ , the clinician can approach patients with these disorders that have fevers  $>102^\circ\text{F}$  by looking for an alternate explanation. The difficulty usually arises when the patient has a multiplicity of conditions and sorting out the infectious from the noninfectious causes can be a daunting task (Tables 3 and 4) (1–6,10).

**Table 3** Clinical Syndromic Approach to Fever in the CCU

System	Community-acquired fevers	Nosocomial fevers	Either community-acquired or nosocomial fever	Usual maximum temperature	
				≥102°F	≤102°F
CNS	<ul style="list-style-type: none"> <li>• Meningitis</li> <li>• Encephalitis</li> <li>• Brain abscess</li> </ul>	<ul style="list-style-type: none"> <li>• Neurosurgical shunt infection</li> <li>• Posterior fossa syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Central fevers</li> <li>• CVAs</li> <li>• Massive ICH</li> <li>• Seizures</li> </ul>	+	+
				+	+
Cardiovascular	<ul style="list-style-type: none"> <li>• SBE</li> </ul>	<ul style="list-style-type: none"> <li>• CVC infections</li> <li>• Lead/generator infected pacemaker associated infections</li> <li>• Postpericardiotomy syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• ABE†</li> <li>• Myocardial infarction</li> </ul>	+	+
				+	+
	<ul style="list-style-type: none"> <li>• Viral pericarditis</li> </ul>	<ul style="list-style-type: none"> <li>• Postperfusion syndrome (CMV)</li> </ul>	<ul style="list-style-type: none"> <li>• Myocardial/ perivalvular abscess</li> </ul>	+	+
		<ul style="list-style-type: none"> <li>• “Balloon pump fever”</li> <li>• Sternal osteomyelitis</li> </ul>		+	+

(Continued)





Urinary tract	<ul style="list-style-type: none"> <li>• CAB</li> </ul>	<ul style="list-style-type: none"> <li>• Urosepsis</li> </ul>	+
	<ul style="list-style-type: none"> <li>• Pyelonephritis</li> <li>• Cystitis</li> </ul>		+
Skin/soft tissue	<ul style="list-style-type: none"> <li>• Cellulitis</li> <li>• Gas gangrene</li> <li>• Mixed soft gas tissue infection</li> </ul>	<ul style="list-style-type: none"> <li>• Uncomplicated wound infection</li> </ul>	+
Bone/joint	<ul style="list-style-type: none"> <li>• Acute osteomyelitis</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic osteomyelitis</li> </ul>	+
Other	<ul style="list-style-type: none"> <li>• Fat emboli</li> <li>• Transient bacteremias</li> <li>• Blood/blood product transfusions</li> </ul>	<ul style="list-style-type: none"> <li>• Septic arthritis</li> <li>• Acute gout/pseudogout</li> <li>• RA flare</li> <li>• SLE flare</li> </ul>	+
	<ul style="list-style-type: none"> <li>• Alcohol withdrawal syndrome</li> <li>• Delirium tremens</li> </ul>	<ul style="list-style-type: none"> <li>• Acute/relative adrenal insufficiency</li> <li>• Hematomas</li> </ul>	+

*Abbreviations:* CNS, central nervous system; RA, rheumatoid arthritis; SBE, subacute bacterial endocarditis; ABE, acute bacterial endocarditis; BOOP, bronchiolitis obliterans organizing pneumonia; ICH, intracranial hemorrhage; CMV, cytomegalovirus; CVC, central venous catheter; CAP, community-acquired pneumonia; GI, gastrointestinal; CAB, catheter-associated bacteriuria; SLE, systemic lupus erythematosus; CVA, cerebral vascular accident; VAP, ventilator-associated pneumonia.  
<sup>†</sup>In normal hosts (excluding IVDAs).

**Table 4** Clinical Approach to Fever in CCU

## Early infectious disease consultation

- All critically ill febrile CCU patients should have infectious disease consultation
- Infectious disease consultation also useful to evaluate mimics of infection (pseudosepsis) and interpretation of complex microbiologic data

Low-grade fevers ( $\leq 102^\circ\text{F}$ )

- *Noninfectious disorders most likely causes of low-grade fevers*

*Common medical disorders with fevers  $\leq 102^\circ\text{F}$  in CCU:*

MI/CHF	Hematomas
Pulmonary embolus/infarction	GI hemorrhage
Acute pancreatitis	Cholecystitis
Atelectasis/dehydration	Uncomplicated wound infections
Thrombophlebitis	

- *Infectious diseases are less likely causes*

High spiking fevers ( $\geq 102^\circ\text{F}$ ) in CCU:

- *Infectious cause most likely*

Most common causes of *noninfectious fevers*  $\geq 102^\circ\text{F}$  in CCU:

- Drug fevers
- Malignant neuroleptic syndrome
- Central fevers
- Relative adrenal insufficiency
- SLE flare
- Vasculitis
- Blood transfusion
- Transient bacteremias ( $2^\circ$  to manipulation of colonized/infected mucosa surface)

**Infectious Causes of Fever in the CCU**

Most infections that are not toxin mediated elicit a febrile response. While all infections do not manifest temperatures  $>102^\circ\text{F}$ , they have the potential to be  $>102^\circ\text{F}$ , e.g., nosocomial pneumonia may be associated with temperatures  $<102^\circ\text{F}$  or  $>102^\circ\text{F}$ . Although all infectious diseases will not present with temperatures  $\geq 102^\circ\text{F}$ , they are the disorders most frequently associated with temperatures in the  $102^\circ\text{F}$ – $106^\circ\text{F}$  range. Infectious diseases encountered in the CCU usually associated with temperatures  $\geq 102^\circ\text{F}$  include postoperative abscesses, acute meningitis, acute encephalitis, brain abscess, suppurative thrombophlebitis, jugular septic vein thrombophlebitis, septic pelvic thrombophlebitis, septic pulmonary emboli, pericarditis, acute bacterial endocarditis, perivalvular/myocardial abscess, community-acquired pneumonia (CAP), pleural empyema, lung abscess, cholangitis, intrarenal/perinephric abscess, prostatic abscess, urosepsis, central-line infections, contaminated infusates, pylephlebitis, liver abscess, *C. difficile* colitis, complicated skin and soft tissue infections/abscesses, AV graft infections, foreign body-related infections [infected pacemakers, defibrillators, semipermanent central intra-venous (IV) catheters, Hickman/Broviac catheters], and septic arthritis. Infectious diseases likely to be seen in the ICU setting with temperatures  $<102^\circ\text{F}$  include osteomyelitis, sacral decubitus ulcers, uncomplicated wound infections, cellulitis, etc. (5,19,21,23).

The clinician should analyze the fever relationships in the clinical context and correlate these findings with other aspects of the patient's clinical condition to arrive at a likely cause for the temperature elevation. The clinical approach utilizes not only the height of the fever but the abruptness of onset, the characteristics of the fever curve, the duration of the fever, and defervescence pattern, all of which have diagnostic importance (Table 5) (5).

**SINGLE FEVER SPIKES  $>102^\circ\text{F}$** 

Patients in the CCU who have been afebrile or had low-grade fevers, i.e.,  $\leq 102^\circ\text{F}$  may suddenly develop a single fever spike  $>102^\circ\text{F}$ . Single fever spikes are never infectious in origin. The causes of single fever spikes include insertion/removal of a urinary catheter, insertion/removal of a venous catheter, suctioning/manipulation of an endotracheal tube, wound packing/lavage, wound irrigation, etc. Any manipulative procedure that involves a

**Table 5** Clinical Applications of the “102°F Fever Rule” in the CCU

Common causes of fever <102°F	Comments
Acute myocardial infarction	<ul style="list-style-type: none"> <li>• H/O chest pain/community-acquired pneumonia</li> <li>• EKG/cardiac enzymes</li> </ul>
Pulmonary embolism/infarction	<ul style="list-style-type: none"> <li>• H/O pulmonary emboli underlying reasons predisposing to pulmonary emboli</li> <li>• VQ scan positive (pulmonary angiography for large emboli)</li> <li>• ↑ FSPs with multiple small pulmonary emboli</li> </ul>
GI bleed	<ul style="list-style-type: none"> <li>• Hyperactive bowel sounds, bleeding per rectum/melena</li> <li>• ↑ BUN (except in alcoholic liver disease)</li> <li>• Endoscopy/abdominal CT scan → bleeding source</li> </ul>
Acute pancreatitis	<ul style="list-style-type: none"> <li>• Severe abdominal pain: often associated with ARDS</li> <li>• Grey–Turner’s/Cullen’s sign</li> <li>• ↑ Amylase and ↑ lipase or pancreatitis on abdominal CT scan</li> </ul>
Hematomas	<ul style="list-style-type: none"> <li>• H/O recent surgery/bleeding diathesis</li> </ul>
Phlebitis	<ul style="list-style-type: none"> <li>• Local erythema without suppuration/vein tenderness</li> </ul>
CAB	<ul style="list-style-type: none"> <li>• Bacteriuria and pyuria represents colonization, not infection</li> <li>• Bacteremia (urosepsis) does not result from bacteriuria unless there is preexisting renal disease, urinary tract obstruction, or patient has SLE, DM, steroids, etc.</li> </ul>
Pleural effusions	<ul style="list-style-type: none"> <li>• Bilateral effusions are never due to infection: look for a noninfectious etiology</li> </ul>
Uncomplicated wound infections	<ul style="list-style-type: none"> <li>• Except for gas gangrene and streptococcal cellulitis, temperatures are usually low grade</li> <li>• “Wounds” with temperatures <math>\geq 102^\circ\text{F}</math> should prompt a search for an underlying abscess</li> </ul>
Atelectasis/dehydration	<ul style="list-style-type: none"> <li>• Temperatures usually <math>\leq 101^\circ\text{F}</math></li> <li>• May be confused with pulmonary emboli/early pneumonia</li> </ul>
Tracheobronchitis	<ul style="list-style-type: none"> <li>• Purulent endotracheal secretions with negative CXR</li> <li>• Tracheobronchitis → temperatures <math>&lt; 102^\circ\text{F}</math></li> </ul>
Thrombophlebitis	<ul style="list-style-type: none"> <li>• Warm, tender calf/foot veins <math>\pm</math> palpable cord</li> <li>• Thrombophlebitis does not → pulmonary emboli</li> <li>• Phlebothrombosis → pulmonary emboli</li> </ul>
<i>C. difficile</i> diarrhea	<ul style="list-style-type: none"> <li>• Stools positive for <i>C. difficile</i> toxin</li> <li>• Fecal WBC positive <math>\sim 50\%</math></li> <li>• Temperatures <math>&lt; 102^\circ\text{F}</math></li> </ul>

*Abbreviations:* ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CT, CAT scan; CAB, catheter-associated bacteriuria; DM, diabetes mellitus; FSPs, fibrin split products; PE, pulmonary edema; SLE, systemic lupus erythematosus.

manipulation of a colonized/infected surface can induce a transient bacteremia. Such transient bacteremias are unsustained and because of their short duration, i.e., less than five minutes, they do not result in sustaining infection or spread infection to other organs, and for this reason may not be treated. Single fever spikes of the transient bacteremias are a diagnostic not a therapeutic problem. The other common cause of single fever spikes in the CCU is blood product transfusions. Fever secondary to blood products/blood transfusions are a frequent occurrence, and are most commonly manifested by fever following the infusion. The distribution of fever is bimodal following a blood transfusion. Most reactions occur within the first 72 hours after the blood/blood product transfusion, and most reactions within the 72-hour period occur in the first 24 to 48 hours. There are very few reactions after 72 hours, but there is a smaller peak five to seven days after the blood transfusion, which although very uncommon, may occur. The temperature elevations associated with late blood transfusion reactions are lower than those with reactions occurring soon after blood transfusion. The fever subsequent to the transient bacteremia results from cytokine release and is not indicative of a prolonged exposure to the infecting agent, but rather represents the post-bacteremia chemokine-induced febrile response. The temperature

elevations from manipulation of a colonized infected mucosal surface persist long after the bacteremia has ceased (1,3-5,24-27).

In patients with fever spikes due to transient bacteremias following manipulation of a colonized or infected mucosal surface, or secondary to a blood/blood product transfusion, may be inferred by the temporal relationship of the event and the appearance of the fever. In addition to the temporal relationship between the fever and the transient bacteremia or transfusion-related febrile response is the characteristic of the fever curve, i.e., a single, isolated temperature spike that resolves spontaneously without treatment (1,5,11,32).

### **MULTIPLE FEVER SPIKES >102°F**

Multiple fever spikes >102°F may be infectious or noninfectious in origin, because a hectic septic fever pattern does not in itself suggest a particular etiology. The clinician must rely upon associated findings in the history and physical, or among laboratory or radiology tests to narrow down the cause of the fever. Pulse-temperature relationships are also of help in differentiating the causes of fever in patients with multiple temperature spikes over a period of days (1-5,10). Assuming that there is no characteristic fever pattern, the presence or absence of a pulse-temperature deficit is useful. Patients with a pulse-temperature deficit, i.e., relative bradycardia, are limited to relatively few infectious and noninfectious disorders. In the CCU setting, patients with multiple spiking fevers and a pulse-temperature deficit should suggest Rocky Mountain spotted fever (RMSF), typhus, arboviral hemorrhagic fevers, central fevers, lymphoma-related fevers, Legionnaires' disease, Q fever, psittacosis, or drug fever. The diagnostic significance of relative bradycardia can only be applied in patients who have normal pulse-temperature relationships, i.e., those who do not have pacemaker-induced rhythms, have third-degree heart block, those with arrhythmias, or those on verapamil, diltiazem, or  $\beta$ -blocker therapy. Any patient on these medications who develop fever will develop relative bradycardia, thus eliminating the usefulness of this important diagnostic sign in patients with relative bradycardia (Table 6) (1,5,33-35).

### **CAUSES OF ACUTE LOW-GRADE FEVERS IN THE CCU**

Most of the acute, noninfectious disorders that occur in the CCU are accompanied by low-grade fevers, i.e.,  $\leq 102^\circ\text{F}$  for a short period of time. Fever secondary to acute myocardial infarction, pulmonary embolus, acute pancreatitis, are all associated with fevers of short duration. If present in patients with these underlying diagnoses, a fever  $>102^\circ\text{F}$  or one that lasts for more than three days should suggest a complication or an alternate diagnosis. Other condition that may present in this way include dehydration, atelectasis, wound healing, hematoma, seromas, ARDS, BOOP, deep vein thromboses, pleural effusions, tracheobronchitis, decubitus ulcers, cellulitis, phlebitis, etc. Prolonged low-grade fevers are, in the main, not infectious. Clinicians should try to determine what noninfectious disorder is causing the fever so that undue resources will not be expended looking for an unlikely infectious disease explanation for the fever (1-10,24-30).

### **CAUSES OF PROLONGED LOW-GRADE FEVERS IN THE CCU**

There are relatively few causes of prolonged fevers in the CCU that last for over a week. Such low-grade prolonged fevers lasting over a week have been termed nosocomial fevers of unknown origin (FUOs). There are relatively few causes of nosocomial FUOs in contrast to its community-acquired counterpart. Low-grade infections or inflammatory states account for most of the causes of nosocomial FUOs. Nosocomial FUOs are usually due to central fevers, drug fevers, postperfusion syndrome, atelectasis, dehydration, undrained seromas, tracheobronchitis, and catheter-associated bacteriuria. Prolonged fevers that become high spiking fevers should suggest the possibility of nosocomial endocarditis related to a central line or invasive cardiac procedure. Prolonged high spiking fevers can also be due to septic thrombophlebitis or an undrained abscess. Nosocomial sinusitis due to prolonged nasotracheal intubation is a rare cause of prolonged fever in the CCU (2,5,6,36-40).

**Table 6** Clinical Applications of the “102°F Rule” in the CCU

Common causes of fever >102°F	Comments
NP/VAP	<ul style="list-style-type: none"> <li>• Temperatures usually <math>\leq 102^\circ\text{F}</math></li> <li>• Pulmonary infiltrate consistent with a bacterial pneumonia occurring &gt;5 days after hospitalization</li> <li>• NP/VAP must be differentiated on CXR from ARDS, LVF, etc.</li> <li>• Endotracheal secretion isolates represent upper airway colonization and are not reflective of lower respiratory tract organisms causing VAP</li> <li>• Endotracheal respiratory secretion isolates should not be “covered” with empiric antibiotics</li> </ul>
Central venous catheter (CVC) infections	<ul style="list-style-type: none"> <li>• Usually CVCs in for &gt;7 days</li> <li>• Organisms from blood cultures taken from noninvolved extremity same as positive semiquantitative catheter tip culture (<math>\geq 15</math> colonies)</li> <li>• If all other sources of fever are ruled out, consider CVC infection, especially with lines in for &gt;7 days (even if site not infected visually)</li> </ul>
Septic thrombophlebitis	<ul style="list-style-type: none"> <li>• Pus at CVC insertion site after CVC removal</li> <li>• Temperatures usually <math>&gt; 102^\circ\text{F}</math></li> <li>• Blood cultures positive</li> </ul>
<i>C. difficile</i> colitis	<ul style="list-style-type: none"> <li>• Stools positive for <i>C. difficile</i> toxin</li> <li>• Abrupt <math>\uparrow</math> WBC count to 30–50 k/mm<sup>3</sup></li> <li>• Abrupt cessation of diarrhea in a patient with <i>C. difficile</i> diarrhea</li> <li>• New abdominal pain in patient with <i>C. difficile</i> diarrhea</li> <li>• Abdominal CT scan shows colonic “thumbprinting”/pancolitis/toxic <math>\pm</math> megacolon</li> </ul>
Drug fever	<ul style="list-style-type: none"> <li>• Consider drug fever in patients with otherwise unexplained temperatures</li> <li>• Blood cultures are negative (excluding contaminants)</li> <li>• Patients with drug fever usually have <math>\geq 102^\circ\text{F}</math> with relative bradycardia<sup>a</sup></li> <li>• <math>\uparrow</math> WBC with left shift</li> <li>• Mild/moderate serum transaminases</li> <li>• Eosinophils present (eosinophilia less commonly)</li> <li>• <math>\uparrow</math> ESR</li> <li>• Commonest causes of drug fever are diuretics, pain/sleep medications, sulfa-containing stool softeners/drugs or <math>\beta</math>-lactam antibiotics (see Table 6)</li> </ul>
Blood/blood product transfusion	<ul style="list-style-type: none"> <li>• Single fever spike (1–3 or 5–7 days posttransfusion)</li> </ul>
Transient bacteremia due to manipulation of a colonized/infected mucosal surface	<ul style="list-style-type: none"> <li>• Single temperature spike 1–3 days, postmanipulative, that spontaneously resolves without treatment</li> </ul>
Serious systemic infectious diseases	<ul style="list-style-type: none"> <li>• Most normal hosts have fevers <math>\geq 102^\circ\text{F}</math></li> </ul>

<sup>a</sup>Patients without heart block/arrhythmias, pacemaker rhythm, or on  $\beta$ -blockers, diltiazem, or verapamil  
 Abbreviations: BBB, bundle branch block; BAL, bronchioalveolar lavage; CT, CAT scan; CVC, central venous catheter; ESR, erythrocyte sedimentation rate; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia

## COMMON DIAGNOSTIC PROBLEMS IN THE CCU

### Drug Fever

Drug fevers are so important in the CCU setting because of the multiplicity of medications. Physicians should always be suspicious of the possibility of drug fever when other diagnostic possibilities have been exhausted. Drug fever may occur in individuals who have just recently been started on the sensitizing medication, or more commonly who have been on a sensitizing medication for a long period of time without previous problems. Patients with drug fever do not necessarily have multiple allergies to medications and are not usually atopic. However, the likelihood of drug fever is enhanced in patients who are atopic with multiple drug allergies.

Patients with drug fever, i.e., hypersensitivity reaction without rash may present with any degree of fever, but most commonly drug fevers are in the 102°F–104°F range. Other conditions aside, patients look “inappropriately well” for the degree of fever, which is different from that of the toxemic patient with a serious bacterial systemic infection. Relative bradycardia is invariably present excluding patients on  $\beta$ -blocker therapy, those with arrhythmias, heart block, or pacemaker-induced rhythms (1,5,41,42). Laboratory tests include an increase in WBC count with a shift to the left. Eosinophils are often present early in the differential count, but less commonly is their actual eosinophilia. The ESR also goes up with drug fever, but this may be compounded by other causes of increased ESR with the multitude of disorders in CCU patients. The sedimentation rate also is increased after surgical procedures, negating the usefulness of this test in the postoperative fever patient. Serum transaminases, i.e., SGOT/SGPT are also mildly/transiently elevated early in cases of drug fever. Often such mild increases in the serum transaminases are overlooked by clinicians as acute-phase reactants or as not being very elevated. However, in a patient with an obscure otherwise unexplained fever, the constellation of nonspecific findings including relative bradycardia, slightly increased serum transaminases, and eosinophils in the differential count is sufficient to make a presumptive diagnosis of drug fever (Tables 7 and 8)(1–5,8,30–35).

It is a popular misconception that antibiotics are the most common cause of drug fever. Among the antibiotics,  $\beta$ -lactams and sulfonamides are the most common causes of drug fever in the CCU setting. More common causes of fever in the CCU setting are antiarrhythmics; antiseizure medications; sulfa-containing loop diuretics, e.g., furosemide, tranquilizers, sedatives, sleep medications, antihypertensive medications; sulfa-containing stool softeners, e.g., Colace; and to a lesser extent,  $\beta$ -blockers. Since patients are usually receiving multiple medications, it is not always possible to discontinue the one agent likely to be the cause of the drug fever. Often two or three agents have to be discontinued simultaneously. The clinician should discontinue the most likely agent that is not life supporting or essential first, in order to properly interpret the decrease in temperature if indeed that was the sensitizing agent responsible for the drug fever. If the agent that is likely to cause the drug fever cannot be discontinued, every attempt should be made to find an equivalent nonallergic substitute, i.e., ethacrynic acid in place of furosemide as a loop diuretic for CHF, a carbapenem in place of a  $\beta$ -lactam. If the agent responsible for the drug fever is discontinued, temperatures will decrease to near normal/normal within 72 hours. If the temperature does not decrease within 72 hours, then the clinician should discontinue sequentially one drug at a time, those that are likely to be the causes of drug fever. Resolution of drug fever means that not only the temperature returns to normal, but the leukocytosis decreases and the eosinophils disappear in the differential WBC count (Tables 7 and 8) (5,33,35). If the patient has a drug rash and fever, the diagnosis is drug rash. If the fever is associated with drug rash, it may take days to weeks to return to normal after the sensitizing drug is discontinued (Tables 7 and 8) (5,27,41–43).

### **Central Venous Catheter (CVC) Related Infections**

Any invasive intravascular device may be associated with infection, but central IV lines are the ones most likely to result in CVC related sepsis. Other causes of CVC related sepsis that may be encountered in the CCU are an infected Hickman/Broviac, PICC line, or pacemaker lead/generator infection, or Quinton catheter. Patients with AV-graft infections resemble, in clinical presentation, those with CVC related sepsis. The diagnosis of CVC related infection may be obvious or less straightforward. The likelihood that a patient in the CCU has CVC related infection is related to the duration that the CVC line is in place. CVC related infections are rare in less than or equal to seven days after line placement. There is progressive increase in the incidence of CVC related infection following seven days of catheter insertion, i.e., the longer the central IV line is in the more likely that IV sepsis will ensue. CVC related infections often present as otherwise unexplained obscure fevers. Half the patients will have obvious sign of infection at the catheter entry site. This is all that is required for a presumptive diagnosis of CVC related infection, and the catheter should be removed and semiquantitative catheter tip cultures and blood cultures should be obtained to confirm the diagnosis. However, the more common problem is in the other half of patients who have no local signs of infection at the site of CVC insertion. With these patients, CVC related infection should be suspected after other

**Table 7** Clinical Features of Drug Fever

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*History*

- Individuals often atopic
- Patients on a “sensitizing medication” for days or more commonly, months/years

*Physical examination*

- Low- to high-grade fevers (usually >102°F)
- Relative bradycardia (with temperature ≥102°F)†
- Patients appear “inappropriately well” for degree of fever (don’t look septic<sup>a</sup>)
- No rash<sup>b</sup>

*Laboratory tests*

- Leukocytosis (with left shift)
- Eosinophils are usually present (eosinophilia is uncommon)
- Elevated ESR (may reach ≥100 mm/h)
- Mildly elevated serum transaminases (early/transient)

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<sup>a</sup>Excluding septic patients who also have drug fever.

<sup>b</sup>Rash, if present, represents drug rash (not drug fever), which is usually accompanied by fever. Drug rashes usually maculopapular (occasionally with a petechial component), central, and may involve palms/soles.

†Excluding those on β-blockers, verapamil, or diltiazem.

**Table 8** Causes of Drug Fever: Sensitizing Medications

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Common Causes	Uncommon Causes	Rare Causes
Sulfa-containing drugs	All other medications	Digoxin
Stool softeners (Colace)		Steroids
Diuretics (Lasix)		Diphenhydramine (Benadryl)
Sleep medications		Aspirin
Antiseizure medications		Vitamins
Antidepressants/tranquillizers		Aminoglycosides
Antiarrhythmics		Tetracyclines
NSAIDs		Macrolides
Antibiotics (β-lactams, sulfonamides)		Clindamycin
		Chloramphenicol
		Vancomycin
		Aztreonam
		Quinolones
	Carbapenems	
	Tigecycline	
	Daptomycin	
	Quinupristin/dalfopristin	
	Linezolid	

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*Abbreviation:* NSAIDs, nonsteroidal anti-inflammatory drugs

diagnostic possibilities have been eliminated in patients who have had a CVC in place for days/weeks. Blood cultures should be obtained and the catheter removed for semiquantitative culture of the CVC catheter tip. The finding of a positive catheter tip culture is one with ≥15 colonies plated in the method of Maki/Cleri. Positive catheter tip culture without bacteremia indicates only a colonized catheter. Bacteremia without positive catheter tip culture with the same organism indicates bacteremia but not secondary to the CVC. CVC related infections are diagnosed by demonstrating the same organism in the blood and the catheter tip. The treatment for CVC related infection is to remove the CVC. If no further central venous access is necessary, the line may be discontinued, but if continued central IV line access is required, then the catheter may be changed over a guidewire. Changing the catheter over a guidewire does not subject the patient to the possibility of a pneumothorax from a subclavian insertion (8,10,21,32,38,39).



Alternately, after the catheter is removed, another may be placed in a different anatomical location. Femoral catheters are the ones most likely to be infected followed by internal jugular have been in place for months inserted catheters. The subclavian inserted central IV lines are those least likely to be infected over time. Central venous catheter (CVC) related infections are treated by catheter removal and antibiotics are usually given, even though the source of the bacteremia has been removed. The organisms from the skin, i.e., *Staphylococcus aureus*, *Staphylococcus epidermidis*/coagulase-negative staphylococci (CoNS), are the most frequent cause, but aerobic gram-negative bacilli and to a lesser extent enterococci are also important causes of IV-line sepsis in the CCU. Many times catheters are often needlessly changed when patients, particularly postoperative patients spike a fever in the first two to three days postoperatively. CVC change so early is unnecessary because IV-line infections are rare before being in place for at least seven days. If antibiotics are used to treat CVC related infections after the central line is removed, treatment is ordinarily for seven days for gram-negative organisms, and for two weeks for gram-positive organisms (excluding CoNS). CoNS are not ordinarily treated because they are low-virulence pathogens and are incapable of infection in the absence of prosthetic metal or plastic materials. Even if devices/prosthetic materials are in place in a patient with a CoNS bacteremia, patients who have endothelialized their devices/prosthetic materials the likelihood of infection from a transient bacteremia associated with a CVC is very low. It cannot be emphasized too strongly that the clinician should have a high index of suspicion for CVC related infection the longer the catheter has been in place in patients without an alternate explanation for their prolonged fevers. CVCs should not be changed/removed prophylactically if they are in place for less than days unless there are obvious signs of infection at the catheter site entry point (4,5,38,39).

### **Diagnostic Significance of Relative Bradycardia**

Relative bradycardia combined in a patient with an obscure fever is an extremely useful diagnostic sign. Fever plus relative bradycardia immediately limits diagnostic possibilities to central fevers, drug fevers, lymphomas, among the noninfectious disorders commonly causing fever in the CCU. Among the infectious causes of fever in the CCU, relative bradycardia in patients with pneumonia narrows diagnostic possibilities to *Legionella*, psittacosis, or Q fever pneumonia. Patients without pneumonias, with fevers in the CCU, limit diagnostic possibilities to a variety of arthropod-borne infections, i.e., RMSF, typhus; typhoid fever, arthropod-borne hemorrhagic fevers, i.e., yellow fever, Ebola, dengue fever. Relative bradycardia, like other signs, should be considered in concert with other clinical findings to prompt further diagnostic testing for specific infectious diseases and to eliminate the noninfectious disorders associated with relative bradycardia from further consideration (Tables 9 and 10) (5,41,42).

### **Diagnostic Fever Curves**

Fever patterns are often considered nonspecific, therefore, have limited diagnostic specificity. It is true that patients being intermittently given antipyretics and being instrumented in a variety of anatomical locations do have complex fever patterns. However, these are usually easily sorted out on the basis of clinical findings. Fever patterns, i.e., "dromedary" or "camel back," remain useful in diagnosing enigmatic fevers in hospitalized patients. A "camel back" pattern should suggest the possibility of Colorado tick fever, dengue, leptospirosis, brucellosis, lymphocytic choriomeningitis, yellow fever, the African hemorrhagic fevers, rat bite fever, and smallpox (5,41-46).

A relapsing fever pattern suggests malaria, rat bite fever, chronic meningococemia, dengue, brucellosis, cholangitis, smallpox, yellow fever, and relapsing fever. The causes of continuous/sustained fevers include typhoid fever, drug fever, scarlet fever, RMSF, psittacosis, Kawasaki's disease, brucellosis, human herpesvirus-6 (HHV-6) infections, and central fevers.

Remittent fevers are characteristic of viral respiratory tract infection, malaria, acute rheumatic fever, Legionnaires' disease, *Legionella*/*Mycoplasma* CAP, tuberculosis, and viridans streptococcal subacute bacterial endocarditis (SBE). Hectic/septic fevers may be due to gram-negative or gram-positive sepsis, renal, abdominal, or pelvic abscesses, acute bacterial endocarditis, Kawasaki's disease, malaria, miliary TB, peritonitis, toxic shock syndrome, or may be due to overzealous administration of antipyretics (5,44).

**Table 9** Determination of Relative Bradycardia

Criteria:

Inclusive

- Patient must be an adult, i.e.,  $\geq 13$  years
- Temperature  $\geq 102^\circ\text{F}$
- Pulse must be taken simultaneously with the temperature elevation

Exclusive

- Patient has no arrhythmia, second-/third-degree heart block or pacemaker-induced rhythm
- Patient not on  $\beta$ -blocker, verapamil, or diltiazem

Temperature–pulse relationships

Temperature	Appropriate pulse response	Pulse rate in relative bradycardia
106°F (41.1°C)	150/min	<140/min
105°F (40.6°C)	140/min	<130/min
104°F (40.7°C)	130/min	<120/min
103°F (39.4°C)	120/min	<110/min
102°F (38.9°C)	110/min	<100/min

Source: Adapted from Ref. 41.

**Table 10** Causes of Relative Bradycardia

Infectious causes	Noninfectious causes
<ul style="list-style-type: none"> <li>• Legionella</li> <li>• Psittacosis</li> <li>• Q fever</li> <li>• Typhoid fever</li> <li>• Typhus</li> <li>• Babesiosis</li> <li>• Malaria</li> <li>• Leptospirosis</li> <li>• Yellow fever</li> <li>• Dengue fever</li> <li>• Viral hemorrhagic fevers</li> <li>• RMSF</li> </ul>	<ul style="list-style-type: none"> <li>• Drugs                             <ul style="list-style-type: none"> <li><math>\beta</math>-blockers</li> <li>Verapamil</li> <li>Diltiazem</li> </ul> </li> <li>• CNS lesions</li> <li>• Lymphomas</li> <li>• Factitious fevers</li> <li>• Drug fever</li> </ul>

Abbreviations: CNS, central nervous system; RMSF, Rocky Mountain spotted fever.

Double quotidian fevers, i.e., two fever spikes in 24 hours, not artificially induced by antipyretics, should suggest right-sided gonococcal endocarditis, mixed malarial infections, miliary TB, visceral leishmaniasis, or adult Still’s disease. These findings should limit diagnostic possibilities and prompt the clinician to order specific diagnostic testing for likely diagnostic possibilities (1,5,44).

**Diagnostic Significance of Fever Defervescence Patterns**

Most of this chapter has been concerned with the diagnosis of fever in the CCU. This is done by analyzing the rapidity of onset of the fever, the height of the fever, the relationship of the fever to the pulse, the fever patterns, and the duration of the fever. Particularly in perplexing cases of fever, the characteristics of fever resolution also have diagnostic significance. Fever defervescence patterns may be interpreted in two ways. The rapidity and completeness of the fever pattern resolution attests to the effective treatment or resolution of the noninfectious or infectious process. Fever defervescence patterns are as predictable as fever patterns and are also useful in predicting complications secondary to the disorder or therapy.

With bacterial meningitis, temperature resolution with appropriate therapy is related to the pathogen causing the meningitis. Meningococcal meningitis defervesces quickly over one to three days whereas *Haemophilus influenzae* meningitis resolves over three to five days, and severe pneumococcal meningitis may take a week or longer for the fever to decrease/become afebrile. Viral causes of meningitis or encephalitis defervesce very slowly over a seven-day period, and by monitoring the fever defervescence pattern a clinician can easily differentiate viral meningitis/encephalitis from bacterial meningitis. Because fever defervescence patterns may also point to complications, the astute clinician will monitor the fever pattern post therapy, looking for an unexpected temperature spike after the patient has defervesced.

*H. influenzae* meningitis, for example, defervesces after three to five days but if the patient spikes a temperature after five days, this would suggest either a complication of the infection, i.e., subdural empyema, or a complication of therapy, i.e., drug fever secondary to antimicrobial therapy (1,2,5).

In patients with endocarditis, the fever defervescence pattern is also pathogen related. Patients with SBE have fevers  $<102^{\circ}\text{F}$ , and defervesce after a few days of effective antimicrobial therapy. A subsequent temperature spike after the fever with *Streptococcus viridans* SBE has resolved should suggest either a complication of SBE, i.e., septic emboli/infarcts, or a complication of SBE therapy, i.e., drug fever. With *S. aureus* acute bacterial endocarditis (ABE), patients initially have temperatures  $\geq 102^{\circ}\text{F}$  [excluding SBE and intravenous drug abusers (IVDAs)]. Patients with *S. aureus* endocarditis defervesce within three to five days after initiation of effective anti-*S. aureus* therapy. The persistence of fever in a patient being treated appropriately should suggest the possibility of a paravalvular/mild myocardial abscess. With *S. aureus* ABE, the reappearance of fever after initial defervescence should suggest a septic complication, i.e., septic emboli/infarcts, paravalvular/myocardial abscess, or complication of antimicrobial therapy, e.g., drug fever. Patients with enterococcal endocarditis have a fever defervescence pattern intermediate between *S. viridans* SBE and ABE. Patients with enterococcal endocarditis usually defervesce slowly over five days and recrudescence of fever in patients with enterococcal endocarditis should suggest a septic complication or drug fever (1,5,21,43).

Fever defervescence patterns are also important in patients with CAP as well as nosocomial pneumonias. In normal hosts with CAP due to typical bacterial pathogens, i.e., *S. pneumoniae*, *H. influenzae*, or *Moraxella catarrhalis*, fever resolves rapidly over the first few days with effective treatment. *S. pneumoniae* CAP has three possible fever defervescence patterns, the first and most common is a rapid decrease in temperature similar to that found in *H. influenzae* or *M. catarrhalis* CAP in normal hosts. The second with pneumococcal pneumonia is that of initial defervescence followed in three to five days by a secondary rise in fever. A secondary fever rise is a normal variant and does not indicate an infectious complication. The third with *S. pneumoniae* is found in patients with impaired humoral immunity, i.e., patients with alcoholic cirrhosis, multiple myeloma, chronic lymphatic leukemia (CLL), etc. With patients with impaired B-lymphocyte function, the fever slowly remits during the first week of therapy. Patients with overwhelming pneumococcal sepsis, with no humoral immunity, i.e., asplenia, remain febrile and critically ill until the infection resolves or there is a fatal outcome.

Patients with nosocomial pneumonias NP/VAP may have temperature elevations that are above/below  $102^{\circ}\text{F}$ , and fever is not a way to rule in or rule out the diagnosis of nosocomial pneumonia. The NP/VAP is an imprecise diagnosis and is routinely given to most patients in the CCU who have fever, leukocytosis, and pulmonary infiltrates. Therefore, most patients who have a working diagnosis of NP/VAP in fact do not have NP/VAP but have infiltrates, fever, and leukocytosis due to other causes. Patients being treated appropriately with monotherapy or combination therapy for NP/VAP defervesce rapidly if the infiltrates do in fact represent NP/VAP (5,47–50).

Monotherapy or combination therapy for NP/VAP should be with at least one agent that has a high degree of anti-*Pseudomonas aeruginosa* activity. Patients with bona fide NP/VAP defervesce quickly within a week. The persistence of fever, i.e., lack of a fever defervescence pattern in patients with NP/VAP suggests two possibilities, firstly, the patient has a noninfectious disorder that is mimicking NP/VAP and for this reason is not responding to antimicrobial therapy. Secondly, the patient could have an infectious disease, a process that is

unresponsive to antipseudomonal antimicrobial therapy, i.e., Herpes simplex virus 1 (HSV-1) pneumonia. HSV-1 pneumonia is common in the CCU setting and presents as persistent fever and infiltrates unresponsive to antibiotics, or as “failure to wean” in ventilated patients. In patients who present as “failure to wean,” these patients have persistent fevers and did not have antecedent severe lung disease that would compromise their ability to come off the respirator. NP/VAP with empiric treatment should see an improvement/resolution of infiltrates and a defervescence of fever within two weeks. Persistence of fever with or without infiltrates after two weeks, in the absence of another cause for the fever, should suggest HSV-1 pneumonia until proven otherwise. HSV-1 pneumonia is easily diagnosed by bronchoscopy, demonstrating cytopathic effects from cytology specimens or direct fluorescent antibody test (DFA)/monoclonal tests of respiratory secretions will be positive for HSV. Importantly, no vesicles are present in the bronchi in bronchoscoped patients with HSV-1 pneumonitis (5,51–53).

The clinical approach to the delayed resolution of fever, persistence of fever, or new appearance of fever is related to a complication of therapy, i.e., drug fever. After initial improvements in temperature/fever, a recrudescence of fever manifested by new fever/fever spikes may be related to the infectious process, or may be related to a noninfectious complication unrelated to therapy, i.e., myocardial infarction, gastrointestinal hemorrhage, acute pancreatitis, acute gout, deep vein thrombosis, phlebitis, pulmonary emboli/infarcts. The time that the fever spike occurs in relation to the initial defervescence, pulse–temperature relationships, and other associated findings are the key determinants diagnostically in sorting out possible explanations for the reappearance of fever in CCU patients. The recrudescence of fever is virtually never due to resistant organisms. Recrudescence of fever may be due to other infectious processes, i.e., candidemia, invasive aspergillosis, in patients with central lines, or on prolonged/high-dose steroid or immunosuppressive therapy. Lack of response to antimicrobial therapy suggests inadequate spectrum or insufficient activity against the pathogen in the antibiotic regimen that is selected (3,5,53).

### **CLINICAL APPROACH TO FEVER IN THE CCU**

Patients in the CCU with fever are admitted for a primary problem, but they also arrive with a variety of preexisting disorders that may interact or complicate the primary reason for admission to the CCU. Problems that occur in the CCU related to new problems, complications of the original/new problems, plus the effect of multiple medications make the diagnostic possibilities of explaining fever in the CCU complex. The cause of fever may be suggested by epidemiologic factors as well as the history, physical, laboratory, and radiology tests. If the main thrust of the diagnostic approach is to identify reversible/curable causes of fever, analysis of the fever characteristics is the best way to sort out differential diagnostic possibilities in the CCU. Careful attention should be given to whether the fever spike is isolated or sustained, whether the fever is greater/less than 102°F, the duration of the fever, and the relationship of the temperature to the pulse. Careful review of all the medications is essential not only to recognize drug side effects/interactions, but also to entertain the possibility of drug fever if other diagnoses are unlikely. Clinicians should also be familiar with the fever defervescence patterns of infectious and noninfectious disorders. Most situations are fairly straightforward, e.g., a steroid-dependent patient with SLE and flare who is in the CCU for the management of renal insufficiency and develops fevers >102°F without relative bradycardia, which are sustained. While there are many possibilities to explain these fevers, i.e., superimposed cytomegalovirus (CMV) or bacterial infections, the most important correctable factor to identify as the cause of the fever is inadequate steroid dosage. Patients on chronic corticosteroids when admitted to the CCU require stress doses of corticosteroids. Without increasing the corticosteroid daily dose, patients develop either a fever from a flare of their SLE/relative bradycardia and adrenal insufficiency, which presents as otherwise unexplained fever in such patients (Table 11) (1,5,6,8,54).

If an infectious etiology is suspected/diagnosed, empiric coverage should be based on site/pathogen associations. Specific therapy, if different from empiric therapy, may be used if empiric therapy is ineffective. Duration of therapy is a function of the type/site of infection and the status of the host defenses (55–57).

**Table 11** Diagnostic and Therapeutic Approach to Fever in the CCU

## Microbiologic data evaluation

- Critical to differentiate colonization from infection particularly with: respiratory secretion isolates in ventilated patients with fever, pulmonary infiltrates, and leukocytosis  
urinary isolates in normal hosts with urinary catheters  
analysis of origin of blood culture isolates
- Rule out pseudoinfections

## Common causes of fevers

- NP/VAP  
Chest X ray  
if negative, no nosocomial pneumonia/VAP  
if positive, rule out LVF, ARDS, etc.
- CVCs  
Duration of insertion  
The longer the CVC is in place > 7 days, the more likely the fever is due to CVC related infection  
Otherwise unexplained fevers in a patient with CVC should be regarded as CVC related infection until proven otherwise  
Evidence of infection at insertion site  
If IV insertion site shows sign of infection, remove CVC immediately, send tip for semiquantitative culture, and obtain blood cultures from peripheral vein  
If IV insertion site nonerythematous, CVC related infection not ruled out, remove/replace CVC and send removed catheter tip for semiquantitative culture
- If nosocomial pneumonia and CVC related infection eliminated as a cause of fever, consider drug fever

## Early empiric therapy

- Coverage based on site/organism correlations: colonization should not be treated
- Infectious disease consultant recommendations should be followed

*Abbreviations:* CVC, central venous catheter; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

Noninfectious causes of relapsing fevers include Crohn's disease, Behçet's disease, relapsing panniculitis leukoclastic angiitis, Sweet's syndrome, familial Mediterranean fever, Fapa's syndrome, hyper IgG syndrome, and SLE. The infectious causes of fevers that are prone to relapse include viral infections, i.e., CMV, Epstein-Barr virus (EBV), lymphocytic choriomeningitis (LCM), dengue, yellow fever, and Colorado tick fever. Zoonotic bacterial infections, i.e., leptospirosis, bartonellosis, brucellosis, rat bite fever (*Spirillum minus*), visceral leishmaniasis, malaria, babesiosis, ehrlichiosis, Q fever, typhoid fever, trench fever, and relapsing fever. Fungal infections tend to relapse as do melioidosis and tuberculosis. Chronic meningococcemia by definition is an infection prone to relapse (1,5).

**Suppression/Treatment of Fever**

Fever is an important clinical sign indicating a noninfectious or infectious disorder. The presence of fever should prompt the clinician to analyze its height, frequency, pattern, and associated history, physical findings, and laboratory tests to determine the cause of fever and appropriate treatment (1,4,5,27,42-44,53). Fever, per se, should not be treated unless the fever itself is a threat to the patient, i.e., extreme hyperpyrexia could result with CNS damage. Temperatures >102°F in patients with severe cardiac/pulmonary diseases could precipitate acute myocardial infarction or respiratory failure (5,58). Fever is also an important host defense mechanism that should not be suppressed without a compelling clinical rationale (58-60).

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# 2 | Fever and Rash in Critical Care

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## INTRODUCTION

There are numerous potential etiologic agents that can cause the syndrome of fever and rash. Skin manifestations may be an early sign of a life-threatening infection. The ability to rapidly identify the cause of fever and rash in critically ill patients is essential for the proper management of the patient and protection of the health care worker(s) providing care for that patient.

A rapid method to narrow the potential life-threatening causes of fever and rash has been described by Cunha (1). Patients from the community who are ill enough to be admitted to the critical care unit with the syndrome of fever and rash from outside the hospital will most likely have meningococemia, Rocky Mountain spotted fever (RMSF), community-acquired toxic shock syndrome (TSS), severe drug reactions, severe bacteremia, *Vibrio vulnificus* septicemia, gas gangrene, arboviral hemorrhagic fevers, dengue infection, or measles (Table 1). Patients who develop fever and rash after admission to the hospital will most commonly have drug reactions, staphylococcal bacteremia from central lines, systemic lupus erythematosus (SLE), or postoperative TSS.

The traditional approach to the patient with fever and rash is based on the characteristic appearance of the rash (2,3). The most common types of rash include petechial, maculopapular, vesicular, erythematous, and nodular. Although there can be overlap in presentation, most causes of fever and rash can be grouped into one specific form of cutaneous eruption (3).

A systematic approach requires a thorough history that includes patient age, seasonality, travel, geography, immunizations, childhood illnesses, sick contacts, medications, and the immune status of the host. A detailed history, physical exam, and characterization of the rash will help the clinician reduce the number of possible etiologies. Appropriate laboratory testing will also assist in delineating the cause of fever and rash in the critically ill patient.

## History

A comprehensive history of the events leading up to the development of fever and rash is essential in the determination of the etiology of the illness. Several initial questions should be answered before taking a complete history (4,5).

1. Can the patient or someone who is with the patient provide a history?
2. Does the patient require cardiopulmonary resuscitation?
3. Are special isolation precautions needed?

For example, patients with meningitis due to *Neisseria meningitidis* will need droplet precautions, while patients with *Varicella* infections will need airborne and contact precautions (Table 2). Health care workers should always exercise universal precautions. Gloves should be worn during the examination of the skin whenever an infectious etiology is considered.

4. Are the skin lesions suggestive of a disease process that requires immediate antibiotic therapy?

Patients with infections suggestive of *N. meningitidis*, RMSF, bacterial septic shock, TSS, or *V. vulnificus* will need urgent medical and possibly surgical treatment to improve their chance of survival.

5. Does the patient have an exotic disease due to travel or bioterrorism?



**Table 1** Etiology of Rash and Fever Based on Admission Status

Rash and fever on admission to the critical care unit	Rash and fever after admission to the critical care unit
Meningococemia	Drug reaction
RMSF	Nosocomial acquired TSS
Overwhelming pneumococcal or staphylococcal sepsis	Nosocomial staphylococcal sepsis
TSS	“surgical” scarlet fever
Epidemic typhus	<i>V. vulnificus</i>
Typhoid fever	Cholesterol emboli syndrome
Measles	
Arboviral hemorrhagic fever	
Gas gangrene (clostridial myonecrosis)	
Dengue	
SLE	

*Abbreviations:* RMSF, Rocky Mountain spotted fever; TSS, toxic shock syndrome; SLE, systemic lupus erythematosus.

*Source:* Data in table from text of a review by Cunha B. (Ref. 1).

Agents such as smallpox and viral hemorrhagic fevers (i.e., Ebola and Marburg) produce a generalized rash, while plague and anthrax may produce localized lesions. Isolation precautions will also need to be addressed (Table 2).

After the preliminary evaluation of the patient, the physician can obtain more information, including history of present illness and previous medical, social, and family histories.

Specific questions about the history of the rash itself are often helpful in determining its etiology (Table 3). Such questions should include time of onset, site of onset, change in appearance of the lesions, symptoms associated with the rash (i.e., itching, burning, numbness, tingling), provoking factors, previous rashes, and prior treatments.

The physical exam should focus on the patient’s vital signs, general appearance, and the assessment of lymphadenopathy, nuchal rigidity, neurological dysfunction, hepatomegaly, splenomegaly, arthritis, and mucous membrane lesions (Table 4) (3,4). Skin examination to determine type of the rash (Table 5) includes evaluation of distribution pattern, arrangement, and configuration of lesions.

The remainder of this chapter will provide a diagnostic approach to patients with fever and rash based on the characteristics of the rash. Several clinically relevant causes of each type of rash associated with fever are described in brief.

## PETECHIAL AND PURPURIC RASHES

Petechiae are produced by extravasation of red blood cells and are less than 3 mm in diameter. Petechiae appear as small red or brown spots on the skin. Purpura or ecchymoses are lesions that are larger than 3 mm and often form when petechiae coalesce. Neither petechial nor purpuric lesions blanch when pressure is applied.

Infections associated with diffuse petechiae are generally amongst the most life threatening and require urgent evaluation and management. There are many infectious causes of these lesions (Table 6); several of the most dangerous include meningococemia, rickettsial infection, and bacteremia (1,3,8).

### Acute Meningococemia

*N. meningitidis* is the leading cause of bacterial meningitis in children and young adults (10). Bacterial meningitis associated with a petechial or purpuric rash should always suggest meningococemia (1). The diagnosis of meningococemia is more difficult to make when meningitis is not present.

Meningococemia can occur sporadically or in epidemics and is more commonly diagnosed during the winter months. The risk of infection is highest in infants, asplenic

**Table 2** Transmission-Based Precautions for Hospitalized Patients*Standard precautions*

Use standard precautions for the care of all patients

*Airborne precautions*

In addition to standard precautions, use airborne precautions for patients known or suspected to have serious illnesses transmitted by airborne droplet nuclei. Examples of such illnesses include:

- Measles
- Varicella (including disseminated zoster)<sup>a</sup>
- Tuberculosis<sup>b</sup>

*Droplet precautions*

In addition to standard precautions, use droplet precautions for patients known or suspected to have serious illnesses transmitted by large particle droplets. Examples of such illnesses include:

- Invasive *Haemophilus influenzae* type b disease, including meningitis, pneumonia, epiglottitis, and sepsis
- Invasive *N. meningitidis* disease, including meningitis, pneumonia, and sepsis

Other serious bacterial respiratory infections spread by droplet transmission, including:

- Diphtheria (pharyngeal)
- Mycoplasma pneumoniae*
- Pertussis
- Pneumonic plague
- Streptococcal pharyngitis, pneumonia, or scarlet fever in infants and young children

Serious viral infections spread by droplet transmission, including those caused by:

- Adenovirus
- Influenza
- Mumps
- Parvovirus B19
- Rubella

*Contact precautions*

In addition to standard precautions, use contact precautions for patients known or suspected to have serious illnesses easily transmitted by direct patient contact or by contact with items in the patient's environment.

Examples of such illnesses include:

Gastrointestinal, respiratory, skin, or wound infections or colonization with multidrug-resistant bacteria judged by the infection control program, based on current state, regional, or national recommendations, to be of special clinical and epidemiologic significance

Enteric infections with a low infectious dose or prolonged environmental survival, including those caused by:

*Clostridium difficile*

For diapered or incontinent patients: enterohemorrhagic *Escherichia coli* O157:H7, *Shigella*, hepatitis A, or rotavirus

Respiratory syncytial virus, parainfluenza virus, or enteroviral infections in infants and young children

Skin infections that are highly contagious or that may occur on dry skin, including:

- Diphtheria (cutaneous)
- Herpes simplex virus (neonatal or mucocutaneous)
- Impetigo
- Major (non-contained) abscesses, cellulitis, or decubiti
- Pediculosis
- Scabies
- Staphylococcal furunculosis in infants and young children
- Zoster (disseminated or in the immunocompromised host)

Viral/hemorrhagic conjunctivitis

Viral hemorrhagic infections (Ebola, Lassa, or Marburg)

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CDC infection control guidelines reprinted from Garner JS and the Hospital Infection Control Practices Advisory Committee.

<sup>a</sup>Certain infections require more than one type of precaution.

<sup>b</sup>See Centers for Disease Control and Prevention.

Source: From Refs. 6 and 7.

patients, alcoholics, patients with complement deficiency, and persons who live in dormitories (coeds, military personnel, or prisoners). Initial symptoms include cough, headache, sore throat, nausea, and vomiting. Acute meningococemia progresses rapidly and patients typically appear ill with high spiking fevers, tachypnea, tachycardia, mild hypotension, and a characteristic petechial rash (11,12). Signs and symptoms of meningeal irritation such as

**Table 3** Fever and Rash: History

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Age of patient  
 Season of the year  
 Type of prodrome associated with current illness  
 History of drug or antibiotic allergies  
 Medications taken within the past 30 days (prescription or nonprescription)  
 Drug ingestion  
 Exposure to febrile or ill persons within the recent past  
 Prior illness  
 Occupational exposures  
 Sun exposures  
 Recent travel  
 Exposure to wild or rural habitats  
 Exposure to insects, arthropods, or wild animals  
 Exposure to pets  
 Immunizations  
 Exposure to sexually transmitted diseases  
 HIV risk factors (intravenous drug use, unprotected sex, sexual orientation)  
 Site of rash onset  
 Factors effecting immunological status (chemotherapy, steroid use, hematological malignancy, solid organ or bone marrow transplant, asplenia)  
 Valvular heart disease  
 Rate of rash development (slow versus fast)  
 Direction of rash spread (centrifugal versus centripetal)  
 Evolution of rash (has the appearance of the rash changed)  
 Relationship between rash and fever  
 Presence or absence of pruritus  
 Previous treatment of the rash (topical or oral therapies)

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*Source:* Adapted from Refs. 5 and 8.

**Table 4** Fever and Rash: Physical Examination

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1. Vital signs
    - a. Temperature
    - b. Pulse
    - c. Respiration
    - d. Blood pressure
  2. General appearance
    - a. Alert
    - b. Acutely ill
    - c. Chronically ill
  3. Signs of toxicity
  4. Adenopathy/location of adenopathy
  5. Presence of mucosal, conjunctival, or genital lesions
  6. Hepatosplenomegaly
  7. Arthritis
  8. Nuchal rigidity/neurological dysfunction
  9. Features of rash
    - a. Type of primary rash lesion (Table 5)
    - b. Presence of secondary lesions
    - c. Presence of desquamation
    - d. Presence of excoriations
    - e. Configuration of individual lesions
    - f. Arrangement of lesions
    - g. Distribution pattern: exposed areas; centripetal versus centrifugal
- 

*Source:* Adapted from Refs. 5 and 8.

**Table 5** Type of Rash Lesions

Macule	A circumscribed, flat lesion that differs from surrounding skin by color. Patches are very large macular lesions.
Papule	A circumscribed, solid, elevated skin lesion that is palpable and smaller than 0.5 cm in diameter.
Plaque	A large, solid, elevated skin lesion that is palpable and greater than 0.5 cm in diameter, often formed by confluence of papules.
Nodule	A circumscribed, solid, palpable skin lesion with depth as well as elevation.
Pustule	A circumscribed, raised lesion filled with pus
Vesicle	A circumscribed, elevated, fluid-filled lesion less than 0.5 cm in diameter
Bulla	A circumscribed, elevated, fluid-filled lesion greater than 0.5 cm in diameter

Source: Adapted from Refs. 5 and 9.

**Table 6** Etiology of Rash and Fever Based on Type of Rash

Purpura or petechiae
Meningococcemia
RMSF
Gonococcemia
Staphylococcal/pneumococcal sepsis
Pseudomonas sepsis
Bacterial endocarditis
Typhus
Allergic vasculitis
Echovirus 9
Measles
Centrally distributed maculopapular rash
Viral exanthems (rubeola, rubella, erythema infectiosum, roseola)
Lyme disease
Drug reactions
Peripherally distributed maculopapular rash
Erythema multiforme (Table 7)
Secondary syphilis
Diffuse erythema with desquamation
Scarlet fever
TSS
Scalded skin syndrome
KD
Ehrlichiosis
TEN
<i>Streptococcus viridans</i> bacteremia
Vesicular, bullous, or pustular rash
Varicella
Herpes zoster
Herpes simplex
<i>Staphylococcus aureus</i> bacteremia
<i>Vibrio vulnificus</i>
<i>Rickettsia akari</i>
Nodular rash
Erythema nodosum (Table 8)
Disseminated fungal infections ( <i>Candida</i> , <i>Cryptococcus</i> , <i>Blastomycosis</i> , <i>Histoplasma</i> , <i>Coccidioides</i> , and <i>Sporothrix</i> )
<i>Nocardia</i>
Mycobacteria

Abbreviations: KD, Kawasaki disease; TEN, toxic epidermal necrolysis; RMSF, Rocky Mountain spotted fever; TSS, toxic shock syndrome.

Source: Adapted from Refs. 1, 3, 5, and 8.

headache, vomiting, and change in consciousness occur in up to 88% of patients with meningococcemia (11,13).

The rash associated with meningococcemia begins within 24 hours of clinical illness. The petechia enlarge rapidly, becoming papular and then purpuric. Lesions most commonly occur on the extremities and trunk, but may also be found on the head and mucous membranes (5).



**Figure 1** Purpuric skin lesions on an infant with meningococcal septicemia. *Source:* Courtesy of the CDC Public Health Image Library.

The development of lesions on the palms and soles is usually a late finding (1). Purpuric skin lesions have been described in 60% to 100% of meningococemia cases and are most commonly seen at presentation (Fig. 1) (14,15). Histological studies demonstrate diffuse vascular damage, fibrin thrombi, vascular necrosis, and perivascular hemorrhage in the involved skin and organs. The skin lesions associated with meningococcal septic shock are thought to result from an acquired or transient deficiency of protein C and/or protein S (16). Meningococci are present in endothelial cells and neutrophils, and smears of skin lesions are positive for gram-negative diplococci in many cases (17,18).

The diagnosis of meningococemia is also aided by culturing the petechial lesions. Blood cultures should be drawn. Admission laboratory data usually demonstrate a leukocytosis and thrombocytopenia. Patients with meningococemia but without meningitis will have a normal cerebrospinal fluid (CSF) profile. If meningococcal meningitis is present, the CSF culture is usually positive although the Gram stain may be negative. Typically, the CSF-associated glucose is low and the protein elevated.

### Chronic Meningococemia

Chronic meningococemia is rare, and its lesions differ from those seen in acute meningococemia. Diagnosis of chronic meningococemia is challenging. Patients present with intermittent fever, rash, arthritis, and arthralgias occurring over a period of several weeks to months (19,20). The lesions of chronic meningococemia are usually pale to pink macules and/or papules typically located around a painful joint or pressure point. Nodules may develop in the lower extremities. The lesions of chronic meningococemia develop during periods of fever and fade when the fevers dissipate. These lesions (in contrast to those of acute meningococemia) rarely demonstrate the bacteria on Gram stain or histology (5,8). Polymerase chain reaction (PCR) testing of skin biopsy specimens may prove to be a valuable method of diagnosis for this rare entity (21).

### RSMF

RMSF, the most lethal rickettsial disease in the United States, is caused by *Rickettsia rickettsii* (22–25). Infection occurs approximately seven days after a bite by a tick vector (Dermacentor or Rhicephalus). Two hundred fifty to twelve hundred cases of RMSF are reported annually (26). Patients who have frequent exposure to dogs and live near wooded areas or areas with high grass may be at increased risk of infection. RMSF is more common in men and is most prevalent in the southern Atlantic and southern central states. North Carolina and Oklahoma are the states with the highest incidence, accounting for over 35% of the cases. Over 90% of patients are infected between April and September. During this season, there are increased



**Figure 2** Child's right hand and wrist demonstrating the characteristic spotted rash of RMSF. *Abbreviation:* RMSF, Rocky Mountain spotted fever. *Source:* Courtesy of the CDC Public Health Image Library.

numbers of ticks. Furthermore, research has demonstrated a link between warm temperatures and increased tick aggressiveness (27).

The onset of RMSF can be abrupt with fever, headache, myalgias, shaking chills, photophobia, and nausea. Patients may have periorbital edema, conjunctival suffusion, and localized edema involving the dorsum of the hands and feet (1,28). A notable clinical finding is a pulse-temperature disparity (i.e., relative bradycardia during fever). Localized abdominal pain secondary to liver involvement, renal failure manifested by acute tubular necrosis, pancreatitis, left ventricular failure, adult respiratory distress syndrome (ARDS), and mental confusion or deafness may also be noted (1).

The rash usually begins about four to five days after the start of the illness. The lesions are initially maculopapular and evolve into petechiae within two to four days. Characteristically, the rash starts on the wrists, forearms, ankles, palms, and soles and then spreads centripetally to involve the arms, thighs, trunk, and face (Fig. 2). Centripetal evolution of the rash occurs 6 to 18 hours after the rash develops.

Prompt treatment with tetracycline decreases mortality (29,30). Most patients defervesce within two to three days and these patients should receive treatment for at least three days after showing improvement (31). Chloramphenicol, the only other antimicrobial agent recommended for the treatment of RMSF, causes gray baby syndrome and should not be used for pregnant women who are near term (31). Gray baby syndrome occurs because of a lack of the necessary liver enzymes to metabolize chloramphenicol resulting in drug accumulation, which leads to vomiting, ashen gray skin color, limp body tone, hypotension, cyanosis, hypothermia, cardiovascular collapse, and often death. Pregnant women who are near term may receive tetracycline because the risk of fetal damage or death is minimal. Pregnant women, in the first or second trimester, should not receive tetracycline because of effects on fetal bone and dental development. Chloramphenicol can be administered in early pregnancy because gray baby syndrome is not a risk during the early period of fetal development (31).

Mortality from RMSF may be decreasing over the last decade. Initial mortality in the United States was reported to be about 20%; however, Raoult and Parola (32) suggest that the actual case mortality rate has decreased to 0.7% to 1.4%. This decrease in mortality may be related to infection with less severe rickettsioses or variations in virulence of some *R. rickettsii* strains.

Clinical diagnosis is the basis for treatment. Serological testing is sensitive but does not distinguish between infection with *R. rickettsii* and other rickettsiae of the spotted fever

group (33). Indirect fluorescent antibody testing is the best serological method available; however, the test has poor sensitivity during the first 7 to 10 days of disease onset. Sensitivity increases to greater than 90% when a convalescent serum is available 14 to 21 days later (31). Direct immunofluorescence on tissue specimens has a sensitivity of about 70%. PCR is limited because of poor sensitivity for detecting *R. rickettsii* DNA in blood (33). The Weil–Felix test is no longer recommended because of poor sensitivity and specificity.

Routine admission tests may demonstrate a normal or decreased peripheral white blood cell count and thrombocytopenia. The total bilirubin and serum transaminases may be elevated. If pancreatitis is present, the serum amylase will be elevated. Patients who develop renal failure may demonstrate a rise in blood urea nitrogen (BUN) and creatinine suggestive of pre-renal azotemia secondary to intravascular volume deficit. When the central nervous system is involved, the CSF profile will demonstrate a mild pleocytosis, normal glucose and protein concentrations, and negative Gram stain and culture. Routine blood cultures will also be negative in RMSF.

### Septic Shock

The yearly incidence of sepsis has been increasing about 9% a year and accounts for 2% of all hospital admissions (34). The peak incidence of septic shock occurs in patients who are in their seventh decade of life (35). Risk factors for sepsis include cancer, immunodeficiency, chronic organ failure, and iatrogenic factors. Sepsis develops from infections of the chest, abdomen, genitourinary system, and primary bloodstream in more than 80% of cases (35,36).

Symmetric peripheral gangrene or purpura fulminans is a cutaneous syndrome most commonly associated with septic shock secondary to *N. meningitidis* or *Streptococcus pneumoniae*. This syndrome is usually preceded by petechiae, ecchymosis, purpura, and acrocyanosis. Acrocyanosis, another cutaneous manifestation of septic shock, is a grayish color to the skin that occurs on the lips, legs, nose, ear lobes, and genitalia and does not blanch on pressure. Bacteria are usually absent in smears obtained from these skin lesions.

Sepsis is defined as systemic inflammatory response syndrome with documented infection. Patients with sepsis will therefore have a documented site of infection and display two or more of the following: body temperature greater than 101.3 °F or less than 95 °F; heart rate greater than 90 beats per minute; respiratory rate greater than 20 breaths per minute; arterial CO<sub>2</sub> tension less than 32 mm Hg; WBC greater than 12,000/mm<sup>3</sup> or WBC less than 4,000/mm<sup>3</sup>; or immature forms greater than 10%. With severe sepsis, patients begin to demonstrate areas of mottled skin, capillary refill time greater than three seconds, decreased urine output, changes in mental status, thrombocytopenia, disseminated intravascular coagulopathy (DIC), cardiac dysfunction, and ARDS. When patients can no longer maintain a systemic mean arterial blood pressure of 60 mm Hg, despite volume resuscitation, or they require a vasopressor agent, then they are said to be in septic shock. Mortality varies from 35% to 70% depending on patients' age, sex, ethnic origin, comorbidities, presence of acute lung injury or ARDS, whether the infection is nosocomial or polymicrobial, or whether the causative agent is a fungus (35,36). Gram-negative infections are responsible for 25% to 30% of cases of septic shock, while gram-positive infections now account for 30% to 50% of the cases of septic shock. Multidrug-resistant bacteria and fungi are increasingly reported as causes of sepsis (35,36).

The diagnosis of septic shock requires a causal link between infection and organ failure (35). Some patients may have clinically obvious infection such as purpura fulminans, cellulitis, TSS, pneumonia, or a purulent wound. Without an obvious source of infection, diagnosis will require the recovery of pathogens from blood or tissue cultures. Unfortunately, cultures are negative in 30% of these cases.

Mortality associated with sepsis is high and increasing (37). The rate of hospitalization for severe sepsis has doubled in the 10-year span from 1993 to 2003 (38). During this period of time, the case fatality rate has decreased but because there are so many more cases of sepsis, the overall mortality rate increased (38). Surviving sepsis campaign guidelines were published in 2008 and provide a thorough review of treatment options for severe sepsis and septic shock (38). Important steps to the treatment of sepsis include (*i*) ruling out mimics of sepsis (disorders that present with fever, leukocytosis, and hypotension, such as pulmonary emboli, myocardial infarction, necrotic pancreatitis, acute gastrointestinal hemorrhage, etc.);

(ii) determining the source of sepsis; and (iii) starting empiric antibiotics that cover the predictable pathogens and have a low resistance potential and good safety profile (38,39).

### Bacterial Endocarditis

Infective endocarditis is described as acute or subacute based on the tempo and severity of the clinical presentation (40). Categories of infective endocarditis include native valve infective endocarditis, prosthetic valve endocarditis, infective endocarditis associated with intravenous drug abuse, and nosocomial infective endocarditis (41). The characteristic lesion is vegetation composed of platelets, fibrin, microorganisms, and inflammatory cells on the heart valve. Conditions associated with endocarditis include injection drug use, poor dental hygiene, long-term hemodialysis, diabetes mellitus, HIV infection, long-term indwelling venous catheters, mitral valve prolapse with regurgitation, rheumatic heart disease, other underlying valvular diseases, and prosthetic valves (42–44). Organisms associated with endocarditis include *Staphylococcus aureus*, viridans streptococci, enterococci, gram-negative bacilli (including the HACEK organisms; *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*), and fungi.

Nonspecific symptoms and signs of endocarditis include fever, arthralgias, wasting, unexplained heart failure, new heart murmurs, pericarditis, septic pulmonary emboli, strokes, and renal failure (45). Skin lesions occur less frequently today than they once did but aid in the diagnosis if present (45). Cutaneous manifestations of endocarditis include splinter hemorrhages (Fig. 3), petechiae, Osler's nodes, and Janeway lesions.

Petechiae are the most common skin lesions seen during endocarditis. The petechiae are small, flat, and reddish brown and do not blanch with pressure. They frequently occur in small crops and are usually transient. They are often found on the heels, shoulders, legs, oral mucous membranes, and conjunctiva.

Osler's nodes may be seen in patients with subacute bacterial endocarditis. These nodules are tender, indurated, and erythematous. They occur most commonly on the pads of the fingers and toes, are transient, and resolve without the development of necrosis. The histology of these lesions demonstrates microabscesses and microemboli.

Janeway lesions are small, painless, erythematous macules that are found on the palms and soles. These lesions can be seen with both acute and subacute endocarditis. Histological analysis reveals microabscesses with neutrophil infiltration.

### Disseminated Gonococcal Infection

Disseminated gonococcal infections (DGI) result from gonococcal bacteremia and occur in 1% to 3% of patients with untreated *N. gonorrhoea*-associated mucosal infection (46–48). DGI is most



**Figure 3** Subungual hemorrhages in an adult patient with group B streptococcal endocarditis. *Source:* Courtesy of Dr Lee S. Engel.





**Figure 4** Cutaneous lesions on the left ankle and calf of a patient with disseminated *Neisseria gonorrhoeae* infection. Source: Courtesy of the CDC/Dr S.E. Thompson, Public Health Image Library.

often seen in young women during menses or pregnancy (49). Most patients will present with fever, rash, polyarthrititis, and tenosynovitis (47).

Skin lesions, which occur in 50% to 70% of patients with DGI, are the most common manifestation (49). The rash usually begins on the first day of symptoms and becomes more prominent with the onset of each new febrile episode (50). The lesions begin as tiny red papules or petechiae (1–5 mm in diameter) that evolve to a vesicular and then pustular form (Fig. 4). The pustular lesions develop a gray, necrotic center with a hemorrhagic base (47,50). The rash of DGI tends to be sparse and widely distributed, and the distal extremities are most commonly involved. Gram stain of the skin lesions rarely demonstrates organisms.

Clinical clues of DGI include the symptoms of fever, rash, and arthritis/tenosynovitis. Early in the infection, blood cultures may be positive; later, synovial joint fluid from associated effusions may yield positive cultures. Smears of the cervix and urethral exudates may also yield positive results.

### **Capnocytophaga Infection**

*Capnocytophaga canimorsus* is a fastidious gram-negative bacillus that is part of the normal gingival flora of dogs and cats (51,52). Human infections are associated with dog or cat bites, cat scratches, and contact with wild animals (51,52). Predisposing factors include trauma, alcohol abuse, steroid therapy, chronic lung disease, and asplenia (51,52). The clinical syndrome consists of fever, disseminated intravascular coagulation (DIC), necrosis of the kidneys and adrenal glands, thrombocytopenia, hypotension, and renal failure. The mortality rate approaches 25%.

Skin lesions occur in 50% of infected patients, often progressing from petechiae to purpura to cutaneous gangrene (53). Other dermatologic lesions include macules, papules, painful erythema, or eschars.

Clinical clues include a compatible clinical syndrome and a history of a dog- or cat-inflicted wound. Diagnosis depends on the culture of the bacteria from blood, tissues, or other body fluids. Unfortunately, the diagnosis is missed in greater than 70% of cases because of lack

of familiarity with the bacteria and its microbiological growth characteristics (54). More prompt diagnosis may be made by Gram staining the buffy coat. *C. canimorsus* is found in the neutrophil and has a characteristic, filamentous, rod-shaped morphology (54).

## Dengue

Dengue is a flavivirus comprising four serotypes, i.e., DEN-1, DEN-2, DEN-3, and DEN-4. Dengue viruses are transmitted from person to person through infected female *Aedes* mosquitoes. The mosquito acquires the virus by taking a blood meal from an infected human or monkey. The virus incubates in the mosquito for 7 to 10 days before it can transmit the infection.

Dengue has made an enormous resurgence over the last decade (55,56). More than 2.5 billion people are at risk for dengue infections worldwide (57). The year 2007 was the worst on record since 1985 with almost 1 million cases of dengue fever and dengue hemorrhagic fever reported in the United States (58). The resurgence of dengue has been attributed to multiple factors including global population growth, urbanization, deforestation, poor housing and waste management systems, deteriorating mosquito control, virus evolution, and climate change (56).

Dengue fever (also known as “breakbone fever” or “dandy fever”) is a short-duration, nonfatal disease characterized by the sudden onset of headache, retro-orbital pain, high fever, joint pain, and rash (57,59). The initial rash of dengue occurs within the first 24 to 48 hours of symptom onset and involves flushing of the face, neck, and chest (60). A subsequent rash, three to five days later, manifests as a generalized morbilliform eruption, palpable pinpoint petechiae, and islands of sparing that begin centrally and spread peripherally (1,60). Dengue fever lasts about seven days. Recovery from infection provides lifelong immunity to that serotype, but does not preclude patients from being infected with the other serotypes of dengue virus, i.e., secondary infections.

Dengue hemorrhagic fever and dengue TSS are two deadly complications of dengue viral infection that occur during secondary infection. Dengue hemorrhagic fever is characterized by hemorrhage, thrombocytopenia, and plasma leakage. Dengue shock syndrome includes the additional complications of circulatory failure and hypotension (57,59).

The incubation period for dengue virus infections is 3 to 14 days. If a patient presents greater than two weeks after visiting an endemic area, dengue is much less likely (61). Laboratory abnormalities include neutropenia followed by lymphocytosis, hemoconcentration, thrombocytopenia, and an elevated aspartate aminotransferase in the serum (62). The diagnosis of dengue virus-associated infection can be accomplished by PCR, detection of anti-dengue virus immunoglobulin M (IgM), centrifugation amplification to enhance virus isolation, or flow cytometry for early detection of cultured virus (63).

## MACULOPAPULAR RASH

### Lyme Disease

Lyme disease is the most common tick vector-associated disease in the United States (64–66). Lyme disease is caused by the spirochete *Borrelia burgdorferi*, a microbe that is transmitted by the tick *Ixodes*. Lyme disease is endemic in the northeastern, mid-Atlantic, north, central, and far western regions of the United States. The disease has a bimodal age distribution, with peaks in patients younger than 15 and older than 29 years of age (67). Most infections occur between May and September.

Lyme disease has three stages: early localized, early disseminated, and late disease. Early localized disease is characterized by erythema migrans (EM), which forms 7 to 10 days following the tick bite (68). Erythema migrans occurs in 60% to 80% of the cases and begins as a small red papule at the site of the bite. The lesion expands centrifugally and can get as large as 70 cm in diameter. The lesion develops central clearing in 30% of cases (Fig. 5). If untreated, the lesions resolve over several weeks. Other symptoms associated with early localized disease include fatigue, myalgias, arthralgias, headache, fever, and chills.

Early disseminated disease occurs days to weeks after the tick bite. Patients may not recall having had the typical EM rash. Patients at this stage can present with lymphocytic meningitis, cranial nerve palsies, mild pericarditis, atrial-ventricular block, arthritis, generalized or regional adenopathy, conjunctivitis, iritis, hepatitis, and painful radiculoneuritis



**Figure 5** Characteristic rash, erythema migrans, on the arm of a patient with Lyme disease. *Source:* Courtesy of the CDC.

followed by decreased sensation, weakness, and absent reflexes (64,65,69). Disseminated skin lesions, when present, are similar to EM but smaller and usually multiple in number.

Late disease is characterized by chronic asymmetric oligoarticular arthritis that involves the large joints (most often the knee). The central nervous system may also be affected, manifesting as subacute encephalopathy, axonal polyneuropathy, or leukoencephalopathy.

Diagnosis is based on the history and physical exam. Serology is confirmatory but takes four to six weeks after the onset of symptoms to become positive. CSF should be obtained if neurological signs are present. Synovial fluid can be evaluated if arthritis is present.

### Drug Reactions

Drugs cause adverse skin reactions in 2% to 3% of hospitalized patients (70). Classic drug reactions include urticaria, angioedema, exanthems, vasculitis, exfoliative dermatitis/erythroderma, erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis (TEN) (70–72). There is no predilection for age, gender, or race (8). Diagnosis of a drug reaction is based on a patient's previous reaction to the drug, ruling out alternate etiological causes of the rash, timing of events, drug levels, evidence of overdose, patient reaction to drug discontinuation, and patient reaction to rechallenge.

### Drug Exanthems

Exanthems are the most common skin reaction to drugs. The rash usually appears within the first two weeks after the offending drug is started and resolves within days after the drug is stopped. The rash is often described as morbilliform, macular, and/or a papular eruption. Pruritus is the most common associated symptom of drug-induced rash. Low-grade fever and peripheral blood eosinophilia may also occur in association with drug exanthems.

### Erythema Multiforme

Erythema multiforme is an acute, self-limited, peripheral eruptive maculopapular rash that is characterized by a target lesion. Erythema multiforme most often affects persons between 20 and 30 years of age and has a predilection for men. The rash begins as a dull-red macular eruption that evolves into papules and the characteristic target lesion. Target lesions are often found on the palms, soles, knees, and elbows. Vesicles and bullae occasionally develop in the center of the papules (8,72). There are many causes of this disorder (Table 7).

**Table 7** Causes of Erythema Multiforme

Viral infections	Anticonvulsants
Herpes simplex 1 and 2	Barbiturates
Epstein–Barr virus	Carbamazepine
Hepatitis A, B, C	Phenytoin
Varicella zoster	Antituberculoïds
Parvovirus B19	Rifampin
Bacterial infections	Isoniazid
Hemolytic streptococci	Pyrazinamide
<i>Pneumococcus</i>	Other drugs
<i>Staphylococcus</i> species	Allopurinol
<i>Proteus</i> species	Fluconazole
<i>Salmonella</i> species	Hydralazine
<i>Mycobacterium tuberculosis</i>	NSAIDs
<i>Mycobacterium avium</i> complex	Estrogen
<i>Francisella tularensis</i>	Physical factors/contact
<i>Vibrio parahaemolyticus</i>	Sunlight
<i>Yersinia</i> species	Cold
<i>Mycoplasma pneumonia</i>	X-ray therapy
Fungal infections	Tattooing
<i>Histoplasma capsulatum</i>	Poison ivy
Coccidiomycosis	Other factors
Parasitic infections	Pregnancy
<i>Trichomonas</i> species	Multiple myeloma
<i>Toxoplasma gondii</i>	Leukemia
Antibiotics	Collagen diseases
Penicillin	Idiopathic (50%)
Tetracyclines	
Erythromycin	
Sulfa drugs	
Vancomycin	

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: Adapted from Ref. 72.

Erythema multiforme may present with varying degrees of severity (previously classified as erythema multiforme minor and major) (8). Bullae and systemic symptoms are absent in less severe erythema multiforme. The rash rarely affects the mucous membranes and is usually limited to the extensor surfaces of the extremities. This mild form of erythema multiforme is often associated with herpes simplex virus infection. Conversely, drug reactions are usually associated with more severe manifestations of erythema multiforme. Mucous membranes are involved, and the eruptions often become bullous. Fever, cheilosis, stomatitis, balanitis, vulvitis, and conjunctivitis can also occur (70).

### Stevens–Johnson Syndrome

Stevens–Johnson syndrome is a blistering disorder that is usually more severe than erythema multiforme (73,74). The causes of Stevens–Johnson syndrome are similar to the etiologies of erythema multiforme (Table 7). Patients with Stevens–Johnson syndrome often present with pharyngitis, malaise, and fever. The syndrome evolves over a few days with the evolution of mucous membrane erosions. Small blisters develop on purpuric or atypical target lesions. The blisters eventually result in skin detachment. Stevens–Johnson syndrome affects less than 10% of the total body surface (70,74).

### TEN

TEN is the most serious cutaneous drug reaction and is defined by blistering of over 30% of the total body surface area. More than one mucous membrane is involved. It is usually caused by the same drugs that cause erythema multiforme (Table 7), and its onset is acute. A fever greater than 39°C is often present. Intestinal and pulmonary involvement predict a poor outcome (70,71).

The diagnosis of Stevens–Johnson syndrome and TEN is made by skin biopsy. Sections of frozen skin will demonstrate full-thickness epidermal necrosis. Because extensive skin detachment results in massive transepidermal fluid losses, patients with these maladies are managed similarly to patients who have had extensive burn injuries. Sepsis can result secondary to microbial colonization of denuded skin. Mortality rates are 5% for Stevens–Johnson syndrome and 50% for TEN (70).

### Secondary Syphilis

Syphilis is a systemic disease caused by *Treponema pallidum*. It is classified into primary, secondary, early latent, late latent, and tertiary stages. The lesion of primary syphilis, the chancre, usually develops about 21 days after infection and resolves in one to two months. Patients with secondary syphilis can present with rash, mucosal lesions, lymphadenopathy, and fever. The rash of secondary syphilis may be maculo-papular, papulosquamous, or pustular and is characteristically found on the palms and the soles (Fig. 6).

The diagnosis of syphilis is based on nontreponemal tests [e.g., Venereal Disease Research Laboratory (VDRL), Rapid Plasma Reagin (RPR)] and specific treponemal tests [e.g., Fluorescent Treponemal Antibody Absorbed (FTA-ABS) and *T. pallidum* particle agglutination (TP-PA)]. The nontreponemal tests are used to screen for disease and follow up treatment. The specific treponemal tests are used to rule in the diagnosis of syphilis because false-positive nontreponemal tests can occur. Darkfield examination of skin or mucous membrane lesions can be done to diagnose syphilis definitively during the early stages as well.

### West Nile Virus

West Nile virus (WNV) is transmitted to humans from the bite of an infected mosquito (75). The virus normally circulates between mosquitoes and birds. The first reported outbreak in the United States was in New York in 1999, and since then WNV has spread southward and westward (76–79). WNV has become seasonally endemic, with peak activity for transmission from July to October in temperate zones and from April to December in warmer climates (77,79).



**Figure 6** Papulosquamous rash on wrist and hands of patient with secondary syphilis. *Source:* Courtesy of the CDC/Susan Lindsley, Public Health Image Library.

Though most commonly spread by infected mosquitoes, WNV may also be transmitted by organ transplantation, blood transfusion, and breast milk (80–82). Transplacental infection from mother to fetus has also been reported (80).

WNV replicates at the site of inoculation and then spreads to the lymph nodes and bloodstream (83). The majority of human infections, i.e., 80%, are asymptomatic (84). Most patients with symptoms have self-limited West Nile fever. West Nile fever is characterized by acute onset of fever, headache, fatigue, malaise, muscle pain, difficulty concentrating, and neck pain (85,86). Approximately 57% of patients with West Nile fever will have a transient macular rash on the trunk of the body (85).

Neuroinvasive disease develops in less than 1% of infected patients (84). The clinical severity of WNV encephalitis ranges from disorientation to coma to death (87,88). Advanced age is the most significant risk factor for severe neurologic disease. Risk increases tenfold for persons 50 to 59 years of age and 43 times for persons greater than 80 years of age (77,81). Neuroinvasive disease can present as meningitis, encephalitis, or paralysis (84,86,88,89). Patients with WNV encephalitis or focal neurologic findings will often have persistent deficits for months to years (77,88). Advanced age is also the most important risk factor for death. The overall case fatality rate for neuroinvasive WNV disease is 9% (77).

Diagnosis of WNV disease can be made by a high index of clinical suspicion and detection of WNV-specific immunoglobulin M (IgM) in serum or CSF. The serum IgM can persist for up to eight months; therefore, nucleic amplification tests for WNV such as reverse transcriptase PCR and real-time PCR may be required to prove that the infection is acute (86,90). Neuroinvasive WNV can be diagnosed by the presence of IgM-specific antibody in the CSF. Patients who have been recently vaccinated for yellow fever or Japanese encephalitis or persons recently infected with the St. Louis encephalitis virus or dengue virus may have false-positive results on IgM antibody tests for WNV (91).

## **DIFFUSE ERYTHEMATOUS RASHES WITH DESQUAMATION TSS**

TSS is characterized by sudden onset of fever, chills, vomiting, diarrhea, muscle aches, and rash. TSS can rapidly progress to severe hypotension and multi-organ dysfunction. The overall case fatality rate is 5%.

The microbial etiology of TSS is usually *S. aureus*; however, coagulase-negative staphylococci, group A streptococci, and group B streptococci can also produce this syndrome (92–94).

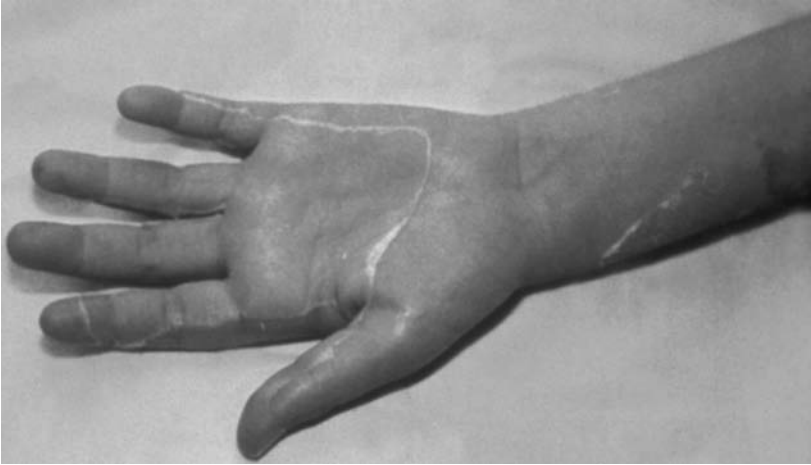
TSS is most commonly seen in menstruating women, women using barrier contraceptive devices, persons who have undergone nasal surgery, and patients with postoperative staphylococcal wound infections (95). Initially, cases associated with menstruation accounted for as many as 91% of the total cases (95). Currently, only half of the reported TSS cases are menses associated (96).

### *Staphylococcal TSS*

Staphylococcal TSS is caused by infection or colonization with toxin-producing bacteria. The most common toxins associated with TSS include toxin 1 and enterotoxin B (97–100). Other toxins that may be involved include enterotoxins A, C, D, E, and H (101).

The clinical presentation of TSS was defined by the Centers for Disease Control (CDC) in 1981 (4). All patients with TSS have high fever (>39°C), hypotension, and skin manifestations. Patients may also present with headache, vomiting, diarrhea, myalgias, pharyngitis, conjunctivitis, vaginitis, arthralgias, abdominal pain, or encephalopathy (102–105). The syndrome can progress to shock, disseminated intravascular coagulation, ARDS, and renal failure.

The rash of TSS may start as erythroderma that involves both the skin and mucous membranes. It is diffuse, red, and macular and may resemble sunburn. The rash can involve the palms and soles. The erythema may be more intense around a surgical wound site. Mucosal involvement can involve the conjunctiva, oropharynx, or vagina (106). One to three weeks after the onset of TSS, the palms and soles may desquamate (Fig. 7) (107).



**Figure 7** Desquamation of left palm of a patient with TSS. *Abbreviation:* TCC, toxic shock syndrome. *Source:* Courtesy of the CDC, Public Health Image Library.

TSS can be divided into menstrual and nonmenstrual. The majority of menstrual cases of TSS are associated with tampon use (108). Nonmenstrual cases are caused by abscesses, cellulitis, bursitis, postpartum infections, vaginal infections, sinusitis, burn wounds, insect bites, and surgical procedures (104,109).

The diagnosis of TSS is based on the CDC diagnostic criteria (4). Although *S. aureus* is isolated from mucosal or wound sites in 80% to 90% of patients with TSS, this criterion is not required for diagnosis. *S. aureus* is only recovered from blood cultures 5% of the time (108). Other laboratory abnormalities may include hypocalcemia, elevated liver enzymes, elevated creatinine, thrombocytopenia, pyuria, and proteinuria (106).

#### *Streptococcal TSS*

The clinical picture of TSS caused by group A and B streptococci is similar to that caused by *S. aureus*. Skin and soft-tissue infections are often the source of invasive group A and B streptococci (92,94). Minor trauma, injuries resulting in hematoma or bruising, surgery, viral infections, and use of nonsteroidal anti-inflammatory drugs are associated with the development of severe streptococcal infections (94). One particular difference from staphylococcus-associated TSS is that streptococci can frequently (60% of the time) be isolated from blood culture (110). The mortality rates for streptococcal TSS are five times higher than those for the staphylococcal TSS (111).

#### **Staphylococcal Scalded Skin Syndrome**

Staphylococcal scalded skin syndrome (SSSS) describes a spectrum of superficial blistering skin disorders caused by *S. aureus* strains that produce exfoliative toxins (112). The clinical spectrum of SSSS includes a localized form, bullous impetigo, and a generalized form, pemphigus neonatorum.

The exfoliative toxins are also known as epidermolytic toxins, epidermolysins, and exfoliatins. Production of exfoliative toxin occurs in 5% of all *S. aureus* strains (113,114). The two main exfoliative toxins are exfoliative toxin A (ETA) and exfoliative toxin B (ETB) (115–117). More recently, two new toxins, exfoliative toxin C (ETC) and exfoliative toxin D (ETD), have been identified (117).

Bullous impetigo (also known as bullous varicella or measles pemphigoid) presents with a few localized, fragile, superficial blisters that are filled with colorless, purulent fluid (118). The lesions re-epithelialize in five to seven days. This form of SSSS is usually seen only in children. Typically, there are no associated systemic symptoms. The lesions are located in the area of the umbilicus and perineum in infants and over the extremities in older children (119).

The generalized form of SSSS is termed pemphigus neonatorum or Ritter's disease. Risk factors for development in adults include renal dysfunction, lymphoma, and immunosuppression (112,119,120). Patients with pemphigus neonatorum present with fever, erythema, malaise, and irritability. They then develop large superficial blisters that rupture easily because of friction (112). A positive Nikolsky sign refers to dislodgement of the superficial epidermis when gently rubbing the skin (121). If untreated, the epidermis will slough off leaving extensive areas of denuded skin that are painful and susceptible to infection. Mucous membranes are not affected in SSSS.

The mortality rate in children remains below 5%. Potentially fatal complications in infants and young children occur because of the loss of protective epidermis. Hypothermia, dehydration, and secondary infections are the leading causes of morbidity and mortality for these age groups affected by generalized SSSS (122). The mortality for adults with generalized SSSS is 60%, probably due to the associated comorbidities such as renal dysfunction, immunosuppression, or malignancy found in this population (123).

Diagnosis of both generalized and localized SSSS is based on clinical characteristics. A thorough exam looking for foci of infection (pneumonia, abscess, arthritis, endocarditis, sinusitis, etc.) should be undertaken. Unfortunately, in most cases, no focus is ever found (112). Blood cultures are usually negative because toxins are produced at a distant site (119,124).

A number of different tests, including PCR, enzyme-linked immunosorbent assays, radioimmune assays, and reverse latex agglutination assays, can be used to demonstrate toxin production by *S. aureus* (125). The diagnostic challenge is that bacteria must first be isolated. When the diagnosis is uncertain, a skin biopsy may be the optimal test. The biopsy typically reveals mid-epidermal splitting at the level of the zona granulosa without cytolysis, necrosis, or inflammation (126). Staphylococci may be seen in bullous lesions of localized disease, but are rarely seen in the bullous lesions of generalized disease (120).

### Scarlet Fever

Scarlet fever is the result of infection with a *Streptococcus pyogenes* strain (i.e., group A streptococcus) that produces a pyrogenic exotoxin (erythrogenic toxin). There are three different toxins, types A, B, and C, which are produced by 90% of these strains. Scarlet fever follows an acute infection of the pharynx/tonsils or skin (8). It is most common in children between the ages of 1 and 10 years (111).

The rash of scarlet fever starts on the head and neck, followed by progression to the trunk and then extremities (8,127). The rash is erythematous and diffuse and blanches with pressure. There are numerous papular areas in the rash that produce a sandpaper-type quality. On the antecubital fossa and axillary folds, the rash has a linear petechial character referred to as Pastia's lines (127). The rash varies in intensity but usually fades in four to five days. Diffuse desquamation occurs after the rash fades (127). Diagnosis of scarlet fever can usually be made on a clinical basis. Confirmation of the diagnosis is supported by isolation of group A streptococci from the pharynx and serologies (111).

### Kawasaki Disease

Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis of childhood (128–130). KD was first described by Tomisaku Kawasaki in Japan in 1961 (128) and is the predominant cause of pediatric-acquired heart disease in developed countries (130). The signs and symptoms evolve over the first 10 days of illness and then gradually resolve spontaneously in most children. The diagnostic criteria for classical KD include the following (128):

1. Fever for five days or more that does not remit with antibiotics and is often resistant to antipyretics.
2. Presence of at least four of the following conditions:
  - a. Bilateral (nonpurulent) conjunctivitis
  - b. Polymorphous rash
  - c. Changes in the lips and mouth: reddened, dry, or cracked lips; strawberry tongue; diffuse erythema of oral or pharyngeal mucosa



- d. Changes in the extremities: erythema of the palms or soles; indurative edema of the hands or feet; desquamation of the skin of the hands, feet, and perineum during convalescence
  - e. Cervical lymphadenopathy: lymph nodes more than 15 mm in diameter
3. Exclusion of disease with a similar presentation, such as scalded skin syndrome, TSS, viral exanthems, etc.

Other clinical features include intense irritability (possibly due to cerebral vasculitis), sterile pyuria, and upper respiratory symptoms (130). The major morbidity of KD is the development of coronary artery aneurysm(s) that occur in 25% of the cases.

There are no specific or sensitive tests that can be used to diagnose KD. The diagnosis is made by clinical assessment of the above criteria. The cause of KD is unknown; however, an infectious etiology is still being sought. KD has seasonal peaks in the winter and spring months, and focal epidemics occurred in the 1970s and 1980s (131). Treatment with aspirin and intravenous immune globulin has reduced the development and severity of coronary artery aneurysms.

### Other Causes of Diffuse Erythematous Rashes

*Streptococcus viridans* bacteremia can cause generalized erythema. Ehrlichiosis can produce a toxic shock-like syndrome with diffuse erythema. Enteroviral infections, graft versus host disease, and erythroderma may all present with diffuse erythema (8).

### VESICULAR, BULLOUS, OR PUSTULAR RASHES

Vesicles and bullae refer to small and large blisters. Pustules refer to a vesicle filled with cloudy fluid. The causes of vesiculobullous rashes associated with fever include primary varicella infection, herpes zoster, herpes simplex, small pox, *S. aureus* bacteremia, gonococemia, *V. vulnificus*, *Rickettsia akari*, enteroviral infections, parvovirus B19, and HIV infection. Other causes that will not be discussed include folliculitis due to staphylococci, *Pseudomonas aeruginosa*, and *Candida*, but these manifestations would not result in admission to a critical care unit.

### Varicella Zoster

Primary infection with varicella (chicken pox) is usually more severe in adults and immunocompromised patients. Although it can be seen year-round, the highest incidence of infection occurs in the winter and spring. The disease presents with a prodrome of fever and malaise one to two days prior to the outbreak of the rash. The rash begins as erythematous macules that quickly develop into vesicles. The characteristic rash is described as "a dewdrop on a rose petal." The vesicles evolve into pustules that umbilicate and crust. A characteristic of primary varicella is that lesions in all stages may be present at one time (8).

Herpes zoster (i.e., shingles) is caused by the reactivation of the varicella zoster virus (VZV), which lies dormant in the basal root ganglia (132). The incidence of zoster is greatest in older age groups because of a decline in VZV-specific cell-mediated immunity. Herpes zoster also occurs more often in immunosuppressed patients such as transplant recipients (133–135) and HIV-infected patients (136–138).

Patients often have a prodrome of fever, malaise, headaches, and dysesthesias that precede the vesicular eruption by several days (139). The characteristic rash usually affects a single dermatome and begins as an erythematous maculopapular eruption that quickly evolves into a vesicular rash (Fig. 8). The lesions then dry and crust over in 7 to 10 days, with resolution in 14 to 21 days (112). Disseminated herpes zoster is seen in patients with solid-organ transplants, hematological malignancies, and HIV-infection (136,137,140–144). Thirty-five percent of patients who have received bone-marrow transplants have reactivation of VZV, and 50% of these patients develop disseminated herpes zoster (142,145,146).

Both immunocompetent and immunocompromised patients can have complications from herpes zoster; however, the risk is greater for immunocompromised patients (147). Complications of herpes zoster include herpes zoster ophthalmicus (140,148), acute retinal



**Figure 8** Lower abdomen of a patient with a herpes zoster outbreak due to varicella zoster virus. *Source:* Courtesy of the CDC, Public Health Image Library.

necrosis (149,150), Ramsay Hunt syndrome (151), aseptic meningitis (152), peripheral motor neuropathy (152), myelitis (152,153), encephalitis (152), pneumonitis (147), hepatitis (145), and pancreatitis (142).

The diagnosis of primary varicella infection and herpes zoster is often made clinically. Diagnosis of the neurological complications can be made with CSF PCR assays (154,155). Patients with ocular involvement should be seen promptly by an ophthalmologist.

### **Smallpox**

Smallpox is caused by the variola virus. The last known case of naturally acquired smallpox occurred in Somalia in 1977. The World Health Organization declared that smallpox had been eradicated from the world in 1980 as a result of global vaccination (156,157). The only known repositories for this virus are in Russia and the United States. With the threat of bioterrorism, there is still a remote possibility that this entity would be part of the differential diagnosis of a vesicular rash.

Smallpox usually spreads by respiratory droplets, but infected clothing or bedding can also spread disease (158). The incidence of smallpox is highest during the winter and early spring. The pox virus can survive longer at lower temperatures and low levels of humidity (159,160).

After a 12-day incubation period, smallpox infection presents with a prodromal phase of acute onset of fever (often  $>40^{\circ}\text{C}$ ), headaches, and backaches (158). A macular rash develops and progresses to vesicles and then pustules over one to two weeks (161). The rash appears on the face, oral mucosa, and arms first but then gradually involves the whole body. The pustules are 4 to 6 mm in diameter and remain for five to eight days, after which time, they umbilicate and crust. The lesions of smallpox are generally all in the same stage of development (Fig. 9). "Pock" marks are seen in 65% to 80% of survivors. Historically, the case mortality rate was 20% to 50% (158). In the United States, almost nobody under the age of 30 years has been vaccinated; therefore, this group is largely susceptible to infection.

The diagnosis of smallpox is based on the presence of a characteristic rash that is centrifugal in distribution. Laboratory confirmation of a smallpox outbreak requires vesicular or pustular fluid collection by someone who is immunized. Confirmation can quickly be made



**Figure 9** Male patient with smallpox. *Source:* Courtesy of the CDC/Barbara Rice, Public Health Image Library.

by electron microscopic examination of the fluid specimen in a high-containment (BL-4) facility. Definitive identification in the laboratory is accomplished with viral cell culture, PCR, and restriction fragment-length polymorphism analysis (162).

### **Herpes Simplex**

Herpes simplex virus type 1 (herpes labialis) commonly causes vesicular lesions of the oral mucosa (163). The illness is characterized by the sudden appearance of multiple, often painful, vesicular lesions on an erythematous base. The lesions last for 10 to 14 days. Recurrent infections in the immunocompetent host are usually shorter than the primary infection. In the immunocompromised host, infections can be much more serious. Aside from vesicular eruptions on mucous membranes, the infection can cause keratitis, acute retinal necrosis, hepatitis, esophagitis, pneumonitis, and neurological syndromes (163–172).

Herpes simplex virus type 1 can cause sporadic cases of encephalitis characterized by rapid onset of fever, headache, seizures, focal neurological signs, and impaired mental function. HSV-1 encephalitis has a high rate of mortality in the absence of treatment (173). Diagnosis can infrequently be made by culture; PCR analysis of the CSF has become the gold-standard technique for making the diagnosis (174).

### ***Staphylococcus aureus* Bacteremia**

*S. aureus* can cause metastatic skin infections that often manifest as pustules (3). The pustular skin eruption due to this organism is often widespread. Risk factors for bacteremia include older age, diabetes, recent surgery, HIV, hemodialysis, neoplasm, neutropenia, and intravenous drug use (175–180). Bacteremia can lead to metastatic complications, such as endocarditis and arthritis. Risk factors for these metastatic complications include underlying valvular heart disease and prosthetic implants.

### ***Vibrio Vulnificus***

*V. vulnificus* is a slightly curved, gram-negative bacillus that is endemic in warm coastal waters around the world. *V. vulnificus* is the leading cause of seafood-related fatalities in the United States (181). There are reports that virtually all oysters and 10 percent of crabs harvested in the warmer summer months from the Gulf of Mexico are culture-positive for *V. vulnificus* (182). Consequently, the illness presents mostly between March and November (183). In the United States, most cases occur in states bordering the Gulf of Mexico or those that import oysters



**Figure 10** Skin lesions associated with *V. vulnificus* septicemia in a 75-year-old patient with liver cirrhosis. Source: Courtesy of CDC/From Ref. 184.

from the gulf states (184). Risk factors for infection include liver disease (most commonly alcoholic), hemochromatosis, HIV infection, steroid use, malignancy, and achlorhydria (181).

*V. vulnificus* has been associated with two distinct syndromes: septicemia and wound infection (185,186). A third syndrome of gastrointestinal illness has also been suggested (187). Primary septicemia is a fulminant illness that occurs after the consumption of contaminated raw shellfish. Consumption of raw oysters within 14 days preceding the illness has been reported in 96% of the cases (188). Wound infection occurs after a pre-existing or newly acquired wound is exposed to contaminated seawater.

The onset of symptoms is abrupt. The most common presenting signs and symptoms are fever, chills, shock, and secondary bullae (186). Skin lesions are seen in 65% of patients and are an early sign of septicemia. The most characteristic skin manifestation is erythema, followed by a rapid development of indurated plaques. These plaques then become violaceous in color, vesiculate, and then form bullae. The necrotic skin eventually sloughs off, leaving large ulcers (Fig. 10) (189). Gangrene of a limb can develop because of blood-vessel occlusion (190).

Diagnosis is aided by clinical presentation and history. The bacteria can be readily cultured from blood and cutaneous lesions (191). A real-time PCR assay has also been reported (192).

The mortality rate for septicemia is about 53% and is higher in patients who present with hypotension and leucopenia (193). Median duration from hospitalization to death is about 1.6 days (186). Failure to initiate antibiotics promptly is associated with higher mortality (184). Debridement of involved tissue is usually necessary.

### ***Rickettsia akari***

Rickettsialpox, which was first described in 1946 in New York City, is caused by *R. akari* (194). *R. akari* infects house mice (*Mus musculus*) and is transmitted to humans by the house mouse-associated mite, *Liponyssoides sanguineus* (195). Most cases have occurred in large metropolitan areas of the northeastern United States (195,196).

Rickettsialpox has an incubation period of 9 to 14 days (197). The initial lesion develops into an eschar at the site of inoculation. Local lymph nodes around the eschar may become enlarged and tender. Approximately one week following the development of the eschar,

patients will develop high fever, headaches, malaise, and myalgias. Some patients will have shaking chills and drenching sweats. Thrombocytopenia may also be noted (196). Within three to seven days of the fever, skin eruptions of red macules, papules, and papulovesicles will develop over the body. These lesions number between 20 and 40 and will resolve within a week. The presence of an eschar, the lack of successive crops of vesicles over time, and the presence of thrombocytopenia will help differentiate this entity from varicella zoster virus infection (196).

Diagnosis can be made by comparing acute and convalescent serum antibody titers. Indirect and direct fluorescent antibody tests using anti-*R. rickettsii* antibodies have also been reported (195). The duration of the disease can be reduced with tetracycline, but even untreated patients typically recover without complication (195).

## NODULAR RASHES

A nodule is a palpable, solid, round, or ellipsoidal lesion that may contain inflammatory cells, organisms (fungi, mycobacterium), or cancer cells (5). Nodules usually result from disease in the dermis.

### Erythema Nodosum

Erythema nodosum is an acute inflammatory process involving the fatty-tissue layer and skin. This condition is more common in woman. There are several causes (Table 8), including infections with streptococci, *Chlamydia* species, and hepatitis C (198–202).

The presentation includes fever, malaise, and arthralgias. The characteristic nodules are painful and tender. The nodules commonly develop over the lower legs, knees, and arms (198). Spontaneous resolution usually occurs within six weeks. Diagnosis is often clinical, but biopsy may be needed in atypical cases.

### Systemic Fungal Infections

The sudden onset of dermal nodules may indicate disseminated candidiasis. Risk factors for disseminated candidiasis include malignancy, neutropenia, antimicrobial therapy, severe burn

**Table 8** Causes of Erythema Nodosum

Infectious	Noninfectious
Bacterial infections	Drug reactions
<i>Streptococcus pyogenes</i>	Oral contraceptives
<i>Mycobacterium tuberculosis</i>	Antibiotics
<i>Mycobacterium leprae</i>	Hepatitis B vaccine
Cat scratch disease	Sulfonamides
<i>Chlamydia</i>	Systemic disease
Enteric pathogens ( <i>Yersinia</i> , <i>Campylobacter</i> , <i>Salmonella</i> )	SLE
Rickettsiae	Ulcerative colitis
Spirochetes (syphilis)	Crohn's disease
Systemic fungal infections	Leukemia
<i>Coccidioides immitis</i>	Lymphoma
<i>Histoplasma capsulatum</i>	Sarcoidosis
Blastomycosis	Idiopathic (55%)
Parasites	
Amebiasis	
Giardiasis	
Ascaris	
Viral infections	
Hepatitis B	
CMV	
EBV	

**Abbreviations:** CMV, cytomegalovirus; EBV, Epstein–Barr virus, SLE, systemic lupus erythematosus.

**Source:** Adapted from Ref. 193.

injuries, intravenous catheters, and systemic steroid administration (203–205). The lesions are raised erythematous papules or nodules that are discrete, firm, and nontender (205–207).

Other fungi, such as blastomycosis, histoplasmosis, coccidioidomycosis, and sporotrichosis, can also produce skin nodules (5,208). Patients with AIDS may present with umbilicated nodules that resemble *Molluscum contagiosum* but are caused by *Cryptococcus neoformans*.

### Rheumatic Fever

Rheumatic fever is a late inflammatory complication of acute group A streptococcal pharyngitis (209,210). Rheumatic fever occurs two to four weeks following the pharyngitis. This disease occurs most frequently in children between the ages of four to nine years. The disease is self-limited, but resulting damage to the heart valves may be chronic and progressive, leading to cardiac decompensation and death.

Rheumatic fever is an acute, systemic, febrile illness that can produce a migratory arthritis, carditis, central nervous system deficits, and rash. The diagnosis is based on major and minor criteria (i.e., modified Jones criteria) (211). The five major criteria are carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. The three minor criteria are fever, arthralgia, and previous rheumatic fever or rheumatic heart disease.

Arthritis is the most frequent and least specific manifestation (212). Large joints are affected most commonly. The arthritis is migratory, with the joints of the lower extremities affected first, followed by those of the upper extremities.

Carditis associated with rheumatic fever manifests as pericarditis, myocarditis, and endocarditis, most commonly involving the mitral valve, followed by the aortic valve (213,214). Rheumatic heart disease is a late sequela of acute rheumatic fever, occurring 10 to 20 years after the acute attack, and is the most common cause of acquired valvular disease in the world (215). The mitral valve is most commonly affected with resultant mitral stenosis that often requires surgical correction.

Sydenham chorea (chorea minor; St. Vitus' dance) is a neurological disorder that manifests as abrupt, purposeless, involuntary movements, muscle weakness, and emotional disturbances (216). The abnormal movements disproportionately affect one side of the body and cease during sleep.

Subcutaneous nodules are firm and painless and are seen most often with patients who have carditis (217). The overlying skin is not inflamed. The nodules can be as large as 2 cm and are most commonly located over bony surfaces or near tendons.

The nodules may be present for one to four weeks.

Erythema marginatum (218) is a pink or faint-red, nonpruritic rash that affects the trunk and proximal limbs and spares the face. Erythema marginatum occurs early in the disease and may persist or recur. The rash is usually only seen in patients with concomitant carditis.

The diagnosis of rheumatic fever is supported by evidence of preceding group A streptococcal infection. Evidence of increased antistreptolysin O antibodies, positive throat culture for group A beta-hemolytic streptococci, positive rapid-direct group A streptococcus carbohydrate antigen test, or recent scarlet fever along with the presence of one major and two minor or two major criteria is considered adequate to make the diagnosis.

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# 3 Physical Exam Clues to Infectious Diseases and Their Mimics in Critical Care

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“Life is short, art long, opportunity fleeting, experience treacherous, judgment difficult.”  
—Hippocrates (460 to 400 B.C.)

Under the best of circumstances, the physical examination (PE) of an ICU patient is quite challenging. To make matters more difficult, many physical findings are neither specific nor sensitive. What have been touted as “pathognomonic” findings are rarely, if ever, so. The astute physician must always consider that a given physical examination finding may be due to more than one disease entity. Premature closure and availability bias can further trip up the unwary clinician. As with various clinical syndromes, physical examination findings in infected patients can be mimicked by a variety of infectious and noninfectious diseases. The table that follows lists many of the physical examination findings one may encounter in the infected ICU patient along with their noninfectious mimics and hints to help distinguish them apart.

System	PE ID findings	Noninfectious mimics	Diagnostic features
Fever	1. Usually the sine qua non of infection	<ul style="list-style-type: none"> <li>• Drug/drug withdrawal fever</li> <li>• Central fever/subarachnoid hemorrhage</li> <li>• Periodic fever syndromes</li> <li>• Sarcoidosis</li> <li>• Neoplasms (lymphoma, renal cell center)</li> <li>• Autoimmune diseases (i.e., SLE)</li> <li>• Neuroleptic malignant syndrome</li> <li>• Malignant hyperthermia</li> <li>• Immune reconstitution in HIV</li> <li>• Reaction to blood products</li> <li>• Jarisch–Herxheimer reaction</li> <li>• Tumor lysis syndrome</li> <li>• Pancreatitis</li> <li>• Organ transplant rejection</li> <li>• Venous thrombosis/pulmonary embolism/fat embolism</li> <li>• Gout</li> <li>• Myocardial infection</li> <li>• Stroke</li> <li>• Adrenal insufficiency</li> <li>• Acalculous cholecystitis</li> <li>• Postoperative</li> <li>• Aspiration syndromes</li> <li>• Atrial myxoma</li> </ul>	<p>Noninfectious causes of fever must always be considered in a patient with fever and no obvious source of infection, especially in the proper clinical setting.</p> <p>Rash and/or eosinophilia suggest a drug fever. Relative bradycardia may be present, but this may be found in infectious causes as well.</p>

System	PE ID findings	Noninfectious mimics	Diagnostic features
Extreme hyperpyrexia (>106°F)	1. Gram-negative bacteremia (rare)	<ul style="list-style-type: none"> <li>• Malignant hyperthermia</li> <li>• Neuroleptic malignant syndrome</li> <li>• Central fever including post craniotomy</li> <li>• Drug fever</li> <li>• Heat stroke</li> <li>• Thyrotoxic crisis</li> <li>• Cocaine/phencyclidine</li> </ul>	Fever of >106°F is almost never due to an infection. Suppressed TSH with elevated T <sub>4</sub> , T <sub>3</sub> in thyrotoxicosis. Muscle rigidity and increased CK in NMS.
Sustained fever	1. Gram-negative pneumonia	<ul style="list-style-type: none"> <li>• Central fever</li> </ul>	Blood cultures positive in bacteremia. There may be relative bradycardia in central fever.
Double quotidian fever	<ol style="list-style-type: none"> <li>1. Gonococcal endocarditis</li> <li>2. Mixed malaria infection</li> <li>3. Visceral leishmaniasis</li> </ol>	<ul style="list-style-type: none"> <li>• Adult-onset JRA</li> </ul>	Blood culture and thick peripheral blood smear. Biopsy of bone marrow, liver, lymph node, or spleen for leishmania. Clinical criteria and elevated ferritin in JRA
Hypothermia	1. Overwhelming sepsis	<ul style="list-style-type: none"> <li>• Exposure/emersion</li> <li>• Drugs (ethanol, phenothiazines, sedative/hypnotics)</li> <li>• Metabolic (hypothyroidism, hypoadrenalism, hypopituitarism, hypoglycemia)</li> <li>• Acute spinal cord transection</li> <li>• Burns/exfoliative dermatitis</li> <li>• Aggressive fluid resuscitation</li> </ul>	Clinical setting. Glucose, TSH, cortisol level.
Relative bradycardia	<ol style="list-style-type: none"> <li>1. Typhoid fever</li> <li>2. Legionellosis</li> <li>3. Babesiosis</li> <li>4. Q fever</li> <li>5. Dengue fever</li> <li>6. Rickettsial organisms</li> <li>7. Yellow fever</li> <li>8. Psittacosis</li> <li>9. Malaria</li> <li>10. Leptospirosis</li> <li>11. Brucellosis</li> <li>12. <i>Chlamydomphila pneumoniae</i> infection</li> </ol>	<ul style="list-style-type: none"> <li>• Cardiac drugs (i.e., beta blockers)</li> <li>• CNS fever</li> <li>• Drug fever</li> <li>• Lymphoma</li> <li>• Factitious fever</li> <li>• Traumatic hypotension</li> </ul>	A pneumonic process and relative bradycardia suggests legionellosis, Q fever, <i>C. pneumoniae</i> , or psittacosis. Hemolytic anemia suggests malaria or babesiosis. Leukopenia suggests typhoid fever.
Orthopnea	<ol style="list-style-type: none"> <li>1. Biapical pneumonia</li> <li>2. Tuberculous pericardial restriction/effusion</li> </ol>	<ul style="list-style-type: none"> <li>• Left-sided CHF</li> <li>• Diffuse interstitial lung disease</li> <li>• Intrathoracic anterior mediastinal mass (i.e., goiter, thymoma, lymphoma, cancer)</li> <li>• Bilateral diaphragmatic paralysis</li> <li>• Pulmonary veno-occlusive disease</li> </ul>	Fever, crackles, and signs of consolidation in the upper lung fields in pneumonia. Increased JVP, edema, S <sub>3</sub> gallop in CHF. Kussmaul sign in pericardial restriction. Fixed diaphragms on percussion in diaphragmatic paralysis. Imaging for mediastinal masses.
Platypnea	1. Bibasilar pneumonia	<ul style="list-style-type: none"> <li>• Cirrhosis</li> <li>• Bilateral pulmonary emboli</li> <li>• Severe emphysema</li> <li>• Bilateral pleural effusions</li> </ul>	Fever suggests pneumonia. Imaging (X Ray, CT) for other pulmonary disorders.

System	PE ID findings	Noninfectious mimics	Diagnostic features
Trepopnea	1. Infectious pleuritis (affected side down)	<ul style="list-style-type: none"> <li>• Left-sided CHF</li> <li>• Unilateral extensive lung disease or post pneumonectomy</li> <li>• Swyer–James syndrome</li> <li>• Endobronchial mass with ball-valve effect</li> </ul>	Fever in infective pleuritis. Chest X Ray or echocardiography in others.
Subcutaneous nodules	<ol style="list-style-type: none"> <li>1. Acute rheumatic fever</li> <li>2. Nocardiosis</li> <li>3. Sporotrichosis</li> <li>4. Mycobacterial infections</li> <li>5. <i>Rochalimaea henselae</i></li> <li>6. <i>Dirofilaria immitis</i></li> <li>7. Cutaneous leishmaniasis</li> <li>8. Onchocerciasis</li> </ol>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• SLE</li> <li>• Tophaceous gout</li> <li>• Sarcoidosis</li> <li>• Granuloma annulare</li> </ul>	Jones criteria in ARF. Fever >102°F suggests, but does not prove, infection. Appropriate cultures and serologies. Synovitis and joint changes in RA. Biopsy for others.
Tender violaceous acral papules	1. Osler's nodes	<ul style="list-style-type: none"> <li>• Cholesterol emboli</li> </ul>	Murmur, fever, positive blood cultures in endocarditis. Livedo reticularis in cholesterol emboli.
Ptosis, miosis, possible hidrosis (i.e., Horner's syndrome)	<ol style="list-style-type: none"> <li>1. Chronic apical pneumonia (staphylococcal, fungal, <i>Aspergillus</i>, <i>Pasteurella</i>)</li> <li>2. Tuberculosis</li> <li>3. Hydatid cyst of the thoracic outlet</li> <li>4. Mycotic thoracic aortic aneurysm</li> <li>5. Thoracic hydatid cyst</li> <li>6. Basal meningitis</li> </ol>	<ul style="list-style-type: none"> <li>• Central lesions—Wallenberg syndrome, TIA/stroke, brain tumors, MS</li> <li>• Preganglionic lesions—thoracic tumors, phrenic nerve syndrome, thyroid enlargement, DISH, neck trauma, carotid dissection, Arnold–Chiari malformation, Syringomyelia</li> <li>• Postganglionic lesions—skull fracture, cluster headaches, migraines, or middle ear infections</li> </ul>	Fever suggests infection. Blood cultures/serologic testing. Imaging (chest X Ray, CT/MRI brain/spinal cord)
Optic papillitis	<ol style="list-style-type: none"> <li>1. Bacterial—esp. Brucellosis, endocarditis, Leptospirosis, Lyme disease, <i>Mycoplasma pneumoniae</i>, syphilis, tuberculosis</li> <li>2. Fungal—Candidiasis, Coccidioidomycosis, Mucormycosis, Cryptococcosis</li> <li>3. Viral—acquired immune deficiency syndrome, varicella zoster virus, Equine encephalitis, hepatitis A, B, C, EBV, influenza, measles, mumps, poliomyelitis, yellow fever, West Nile virus</li> </ol>	<ul style="list-style-type: none"> <li>• Idiopathic</li> <li>• Nonarteritic anterior ischemic optic neuropathy</li> <li>• Demyelinating/degenerative diseases—adrenoleukodystrophy, hereditary ataxia, MS, neuromyelitis optica</li> <li>• Drugs/vaccines/toxins</li> <li>• Inflammatory/autoimmune—Henoch–Schönlein, polyarteritis nodosa, sarcoidosis, Wegener granulomatosis, Behçet disease, progressive systemic sclerosis, RA, SLE, giant cell arteritis, Takayasu syndrome</li> <li>• Buerger disease (thromboangiitis obliterans)</li> <li>• Multiple myeloma</li> </ul>	Distinguished by CSF findings including culture and serology. MRI and CT scanning for demyelinating and degenerative CNS disorders. Clinical criteria and serologic testing for autoimmune disorders

(Continued)



System	PE ID findings	Noninfectious mimics	Diagnostic features
	<ol style="list-style-type: none"> <li>4. Protozoan—malaria, toxoplasmosis, trypanosomiasis</li> <li>5. Rickettsia—typhus, Q fever, Rocky Mountain spotted fever</li> <li>6. Helminths—Acanthamoeba, Echinococcosis, Onchocerciasis, Toxocariasis, Trichinellosis</li> </ol>		
Sudden sensorineural hearing loss (i.e., negative ipsilateral Rinne test and/or contralateral localization on the Weber test)	<ol style="list-style-type: none"> <li>1. Viral cochlear/ vestibular labyrinthitis</li> <li>2. Viral auditory nerve neuritis</li> <li>3. Meningoencephalitis</li> <li>4. Specific viruses: mumps, CMV, EBV, rubella, rubeola, varicella zoster, HSV, parainfluenza, Lassa fever, HIV</li> <li>5. Syphilis</li> <li>6. Scrub typhus</li> <li>7. Leptospirosis</li> <li>8. Psittacosis</li> <li>9. Typhoid fever</li> <li>10. Scrub</li> </ol>	<ul style="list-style-type: none"> <li>• High-viscosity syndromes: macroglobulinemia, P-vera</li> <li>• Small vessel obstruction: sickle cell anemia, micro-emboli, Caisson disease</li> <li>• Diabetes mellitus, atherosclerosis, thrombngitis obliterans</li> <li>• Hypercoagulable states</li> <li>• Autoimmune disorders—inner ear autoimmune disease, relapsing polychondritis, SLE, polyarteritis nodosa, Cogan's syndrome</li> <li>• Neurologic disorders—MS, migraine</li> <li>• Ototoxic drugs</li> </ul>	<p>Historical context. Fever suggests an infection.</p> <p>Autoimmune disorders diagnosed by criteria and serology.</p> <p>Culture and/or serologic testing will identify most, but not all, of the infectious etiologies</p>
Parotid enlargement and tenderness	<ol style="list-style-type: none"> <li>1. Viral parotitis (mumps, parainfluenza, influenza, coxsackie virus, CMV)</li> <li>2. Bacterial parotitis</li> </ol>	<ul style="list-style-type: none"> <li>• Bulimia</li> <li>• Drug induced/iodide parotitis</li> <li>• Sialolithiasis</li> <li>• Parotid neoplasms</li> </ul>	<p>Fever suggests infection. Pus emanating from Stenson's duct in bacterial parotitis.</p>
Erythema/edema external auditory canal	<ol style="list-style-type: none"> <li>1. Acute otitis externa (esp. pseudomonal)</li> </ol>	<ul style="list-style-type: none"> <li>• Allergic contact dermatitis</li> <li>• Eczematous dermatitis</li> <li>• Psoriasis</li> <li>• SLE</li> </ul>	<p>Historical context. Fever favors infection.</p>
Inflamed pinna	<ol style="list-style-type: none"> <li>1. Bacterial perichondritis</li> <li>2. Chronic granulomatous infectious process (TB, fungal, syphilis, leprosy)</li> </ol>	<ul style="list-style-type: none"> <li>• Relapsing polychondritis</li> <li>• Frost bite</li> <li>• Irritant contact dermatitis</li> <li>• Trauma</li> </ul>	<p>Distinguished based on the history. Fever favors an infectious process. Culture and/or biopsy if indicated.</p>
Clear nasal discharge	<ol style="list-style-type: none"> <li>1. CSF rhinorrhea in a patient with meningitis and a basilar skull/ cribriform plate fracture</li> </ol>	<ul style="list-style-type: none"> <li>• Vasomotor rhinitis</li> <li>• Allergic rhinitis</li> <li>• Viral rhinitis</li> </ul>	<p>Beta 2 transferrin level is elevated in CSF and not in other causes of rhinorrhea.</p>

System	PE ID findings	Noninfectious mimics	Diagnostic features
Saddle nose deformity	1. Syphilis	<ul style="list-style-type: none"> <li>Relapsing polychondritis</li> <li>Trauma, including post rhinoplasty</li> <li>Wegener's granulomatosis</li> <li>Leprosy</li> </ul>	Distinguished based on history, serologic testing, and/or biopsy
Intranasal eschar	<ol style="list-style-type: none"> <li>Rhinocerebral mucormycosis</li> <li>Phaeo-hyphomycosis in allergic fungal sinusitis</li> <li>Aspergillosis</li> </ol>	<ul style="list-style-type: none"> <li>Wegener's granulomatosis</li> <li>Cocaine abuse</li> </ul>	Culture first, then biopsy and/or serologic testing if necessary
Nasal septal perforation	<ol style="list-style-type: none"> <li>Syphilis</li> <li>Tuberculosis</li> </ol>	<ul style="list-style-type: none"> <li>Cocaine/oxymetazoline abuse</li> <li>Wegener's granulomatosis</li> <li>Midline granuloma</li> <li>SLE</li> <li>Mixed cryoglobulinemia</li> <li>Rheumatoid arthritis</li> <li>Mixed connective tissue disease</li> </ul>	Culture/biopsy. Serologic testing.
Swelling of the cheek	1. Buccal space infection	<ul style="list-style-type: none"> <li>Angioedema</li> </ul>	Fever and tenderness in infection
Tongue ulcer	<ol style="list-style-type: none"> <li>Histoplasma capsulatum</li> <li>Herpes virus</li> <li>CMV</li> <li>Tuberculosis</li> <li>Syphilis</li> <li><i>Leishmania donovani</i></li> <li>Blastomyces dermatitidis</li> </ol>	<ul style="list-style-type: none"> <li>Oral lichen planus</li> <li>Behcet's disease</li> <li>Wegener's granulomatosis</li> <li>Amyloidosis</li> <li>Crohn's disease</li> <li>Carcinoma</li> <li>TUGSE</li> </ul>	Distinguished by culture, serology and/or biopsy. Wickham's striae are seen in lichen planus, macroglossia in amyloidosis.
Palatal ulcer	<ol style="list-style-type: none"> <li>Mucormycosis</li> <li>Other fungal infection (i.e., phaeo-hyphomycosis)</li> <li>Histoplasmosis</li> <li>Syphilis</li> </ol>	<ul style="list-style-type: none"> <li>Drug induced (esp. methotrexate)</li> <li>Cancer/lymphoma</li> <li>Wegener's granulomatosis</li> <li>Crohn's disease</li> <li>Midline granuloma</li> <li>Major aphthous ulcer</li> <li>Sweet's syndrome</li> </ul>	Distinguished by culture, serology (if necessary) and/or biopsy
Palatal purpura	1. Early Kaposi sarcoma	<ul style="list-style-type: none"> <li>Trauma</li> <li>Coagulopathy</li> </ul>	KS will progress over time whereas true purpura will resolve.
Tonsillar inflammation/enlargement	<ol style="list-style-type: none"> <li>Tonsillar abscess</li> <li>Syphilis</li> </ol>	<ul style="list-style-type: none"> <li>Cancer</li> <li>Amyloidosis</li> <li>Lymphoma</li> <li>Sarcoidosis</li> </ul>	Culture and/or biopsy
Gingival edema, inflammation, ulceration	<ol style="list-style-type: none"> <li>Acute necrotizing ulcerative gingivitis (Vincent's angina)</li> <li>Herpangina</li> </ol>	<ul style="list-style-type: none"> <li>Leukemic gingivitis</li> <li>Scurvy</li> <li>Agranulocytosis</li> <li>Cyclic neutropenia</li> <li>Acatlasia</li> </ul>	Leukopenia suggests agranulocytosis or cyclic neutropenia. Follicular hyperkeratosis, purpura, and corkscrew hairs are seen in scurvy. Premature WBC forms on peripheral smear in leukemia.

(Continued)

System	PE ID findings	Noninfectious mimics	Diagnostic features
Uvular swelling	Acute infectious uvulitis (streptococcal, <i>Hemophilus influenzae</i> )	<ul style="list-style-type: none"> <li>• Angioedema—hereditary or acquired (i.e., ACE inhibitors)</li> <li>• Inhalation injuries or exposures (i.e., marijuana, cocaine, <i>Ecballium elaterium</i>)</li> <li>• Trauma</li> <li>• Post anesthesia and deep sedation (with and without endotracheal intubation)</li> <li>• Obstructive sleep apnea</li> <li>• Heavy chain disease</li> </ul>	Fever and/or cellulitis of the surrounding tissues should prompt a search for infection. Acute infectious uvulitis may be associated with epiglottitis.
Smooth, erythematous tongue	<ol style="list-style-type: none"> <li>1. Infectious glossitis due to type b <i>H. influenzae</i></li> <li>2. Atrophic thrush</li> </ol>	<ul style="list-style-type: none"> <li>• Vitamin B complex deficiency</li> <li>• Nontropical sprue</li> <li>• Pernicious anemia</li> <li>• Iron deficiency</li> <li>• Alcoholism</li> <li>• Amyloidosis</li> <li>• Regional enteritis</li> </ul>	Culture will be positive in bacterial/fungal glossitis.
Blanching of half of the tongue	<ol style="list-style-type: none"> <li>1. Bacterial endocarditis emboli</li> </ol>	<ul style="list-style-type: none"> <li>• Giant cell arteritis</li> <li>• Air embolism (Liebermeister sign)</li> </ul>	Fever >102°F favors endocarditis. Air embolism with petechial rash, confusion.
Buccal/gingival violaceous papule/nodule	<ol style="list-style-type: none"> <li>1. Kaposi sarcoma</li> <li>2. Bacillary angiomatosis</li> </ol>	<ul style="list-style-type: none"> <li>• Venous lake or varicosity</li> <li>• Pyogenic granuloma</li> <li>• Scurvy</li> <li>• Hemangioma</li> </ul>	Biopsy will distinguish the entities.
Preauricular lymphadenopathy/mass	<ol style="list-style-type: none"> <li>1. Parinaud's oculoglandular syndrome (TB, cat scratch disease, syphilis, tularemia, <i>Chlamydia trachomatis</i>, adenovirus, <i>Bartonella</i>)</li> <li>2. Toxoplasmosis</li> <li>3. Acute parotitis</li> <li>4. Actinomycosis</li> <li>5. Infection of the scalp, face, ear</li> <li>6. Orbital adnexal infection</li> </ol>	<ul style="list-style-type: none"> <li>• Metastatic cancer</li> <li>• Branchial cleft cyst</li> <li>• Preauricular sinus</li> <li>• Parotid tumor</li> <li>• Lymphoma</li> </ul>	Culture/serology/biopsy. CT scanning, if needed.
Submental/submandibular lymphadenopathy	<ol style="list-style-type: none"> <li>1. Oral, buccal, dental infections (sialadenitis, diphtheria, primary HSV gingivostomatitis, gonorrhea, syphilis, etc.)</li> <li>2. Parinaud's oculoglandular conjunctivitis.</li> </ol>	<ul style="list-style-type: none"> <li>• Metastatic cancer</li> </ul>	Culture or biopsy. CT scanning, if needed.
Anterior cervical lymphadenopathy	<ol style="list-style-type: none"> <li>1. Oropharyngeal infections</li> <li>2. Toxoplasmosis</li> <li>3. Mycobacterial infections</li> <li>4. HIV</li> </ol>	<ul style="list-style-type: none"> <li>• Metastatic cancer</li> <li>• Kikuchi–Fujimoto disease</li> <li>• Sarcoidosis</li> <li>• Lymphoma</li> </ul>	Culture/serology/biopsy. CT scanning, if needed.

System	PE ID findings	Noninfectious mimics	Diagnostic features
Posterior cervical lymphadenopathy	<ol style="list-style-type: none"> <li>1. Infectious mononucleosis</li> <li>2. Rubella</li> <li>3. HIV</li> <li>4. Scalp infection</li> <li>5. Toxoplasmosis</li> <li>6. Trypanosomiasis</li> <li>7. <i>Neorickettsia sennetsu</i></li> </ol>	<ul style="list-style-type: none"> <li>• Castleman's disease</li> <li>• Kikuchi–Fujimoto disease</li> <li>• Lymphoma</li> <li>• 4. Metastatic cancer</li> <li>• Tornwaldt's disease</li> </ul>	Culture/serology/biopsy. CT scanning, if needed
Occipital lymphadenopathy	<ol style="list-style-type: none"> <li>1. Rubella</li> <li>2. Scalp infection</li> <li>3. Toxoplasmosis</li> <li>4. Cat scratch disease</li> <li>5. Pediculosis</li> <li>6. <i>Tinea capitis</i></li> <li>7. Tularemia</li> <li>8. Orbital cellulitis</li> </ol>	<ul style="list-style-type: none"> <li>• Seborrheic dermatitis</li> </ul>	Culture and/or serology in infectious causes. Scaling, erythematous rash in seborrhea
Supra-clavicular lymphadenopathy	<ol style="list-style-type: none"> <li>1. Thoracic bacterial or fungal infections</li> <li>2. Parinaud's oculoglandular syndrome</li> </ol>	<ul style="list-style-type: none"> <li>• Metastatic cancer (GI, lung, ovarian, GU)</li> <li>• Lymphoma</li> </ul>	Culture, imaging, biopsy.
Axillary lymphadenopathy	<ol style="list-style-type: none"> <li>1. Upper extremity infections</li> <li>2. Cat scratch disease</li> <li>3. Brucellosis</li> </ol>	<ul style="list-style-type: none"> <li>• Lymphoma</li> <li>• Breast cancer</li> <li>• Melanoma</li> <li>• Silicone implants</li> </ul>	Culture, serology, biopsy.
Bicipital/epitrochlear lymphadenopathy	<ol style="list-style-type: none"> <li>1. Upper extremity infections</li> <li>2. Tularemia</li> <li>3. Secondary syphilis</li> <li>4. EBV</li> </ol>	<ul style="list-style-type: none"> <li>• Lymphoma</li> <li>• Sarcoidosis</li> <li>• SLE</li> </ul>	Clinical setting. Culture, serology, biopsy.
Inguinal lymphadenopathy	<ol style="list-style-type: none"> <li>1. Infections of the foot/leg</li> <li>2. STDs (syphilis, chancroid, LGV, genital herpes, granuloma inguinale)</li> <li>3. Plague</li> <li>4. Filariasis</li> <li>5. Onchocerciasis</li> <li>6. Rectal infections with CMV, mycobacteria</li> <li>7. Tularemia</li> <li>8. Cat scratch disease</li> <li>9. EBV</li> <li>10. Orchitis</li> <li>11. Pediculosis</li> <li>12. Intersphincteric abscess</li> <li>13. Mayaro virus infection</li> </ol>	<ul style="list-style-type: none"> <li>• Metastatic cancer (urogenital tract)</li> <li>• Lymphoma</li> <li>• Rosai–Dorfman disease</li> </ul>	Clinical setting. Culture, serology, biopsy.

(Continued)

System	PE ID findings	Noninfectious mimics	Diagnostic features
Generalized lymphadenopathy	<ol style="list-style-type: none"> <li>1. EBV</li> <li>2. CMV</li> <li>3. Rubella</li> <li>4. Tuberculosis</li> <li>5. Secondary syphilis</li> <li>6. Lyme disease</li> <li>7. Hepatitis A, B</li> <li>8. Typhoid fever</li> <li>9. Brucellosis</li> <li>10. Leptospirosis</li> <li>11. Histoplasmosis</li> <li>12. HIV</li> <li>13. HTLV-1 infection</li> <li>14. Bartonellosis</li> <li>15. Mycoplasma</li> <li>16. Toxoplasmosis</li> <li>17. Cryptococcosis</li> <li>18. West Nile virus</li> <li>19. Measles</li> <li>20. Scarlet fever</li> <li>21. <i>Rickettsia</i> (scrub typhus, rickettsial pox)</li> <li>22. Dengue</li> <li>23. Leishmaniasis</li> <li>24. Lassa fever</li> <li>25. Monkeypox</li> <li>26. Chagas' disease</li> <li>27. Trypanosomiasis</li> <li>28. Penicilliosis</li> <li>29. Melioidosis</li> <li>30. Glanders</li> </ol>	<ul style="list-style-type: none"> <li>• Lymphoma</li> <li>• Leukemia</li> <li>• Rheumatoid arthritis</li> <li>• SLE</li> <li>• Drug reaction (phenytoin, sulfonamides, others)</li> <li>• Still's disease</li> <li>• Multicentric Castleman's disease</li> <li>• Kikuchi–Fujimoto disease</li> <li>• Storage diseases (glycogen, lipid, lysosomal)</li> <li>• X-linked lympho-proliferative disease</li> <li>• Serum sickness</li> </ul>	Culture, serology, biopsy. Evanescent salmon rash, elevated ferritin in Still's disease.
Tender thyroid	<ol style="list-style-type: none"> <li>1. Acute suppurative thyroiditis</li> </ol>	<ul style="list-style-type: none"> <li>• Subacute (de Quervain) thyroiditis</li> <li>• Thyroid amyloidosis</li> <li>• Infarction of a thyroid nodule</li> </ul>	Fever >102°F suggests infection. Scanning/biopsy for others
Hemoptysis	<ol style="list-style-type: none"> <li>1. Lung abscess</li> <li>2. Pneumonia</li> <li>3. Tuberculosis</li> <li>4. Mycetoma ("fungus ball")</li> <li>5. Infectious tracheobronchitis</li> <li>6. Bronchiectasis</li> </ol>	<ul style="list-style-type: none"> <li>• Pulmonary neoplasm (malignant or benign)</li> <li>• Pulmonary embolus/infarction</li> <li>• Goodpasture's syndrome</li> <li>• Idiopathic pulmonary hemosiderosis</li> <li>• Wegener's granulomatosis</li> <li>• Lupus pneumonitis</li> <li>• Long trauma/contusion</li> <li>• Foreign body</li> <li>• Arteriovenous malformation</li> <li>• Mitral stenosis</li> <li>• Pseudo-hemoptysis</li> </ul>	Imaging, serologic tests (ANA, anti-GBM antibodies, cANCA), sputum Gram stain/AFB stain. Bronchoscopy on occasion.
Inspiratory stridor	<ol style="list-style-type: none"> <li>1. Epiglottitis</li> <li>2. Laryngeal TB</li> </ol>	<ul style="list-style-type: none"> <li>• Upper airway foreign body</li> <li>• Upper airway tumor</li> </ul>	Endoscopy, sputum AFB.
Tracheal deviation (with the patient sitting up)	<ol style="list-style-type: none"> <li>1. Toward the lung with a lobar pneumonia</li> </ol>	<ul style="list-style-type: none"> <li>• Toward the lung with significant atelectasis</li> <li>• Deviated by a goiter</li> <li>• Away from a pleural effusion</li> </ul>	Fever favors infection. Dullness, decreased fremitus with effusion. Imaging.
Unilateral or focal loss of inspiratory intercostal retractions	<ol style="list-style-type: none"> <li>1. Lobar pneumonia</li> </ol>	<ul style="list-style-type: none"> <li>• Pleural effusion</li> <li>• Tension pneumothorax</li> </ul>	Fever, egophony, increased fremitus in pneumonia. Hyperresonance in pneumothorax.

System	PE ID findings	Noninfectious mimics	Diagnostic features
Chest wall tenderness	<ol style="list-style-type: none"> <li>1. Epidemic pleurodynia</li> <li>2. Septic arthritis of the sternoclavicular, sternomanubrial, or costoclavicular joint</li> <li>3. Necrotizing fasciitis</li> </ol>	<ul style="list-style-type: none"> <li>• Tietze syndrome</li> <li>• Chest trauma</li> <li>• Intercostal/mammary thrombophlebitis (Mondor disease)</li> <li>• SAPHO syndrome</li> <li>• Relapsing polychondritis</li> </ul>	Fever favors infection. Tender chest wall thrombosed vein in Mondor disease. Imaging in SAPHO.
Chest wall mass	<ol style="list-style-type: none"> <li>1. "Pointing" empyema</li> <li>2. TB of a rib</li> <li>3. Actinomycosis</li> <li>4. Nocardiosis</li> <li>5. Aspergillosis</li> </ol>	<ul style="list-style-type: none"> <li>• Neoplasm, malignant or benign</li> </ul>	The skin over a "pointing" empyema is warm. Chest X Ray, culture, and biopsy.
Chest dullness to percussion	<ol style="list-style-type: none"> <li>1. Lobar pneumonia with or without empyema</li> </ol>	<ul style="list-style-type: none"> <li>• Atelectasis</li> <li>• Pleural effusion</li> <li>• Pleural thickening</li> </ul>	Fever favors infection. Imaging.
Wheezing	<ol style="list-style-type: none"> <li>1. Lower respiratory tract infection (esp. with RSV, human metapneumovirus)</li> <li>2. Chronic pneumonia</li> <li>3. PIE (<i>Strongyloides stercoralis</i>, hookworm, <i>Ascaris lumbricoides</i>, or <i>Schistosoma japonicum</i>)</li> <li>4. Tropical pulmonary eosinophilia</li> <li>5. Allergic bronchopulmonary aspergillosis</li> </ol>	<ul style="list-style-type: none"> <li>• Asthma/COPD</li> <li>• CHF</li> <li>• Endobronchial tumors</li> <li>• Sarcoidosis</li> <li>• Cystic fibrosis</li> <li>• Pulmonary embolism</li> <li>• Lymphangioleiomyomatosis</li> <li>• Acute chest syndrome sickle cell disease</li> <li>• Drug-induced bronchospasm</li> <li>• Bronchiectasis</li> <li>• Bronchiolitis obliterans</li> <li>• Hypersensitivity pneumonitis</li> </ul>	Culture, serology for infections. Imaging (X Ray, CT scan). Peripheral smear in SS disease. Occasionally, biopsy (bronchiolitis, hypersensitivity pneumonitis).
Late inspiratory crackles (rales)	<ol style="list-style-type: none"> <li>1. Pneumonia</li> </ol>	<ul style="list-style-type: none"> <li>• Atelectasis</li> <li>• CHF</li> <li>• Pulmonary fibrosis</li> <li>• Sarcoidosis</li> <li>• Collagen vascular disorders (SLE, Wegener's granulomatosis, scleroderma, others)</li> </ul>	Culture, sputum Gram stain, serologic testing (ANA, cANCA, Scl-70). Rarely, lung biopsy. Elevated JVP, S <sub>3</sub> gallop, edema in CHF.
Pleural friction rub	<ol style="list-style-type: none"> <li>1. Viral pleurisy</li> <li>2. Pneumonia</li> <li>3. Tuberculous pleuritis</li> </ol>	<ul style="list-style-type: none"> <li>• Pulmonary embolism/infarction</li> <li>• Sickle cell chest syndrome</li> <li>• Asbestosis/mesothelioma</li> <li>• Postpericardiotomy syndrome</li> <li>• SLE</li> <li>• Post thoracotomy</li> <li>• Drug-induced pleuritis</li> </ul>	Imaging (X Ray, CT). Peripheral smear in SS disease. Pleural biopsy for TB.
Amphoric breath sounds	<ol style="list-style-type: none"> <li>1. Lung abscess</li> <li>2. Tubercular cavity</li> <li>3. Fungal pulmonary cavity</li> </ol>	<ul style="list-style-type: none"> <li>• Cyst, bleb, or bulla of any etiology communicating with a bronchus (i.e., COPD, cavitory cancer, etc.)</li> <li>• Open pneumothorax</li> </ul>	Imaging (X Ray, CT). Sputum culture for TB.
Tender, inflamed superficial vein	<ol style="list-style-type: none"> <li>1. Septic thrombophlebitis</li> </ol>	<ul style="list-style-type: none"> <li>• Trousseau syndrome</li> <li>• Thromboangiitis obliterans</li> <li>• Chemical phlebitis</li> </ul>	Fever >102°F and positive blood cultures in septic thrombophlebitis
Palpable arterial aneurysm	<ol style="list-style-type: none"> <li>1. Mycotic aneurysm</li> </ol>	<ul style="list-style-type: none"> <li>• Polyarteritis nodosa</li> <li>• Traumatic aneurysm</li> <li>• Neurofibromatosis</li> </ul>	Fever, positive blood cultures in mycotic aneurysm. Multiorgan involvement, ANCA positivity in PAN. Cutaneous neurofibromas in NF.

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System	PE ID findings	Noninfectious mimics	Diagnostic features
Right parasternal or suprasternal pulsation	1. Mycotic or luetic ascending aortic aneurysm	<ul style="list-style-type: none"> <li>• Noninfectious ascending aortic aneurysm</li> <li>• Tortuous carotid artery</li> <li>• Dissecting aneurysm of the ascending aorta</li> <li>• Right-sided aortic arch</li> </ul>	Fever, positive blood cultures in mycotic aneurysm. RPR in luetic aneurysm. Echocardiography in other diagnoses.
Pericardial friction rub	1. Acute viral or bacterial pericarditis	<ul style="list-style-type: none"> <li>• Collagen vascular diseases (esp. SLE)</li> <li>• Postpericardiotomy/MI syndrome</li> <li>• Uremia</li> <li>• Pericardial metastases</li> </ul>	Clinical context for post-pericardiotomy syndrome. Serologic testing, BUN/creatinine, echocardiography.
Apical pan-systolic murmur	<ol style="list-style-type: none"> <li>1. Mitral regurgitation in acute rheumatic fever</li> <li>2. Mitral regurgitation in bacterial endocarditis</li> </ol>	<ul style="list-style-type: none"> <li>• Mitral regurgitation due to other causes—mitral valve prolapse, papillary muscle dysfunction/rupture, endocarditis, severe LV dilation.</li> </ul>	Jones criteria in ARF. Echocardiography in other diagnoses.
Apical diastolic rumbling murmur	1. Relative mitral stenosis in acute rheumatic fever (Carey Coombs murmur)	<ul style="list-style-type: none"> <li>• Mitral stenosis—late effect of rheumatic fever or degenerative valvular disease</li> <li>• Austin Flint murmur</li> </ul>	Jones criteria in ARF. Echocardiography in other diagnoses.
Basilar diastolic blowing murmur (LSB)	1. Aortic regurgitation in endocarditis	<ul style="list-style-type: none"> <li>• Aortic regurgitation due to hypertension, rheumatic heart disease, aortoannular ectasia, aortic dissection</li> <li>• Pulmonic insufficiency</li> </ul>	Blood cultures and IE stigmata for IE. Echocardiography for other diagnoses.
Pan-systolic murmur LLSB	<ol style="list-style-type: none"> <li>1. Tricuspid regurgitation in endocarditis</li> <li>2. Tricuspid regurgitation in rheumatic fever</li> </ol>	<ul style="list-style-type: none"> <li>• Tricuspid regurgitation in Ebstein anomaly, prolapse, carcinoid, papillary muscle dysfunction, connective tissue disorders (Marfan), RA, radiation injury</li> </ul>	Blood cultures and IE stigmata for IE. Jones criteria for ARF. Echocardiography for other diagnoses.
Jaundice	<ol style="list-style-type: none"> <li>1. Viral hepatitis (A, B, E, EBV, CMV)</li> <li>2. Ascending cholangitis</li> <li>3. Sepsis-associated cholestasis</li> <li>4. Leptospirosis</li> <li>5. Malaria</li> <li>6. Hemorrhagic fevers</li> <li>7. Relapsing fever</li> </ol>	<ul style="list-style-type: none"> <li>• Alcoholic liver disease</li> <li>• Biliary tract obstruction (stone, tumor, stricture)</li> <li>• Drug induced</li> <li>• Hemolytic anemia</li> <li>• Cancer (primary or metastatic to liver)</li> <li>• Hepatic vein thrombosis</li> <li>• Ischemic hepatitis</li> </ul>	Clinical context. Serologic testing. Culture. Peripheral smear (hemolytic anemia, malaria). US for CBD obstruction, tumors/hepatic vein thrombosis.
Doughy abdomen	1. Tubercular peritonitis	<ul style="list-style-type: none"> <li>• Peritoneal metastases</li> <li>• Recent significant weight loss</li> <li>• Peritoneal mesothelioma</li> </ul>	Imaging (CT, US). Peritoneal/ascites culture or biopsy.
Right lower quadrant tenderness	<ol style="list-style-type: none"> <li>1. Acute salpingitis with a tuboovarian abscess</li> <li>2. Bacterial ileocecolitis (<i>Yersinia enterocolitica</i>, <i>Campylobacter jejuni</i>, <i>Salmonella enteritidis</i>)</li> </ol>	<ul style="list-style-type: none"> <li>• Acute appendicitis</li> <li>• Cecitis/typhlitis</li> <li>• Regional enteritis</li> <li>• Diverticulitis</li> <li>• Epiploic appendagitis</li> <li>• Impaction of a stone in the right ureter</li> <li>• Meckel's diverticulitis</li> <li>• Ovarian cyst</li> </ul>	Stool culture, specific serology in enteric infections. CT scanning/US for noninfectious etiologies.

System	PE ID findings	Noninfectious mimics	Diagnostic features
	<ol style="list-style-type: none"> <li>3. Amebic colitis</li> <li>4. Tuberculous colitis</li> <li>5. Actinomycosis</li> <li>6. <i>Mycobacterium avium</i>-intracellulare (in AIDS)</li> <li>7. <i>Angiostrongylus costaricensis</i></li> <li>8. <i>Balantidium coli</i></li> <li>9. Ascariasis</li> </ol>	<ul style="list-style-type: none"> <li>• Ectopic pregnancy</li> <li>• Cecal adenocarcinoma</li> <li>• Carcinoid</li> </ul>	
Obturator sign	<ol style="list-style-type: none"> <li>1. Appendicitis</li> <li>2. Pelvic abscess</li> </ol>	<ul style="list-style-type: none"> <li>• Pelvic fracture</li> <li>• Obturator muscle spasm/dysfunction</li> </ul>	Fever and leukocytosis in appendicitis/pelvic abscess.
Psoas sign	<ol style="list-style-type: none"> <li>1. Appendicitis</li> <li>2. Psoas abscess</li> </ol>	<ul style="list-style-type: none"> <li>• Psoas hematoma</li> <li>• Iliopsoas bursitis</li> </ul>	Fever and leukocytosis in appendicitis/psoas abscess. CT scanning in psoas hematoma.
Tender hepatomegaly	<ol style="list-style-type: none"> <li>1. Acute viral hepatitis</li> <li>2. Hepatic abscess (pyogenic, amebic, Toxoplasma)</li> <li>3. Typhoid</li> <li>4. Disseminated candidiasis</li> <li>5. Echinococcosis</li> <li>6. Acute schistosomiasis</li> <li>7. Fascioliasis</li> <li>8. Clonorchiasis</li> <li>9. Hepatic capillaritis</li> </ol>	<ul style="list-style-type: none"> <li>• Acute alcoholic hepatitis</li> <li>• Drug-induced hepatitis</li> <li>• Right-sided heart failure/constrictive pericarditis</li> <li>• Hepatic sickle cell crisis</li> <li>• Budd–Chiari syndrome</li> </ul>	Clinical context. There may be a friction rub over a hepatic abscess. Serology, ultrasonography, culture to distinguish the various etiologies.
Splenomegaly	<ol style="list-style-type: none"> <li>1. Acute infections (e.g., EBV, CMV, hepatitis, SBE, psittacosis, cat scratch disease)</li> <li>2. Chronic infections (e.g., miliary TB, malaria, schistosomiasis, AIDS brucellosis, visceral leishmaniasis, syphilis, toxoplasmosis)</li> </ol>	<p>Congestive—cirrhosis, portal hypertension, CHF, compression or thrombosis of portal or splenic vein</p> <ul style="list-style-type: none"> <li>• Neoplasms—lymphoproliferative disorders, myeloproliferative disorders</li> <li>• Inflammatory—sarcoidosis, amyloidosis</li> <li>• Connective tissue diseases—SLE, RA</li> <li>• Hemolytic anemias</li> <li>• Storage diseases (e.g., Gaucher's, Niemann–Pick, etc.)</li> </ul>	Based on the clinical context, blood and other appropriate cultures, serological testing, review of peripheral smear and, rarely, splenic biopsy.
Prostatic nodule	<ol style="list-style-type: none"> <li>1. Tuberculosis</li> </ol>	<ul style="list-style-type: none"> <li>• Cancer</li> <li>• Leiomyoma</li> </ul>	In TB, the seminal vesicle and vas deferens are also involved.
Carpo-metacarpal ulnar deviation	<ol style="list-style-type: none"> <li>1. Jaccoud's arthritis in recurrent polyarthritis of rheumatic fever</li> </ol>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• SLE</li> <li>• Ulnar impaction syndrome</li> <li>• Chronic hemiplegia</li> </ul>	Initially, the deviation in Jaccoud's arthritis is passively reducible. MCP synovitis, swan neck, and boutonniere deformities in RA. Imaging.

(Continued)



System	PE ID findings	Noninfectious mimics	Diagnostic features
Charcot joint	<ol style="list-style-type: none"> <li>1. Syphilis</li> <li>2. Leprosy</li> </ol>	<ul style="list-style-type: none"> <li>• Diabetes</li> <li>• Alcoholism</li> <li>• Trauma</li> <li>• Amyloidosis</li> <li>• Pernicious anemia</li> <li>• Syringomyelia, spina bifida, myelomeningocele</li> <li>• MS</li> <li>• Charcot-Marie-Tooth disease</li> <li>• Connective disorders (RA, scleroderma)</li> <li>• Cauda equine lesions</li> </ul>	Clinical context. Serology, imaging, biopsy/culture.
Mono or pauci-articular arthritis	<ol style="list-style-type: none"> <li>1. Bacterial septic arthritis</li> <li>2. Lyme disease</li> <li>3. Viruses (parvovirus B19, hepatitis B, rubella, mumps, adenovirus, coxsackie, retroviruses, EBV, Chikungunya)</li> </ol>	<ul style="list-style-type: none"> <li>• Gout</li> <li>• Pseudogout</li> <li>• Other crystalline arthritides</li> <li>• Lofgren's syndrome (peri-arthritis of the ankles)</li> <li>• Plant thorn synovitis</li> <li>• Synovial metastases</li> <li>• Charcot joint</li> </ul>	Arthrocentesis with microscopy (including polarized lens) and culture. Serology, imaging.
Sternoclavicular inflammation/tenderness	<ol style="list-style-type: none"> <li>1. Septic arthritis/osteomyelitis (esp. in IVDA)</li> </ol>	<ul style="list-style-type: none"> <li>• Trauma/fracture</li> <li>• Inflammatory arthritis (RA, ankylosis spondylitis, psoriatic)</li> <li>• Gout</li> <li>• Friedrich's syndrome</li> </ul>	Blood and joint fluid culture/microscopy. Imaging.
Acute sacroiliac tenderness	<ol style="list-style-type: none"> <li>1. Septic arthritis/osteomyelitis (IVDA, indwelling catheter)</li> </ol>	<ul style="list-style-type: none"> <li>• Reactive arthritis</li> <li>• Trauma/fracture</li> <li>• Crystalline arthritides</li> </ul>	Blood and joint fluid culture/microscopy. Imaging.
Chronic sacroiliac tenderness	<ol style="list-style-type: none"> <li>1. Brucella arthritis</li> <li>2. Tubercular arthritis</li> </ol>	<ul style="list-style-type: none"> <li>• Spondyloarthropathies (i.e., ankylosing spondylitis, inflammatory bowel disease, psoriatic arthritis)</li> </ul>	Imaging. Serology, joint fluid culture.
Tenderness/inflammation symphysis pubis	<ol style="list-style-type: none"> <li>1. Osteomyelitis of the symphysis pubis</li> </ol>	<ul style="list-style-type: none"> <li>• Osteitis pubis (sterile)</li> <li>• CPPD disease</li> </ul>	Blood/bone culture. Imaging.
Muscle swelling/tenderness	<ol style="list-style-type: none"> <li>1. Pyomyositis</li> <li>2. Necrotizing fasciitis</li> <li>3. Trichinosis</li> <li>4. Infected hematoma</li> </ol>	<ul style="list-style-type: none"> <li>• Bland hematoma</li> <li>• Muscle infarction</li> </ul>	Culture, imaging. Occasional muscle biopsy (trichinosis)
Penile ulcer	<ol style="list-style-type: none"> <li>1. Syphilis</li> <li>2. Herpes simplex</li> <li>3. Chancroid</li> <li>4. Lymphogranuloma venereum</li> <li>5. Donovanosis</li> <li>6. Histoplasma</li> <li>7. Tularemia</li> <li>8. Leishmaniasis</li> <li>9. Amebiasis</li> </ol>	<ul style="list-style-type: none"> <li>• Behçet disease, Crohn's disease, Lichen planus</li> <li>• Cancer</li> </ul>	Extreme tenderness suggests herpes, chancroid. Groove sign in LGV. Bilateral lymphadenopathy in syphilis, herpes. Culture, serology, or biopsy.
Perineal/scrotal purpura	<ol style="list-style-type: none"> <li>1. Early Fournier's gangrene</li> </ol>	<ul style="list-style-type: none"> <li>• Blue scrotum sign of Bryant seen in retroperitoneal hemorrhage</li> </ul>	Recent GU surgery/manipulation fever, prostration in Fournier's gangrene.

System	PE ID findings	Noninfectious mimics	Diagnostic features
Scrotal swelling/ tenderness	<ol style="list-style-type: none"> <li>1. Epididymo-orchitis</li> <li>2. Pyocele</li> </ol>	<ul style="list-style-type: none"> <li>• Testicular cancer</li> <li>• Testicular torsion</li> <li>• Polyarteritis nodosa</li> </ul>	Color Doppler US shows impaired blood flow in torsion and an inhomogeneous collection in a pyocele.
Epididymal beading	<ol style="list-style-type: none"> <li>1. Genitourinary tuberculosis</li> </ol>	<ul style="list-style-type: none"> <li>• Epididymal cysts in polycystic kidney disease</li> <li>• Young's syndrome</li> </ul>	Upper and lower GU tract scarring in TB. Imaging.
Nuchal rigidity, meningismus	<ol style="list-style-type: none"> <li>1. Infectious meningitis (bacterial, viral)</li> </ol>	<ul style="list-style-type: none"> <li>• Noninfectious meningitis (drug induced, SLE, Behcet's syndrome, Sjogren's syndrome, sarcoidosis)</li> <li>• Leptomeningeal metastases</li> <li>• Primary CNS angiitis</li> <li>• Degenerative cervical spine disease</li> </ul>	Fever >102°F suggests infection. CSF culture/Serology. Imaging.
Chorea	<ol style="list-style-type: none"> <li>1. Acute rheumatic fever (Sydenham's chorea)</li> <li>2. HIV</li> <li>3. Creutzfeldt–Jakob disease</li> </ol>	<ul style="list-style-type: none"> <li>• CNS ischemic/hemorrhage</li> <li>• Neurologic disorders (Huntington's chorea, neuro-acanthocytosis)</li> <li>• SLE</li> <li>• Drugs (l-dopa, lithium, methadone, lamotrigine)</li> <li>• Toxins</li> <li>• Paraneoplastic</li> <li>• Antiphospholipid syndrome</li> <li>• Metabolic—hyper-thyroidism, hyperglycemia, hypocalcemia</li> <li>• Other—P vera, basal ganglia calcification, senile</li> </ul>	Fever suggests infection but does not exclude CNS lesions, SLE, hyperthyroidism. Serology, routine blood work, and imaging for other possibilities.
Cranial nerve palsies (isolated or in various combinations)	<ol style="list-style-type: none"> <li>1. Suppurative intracranial thrombophlebitis—CN II, IV, V, VI, VII</li> <li>2. Acute bacterial meningitis—III, IV, VI, VII</li> <li>3. Rhinocerebral Mucormycosis—II through VII, IX, and X</li> <li>4. Lyme disease—primarily CN VII (at times bilateral). Less common II, III, the sensory portion of V, VI, and the acoustic portion of VIII</li> <li>5. Acute HIV meningitis—V, VII, and VIII</li> <li>6. Malignant otitis externa—VII, less commonly X, X, XII</li> <li>7. Orbital cellulitis—III, IV, VI; V1</li> </ol>	<ul style="list-style-type: none"> <li>• Nerve infarction (i.e., diabetic)</li> <li>• Supratentorial mass with herniation</li> <li>• Migraine</li> <li>• Aneurysm</li> <li>• Subarachnoid hemorrhage</li> <li>• Sarcoidosis</li> <li>• Meningeal carcinomatosis/lymphoma</li> <li>• Tolosa–Hunt</li> <li>• Neurologic syndromes—Weber's, Benedikt's, Nothnagel's)</li> <li>• Neoplasms (pituitary, meningioma)</li> <li>• Trauma</li> <li>• Pseudotumor cerebri</li> <li>• Multiple sclerosis</li> <li>• Ciguatera fish poisoning</li> </ul>	Clinical setting. Culture, serology, and imaging to distinguish the various possibilities.

(Continued)

System	PE ID findings	Noninfectious mimics	Diagnostic features
	8. Septic cavernous sinus thrombosis—III, IV, V, and VI		
	9. Cryptococcal meningitis		
	10. Herpes meningoencephalitis		
	11. CMV mononucleosis		
	12. Syphilis—VII and VIII, followed by II, III, IV, VI, V		
	13. Acute botulism—III, IV, VI, IX, X, XI, XII (with a fixed dilated pupil)		
	14. Tuberculous meningitis—VI, VII, VIII		
	15. Primary amebic meningoencephalitis		
	16. Mumps		
	17. Eastern equine encephalitis—VI, VII, XII		
	18. Bulbar poliomyelitis—IX, X		
	19. Diphtheria—III, VI, VII, IX, and X		
	20. Tick borne encephalitis—III, VII, IX, X, and XI		
	21. Progressive multifocal leukoencephalopathy		
	22. Listerial brainstem encephalitis (rhombencephalitis)		
	23. St. Louis encephalitis		
	24. Japanese encephalitis		
	25. Cerebral cysticercosis		
	26. Subacute progressive disseminated histoplasmosis		
	27. Cephalic tetanus (following a head wound)		
	28. Relapsing fever		
	29. Q fever		
	30. Psittacosis		
	31. Eosinophilic meningitis ( <i>Angiostrongylus cantonensis</i> )—IV, VI		
	32. Melioidosis—VII		

System	PE ID findings	Noninfectious mimics	Diagnostic features
Peripheral neuropathy (stocking sensory deficit with or without weakness)	<ol style="list-style-type: none"> <li>1. HIV</li> <li>2. Leprosy</li> <li>3. CMV</li> <li>4. <i>M. pneumoniae</i></li> <li>5. Lyme disease</li> <li>6. Hepatitis B, C</li> <li>7. VZV</li> <li>8. Parvovirus</li> <li>9. Neuroborreliosis</li> <li>10. Neurosyphilis</li> <li>11. Trypanosomiasis</li> <li>12. Botulism</li> <li>13. Diphtheria</li> <li>14. <i>Tropheryma whipplei</i></li> </ol>	<ul style="list-style-type: none"> <li>• Diabetes mellitus</li> <li>• Alcohol abuse</li> <li>• Drugs</li> <li>• Vasculitis</li> <li>• Myxedema</li> <li>• Renal failure</li> <li>• Rheumatoid arthritis</li> <li>• Sarcoidosis</li> <li>• Monoclonal gammopathy/amyloidosis</li> <li>• Acromegaly</li> <li>• Multifocal CIDP</li> <li>• Porphyria</li> <li>• Hereditary (i.e., Charcot-Marie-Tooth)</li> <li>• Vitamin B deficiency</li> <li>• Heavy metal poisoning</li> </ul>	Clinical setting. Culture, serology, and imaging to distinguish the various possibilities.
Brachial plexopathy	<ol style="list-style-type: none"> <li>1. Parvovirus B19</li> <li>2. EBV mononucleosis</li> <li>3. HIV</li> <li>4. Lyme disease</li> </ol>	<ul style="list-style-type: none"> <li>• Pancoast tumor</li> <li>• Trauma/compression</li> <li>• Parsonage–Turner syndrome</li> <li>• Post irradiation</li> <li>• Tumor infiltration</li> <li>• Paraneoplastic</li> </ul>	Clinical setting. Culture, serology, and imaging to distinguish the various possibilities.
Lumbosacral plexopathy (a) T12 to L4—decreased flexion, adduction, and eversion of thigh. Absent patellar reflex (b) L5 to S3—hip extension, abduction, and internal rotation of thigh, flexion of leg, and all movements of foot. Absent Achilles reflex (c) Entire plexus—variable weakness of hip girdle, thigh and foot muscles	<ol style="list-style-type: none"> <li>1. CMV (in AIDS)</li> <li>2. Herpes zoster</li> <li>3. <i>C. pneumoniae</i></li> </ol>	<ul style="list-style-type: none"> <li>• Trauma/parturition</li> <li>• Retroperitoneal hemorrhage</li> <li>• Neoplastic</li> <li>• Diabetic</li> <li>• Vasculitic (RA, SLE, PAN)</li> </ul>	Clinical setting. Culture, serology, and imaging to distinguish the various possibilities.
Paraplegia/paresis with a sensory level	<ol style="list-style-type: none"> <li>1. Spinal epidural abscess</li> <li>2. Tuberculous adhesive arachnoiditis</li> <li>3. Transverse myelitis (mycoplasma, TB, Lyme disease, syphilis, viral, HTLV-1)</li> </ol>	<ul style="list-style-type: none"> <li>• Arachnoiditis due to epidural drug injection, hemorrhage or postsurgical</li> <li>• Arachnoiditis due to seeding of a CNS or metastatic cancer</li> <li>• Transverse myelitis (MS, autoimmune/vasculitis, drugs, Devic's syndrome)</li> </ul>	Significant spinal pain suggests epidural abscess. Blood and CSF culture/serology. Imaging and serologic testing for vasculitis.

(Continued)

System	PE ID findings	Noninfectious mimics	Diagnostic features
Cerebellar ataxia	<ol style="list-style-type: none"> <li>1. Lyme disease</li> <li>2. Brain abscess</li> <li>3. Toxoplasma encephalitis</li> <li>4. Listeria monocytogenes meningitis</li> <li>5. CNS syphilis</li> <li>6. Tick borne encephalitis</li> <li>7. Viral encephalitis (Japanese, St. Louis, West Nile, enteroviral, Varicella meningitis, Venezuelan equine, CMV)</li> <li>8. Rickettsia (<i>Rickettsia rickettsii</i>, <i>Coxiella burnetii</i>)</li> <li>9. JC virus (including PML)</li> <li>10. Cerebral malaria</li> <li>11. Neurotoxic shellfish poisoning</li> <li>12. Subacute progressive disseminated histoplasmosis</li> <li>13. West African trypanosomiasis</li> <li>14. Whipple's disease</li> <li>15. Primary amoebic meningoencephalitis</li> <li>16. Hendra virus</li> <li>17. Francisella <i>Tularensis</i></li> </ol>	<ul style="list-style-type: none"> <li>• CNS tumors</li> <li>• Drugs</li> <li>• Multiple sclerosis</li> <li>• Miller Fisher syndrome</li> <li>• Ataxia-telangiectasia syndrome</li> <li>• Friedrich's ataxia</li> <li>• Spinocerebellar ataxia</li> <li>• Celiac disease</li> <li>• Posterior circulation ischemia/ stroke</li> <li>• Alcoholic cerebellar disease</li> <li>• Idiopathic cerebellar degeneration</li> <li>• Paraneoplastic syndrome</li> <li>• MELAS</li> <li>• Vitamin E deficiency</li> <li>• Dominant periodic ataxia</li> <li>• Olivopontocerebellar atrophy</li> <li>• Paraneoplastic disorder</li> <li>• Vitamin E deficiency</li> <li>• Exposure to toxins (lead, anticonvulsants, salicylates, aminoglycosides, sedatives)</li> <li>• Autoimmune disorders (SLE, Sjogren's)</li> </ul>	<p>Fever favors an infectious etiology. Chronicity suggests hereditary syndrome. Culture (including CSF), serology, imaging to distinguish among the other etiologies.</p>
Descending paralysis with absent MSRs	<p>Botulism Bulbar poliomyelitis</p>	<ul style="list-style-type: none"> <li>• Miller-Fisher syndrome</li> </ul>	<p>Fever and asymmetry suggest polio. Ataxia and diffuse areflexia seen in Miller-Fisher syndrome</p>

**Abbreviations:** ACE, angiotensin converting enzyme; AFB, acid fast bacillus; AIDS, autoimmune deficiency syndrome; ANA, antinuclear antibody; ARF, acute rheumatic fever; cANCA, cytoplasmic staining antineutrophil cytoplasmic antibody; CBD, common bile duct; CHF, congestive heart failure; CK, creatine kinase; CMV, cytomegalovirus; CN, cranial nerve; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPPD, calcium pyrophosphate dehydrate; CSF, cerebrospinal fluid; CT, computed tomography; DISH, diffuse idiopathic skeletal hyperostosis; EBV, Epstein-Barr virus; GBM, glomerular basement membrane; GI, gastrointestinal; GU, genitourinary; HIV, human immunodeficiency virus; HTLV, human T cell lymphotropic virus; IE, infectious endocarditis; IVDA, intravenous drug abuse; JC, Jakob Creutzfeldt; JRA, juvenile rheumatoid arthritis; JVP, jugular venous pressure; LGV, lymphogranuloma venereum; LV, left ventricle; MCP, metacarpophalangeal; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; MI, myocardial infarction; MRI, magnetic resonance imaging; MS, multiple sclerosis; NF, neurofibromatosis; NMS, neuroleptic malignant syndrome; PAN, polyarteritis nodosa; PIE, pulmonary infiltrate with eosinophilia; PML, progressive multifocal leukoencephalopathy; P-vera, polycythemia vera; RA, rheumatoid arthritis; RPR, rapid plasma reagent; RSV, respiratory syncytial virus; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus; SS, sickle cell disease; STDs, sexually transmitted diseases; TB, tuberculosis; TIA, transient ischemic attack; TSH, thyroid stimulating hormone; TUGSE, traumatic ulcerative granuloma with stromal eosinophilia; US, ultrasound; VZV, varicella zoster virus.

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# 4 | Ophthalmologic Clues to Infectious Diseases and Their Mimics in Critical Care

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*The eyes, like a sentinel, occupy the highest place in the body.*

*—Marcus Tullius Cicero*

Eye exam is one element of physical examination that is frequently overlooked by clinicians despite its ability to provide key diagnostic clues. Often an eye exam is deferred because of a lack of comfort or familiarity with funduscopic and, to a lesser degree, external ocular examination. However, clinicians should take time to carefully inspect the internal and external anatomy of the eye in search of a physical finding that may tip the scales toward one diagnosis over another.

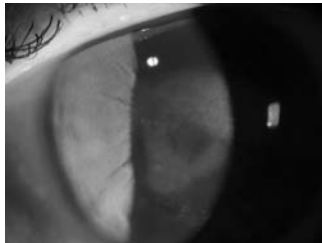
Nowhere is this more the case than in critically ill patients, who are often unable to provide historical clues as to the nature of their condition. We should, therefore, not relegate this exam solely to the purview of ophthalmologists, but rather add it to our armamentarium of diagnostic tools.

This chapter, presented in tabular form, contains a collection of both internal and external eye findings in conditions that may be seen in an intensive care setting. This is designed to act as a guide to supplement the internists ocular exam of critically ill patients—to be used for initial evaluation of a patient or when an ophthalmologist is not readily available. These findings, in concert with the history, physical, and laboratory analyses, may help to identify the etiology of the patient's illness (1–4).

Note that physical findings that will be visible on slit lamp exam will be found under "SL:" All other findings should be visible on general examination of the eye.

**INFECTIOUS DISEASES**

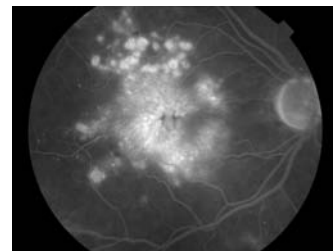
Disease	External eye findings	Fundoscopy findings
<b>M. tuberculosis (TB)</b>	<ul style="list-style-type: none"> <li>• Chronic conjunctivitis (often unilateral)</li> <li>• Conjunctival granulomas</li> <li>• Phlyctenulosis (focal translucent nodules along the limbus of the eye)</li> <li>• Ulcerative/interstitial keratitis</li> <li>• Scleritis</li> <li>• Orbital tuberculoma</li> </ul> SL: <ul style="list-style-type: none"> <li>• Chronic granulomatous iritis</li> <li>• Panuveitis</li> <li>• Interstitial keratitis</li> <li>• Keratic precipitates</li> </ul>	<ul style="list-style-type: none"> <li>• Tuberculoma of the choroid (usually unilateral, but diffuse choroidal granulomas may be seen in miliary TB)</li> </ul>



**Figure 1** Interstitial keratitis (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Adenovirus</b>	<ul style="list-style-type: none"> <li>• Follicular conjunctivitis with watery/mucoid discharge (often begins with unilateral involvement and later spreads to contralateral eye)</li> <li>• Subepithelial corneal infiltrates</li> <li>• Eyelid edema</li> <li>• Subconjunctival hemorrhage</li> <li>• Ciliary flush</li> <li>• Corneal haziness</li> <li>• Pre-auricular lymph node enlargement</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>

Disease	External eye findings	Fundoscopy findings
<b>Toxic shock syndrome (TSS)</b>	<ul style="list-style-type: none"> <li>• Conjunctival suffusion</li> <li>• Anterior scleritis</li> <li>• Scleral ectasia</li> </ul> SL: <ul style="list-style-type: none"> <li>• Uveitis</li> <li>• Keratic precipitates</li> <li>• Vitreous opacities</li> <li>• Choroiditis</li> </ul>	<ul style="list-style-type: none"> <li>• Retinal detachments</li> <li>• Cystoid macular edema</li> </ul>

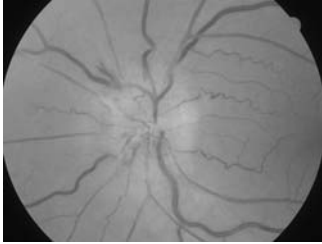


**Figure 2** Cystoid macular edema (see color insert).



Disease	External eye findings	Fundoscopy findings
<b>Leptospirosis (Weil's syndrome)</b>	<ul style="list-style-type: none"> <li>• Conjunctival suffusion (often dramatic hemorrhagic )</li> <li>• Conjunctival discharge</li> <li>• Subconjunctival hemorrhage</li> <li>• Hypopyon (a small hypopyon may require SL evaluation)</li> <li>• Scleral icterus +/-</li> </ul> SL: <ul style="list-style-type: none"> <li>• Mutton fat keratic precipitates</li> <li>• Uveitis (anterior or posterior)</li> </ul>	<ul style="list-style-type: none"> <li>• Retinal hemorrhage</li> <li>• Retinal exudates</li> <li>• Optic neuritis</li> </ul>

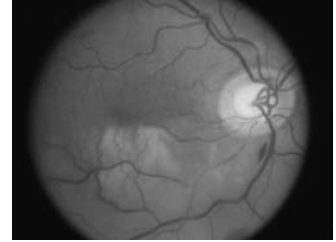
Disease	External eye findings	Fundoscopy findings
<b>Rocky Mountain spotted fever (RMSF)</b>	<ul style="list-style-type: none"> <li>• Conjunctivitis with papillae</li> <li>• Conjunctival petichiae</li> <li>• Subconjunctival hemorrhage</li> <li>• Corneal ulceration</li> </ul> SL: <ul style="list-style-type: none"> <li>• Panuveitis</li> <li>• Iritis</li> </ul>	<ul style="list-style-type: none"> <li>• Retinal hemorrhage</li> <li>• Retinal exudates</li> <li>• Optic nerve pallor</li> <li>• Roth spots</li> </ul>

Disease	External eye findings	Fundoscopy findings
<b>Tularemia (oculoglandular)</b>	<ul style="list-style-type: none"> <li>• Conjunctivitis with purulent discharge</li> <li>• Conjunctival nodules (1–5 mm)</li> <li>• Chemosis</li> <li>• Necrosis of conjunctivae</li> <li>• Eyelid edema</li> <li>• Periorbital edema</li> <li>• Eyelid ulceration</li> </ul> SL: <ul style="list-style-type: none"> <li>• Corneal edema</li> <li>• Peripheral corneal infiltrates (relatively rare, but have a very high specificity when present)</li> <li>• Nodules along the limbus</li> </ul>	<ul style="list-style-type: none"> <li>• Optic neuritis</li> </ul> 

**Figure 3** Optic neuritis (see color insert).

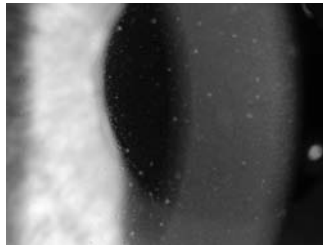
Disease	External eye findings	Fundoscopy findings
<b>Hantavirus pulmonary syndrome (HPS)</b>	<ul style="list-style-type: none"> <li>• Conjunctival suffusion</li> </ul> SL: <ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>

Disease	External eye findings	Fundoscopic findings
<b>Bacterial endocarditis</b>	<ul style="list-style-type: none"> <li>• Conjunctival hemorrhage</li> <li>• Subconjunctival hemorrhage</li> </ul> SL: <ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Roth spots</li> <li>• Cotton-wool spots</li> <li>• Retinal hemorrhages</li> <li>• Branch/central retinal artery occlusion</li> </ul>

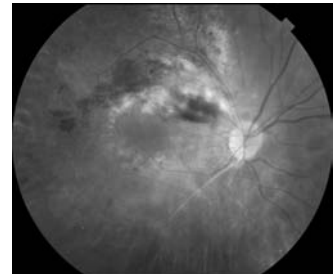


**Figure 4** Branch retinal artery occlusion (see color insert).

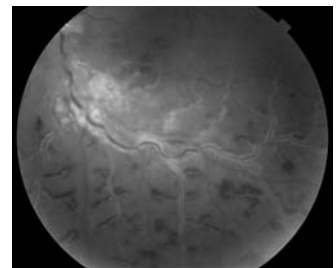
Disease	External eye findings	Fundoscopic findings
<b>Cytomegalovirus (CMV)</b> Ocular CMV seen in HIV-infected patients with CD4 <50 cells/ mm <sup>3</sup>	<ul style="list-style-type: none"> <li>• Often has no remarkable external ocular manifestations</li> </ul> SL: <ul style="list-style-type: none"> <li>• Fine keratic precipitates</li> <li>• Anterior uveitis +/-</li> </ul>	<ul style="list-style-type: none"> <li>• Granular yellow–white opacities with irregular borders (lesions usually originate on the periphery and spread centrally)</li> <li>• Retinal hemorrhage “Cheese Pizza” appearance</li> <li>• “Frosted branch angiitis” (vascular sheathing)</li> </ul>



**Figure 5** Keratic precipitates (see color insert).

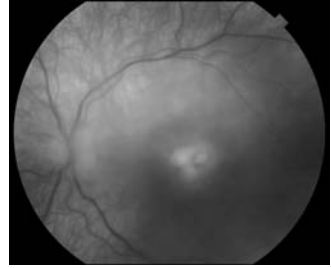


**Figure 6** CMV retinitis (see color insert).



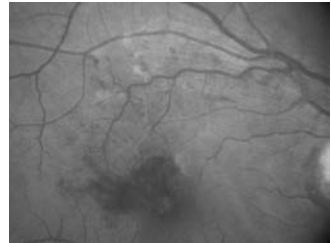
**Figure 7** “Frosted branch angiitis” (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Toxoplasmosis</b>	<ul style="list-style-type: none"> <li>Nystagmus</li> </ul> SL: <ul style="list-style-type: none"> <li>Granulomatous iridocyclitis</li> </ul>	<ul style="list-style-type: none"> <li>“Headlight in the fog” (focal necrotizing retinitis with overlying vitritis)</li> <li>Chorioretinitis</li> <li>Papilledema</li> <li>Retinal hemorrhage</li> <li>Retinal vasculitis</li> <li>Retinal vein/artery occlusion</li> </ul>



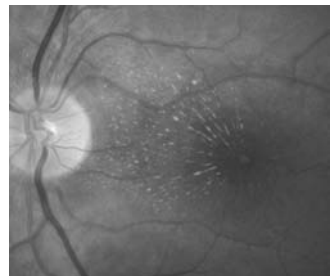
**Figure 8** “Headlight in the fog” (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Meningococemia</b>	<ul style="list-style-type: none"> <li>Severe bilateral eyelid edema (this is a relatively common, but overlooked, early sign of meningococcal meningitis as well as disseminated disease)</li> <li>Purulent, bilateral conjunctivitis (this may be the presenting feature of meningococcal infection)</li> <li>Chemosis</li> <li>Petechiae on the eyelids</li> <li>Subconjunctival hemorrhage</li> </ul> SL: <ul style="list-style-type: none"> <li>Anterior uveitis</li> </ul>	<ul style="list-style-type: none"> <li>Retinal detachment</li> <li>Retinal vein occlusion</li> </ul>



**Figure 9** Branch retinal vein occlusion (see color insert).

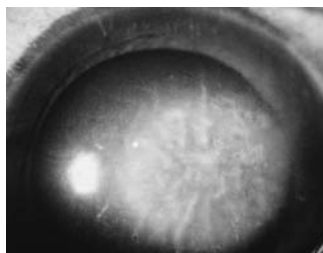
Disease	External eye findings	Fundoscopy findings
<b>Cat scratch disease (CSD)</b>	<ul style="list-style-type: none"> <li>Unilateral conjunctivitis with papillae (Parinaud’s oculoglandular syndrome)</li> <li>Bacillary angiomatosis (relatively uncommon)</li> </ul> SL: <ul style="list-style-type: none"> <li>Intermediate uveitis</li> </ul>	<ul style="list-style-type: none"> <li>Optic nerve edema with “macular star” (typically unilateral)</li> <li>Cotton-wool spots</li> </ul>



**Figure 10** “Macular star” (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Invasive fungal infection (disseminated histoplasmosis and candidiasis)</b>	<ul style="list-style-type: none"> <li>• Conjunctival suffusion</li> <li>• Strabismus</li> <li>• Corneal infiltrates</li> <li>• Dacryocystitis</li> <li>• Proptosis</li> <li>• CN palsies</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• Anterior uveitis (+/- hypopyon)</li> </ul>	<ul style="list-style-type: none"> <li>• Chorioretinitis</li> <li>• Roth spots</li> <li>• Vitreous opacities ("string of pearls" appearance)</li> <li>• Candidal endophthalmitis</li> </ul>

Disease	External eye findings	Fundoscopy findings
<b>Herpes zoster (VZV)</b>	<ul style="list-style-type: none"> <li>• Unilateral conjunctivitis</li> <li>• Blepharitis</li> <li>• Scleritis</li> <li>• Hutchinson's sign</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• Pseudodendritic keratitis</li> <li>• Interstitial keratitis</li> <li>• Uveitis</li> <li>• Iritis</li> </ul>	<ul style="list-style-type: none"> <li>• Retinitis</li> </ul>



**Figure 11** Pseudodendritic keratitis (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Lyme disease</b>	<ul style="list-style-type: none"> <li>• Scleritis</li> <li>• Proptosis</li> <li>• Follicular conjunctivitis</li> <li>• Keratitis</li> <li>• CN palsies (CN III, VI, VII)</li> <li>• Eyelid edema</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• Uveitis</li> <li>• Iritis</li> </ul>	<ul style="list-style-type: none"> <li>• Papilledema</li> <li>• Retinal detachment</li> <li>• Optic neuritis</li> <li>• Choroiditis</li> <li>• Retinal vasculitis</li> </ul>

Disease	External eye findings	Fundoscopy findings
<b>Primary syphilis</b>	<ul style="list-style-type: none"> <li>• Lid ulcer (chancres)</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Secondary syphilis</b>	<ul style="list-style-type: none"> <li>• Conjunctivitis</li> <li>• Eyebrow loss/thinning</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• Uveitis</li> <li>• Interstitial keratitis</li> <li>• Scleritis</li> </ul>	<ul style="list-style-type: none"> <li>• Optic neuritis</li> <li>• Chorioretinitis</li> <li>• Retinal vasculitis</li> </ul>

Disease	External eye findings	Fundoscopic findings
<b>Tertiary syphilis</b>	<ul style="list-style-type: none"> <li>• Argyll Robertson pupil</li> <li>• Conjunctival gumma</li> </ul>	<ul style="list-style-type: none"> <li>• Optic atrophy</li> <li>• Retinal scarring</li> </ul>

SL:

- Interstitial keratitis



**Figure 12** Optic atrophy (see color insert).

## NON-INFECTIOUS DISEASES

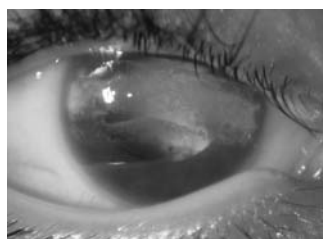
Disease	External eye findings	Fundoscopic findings
<b>Sarcoidosis</b>	<ul style="list-style-type: none"> <li>• Conjunctival granuloma</li> <li>• Eyelid nodules</li> <li>• Painless dacryoadenitis</li> <li>• Argyll Robertson or Adie's pupil anomalies</li> <li>• CN palsies (CN III, IV, VI, VII)</li> <li>• Proptosis</li> <li>• Scleritis</li> </ul>	<ul style="list-style-type: none"> <li>• Candle wax drippings</li> <li>• Retinal granuloma</li> <li>• Retinal neovascularization</li> <li>• Optic disk edema</li> <li>• Optic neuritis</li> <li>• Optic atrophy</li> <li>• Retinal venous sheathing</li> <li>• Branch retinal vein occlusion</li> <li>• Chorioretinitis</li> <li>• Retinal hemorrhage</li> <li>• Cystoid macular edema</li> </ul>

SL:

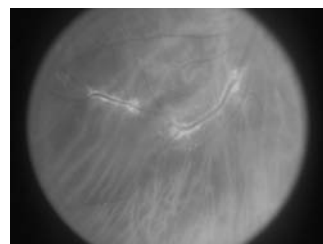
- Mutton fat keratic precipitates
- Band keratopathy
- Keratoconjunctivitis sicca
- Anterior uveitis
- Koeppe nodules (pupil margin)
- Busacca nodules (stromal)
- Cataracts



**Figure 13** Keratic precipitates (see color insert).

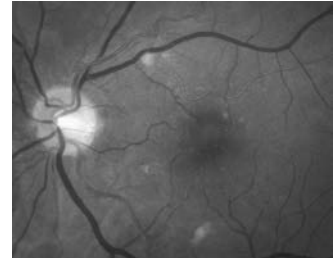


**Figure 14** Band keratopathy (see color insert).



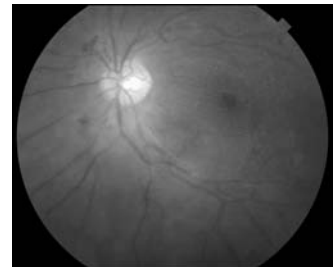
**Figure 15** Candle wax drippings (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Systemic lupus erythematosus (SLE)</b>	<ul style="list-style-type: none"> <li>• Eyelid nodules</li> <li>• Conjunctivitis</li> <li>• Scleritis</li> <li>• Internuclear ophthalmoplegia</li> <li>• One and a half syndrome (a conjugate horizontal gaze palsy in one direction and an internuclear ophthalmoplegia in the other)</li> </ul>	<ul style="list-style-type: none"> <li>• Cotton-wool spots</li> <li>• Roth spots</li> <li>• Hard exudates</li> <li>• Macular ischemia</li> <li>• Retinal neovascularization</li> <li>• Papillitis</li> <li>• Chorioretinitis</li> </ul>
	SL: <ul style="list-style-type: none"> <li>• Keratoconjunctivitis sicca</li> <li>• Uveitis</li> </ul>	



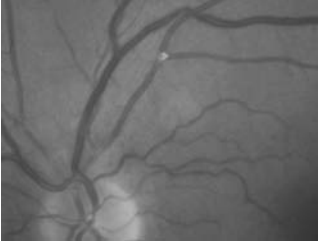
**Figure 16** Cotton-wool spots (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Wegener's granulomatosis</b>	<ul style="list-style-type: none"> <li>• Conjunctival suffusion</li> <li>• Bilateral eyelid edema</li> <li>• Eyelid nodules</li> <li>• Painful ptosis</li> <li>• Necrotizing sclerokeratitis (corneal ulceration)</li> <li>• Proptosis</li> <li>• Orbital cellulitis</li> <li>• Orbital pseudotumor</li> <li>• Painful dacryoadenitis/ dacryocystitis</li> <li>• CN palsies (can involve any, but most common are CN II, VI, VII)</li> </ul>	<ul style="list-style-type: none"> <li>• Cotton-wool spots</li> <li>• Retinal hemorrhages</li> <li>• Retinal vasculitis (perivascular sheathing)</li> <li>• Central retinal artery occlusion</li> <li>• Central/branch retinal vein occlusion</li> </ul>
	SL: <ul style="list-style-type: none"> <li>• Posterior uveitis</li> </ul>	

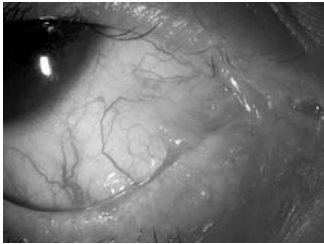
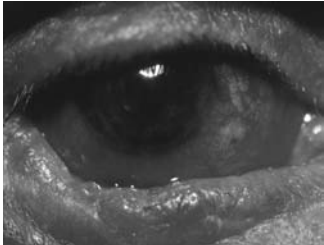


**Figure 17** Retinal vasculitis (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Temporal arteritis/ giant cell arteritis (TA/GCA)</b>	<ul style="list-style-type: none"> <li>• Decreased visual acuity</li> <li>• Amaurosis fugax</li> <li>• Relative afferent pupillary defect</li> <li>• Horner's syndrome</li> <li>• Scleritis</li> </ul>	<ul style="list-style-type: none"> <li>• Cotton-wool spots</li> <li>• Central retinal artery occlusion</li> <li>• Chorioretinal scarring (secondary to choroidal infarctions)</li> </ul>
	SL: <ul style="list-style-type: none"> <li>• Marginal corneal ulceration</li> </ul>	

Disease	External eye findings	Fundoscopy findings
<b>Cholesterol emboli syndrome</b>	<ul style="list-style-type: none"> <li>• Amaurosis fugax</li> </ul> SL: <ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Hollenhorst plaques</li> <li>• Retinal infarction</li> </ul> 

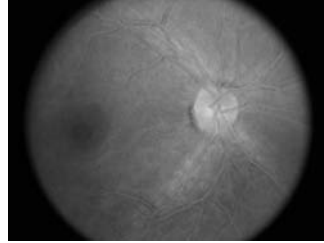
**Figure 18** Hollenhorst plaque (see color insert).

Disease	External eye findings	Fundoscopy findings
<b>Stevens–Johnson syndrome</b>	<ul style="list-style-type: none"> <li>• Bilateral hemorrhagic conjunctivitis</li> <li>• Ulcerative keratitis</li> <li>• Symblepharon</li> <li>• Entropion</li> <li>• Trichiasis</li> </ul> SL: <ul style="list-style-type: none"> <li>• Stromal opacification</li> </ul> 	<ul style="list-style-type: none"> <li>• None</li> </ul> 

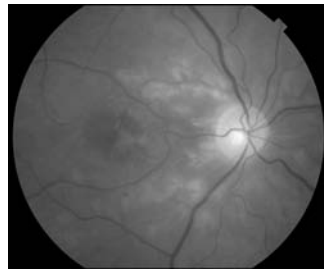
**Figure 19** Symblepharon (see color insert).

**Figure 20** Hemorrhagic conjunctivitis (see color insert).

Disease	External eye findings	Fundoscopic findings
<b>Acute pancreatitis</b>	<ul style="list-style-type: none"> <li>• Xanthlasma (seen in hypertriglyceridemia-related pancreatitis)</li> <li>• Corneal arcus (seen in hypertriglyceridemia-related pancreatitis)</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Lipemia retinalis (seen in hypertriglyceridemia-related pancreatitis)</li> <li>• Purtscher's-like Retinopathy (seen in alcoholic pancreatitis)</li> </ul>



**Figure 21** Lipemia retinalis (see color insert).



**Figure 22** Purtscher's-like retinopathy (see color insert).

Disease	External eye findings	Fundoscopic findings
<b>Kawasaki's disease</b>	<ul style="list-style-type: none"> <li>• Bilateral nonexudative bulbar conjunctivitis (limbal sparing)</li> <li>• Subconjunctival hemorrhage</li> </ul> <p>SL:</p> <ul style="list-style-type: none"> <li>• Anterior uveitis</li> <li>• Superficial keratitic precipitates</li> </ul>	<ul style="list-style-type: none"> <li>• Papilledema</li> </ul>

**ACKNOWLEDGMENTS**

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# 5 | Radiology of Infectious Diseases and Their Mimics in Critical Care

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## INTRODUCTION

Radiologic diagnosis of infection in the critically ill population can be challenging. Various imaging modalities are usually needed in the workup of infection in these patients to exclude or diagnose alternate disorders such as malignancy and autoimmune disease. In this chapter, the radiologic presentation of various abdominal, neurologic, and thoracic infections as well as the findings in other diseases that may mimic infection on imaging are discussed, as are potentially helpful differentiating factors.

## ABDOMINAL AND PELVIC INFECTIOUS PROCESSES AND THEIR MIMICS

### Clinical and Radiologic Diagnosis of Acute Pyelonephritis

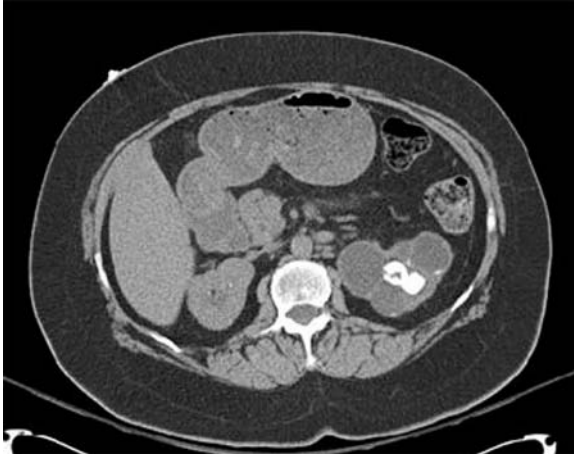
Acute pyelonephritis is a bacterial infection involving the renal pelvis, tubules, and interstitium. The most common pathogen is *Escherichia coli*. Infection occurs primarily via ascending spread of a urinary tract infection, although hematogenous spread can occur less frequently. Uncomplicated disease is rarely, if ever, fatal. However, complications such as emphysematous pyelonephritis in diabetics, abscess formation, or sepsis increase the morbidity and mortality substantially. Risk factors for the development of complications include age greater than 65, bedridden status, immunosuppression, and a long-term indwelling urinary tract catheter (1).

The diagnosis of acute pyelonephritis is usually made via history and physical exam in conjunction with positive urinalysis, and imaging is not generally needed except for cases of atypical presentation or a suspected complication. Contrast-enhanced CT is the imaging method of choice in adult patients. The classic findings of acute pyelonephritis on CT are wedge-shaped and striated areas of decreased enhancement (“patchy” nephrogram). There is also usually stranding of the perinephric fat and thickening of Gerota’s fascia. The kidney involved may also be enlarged or demonstrate areas of focal swelling in the acute setting and then may become scarred and contracted if the infection progresses to a chronic state. Ultrasound may be used for screening, although it is not as sensitive or specific as CT. Findings include a normal or enlarged kidney with decreased echogenicity and wedge-shaped zones of hypoechogenicity (hyperechogenic foci, which are less likely, usually indicate a hemorrhagic component). There is also blurring of the corticomedullary junction. Anechoic regions are indicative of abscess formation. A Tc-99m DMSA (nuclear medicine) scan is equally sensitive for the detection of renal infection, demonstrating decreased uptake at foci of inflammation, and is the diagnostic and follow-up method of choice in children, to lessen radiation exposure (1–3).

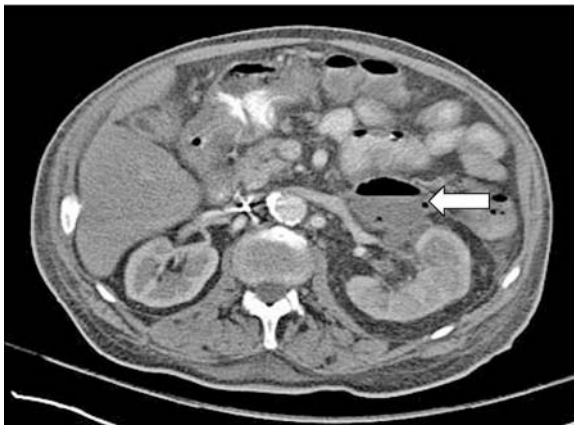
### Mimic of Acute Pyelonephritis

Xanthogranulomatous pyelonephritis (XGPN) is a relatively rare form of pyelonephritis associated with a chronically obstructed kidney, usually in conjunction with a staghorn calculus. The disease results in destruction of the renal parenchyma and a nonfunctioning kidney. Unlike conventional bacterial pyelonephritis, which can be treated medically, the treatment for XGPN is nephrectomy, once the patient is stable. XGPN is most frequently seen in diabetic or immunocompromised patients (1,2).

The CT findings of XGPN include low-attenuation collections in the kidney involved, which represent dilated calyces filled with pus and debris, as well as a dilated renal pelvis (Fig. 1). There is bright enhancement of the rims of the collections secondary to inflammation and formation of granulation tissue. There is also little to no excretion of IV contrast into the



**Figure 1** CT scan of the abdomen in a 53-year-old female demonstrates a large obstructing staghorn calculus in the pelvis of the left kidney with diffuse calyceal dilatation and diffuse cortical thinning. These findings are essentially diagnostic of XGPN, when combined with a history of recurrent urinary tract infection. *Abbreviation:* XGPN, xanthogranulomatous pyelonephritis.



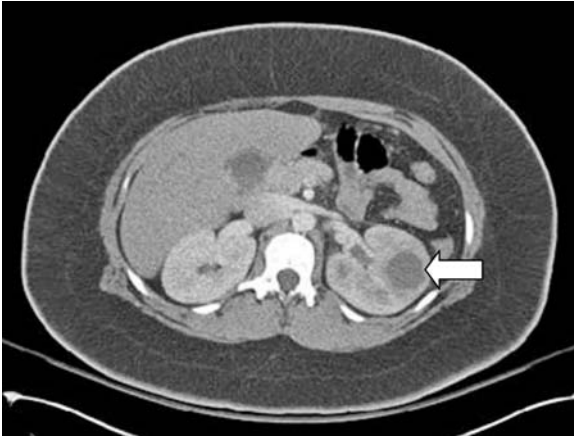
**Figure 2** CT scan of the abdomen in a 72-year-old male demonstrates an abscess in the left anterior pararenal space containing gas and fluid (arrow).

collecting system as the kidney is nonfunctioning. As in conventional pyelonephritis, there is inflammatory change of the perinephric fat, but in contrast, there is much more frequent involvement of adjacent structures, particularly the ipsilateral psoas muscle, with rare involvement of other structures such as the colon. Unlike in conventional pyelonephritis, the previously mentioned staghorn calculus is usually present or rarely some other chronically obstructing lesion, such as tumor. Gas within the kidney may also rarely be seen (1–3).

### Clinical and Radiologic Diagnosis of Renal Abscess

Focal or multifocal bacterial infections can result in formation of renal abscess. The location of the abscess is indicative of its etiology. Cortical abscesses result from hematogenous spread of infection, with *Staphylococcus aureus* being the most common pathogen. Much more commonly, in contrast, corticomedullary abscesses result from ascending spread of infection from organisms in the urine. The latter type of abscess is more likely to extend to the renal capsule and perforate, resulting in perinephric abscess formation (Fig. 2). Corticomedullary abscesses are uncommon complications of urinary tract infections; risk factors for their development include recurrent infections, untreated or ineffectively treated infections, renal calculi, instrumentation, vesicoureteral reflux, and diabetes mellitus (4).

There are multiple options for imaging a patient with a suspected renal abscess, with CT considered the method of choice. Plain radiographs may show radiopaque stones or intraparenchymal gas in patients with emphysematous pyelonephritis, but are generally not helpful for the identification of abscess alone. Ultrasound findings include an ill-defined mass



**Figure 3** Contrast-enhanced CT scan of the abdomen in a 15-year-old female demonstrates as abscess in the interpolar region of the left kidney (*arrow*) with rim enhancement and adjacent diffuse low density and left renal swelling representing pyelonephritis.



**Figure 4** Non-enhanced CT scan of the abdomen in a 47-year-old male, who presented with left flank pain, demonstrates a large mixed solid and cystic tumor in the upper pole of the right kidney, containing internal foci of calcification, which subsequently proved to be renal cell carcinoma.

that is either hyperechoic or hypoechoic, with low-level internal echoes and disruption of the corticomedullary junction. The “comet sign,” consisting of internal echogenic foci, indicates the presence of gas within the lesion. Contrast-enhanced CT demonstrates a round, well-margined, low-attenuation mass with wall enhancement (Fig. 3). Gas may or may not be present within the lesion, and there is no enhancement centrally within the lesion. Perinephric inflammatory change is also often seen. A white blood cell scan may also be helpful for diagnosis. Uptake of indium-111-labeled leukocytes within the abscess can be seen, although false-negative results may occur if the patient has already been on antibiotic therapy, if the abscess is walled off, or if there is a poor inflammatory response (3,4).

#### **Mimic of Renal Abscess**

Renal cell carcinoma may mimic renal abscess on imaging examinations. Both are mass-like lesions within the kidney; however, unlike renal abscess, which does not enhance centrally, renal cell carcinoma typically demonstrates heterogeneous enhancement. Internal calcifications may or may not be present (Fig. 4). For this reason, the recommendation for imaging known or suspected renal masses that could be cancers rather than abscesses includes non-enhanced CT followed by multiphasic contrast-enhanced CT performed at the same sitting (3,5).

#### **Clinical and Radiologic Diagnosis of Psoas Abscess**

Primary psoas abscess is rare and usually idiopathic. The most common causative pathogens are *S. aureus* and mixed Gram-negative organisms. Immunocompromised patients are at risk

for infection by opportunistic agents. Secondary psoas abscess is more common and may result from spread of infection from adjacent structures, including colon, kidney, and bone (6).

The CT findings of psoas abscess include enlargement of the muscle by a low-attenuation lesion that displays rim enhancement after IV contrast administration. Other findings include obliteration of normal fat planes as well as bone destruction and gas formation. Gas within a psoas abscess may also be related to an underlying bowel fistula, such as in Crohn's disease or diverticulitis. MRI has generally shown no increased diagnostic benefit and has no role in the diagnosis of psoas abscess, unless concurrent examination of the spine and thecal sac is indicated. Abnormal uptake on a Ga-67 scan may also be used for diagnosis, although other entities, such as lymphoma, also show increased uptake; this finding is therefore not specific. An indium-111 white blood cell scan alternatively can be used to confirm infection if needed and should be more specific, although percutaneous aspiration (and drainage) can be performed for more definitive diagnosis and therapy (6-8).

### **Mimic of Psoas Abscess**

Differentiation from tumor, such as lymphoma, can be difficult with imaging alone, as both can present as low-attenuation lesions, although the presence of gas makes the diagnosis of abscess far more likely. Adjacent structures should be examined to determine if there is a source of secondary infection. In the case of lymphoma originating from para-aortic lymph nodes, a potential helpful differentiating feature is that there may be medial or lateral displacement of the muscle by tumor, rather than extension into the muscle, as would be seen in an abscess (9,10).

### **Clinical and Radiologic Diagnosis of Prostate Abscess**

Prostatic abscess occurs as a complication of acute bacterial prostatitis. The most common organism is *E. coli*. Diabetic and immunocompromised patients are especially prone to this complication. The symptoms are similar to acute bacterial prostatitis, including fever, chills, and urinary frequency, with focal prostatic tenderness on physical exam (11).

Both CT and ultrasound are used for diagnosis, with ultrasound also having therapeutic utility in transrectal drainage. Abscesses can occur anywhere in the prostate, although they are usually centered away from the midline. Findings on ultrasound include focal hypoechoic or anechoic masses, with thickened or irregular walls, septations, and internal echoes. On CT, findings include an enlarged gland containing multiple well-demarcated, non-enhancing fluid collections within the gland and/or periprostatic tissues. These collections may be multi-septated or demonstrate enhancing rims (3,12).

### **Mimic of Prostate Abscess**

A potential mimicker of prostate abscess is prostate carcinoma. Prostate cancer is the most common noncutaneous cancer in American men and the second most common cause of male cancer deaths after lung cancer. Unlike prostate abscess, which can occur anywhere in the gland, prostate cancer occurs mainly in the peripheral zones. Diagnosis is made via a combination of digital rectal exam findings, elevated PSA level, transrectal ultrasound, and MR, with a definitive diagnosis established by biopsy (3,13).

Ultrasound findings are somewhat similar to abscess in that carcinoma appears as an anechoic to hypoechoic mass. The contour is classically asymmetric or triangular with the base close to the capsule and extending centrally into the gland based on the pattern of tumor growth. While CT is an excellent means for diagnosing and following treatment of prostatic abscess, it has limited use in the diagnosis of carcinoma due to relatively poor sensitivity and specificity for detection of cancer within the gland compared with MRI. CT findings may include an enlarged gland with evidence of extracapsular extension in more advanced tumors (obliterated periprostatic fat plane, invasion of adjacent bladder or rectum) and pelvic lymphadenopathy (Fig. 5). T2-weighted MRI demonstrates prostate cancer as a low-intensity area within the gland, whereas abscess should demonstrate areas of central high signal intensity related to the fluid content (13,14).



**Figure 5** CT scan of the pelvis in a 91-year-old male with known prostate cancer demonstrates a large, slightly heterogeneous prostate (*large arrow*) protruding into the bladder base (*small arrow*).



**Figure 6** CT scan of the abdomen demonstrating an abscess in the right hepatic lobe (*arrow*) in a 36-year-old male with fever and abdominal pain following recent laparoscopic appendectomy for perforated appendicitis.

### Clinical and Radiologic Diagnosis of Liver Abscess

There are three main types of liver abscess: pyogenic, amebic, and fungal. Pyogenic abscesses occur most often in the United States and are usually polymicrobial. Pyogenic liver abscesses occur by direct extension from infected adjacent structures or by hematogenous spread via the portal vein or hepatic artery. Clinical presentation may be insidious, with fever and right upper quadrant pain being the most common presenting complaints. The right lobe of the liver is more often affected secondary to bacterial seeding via the blood supply from both the superior mesenteric and portal veins. Untreated, the disease is usually fatal, but with prompt abscess identification and then antibiotic administration and drainage, mortality is significantly decreased (15).

Both CT and ultrasound can be used for diagnosis and follow-up of liver abscess as well as for guiding percutaneous drainage. The CT appearance of a liver abscess is a round, well-defined hypodense mass that may contain gas centrally (Fig. 6). A commonly seen finding is the “cluster sign” representing a conglomerate of small abscesses coalescing into a single large cavitating lesion. An associated capsule or septations may be present, which enhance with IV contrast administration. Secondary findings include right pleural effusion and right lower lobe atelectasis. On ultrasound, the lesion is usually spherical or ovoid with hypoechoic, irregular walls. Centrally, the abscess may be anechoic or less often hyperechoic or hypoechoic, depending on the presence of septa, debris, or necrosis (3,7).



**Figure 7** Non-enhanced CT scan of the abdomen in a 77-year-old male with colon cancer demonstrating multiple low-density lesions throughout the liver (stars), representing metastases.

### Mimic of Liver Abscess

A nonliquefied abscess (particularly from *Klebsiella* species) can sometimes be confused with hepatic tumor such as hepatocellular carcinoma (HCC) or metastatic disease from gastrointestinal primary tumors or vice-versa (Fig. 7), particularly when solitary. Like abscess, these also appear more often on the right side of the liver when solitary. A helpful differentiating factor is that most cases of HCC occur in patients with underlying cirrhosis (3).

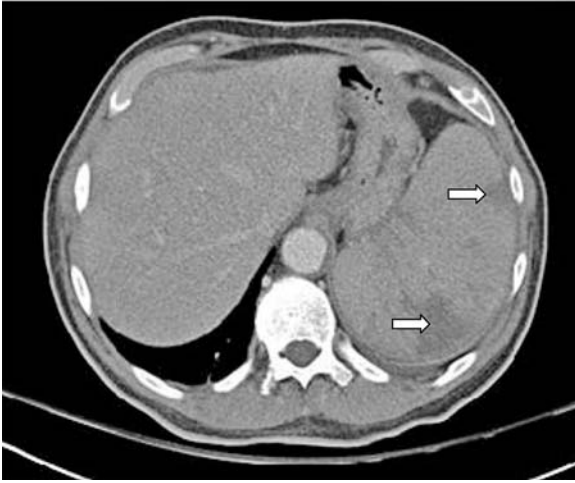
On ultrasound, the mass appears mixed in echogenicity and demonstrates increased vascularity on color Doppler interrogation. The appearance on portal venous phase (i.e., routine delay following IV contrast) CT is usually that of a hypodense mass with or without necrosis. The tumor may have a capsule, which enhances after contrast administration. Portal vein thrombosis occurring in conjunction with liver abscess is clinically and radiologically difficult to differentiate from tumor thrombus in HCC. HCC demonstrates characteristic enhancement patterns on multiphasic CT scans performed with at least both arterial and portal venous phases, which aids in diagnosis and differentiation from other entities. The tumor is heterogeneous on arterial-phase CT (or MR) imaging, intermixed with areas of hypoperfusion from portal vein occlusion by tumor thrombus. There is then washout of contrast on the portal venous phase, as the tumor is supplied almost exclusively by the hepatic artery, and, if performed, on the delayed phase (3,16,17).

MR can also be used, although it is mostly reserved for those cases that are indeterminate on CT or when there is a contraindication to iodinated contrast for CT and IV gadolinium can be administered for MR. On T1-weighted imaging, HCC is typically hypointense, whereas on T2-weighted images, it is usually somewhat hyperintense. With gadolinium administration, the enhancement pattern varies from central to peripheral and from homogeneous to rim enhancing. Also on T2-weighted imaging, the hyperintensity surrounding an abscess is typically much greater than that which would be seen for HCC (3,16,17).

### Clinical and Radiologic Diagnosis of Splenic Abscess

Splenic abscess is a rare entity with a high mortality rate. The most common etiology is hematogenous spread of infection from elsewhere in the body. Alcoholics, diabetics, and immunocompromised patients are most susceptible. There are a diverse array of pathogens, including bacteria (aerobic and anaerobic) and fungi (18).

Diagnosis cannot be made solely through history and physical examination. CT is the standard imaging modality for diagnosis and therapeutic drainage planning. CT findings include a low-attenuation, ill-defined mass within the splenic parenchyma. As with abscesses elsewhere in the abdomen and pelvis, there may be gas or an air-fluid level. There is no enhancement of the central portion after IV contrast administration, although as with hepatic abscesses, there is often perilesional enhancement as well as surrounding edema. There may be



**Figure 8** CT scan of the abdomen in an 82-year-old male demonstrating multiple peripheral, wedge-shaped, low-density lesions in a mildly enlarged spleen (arrows) that are acute and subacute infarcts.

inflammatory stranding of the perisplenic fat. Ultrasound demonstrates a hypoechoic lesion that may contain internal septations and low-level internal echoes, representing either debris or hemorrhage. There is no blood flow within the central areas on Doppler interrogation (3,19).

### Mimic of Splenic Abscess

Splenic infarct may have a similar clinical presentation, including fever, chills, and left upper quadrant pain. Differentiating the two entities is important, as an infarct can be managed conservatively, whereas abscess requires antibiotic therapy and possibly drainage. On CT, a splenic infarct is classically a peripheral, wedge-shaped low-attenuation region after IV contrast administration (Fig. 8). However, the lesion may be rounded, similar to an abscess, or irregular. Lack of mass effect on the splenic capsule may be a helpful differentiating factor from abscess. Further complicating matters, in patients with septic emboli (e.g., from endocarditis), the CT findings may be identical to those of bland infarction (e.g., from atrial fibrillation), and differentiating between these two entities is difficult to impossible without clinical correlation (3,19).

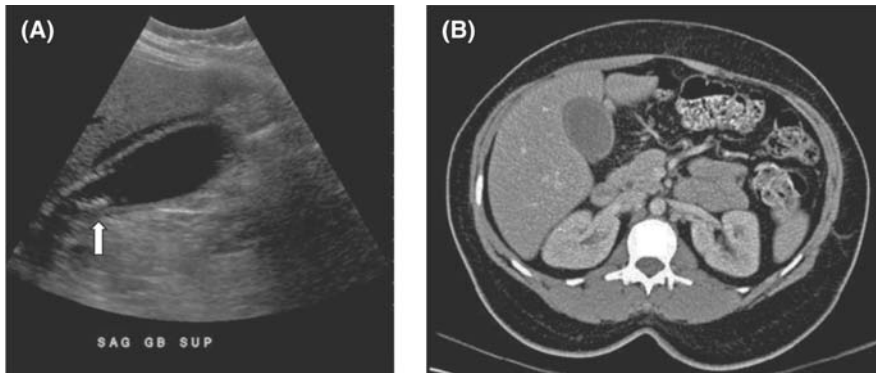
Unlike abscess, on follow-up cross-sectional imaging, an infarct should become better demarcated and eventually resolve, leaving an area of fibrotic contraction and volume loss. A deviation from this expected course suggests a complication such as hemorrhage or superimposed infection (19).

### Clinical and Radiologic Diagnosis of Cholangitis/Calculous Cholecystitis

Acute infection of the biliary system is often associated with biliary obstruction from gallbladder calculi. Obstruction leads to intraluminal distention, which interferes with blood flow and drainage, predisposing to infection. The most common pathogens are *E. coli*, *Klebsiella*, enterobacter, enterococci, and group D streptococci. Elderly patients are particularly predisposed to infection (20).

On ultrasound, cholangitis appears as thickened walls of the bile ducts, which may be dilated and contain pus or debris. Visualization of an obstructing stone increases diagnostic certainty, although MR cholangiography (see below) is more accurate for identification of such stones. The ultrasound criteria for acute cholecystitis include cholelithiasis and a sonographic Murphy's sign, considered the most sensitive findings, with additional findings of a thickened gallbladder wall (>3 mm) and pericholecystic fluid (Fig. 9A) (3,20,21).

CT is somewhat less sensitive due to a minority of gallstones being calcified and therefore radiopaque. CT findings include a distended gallbladder, gallbladder wall thickening, pericholecystic fat stranding and calcified gallstones, when present. There is also mural enhancement with IV contrast administration (Fig. 9B). Complications including gangrenous changes in the wall, with heterogeneity of enhancement, and pericholecystic abscess, are also identifiable on CT (3,21).



**Figure 9** (A) Ultrasound examination demonstrates a thickened gallbladder wall, pericholecystic fluid, and gallstones (*arrow*). Correlating with a positive sonographic Murphy's sign, these findings were diagnostic of acute cholecystitis in this patient. (B) Contrast-enhanced CT scan of the abdomen in the same patient demonstrates increased enhancement of the gallbladder wall and pericholecystic fluid, but the gallstones are not identifiable.

Nuclear scintigraphic studies are useful in confirming cholecystitis and for differentiating between acute and chronic cases, in selected patients.  $^{99m}\text{Tc}$  iminodiacetic acid derivatives (i.e., HIDA and its derivatives) are injected intravenously, are taken up by hepatocytes, and are then transported into the biliary system in a fashion similar to bilirubin. Nonvisualization of the gallbladder at four hours has 99% specificity for diagnosing cholecystitis. Intravenous morphine may be administered if initial images do not demonstrate the gallbladder, to cause sphincter of Oddi spasm, increasing biliary pressure and forcing radiotracer into a chronically inflamed gallbladder, but not in acute gallbladder inflammation (3).

MRI findings of acute cholecystitis include a distended gallbladder with stones, gallbladder wall thickening and edema, and increased signal in the pericholecystic fat on T2-weighted images. MR cholangiopancreatography (MRCP, i.e., multi-planar heavily T2-weighted images) can be used to visualize obstructing stones within the biliary tree with a high degree of accuracy in patients with suspected cholecystitis and/or cholangitis, which are seen as filling defects and/or a cutoff of the common duct (3).

### Mimic of Calculous Cholecystitis

Approximately 90% of cases of cholecystitis are associated with stones, but 10% occur without them, i.e., acalculous cholecystitis (AC). The precise etiology of AC is still not fully understood. Existing theories propose the noxious effect of superconcentrated bile due to prolonged fasting and the lack of cholecystokinin-stimulated emptying of the gallbladder. Gallbladder wall ischemia from low-flow states in patients with fever, dehydration, or heart failure has also been proposed. The disease occurs in very ill patients, such as those on mechanical ventilation or those having experienced severe trauma or burns. Mortality is much higher with AC, as the entity is much more prone to gangrene and perforation (20,22,23).

AC has proven to be an elusive diagnosis to make, both clinically and radiologically. In the appropriate clinical context, in any patient with presumed cholecystitis without demonstration of stones on either ultrasound, CT, or MR, AC should be the leading diagnosis. Prior studies have shown decreased sensitivity for both ultrasound and nuclear medicine studies in the detection of AC. Sonographic findings include an enlarged gallbladder, diffuse or focal wall thickening with focal hypoechoic regions, pericholecystic fluid, and diffuse homogeneous echogenicity (possibly from debris) in the gallbladder lumen without identifiable calculi. Visualization of the gallbladder on HIDA scans is possible in some cases of AC due to a patent cystic duct, leading to false negatives. False positives on HIDA scans may also occur since parenteral alimentation, prolonged fasting, and hepatocellular dysfunction, all seen in the critically ill, are the same factors that cause nonvisualization of the gallbladder despite lack of acute or chronic inflammatory gallbladder disease (23,24).





**Figure 10** CT scan of the abdomen demonstrates air in the gallbladder [which also contains gallstones (*arrow*)], secondary to erosion of the stomach into the biliary system in a 71-year-old male with metastatic gastric cancer. A gastrostomy tube is also present.

### Clinical and Radiologic Diagnosis of Emphysematous Cholecystitis

Emphysematous cholecystitis is a form of cholecystitis caused by gas-forming organisms, most commonly *E. coli* and *Klebsiella*. Gallstones are often present, although there are cases associated with AC. Those most prone to infection are diabetics and the elderly. Mortality rates are much higher than with nonemphysematous cholecystitis (21,25).

Gas within the gallbladder wall may be identified on radiographs. The most sensitive and specific test is CT, which not only demonstrates gas in the gallbladder wall, but also may show spread of inflammation and, in some cases, gas into surrounding tissues and into the rest of the biliary system (21,25).

### Mimic of Emphysematous Cholecystitis

Aside from calculous and AC, gas in the biliary system from a biliary-enteric fistula (spontaneous or iatrogenic) is a differential consideration in the diagnosis of emphysematous cholecystitis, although relatively rare (Fig. 10). Specific considerations include gallstone ileus (i.e., chronic cholecystitis with fistula to the adjacent small bowel) and malignancy. Extension of inflammation into the pericholecystic tissues and extrahepatic ducts may be a helpful differentiating feature, as this is considered more specific for emphysematous cholecystitis (25).

### Clinical and Radiologic Diagnosis of Pancolitis

Colonic infection results from bacterial, viral, fungal, or parasitic infections. An increasingly prevalent agent in both hospitalized and nonhospitalized patients is *Clostridium difficile*.

Plain film findings of *C. difficile* colitis include polypoid mucosal thickening, haustral fold thickening or “thumbprinting” represented by widened opaque transverse bands, and gaseous distention of the colon. On CT, the colonic wall is thickened and low in attenuation, secondary to edema (Fig. 11). Wall thickening may be circumferential, eccentric, smooth, irregular, or polypoid, and ranges from 3 mm to 32 mm. There is mucosal and serosal enhancement. Inflammation of the pericolonic fat and ascites may be present. The “target sign” consists of two to three concentric rings of different attenuation within the colonic wall and represents mucosal hyperemia and submucosal edema or inflammation. This sign is helpful, but not very specific, as it is also seen in inflammatory bowel disease, including ulcerative colitis (UC), amongst other disorders. The “accordion sign” is due to trapping of oral contrast between markedly thickened haustral folds, resulting in alternating bands of high and low attenuation, oral contrast, and edematous bowel wall, respectively. Pericolonic fat stranding, while often present, is generally mild in comparison with the degree of bowel wall thickening, which may be helpful in differentiating *C. difficile* from inflammatory colitis (3,26).



**Figure 11** Contrast-enhanced CT scan of the abdomen demonstrates wall thickening of the sigmoid colon with intramural low density, representing submucosal edema. Mild pericolic inflammation is noted. These findings are compatible with colitis. A small amount of ascites is also present (*arrow*).

### Mimic of Pancolitis

#### *Ulcerative Colitis*

UC is an inflammatory bowel disorder that primarily involves the colorectal mucosa and submucosa. The wall thickening in UC is characteristically diffuse and symmetric. Barium enema (BE) can be helpful in differentiating UC from infectious colitis, although it is relatively contraindicated in the latter to prevent proximal spread of infection. BE demonstrates mucosal stippling, representing crypt abscess formation, and “collar button” ulcers, representing lateral extension of ulcers within the submucosal space. CT findings are typically of a nonspecific, contiguous colitis involving a portion of the distal colon or the entire colon, without skip areas, that is in and of itself difficult if not impossible to differentiate from infection at initial presentation; CT is used to determine extent/severity of colitis and any complications (obstruction, perforation, etc.) (3,27).

#### *Ischemic Colitis*

Ischemic colitis results from compromise to the mesenteric blood supply. As such, findings occur in a territorial distribution, typically in watershed areas, such as the splenic flexure (superior mesenteric artery/inferior mesenteric artery junction) and the rectosigmoid junction (inferior mesenteric artery/hypogastric artery junction). Again, bowel wall thickening, mucosal irregularity, and pericolic inflammatory changes may be seen on CT. Specific findings for bowel ischemia include pneumatosis (in the correct clinical context), which may be difficult to distinguish from intraluminal gas in some patients, and lack of submucosal enhancement in the region of infarction (3).

## CNS INFECTIONS AND THEIR MIMICS

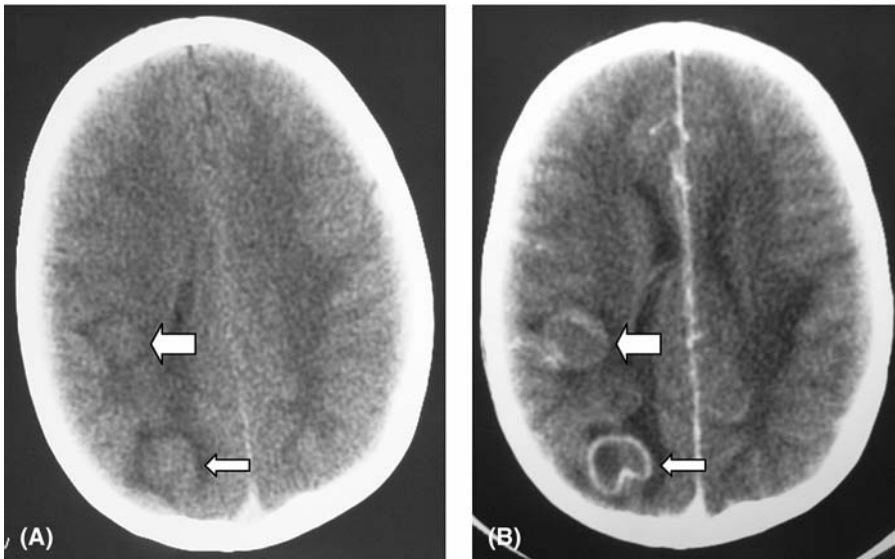
### Clinical and Radiologic Diagnosis of Brain Abscess

Focal infection in the brain is most often bacterial, although fungal and parasitic infections also occur. Pathogens can be introduced into the brain via direct extension (such as from sinus or dental infection), hematogenous spread, or after penetrating injury or brain surgery. There is a substantially increased incidence of CNS infection in immunocompromised patients. There are four stages of infection: early and late cerebritis and early and late abscess capsule formation. Capsule formation typically occurs over a period of two to four weeks (28,29).

CT and MRI are both utilized in diagnosis. The appearance of the lesion on either depends on the stage of infection. Classically, a brain abscess appears as a smooth, ring-enhancing lesion; gas-containing lesions are rarely seen. Early cerebritis is more readily detected on MR than CT. CT during this stage may demonstrate a poorly defined, low-attenuation subcortical lesion with mass effect or may alternatively be normal. On MR, an ill-defined, heterogeneous lesion is seen, hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images. During the late cerebritis stage, a rim appears on MR,



**Figure 12** Contrast-enhanced T1-weighted axial MR image of the brain demonstrates two ring-enhancing lesions in the temporal lobes (*arrows*) in a 52-year-old female with *Nocardia* cerebritis.



**Figure 13** (A) Axial CT image of the brain in a three-year-old male with congenital heart disease demonstrates two subcortical, low-attenuation lesions in the right cerebral hemisphere (*arrows*). (B) After IV contrast administration, both lesions demonstrate thin, peripheral enhancement (*arrows*) with central low density consistent with brain abscesses.

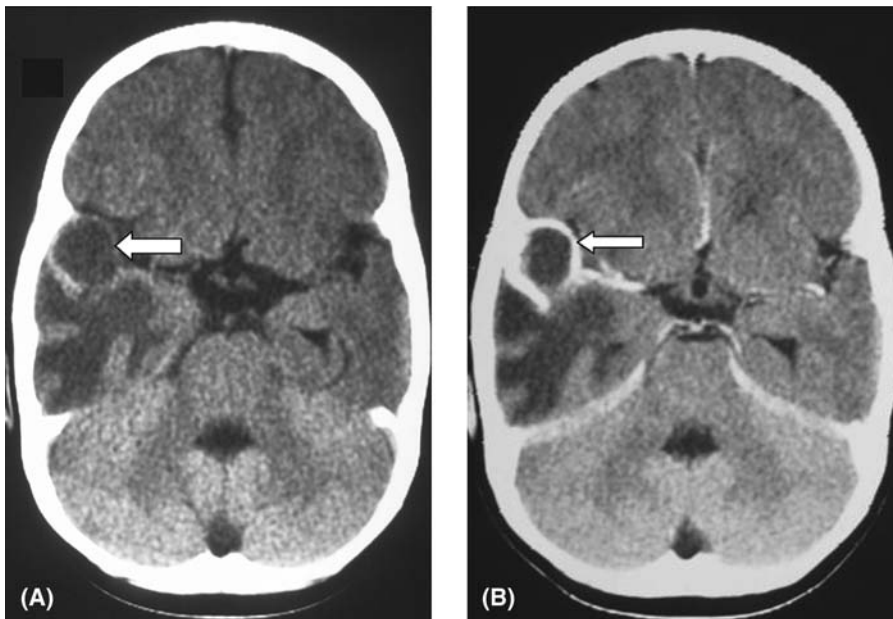
high intensity on T1-weighted images (Fig. 12) and low on T2-weighted images, as well as increasing mass effect and vasogenic edema on both CT and MR. The early capsule on CT appears as a thin, enhancing rim, with low attenuation in the center of the lesion (Fig. 13A and B). On MR, the rim becomes increasingly well defined, and the center of the lesion

demonstrates increased signal relative to cerebrospinal fluid (CSF) on T1-weighted images. The rim is typically thickest on the cortical aspect and thinnest in its deep aspect, which is a phenomenon believed to be related to the higher oxygenation of blood flow closer to the gray matter. A feature that can be used to differentiate late cerebritis from the early capsular stage, as both demonstrate rim formation, is the phenomenon of “filling in,” in which a 20- to 40-minute delay on a contrast-enhanced MR will show enhancement in the central portion of the lesion during late cerebritis, but not once the actual capsule has formed. The center of the abscess also demonstrates high signal on diffusion-weighted MR imaging, presumably due to the elevated viscosity of the necrotic material (28,30).

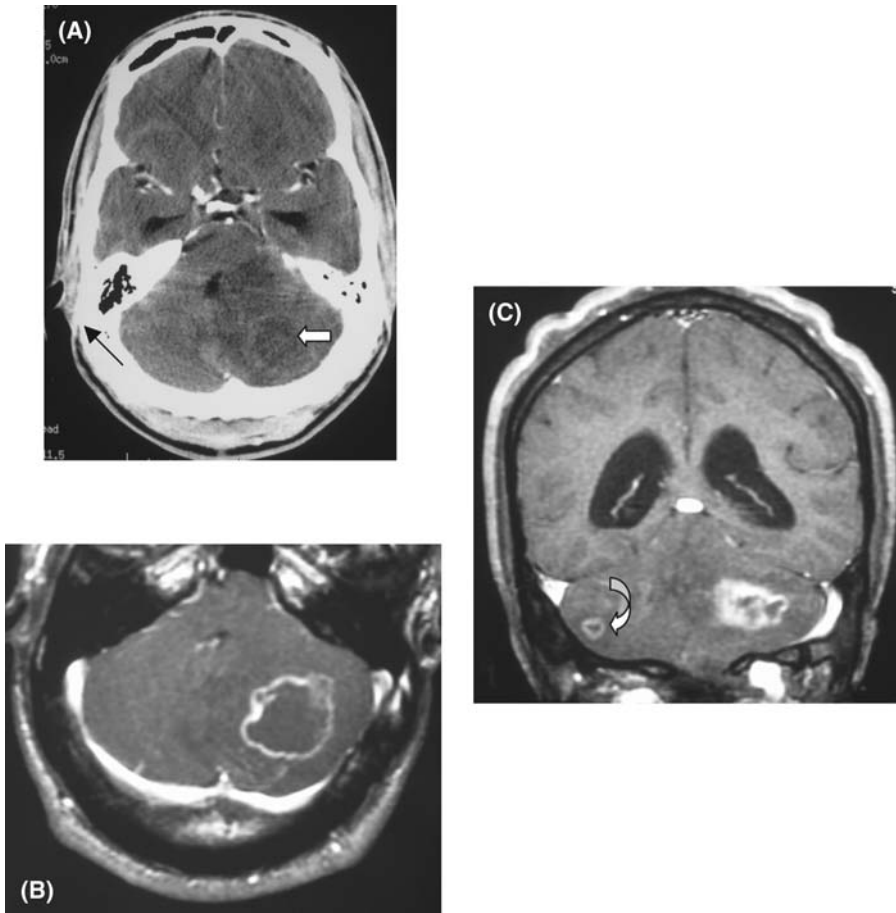
### Clinical and Radiologic Diagnosis of CNS Tuberculosis

While isolated involvement of the central nervous system in tuberculosis is rare, CNS involvement is seen in approximately 5% of cases of tuberculosis, with increased prevalence in immunocompromised individuals. Infection mostly occurs via hematogenous spread. Various forms of cerebral involvement can occur including tuberculous meningitis, cerebritis, tuberculoma, abscess, or miliary tuberculosis. Tuberculoma (or tuberculous granuloma) is the most common CNS parenchymal lesion of tuberculosis. The lesions may be solitary or multiple and can occur anywhere in the brain, although there is a predilection for the frontal and parietal lobes (31,32).

On CT, the lesions may be round or lobulated, high or low in attenuation, and enhancement patterns vary from homogeneous to ring enhancing (Fig. 14A and B). The lesions may also have irregular walls of varying thickness. When chronic, they are associated with mass effect, surrounding edema, and calcification. The “target sign,” consisting of central calcification, surrounding edema, and peripheral enhancement, is suggestive of, but not entirely diagnostic for, tuberculoma. On MR, the lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images and homogeneously enhance, although once there is central caseation and necrosis, there is central hypointensity on T1-weighted images (and hyperintensity on T2-weighted images) and peripheral hyperintensity on T1-weighted images (and hypointensity on T2-weighted images) as well as rim enhancement (28,32).



**Figure 14** (A) Axial CT image of the brain in a male patient demonstrates a round, low-attenuation lesion in the right temporal lobe (*arrow*) with surrounding vasogenic edema. (B) After IV contrast administration, the lesion demonstrates thick peripheral enhancement, which subsequently proved to be a tuberculoma.



**Figure 15** (A) Axial CT image of the brain in a 34-year-old immunocompromised male demonstrates a 3-cm area of low attenuation in the left cerebellar hemisphere (*arrow*) with associated mass effect on the fourth ventricle and acute hydrocephalus. (B) Axial T1-weighted MR image with gadolinium demonstrates peripheral ring enhancement. (C) Coronal T1-weighted gadolinium-enhanced MR image from the same patient demonstrates a second lesion in the right cerebellar hemisphere (*curved arrow*), in this patient with toxoplasmosis.

### Clinical and Radiologic Diagnosis of Toxoplasmosis

In the immunocompetent individuals, toxoplasmosis causes a self-limited flu-like illness. However, in the immunocompromised patient, there is fulminant infection with significant morbidity and mortality. Toxoplasmosis is the most common focal neurologic lesion in the AIDS population. Multiple ring-enhancing lesions are the most common imaging finding (Figs. 15A, B, and C). The lesions vary in size and demonstrate surrounding edema. The lesions are hypodense to isodense on nonenhanced CT. With IV contrast administration, rim enhancement is present and can be either thin and smooth or solid and nodular. The lesions are hypointense on nonenhanced T1-weighted imaging and typically hyperintense on T2-weighted imaging, although this is variable. (28,33)

### Mimics of Brain Abscess, CNS Tuberculosis, and Toxoplasmosis

#### Brain Tumor

Necrotic brain tumors, both primary and metastatic, may also present as ring-enhancing parenchymal lesions. Unlike an abscess, which typically has smooth margins, a tumor classically demonstrates thick, nodular rim enhancement. The lesion may be multi-loculated and complex. The entities can further be differentiated via diffusion-weighted imaging, in

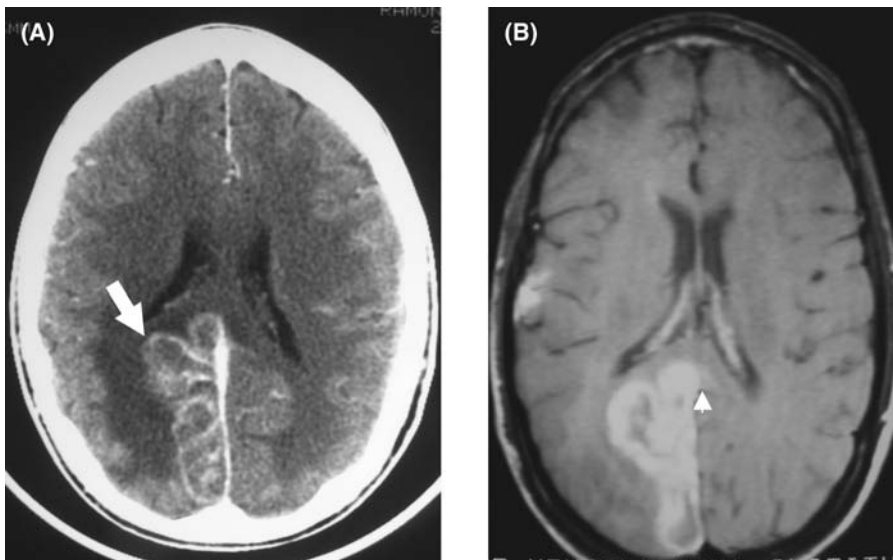
which the tumor will usually be low in signal, consistent with lack of restricted diffusion, whereas an abscess usually does exhibit increased intensity due to restricted diffusion. The enhancement pattern is also different, as residual foci of viable tumor within a necrotic center will continue to enhance, resulting in a heterogeneous enhancement pattern. The center of an abscess does not enhance (28,30).

Differentiation of tuberculoma from tumor can be difficult. Imaging characteristics on MRI can be nearly indistinguishable. MR spectroscopy is one potential technique that has been utilized to successfully differentiate an unusual presentation of extra-axial tuberculoma from meningioma. The high lipid and lactate peaks and lack of amino acid resonances may prove useful for distinguishing tuberculoma from other entities in the correct clinical context, potentially sparing unnecessary biopsy (34).

### CNS Lymphoma

Primary CNS lymphoma is a B-cell lymphoma that originates from and generally remains within the brain, spinal cord, optic tract, or leptomeninges. Disease incidence in both immunocompetent and immunocompromised patients has been increasing for as yet undetermined reasons. Differential diagnoses differ between immune competent and compromised patients, with primary or metastatic tumor considered for the former and opportunistic infection, such as toxoplasmosis, for the latter. The enhancement pattern of lymphoma on imaging studies is usually heterogeneous on both CT and MR. However, in the immunocompromised population, enhancement can be heterogeneous or ring enhancing (Fig. 16A and B). Lesions are isointense to hypointense on T1-weighted images and hyperintense on T2-weighted images. There is often leptomeningeal or periventricular/intraventricular extension (28,30).

Toxoplasmosis is difficult to differentiate from primary CNS lymphoma. Both affect gray and white matter, particularly the basal ganglia, and affect immunocompromised patients. Lesion multiplicity can be observed in both conditions. Lymphoma may demonstrate ependymal spread, which is not characteristic of toxoplasmosis. Positron emission tomography (PET) findings do differ, as toxoplasmosis is usually hypometabolic, whereas CNS lymphoma is usually hypermetabolic (28).



**Figure 16** (A) Contrast-enhanced axial CT image of the brain in an HIV-positive male demonstrates a gyriform-enhancing mass in the right occipital lobe associated with vasogenic edema (arrow). (B) Contrast-enhanced T1-weighted axial MR image demonstrates intense right occipital lobe enhancement as well as a second small right frontal cortical focus of enhancement in this patient with lymphoma.

### **Clinical and Radiologic Features of Cerebritis**

Cerebritis is a term used to describe an acute inflammatory reaction in the brain, with altered permeability of blood vessels, but not angiogenesis. Cerebritis is the earliest form of brain infection that may then progress to abscess formation, as previously noted. Cerebritis alone can be managed nonsurgically with antibiotics (30).

The appearance of early cerebritis on T1-weighted MR imaging is a hypointense or isointense area with minimal mass effect and little to no enhancement after IV contrast administration. The affected area is hyperintense on T2-weighted images and FLAIR images and may demonstrate restricted diffusion on diffusion-weighted imaging; this has been attributed to increased cellularity (from infiltrating neutrophils), ischemia, and cytotoxic edema (28).

### **Mimic of Cerebritis**

As opposed to infectious cerebritis, autoimmune cerebritis occurs with systemic lupus erythematosus (SLE). CNS involvement in SLE typically occurs within three years of diagnosis and may even precipitate full-blown SLE presentation. On CT, there is cerebral atrophy and possible focal infarcts or calcification as well as extensive, potentially reversible white matter changes (28).

MRI is superior for demonstrating active lesions that appear as hyperintense white matter spots on FLAIR imaging, with restricted diffusion and IV contrast enhancement. Differentiating old lesions from infectious cerebritis may be difficult as both are bright on T2-weighted imaging, and neither entity enhances with IV contrast administration. MR spectroscopy (MRS) and PET imaging can be utilized to further evaluate for suspected lupus cerebritis in difficult cases. MRS findings, though nonspecific, include a decreased *N*-acetyl aspartate peak and increased choline and lactate peaks. PET imaging demonstrates parieto-occipital hypometabolism, even in MR-negative cases (28).

### **Clinical and Radiologic Diagnosis of Meningitis**

Meningitis is an inflammatory infiltration of the pia mater, the arachnoid, and the CSF. The disease can have an infectious or noninfectious etiology. Early in the course of disease, the initial diagnosis is made on clinical evaluation, including lumbar puncture, as imaging findings are often normal. On CT, there may be hydrocephalus with enlargement of the subarachnoid space and effacement of the basal cisterns. There is enhancement within the sulci and cisterns after IV contrast administration, secondary to breakdown in the blood-brain barrier, as well as areas of low attenuation from altered perfusion patterns. On MR, exudate in the subarachnoid space is isointense on T1-weighted images and hyperintense on T2-weighted images. Again, there is leptomeningeal enhancement after IV contrast administration, which is typically smooth and linear (Fig. 17). Diffusion-weighted imaging findings depend on altered perfusion and the presence of vascular complications such as arterial occlusion (28,30).

### **Mimic of Meningitis**

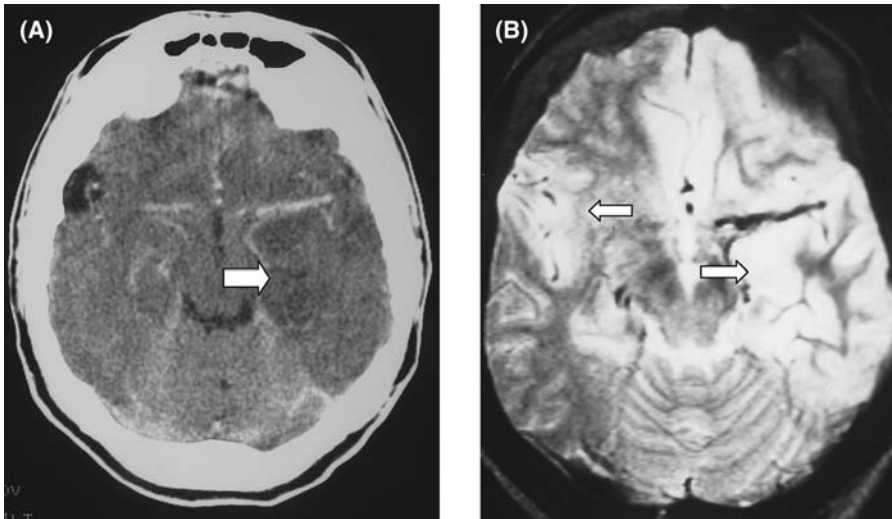
Carcinomatous meningitis occurs from both secondary and primary brain tumors. The most common distant primary tumors include breast and lung cancer. Glioblastoma multiforme, pineal tumors, and choroid plexus tumors can also extend along the leptomeninges. The enhancement pattern of carcinomatous meningitis is often thicker and irregular compared with that which is seen with infectious meningitis, although thin and linear enhancement can also occur. In such cases, clinical information, including presence of a primary malignancy, and CSF analysis may be needed to definitively differentiate between the two entities (28,30).

### **Clinical and Radiologic Diagnosis of Encephalitis**

Encephalitis is an inflammation of the brain parenchyma that may be focal or diffuse and is most commonly associated with viral infection (rather than cerebritis, which is associated with bacterial infection). Potential agents include eastern and western equine, herpes simplex, Epstein-Barr, and varicella viruses as well as cytomegalovirus (CMV). Herpes encephalitis, to which the elderly are particularly vulnerable, is a dangerous form of the disease with high



**Figure 17** Contrast-enhanced sagittal MR image of the brain demonstrates mild leptomenigeal enhancement, most pronounced in the posterior fossa (*arrow*), in a 53-year-old male with cryptococcal meningitis on CSF analysis.



**Figure 18** (A) Contrast-enhanced axial CT image of the brain in a patient with herpes encephalitis demonstrates low attenuation in the left temporal lobe (*arrow*). (B) A corresponding T2-weighted axial MR image from the same patient demonstrates high signal intensity in both medial temporal lobes (*arrows*) consistent with the diagnosis of herpes encephalitis.

mortality rates if therapy is not promptly initiated. CT is often negative in these patients. Abnormal findings on MR and nuclear imaging studies depend on the specific virus. Herpes typically involves the medial temporal and inferior frontal lobes (Fig. 18A), whereas Japanese encephalitis affects the thalami, brain stem, cerebellum, spinal cord, and cerebral cortex. Abnormal high-intensity lesions can be demonstrated on T2-weighted and FLAIR sequences (Fig. 18B). Contrast enhancement may range from none to intense (28,30,35).



### **Mimic of Encephalitis**

Restricted diffusion may be present, which, depending on clinical presentation, may rarely lead to confusion of the entity with acute infarction. In such cases, MR spectroscopy and nuclear medicine imaging may be helpful. Tc-99m HMPAO single-photon emission CT has shown utility for the detection of both herpes encephalitis and Japanese encephalitis (36).

### **Clinical and Radiologic Diagnosis of HIV Encephalopathy/Encephalitis**

HIV encephalopathy/encephalitis (HIVE) is a syndrome of cognitive, behavioral, and motor abnormalities attributed to the effect of HIV infection on the brain in the absence of other opportunistic infection. HIVE is the most common neurologic manifestation of HIV. Diffuse cortical atrophy is the most common finding on both CT and MR. White matter disease is also present, and the areas most affected are the periventricular regions and centrum semiovale, the basal ganglia, cerebellum, and the brainstem. On T2-weighted MR images, white matter signal changes may be focal or diffuse, and the distribution and extent of the lesions do not necessarily correlate with clinical presentation. FLAIR sequences may demonstrate lesions not detected on T2-weighted images, such as those smaller than 2 cm. HIVE lesions do not enhance on MR examination after gadolinium administration, a characteristic feature (28).

### **Mimic of HIVE**

The differential for white matter lesions is broad, encompassing infectious, inflammatory, and autoimmune causes. Multiple sclerosis lesions are usually focal, although with severe illness they can become confluent (Fig. 19A, B, and C). Unlike lesions in HIV, active multiple sclerosis (MS) lesions do enhance. The lesions are isointense to hypointense on T1-weighted imaging, whereas such lesions are not visualized on T1-weighted images in HIVE (28).

Acute disseminated encephalomyelitis (ADEM) is a condition whereby multifocal white matter and basal ganglia lesions occur, typically 10–14 days after infection or vaccination. The lesions involve both the brain and spinal cord. CT is initially negative, but with time demonstrate low-density, flocculent, and asymmetric lesions. These abnormalities are better visualized on FLAIR MR sequences. Contrast enhancement may be punctate or ringlike (complete or incomplete). Again, contrast enhancement of the lesions is one helpful differentiating feature from HIVE (28).

## **THORACIC INFECTIONS AND THEIR MIMICS**

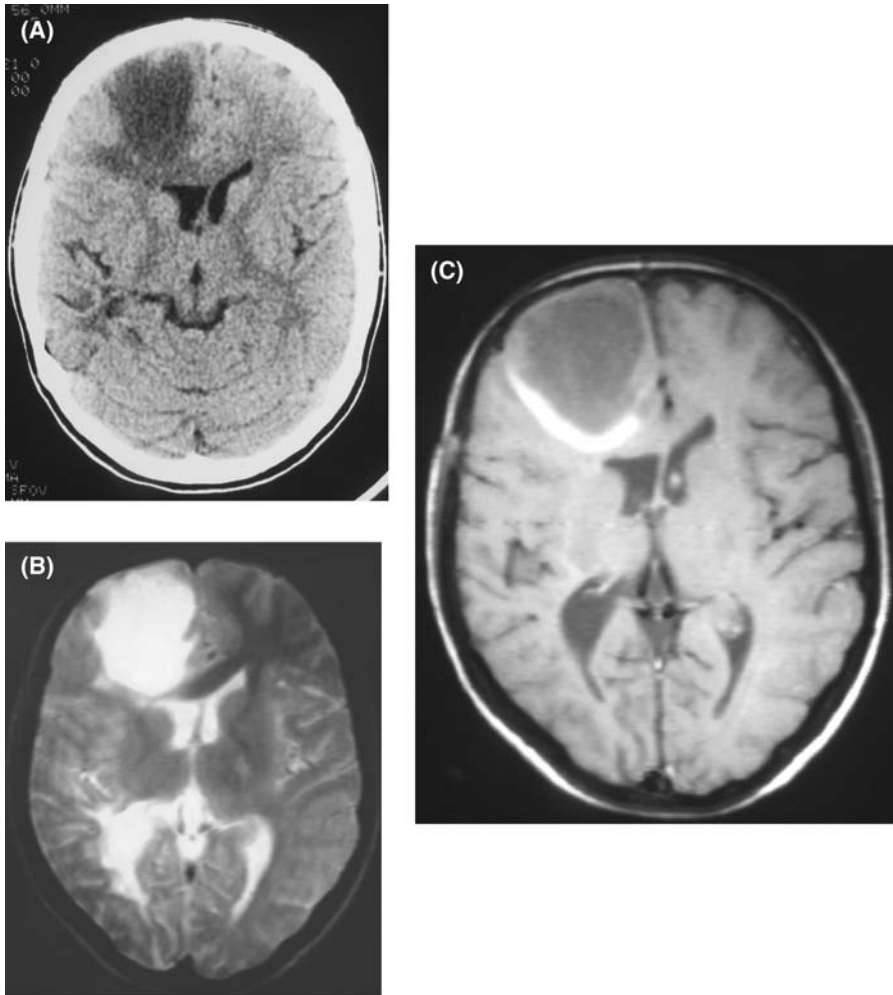
### **Clinical and Radiologic Diagnosis of Focal/Segmental Pneumonia**

Bacterial pneumonia can be divided into three main categories: lobar, lobular or bronchopneumonia, and interstitial. The causative organism generally determines what type of pneumonia results. Bronchopneumonia is the most common type, with the prototype causative agent being staphylococcus. The classic appearance on chest radiography and CT is a “patchwork-quilt” pattern of air-space opacification, reflecting diseased and adjacent non-diseased pulmonary lobules and the presence of air bronchograms, reflecting air-filled bronchi within diseased parenchyma (Fig. 20A and B) (37,38).

### **Mimics of Focal/Segmental Pneumonia**

#### *Pulmonary Embolus*

Although many chest radiographs in patients with pulmonary embolus (PE) are not entirely normal, the findings are usually not specific for PE, and confirmation with additional modalities, such as pulmonary CT angiography (the current imaging reference standard), ventilation/perfusion (V/Q) scan, and lower extremity venous Doppler, are required for diagnosis. Radiographic findings include right heart enlargement, central pulmonary artery enlargement (usually when chronic, but occasionally when acute with a large clot burden), localized peripheral oligemia with or without distention of more proximal vessels (“Westermark sign”), and peripheral air-space opacification due to localized pulmonary hemorrhage. When lung infarction occurs, in a minority of cases, a pleural-based, wedge-shaped opacity can be identified, the “Hampton’s Hump.” Lung infarction can have a similar appearance to segmental pneumonia, and correlation with CT angiography is usually needed to differentiate the two entities (Fig. 21A and B). The utility of chest radiography is more for identifying



**Figure 19** (A) Axial CT image of the brain in a 15-year-old female with known multiple sclerosis demonstrates a low-attenuation “mass” in the right frontal lobe with little mass effect relative to the size of the lesion. (B) T2-weighted axial MR image demonstrates high signal intensity within the lesion. (C) Gadolinium-enhanced T1-weighted axial MR image demonstrates partial rim enhancement in this patient with tumefactive multiple sclerosis.

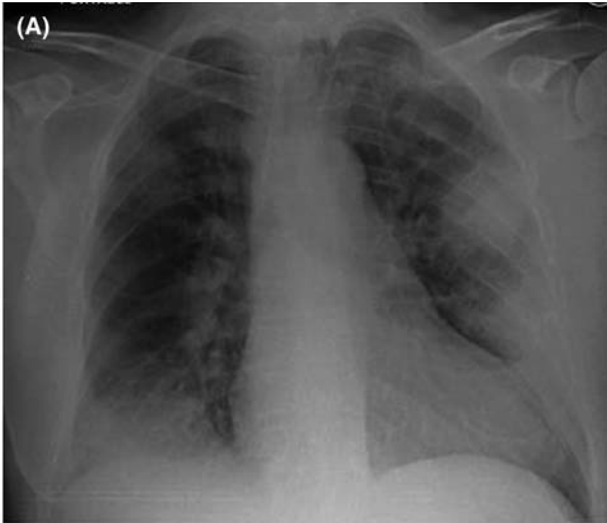
alternate diagnoses and for interpretation of V/Q scans, to correlate with abnormal areas of perfusion or ventilation (37).

#### *Lupus Pneumonitis*

Pulmonary manifestations of SLE include acute lupus pneumonitis and chronic interstitial disease. The former is rapid in onset and may mimic a focal pneumonia, with CT findings of ground-glass attenuation and consolidation that then coalesces (Fig. 22). Additional radiographic findings include elevated hemidiaphragms due to myopathy and resultant low lung volumes with linear bibasilar atelectasis. The opacities will respond to steroids, unlike pneumonia and chronic interstitial disease (37,39).

#### *Congestive Heart Failure*

Congestive heart failure (CHF) is usually bilateral and symmetric, but unilateral disease can also occur much less commonly. A specific condition associated with pulmonary edema



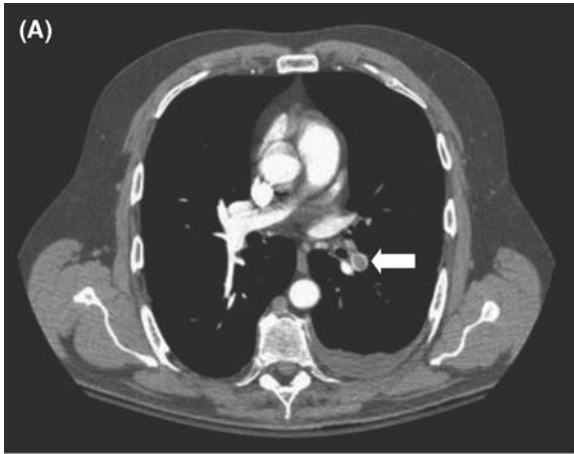
**Figure 20** (A) Chest radiograph demonstrates dense opacification in the left upper lobe and at the right lung base in an adult patient with multilobar pneumonia. (B) CT scan of the chest in the same patient demonstrates consolidation in the left lower and right upper lobes containing air bronchograms, again consistent with multifocal pneumonia. Bilateral pleural effusions are also present posteriorly.

isolated to the right upper lobe is mitral regurgitation. The radiographic findings may easily be confused with pneumonia. As in the case of diffuse CHF changes, initiation of therapy should rapidly reverse the findings, unlike in pneumonia (40).

### **Clinical and Radiologic Diagnosis of Cavitory Pneumonia**

The term “cavity” with respect to the lung is used to describe an air-containing lesion with a thick wall (>4 mm) or within a surrounding area of pneumonia or an associated mass. Cavitory lung lesions result from neoplastic, autoimmune, and infectious processes. The common bacterial pneumonias that may progress to cavitation are *S. aureus*, *Klebsiella*, and *P. aeruginosa* (41).

Hospitalized, debilitated patients are most prone to the development of *S. aureus* pneumonia. Staph pneumonia is a bronchopneumonia that initially appears on chest radiographs



**Figure 21** (A). CT scan of the chest demonstrates an embolus in the left lower lobe pulmonary artery (*arrow*) as well as a small left pleural effusion. (B) An area of consolidation in the left lower lobe posteriorly represents pulmonary infarction. Although the appearance may be similar to pneumonia in some patients, the presence of embolus and absence of other clinical signs of infection in this patient establishes the diagnosis pulmonary infarction with certainty.



**Figure 22** CT scan of the chest demonstrates bilateral alveolar and ground-glass opacities as well as interlobular septal thickening in a 38-year-old female with a history of lupus. These findings were not present on a CT performed four days earlier and are compatible with lupus pneumonitis and/or hemorrhage. Bilateral pleural effusions as well as a pericardial effusion are also present.

as patchy opacities. There is progressive confluence of the opacities resulting in lobar opacification. The process is often bilateral. Abscess formation occurs late in the infection and is demonstrated by increasing demarcation of an initially ill-defined opacity with evolution into a round cavity with an irregular thick wall and possibly an air-fluid level (37).

Gram-negative agents include *Klebsiella* and *Pseudomonas*, each of which has relatively specific radiographic features that can facilitate diagnosis, in addition to clinical history and sputum culture. In general, Gram-negative pneumonia can present as ill-defined pulmonary

nodules, patchy to confluent areas of opacification, or even lobar pneumonia. Infection is usually bilateral and multifocal, with the lower lobes affected more often. *Klebsiella* classically occurs in older, alcoholic patients. The infection manifests as lobar opacification with an exuberant inflammatory reaction, resulting in bulging fissures and a high incidence of effusion and empyema compared with other organisms. *Pseudomonas* affects debilitated, chronically ventilated patients in particular. Infection may occur via the tracheobronchial tree, resulting in patchy opacities and abscess formation, or hematogenously, which is seen as diffuse, bilateral ill-defined nodular opacities (37).

### Mimics of Cavitory Pneumonia

#### *Septic Emboli*

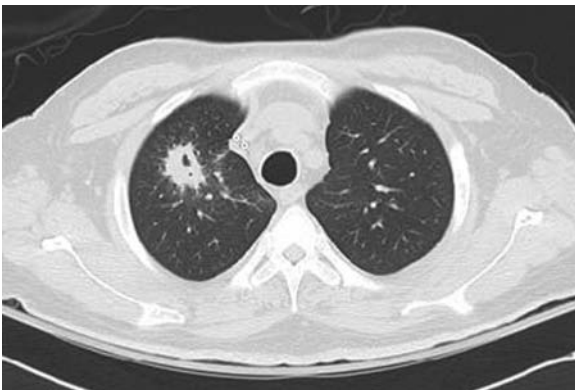
Cavitations caused by septic emboli may be thick or thin walled on chest radiographs and CT. On CT, the lesions are peripherally distributed and frequently have associated feeding vessels (Fig. 23). The lesions may be at different stages of development and healing (41).

#### *Aspergillosis*

Invasive pulmonary aspergillosis is another entity that frequently results in focal lung infarctions and cavitory formation. The organism invades small blood vessels in the lung, the early appearance of which is relatively small pulmonary nodules with surrounding hemorrhage seen as ground-glass opacity secondary to hemorrhagic infarction, the "CT halo" sign (Fig. 24). The vessel(s) involved can sometimes be identified ("feeding vessel" sign). The classic "air crescent" sign appears during the healing process and is due to separation of



**Figure 23** CT scan of the chest in a 30-year-old male with endocarditis demonstrates multiple nodular lesions throughout both lungs, some cavitating, as well as left lower lobe pneumonia. The nodular lesions represent septic pulmonary emboli.



**Figure 24** CT scan of the chest in an immunocompromised 29-year-old male demonstrates a thick-walled cavitary lesion in the right lung apex. Additional nodular lesions with surrounding ground-glass opacity, some of which were cavitating, were also seen throughout both lungs. The findings combined with the clinical information are highly compatible with invasive aspergillosis.



**Figure 25** CT scan of the chest demonstrates two cavitary lesions in the left lung apex containing soft-tissue material with lucent areas and a surrounding crescent of air (“air crescent” sign) compatible with aspergillomas. There is also tracheal dilatation and preexistent bronchiectasis as well as architectural distortion of the upper lobes.

infected necrotic lung from normal lung parenchyma or an aspergilloma that develops within a preexistent cavity (Fig. 25). Aspergillomas, which are not frankly angioinvasive in contrast to invasive aspergillosis, but which may cause hemoptysis or may be asymptomatic, move freely within the cavity and thus should change position between prone and supine imaging, a helpful identifying feature (37,38).

#### *Tuberculosis*

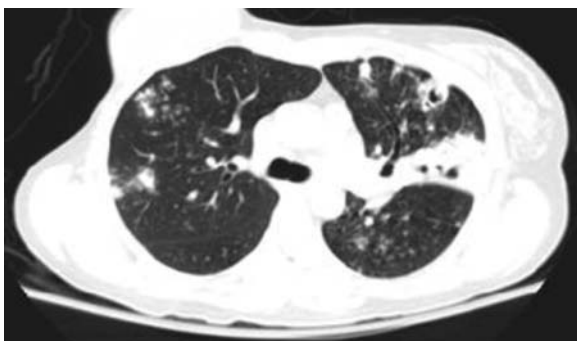
Tuberculous cavitations have a preponderance for the upper lobes. The inner wall of a tuberculous lesion can be either smooth or irregular in appearance (Fig. 26) (42).

#### **Clinical and Radiologic Diagnosis of Diffuse Bilateral Pneumonia**

Truly diffuse pneumonias are often viral in etiology. The infections can be divided into two broad categories: those in immunocompetent hosts, most often influenza A and B, and those in immunocompromised hosts, such as CMV, herpes simplex virus (HSV), and pneumocystis pneumonia (37).

On radiographs, diffuse pneumonia appears as patchy or diffuse opacification. Areas of air-space disease or reticular opacity may or may not be present. Influenza pneumonia in a normal, healthy host usually has a mild course. In the elderly or debilitated patient, infection can be fulminant and potentially fatal within a matter of days. Influenza pneumonia initially appears on chest CT as diffuse bilateral reticulonodular areas, 1 to 2 cm in diameter, and patchy ground-glass opacities. There may be small centrilobular nodules representing alveolar hemorrhage. Over the course of days to weeks, depending on the condition of the patient, diffuse consolidation may develop. Pleural effusions are rarely demonstrated. In a healthy host, the findings should resolve within approximately three weeks (37,43).

Herpes simplex virus is a rare entity, occurring primarily in the immunocompromised or those with airway trauma, such as the chronically intubated. Infection occurs either via aspiration, via extension from oropharyngeal infection, or hematogenously in cases of sepsis.



**Figure 26** CT scan of the chest in a 39-year-old female with pulmonary tuberculosis demonstrates left upper lobe consolidation along the left major fissure with areas of cavitation. Additional opacities are seen diffusely in both lungs, some of which demonstrate a “tree-in-bud” configuration.



**Figure 27** CT scan of the chest demonstrates emphysematous change with superimposed diffuse ground-glass opacity in a 58-year-old immunocompromised female with pneumocystis pneumonia.

On radiographs, the most common findings are patchy segmental or subsegmental areas of air-space disease. CT demonstrates multifocal segmental and subsegmental areas of ground-glass opacity with smaller areas of focal consolidation. Pleural effusion is commonly present with herpes pneumonia (43).

CMV pneumonia is seen most often in transplant patients as well as AIDS patients. On CT, the appearance may vary. Mixed alveolar and interstitial abnormalities; consolidation; nodules; small, ill-defined centrilobular nodules; bronchial dilatation; and thickened interlobular septa are all potential findings. (43,44)

Unlike the typical viral diffuse pneumonias, pneumocystis pneumonia is caused by the fungus *P. jiroveci*, a common organism found in otherwise normal human lungs, but which in the immunocompromised host may cause pneumonia. The radiographic appearance of pneumocystis pneumonia varies widely. Chest radiographs are often completely normal early in the infection. Fine reticular or ground-glass opacities, predominantly in the hilar regions, may be seen on CT (Fig. 27). Progressive disease results in formation of confluent areas of air-space opacification. Asymmetric or focal areas of interstitial disease are also highly suggestive of pneumocystis pneumonia in the correct clinical context. Significant adenopathy and pleural effusions are highly unusual, and their presence usually indicates an alternate diagnosis. Thin-walled cysts or pneumatoceles can also be seen with pneumocystis pneumonia, as can pneumothorax (25,38,43).

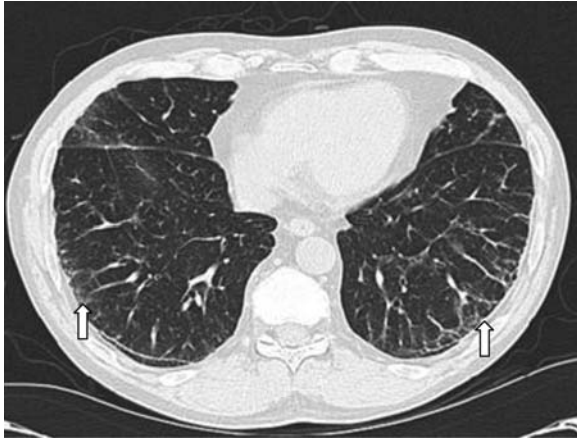
### **Mimics of Diffuse Bilateral Pneumonia**

#### *Congestive Heart Failure*

Congestive changes occur in two phases: interstitial edema and alveolar flooding or edema. With increased transmural arterial pressure, the earliest findings are loss of definition of subsegmental and segmental vessels; enlargement of peribronchovascular spaces; and the appearance of Kerley A, B, and C lines, reflecting fluid in the central connective septa, peripheral septa, and interlobular septa, respectively. If allowed to progress, increasing accumulation of fluid results in spillage into the alveolar spaces, which is exhibited by confluent opacities primarily in the mid and lower lungs. A “bat’s wing” or “butterfly” appearance is classic for CHF, although this is relatively rarely seen. A potentially helpful differentiating feature from other causes of diffuse bilateral air-space opacities is the rapid time frame in which these changes occur. CT findings can also be helpful for demonstrating thickening of subpleural, septal, and bronchovascular structures, along with ground-glass opacities with a gravitational anterior–posterior gradient. Common associated findings are cardiomegaly, pulmonary venous distention, and pleural effusion (37,45).

#### *Pulmonary Hemorrhage*

Pulmonary hemorrhage may result from trauma, bleeding diathesis, infection, and autoimmune causes. Radiographic findings include bilateral coalescent air-space opacities that develop rapidly and that commonly improve rapidly with a time course of hours, as opposed to days or weeks, such as with most cases of pneumonia (37).



**Figure 28** CT scan of the chest in a female with rheumatoid arthritis demonstrates peripheral fibrotic changes (*arrows*) compatible with rheumatoid arthritis (RA)-associated interstitial lung disease.

### *Adult Respiratory Distress Syndrome*

Adult respiratory distress syndrome (ARDS) occurs as a response to a variety of insults including trauma, sepsis, pancreatitis, and drug overdose. Leakage of protein-rich fluid from damaged capillary membranes into the interstitial and alveolar spaces leads to decreased inflated lung volumes and decreased lung compliance (37).

On chest radiographs, there are diffuse bilateral opacities located more peripherally due to predominance of capillaries in the periphery of the lung. Presumably, proteinaceous fluid remains in the periphery rather than migrating centrally due to poor diffusion, and there is decreased clearance of the material leading to persistence of the opacities for days to weeks with little change in appearance. CT findings include bilateral ground-glass opacities, consolidation, or a combination of both. Opacities are most often most severe in dependent portions of the lung (44,46).

### *Interstitial Lung Disease*

Interstitial lung diseases (ILDs) are, in general, chronic inflammatory processes that may result in fibrotic change. There are many classifications of the disease, describing both etiology and pattern of pulmonary change. Usual interstitial pneumonia (UIP), the most common of the ILDs, is initially seen on chest radiographs as bibasilar fine reticular opacities progressing to a coarse reticular or reticulonodular pattern and eventual honeycombing and loss of lung volume. On CT, areas of ground-glass opacity are seen with irregular septal and subpleural thickening and eventual honeycombing and traction bronchiectasis. Pulmonary fibrosis, while not always seen in ILD, is a helpful feature in differentiating it from pneumonia (Fig. 28). The time course is also more likely to be chronic, based on months to years, rather than acute or subacute as with pneumonia (37).

### *Bilateral Massive Aspiration*

Aspirated material may include food, water, or sand (as in near drowning) or other foreign objects such as dental material. On chest radiographs, the characteristic appearance is of dependent pulmonary opacities, which then typically coalesce. In healthy individuals, the opacities should resolve rapidly because of mucociliary clearance. There are other specific findings on both radiographs and CT depending on the material aspirated. A specific foreign body may be identified within a bronchus. Legumes, such as lentils, are known to cause a granulomatous pneumonitis. Also, sand or gravel particles may become lodged in small airways, leading to the diagnostic appearance of sand or gravel bronchograms (37,47).

## **CONCLUSION**

In conclusion, imaging is extremely helpful and often necessary in the diagnosis of infection in a critically ill patient. However, neoplastic and autoimmune processes can have very similar appearances on imaging. Subtle findings are often relied upon to separate these entities and in



many cases diagnostic certainty is not achieved solely through imaging, but in combination with pertinent clinical and laboratory information and, where necessary, with more invasive procedures, including imaging-guided aspiration and biopsy.

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# 6 Methicillin-Resistant *Staphylococcus aureus*/Vancomycin-Resistant Enterococci Colonization and Infection in the Critical Care Unit

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## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are among the most common antibiotic-resistant nosocomial pathogens in health care in general and in critical care units (CCUs) in particular. Although discovered shortly after its introduction, resistance to methicillin was first reported in the United States in 1968 (1,2). Since then, MRSA has spread throughout the world and has continued to spread in the United States. In many health care facilities,  $\geq 50\%$  of *S. aureus* isolates are MRSA. In intensive care units (ICUs), MRSA now makes up 60% of *S. aureus* isolates (3).

As hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) continues to spread within health care facilities, sites where health care is delivered face a new threat from community-acquired methicillin-resistant *S. aureus* (CA-MRSA). These latter strains from the community first appeared in the 1990s and now have been detected throughout the United States and in many other countries throughout the world (4–12). Infections due to CA-MRSA occur in patients with no risk factors or recent contact with health care facilities. They commonly occur in healthy children and most commonly manifest as skin and soft tissue infections (13–15). Most patients require treatment, and 23% to 29% have required hospitalization (14,15).

Over the past 10 years, CA-MRSA has continued to spread in the general population in the United States and in other countries (16,17). The widespread dissemination of CA-MRSA in the general population has been accompanied by an increasing prevalence of the pathogen in hospitals and in other health care settings (18–21). Mathematical modeling indicates that CA-MRSA will quickly replace the traditional HA-MRSA over the next few years (22). It is anticipated that CA-MRSA may also be a more virulent pathogen for hospitalized patients. Under these circumstances, patients in ICUs are going to be at even greater risk of infection caused by more virulent pathogens. In the near future, infection control in ICUs will require more resources and a much more intense application of preventive procedures and programs.

VRE are resistant gram-positive cocci that have appeared more recently in hospitals and ICUs. VRE were first noted in November 1986 and reported in January 1988 (23). In July 1988, VRE colonization of hematology patients was reported from Paris (24). In 1989, 0.3% of enterococci (0.1% in ICUs) isolated from patients in hospitals participating in the National Nosocomial Infection Surveillance (NNIS) system at the Centers for Disease Control and Prevention (CDC) were resistant to vancomycin (25). In 1993, 7.9% of enterococci isolated in NNIS system hospitals (13.6% in ICUs) were resistant to vancomycin. By 2003, 28.5% of enterococci isolated in NNIS system hospital ICUs were resistant to vancomycin (26).

As normal flora, enterococci are not nearly as invasive as are *S. aureus*. Approximately 1 in 10 patients colonized with VRE develop infection (27), although this may vary with the degree of immunosuppression of the patients (28,29). However, there is a growing body of evidence that VRE are acquiring both genes that code for virulence and a putative pathogenicity island, including the *esp* gene (30,31). The most serious infections with VRE are bacteremia, endocarditis, and meningitis. Urinary tract infections are less serious and

easier to treat. Infections at other body sites are difficult to document, because VRE isolated from other sites frequently represent colonization and not infection (32,33).

## METHICILLIN-RESISTANT *S. AUREUS*

### Types of MRSA

#### HA-MRSA

HA-MRSA first appeared in the United States in 1968 (2). It has spread across the country over the last three-and-a-half decades by lateral transfer among hospital patients, by transfer of patients between hospitals, and between hospitals and long-term care facilities. Most circulating strains of HA-MRSA appear to have originated from two or three clones of MRSA (34,35).

Methicillin resistance and resistance to all  $\beta$ -lactam antibiotics are conferred by the staphylococcal cassette chromosome *mec* (SCC*mec*), which carries the *mecA* gene that encodes a protein designated "penicillin-binding protein 2a" or "penicillin-binding protein 2'." These altered penicillin-binding proteins bind  $\beta$ -lactam antibiotics poorly, permitting cell wall synthesis to continue in the presence of these antimicrobial agents.

There are three types of SCC*mec* in HA-MRSA: types I, II and III (4,36). Type I contains no additional resistance determinants, but types II and III contain resistance determinants in addition to *mecA*; these additional genetic elements account for the antimicrobial resistance to many antibiotics in addition to the  $\beta$ -lactam agents. The three SCC*mec* types contained in HA-MRSA have an identical chromosomal integration site and cassette chromosome recombinase genes, which are responsible for horizontal transfer of SCC*mec* (4). Thus, HA-MRSA are resistant to many antibiotics and have a selective advantage as they are spread among patients by the hands of personnel and contaminated environmental surfaces. The presence of underlying diseases and multiple types of instrumentation and procedures predisposes patients to colonization and infection by the multiply resistant strains of HA-MRSA.

**CA-MRSA.** CA-MRSA have appeared gradually over about the last 15 years. Early on there was uncertainty about the origin of CA-MRSA, and it was unclear whether CA-MRSA were different from HA-MRSA. Some investigators believed that most of the CA-MRSA infections could be traced back to some previous contact with the health care system. More recently, it has become clear that these infections occur in young healthy persons with no recent health care contacts and no risk factors for HA-MRSA. It has also become clear that CA-MRSA have evolved in the community through an evolutionary pathway entirely separate from HA-MRSA.

It appears that all four of the SCC*mec* types have risen from *Staphylococcus sciuri*, the most ubiquitous and ancient species of *Staphylococcus* (37). Because of their large size, SCC*mec* types I, II, and III have rarely been transferred to the cells of methicillin-susceptible *S. aureus* (MSSA). On the contrary, CA-MRSA has an SCC*mec* type IV that is small enough to be transferred between cells by transduction or phage-mediated transformation (37). There is some evidence that transfer of type IV SCC*mec* from CA-MRSA to MSSA can occur (38).

Given that many infections caused by CA-MRSA are treated in hospitals and other health care facilities, there must be some concern that this pathogen may become another type of MRSA in hospitals. In addition to infections, it is likely that patients admitted to hospitals for a variety of indications will be colonized with CA-MRSA.

In addition to adding to the burden of MRSA in the hospital, CA-MRSA appear to be more virulent than HA-MRSA. The MW2 strain of CA-MRSA, a common strain in the United States, has 18 toxins that were not found in five comparative *S. aureus* genomes (39). The majority of CA-MRSA contain the genetic element for the Pantone-Valentine leukocidin. This toxin has been associated with necrotizing pneumonia in healthy children (6). The MW2 strain of CA-MRSA contains genes for 11 exotoxins and four enterotoxins. All of these toxins are super-antigens (39). CA-MRSA may also contain genes for exfoliative toxins and for hemolysins (40).

CA-MRSA most commonly cause skin and soft tissue infections in persons with no risk factors for HA-MRSA. However, they may cause severe disease, and hospital patients may be at particularly high risk for serious disease. It is very important that infection control programs be on guard for ingress of CA-MRSA into hospitals, and this is particularly true for ICUs.

**Table 1** Sites of Infection Due to Nosocomial MRSA in Patients in Neonatal Intensive Care Units

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Sites of infection
Bacteremia
Pneumonia
Skin and soft tissue abscess
Peritonitis or necrotizing enterocolitis
Ventriculitis or meningitis
Osteomyelitis or septic arthritis
Urinary tract infection
Eye infection
Wound infection
Endocarditis
Thrombophlebitis
Ear, nose, and throat infection
Omphalitis

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*Abbreviation:* MRSA, methicillin-resistant *Staphylococcus aureus*.

*Source:* From Refs. 47–51.

## Types of Infections Caused by MRSA

### *Infections Caused by HA-MRSA*

**Adult ICUs.** Bacteremia and pneumonia are the most common HA-MRSA infections encountered when all types of ICUs are considered (41–46). Other HA-MRSA infections reported include urinary tract infections (41,42), empyema (42), and bacteremia associated with hemofiltration (45). Surgical site infections due to HA-MRSA are reported from ICUs that care for surgical patients, although most all of these infections were acquired in the operating room and not in the ICU (42,43).

**Neonatal ICUs.** HA-MRSA are recovered from many more sites of infection in patients in neonatal intensive care units (NICUs) compared with patients in adult ICUs. As is the case in adult ICUs, reports on sites of infection due to HA-MRSA in neonates are from publications of outbreak investigations (47–51). Table 1 shows the sites of infection due to HA-MRSA reported from outbreaks in NICUs.

### *Infections Caused by CA-MRSA*

**Adult ICUs.** The earliest cases of CA-MRSA acquired in the hospital by adults were reported from Australia (52–54). There were no reports of outbreaks in the ICUs of these hospitals. More recent studies report on CA-MRSA in hospitals in the United States and other countries, but there are no reports of outbreaks due to CA-MRSA in adult ICUs (55,56). Given the invasion of hospital populations by CA-MRSA and the results of the recently published mathematical modeling studies on the same, it is likely that CA-MRSA are present in many ICUs and will account for increasing numbers of MRSA infections in ICUs (22).

**Neonatal ICUs.** Outbreaks due to CA-MRSA have been reported from NICUs. In one outbreak nine neonates of low gestational age and birthweight had bacteremia due to CA-MRSA with an SCC*mec* type IV but no Pantón–Valentine leukocidin (*pvl*) genes (57). In a second outbreak in an NICU due to CA-MRSA, the outbreak strain was USA300 and contained the *pvl* genes. Infections included skin and soft tissue abscesses, necrotizing pneumonia, and bacteremia (58).

An outbreak has also been reported in a nursery for newborns and associated maternity units (59). The isolates from this outbreak were shown to have the type IV SCC*mec* and genes for Pantón–Valentine leukocidin and staphylococcal enterotoxin K.

## Epidemiology of HA-MRSA Infections in Critical Care

### *Epidemiology of HA-MRSA*

**Adult ICUs.** The risk for adult patients who are culture-negative for HA-MRSA on admission to an ICU, where HA-MRSA is endemic, for acquiring HA-MRSA ranges between 4.5% and

11.7% for cumulative incidence (43,60) and between 7.9 and 9.9 per 1000 patient days for incidence density (61,62). In one study, it was observed that HA-MRSA was acquired at about 1% per day in the first week after admission and then at 3% per day thereafter (45). In a more recent study the risk per day for acquisition of MRSA was less than 1% at ICU admission and then was greater than 2% by day 12 and then leveled out (63).

**Sources of HA-MRSA.** The sources of HA-MRSA include colonized or infected patients, colonized or infected health care workers (HCWs), and contaminated environmental surfaces. One of the best indications of the importance of colonized and infected patients as an important source of HA-MRSA is the significant relationship between colonization pressure and acquisition of HA-MRSA colonization, or infection by patients who have no colonization or infection due to HA-MRSA at the time of admission to an ICU (60). Colonization pressure is defined as the number of patient days for patients with cultures positive for HA-MRSA divided by the number of total patient days (64). It can be calculated for any day or for a given period of time. The most common site of MRSA colonization in adults is the external nares (42,65,66). The second most common site of colonization is skin and soft tissue other than surgical sites (34%) (65). Other sites of colonization include rectal (11% to 28.9%), respiratory tract (11%), and urinary tract (6%) (42,65,66).

Another source of HA-MRSA is colonized or infected health care personnel. Acquisition of HA-MRSA in an ICU from a respiratory therapist with chronic sinusitis due to HA-MRSA has been reported, as well as surgical site infections due to colonization of the external nares and an area of dermatitis on the hand of a surgeon (67,68). The surgical site infections caused by the colonized surgeon were initiated at the time of surgery but became manifest postoperatively in the ICU. HCWs often become colonized with HA-MRSA from contacts with patients when providing health care but are not often implicated in transmission to patients. To implicate a colonized HCW as a source for colonization or infection of patients, it is first necessary to epidemiologically establish an association between contact with the colonized or infected HCW and acquisition of HA-MRSA by patients. Then it is necessary to prove that the strain from the HCW and the patient is the same using molecular techniques such as pulsed-field gel electrophoresis (PFGE) after restriction endonuclease digestion of genomic DNA.

Contaminated surfaces of equipment and environmental surfaces appear to make up another source of HA-MRSA for transmission to patients (69,70). HA-MRSA has been recovered from cultures of computer terminals, the floor next to the patient's bed, bed linens, patient gowns, over-bed tables, blood pressure cuffs, bedside rails, infusion pump buttons, door handles, bedside commodes, stethoscopes, and window sills. In the latter study, 27% of 350 environmental surface cultures yielded HA-MRSA (70). It has also been shown in *in vitro* studies that outbreak isolates of HA-MRSA survive at significantly higher concentrations and for longer periods of time on an inanimate surface than do sporadic HA-MRSA isolates (71). Thus, environmental contamination is likely another important source for transmission of HA-MRSA to patients.

**Mode of transmission of HA-MRSA.** The most common mode of transmission of HA-MRSA to patients is by indirect contact. Several studies have shown that HA-MRSA is frequently transmitted to the hands and clothing of HCWs from colonized or infected patients. Two studies have shown that HA-MRSA can be recovered from 14% to 17% of HCWs' hands after patient contact (72,73). Another study showed that 7 out of 12 (58%) nurses who cared for patients with HA-MRSA in a wound or urine had HA-MRSA on their gloves, recoverable by direct plating to solid media (70). Culture of 13 of 20 (65%) nurses' uniforms or gowns who cared for these same patients yielded HA-MRSA. When cultures were taken from gloves of 12 personnel who touched only environmental surfaces in the rooms of these patients, five (42%) had HA-MRSA recovered on culture. Arbitrary-primed polymerase chain reaction (PCR) typing demonstrated that isolates recovered from patients and environment had very similar banding patterns (70). Although additional studies are needed, data continue to accumulate in support of indirect transfer of HA-MRSA to patients from contaminated hands and clothing of HCWs.

HA-MRSA also appear to have an advantage over MSSA in colonizing patients after transmission (74). During an epidemic of HA-MRSA colonizations and infections in a surgical ICU, 23 patients were exposed to six patients admitted to the ICU with HA-MRSA colonization. PFGE of isolates showed that all secondary cases had HA-MRSA PFGE patterns identical to the PFGE patterns of the strain recovered from the patients to whom they were exposed. None of the PFGE patterns of the isolates of MSSA cultured from patients and HCWs were the same. The authors concluded that HA-MRSA may have spread more easily between patients due to selection through antibiotic pressure.

Airborne transmission of HA-MRSA may occur, but the importance of this route of transmission has not been established. The CDC has not recommended airborne precautions for patients with HA-MRSA colonization or infection (75). Theoretically, HA-MRSA could be transferred by the airborne route after aerosolization from contaminated environmental surfaces or by aerosolization from nasal carriers. One study has shown that HA-MRSA can be aerosolized from environmental surfaces, i.e., changing bed sheets (76). Molecular typing showed that environmental isolates and patient isolates were identical. However, the authors did not investigate other possible routes of transmission of HA-MRSA to the patients.

Several studies have been published on the dissemination of *S. aureus* from the upper respiratory tracts of HCWs. To the author's knowledge, no such studies have been published on dissemination of HA-MRSA from HCWs. One study has epidemiologically implicated a HCW with chronic sinusitis and nasal colonization with *S. aureus* in the spread of *S. aureus* to patients. The relationship was confirmed by molecular typing (67). There appears to be a strong relationship between shedding of *S. aureus* by HCWs and having a viral upper respiratory tract infection (77,78). In one study, nasal carriers of *S. aureus* who volunteered were experimentally infected with rhinovirus (78). Investigators were able to quantify the *S. aureus* colony-forming units (CFU) released into the air under varying conditions, including type of clothes worn and whether or not a mask was worn. They documented that the *S. aureus* released into the air was from the experimentally infected volunteers by molecular typing. Studies on airborne dissemination of HA-MRSA using these techniques are needed.

**Risk factors for acquisition of HA-MRSA.** Risk factors for acquisition of HA-MRSA in ICUs vary depending on the type of ICU. Risk for HA-MRSA colonization/infection identified in recent well-designed studies making use of multivariable analysis is shown in Table 2.

**Neonatal ICUs.** The epidemiology of HA-MRSA colonization and infection has been less well studied in NICUs than in adult ICUs. Few, if any, reports on outbreaks of HA-MRSA in NICUs published in the 1990s and up to the present have included data on the risk of acquisition of HA-MRSA during outbreaks or analytic epidemiologic studies to identify risk factors for acquisition. One study provided time-and-intensity-of-care-adjusted incidence density for infections. In the intensive care section of the unit this incidence density was 0.73 infections/1000 patient-care hours (47). In the intermediate-care area the incidence density was 0.62 infections/1000 patient-care hours. There are no data on the rate of acquisition of HA-MRSA colonization.

There are few data on the source of HA-MRSA in NICUs. In one recent study, patients would have to be presumed to be the source of HA-MRSA, as personnel or the environment could not be implicated (49). In another study based on molecular typing, environmental cultures were all negative and a HCW was thought to have transferred the HA-MRSA outbreak strain from an adult hospital (51). However, the HCW was not epidemiologically implicated as the source. In all of the latter studies, transmission between patients by the hands of HCWs is suggested (47,49,51). In a prospective surveillance study in an NICU risk factors for colonization with HA-MRSA included delivery by cesarean section and receipt of systemic antibacterial therapy immediately before delivery. Absence of smoking by the mother appeared to be protective (21). No case-control studies to identify risk factors for colonization or infection with HA-MRSA in NICUs have been published to the author's knowledge. Using a different approach, one study implicated overcrowding and understaffing as risk factors for acquisition of HA-MRSA colonization or infection (47).

**Table 2** Risk Factors for Acquisition of Nosocomial MRSA in Adults

Publications	Type of ICU	Risk Factors	Adjusted Odds Ratio (95% CI)	p Value
Marshall et al. (43)	Medical-surgical	Previous admission to the ICU	3.3 (1.7–6.6).	
		Previous admission to trauma/orthopedics ward	2.9 (1.2–7.2)	
		Previous admission to the neurology/endocrinology/rheumatology/renal ward	2.6 (1.0–6.9)	
		LOS more than three days prior to admission to the ICU	8.6 (4.4–16.9)	
		Being a trauma patient	3.9 (1.8–8.7)	
		LOS two to seven days in the ICU	11.1 (1.4–86)	
		LOS more than seven days in the ICU	109.8 (14.5–833)	
Merrer et al. (60)	Medical	Weekly colonization pressure >40%	5.8 (1.7–20.1)	<0.0001
Grundmann et al. (62)	Interdisciplinary	Clustered cases		
		Days of staff deficit	1.05 (1.020–1.084)	0.001
		Sporadic cases		
		Urgent/emergency admission	3.50 (1.328–9.209)	0.011
		APACHE II score at 24 hours	1.07 (1.002–1.147)	0.044
Marshall et al. (79)	Trauma	Bronchoscopy	3.68 (1.38–9.84)	0.009
		Laparotomy	6.3 (1.4–28.9)	
		Motor vehicle accident	10.4 (1.2–93.7)	
		Ticarcillin–clavulanic acid	4.5 (1.3–15.0)	
		Glycopeptide	5.9 (1.7–21.0)	

*Abbreviations:* MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; LOS, length of stay; APACHE, acute physiology and chronic health evaluation.

### *Epidemiology of CA-MRSA*

**Adult ICUs.** Outbreaks of CA-MRSA infections have been described in hospitals in Australia, and CA-MRSA has spread to hospitals around the world (16,18,19,52–54). However, there have been no reports of outbreaks in ICUs due to CA-MRSA.

**Neonatal ICUs.** There have been several published reports of transmission of CA-MRSA in NICUs (21,57,58,80). In one report six patients had severe disease due to CA-MRSA and three (50%) died (80). One study identified infections due to CA-MRSA, HA-MRSA and methicillin-sensitive *S. aureus* (MSSA) in neonates but was unable to identify risk factors for colonization with CA-MRSA (57). There was no difference in mortality between the three groups. In an investigation of the emergence of CA-MRSA PFGE type USA300 in an NICU the epidemiology was unique in that it involved transmission between patients, HCWs, and family members (58). Three HCWs acquired soft tissue infections from the colonized/infected infants and four members of two of the HCW families developed soft tissue infections (58). Eight of nine isolates typed by PFGE were USA300. Only one study has provided data on risk factors for colonization by CA-MRSA in NICU patients (21). In this article it was noted that vaginal delivery and maternal tobacco or marijuana use were significant predictors for CA-MRSA colonization among infants whose mothers had received systemic antibacterial therapy immediately before delivery. Although there are few published epidemiologic data on the spread of CA-MRSA in NICUs, it is clear that CA-MRSA may enter NICUs and cause outbreaks with resultant colonization and infection of neonates. It is likely that CA-MRSA will continue to enter many areas of hospitals, and more definitive studies will be needed to better understand how to prevent entry of CA-MRSA and to control it once present in health care facilities.



## Prevention and Control of MRSA in ICUs

Prevention of MRSA transmission and control of ongoing dissemination among patients receiving health care requires a number of preventive and control measures. The approach to control is similar for adult and neonatal patients and for HA-MRSA and CA-MRSA. Differences for adults versus neonates and for HA-MRSA versus CA-MRSA will be noted.

### *Screening Patients on Admission and During Hospitalization*

The most important measures for control of MRSA in ICUs are active surveillance for patients infected or colonized with MRSA at the time of admission followed by prompt isolation of those patients identified as colonized or infected and weekly cultures for all other patients in the ICU to detect acquisition of MRSA from patients who may have escaped detection on admission, from colonized or infected HCWs, or from contaminated environmental surfaces (41,51,74,81–98). It is important to identify every colonized patient so that all colonized as well as infected patients can be placed on contact precautions. Surveillance cultures for MRSA should always include samples from the anterior nares (81).

Patients are screened for colonization with MRSA by taking swab samples from the anterior nares and other sites of possible MRSA colonization, such as the oropharynx, axilla, inguinal area, perirectal areas, and from open wounds and skin eruptions. Samples are then inoculated to broth or solid media containing antibiotics or other agents to select out MRSA. Although effective, results are not immediately available due to the delay for incubation and identification of isolates. More rapid techniques for detection of MRSA based on PCR have been developed and published (99). Such techniques permit detection of MRSA from swab specimens within two hours.

Screening for MRSA colonization and infection on admission is particularly important for patients admitted from other hospitals, from long-term care facilities, or who have been hospitalized in the past year. Although it is not yet clear as to the impact of CA-MRSA on the influx of MRSA into hospitals, this potential reservoir for MRSA must be kept in mind. It may be necessary to screen everyone entering the hospital from the community regardless of whether they have one of the above-mentioned risk factors for MRSA colonization or infection.

### *Barrier Precautions*

Gloves and a gown should be worn before entry of HCWs into rooms of patients isolated for MRSA (100,101). There is good evidence that HCWs acquire MRSA on gloved and ungloved hands and on gowns when in contact with patients colonized or infected with MRSA (72,73,101). Hand hygiene should be practiced before and after glove use.

Whether or not masks are needed for contact precautions for MRSA is controversial. The CDC has not recommended that masks be used for isolation of patients colonized or infected by MRSA (75). Masks are recommended by the Society for Healthcare Epidemiology of America (SHEA) Guidelines for preventing nosocomial transmission of multidrug-resistant strains of *S. aureus* and *Enterococcus* (81). However, the recommendation is categorized as a type II. Definitive studies are needed to determine whether or not masks are needed for isolation of patients with MRSA colonization or infection.

### *Decontamination of the Environment*

There is evidence that the environment may be an important source for MRSA for patient colonization and infection (70,102,103). One study has shown that strains of MRSA survive for about 7 to 10 months on glass surfaces (71). It was also shown that outbreak strains of MRSA survived longer than sporadic strains. There is also evidence that enhanced disinfection is an important measure for controlling epidemic MRSA (104,105). Thus, attention should be paid to thorough cleaning and disinfection of environmental surfaces in patient rooms and other areas where patients receive care.

### *Hand Hygiene*

Hand hygiene is very important in conjunction with barrier precautions in preventing the spread of MRSA between patients and from patients to HCWs (82). Hand hygiene practices

have been suboptimal for many years, and efforts to improve them have had little impact on compliance rates, which average about 40%. Risk factors for poor compliance include being a physician or a nursing assistant, working in an ICU, working during weekdays performing activities with a high risk for transmission, and having many opportunities for hand hygiene per hour of patient care (81). Most of these risk factors for poor hand hygiene are commonly present in ICUs.

HCWs must be taught to decontaminate their hands with an antiseptic-containing agent (an alcohol-based hand rub or a hand-washing preparation containing an antiseptic agent). If hands are visibly soiled with urine, feces, blood, or other body fluids, they must be washed with soap and water followed by application of an alcohol-based hand rub or washed with soap containing an antiseptic.

Hands must be decontaminated before and after contact with each patient. This includes decontamination by washing with an antimicrobial soap or application of an alcohol-based hand rub after removal of gloves (106). HCWs should be strongly encouraged to apply moisturizing hand lotions, but it is important to establish that such preparations are compatible with the cleansing products and glove materials used by the HCWs. They must be thoroughly educated about microbial contamination of their hands and why hand hygiene is important. Hand hygiene should be monitored and feedback should be given to the HCWs about their performance on a continuous basis. It is unlikely that occasional feedback will change hand-hygiene practice.

#### *Decolonization of Patients Who Are Carriers of MRSA*

Decolonization of patients as a way to prevent and control outbreaks of colonization and infections due to both MRSA and MSSA has been studied for decades. In spite of the introduction of mupirocin as one of the most potent topical anti-staphylococcal antibiotics discovered to date, decolonization of patients colonized with MRSA remains a challenge (107). In a number of studies, patients often become recolonized with the same or a different strain of MRSA. Few randomized controlled clinical trials with long-term follow-up ( $\geq 12$  weeks after intranasal application of mupirocin) have been conducted. Decolonization is often attempted using a combination of mupirocin applied to the nares and showers with an antiseptic agent such as chlorhexidine. Very little published data suggest that chlorhexidine baths may add to the efficacy of mupirocin (108). One of the major problems in the use of mupirocin for decolonization of patients, in addition to failure to maintain long-term decolonization, is development of resistance (109). Resistance is particularly likely to develop with extensive use such as application to wounds. Resistance to mupirocin after use for treatment of both colonization and infection can be effectively controlled by limiting its use to the treatment of colonization (109).

Use of mupirocin for decolonization of patients in ICUs must be very judicious. Several of the risk factors for failure are present in many ICU patients (107). These include (i) colonization of multiple body sites; (ii) chronic non-healing wounds; and (iii) the presence of colonized foreign bodies such as tracheostomy tubes or gastrostomy tubes. Treatment for colonization should be limited to the nares. Attempts at decolonization of patients with colonization at multiple body sites, with chronic non-healing wounds, and the presence of foreign bodies should be avoided. If mupirocin is used on multiple patients over long periods of time (months), MRSA isolates from patients should be tested for susceptibility to mupirocin.

Another approach to decolonization of MRSA carriers has been instillation of vancomycin into the gastrointestinal tract by way of a nasogastric tube. In one study, the ICU patients had surveillance cultures of throat and rectum for MRSA over an eight-month period (110). The patients were part of a study of prevention of infection in mechanically ventilated patients. The patients were receiving oral antimicrobial agents for selective decontamination of the digestive tract. The authors designed a study to determine whether oral administration of vancomycin could eliminate MRSA from the intestinal tract. The study was not randomized and did not have concurrent controls. The authors noted a significant decrease in MRSA infections in the treated group compared with the historical group. They were able to show elimination of MRSA from the gastrointestinal tract based on rectal swab cultures. The weaknesses of the study included nonrandomization, the use of historic controls,

and the simultaneous administration of other oral antimicrobial agents. The strengths included eradication of gastrointestinal carriage of MRSA and the careful monitoring of vancomycin resistance in MRSA and enterococci. No resistance was detected in many isolates of MRSA and enterococci tested for vancomycin susceptibility during the study. The authors also noted that by eradicating rectal carriage with vancomycin and preventing infection, they administered only 25% as much vancomycin to the group given oral vancomycin prophylaxis as was needed to treat the infections in the control group. A four-year prospective observational study in a pediatric intensive care unit in which cultures for MRSA were taken from throat and rectum of patients on admission and then twice weekly thereafter assessed the effect of enteral vancomycin on the prevention of primary and secondary endogenous infections due to MRSA (111). Patients with colonization or infection were treated for five days with enteral vancomycin. The MRSA carrier state was eradicated in 11 (79%) of 14 patients in a median of six days (IQR 3.5–9.75). Five primary endogenous infections occurred in patients who came into the hospital colonized with MRSA. There were no secondary endogenous infections in patients who acquired MRSA in the hospital. Over the four-year period of the study, no VRE or vancomycin-intermediate *S. aureus* (VISA) was isolated from 1611 cultures taken from infected and colonized sites in these patients (111). Another approach to decolonize patients who are MRSA carriers is application of a topical antimicrobial agent to the nares and total body bathing with chlorhexidine (112,113). Both of the latter studies observed a significant decrease in infections due to MRSA.

Decolonization of patients in NICUs is similar to that in adult ICUs but has not been as well studied. In one report of an MRSA outbreak, four patients were treated with nasal mupirocin three times a day for five days and bathed with diluted (1:10) 4% chlorhexidine gluconate once daily for three days (114). Two of the four neonates were successfully decolonized and two remained colonized with MRSA. The latter two were decolonized after the regimen was repeated. In a report of a second outbreak, colonized neonates were treated with mupirocin twice daily to the anterior nares and the umbilical area for seven days (115). The authors did not report the results of their decolonization regimen.

In an account of an MRSA outbreak in an NICU, one control measure was application of triple dye to the umbilical area of the patients (47). This was one of several control measures implemented. Other control measures instituted included reducing overcrowding and understaffing, and placing an infection control nurse in the NICU. Because all of these control measures were implemented at the same time, it was not possible to determine what effect the triple dye had in controlling the outbreak.

#### *Decolonization of HCWs Who Are MRSA Carriers*

Decolonization of HCWs is necessary when they have been epidemiologically implicated in the transmission of MRSA to patients from a colonized body site, which is most often the nose. Eradication of MRSA carriage from HCWs has been shown to help control outbreaks (68). For MRSA, mupirocin will decolonize the external nares effectively 91% of the time, although recolonization may occur in about one quarter of treated individuals within four weeks (116). It has also been shown that decolonization of HCWs with nasal carriage of MSSA results in a substantial decrease in hand carriage (117). Temporary decolonization of most of the colonized HCWs in an ICU for a few weeks may help control an outbreak. Although there are few data on decolonization of HCWs carrying MRSA, it is likely that mupirocin will eradicate MRSA from the nares of HCWs.

A second area where HCWs may be colonized with MRSA is at the site of dermatitis on their hands or forearms. It is important that hands and forearms of HCWs be examined and areas of dermatitis be cultured during an outbreak investigation. Other sites of colonization or infection are less common but may have to be sought if epidemiologically indicated. Table 3 lists the control measures for MRSA in ICUs.

#### *Cost Effectiveness of MRSA Control*

One study of the cost-effectiveness of MRSA control in a medical intensive care unit (MICU) has concluded that identification of patients who are carriers of MRSA on admission and during hospitalization and isolating of these carriers is cost-effective (41). In spite of an

**Table 3** Control Measures for MRSA in ICUs

Measure	Comments
Culture all patients on admission and weekly while in the ICU until they become positive for MRSA or they are discharged	Use selective culture media Always take cultures from the external nares Culture wounds and skin eruptions Consider perirectal cultures if other sites are negative Flag patients' charts or flag patients in the hospital computer system who are MRSA positive
Place patients with MRSA infection and colonization on contact precautions	Place patients flagged for MRSA on contact precautions on admission Wear gloves and a gown to enter the room Remove gloves and gown prior to leaving the room
Practice hand hygiene after leaving room	Wash hands with soap containing an antiseptic or apply an alcohol hand rub If hands are visibly soiled, wash with a soap containing an antiseptic or wash with plain soap followed by application of an alcohol hand rub
Culture environmental surfaces to assess extent of contamination with MRSA	Obtain specimens with sterile swabs moistened with sterile saline without bacteriostatic agents Use selective culture media to maximize efficiency of laboratory identification of MRSA
Decontaminate environmental surfaces often enough to keep them free of MRSA	Thoroughly clean surfaces followed by application of a hospital-grade disinfectant Culture environmental surfaces to determine effectiveness of cleaning and disinfection methods Do not use phenolic disinfectants in NICUs for environmental decontamination
Determine what sites to clean and the frequency of cleaning based on environmental culture data	
Attempts at decolonization of patients with MRSA should be done only under the supervision of infection control staff	Mupirocin is the agent of choice Follow the manufacturer's instructions for use Decolonization should be attempted for nasal colonization only Total body bathing with chlorhexidine may be combined with nasal mupirocin for decolonization Attempts at nasal decolonization should not be done for patients with the following conditions: Colonization of multiple body sites Chronic nonhealing wounds Presence of colonized foreign bodies such as tracheostomy tubes or gastrostomy tubes Take cultures after treatment for decolonization and 12 wk later Nasal decolonization is the same in NICUs
Health care workers who have nasal colonization with MRSA and who have been epidemiologically implicated in transmission to patients should be furloughed from patient care and treated with mupirocin for decolonization	Mupirocin should be applied to the external nares according to manufacturer's instructions Follow up cultures of the external nares should be taken after therapy and again at 2, 6, and 12 wk to detect relapse or recolonization When decolonization is unsuccessful on the first attempt, retreatment may be successful
When health care workers are infected with MRSA or have colonization of dermatitis, they should be furloughed from patient care and treated for infection or dermatitis until the condition clears	Sites of infection or colonization should be culture negative before the health care worker returns to patient care

*Abbreviations:* MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; NICUs, neonatal intensive care units.

ongoing MRSA carriage prevalence in admitted patients of 4%, the authors were able to reduce the incidence of ICU-acquired MRSA infection and colonization by fourfold. They observed that costs for single-room isolation of patients were \$1480 and that the extra cost of an MRSA infection was \$9275. They estimated that control was cost-effective when MRSA carriage on admission is between 1% and 7% and when the MRSA transmission rate from colonized to isolated patients is at least fivefold less than to patients not isolated. Additional studies are needed on the cost-effectiveness of MRSA control.

## VANCOMYCIN-RESISTANT ENTEROCOCCI

### Mechanism of Resistance

Although there are many species of *Enterococcus*, relatively few species make up the VRE that cause endemic and epidemic nosocomial colonization and infection in health care facilities. The most important species are *Enterococcus faecium* and *Enterococcus faecalis*. Two other species, *Enterococcus gallinarium* and *Enterococcus casseliflavus*, are motile and display intrinsic vancomycin resistance (118).

Vancomycin resistance in enterococci is mediated by the production of D-Alanine:D-Alanine ligases of altered substrate specificity (119). The most common ligases with altered substrate specificity are *vanA* and *vanB*. Both of these ligases condense D-Ala with D-Lac (lactate). Vancomycin does not bind to D-Lac, thus permitting cell wall synthesis to continue. The *vanA* trait is carried on a transposon Tn1546. This transposon is most often carried on a plasmid and can be transferred to other gram-positive cocci. The genes that code for both *vanA* and *vanB* are similar. The *vanB* genes are carried on a large mobile element found on the chromosome. The *vanB* trait can be transferred to other enterococci (118). VRE containing the *vanA* ligase are resistant to vancomycin and another glycopeptide, telcoplanin, whereas *vanB* isolates are resistant to vancomycin but are susceptible to telcoplanin. Enterococci carrying *vanA* have minimal inhibitory concentrations (MICs) to vancomycin of >64 µg/mL, whereas isolates with *vanB* have MICs to vancomycin of 16 to >1000 µg/mL (118).

Other types of ligases with altered substrate specificities are *vanC* [D-Ala- D-Ser (serine)], *vanD* (D-Ala- D-Lac), and *vanE* (D-Ala- D-Ser). The *vanE* genes are found on the chromosomes of *E. gallinarium* and *E. casseliflavus*. These latter species have intrinsic low-level resistance to vancomycin (8 to 16 µg/mL).

More recently, it has been discovered that *E. faecium* strains of VRE have acquired genes that appear to code for two virulence factors (120,121). The *esp* gene was found only in outbreak strains of *E. faecium* on three continents and not in nonepidemic isolates and isolates from healthy individuals or farm animals (120). Isolates carrying the *esp* gene seem to be associated with in-hospital spread and possibly with increased virulence. The *hyl<sub>Efm</sub>* gene is found primarily in vancomycin-resistant *E. faecium* in nonstool cultures obtained from patients hospitalized in the United States (121). This observation suggests that specific *E. faecium* strains may contain determinants that are associated with clinical infections. The appearance of virulence determinants in microorganisms that were considered nonvirulent normal flora in the past makes control of VRE even more urgent than when the only concern was resistance to glycopeptides.

## Types of Infections Caused by VRE

### Adult ICUs

The most important type of infection caused by VRE is bacteremia. Such infections are usually related to intravascular catheters (122–128). Mortality due to VRE bacteremia has not been studied extensively. One study concluded that VRE bacteremia had a negative impact on survival (126). The best study was a historical cohort study that found an attributable mortality of 37% (95% CI 10% to 64%) (125). Nosocomial meningitis has been reported rarely (129,130). VRE is frequently cultured from urine, but only about 13% of patients with positive urine cultures have a urinary tract infection. Bacteremia from the infected urinary tract occurs but is uncommon (131). A univariate analysis of patients with and without a urinary tract infection revealed a significant relationship between having a malignancy and a urinary tract infection (131).

### *Neonatal ICUs*

As in adults, neonates may also develop serious infections caused by VRE (132–134). The most common infection is bacteremia. Meningitis due to VRE has been reported in neonates, and two cases of VRE meningitis developed in patients after ventriculoperitoneal shunt placement (133). Urinary tract infection and lower respiratory tract infection with VRE has also been reported (133). However, there is no evidence that VRE cause pneumonia. Similar to adult patients, only about 1 in 10 colonized patients develop infection.

## **Epidemiology of VRE in ICUs**

### *Sources of VRE*

The main source/reservoir for VRE in hospitalized patients is the gastrointestinal tract (135–138). The first sites from which VRE are recovered on culture in newly colonized patients 86% of the time are the rectum or groin (135). Rectal cultures for VRE remain positive 100% of the time while patients are hospitalized. Gastrointestinal colonization may be very prevalent in ICU patients even in the absence of an outbreak (137). Patients with gastrointestinal colonization with VRE have very high concentrations of VRE in stool (median  $10^8$  CFU/g) (136). VRE are the predominant aerobic microorganisms in the gastrointestinal tracts of colonized patients, outnumbering gram-negative bacilli and vancomycin-susceptible enterococci. Given the high concentrations of VRE in stool, it is not surprising that many body sites in the patient carrying VRE become colonized (135).

### *Transmission of VRE in the ICU*

Transmission of VRE to patients is by indirect contact with the hands of HCWs and fomites. There is no evidence that VRE are spread by the airborne route. Five studies show that gloved hands in contact with colonized patients and their environments become culture positive for VRE (139–143). When patients have diarrhea, the likelihood of HCWs picking up VRE on their gloves when in contact with these patients is greater than when in contact with patients who do not have diarrhea (140). It has also been shown that VRE in the environment surrounding a colonized patient are easily transferred on to the gloved hands of HCWs after contact with environmental surfaces (141,143). Isolates from patients, environmental surfaces, and gloved hands of HCWs were the same strains by PFGE (141). Isolates from patients' intact skin or environmental surfaces may also be transferred to clean sites on patients by HCWs' hands or gloves (142).

Two studies have shown that environmental surfaces have a lower density of VRE than do perirectal swabs (142,144). Both studies showed that broth amplification was often necessary to recover VRE from environmental surface samples. However, low density of VRE on environmental surfaces did not prevent transfer. Sixty-nine percent of surfaces from which VRE were transferred were positive by broth amplification culture only (142).

Another concern about transfer of VRE from environmental surfaces is that the microorganism can survive on inanimate surfaces from seven days to two months (145,146). Further evidence that VRE may survive for a prolonged period on an inanimate surface and then be transferred to a patient is provided by a report on a VRE outbreak in a burn unit (138). After initial control of the outbreak for five weeks, the outbreak recurred from an electrocardiogram (EKG) lead that had not been cleaned since use on the last patient. In the five-week period, during which the outbreak had been cleared, all weekly patient surveillance cultures and 317 environmental cultures were negative for VRE. The VRE cultured from the EKG lead, the prior patient on which the lead had been used, and the patient who acquired the VRE from the EKG lead were shown to be the same strain by PFGE. The time from use of the EKG lead on the first patient to use on the second patient was 38 days. VRE have also been transmitted between patients by electronic thermometers during an outbreak (147). Restriction endonuclease analysis of plasmid DNA indicated that all clinical isolates and isolates from handles of the electronic thermometers were identical.

### *Risk Factors for Acquisition of VRE in ICUs*

**Adult ICUs.** Although many published studies have examined risk factors for nosocomial acquisition of VRE, most have not been well designed. When trying to ascertain risk factors for

acquisition, it is important to determine the exact time of colonization or infection by VRE, to use controls that are negative for VRE [as opposed to controls positive for vancomycin-susceptible enterococci (VSE)], and to use multivariable statistics to identify independent risk factors. Some studies of risk factors have included ICUs in addition to other areas of the hospital (Table 4), and others have been limited to ICUs (Table 5).

Several of the studies included in Tables 4 and 5 have identified a significant relationship between prior administration of an antimicrobial agent and acquisition of VRE. Drugs listed included cephalosporins, metronidazole, vancomycin, carbapenems, ticarcillin–clavulanate, and quinolones. The antibiotic most often identified as a risk factor was vancomycin. In an extensive study of the effects of antimicrobial agents on fecal flora, it was found that antianaerobic antibiotics promoted high-density colonization of stool with VRE (157). Administration of vancomycin had no effect on the concentration of VRE in stool. Although antianaerobic agents increased the concentration of VRE in stool, it is unclear whether these agents or vancomycin predispose to acquisition of VRE.

Several case-control studies have shown that vancomycin is a risk factor for acquisition of VRE. In an assessment of studies showing a relationship between vancomycin and acquisition of VRE by meta-analysis, the authors concluded that the apparent relationship between administration of vancomycin and colonization with VRE is due to selection of VSE as the reference group, confounding by duration of hospitalization and publication bias (158). However, several studies have shown a significant relationship between receipt of vancomycin and colonization with VRE (150,151,159). In these studies the reference group was appropriately selected (VRE-negative patients and not VSE-culture positive) and duration of hospitalization was included to control for confounding due to longer exposure time. Thus, the issue of whether vancomycin is a risk factor for acquisition of VRE is unsettled.

Risk factors from Tables 4 and 5 that appear multiple times are use of antacids and enteral feedings. One study noted that a length of stay of less than or equal to five days in an MICU was protective against VRE acquisition, whereas another study observed that hospitalization for more than one week prior to MICU admission was a risk factor for acquisition of VRE. In summary the most frequently identified risk factors for acquiring VRE from these studies were administration of antibiotics and antacids and enteral feedings.

**Neonatal ICUs.** There are seven reports of outbreaks of VRE in NICUs (132–134,160–163). Analytical epidemiology was used in two of the studies to identify risk factors for acquisition of VRE (132,163). The first study examined a large number of variables by univariate analysis and found many variables apparently related to VRE colonization. However, multivariable analysis by logistic regression identified days of antimicrobial therapy (OR 1.21, 95% CI 1.045–1.400,  $p = 0.01$ ) and birth weight (OR 0.92, 95% CI 0.862–0.979,  $p = 0.009$ ) as the only independent associations with acquisition of VRE. The second study also examined a large number of variables, but on multivariable analysis, no risk factors were identified for colonization or infection by VRE. Additional studies are needed to further define the variables associated with acquisition of VRE in this population.

**Table 4** Risk Factors for Acquisition of VRE from Studies of Mixed Patient Populations

Publications	Risk Factors	Adjusted Odds Ratio (95% CI)	$p$ Value
Loeb et al. (148)	Cephalosporin use	13.8 (2.5–76.3)	0.01
Byers et al. (149)	Proximity to an unisolated patient	2.04 (1.32–3.14)	0.0014
	History of major trauma	9.27 (1.43–60.3)	0.020
	Therapy with metronidazole	3.04 (1.05–8.77)	0.040
Cetinkaya et al. (150)	Vancomycin use	3.2 (1.7–6.0)	0.0003
	Gastrointestinal bleeding <sup>a</sup>	0.26 (0.08–0.79)	0.02
	Presence of central venous lines	2.2 (1.04–4.6)	0.04
	Antacid use	2.9 (1.5–5.6)	0.002
	Mean daily dose of Vicodin <sup>Ⓜa</sup>		0.0003

<sup>a</sup>Protective factors.

Abbreviation: VRE, vancomycin-resistant enterococci.

**Table 5** Risk Factors for Acquisition of VRE from Studies in ICUs

Publications	Type of ICU	Risk Factors	Adjusted Odds Ratio (95% CI)	p Value
Karanfil et al. (151)	Cardiothoracic	Vancomycin use	Sole predictor in the logistic regression model	
Slaughter et al. (152)	Medical	Length of stay in ICU $\leq$ 5 day Enteral feeding Sucralfate	0.08 (0.02–0.39) <sup>a</sup> 6.09 (1.56–23.7) 3.26 (1.09–9.72)	
Bonten et al. (64)	Medical	Colonization pressure Proportion of days with enteral feeding Proportion of patient days with cephalosporin use	1.032 (1.012–1.052) <sup>b</sup> 1.009 (1.000–1.017) <sup>b</sup> 1.007 (0.999–1.015) <sup>b</sup>	0.002 0.05 0.11
Falk et al. (138)	Burn	Presence of diarrhea Administration of an antacid	43.9 (5.5 to infinity) 24.2 (2.9 to infinity)	0.0001 0.002
Gardiner et al. (153)	Medical	Enteral feedings	19 (2.02–177.9)	<0.05
Padiglione et al. (154)	Multicenter study—mixed ICUs and transplant units	Renal unit patients Carbapenems Ticarcillin–clavulanate	4.62 (1.22–17) <sup>b</sup> 2.84 (1.02–7.96) <sup>b</sup> 3.64 (1.13–11.64) <sup>b</sup>	0.02 0.048 0.03
Martinez et al. (155)	Medical	Hospitalization for more than one week before MICU admission Administration of vancomycin before or during an ICU admission	18.5 (1.1–301.0) 6.3 (1.2–34.0)	0.04 0.03
Warren et al. (156)	Medical	Administration of quinolones before or during MICU admission Location in a high-risk MICU room <sup>c</sup> Increasing age Hospitalization in the 6 months prior to current admission Admission from a long-term care facility	14.8 (1.2–180.0) 81.7 (2.2–3092.0) 1.02 (1.01–1.03) 2.74 (2.21–3.40) 1.30 (1.14–1.47)	0.04 0.02

<sup>a</sup>Protective factor.

<sup>b</sup>Hazard ratios.

<sup>c</sup>A room that proved to be contaminated after postpatient discharge cleaning.

Abbreviations: VRE, vancomycin-resistant enterococci; ICU, intensive care unit; MICU, medical intensive care unit.



## Prevention and Control of VRE in ICUs

Although less data were available 14 years ago on the epidemiology and control of VRE, recommendations of the CDC's Hospital Infection Control Practices Advisory Committee (HICPAC) have stood the test of time (164). Virtually all of HICPAC's recommendations to prevent and control the spread of VRE have been supported by the studies published in the last 14 years. Thus, the focus for control and prevention is on the following: (i) detection of colonized patients by surveillance cultures; (ii) barrier isolation; (iii) hand hygiene; (iv) environmental decontamination; and (v) control of antimicrobial (particularly vancomycin) use. The HICPAC guideline also emphasized that prevention and control should start in ICUs and other areas where the VRE transmission rate is the highest.

### *Culture Surveillance*

Because only about 10% of patients colonized with VRE develop infection, most patients who make up the reservoir of VRE in the hospital are colonized and not infected. Colonization can be detected only by surveillance cultures. Colonized patients have been detected by screening stool specimens submitted to the clinical microbiology laboratory for *Clostridium difficile* toxin assay (165). Stool may be collected and sent from the ICU to the clinical microbiology laboratory, but in most cases perirectal swab specimens are cultured in broth or streaked to solid agar. One group of authors found that a rectal swab sample had a sensitivity of 58% in detecting VRE compared with culture of stool (166). These authors also noted that the concentration of VRE in stool increased with the number of antibiotics administered and duration of their administration. It is likely that perirectal swab cultures will have a higher sensitivity for detection of VRE in ICUs where many patients are on antibiotics.

In another study in a burn unit, the authors observed that perirectal swabs had the same sensitivity for detecting VRE whether inoculated to broth or to solid media (144). This suggests that small numbers of VRE detected by broth amplification can also be detected by growth on solid media. This may have been due to the extensive use of antimicrobial agents in the burn unit where the study was performed. The HICPAC guideline also recommends culturing urine and wounds for VRE (164). This will likely increase the sensitivity of surveillance cultures.

Surveillance cultures can be made more efficient by using a selective culture media to suppress growth of other microorganisms that will likely contaminate the specimens (144,164). It is likely that most patients who are colonized with VRE in an ICU will be detected by perirectal swabs and swabs of open wounds and other skin sites inoculated to selective media. This recommendation is further supported by a study that found that rectal and perirectal swabs had approximately the same sensitivity (79%) (167).

Surveillance cultures and isolation of colonized and infected patients has been shown in many studies to control VRE in both acute care and long-term care facilities (136,138,139, 149,168–172). One publication describes the effective control of VRE in four acute-care hospitals and in 26 long-term care facilities in the Siouxland region of Iowa, Nebraska, and South Dakota (168).

### *Barrier Precautions*

Patients with VRE infections and VRE colonization detected by surveillance cultures should be immediately placed on contact precautions. The HICPAC guideline recommends placement of patients in a single room or in the same room as other patients with VRE (164). The guideline also recommends donning clean nonsterile gloves prior to entering the room. The CDC 2006 MDRO Guideline now recommends that both gloves and gown be donned prior to entering the room of a patient on contact precautions (100).

There are few data on when patients colonized or infected with VRE may be taken off isolation. The CDC's HICPAC recommendation was that isolation be discontinued when three sets of cultures taken from stool or by rectal swab and all previous positive body sites were culture negative for VRE on three occasions at least one week apart (164). One study has been published that supports the recommendation made by HICPAC that patients may be taken off isolation after three consecutive negative cultures taken at least one week apart (173).

### *Decontamination of the Environment*

That VRE can remain viable on inanimate surfaces from seven days to two months has already been established (138,145,146). In addition to hard surfaces, upholstered surfaces in hospitals can be contaminated with VRE (174). VRE were recovered at 72 hours and one week after inoculation to an upholstered surface. VRE were also recovered from 3 of 10 seat cushions that were cultured in the room of a VRE patient. The authors state that an easily cleanable nonporous material is the preferred upholstery in hospitals.

Extensive cultures of environmental surfaces in rooms of patients colonized with VRE in an MICU and a burn ICU identified contaminated surfaces in 12% and 13.5%, respectively (135,138). It has also been shown that at least one environmental surface was positive in the rooms of 63% to 92% of patients colonized with VRE (135,141). Five studies have demonstrated that VRE are easily transferred to gloves or hands of HCWs after contact with the environment (101,140–143). In one of the latter studies, VRE were transferred from a culture-positive site to a culture-negative site in 10.6% of the opportunities (143). VRE were transferred from patient to environment and from environment to patient. VRE were transferred from sites with low-density contamination or colonization (cultured from broth only) 69% of the time. Room contamination by VRE has been shown to be an important risk factor for colonization of patients (175,176).

The effectiveness of decontamination of the environment depends on the method used. In one study, the investigators observed that cleaning environmental surfaces with a cleaning rag sprayed with a quaternary ammonium disinfectant was significantly less effective than dipping the cleaning rag into a bucket of the same disinfectant, drenching all surfaces, allowing the surfaces to remain wet for 10 minutes, and then wiping the surfaces dry with a clean towel (177). The authors referred to the latter as the bucket method. Using the method in which the disinfectant was sprayed on the cleaning rag took 2.8 applications to eradicate VRE from environmental surfaces compared with one application using the bucket method. In addition to a greater efficiency at removing VRE from surfaces, the bucket method also cost less than the method of spraying disinfectant on a cleaning rag. Based on this study, the bucket method is the preferred method for decontaminating environmental surfaces.

In another study investigators examined the elements of environmental cleaning to determine whether changes in cleaning products, cleaning procedures, or performance of cleaning personnel would lead to more effective cleaning of the environment (178). The authors noted that the performance of cleaning personnel was the most important factor in the effective decontamination of the environment. The effectiveness of cleaning personnel performance was related to the number of environmental sites cleaned. The investigators noted a decrease of 6% in prevalence of VRE with every 10% increase in percentage of sites cleaned after adjustment for other factors.

### *Hand Hygiene*

Excellent hand hygiene must always be practiced for the prevention of nosocomial infections, but it is particularly important for providing effective isolation of patients with VRE. Given the frequent contamination of gloved and ungloved hands of HCWs in contact with VRE-colonized patients and environmental surfaces, excellent hand hygiene must be an integral part of barrier precautions for VRE (140–142). After patient contact, hands should be washed with an antiseptic-containing soap or an alcohol hand rub should be applied.

### *Colonization of HCWs*

Colonization of HCWs with VRE has not been reported in the literature during outbreaks of VRE infection and colonization. A study of 55 stool specimens from HCWs in a hospital, where 15% of enterococci were VRE found that all cultures of stool specimens were negative for VRE (179). The authors concluded that colonization resistance was sufficient to prevent colonization of HCWs' gastrointestinal tracts in the absence of acute illness or severe underlying comorbidities.

### *Antimicrobial Agents*

Antimicrobial agents have been identified as risk factors for acquisition of VRE as shown in Tables 4 and 5. Vancomycin has been considered as a risk factor for acquisition of VRE, but

several studies have failed to identify vancomycin as a risk factor (148,149,152,154). The HICPAC recommendations included a list of indications for use of vancomycin and a list of contraindications for use of this antibiotic (164). A more recent publication from the CDC reports on a study performed in cooperation with 20 hospitals in the NNIS system that joined the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project. These hospitals contributed data from 50 ICUs on grams of selected antibiotics used each month and on susceptibility tests for selected microorganisms recovered from patients in these units each month (180). The data submitted to Project ICARE was used to create benchmarks for vancomycin use. Those ICUs that instituted changes in practice observed significant decreases in vancomycin use and in VRE prevalence. Although some controversy remains about whether vancomycin use is a risk factor for acquisition of VRE, the bulk of the data to date is in favor of limiting vancomycin use in ICUs as part of control programs for VRE.

Other antibiotics that have been identified as risk factors for acquisition of VRE include cephalosporins, metronidazole, carbapenems, ticarcillin–clavulanate, and quinolones (148,149,154,155). A study of the effect of antimicrobial therapy on the concentration of VRE in patients' stools observed that concentrations of VRE increased significantly in stools of those patients who received antianaerobic antibiotics. The authors made the point that vancomycin has antianaerobic activity and showed that VRE increased in concentration in stools of patients who were treated with vancomycin (157). The authors also showed that patients with high concentrations of VRE in stools caused greater environmental contamination and observed that eight patients with VRE cultured from blood, urine, and a sacral wound had greater than six logs of VRE per gram of stool. Therefore, avoiding the use of antianaerobic antimicrobial therapy in patients when possible may aid in control of VRE by reducing environmental contamination. Limiting the concentration of VRE in stool may also reduce the risk of invasive disease due to VRE. Limiting the use of antianaerobic agents and vancomycin appears important in the control of VRE.

Another approach to controlling VRE through changes in the use of antimicrobial agents is to replace the use of antimicrobials to which VRE are resistant with antimicrobials to which VRE are more susceptible. Piperacillin/tazobactam has been considered to be a good candidate for suppressing the growth of VRE, because it has good antimicrobial activity against *E. faecium*, which is the most common VRE species, and because it is concentrated in bile. Six studies on the use of piperacillin–tazobactam in place of third-generation cephalosporins and ticarcillin–clavulanate have been published (181–186). One study found no difference between patients treated with cefepime and those treated with piperacillin–tazobactam in the acquisition of VRE (186). However, there were several significant differences between the two groups and the authors did not apply multivariable analysis to obtain a clearly unconfounded conclusion of their results. Only one of the latter studies was adequately designed to provide definitive results (185). There was a significant reduction in the acquisition of VRE after ticarcillin–clavulanate was replaced by piperacillin–tazobactam. As the authors pointed out, additional studies are needed for this control strategy as the study was carried out in a single institution and the reduction in acquisition of VRE was associated with the formulary change, but causality could not be established. When other measures have failed to control the spread of VRE, this approach could be tried.

In summary when measures are being instituted in an attempt to control VRE, it would appear prudent to limit the use of vancomycin, cephalosporins, metronidazole, clindamycin, and ticarcillin–clavulanate. Initiating the use of piperacillin–tazobactam might add to the effectiveness of manipulating antimicrobials as part of the control measures for VRE.

Other risk factors that should be addressed are the use of enteric feedings, the use of antacids, and effectively removing VRE from environmental surfaces. Table 6 lists the control measures for VRE in ICUs.

#### *Cost Effectiveness of VRE Control*

The high cost of VRE control is often mentioned in the literature, and many infection control programs have decided to apply very limited control measures to prevent and control the spread of VRE. However, several recent studies on the cost-effectiveness of VRE control have

**Table 6** Control Measures for VRE in ICUs

Measure	Comments
When there is one or more patients in the ICU with infection or colonization due to VRE, culture each of the other patients in the ICU weekly until discharge to identify all patients colonized with VRE	Use selective culture media Take specimens for culture from perirectal area and wounds Flag patients' charts or flag patients in the hospital computer system who are VRE positive
Place patients with VRE infection and colonization on contact precautions	Place patients flagged for VRE on contact precautions on admission Health care workers should wear both gown and gloves to enter the room of a patient on contact precautions Masks are not needed Remove gown and gloves prior to leaving the room
Practice hand hygiene after leaving the room	Wash hands with a soap containing an antiseptic or apply an alcohol hand rub If hands are visibly soiled, wash with a soap containing an antiseptic or wash with plain soap followed by application of an alcohol hand rub
Culture environmental surfaces to assess extent of contamination with VRE	Obtain specimens with sterile swabs moistened with sterile saline without bacteriostatic agents Use selective culture media to maximize efficiency of laboratory identification of VRE Use bucket method to clean and disinfect environmental surfaces Identify and clean all surfaces that may become contaminated Culture environmental surfaces to determine the effectiveness of the cleaning and disinfection methods Do not use phenolic disinfectants in NICUs for environmental decontamination
When possible, limit use of those antimicrobial agents that have been identified as risk factors for VRE acquisition or that increase the concentration of VRE in stool	Antimicrobial agents that have been identified as risk factors for the acquisition of VRE include cephalosporins (particularly third-generation cephalosporins), vancomycin, metronidazole, carbapenems, and ticarcillin-clavulanate Antimicrobial agents that have been shown to increase the concentration of VRE in stools include clindamycin, metronidazole, cefoxitin, and ceftriaxone Piperacillin-tazobactam may protect against acquisition of VRE
Patients may be taken off of contact precautions when they have had three consecutive sets of negative cultures for VRE, each taken $\geq 1$ wk apart	Cultures should be taken from the perirectal area and all previously positive sites

*Abbreviations:* VRE, vancomycin-resistant enterococci; ICU, intensive care unit; NICUs, neonatal intensive care units.

all concluded that effective VRE control with a reduction in infections caused by VRE is cost-effective (187–190). In three of the studies, control of VRE was cost-effective with savings to the hospitals of between \$100,000 and \$500,000 per year (187,188,190). The other study estimated the costs of VRE infections in a hospital using a retrospective matched cohort study (189). The authors estimated that the effects of VRE infections on patients would include 15 cases of in-hospital deaths, 22 major operations, 26 ICU admissions, and 1445 additional hospitalization days with excess costs of \$2,974,478 during the study period. It is reasonable to conclude from the available data that control of VRE is cost-effective.

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# 7 Clinical Approach to Sepsis and Its Mimics in Critical Care

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## INTRODUCTION

Sepsis refers to bacteremia or fungemia with hypotension and organ dysfunction. The main clinical problem with the “septic” patient is to determine whether the patient is septic or has a disorder noninfectious mimic of sepsis by hemodynamic or laboratory parameters. In the intensive care setting, it is of critical importance to differentiate between sepsis and its mimics (1–6).

## Diagnostic Approach

Many patients with fever and hypotension are not septic. Several clinical disorders resemble sepsis. Patients do not become septic without a major breach in host defenses. The most important clinical consideration in determining whether a patient is septic is to identify the source of infection. Sepsis is a complication with only relatively few infections. Infections limited to specific infections in a few organ systems are the only ones with septic potential. Most sepsis derives from perforated obstructions or abscesses of the gastrointestinal (GI) tract/pelvis, hepatobiliary tract, genitourinary (GU) tract, or may be related to central intravenous (IV) lines. Even though the GI tract is the most frequent focus of infection leading to sepsis, not all gastrointestinal disorders including infections have a septic potential. Lower gastrointestinal tract perforations, intra-abdominal/pelvic abscesses, pylephlebitis, commonly result clinically in sepsis. In contrast, gastritis and nonperforating gastric ulcer are rarely associated with sepsis. Cholangitis in the hepatobiliary tract results in sepsis, but rarely, if ever, complicates acute/chronic cholecystitis (6–13). IV line sepsis represents the ultimate breach in host defenses since the pathogenic organisms from central catheters are introduced directly into the bloodstream in high concentrations (14,15).

The primary task is to search for GI, GU, or an intravenous source of sepsis. It is almost always possible to identify the septic source by physical exam, laboratory, or radiology tests. Without local signs of entry site infection, IV-line sepsis should not be entertained if the central IV line has been in place less than seven days.

If intra-abdominal and GU sources have been eliminated as diagnostic possibilities, central IV lines, either temporary or long term, should be considered as a cause of sepsis. The longer a central IV line is in place, the more likely the central IV line may be the cause of fever/hypotension. Signs of infection at entry sites of central IV lines indicate likely IV-line sepsis, but no superficial erythema/swelling does not rule out IV-line sepsis (14–16).

Disorders that mimic sepsis should be recognized to treat the condition and not to avoid inappropriate treatment with antibiotics. Disorders that mimic sepsis (pseudosepsis) include gastrointestinal hemorrhage, pulmonary embolism, myocardial infarction, acute pancreatitis, diabetic ketoacidosis, systemic lupus erythematosus (SLE) flare, relative adrenal insufficiency, inadequate steroid therapy, rectus sheath hematoma, and diuretic-induced hypovolemia (6,17–21) Table 1.

## CLINICAL SIGNS OF SEPSIS

Excluding the elderly, compromised hosts, and uremic patients, fever is a cardinal sign of inflammation or infection. Fever should not be equated with infection since the chemical mediators of inflammation and infection, i.e., cytokines, induce a febrile response mediated via the preoptic nucleus of the anterior hypothalamus. All that is febrile is not infectious, and most, but not all diseases causing sepsis are accompanied by temperatures  $\geq 102^{\circ}\text{F}$ . With the exceptions of drug fever and adrenal insufficiency, the disorders that mimic sepsis and

**Table 1** Clinical Conditions Associated with Sepsis

Associated with sepsis (fevers $\geq 102^{\circ}\text{F}$ )	Not associated with sepsis (fevers $\leq 102^{\circ}\text{F}$ )
<ul style="list-style-type: none"> <li>● <i>GI source</i> <ul style="list-style-type: none"> <li>Liver Abscess</li> <li>Gallbladder</li> <li>Gallbladder “wall abscess”</li> <li>Cholangitis</li> <li>Colon</li> <li>Colitis               <ul style="list-style-type: none"> <li>Ischemic <i>C. difficile</i></li> </ul> </li> <li>Diverticulitis</li> <li>Toxic megacolon</li> <li>Perforation</li> <li>Obstruction</li> <li>Abscess</li> </ul> </li> <li>● <i>Genitourinary source</i> <ul style="list-style-type: none"> <li>Renal               <ul style="list-style-type: none"> <li>Pyelonephritis</li> <li>Intra/perinephric abscess</li> <li>Calculi</li> </ul> </li> <li>Urinary tract obstruction               <ul style="list-style-type: none"> <li>Partial</li> <li>Total</li> </ul> </li> <li>Prostate Abscess</li> </ul> </li> <li>● <i>Pelvic source</i> <ul style="list-style-type: none"> <li>Pelvic peritonitis</li> <li>Tubo-ovarian abscess</li> <li>Pelvic septic thrombophlebitis</li> </ul> </li> <li>● <i>Lower respiratory source</i> <ul style="list-style-type: none"> <li>CAP               <ul style="list-style-type: none"> <li>Asplenia/hyposplenism</li> <li>Empyema</li> <li>Lung abscess</li> </ul> </li> <li>Nosocomial pneumonia</li> </ul> </li> <li>● <i>Intravascular source</i> <ul style="list-style-type: none"> <li>IV line infection               <ul style="list-style-type: none"> <li>Central venous catheters (CVC)</li> <li>PICC lines</li> <li>Hickman/Broviac catheters</li> </ul> </li> <li>Infected prosthetic devices               <ul style="list-style-type: none"> <li>AV grafts</li> <li>Jugular vein septic thrombophlebitis</li> </ul> </li> </ul> </li> <li>● <i>Cardiovascular source</i> <ul style="list-style-type: none"> <li>Acute bacterial endocarditis (ABE)               <ul style="list-style-type: none"> <li>Myocardial abscess</li> <li>Paravalvular abscess</li> </ul> </li> </ul> </li> <li>● <i>Other</i> <ul style="list-style-type: none"> <li>Toxic shock syndrome</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● <i>GI source</i> <ul style="list-style-type: none"> <li>Esophagitis</li> <li>Gastritis</li> <li>Pancreatitis</li> <li>GI bleed</li> </ul> </li> <li>● <i>Genitourinary source</i> <ul style="list-style-type: none"> <li>Urethritis</li> <li>Cystitis (normal hosts)</li> <li>Cervicitis</li> <li>Vaginitis</li> <li>PID</li> <li>Catheter-associated bacteriuria (CAB) in normal hosts</li> </ul> </li> <li>● <i>Upper respiratory source</i> <ul style="list-style-type: none"> <li>Pharyngitis</li> <li>Sinusitis</li> <li>Mastoiditis</li> <li>Bronchitis</li> <li>Otitis</li> </ul> </li> <li>● <i>Lower respiratory source</i> <ul style="list-style-type: none"> <li>CAP (normal host)</li> </ul> </li> <li>● <i>Skin/soft tissue source</i> <ul style="list-style-type: none"> <li>Osteomyelitis</li> <li>Uncomplicated wound infections</li> </ul> </li> <li>● <i>Cardiovascular source</i> <ul style="list-style-type: none"> <li>Subacute bacterial endocarditis (SBE)</li> </ul> </li> <li>● <i>Central nervous system source</i> <ul style="list-style-type: none"> <li>Bacterial meningitis (excluding meningococcal meningitis with meningococcemia)</li> </ul> </li> <li>● <i>Intravascular source</i> <ul style="list-style-type: none"> <li>A-lines</li> <li>Peripheral IV lines</li> <li>Phebits</li> </ul> </li> </ul>

*Abbreviations:* GI, gastrointestinal; IV, intravenous; PID, pelvic inflammatory disease; CAP, community acquired pneumonia; BPH, benign prostatic hyperperthrophy; PICC, peripherally inserted central catheter; AV, arteriovenous. *Source:* From Refs. 9 and 22.

pseudosepsis have temperatures  $\leq 102^{\circ}\text{F}$ . The temperature relationships are critical when considered together with organ involvement, such as GI, GU, etc. are key factors in determining if the patient is septic or has a noninfectious disorder resembling sepsis. Hyperthermia  $\geq 106^{\circ}\text{F}$  is only caused by noninfectious disorders. Hypothermia is an important clinical clue to bacteremia, particularly in renal insufficiency. In normal hosts with fever, sepsis should not be a diagnostic consideration if temperatures are  $< 102^{\circ}\text{F}$  or  $> 106^{\circ}\text{F}$  (22–25) (Table 2).

**Table 2** Clinical Mimics of Sepsis

- 
- Acute gastrointestinal hemorrhage
  - Acute pulmonary embolism
  - Acute myocardial infarction
  - Acute pancreatitis
  - Diabetic ketoacidosis
  - SLE flare
  - Relative adrenal insufficiency
  - Diuretic-induced hypovolemia
  - Rectus sheath hematoma
- 

Source: From Refs. 9 and 22.

## LABORATORY ABNORMALITIES IN SEPSIS

The usual hemodynamic parameters associated with sepsis include decreased peripheral resistance (PR) with increased cardiac output (CO) accompanied by tachycardia/respiratory alkalosis. Patients with fever are often diagnosed as septic. Although sepsis is associated with hemodynamic abnormalities, i.e., ↓ PR/↑ CO, many disorders mimicking sepsis also have similar findings, such as acute pancreatitis, GI bleed, etc. If hemodynamic abnormalities are present, but not accompanied by GI, GU, or intravenous clinical disorders associated with sepsis, then it should be assumed that the patient has a noninfectious mimic of sepsis.

As with hemodynamic parameters, laboratory data may mislead the unwary into incorrectly ascribing laboratory abnormalities to an infectious rather than a noninfectious process. An increase in white peripheral blood cell count with a shift to the left is a nonspecific reaction to stress, and is not specific for infection. Leukocytosis does not differentiate bacterial from viral infections. An increase in white count with a shift to the left is a measure of the intensity of the systemic response to stress of infectious or noninfectious disorders. Similarly, an increase in fibrin split products (FSPs), increase in lactic acid, decrease in serum albumin, decrease in  $\alpha$ -2 globulins, decrease in fibrinogen, or an increase in PT/PTT are compatible but not characteristic of infection.

Laboratory parameters that are more indicative of infection include leukopenia or thrombocytopenia. The only laboratory abnormalities that are specific for sepsis are organisms in the blood, i.e., gram/acridine orange stains of buffy coat smears/high grade positivity in blood cultures (excluding contaminants). Increased cytokine/endotoxin levels are also suggestive. Highly elevated C-reactive protein (CRP) levels have also been described as a marker for sepsis. Positive buffy coat smears are not present in all patients with bacteremia, and when positive are diagnostic and rapid. The bacteria/fungi present in buffy coat smears are helpful in determining the origin of the septic process by their association with particular organ system involvement, i.e., poorly stained pleomorphic gram-negative bacilli (*Bacteroides fragilis*) point to a GI, but not GU/IV source. The morphology/arrangement of the bacteria in buffy coat smears is also useful in selecting appropriate empiric antibiotic coverage (26–30) (Table 3).

## EMPIRIC ANTIMICROBIAL THERAPY

The selection of appropriate antibiotic therapy for sepsis depends on accurate localization of the infectious process to the abdomen/pelvis, GU tract, or IV line. Because each organ has its normal resident flora that becomes the pathogenic flora when the organ function is disrupted, empiric coverage is directed against the normal resident flora (Table 4). Factors in antibiotic selection include hepatic/renal insufficiency, allergic status of the patient, tissue penetration of the antibiotic, safety profile of the antibiotic, resistance potential of the antibiotic, and cost.

If the spectrum is appropriate for the source of sepsis, no regimen is superior to others in terms of clinical outcome. However, clinicians should utilize the most clinically/cost-effective regimens with a low resistance potential and begin therapy as soon as the diagnosis of sepsis is made. The basis of empiric therapy for sepsis depends on eliminating the source of sepsis and covering the patient with antibiotic therapy appropriate for the septic source (31–42). The use of steroids and anti-cytokine therapies remain controversial and of unproven benefit (43–46).

**Table 3** Sepsis Vs. Mimics of Sepsis

Parameters	Disorders mimicking sepsis	Sepsis (bacteremia from GI/pelvic GU, IV source)
● Microbiologic	Negative blood cultures (excluding skin contaminants)	Positive buffy-coat smear Bacteremia (excluding skin contaminants)
● Hemodynamic	↓ PVR ↑ CO	↓ PVR ↑ CO
● Laboratory	↑ WBC (with left shift) Normal platelet count ↓ Albumin ↑ FSP ↑ Lactate ↑ D-dimers ↑ PT/PTT ↓ Fibrinogen ↓ α <sub>2</sub> globulins	↑ WBC (with left shift) ↓ Platelet count ↓ Albumin ↑ FSP ↑ Lactate ↑ D-dimers ↑ PT/PTT
● Clinical	≤102°F Hypotension Tachycardia Respiratory alkalosis	≥102°F Hypotension Tachycardia Respiratory alkalosis

*Abbreviations:* PVR, peripheral vascular resistance; CO, cardiac output; FSP, fibrin split products; WBC, white blood cell; PT/PTT, prothrombin time/partial thromboplastin time; GI, gastrointestinal; GU, genitourinary; IV, intravenous.

*Source:* From Refs. 9 and 22.

**Table 4** Empiric Therapy of Sepsis Based on Organ System Involved

Source/usual organisms	Empiric therapy usual organisms	
	Monotherapy	Combination therapy
● Lower GI tract/pelvis (common coliforms plus <i>Bacteroides fragilis</i> )	Meropenem Tigacycline Ertapenem Piperacillin/tazobactam moxifloxacin	Aztreonam or aminoglycoside plus either clindamycin or metronidazole
● GU tract/kidneys/prostate (aerobic gram-negative bacilli)	Levofloxacin Third-generation cephalosporin Aztreonam Amikacin	
● <i>E. faecalis</i> (VSE)	Ampicillin Meropenem	
● <i>E. faecium</i> (VRE)	Linezolid Daptomycin Quinupristin/dalfopristin Meropenem <sup>b</sup>	Cefepime plus vancomycin
● Bloodstream (CVC) (aerobic gram-negative bacilli, <i>Staphylococcus aureus</i> , Enterococci)		
● Lung nosocomial pneumonia/vent-associated pneumonia (aerobic gram-negative bacilli)	Meropenem Cefepime Cefoperazone Levofloxacin	Meropenem or cefepime plus either levofloxacin or aztreonam or amikacin
● Organism unknown	Meropenem Piperacillin/tazobactam Tigacycline <sup>a</sup>	

<sup>a</sup> if *Proteus* and *P. aeruginosa* unlikely.

<sup>b</sup>plus vancomycin, daptomycin, or linezolid if most CVC infections in hospital due to methicillin-resistant *Staphylococcus aureus* (MRSA).

*Abbreviations:* IV, intravenous; GI, gastrointestinal; GU, genitourinary; VSE, vancomycin susceptible enterococci; VRE, vancomycin-resistant enterococci.

*Source:* From Ref. 32.



## SUMMARY

The immediate task of the clinician is to determine whether the patient has sepsis or a mimic of sepsis. Diagnostic approach may be approached from the negative perspective, i.e., if the patient does not have a GI, GU, IV process usually associated with sepsis, then the patient in all probability does not have sepsis, and the workup should be directed to diagnosed disorders that mimic sepsis.

The temperature of the patient is of key importance in determining if the patient has sepsis or a noninfectious mimic. In temperatures  $\geq 106^{\circ}\text{F}$  and  $\leq 102^{\circ}\text{F}$ , a noninfectious disease process is likely and argues against a diagnosis of sepsis. Antibiotic therapy should be instituted as soon as there is a basis for the diagnosis of sepsis, i.e., characteristic (perforation, obstruction, or abscess) organ system of infection, GI, GU, or IV site. Coverage should be based on the usual pathogens associated with the involved organ system. Antibiotics with appropriate spectrum, good safety profile, low resistance potential, and anti-endotoxin qualities are preferred. In sepsis related to perforation, obstruction, or abscess, surgical intervention is paramount and should be done as soon as the diagnosis is confirmed.

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# 8 Meningitis and Its Mimics in Critical Care

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## INTRODUCTION

There are several diagnostic difficulties in patients presenting with the possibility of acute bacterial meningitis (ABM). Critically ill patients with meningitis are usually transferred to the critical care unit (CCU) for intensive supportive care. Meningitis may be mimicked by a variety of infectious and noninfectious disorders. The mimics of meningitis are readily ruled out on the basis of the history/physical exam and, if any doubt remains, then a lumbar puncture with cerebrospinal fluid (CSF) analysis will include or exclude the diagnosis of ABM. Early and appropriate empiric antimicrobial therapy of ABM in the CCU may be lifesaving. In contrast to differential of diagnostic problem of encephalitis in the CCU, ABM in the CCU is not usually a diagnostic problem but is primarily a therapeutic problem.

ABM is primarily caused by bacterial neuropathogens. It occurs in normal and compromised hosts and may be acquired naturally or as a complication of open head trauma or neurosurgical procedures. Regardless of the pathogen or mode of acquisition, the definitive diagnosis of ABM rests on analysis of the CSF profile and Gram stain/culture of the CSF. In normal and compromised hosts, ABM presents clinically with meningeal irritation, i.e., nuchal rigidity. Nuchal rigidity must be differentiated from other causes of neck stiffness, i.e., meningismus associated with the mimics of meningitis. There are relatively few nonbacterial causes of meningitis, and it is important to differentiate aseptic or viral meningitis from bacterial meningitis. In general, patients with aseptic or viral meningitis are less critically ill than are those with ABM. Patients ill enough to be admitted to the CCU usually are more likely to have bacterial versus viral meningitis. Aseptic viral meningitis may be diagnosed by analysis of the CSF profile, as well as specific viral culture/PCR determinations. Patients with acute meningitis, either bacterial or viral, will have various degrees of nuchal rigidity with intact mental status. Patients with mental confusion, i.e., encephalopathy, have encephalitis and these patients do not have nuchal rigidity. Central nervous system (CNS) infection caused by a few organisms, i.e., herpes simplex virus (HSV)-1, *Mycoplasma pneumoniae*, *Listeria monocytogenes*, may present with a combination of stiff neck and mental confusion, i.e., meningoencephalitis. Any patient with fever and otherwise unexplained neck stiffness should have a lumbar puncture performed to confirm the diagnosis of ABM. If ABM is suspected, lumbar puncture should be performed prior to head CT/MRI scanning (1–6).

Therefore, the challenge of meningitis in the CCU setting is to arrive at a correct diagnosis by ruling out the noninfectious mimics of meningitis, and then differentiating viral meningitis from bacterial meningitis. Patients with signs of meningeal irritation and mental confusion, i.e., meningoencephalitis, are diagnosed on the basis of the CSF profile and extra-CNS signs, symptoms, and/or laboratory abnormalities. The objective of arriving at a presumptive diagnosis of ABM is to begin appropriate empiric therapy as soon as possible. Appropriate empiric therapy for ABM is determined by predicting the likely range of pathogens. In ABM, the most likely pathogen is determined by the age of the patient, mode of onset, epidemiological history/predisposing factors, physical signs, e.g., rash, rhinorrhea, and cranial nerve abnormalities, and specific host defense defects and associated underlying disorders, and the morphology/arrangement of organisms seen on the Gram stain of the CSF (1–7).

## CLINICAL APPROACH IN MENINGITIS

Excluding open CNS trauma or neurosurgical procedures, bacteria causing acute meningitis reach the CSF hematogenously. Many bacteria have a bacteremic potential, i.e., bacteremias are part of their infection process, but relatively few are able to cross the blood/brain barrier and cause meningitis. ABM usually involves the leptomeninges or the covering of the brain. Leptomeningeal irritation is responsible for the nuchal rigidity, Kernig's and Brudzinski's signs associated with ABM (7,8) Because the leptomeninges cover the brain parenchyma, meningitis is not associated with changes in mental status that require parenchymal invasion. The majority of pathogens causing ABM are respiratory tract organisms.

ABM may also result from contiguous spread from a local source in close proximity to the brain. Infections that cause meningitis by contiguous spread include sinusitis or mastoiditis. Cracks in the cribriform plate are another example of a mode of entry via a contiguous bacterial source. Meningitis may also occur by hematogenous spread of nonrespiratory pathogens, e.g., *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus aureus*, as part of secondary bacteremia with CNS seeding. Acute bacterial endocarditis due to *S. aureus* is not infrequently complicated by acute purulent bacterial meningitis as a suppurative complication (1,2,9). The insertion of CNS shunts for hydrocephalus/increased intracranial pressure, if complicated by meningitis, reflects either the flora of the skin introduced during the insertion process, or the flora at the distal end of the shunt, i.e., a ventricular peritoneal shunt. Open head trauma introduces the bacteria into the CSF/brain parenchyma (1–5,10–13) (Table 1).

Meningoencephalitis due to *L. monocytogenes* is recognizable by clues from the CSF profile and is common in the elderly/immunosuppressed. *M. pneumoniae* meningoencephalitis is being recognized as part of the clinical presentation of *M. pneumoniae* atypical pneumonia. *M. pneumoniae* meningoencephalitis occurs in patients with *Mycoplasma* community-acquired pneumonia with very high cold agglutinin levels (>1:512) (1,2,5).

The viruses, e.g., enteroviruses, that cause meningitis are relatively few compared with their bacterial counterparts. Some viruses, i.e., HSV-1 cause a spectrum of CNS infections in normal hosts from aseptic meningitis to encephalitis. Partially treated meningitis is bacterial meningitis following initial treatment for meningitis. Partially treated bacterial meningitis is diagnosed by history, and findings in the CSF, i.e., pleocytosis with a variably decreased glucose and a moderately elevated CSF lactic acid (4–6 mmol/L). Partially treated meningitis requires re-treatment with antimicrobials with the same spectrum and dosage as to treat ABM (1,5,6,14,15).

## THE MIMICS OF MENINGITIS

Because a stiff neck or nuchal rigidity is the hallmark of ABM, any condition that is associated with neck stiffness may mimic meningitis. Patients with acute torticollis, muscle spasm of the head/neck, cervical arthritis, or meningismus due to a variety of head and neck disorders can all mimic bacterial meningitis. Fortunately, most of these causes of neck stiffness or meningismus are not associated with fever. Fever plus nuchal rigidity is the distinguishing hallmark of ABM. It may be difficult in elderly patients to rule out meningitis on the basis of fever and nuchal rigidity alone since many elderly individuals have fever due to a variety of non-CNS infections, and may have a stiff neck due to cervical arthritis. In such situations, analysis of the CSF profile will readily distinguish the mimics of meningitis from actual infection (1,4,5,18).

**Table 1** Symptoms and Signs of ABM

Symptoms	Signs
Headache	Fever
Photophobia	Meningismus
Nausea and vomiting	Kernig's sign
	Brudzinski's sign
	Acute deafness
	Cranial nerve palsies
	Seizures

## NONINFECTIOUS MIMICS OF MENINGITIS

Disorders that commonly may be mistaken for meningitis include drug-induced meningitis, meningeal carcinomatosis, serum sickness, collagen vascular diseases, granulomatous angiitis of the CNS, Beçhet's disease, systemic lupus erythematosus (SLE), and neurosarcoidosis (1,8,14–17). The diagnostic approach to the mimics of meningitis is related to the clinical context in which they occur. For example, lupus cerebritis may rarely present as the sole manifestation of SLE. Similarly, with Beçhet's disease, patients developing neuro-Beçhet's disease have established Beçhet's, and have multiple manifestations, which should lead the clinician to suspect the diagnosis in such a patient. Similarly, with neurosarcoidosis, the presentation is usually subacute or chronic rather than acute, and occurs in patients with a known history of sarcoidosis (1,4,5,19–24) (Table 2).

### Drug-Induced Aseptic Meningitis

Drug-induced meningitis may present with a stiff neck and fever. The time of meningeal symptoms after consumption of the medication is highly variable. The most common drugs associated with drug-induced meningitis include use of nonsteroidal inflammatory drugs. In addition, trimethoprim–sulfamethoxazole (TMP–SMX) alone, and to a lesser extent,

**Table 2** Mimics of Meningitis

- 
- *Drug-induced aseptic meningitis*
    - Toxic/metabolic abnormalities
    - NSAIDs
    - OKT3
    - ATG
    - TMP–SMX
    - Azathioprine
  - *CNS vasculitis*
  - *SLE cerebritis*
  - *Sarcoid meningitis*
  - *Bland emboli from SBE or marantic endocarditis (nonbacterial thrombotic endocarditis)*
  - *Tumor Emboli*
  - *Primary or metastatic CNS malignancies (meningeal carcinomatosis)*
    - AML
    - ALL
    - Hodgkin's lymphoma
    - Non-Hodgkin's lymphoma
    - Melanoma
    - Breast carcinomas
    - Bronchogenic carcinomas
    - Hypernephromas (renal cell carcinomas)
    - Germ cell tumors
  - *Legionnaires' disease*
  - *Posterior fossa syndrome*
  - *Subarachnoid hemorrhage*
    - Intracerebral hemorrhage
    - CNS leukostasis
    - Thrombocytopenia
    - DIC
    - Abnormal platelet function
    - Coagulopathy
    - CNS metastases
  - *Embolic and thrombotic strokes*
  - *Partially treated bacterial meningitis*
  - *Meningoencephalitis*
- 

*Abbreviations:* NSAIDs, nonsteroidal anti-inflammatory drugs; TMP–SMX, trimethoprim–sulfamethoxazole; SLE, systemic lupus erythematosus; SBE, subacute bacterial endocarditis; ATG, antithymoglobulin; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; DIC, diffuse intravascular coagulation; CNS, central nervous system.

azithromycin may present as a drug-induced aseptic meningitis. Leukocytosis in the CSF with a polymorphonuclear predominance is typical with drug-induced meningitis, and the clinical clue to the presence of drug-induced meningitis is the presence of eosinophils in the CSF. In drug-induced meningitis, the CSF also contains increased protein, but the CSF glucose is rarely decreased. Red blood corpuscles (RBCs) or an increased CSF lactic acid level are not features of drug-induced meningitis. Treatment is discontinuation of the offending agent (1,5,16,17).

### **Serum Sickness**

Serum sickness is a systemic reaction to the injection of, or serum-derived antitoxin derivatives. Since such toxins are not used much anymore, serum sickness is now most commonly associated with the use of certain medications, including  $\beta$ -lactam antibiotics, sulfonamides, and streptomycin among the antimicrobials. Non-antimicrobials associated with serum sickness include hydralazine, alpha methyl dopa, propranolol, procainamide, quinidine, phenylbutazone, naproxen, catapril, and hydantoin. Symptoms typically begin about two weeks after the initiation of drug therapy and are characterized by fever, arthralgias/arthritis, and immune complex mediated renal insufficiency. Urticaria, abdominal pain, or lymphadenopathy may or may not be present. Neurologic abnormalities are part of the systemic picture and include a mild meningoencephalitis, which occurs early in the first few days with serum sickness. Ten percent of patients may have papilledema, seizures, circulatory ataxia, transverse myelitis, or cranial nerve palsies. The clues to serum sickness systemically are an increased sedimentation rate, a decreased serum complement, microscopic hematuria/RBC casts, and hypergammaglobulinemia. The CSF typically shows a mild lymphocytic pleocytosis, protein is usually normal but may be slightly elevated as is the CSF glucose. The cause of the patient's fever and meningeal symptoms may be related to serum sickness if the clinician appreciates the association of the CNS findings and extra-CNS manifestations of serum sickness. Treatment is with corticosteroids (1–5).

### **Collagen Vascular Diseases**

SLE often presents with CNS manifestations ranging from meningitis to cerebritis, and encephalitis. The most frequent CNS manifestation of SLE is aseptic meningitis, which needs to be differentiated from ABM. CNS manifestations of SLE usually occur in patients who have established multisystem manifestations of SLE. CNS SLE is usually present as part of a flare of SLE. SLE flare may be manifested by fever, an increase in the signs/symptoms of SLE manifested in previous flares. Laboratory tests suggesting flare include new or more severe leukopenia, thrombocytopenia, increased erythrocyte sedimentation rate (ESR), polyclonal gammopathy, proteinuria/microscopic hematuria. The CSF in patients with SLE includes a lymphocytic predominance (usually  $<100$  WBCs/mm<sup>3</sup>). Polymorphonuclear neutrophils (PMNs) may predominate early in SLE and aseptic meningitis. The RBCs are not present in the CSF with SLE, aseptic meningitis, and the CSF lactic acid level is also normal. The definitive test for diagnosing CNS SLE is to demonstrate a decreased C<sub>4</sub> level in the CSF. Unfortunately, patients with a flare of CNS lupus are predisposed to bacterial meningitis/viral encephalitis. CCU clinicians must be careful to be sure that the patient with an SLE flare with CNS manifestations does not have a superimposed ABM or acute viral encephalitis (1,8,19–24).

Granulomatous angiitis of the CNS is an uncommon cause of aseptic meningitis. The fever and encephalopathy are the most common manifestations of granulomatous angiitis of the CNS, but the focal abnormalities, including seizures and cranial nerve palsies, may mimic bacterial meningitis. Systemic laboratory tests are unhelpful. The ESR is usually elevated. The CSF profile includes a lymphocytic predominance (usually  $<200$  cells/mm<sup>3</sup>), a low CSF glucose may occur, RBCs are rarely present. Such findings are also compatible with the diagnosis of HSV meningoencephalitis, or aseptic meningitis. The diagnosis of granulomatous angiitis of the CNS is made by head CT/MRI imaging demonstrating vasculitic lesions in the CSF (19,20).

Behçet's disease is multisystem disorder of unknown etiology characterized by oral aphthous ulcers, genital ulcers, eye findings, and neurological manifestations in up to one quarter of patients. CNS presentation of Behçet's may be the presenting finding in about 5% of

patients. Neuro-Behçet's disease is characterized by fever, headache, and meningeal signs that closely mimic a bacterial process. Aseptic meningitis, meningoencephalitis, or encephalitis may also be present. The CSF profile is indistinguishable from aseptic viral meningitis/encephalitis. There are no distinguishing features on the EEG or head CT/MRI imaging. The diagnosis of neuro-Behçet's disease is based on recognizing that the patient has Behçet's disease and has neurologic manifestations not attributable to another or superimposed process (20,21).

Neurosarcoidosis is a common manifestation of sarcoidosis. Signs of CNS sarcoid include headaches, mental confusion and cranial nerve palsies. Any of the cranial nerves may be affected. Patients with sarcoidosis may often present with polyclonal gammopathy on serum protein electrophoresis (SPEP), an elevated ESR, leukopenia and mild anemia, and increased levels of serum angiotensin-converting enzyme (ACE). Chest X ray shows one of the four stages of sarcoidosis ranging from bilateral hilar adenopathy to parenchymal reticular nodular fibrotic changes. In neuro sarcoid, the CSF is usually abnormal. A lymphocytic pleocytosis ( $\leq 300$  cells/mm) is usual. Protein levels in the CSF are usually elevated, and  $\sim 20\%$  of patients have a decreased CSF glucose level. RBCs are not a feature of neurosarcoidosis. Aseptic meningitis with sarcoidosis may present as acute meningitis mimicking/viral aseptic meningitis. Sarcoid meningoencephalitis is more chronic, mimicking the chronic causes of meningitis due to acid fast bacilli or fungi. Patients usually have a history of sarcoidosis, which is a clue to the diagnosis. Diagnosis of neurosarcoidosis is a diagnosis of association and exclusion. Neurosarcoidosis occurs in the setting of systemic sarcoidosis and is characterized by a negative CSF Gram stain and culture. Treatment is with corticosteroids/immunosuppressives (1,20,23,24) (Table 3).

### **CLINICAL AND LABORATORY FEATURES OF MENINGITIS**

The clinical diagnosis of ABM concerns differentiating it from its mimics as well as the viral/aseptic causes of meningitis. Patients with ABM have a more fulminant course and tend to be more critically ill than those with a meningitis mimic or a virally mediated meningeal process. Many meningeal pathogens have associated systemic manifestations, which, if appreciated and related to the CNS findings, make the diagnosis of the underlying condition relatively straightforward. However, in spite of an analysis of predisposing factors, host defense defects, age of the patient, history of systemic disorders and cutaneous findings, the diagnosis of meningitis remains based on the analysis of CSF findings. Analysis of the CSF obtained by lumbar puncture is critical in ruling in the diagnosis of ABM, as well as ruling out viral or noninfectious causes of meningitis (1,4,8,10,25).

### **PREDICTING THE PATHOGEN IN MENINGITIS**

Normal hosts with ABM may or may not have a variety of historical epidemiologic clues as well as physical findings that may suggest a particular organism. Patients with chronic meningitis are diagnostic not therapeutic problems and are not included in this chapter concerned primarily with the diagnosis and management of patients in the CCU with ABM. In compromised hosts, the diagnosis of ABM depends on correlating the underlying disorder with its host defense defect, which predicts the meningeal pathogen. Compromised hosts with impaired cellular-mediated immunity (CMI) usually present with chronic rather than bacterial meningitis. Such patients presenting with ABM should be viewed as normal hosts from the standpoint of pathogen predictability, i.e., the underlying disorder is not responsible for their meningitis. If a patient who has had an organ transplant or has HIV, for example, is involved in an outbreak of meningococcal meningitis, the underlying disorder does not predispose the patient to this pathogen. With ABM, compromised hosts with impaired CMI are afflicted with the same infectious diseases as are normal hosts. Compromised hosts are not exempt from the spectrum of infectious diseases that affect immunocompetent hosts. Compromised hosts with defects in humoral immunity (HI) or those with combined CMI and HI defects, e.g., chronic lymphatic leukemia (CLL), are predisposed to meningitis due to encapsulated organisms, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Klebsiella pneumoniae* (1–6,8,18) (Tables 4 and 5).

**Table 3** Mimics of Meningitis

Meningeal mimics	Differential features and diagnostic clues
● Enteroviral meningitis	Seasonal distribution: summer (recent fresh water/sick person exposure) History: sore throat, facial/maculopapular rash, loose stools/diarrhea Onset: subacute; not as ill as bacterial meningitis CSF: Gram stain: – Lactic acid: normal (<3 mmol/L)
● Partially treated bacterial meningitis (usually 2° to <i>influenzae</i> )	History: meningitis symptoms + previous antibiotic therapy Onset: subacute CSF: Gram stain: ± Lactic acid: mildly ↑ (4–6 mmol/L)
● HSV-1	Season: nonseasonal History: antecedent herpes labialis (not concurrent) Onset: aseptic meningitis/meningoencephalitis (subacute); encephalitis (acute) Presentation: viral/aseptic meningitis, meningoencephalitis, or encephalitis EEG: unilateral temporal lobe focus Head MRI/CT scan: unilateral temporal lobe focus (negative early) CSF: Gram stain: – RBCs (negative early; present later) ↑ PMNs ( may be >90%) Glucose may be ↓/normal ↑ Lactic acid ~ RBCs in CSF
● Meningeal carcinomatosis	History: leukemias, lymphomas, carcinomas, or without known primary neoplasm; mental status changes: ± Onset: subacute Presentation: 80% have cranial nerve involvement, (CNs III, IV, VI, VII, or VIII most common) CSF: Gram stain: – RBCs: ± protein: highly ↑ lactic acid: variably ↑ Cytology: abnormal in 90%
● Amebic meningoencephalitis ( <i>Naegleria fowleri</i> )	History: recent swimming in fresh water Onset: rapid Presentation: olfactory/gustatory abnormalities: early Head MRI/CT: mass lesions CSF: RBCs: + glucose: ↓ lactic acid: variably ↑ Gram stain: “motile WBCs” (ameba) on wet prep
● Brain abscess (with ventricular leak)	History: source usually suppurative lung disease (bronchiectasis), cyanotic heart disease Onset: acute (R → L shunts), mastoiditis, dental abscess, etc. Presentation: meningitis Head MRI/CT: mass lesions CSF: mimics bacterial meningitis (with ventricular leak) Protein: highly ↑ Without leak: usually <200 WBCs With leak: ≤100,000 WBCs
● Leptospirosis	History: water/rat urine exposure Onset: acute Presentation: clinically ill, jaundiced, conjunctival suffusion, ↑SGOT/SGPT. Usually associated with severe leptospirosis (Weil’s syndrome) CSF: Bacterial profile CSF: ↑ bilirubin (> serum bilirubin) RBCs: +
● Tuberculous/fungal meningitis	History: TB exposure Onset: subacute Presentation: basilar meningitis, usually with evidence of primary infection. Lung lesions not always apparent in TB (chest X ray negative in 50%).

(Continued)



**Table 3** Mimics of Meningitis (*Continued*)

Meningeal mimics	Differential features and diagnostic clues
	<p>Fundi: choroidal tubercles            CNS: unilateral CN VI abducens palsy, MRI/CT scans: hydrocephalus/arachnoiditis            CSF:              WBCs: &lt;500              PMNs (early)              Lymphs (later)              Glucose: ↓ (may be normal)              RBCs: ↑              TB smear/culture + ~80%            Serial CSFs:              Over time ↓ glucose/↑ protein              Lactic acid: ↑ (variably elevated)</p>
● Neurosarcoidosis	<p>History: systemic sarcoidosis (bilateral hilar adenopathy/interstitial infiltrates, skin lesions, uveitis, erythema nodosum, arthritis, hypercalciuria, ↑ ACE levels)            Onset: subacute            Fundi: “candle wax drippings”            Cranial nerves: unilateral/bilateral CN VII (facial nerve palsy characteristic also CN palsies II, VII, VIII, IX, X)            CSF:              Lymphs: ↑              Glucose : ↓              WBCs: &lt;100              RBCs: none (vs TB or malignancy)</p>
● SLE cerebritis	<p>History/signs of SLE (pneumonitis, nephritis, skin lesions)            Onset: subacute            Presentation: seizures/encephalopathy: ±            Fundi: cytoid bodies/cotton wool spots in fundi            CSF:              CSF ANA: +              CSF C<sub>4</sub>: ↓</p>
● LCM	<p>Seasonal distribution: fall            History: hamster/mouse/rodent contact            Onset: subacute            Presentation: biphasic “flu-like” illness followed by recovery, then headache, fever, mental confusion/meningismus, myalgias            CBC:              WBCs: ↓              Platelets ↓              CSF: resembles aseptic meningitis if glucose normal              Glucose: normal/↓              WBCs: &gt;1,000 lymphs</p>
● RMSF	<p>Seasonal distribution: spring/fall            History: woods/animal exposure            Onset: sudden            Presentation: severe headache, myalgias, and mild nuchal rigidity              conjunctival suffusion, periorbital edema/edema of dorsum of hands/feet, wrists/ankles rash            CSF:              WBCs: &lt;100 lymphs              Lactic acid: normal/slightly ↑              Glucose: normal/↓              Protein: ↑ (variably)</p>
● <i>Mycoplasma</i> meningoenzephalitis	<p>History: <i>Mycoplasma</i> CAP            Onset: subacute            Presentation: nonexudative pharyngitis, otitis/bullous myringitis, loose stools/diarrhea, erythema multiforme            Cold agglutinin titers: &gt;1:512            CSF:              Culture for <i>Mycoplasma pneumoniae</i>: ±</p>

*Abbreviations:* CSF, cerebrospinal fluid; CNS, central nervous system; SLE, systemic lupus erythematosus; PMNs, polymorphonuclear leukocytes; LCM, lymphocytic choriomeningitis; RMSF, Rocky Mountain spotted fever; HSV, Herpes simplex virus; ACE, angiotensin-converting enzyme; SGOT, serum glutamate oxaloacetate transaminase; SGPT, serum glutamate pyruvate transaminase; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography.

**Table 4** Host–Pathogen Association in Meningitis

Host	Pathogen
• Sinopulmonary function	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i>
• Elderly	<i>H. influenzae</i> <i>Listeria monocytogenes</i> Brain abscess (2° dental focus)
• Sickle cell disease	<i>S. pneumoniae</i> <i>Salmonella</i> <i>N. meningitidis</i> <i>H. influenzae</i>
• Splenectomy	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>N. meningitidis</i> <i>Klebsiella pneumoniae</i>
• HIV	HIV CMV <i>Toxoplasma gondii</i> <i>Listeria monocytogenes</i> <i>Nocardia</i> sp. <i>Cryptococcus neoformans</i> TB/MAI Lymphomas
• Complement deficiencies	<i>S. pneumoniae</i> <i>N. meningitidis</i>
• CSF leak	<i>S. pneumoniae</i>
• IVDAs	<i>Staphylococcus aureus</i> Aerobic GNBs
• Alcoholism/cirrhosis	<i>S. pneumoniae</i> <i>Klebsiella</i> TB
• Hypogammaglobulinemia	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>N. meningitidis</i> Enteroviruses
• VA/VP shunts	<i>S. epidermidis</i> (CoNS) <i>S. aureus</i> Aerobic GNBs
• Recurrent meningitis (usually 2° to immune/anatomic defects)	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>N. meningitidis</i> Recurrent noninfectious CNS diseases SLE Neuro-sarcoidosis Neuro-Beçhet's CNS granulomatosis Vasculitis
• ABE	<i>S. pneumoniae</i> <i>S. aureus</i>
• Brain abscess	Oral anaerobes <i>Citrobacter</i> (children) <i>S. aureus</i> Aerobic GNBs

**Abbreviations:** IVDAs, IV drug abusers; VA, ventriculo-atrial; VP, ventriculo-peritoneal; ABE, acute bacterial endocarditis; CoNS, coagulase-negative staphylococcal; CMV, cytomegalovirus; CNS, central nervous system; SLE, systemic lupus erythematosus; MAI, mycobacterium arium-intracellulare; TB, tuberculosis; GNB, gram-negative bacilli.

**Table 5** Complications of Meningitis

Complications	Associated Organisms
• Deafness/hearing loss	<i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> TB RMSF Mumps
• Seizures	<i>Streptococcus pneumoniae</i> (early) <i>H. influenzae</i> Group B streptococci HSV-1 Septic arthritis Histoplasmosis TB Brain abscess <i>H. influenzae</i>
• Subdural effusions	<i>S. pneumoniae</i> <i>N. meningitidis</i>
• Septic arthritis	<i>S. aureus</i>
• Hemiplegia	<i>S. pneumoniae</i>
• Cerebral-vein thrombosis	<i>H. influenzae</i> (associated Jacksonian seizures)
• Hydrocephalus	<i>H. influenzae</i> TB Neurosarcoidosis Neurocysticercosis
• Cranial nerve abnormalities	<i>N. meningitidis</i> (CN VI, VII, VIII) Tuberculosis (CN VI) Neurosarcoidosis (CN VII) Meningeal carcinomatosis (multiple CNs)
• Herpes labialis	<i>N. meningitidis</i> <i>S. pneumoniae</i>
• Panophthalmitis	<i>N. meningitidis</i> <i>S. pneumoniae</i>
• Purpura/petechiae or shock	<i>H. influenzae</i> <i>N. meningitidis</i> <i>S. pneumoniae</i> <i>Listeria monocytogenes</i> <i>Staphylococcus aureus</i>

*Abbreviations:* RMSF, Rocky Mountain spotted fever; HSV, herpes simplex virus.

The critical laboratory test in ABM is analysis of the CSF. In ABM, there is usually a pleocytosis of the CSF. In ABM, the cells in the CSF are nearly all PMNs. As the meningeal infection is treated, the number of PMNs decreases and there is a parallel rise in the number of CSF lymphocytes. Bacterial meningitis begins with a PMN predominance and ends with a lymphocytic predominance. Other CNS infections, e.g., tuberculosis, viral infections, fungal infections, and syphilis, may all present initially with a PMN-predominant pleocytosis. These disorders are characterized by a lymphocytic CSF pleocytosis, but initially may present with a PMN predominance. Importantly, with the exception of HSV-1,  $\geq 90\%$  PMNs in the CSF initially always indicates ABM. A PMN predominance of  $< 90\%$  is compatible with a wide variety of CNS pathogens and does not, of itself, indicate a bacterial etiology. In patients with fever and nuchal rigidity, a lumbar puncture should always be performed before a head CT/MRI scan is obtained. Patients with bacterial meningitis are acutely ill and have a potentially rapidly fatal disorder. To waste valuable time obtaining a head CT/MRI can result in a fatal outcome. Fear of supratentorial herniation is the main reason why head imaging studies are done before lumbar puncture, which is appropriate if a mass lesion is suspected, but not if the diagnosis includes ABM. Far more people will die from a delay in therapy than have died from supratentorial herniation (1–5,18,25,26) (Table 6 to 9).

**Table 6** Central Nervous System Infections in Normal versus Compromised Hosts

- 
- CNS infection in normal hosts
    - Usually *acute* onset of signs and symptoms of meningitis
    - Single* pathogen
    - Predictable pathogen* based on epidemiology, patient age, head and neck/CNS anatomic abnormalities, and host defense defects
    - Meningitis* or *encephalitis* most frequent manifestation of CNS infection
  - CNS infection in compromised hosts
    - Subacute/indolent onset* of signs and symptoms of CNS infection
    - Single or sequential pathogens*
    - Pathogen determined by type of immune defect and degree/duration of immunosuppression*
    - Encephalitis or mass lesions (brain abscess) most common manifestations of CNS infection
- 

*Abbreviation:* CNS, central nervous system.

**Table 7** CNS Pathogens and Disorders Associated with Impaired B-Lymphocyte–Mediated Humoral Deficiency

- 
- *Disorders associated with impaired B-lymphocyte function/humoral immunity*
    - Multiple myeloma
    - B-cell lymphoma
    - Splenic infarcts
    - Advanced age
    - Infiltrative diseases of the spleen
    - Splenectomy
    - Waldeström’s macroglobulinemia
    - Hereditary immunoglobulin deficiencies
    - CLL
    - IgA deficiency
    - Hyposplenism/decreased splenic function
  - *Disorders associated with impaired splenic function include:*
    - Hyposplenism of the elderly: Congenital asplenia
    - Chronic alcoholism: Sickle cell trait or disease
    - Amyloidosis: Splenic infarcts
    - Chronic active hepatitis: Splenic malignancies
    - Fanconi’s syndrome: Systemic mastocytosis
    - IgA deficiency: Rheumatoid arthritis
    - Intestinal lymphangiectasia: Systemic necrotizing vasculitis
    - Myeloproliferative disorders: Thyroiditis
    - Waldenstrom’s macroglobulinemia: Steroid therapy
    - Non-Hodgkin’s lymphoma:  $\gamma$ -Globulin therapy
    - Celiac disease: Splenectomy
    - Regional enteritis: Ulcerative colitis
    - Sezary syndrome

*CNS pathogens associated with impaired B-Lymphocyte function/humoral immunity*

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Common	Uncommon	Rare
<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>	<i>Pseudomonas aeruginosa</i>
<i>Haemophilus influenzae</i>	<i>Klebsiella pneumoniae</i>	Echovirus
		Poliovirus

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*Abbreviation:* CNS, central nervous system.

### CSF Profile in Meningitis

The evaluation of the CSF is the definitive diagnostic test in patients with ABM. Microscopic examination of the CSF by Gram stain provides rapid information regarding the CSF cellular response as well as the concentration morphology/arrangement of potential neuropathogenic bacteria. The typical “purulent profile” in the CSF of bacteria causing acute meningitis includes an early PMN predominance, a decreased CSF glucose, a variabilitated CSF protein, no RBCs, and a highly elevated CSF lactic acid level (1,3–6). The positivity of the CSF Gram stain depends on the concentration and type of organism present. The CSF Gram stain is negative half the time

**Table 8** CNS Pathogens and Disorders Associated with Impaired T-Lymphocyte/Macrophage-Mediated Cellular Immunity

- Disorders associated with impaired T-lymphocyte/macrophage-mediated cellular immunity
  - HIV/AIDS
  - Lymphoreticular malignancies
  - Hodgkin's lymphoma
  - Chronic immunosuppressive therapy
  - Organ transplantation (bone marrow, renal, cardiac, pancreatic, hepatic, etc.)
  - Chronic corticosteroid therapy
    - Collagen vascular diseases
    - Systemic vasculitis
    - Chronic renal failure
    - Rheumatoid ailments
  - CMV

*CNS pathogens associated with impaired T-lymphocyte/macrophage-mediated cellular immunity*

Common	Uncommon	Rare
<i>Listeria</i>	<i>M. tuberculosis (TB)</i>	PML
<i>Nocardia</i>	Brucellosis	<i>Strongyloides stercoralis</i>
<i>Cryptococcus neoformans</i>	<i>Aspergillus</i>	<i>Toxicara canis</i>
CMV	<i>Mucor</i>	<i>Pneumocystis (carinii) jiroveci (PCP)</i>
HSV		<i>Pseudallescheria boydii</i>
VZV		
<i>Toxoplasma gondii</i>		

*Abbreviations:* CNS, central nervous system; CMV, cytomegalovirus; VZV, varicella zoster virus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy.

**Table 9** Diagnostic Approach in Compromised Hosts with Symptoms/Signs of Central Nervous System Infection

Syndrome presentation	Diagnostic procedures	Comments
• Meningeal signs	LP with CSF: WBC cell count/differential RBC count Glucose/protein Lactic acid Cytology Bacterial signs/culture AFB fungal smears/culture	Determine host defense defect to predict most likely CNS pathogens Rule out mimics of meningitis Empiric therapy is based on cerebrospinal fluid findings
• Encephalitis/encephalopathy or mass lesion	Head CT/MRI: To rule out cerebritis To rule out mass lesions To rule out hydrocephalus To rule out CNS hemorrhage LP if papilledema not present: WBC cell count/differential Glucose/protein/RBCs Lactic acid Cytology Bacterial strains/culture AFB fungal smears/culture	Determine host defense defect to predict most likely CNS pathogens Rule out noninfectious causes by history/physical exam, and CT/MRI appearance Specific therapy based on tissue diagnosis, or empiric therapy for the most likely diagnostic possibility

*Abbreviations:* CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CT, computed tomography; AFB, acid-fast bacilli; LP, lumbar puncture.

with *L. monocytogenes* meningitis, for example, but the organism is virtually always culturable from the CSF. With ABM due to the meningococcus, no organisms may be seen on CSF Gram stain, even in the presence of overwhelming infection due to autolysis by the organism. The CSF may appear turbid or cloudy due to the abundance of WBCs present. Organisms may not be visible on the CSF Gram stain, but culture is invariably positive for *Neisseria meningitidis*. The typical purulent profile of ABM may also be present in patients with early tuberculous or fungal meningitis, but more typically present as subacute/chronic meningitis (1,8,27).

The various causes of viral/aseptic meningitis are uniformly associated with a normal CSF glucose with a few important exceptions. The presence of a normal CSF glucose in a patient with suspected meningitis argues strongly against a bacterial tuberculous or fungal etiology and suggests a viral or noninfectious mimic of meningitis, i.e., carcinomatous meningitis. The viruses that are capable of decreasing the CSF glucose include HSV, lymphocytic choriomeningitis (LCM), mumps, and occasionally enteroviruses. With these exceptions aside, a normal CSF glucose virtually excludes a bacterial etiology of ABM (1,5,8,14,18,28,29).

RBCs are not a feature of ABM, and the physician should suggest an alternate explanation for the patient's symptoms. Excluding a traumatic tap, CNS leaking aneurism, etc., RBCs in the CSF limit diagnostic possibilities to *L. monocytogenes*, amebic meningoencephalitis, leptospirosis, tuberculous meningitis, HSV, and anthrax. RBCs in the CSF can also decrease the CSF glucose and increase the CSF lactic acid. The abnormalities in CSF glucose and lactic acid are proportional to the number of RBCs present in the CSF, and can account for mild to moderate abnormalities in these two CSF parameters (1,5,8,18,27).

The white blood cell response in the CSF typically is early and brisk with bacterial meningitis. Many CNS infections characteristically associated with a lymphocytic predominance often present acutely with a PMN predominance, e.g., tuberculosis (TB), fungi, syphilis, and viruses. With the exception of HSV-1, only ABM presents with a CSF PMNs  $\geq 90\%$ . Patients with partially treated meningitis have a mixed picture with both PMNs and lymphocytes as well as a moderately decreased glucose versus the profoundly decreased glucose and untreated ABM, and will have CSF lactic acid levels that are intermediate between aseptic/viral meningitis and ABM. The clinician uses not only the CSF Gram stain but analyzes the patient's clinical information integrating the CSF findings of the number of WBCs in relationship to the PMN predominance glucose levels, CSF lactic acid levels, and the presence or absence of RBCs in the absence of trauma to correctly analyze CSF findings (1,5,8,30) (Tables 10 and 11).

**Table 10** CSF Gram Stain Clues in Meningitis

<ul style="list-style-type: none"> <li>● Purulent CSF/no organisms seen               <ul style="list-style-type: none"> <li><i>Neisseria meningitidis</i></li> <li><i>Streptococcus pneumoniae</i></li> </ul> </li> <li>● Cloudy CSF/without WBCs               <ul style="list-style-type: none"> <li><i>S. pneumoniae</i></li> </ul> </li> <li>● Gram-positive bacilli               <ul style="list-style-type: none"> <li><i>Listeria monocytogenes</i></li> <li>Pseudomeningitis (<i>Bacillus</i>, <i>Corynebacterium</i>, etc)</li> </ul> </li> <li>● Gram-negative bacilli               <ul style="list-style-type: none"> <li><i>Haemophilus influenzae</i> (small encapsulated, pleomorphic)</li> <li>Enteric aerobic GNBs (larger, unencapsulated)</li> </ul> </li> <li>● Gram-positive cocci               <ul style="list-style-type: none"> <li>Group A, B streptococci (pairs and chains)</li> <li><i>S. pneumoniae</i> (pairs)</li> <li><i>Staphylococcus aureus</i> (clusters)</li> <li><i>Staphylococcus epidermidis</i></li> <li>VA/VP shunt infections only (clusters)</li> </ul> </li> <li>● Gram-negative cocci               <ul style="list-style-type: none"> <li><i>N. meningitidis</i></li> </ul> </li> <li>● Mixed organisms/polymicrobial               <ul style="list-style-type: none"> <li>Pseudomeningitis</li> <li>Brain abscess with meningeal leak</li> <li>VP shunt infection</li> <li>Disseminated <i>Strongyloides stercoralis</i></li> <li>Meningitis (2° to penetrating head trauma)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Clear CSF/no organisms seen               <ul style="list-style-type: none"> <li>Viral meningitis</li> <li>TB/fungal meningitis</li> <li>Neurosarcoidosis meningitis</li> <li>Early bacterial meningitis</li> <li>Partially treated bacterial meningitis</li> <li>Meningitis in leukopenic hosts</li> <li>Meningeal carcinomatosis</li> <li>Brain abscess</li> <li>Parameningeal infection</li> <li>Bland emboli (2° to SBE)</li> <li>Cerebritis</li> <li>Neuroborreliosis</li> <li>LCM</li> <li><i>L. monocytogenes</i></li> <li>HIV</li> <li>Syphilis</li> <li>Leptospirosis</li> </ul> </li> </ul>
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**Abbreviations:** RMSF, Rocky Mountain spotted fever; SBE, subacute bacterial endocarditis; HIV, human immunodeficiency virus; VA, ventriculo-atrial; VP, ventriculo-peritoneal; LCM, lymphocytic choriomeningitis.

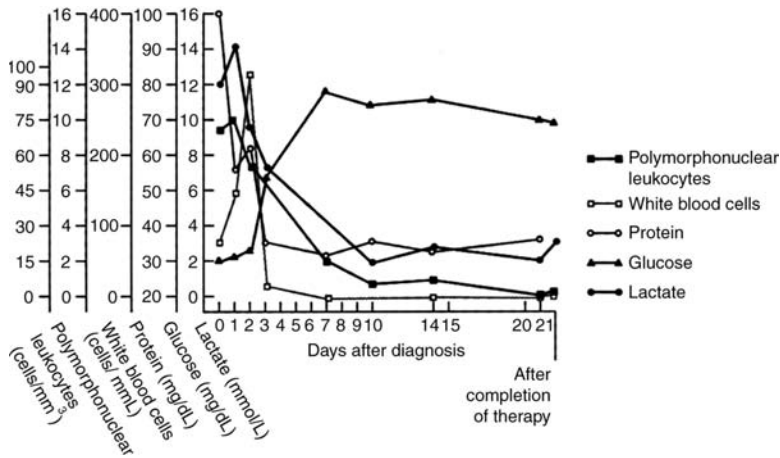
**Table 11** Differential Diagnosis of CSF with a Negative Gram Stain

<ul style="list-style-type: none"> <li>● Predominantly PMNs/decreased glucose               <ul style="list-style-type: none"> <li>Partially treated bacterial meningitis</li> <li><i>Listeria monocytogenes</i></li> <li>HSV-1</li> <li>Tuberculosis (early)</li> <li>Syphilis (early)</li> <li>Neurosarcoidosis</li> <li>Parameningeal infection</li> <li>Septic emboli (2° to ABE)</li> <li>Amebic meningoencephalitis</li> <li><i>N. fowleri</i></li> <li>Syphilis (early)</li> <li>Posterior fossa syndrome</li> </ul> </li> <li>● CSF lactic acid               <ul style="list-style-type: none"> <li>&lt;3 mmol/L                   <ul style="list-style-type: none"> <li>Aseptic “viral” meningitis</li> <li>Parameningeal infections</li> </ul> </li> <li>3-6 mmol/L                   <ul style="list-style-type: none"> <li>Partially treated meningitis</li> <li>RBCs</li> <li>TB/fungal meningitis</li> </ul> </li> <li>&gt;6 mmol/L                   <ul style="list-style-type: none"> <li>Bacterial meningitis</li> </ul> </li> </ul> </li> <li>● CSF protein               <ul style="list-style-type: none"> <li>Elevated (any CNS infection/ inflammation)</li> <li>Very highly elevated                   <ul style="list-style-type: none"> <li>Brain tumor</li> <li>Brain abscess</li> <li>TB (with subarachnoid block)</li> <li>Demyelinating CNS disorders</li> <li>Multiple sclerosis</li> </ul> </li> </ul> </li> <li>● RBCs               <ul style="list-style-type: none"> <li>Traumatic tap</li> <li>Posterior fossa syndrome</li> <li>CNS bleed/tumor</li> <li>HSV-1</li> <li><i>L. monocytogenes</i></li> <li>Leptospirosis</li> <li>TB meningitis</li> <li><i>Naegleria fowleri</i> meningoencephalitis</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Predominantly lymphocytes/normal glucose               <ul style="list-style-type: none"> <li>Partially treated bacterial meningitis</li> <li>Neurosarcoidosis</li> <li>Neuroborreliosis</li> <li>HIV</li> <li>Leptospirosis</li> <li>RMSF</li> <li>Viral meningitis</li> <li>Bland emboli (2° to SBE)</li> <li>Parameningeal infection</li> <li>TB/fungal meningitis</li> <li>Meningeal carcinomatosis</li> </ul> </li> <li>● Predominantly lymphocytes/decreased glucose               <ul style="list-style-type: none"> <li>Partially treated bacterial meningitis</li> <li>LCM</li> <li>Enteroviral meningitis</li> <li><i>L. monocytogenes</i></li> <li>Mumps</li> <li>Leptospirosis</li> <li>TB/fungal meningitis</li> <li>Neurosarcoidosis</li> <li>Meningeal carcinomatosis</li> </ul> </li> <li>● CSF eosinophils               <ul style="list-style-type: none"> <li>CNS vasculitis</li> <li>NSAIDs</li> <li>Coccidioidomycosis</li> <li>Neurocysticercosis</li> <li>Angiostrongyliasis</li> <li>Gnathostomiasis</li> <li>Paragonimiasis</li> <li>Shistosomiasis</li> <li><i>Toxocara canis/cati</i> (VLM)</li> <li>CNS lymphomas</li> <li>VA/VP shunts</li> <li>Interventional contrast materials</li> </ul> </li> </ul>
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**Abbreviations:** CSF, cerebrospinal fluid; HSV, herpes simplex virus; CNS, central nervous system; ABE, acute bacterial endocarditis; LCM, lymphocytic choriomeningitis; SBE, subacute endocarditis; PMNs, polymorphonuclear leukocytes; RMSF, Rocky Mountain spotted fever; VA, ventriculo-atrial; VP, ventriculo-peritoneal; NSAIDs, nonsteroidal inflammatory drugs. VLM, visceral larva migrans

### The Diagnostic Significance of CSF Lactic Acid Levels in Meningitis

In the diagnosis of ABM, the CSF lactic acid levels are second only to the CSF Gram stain as a rapid and reliable indicator of ABM. It has been said that the CSF lactic acid levels offer no information that cannot be inferred from CSF glucose levels. This is not the case. The CSF glucose levels and CSF lactic acid levels are inversely proportional to each other. As the CSF glucose decreases, the CSF lactic acid increases. With successful treatment, the CSF lactic acid levels and CSF glucose levels are the first to normalize. It takes days for the initial PMN predominance in the CSF to become lymphocytic, and a lymphocytic pleocytosis may persist in the CSF for weeks after clinical resolution of the patient's bacterial meningitis. The CSF lactic acid level decreases more rapidly and acutely than does the CSF glucose. For example, if a patient has *S. aureus*, acute bacterial endocarditis, and has seeded the CSF resulting in an early purulent meningitis, the CSF lactic acid level will be elevated before the Gram stain is positive or the CSF glucose levels have dropped. The CSF lactic acid test is invaluable in separating viral from bacterial meningitis as well as for identifying patients with partially treated meningitis (1,30–32).



**Figure 1** Temporal relationships of CSF lactic acid levels in bacterial meningitis. *Source:* adapted from Ref. 31.

CSF lactic acid levels are also useful in assessing the significance of RBCs in the CSF in patients with a decreased CSF glucose. If the diagnosis is between HSV-1 and *L. monocytogenes* meningitis, in *L. monocytogenes* meningoencephalitis, CSF lactic acid levels will be highly elevated, i.e.,  $\geq 6$  mmol/dL, whereas the CSF lactic acid levels will be normal/near normal in HSV-1. A normal CSF lactic acid level in the absence of RBCs from a trauma or traumatic tap is the best way to differentiate aseptic from septic meningitis. If the Gram stain is negative and CSF lactic acid levels are normal, then the clinician can confidently wait for CSF cultures to be reported as negative during the next one to three days. No empiric antimicrobial therapy is needed if the CSF lactic acid level is normal and the CSF Gram stain is normal. CSF lactic acid levels may be obtained serially to determine if antimicrobial therapy of the meningitis is effective, and also may be used at the end of therapy as a test of cure (1,30–34) (Fig. 1).

### Other CSF Tests (CRP, PCT, LDH)

Another test that has been used to differentiate aseptic/viral meningitis from ABM is C-reactive protein (CRP). CSF CRP is elevated in bacterial meningitis but is not as highly elevated in viral/aseptic meningitis. CSF procalcitonin (PCT) levels are highly elevated in ABM but not in aseptic/viral meningitis (35).

Other CSF parameters have been used, i.e., lactate dehydrogenase (LDH) to differentiate the various types of meningeal pathogens, but lack sensitivity and specificity. The CSF antigen tests, i.e., counter immunoelectrophoresis (CIE) techniques of the CSF are generally unhelpful. The problems with the CSF CIE assays are lack of sensitivity and specificity. When a CNS pathogen is demonstrated by Gram stain and culture and there is no doubt about the diagnosis, the CIE is not infrequently negative (1,3–5,8).

Other tests are useful in selected CNS disorders. The CSF  $C_4$  level is decreased and diagnostic of SLE meningitis/ cerebritis although clonal bands in the CSF may be present in SLE as well as multiple sclerosis. Cytology of the CSF may indicate meningeal carcinomatosis, which may mimic ABM (1,19–21,28,29).

Other tests are useful in the CSF for selected pathogens. PCR technique is useful to make the diagnosis of enteroviral meningitis, HSV-1/2 and HHV-6 aseptic meningitis. PCR is also useful to diagnose acute TB meningitis (1,5,25,27,36).

### Serum Tests (CRP, PCT, and Ferritin Levels)

The serum CRP has also been useful to differentiate ABM from aseptic/viral meningitis. In ABM, serum CRP levels are higher than in viral/aseptic meningitis. Similarly, serum PCT levels are more highly elevated than viral/aseptic meningitis versus ABM (35,37,38).

Highly elevated serum ferritin levels appear to be a marker for West Nile encephalitis (WNE). In WNE, serum ferritin levels are highly elevated but are unelevated/minimally elevated in aseptic/viral and bacterial meningitis (39,40).



## Radiologic Tests

Neuroimaging tests are primarily valuable for ruling out the mimics of ABM. In ABM, head CT/MRI scans are of limited value and are done primarily to rule out parameningeal suppurative focus or brain abscess, or systemic mimics of meningitis. As mentioned previously, lumbar puncture takes precedence over neuroimaging if the diagnosis of ABM is being considered. The EEG is primarily useful in diagnosing encephalitis and is non-diagnostic in ABM. The main use for EEG is in the early diagnosis of HSV meningoencephalitis because of the propensity of HSV to localize to the frontal/temporal lobe. In normal hosts, HHV-6 encephalitis may also localize to the frontal/temporal lobe. EEG abnormalities are diffuse with most causes of acute viral encephalitis, but is localized very early with HSV-1 meningoencephalitis, which is an important diagnostic clue to its presence (1-5,26,27,41).

## EMPIRIC THERAPY OF MENINGITIS

Empiric therapy of ABM depends upon demonstrating or predicting the CNS pathogens so that an appropriate antibiotic may be selected. If the pathogen can be demonstrated by Gram stain or inferred from aspects of the history, epidemiological data, systemic laboratory tests, or physical findings then an antibiotic with an appropriate spectrum can be selected to begin treatment. Early treatment with an appropriate antibiotic is crucial to the outcome in patients with ABM (1,42-50).

Not only must the antimicrobial being selected to treat ABM be effective against the pathogen, but it must reach bactericidal concentrations in the CSF with the usual "meningeal doses." Certain antibiotics achieve a therapeutic CSF concentration when being in the usual dose, e.g., chloramphenicol, TMP-SMX, doxycycline, minocycline, and anti-tuberculous drugs, whereas others require higher than usual doses to penetrate the CSF, e.g., cefepime, meropenem, and anti-viral drugs. Most other antimicrobials do not achieve sufficient CSF concentration with usual or even with high dosing, e.g., first/second-generation cephalosporins, vancomycin, amphotericin (1-3,42-45).

After selecting a drug with the appropriate spectrum for the presumed neuropathogen and delivering the drug intravenously in a dose that will rapidly achieve bactericidal concentrations in the CSF, patients are ordinarily treated for a total of two weeks. The main determinants of antibiotic penetration of the CSF are antibiotic size and the lipid solubility characteristics of the antibiotic. In general, highly lipid soluble antibiotics penetrate the CSF in the presence or absence of inflammation.  $\beta$ -Lactam antibiotics do not penetrate the CSF well in the absence of inflammation. Third- and fourth-generation cephalosporins given in "meningeal doses" do not penetrate the CNS well, but penetrate sufficiently with sufficiently high degree of activity that they are effective against common neuro-pathogens except *L. monocytogenes* (1,42-48).

*Listeria meningitis* is ordinarily treated with "meningeal doses" of ampicillin, i.e., 2 g (IV) q4h, in penicillin tolerant patients. In patients with *Listeria meningitis* intolerant of penicillin, chloramphenicol or TMP-SMX may be used. For the treatment of staphylococcal meningitis due to methicillin-sensitive strains, "meningeal doses" of an anti-staphylococcal penicillin, e.g., nafcillin, may be given as a 2 g (IV) q4h dose.

Drugs used to treat methicillin-resistant *S. aureus* (MRSA) causing ABM include minocycline and linezolid. Vancomycin does not penetrate the CSF well. Vancomycin CSF concentrations are ~15% of simultaneous serum concentrations. Therefore at the usually used dose of 1 g (IV) q12h (15 mg/kg/day), CSF concentrations may be inadequate. If vancomycin is selected to treat MRSA CNS infections, then either 30 to 60 mg/day of vancomycin is necessary, or the usual dose of vancomycin [15 mg/kg/day (IV)] may be supplemented 20 mg of intrathecal (IT) vancomycin daily. Linezolid and minocycline penetrate the CSF well and achieve therapeutic concentrations (42).

The treatment of shunt-related ventriculo-atrial/ventriculo-peritoneal (VA/VP) infections usually requires shunt removal and the administration of an antibiotic that has a high degree of activity against *Staphylococcus epidermidis* or *S. aureus* (depending upon the pathogen isolated that penetrates the CSF in therapeutic concentrations). In patients with meningitis secondary to open CNS trauma, the antibiotics selected should have a high degree of aerobic gram-negative bacillary coverage as well as sufficient anti-staphylococcal activity (1,42,51,52).

The preferred drugs for each pathogen-causing meningitis are presented in tabular form here (Table 12) (1,42).

**Table 12** Empiric Therapy of Acute Bacterial Meningitis (ABM)

Subset	Usual pathogens	Preferred IV therapy	Alternate IV therapy	IV-to-PO switch
Normal Host	<i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i>	Ceftriaxone 2 g (IV) q12h × 2 wk	Meropenem 2 g (IV) q8h × 2 wk or Cefotaxime 3g (IV) q6h × 2 wk or Ceftizoxime 3 g (IV) q6h × 2 wk	Chloramphenicol 500 mg (PO) q6h × 2 wk
Elderly or malignancy	<i>Listeria monocytogenes</i> (plus usual meningeal pathogens in normal hosts)	Before culture results: Ceftriaxone 2 g (IV) q12h × 2 wk plus Ampicillin 2 g (IV) q4h × 2 wk	After culture results: <i>Listeria</i> present Ampicillin 2 g (IV) q4h × 2 wk or Chloramphenicol 500 mg (IV) q6h × 2 wk  <i>Listeria</i> not present: Treat as normal host	After culture results for <i>Listeria</i> present: TMP-SMX 5 mg/kg (PO) q6h × 2 wk or Chloramphenicol 500 mg (PO) q6h × 2 wk  <i>Listeria</i> not present: Chloramphenicol 500 mg (PO) q6h × 2 wk
CNS shunt infections (VA shunts)* (Treat initially for MSSA; if later, identified as MRSA, MSSE, or MRSE, treat accordingly.)	<i>Staphylococcus aureus</i> <i>Staphylococcus</i> <i>epidermidis</i> (CoNS)	Treat as normal host MSSA/MSSE Cefotaxime or Ceftizoxime 3 g (IV) q6h <sup>a</sup> or Linezolid 600 mg (IV) q12h <sup>a</sup> MRSA/MRSE Linezolid 600 mg (IV) q12h <sup>a</sup>	MSSA/MSSE Meropenem 2 g (IV) q8h × 2 wk <sup>a</sup> or Cefepime 2 g (IV) q8h <sup>a</sup> MRSA/MRSE Vancomycin 1 g (IV) q12h <sup>a</sup> plus 20 mg (IT) q24h until shunt removal	MSSA/MRSE Linezolid 600 mg (PO) q12h <sup>a</sup> MSSA/MRSA Minocycline 100 mg (PO) q12h <sup>a</sup> or Linezolid 600 mg (PO) q12h <sup>a</sup>
CNS shunt infections (VP shunts)*	<i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Enterobacter</i> <i>Acinetobacter baumannii</i>	Ceftriaxone 2 g (IV) q12h × 2 wk after shunt removal or Ceftizoxime or Cefotaxime 3 g (IV) q6h × 2 wk after shunt removal Meropenem 2 g (IV) q8h × 2 wk after shunt removal	Meropenem 2 g (IV) q8h × 2 wk after shunt removal. TMP/SMX 5 mg/kg (IV) q6h × 2 wk after shunt removal Subactam/ampicillin 4.5 g (IV) q6h × 2 wk after shunt removal	TMP-SMX 5 mg/kg (PO) q6h × 2 wk after shunt removal None

*Note:* Duration of therapy represents total time IV or IV+PO. Most patients on IV therapy able to take PO meds should be switched to PO therapy after clinical improvement.

\*Remove CNS shunt as soon as possible.

<sup>a</sup>Treat for 1 wk after shunt removal.

*Abbreviations:* ABM, acute bacterial meningitis MSSA/MRSA, methicillin-sensitive/resistant *S. aureus*; MSSE/MRSE, methicillin-sensitive/resistant *S. epidermidis*.

*Source:* Adapted from Ref. 42.

The use of steroids as an adjunctive measure to treat ABM remains controversial. Steroids have long been used together with antituberculous therapy in acute tuberculous meningitis, but there is relatively little information on the use of steroids in the treatment of ABM in adults. Steroids have been shown to be beneficial in the treatment of meningitis in children due to *H. influenzae*, but have been limited to *H. influenzae*. Because steroids affect blood/brain barrier permeability, if used steroids should be given after antimicrobial therapy has been initiated (46–50).

### REPEAT LUMBAR PUNCTURE

The diagnosis of ABM rests on analysis of the CSF and demonstration of the putative organism in the CSF by Gram stain or culture. Corroborative evidence includes a PMN predominance in the CSF, a decreased CSF glucose, and a highly increased CSF lactic acid level. A repeat lumbar puncture is indicated if the patient has not responded to therapy within 72 hours. If the antibiotic is ineffective, the CFS profile will remain relatively unchanged and most importantly, the CSF lactic acid levels will have not decreased. CSF lactic acid levels decrease rapidly with appropriate antimicrobial therapy and CSF glucose levels also quickly return to normal. If the patient is clinically not responding to antimicrobial therapy and the repeat lumbar puncture shows the same or only slightly increased CSF glucose levels with the same or only slightly decreased lactic acid levels, then the clinician should reassess the antimicrobial regimen (1,5,30–33,45).

Reevaluation of the antibiotic should include a reassessment of its spectrum, degree of activity, dosage, CSF penetration, to determine if a change in therapy is warranted. The only CNS infection that may present with ABM that would change quickly as the result of appropriate therapy would be a brain abscess that has ruptured into the ventricular system. Such a large number of organisms released from the brain abscess into the CSF would be overwhelming to the host and in spite of appropriate antimicrobial therapy, would not change the CSF parameters within three days without drainage of the brain abscess. There is no need to repeat the lumbar puncture if the patient is responding to therapy, suggesting that the proper antibiotic has been chosen and given in the correct dose, and that it is effectively cidal at CNS concentrations resulting in a rapid clinical response as well as a rapid response to the key CSF parameters of the lactic acid/CSF glucose (1–5,45,53).

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# 9 | Encephalitis and Its Mimics in Critical Care

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## INTRODUCTION

A critically ill patient presents to the emergency department with a low-grade fever and altered mental status. Is this a brain infection? Is it a stroke? Is it the “toxic metabolic” encephalopathy so commonly seen in patients who are septic, hypotensive, hypoxic, or otherwise severely compromised? How far must one go to exclude the possibility of a central nervous system (CNS)-damaging process? How does one most rationally approach this all too frequent occurrence? This chapter will attempt to provide a framework to address these frequent and challenging questions.

The neurologist’s approach to the patient with impaired nervous system function is firmly rooted in the classic clinical approach of characterizing the disease process in space and time. Although technology, including magnetic resonance imaging (MRI) and electroencephalography (EEG), can augment the neurologic examination, much of the necessary information can be quickly ascertained by performing a limited but directed bedside assessment.

A basic premise of clinical neurology is that brain infections, like other CNS-damaging processes, cause constant or progressive impairment of specific neurologic functions related to the location of the responsible CNS damage. In contrast, many systemic illnesses will cause impairments that wax and wane in both time and space—deficits may appear focal, but improve, only to be followed by transient impairment of other functions. Simple and repeated clinical assessments of brainstem function, and of specific cortical functions such as language, memory, and vision, can raise or lower the index of suspicion for a primary CNS process.

## BRAIN INFECTION OR NOT?

A key conceptual first step is to differentiate among three distinct entities—encephalopathy, meningitis, and encephalitis. All may initially present in strikingly similar fashion, with systemic symptoms accompanied by changes in level of alertness and cognitive function.

Encephalopathy is by far the most common of the three, and, from a neurologic perspective, the most benign. Although the word can be defined to include any abnormality of brain function, it is most commonly used to describe alterations of consciousness and cognition in response to systemic disorders, without necessarily any underlying structural brain damage. Common causes of “toxic metabolic encephalopathy” include hyper- or hypo-glycemia, hyponatremia, hypoxia, hyperthermia, sepsis, and organ system failure such as significant renal or hepatic insufficiency. The unifying theme of these disorders is that, by altering the brain’s physiologic milieu, they alter brain function. Although all can result in nervous system damage if sufficiently severe or prolonged, each can cause transient neurobehavioral changes that are completely reversible.

Meningitis refers to inflammation in the subarachnoid space—the fluid-filled space that surrounds the brain and spinal cord. Infections that remain limited to this space, such as viral meningitis, are benign, though unpleasant. “Aseptic meningitis” (a term dating to a time when only bacterial pathogens could be readily identified) typically causes severe headaches and systemic symptoms but rarely has serious sequelae. Changes in neurologic function are generally nonfocal and simply reflect the fact that the patient is ill and very uncomfortable.

Bacterial meningitis, on the other hand, can be devastating. This infection starts in the subarachnoid space, but bacteria then invade and damage the arteries and veins passing into the adjacent brain, and invade the brain directly. It is this vascular-related damage, combined with focal cerebritis and abscess formation, as well as the effects of having a purulent exudate in the subarachnoid space obstructing cerebrospinal fluid (CSF) flow, that lead to severe neurologic sequelae. This, in combination with the systemic effects of the bacteremia, can result in a lethal outcome.

Finally, encephalitis refers to inflammation within the substance of the brain itself. This can lead to severe parenchymal CNS damage, resulting in irreversible neurologic impairment or death. Most often infectious, there are also rare disorders in which this occurs on a primarily immunologic basis. Fortunately encephalitis of all types is quite rare (10,000 to 20,000 cases per year in the United States).

Brain infections of all types are uncommon, in large part because the nervous system is so well protected. Bacterial infection, which most typically starts as a meningitis, occurs primarily in three settings—mechanical injury to the skull (traumatic or surgical), contiguous untreated infection in the sinuses or mastoids, eroding through bone, or bacteremia with an organism able to cross the blood–brain barrier.

Other organisms, particularly neurotropic viruses, have developed unique strategies to enable CNS invasion. Herpes simplex is thought to use one of two routes—either tracking from the olfactory epithelium to the olfactory tracts and then into the medial temporal lobes or binding peripheral sensory nerve terminals, migrating intra-axonally to the sensory ganglia, then tracking centrally along trigeminal branches innervating the meninges (1). Poliovirus specifically binds receptors on motor neuron terminals, then migrates centrally within axons (2). Other strains of organisms have developed mechanisms to cross the blood–brain barrier, but lack the ability to bind to neurons or glia; these cause infections limited to the meninges, and not encephalitis. In the absence of such specialized mechanisms, very few microorganisms are capable of invading and infecting the CNS.

### **CLINICAL APPROACH**

Given the remarkably low incidence of encephalitis in the United States, only a small subset of febrile patients with altered mental status will actually have encephalitis. In most instances alterations of consciousness and cognitive function will be a nonspecific response to the febrile state, probably caused by circulating cytokines or other small molecules that cross the blood–brain barrier and are then neuroactive (3).

Two key elements are involved in differentiating between such encephalopathies and primary brain processes. From the systemic perspective, identification of a specific underlying medical abnormality is the key. Neurologically, it is essential to establish whether the observed changes are focal or not—brain disorders resulting from localized damage to the brain cause abnormalities of function related to the site of damage. Damage to the cerebral cortex can cause seizures, an altered level of consciousness, and cognitive difficulty. Damage to the deep white matter causes spasticity, ataxia, visual and sensory problems, but not seizures and has a less severe impact on alertness and cognition. Damage to the brainstem can affect level of consciousness, long tracts that pass through the brainstem, but most importantly cranial nerve function.

Within the brain, different functions have discrete localization as well. Damage to the temporal lobes can cause memory and olfactory problems, frontal lobe damage affects behavior, occipital lobe damage affects vision, etc. In brief, location dictates the specific functions that are affected. Typically if there is a brain-damaging process, functions that are affected remain affected throughout. In contrast, in patients with an encephalopathy abnormalities fluctuate in space and time. Hence a detailed clinical neurologic assessment can help differentiate between a structural process—i.e., potentially an encephalitis—and a systemic abnormality altering the brain's metabolic milieu, and secondarily inducing a time-varying abnormality of brain function.

In assessing patients' mental status, one of the first steps must be assessing language. Without establishing meaningful communication with the patient, further assessment of brain function can be uninterpretable. Aphasic patients are commonly described as "confused" because what they say makes no sense. If a patient's language sounds fluent but its content is incomprehensible, it is understandable to interpret this as evidence of confusion. However, several simple steps—asking the patient to follow several simple verbal commands (without helpful gesticulations), asking him/her to name a few objects or repeat a few words—should readily differentiate between a language disorder and a confusional state.

Similarly, the behavior of a patient with psychosis may seem inexplicable and may be interpreted as evidence of confusion. Remarkably, although psychotic patients may

demonstrate extraordinarily bizarre behavior, they almost always retain orientation and memory. Testing these simple functions usually will be very helpful.

Many disorders other than infections can produce focal brain damage—strokes and tumors being the most common. Differentiating between these disorders and infections should usually be straightforward, based on the clinical context. Stroke usually has a virtually instantaneous onset and causes abnormalities related to the specific blood vessel involved. Tumors typically cause symptoms that develop insidiously (over weeks or longer) and are not usually accompanied by systemic symptoms of infection.

Often, most challenging are epileptic disorders. If there is no past history of epilepsy, and if no motor seizure activity was witnessed, these can be particularly perplexing. Post-ictal confusional states usually clarify themselves by resolving over minutes to hours. However non-convulsive status epilepticus, in which part of the brain seizes continuously but with no corresponding motor activity, can result in a patient with profoundly altered cognitive function, but with a cause only identifiable by EEG monitoring. Although, as in patients with brain tumors, these patients do not typically have systemic symptoms of infection, assuming that this excludes encephalitis can be dangerous—not all patients with encephalitis have systemic signs at the onset, and encephalitis can present as non-convulsive status!

## **INFECTIOUS ENCEPHALITIS**

All encephalitides, regardless of cause, share several key characteristics—all are inflammatory processes involving the substance of the brain, resulting in at least a transient alteration of brain function, but ultimately potentially causing irreversible CNS damage. All are potentially devastating and much-feared diseases—think of rabies or “sleeping sickness” as just two examples. On the other hand, most of the viruses that can cause encephalitis cause many more asymptomatic infections than symptomatic ones, and typically even among patients with symptomatic infection only a small subset develops neuroinvasive disease (2).

The initial presentation of these infections is often unimpressive—typically much less dramatic than that of meningitis, where infection of the brain lining causes severe pain, sensitivity to light and sound, and reflex protective neck stiffness. The meninges and cortical blood vessels have nociceptive receptors, so inflammation is painful; the brain itself has no nociceptors. Fever, often low grade, is common—but less so in the very young, the elderly, and the immunocompromised. Neurologic changes are often initially limited to subtle alterations of consciousness or cognition—easily confused with the mild changes typically seen as a nonspecific result of systemic infection. Specific etiologic agents may cause more specific symptoms. Enteroviruses and listeria often cause prominent associated gastrointestinal symptoms. Some arboviruses similarly can present with gastrointestinal (GI) or other nonlocalizing symptoms.

Most CNS bacterial infections do not need to be considered further in this discussion, as affected patients generally present acutely toxic with little doubt about the diagnosis. However some bacteria, typically more slow growing ones that elicit a less dramatic immunologic response, cause much more indolent CNS infections—typically spirochetes, listeria, and mycobacteria.

### **Specific Encephalitides**

A consideration of the specific infections (Table 1) that cause encephalitis should begin with those that are most treatable—spirochetoses, mycobacteria, and herpes viruses—all of which cause meningitis with varying degrees of parenchymal brain involvement. Consideration should next turn to disorders with significant prevalence—the arboviruses and most specifically West Nile Virus. Finally, there is a broad array of other agents that must be identified—if for no other reason than for epidemiologic recognition and prevention of additional victims (e.g., rabies).

### **Bacterial Brain Infections**

#### *Tuberculosis*

Worldwide, tuberculosis (TB) remains a significant public health problem, particularly in the less developed world. In the United States, it occurs primarily in patients who have emigrated



**Table 1** Common Etiologic Agents and Diagnostic Approach

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<i>Acute Bacterial Meningitis</i>	
	Brain imaging
	Blood cultures
	CSF examination
	Identify source (skin, sinuses, mastoids, dental, cardiac, other)
<i>Indolent Bacterial</i>	
	TB
	Chest X Ray
	Brain MRI with contrast (basal cisterns)
	CSF examination
	Neuroborreliosis (Lyme disease)
	Peripheral blood serologic testing
	Consider CSF examination including Lyme ELISA
	Neurosyphilis
	Serum reaginic and specific serologic testing
	CSF reaginic and specific serologic testing
<i>Listeria</i>	
	Brain MRI with contrast (brainstem)
	CSF examination
<i>Mycoplasma</i>	
	Chest X Ray
	Serum cold agglutinins
	IgM mycoplasma ELISA
<i>Viral</i>	
	Herpes simplex
	Brain MRI with contrast (frontal and temporal lobes)
	CSF with PCR
	West Nile virus
	Brain MRI with contrast (brainstem)
	Serum IgG and IgM specific serologies (acute and convalescent)
	CSF serology and PCR
	Rabies
	Immunofluorescence for virus in skin biopsy
	Serology
	Saliva PCR

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*Abbreviations:* CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TB, tuberculosis.

from Southeast Asia, Africa, and eastern Europe, and in the immunocompromised, particularly among patients with HIV infection. TB, caused by *Mycobacterium tuberculosis*, is spread primarily by airborne droplets, initially causing pulmonary infection. Although this infection is typically controlled by cell-mediated immunity, some degree of hematogenous dissemination occurs frequently. Bacilli can seed the CNS where tuberculomas most commonly occur along the meninges, but can occur at typical intraparenchymal sites of hematogenously disseminated infection such as the cortical-subcortical gray-white junction. At some point long after initial infection, a tuberculoma may rupture into the subarachnoid space causing meningitis. This meningitis tends to involve the meninges at the base of the brain (regardless of where the tuberculoma was), where involvement of the cranial nerves and blood vessels that pass through the subarachnoid space is commonplace. This results in cranial neuropathies, obstructive hydrocephalus, and strokes (4).

In the absence of obvious chest X-ray findings, diagnosis can be challenging. In a small percentage of patients, brain imaging will demonstrate thick enhancement of the basilar meninges. Skin tests are usually but not invariably positive. CSF analysis typically demonstrates a significant lymphocytic pleocytosis (cell count in the 100's to 1000's) with increased protein, low glucose (sometimes immeasurably so), and elevated adenosine deaminase concentration (5). The latter, indicative of a vigorous T-cell response, is said to have approximately 90% sensitivity

and specificity. Culture, acid fast stain, and even polymerase chain reaction (PCR)-based testing for mycobacteria are available but of incomplete sensitivity, and empiric treatment is necessary in up to half affected patients.

Outcome is heavily dependent on the patient's level of function at the time treatment is initiated. If treatment begins while the patient is neurologically normal, outcomes are excellent. If initiated in comatose individuals, outcomes are predictably quite poor. Although treatment for TB in general has been well studied, fewer studies have specifically addressed TB meningitis (6). If multidrug resistant (MDR) TB is unlikely, three-drug regimens with isoniazid, rifampin, and pyrazinamide are usually given for two months; at the end of that time the pyrazinamide is usually stopped and the other drugs continued for up to 10 additional months. If MDR TB is likely, ethambutol or streptomycin is typically added for the first two months. Corticosteroids are often added initially (except in HIV-infected individuals) and seem to improve outcomes (4). Neurologic sequelae are common.

### *Spirochetal Infections*

Two spirochetal infections commonly invade the nervous system—*Borrelia burgdorferi* (the agent of Lyme disease) and *Treponema pallidum* (syphilis). Both commonly cause meningitis quite early in infection. In both, the basilar meningitis can be accompanied by cranial neuropathies. Both may develop parenchymal nervous system involvement later in infection, although this appears to be far more common in neurosyphilis.

### *Lyme Disease*

*B. burgdorferi* infection, transmitted virtually exclusively by bites of hard-shelled *Ixodes* ticks, typically begins with an asymptomatic skin lesion at the site of inoculation, known as erythema migrans. Prevalent in areas of the Northeast and Upper Midwest United States (7), as well as much of temperate Europe, this is a multisystem infectious disease that involves the nervous system in 10% to 15% of untreated patients (8). Meningitis occurs in up to 10% of patients, who also can develop cranial neuritis and peripheral nerve involvement. Only rarely is the brain or spinal cord parenchyma directly involved, although many patients with systemic infection may develop a "toxic metabolic" encephalopathy as a result of the systemic inflammatory response (9–11).

This encephalopathy well exemplifies the difficulty many nonneurologists have had differentiating between brain infection and the physiologic effects systemic infection (and the immune response to it) can exert on the nervous system. Affected patients often describe cognitive slowing, memory difficulty, and other nonspecific symptoms reflecting the ongoing presence of a chronic indolent infection—symptoms that typically resolve with successful treatment. Unfortunately many patients and physicians conclude that these symptoms mean that the spirochetes have infected the brain and fear that this will lead to inevitable and progressive neurologic decline. It is now quite clear that most of these patients do not have CNS infections and that simple oral antimicrobial regimens will cure virtually all of them.

Very rare patients with neuroborreliosis will develop infection within the parenchyma of the brain or spinal cord—encephalomyelitis. Such individuals, who generally have abnormal neurologic examinations, abnormal MRI scans, and abnormal spinal fluid, are similarly responsive to conventional courses of antimicrobials (12).

Diagnosis in general is confirmed with two-tiered antibody testing. An initial screen is performed using an ELISA; sera judged to be borderline or positive (antibody concentration 2 and 3 standard deviations above the mean, respectively) are then assessed for specificity with a Western blot (13). The serologic response may take four to eight weeks to be measurable, so in patients suspected of having very early disease, a follow up ELISA in one to two months is reasonable. However the rash, erythema migrans, is virtually pathognomonic; in endemic areas patients with this rash should be treated regardless of serologic results (which can be negative in up to 50% of these individuals) (14).

In patients without parenchymal involvement (a group that includes those with meningitis) oral doxycycline 200 mg daily for two to four weeks is generally effective. In

children under eight years of age, in pregnant women, and in patients allergic to doxycycline, amoxicillin 500 mg three times daily or cefuroxime axetil 500 mg twice daily are probably as effective, though less well studied. In those with parenchymal CNS involvement, or those who fail these oral regimens, intravenous ceftriaxone (2 g daily), cefotaxime (2 g three times daily), or penicillin 24 million units daily, all for two to four weeks, are highly effective (12).

### *Neurosyphilis*

Transmitted primarily by sexual contact, syphilis typically begins with an asymptomatic skin lesion at the site of inoculation, the chancre. Spirochetes disseminate quite early in infection, with seeding of the neuraxis in about 40% of individuals (15). Almost all of these patients develop meningitis, which can be variably symptomatic. However, virtually all develop CSF changes including a lymphocytic pleocytosis, modest elevation of protein, and minimal changes in glucose. In most, nonspecific “reaginic” (anti-cardiolipin) antibodies are detectable in the CSF; treatment success can be monitored by measuring the decline in these antibodies as well as in the cell count.

Parenchymal CNS involvement is grouped into three syndromes. Meningovascular syphilis tends to occur on average seven years after initial infection and results from inflammatory damage to the blood vessels in the subarachnoid space. This causes a series of primarily small-artery strokes, often somewhat slowly evolving, typically accompanied by chronic headaches from the meningitis. One to two decades after disease onset other patients will develop “general paresis of the insane,” a more diffuse picture thought to result from a combination of chronic hydrocephalus and parenchymal gummas. Finally, some patients will develop tabes dorsalis two to three decades after initial infection—primarily a disorder of the dorsal roots (which cross through the chronically inflamed subarachnoid space). These same patients often develop parenchymal inflammation in the midbrain causing Argyll Robertson pupils.

Diagnosis is primarily serologic, using both reaginic antibody tests such as the rapid plasma reagent (RPR) and venereal disease research laboratory (VDRL) assays and more specific tests such as the fluorescent treponemal antibody (FTA) and more recently ELISA technology.

Treatment when the CNS parenchyma is involved is typically with parenteral penicillin, typically 18 to 24 million units daily for 10 to 14 days. Oral doxycycline (200 mg daily for four weeks) is recommended and used as an alternative in penicillin-allergic patients, despite a paucity of supportive studies.

### *Listeria*

*Listeria* is a widely prevalent organism that only rarely causes human disease. Infection most often occurs by exposure to contaminated food, most often dairy products. The organism is ingested by, and survives within, a number of types of cells. It seems particularly able to invade the placenta and the CNS, probably hiding intracellularly within trafficking monocytes (16).

Initial symptoms are primarily gastrointestinal. Infections are particularly problematic in pregnant women (causing miscarriages) and newborns (causing disseminated infection). Neurologic involvement takes several forms, most typically meningitis, being the commonest cause of bacterial meningitis in the immunocompromised and the second most common in healthy adults over age 50. The clinical picture of this meningitis is often more indolent than in other meningitides; patients appear less ill and the time course is more protracted. A subset of patients—often younger and otherwise healthy—develops a brainstem encephalitis, or rhombencephalitis, with cranial nerve and long tract signs (ataxia, paresis) referable to this anatomic segment of the CNS (17).

MR imaging can demonstrate microabscesses, particularly in the brainstem. Diagnosis is typically by culture of blood or CSF. The organism is very sensitive to ampicillin and penicillin, but perhaps because of its intracellular location, slow to respond. Consequently, gentamicin is often added for synergy and treatment is typically prolonged. Meningitis is typically treated for three weeks; rhombencephalitis for six.

### *Mycoplasma Pneumonia*

Most patients with mycoplasma pneumonia have prominent headaches (18); however actual CNS involvement, or even alteration of cognitive function or alertness, is quite rare. When encephalitis does occur there are few specific features. Diagnosis is generally by measuring either cold agglutinins or specific antibody titers. Prognosis is generally excellent.

### **Viral Brain Infections**

#### *Herpes Simplex Encephalitis*

Human herpes viruses, similar to polioviruses, differ from many other encephalitis-causing viruses in that they have just one host—humans. Because of this it is at least theoretically possible to eliminate these pathogens entirely—primarily through effective vaccines. While sufficiently potent vaccines are not yet available for herpes simplex, this strategy has eliminated smallpox and hopefully will eliminate polio in the not too distant future. Unfortunately, this approach cannot eliminate the innumerable other viruses, such as West Nile and rabies, which are zoonoses, existing in multiple species. Even with successful vaccination, the best that can be hoped for with zoonotic infections is temporary protection of the immunized individuals, not permanent elimination of the virus and therefore the disease.

Herpes virus is the most commonly identified agent of sporadic encephalitis (19). Herpes simplex virus (HSV) 1 and 2 are ubiquitous; following initial infection, primarily via the mucous membranes, the virus generally establishes permanent residence in the innervating dorsal root ganglion neurons. Periodically the virus will migrate back down the axon, causing a recurrent cutaneous eruption. A similar mechanism is thought to underlie HSV1 encephalitis. The sensory neurons of the trigeminal nerve, which innervate the lips, also innervate the meninges of the middle and anterior cranial fossa. Experimentally, reactivating virus can be shown to migrate centrally, affecting the medial temporal and frontal lobes, the primary site of involvement in herpes simplex encephalitis.

HSV1 encephalitis is potentially a devastating illness with mortality approaching 90% in the pretreatment era. Initial presentation can be as a nonspecific febrile prodrome with headaches. Often mild personality changes are noted for a few days. Two important (and probably interrelated) functions of the medial temporal lobes are olfaction and memory. Early manifestations of this necrotizing, localized infection often consist of focal seizures manifest as olfactory hallucinations and perceptions of déjà vu or jamais vu. Often a diagnosis is not made until the patient has a generalized or at least focal motor seizure.

The diagnosis should be considered in a previously healthy individual with abrupt onset of altered mental status and fever; headache is present in most. Clinically evident seizures are a presenting symptom in up to half. Since other brain infections can be clinically similar, confirmatory testing is necessary. Imaging, particularly MRI scans, classically will demonstrate changes in the medial temporal lobes, though this may take a few days to be evident. EEG can show paroxysmal periodic discharges—but again usually only after several days. CSF examination is the most helpful—although cases have been reported in which CSF is initially normal; typically it shows a modest lymphocytic pleocytosis with a significant number of erythrocytes, and mild hypoglycorrhachia. Most importantly, CSF PCR for herpes viruses is highly sensitive and specific.

Speed is of the essence in treating HSV encephalitis—there is a much higher probability of successful outcome if treatment is initiated when the patient is awake and unimpaired than if it can only be started when the patient is comatose (20). Therefore it is common practice to perform an MRI and lumbar puncture rapidly, initiate treatment immediately, and then stop treatment if PCR and other testing do not support the diagnosis. Treatment consists of acyclovir 10 mg/kg every 8 hours for 21 days. Its major complication is renal toxicity; this risk can be decreased with aggressive hydration. However the requisite fluid load can be somewhat problematic since patients with HSV encephalitis frequently develop significant hyponatremia and significant cerebral edema, both requiring fluid restriction. Most patients require anticonvulsants. The role of steroids is unclear, without substantial evidence supporting their use.

#### *Other Herpes Viruses*

Neurologic complications used to accompany about 1 of every 10,000 cases of chickenpox (19). With widespread vaccination, this is now rarely seen. Cytomegalovirus can cause

ventriculoencephalitis and dementia in the immunocompromised. HSV6 can cause encephalitis similar to HSV1 and has been associated with febrile seizures in infants. Epstein–Barr virus has been associated with a similar clinical picture, but has not been shown to respond to acyclovir or other antivirals.

### *West Nile Virus*

With over 1,200 cases of neuroinvasive disease in 2007 (21), West Nile virus is now probably the commonest cause of encephalitis in the United States (with virtually the same number of cases as there are due to HSV1). Unlike herpes, West Nile is one of the large group of diseases referred to as arthropod borne, or arboviruses. These agents, which include the equine encephalitis viruses, Venezuela, St. Louis, and others, share the ability to infect multiple species. West Nile appears to have been brought to the United States by infected birds and was originally recognized for being highly lethal in some but not all bird species.

Key to the transmissibility of any of these infections is its production of prolonged viremia in some host species, and the presence of mosquitoes or other vectors that feed on both the infected reservoir species and on humans (22). This interspecies promiscuity is essential to the transmission of this large group of pathogens, which can persist in the environment in reservoir hosts, and periodically infect humans when a large group of nonimmune individuals is exposed. Since there are hundreds of asymptomatic or minimally symptomatic infections for every neuroinvasive case, “herd immunity” normally takes over after the infection is present in the environment for a period of time—presumably the reason the incidence of cases has moved like a wave across the United States from east to west since its initial introduction.

West Nile is a flavivirus (the family that includes and is named for Yellow Fever virus), a broad group that includes dengue, tick borne encephalitis, Japanese encephalitis, and St. Louis encephalitis viruses. It was first detected in North America in 1999. In the Middle East, serologic studies indicate up to 40% of the population has had asymptomatic infection. Studies in the United States suggest 80% of infections are asymptomatic with most of the remainder developing nonspecific symptoms with fever, head and back pain, and GI symptoms all occurring with some frequency. Neuroinvasive disease develops in fewer than 1% of infected individuals. Mortality among these is about 10%. Disease severity increases with age, with most mortality occurring in individuals over 50. Over half the survivors of neuroinvasive disease have sequelae (22).

Neuroinvasive disease causes meningitis; a polio-like syndrome of flaccid lower motor neuron-type weakness occurs in about half. Involvement of the brainstem and basal ganglia appears to be common with extrapyramidal syndromes, tremors and ataxia occurring with some frequency. Patients often have a peripheral leucopenia and CSF lymphocytosis. Diagnosis is by serologic testing [IgG (immunoglobulin G) and IgM (immunoglobulin M) antibodies in serum and CSF] and PCR. MRIs have shown abnormalities in the spinal cord, brainstem, and basal ganglia. No specific treatment is available.

### *Rabies*

Fortunately human rabies is extremely rare in the United States, with typically 1 case per year nationwide. However there is a significant incidence among animals, and when human cases occur, there often is some delay in diagnosis, resulting in additional individuals being exposed, and then requiring prophylaxis. This too is a zoonosis, existing in innumerable mammalian species. Transmission requires transfer of virus-containing secretions or tissue through mucosa or broken skin. Since the virus has an affinity for the muscle endplates, infection is particularly efficient when a bite introduces the virus directly into muscle. Once introduced, virions are transported within axons to the dorsal root ganglion neurons and multiply, then on to the spinal cord and brainstem. This asymptomatic incubation period lasts weeks to years (23). Once the virus is in the nervous system, patients develop fever, anxiety, muscle aches, and nonspecific symptoms. Neuropathic symptoms ranging from itching to pain may develop at the inoculation site. Ultimately patients develop either paralytic rabies or the encephalitic form. In the former, patients develop a Guillain Barre-like picture, with fever, sensory and motor symptoms, facial involvement, and sphincter dysfunction. More common is the encephalitic form in which patients develop inspiratory spasms, precipitated by any

contact with the face, including trying to drink (hydrophobia). Hallucinations and fluctuating consciousness proceed to coma, paralysis, and death within a week.

Diagnosis can be challenging. Presence of antibodies in serum (if unvaccinated) or CSF is diagnostic but not terribly sensitive. Immunofluorescence can often detect virus in nerve twigs surrounding hair follicles in skin biopsied from the nape of the neck. PCR has been used to detect virus in saliva. Despite numerous attempts at treatment, only one or two individuals have survived (24).

### ENCEPHALITIS MIMICS

Mental status changes are common in many patients with systemic infections, particularly in older individuals—typically in the absence of nervous system infection. Confusional states in septic patients—even with sources as localized as urinary tract infections or pneumonia—are so commonplace that clinicians rarely question the underlying pathophysiology. However in some infections CNS changes can be disproportionately prominent; in these a number of mechanisms may underlie these changes.

Patients with rickettsia [particularly Rocky Mountain spotted fever (RMSF)] and ehrlichia/anaplasma (particularly human monocytic and granulocytic ehrlichiosis) infections can have severe headaches and prominent mental status changes. In both, the disorder caused by these intracellular organisms probably is less an encephalitis than an infectious vasculitis. RMSF in particular can be associated with significant cerebral edema and stupor. CSF typically demonstrates a modest lymphocytic pleocytosis and increased protein; CSF glucose is most often normal. Autopsy studies demonstrate perivascular inflammatory infiltrates and occasionally intravascular thrombi in the brain, pathologic changes that could easily explain the seizures that sometimes accompany RMSF. Focal CNS findings are relatively infrequent in patients with these infections and survivors typically do not have prominent neurologic sequelae. Whether ehrlichia infections have significant neurologic involvement remains unclear—although headaches and alterations of consciousness are described frequently, only a few case reports have described focal brain abnormalities.

Diagnosis can be quite challenging. Organisms can sometimes be identified in buffy coat isolates, using special stains. Serologic studies using immunofluorescence or ELISA can be useful but titers may be negative very early in infection and often comparison of acute and convalescent sera is necessary for diagnosis. Treatment with doxycycline is quite effective.

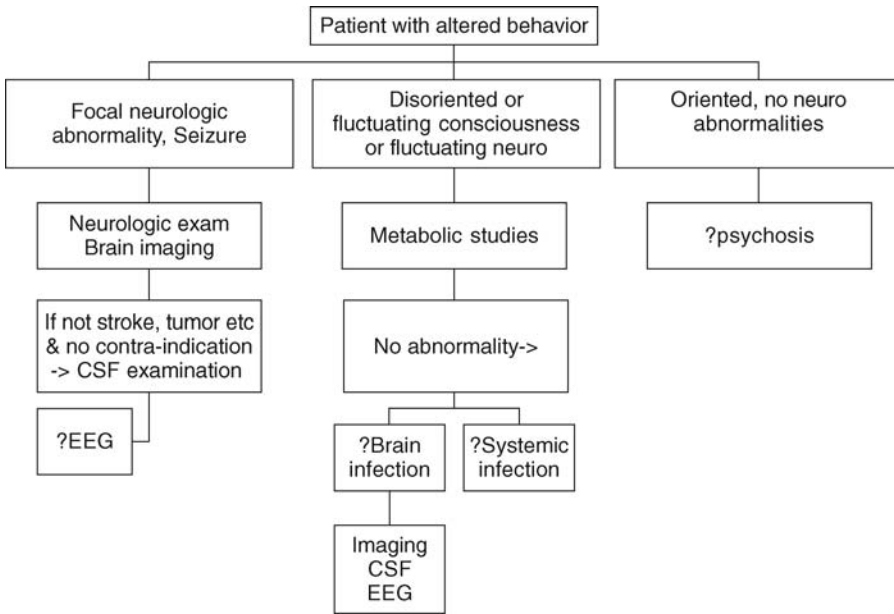
Legionnaire's disease similarly does not infect the brain but causes altered cognitive function with remarkable frequency—out of proportion to any associated hypoxia or other metabolic abnormalities. This infection can often be suspected clinically by its multisystem involvement—often with prominent early gastrointestinal symptoms (diarrhea and abdominal pain), bradycardia, and hepatic and renal involvement. Diagnosis typically rests on the combination of rapidly worsening changes on chest radiograms, and either serologic or urinary antigen testing.

Patients with bacterial endocarditis similarly can have CNS manifestations related more to involvement of the cerebral vasculature than of the brain itself. Signs and symptoms are typically nonspecific—except when a septic embolism causes either a stroke or a mycotic aneurysm that ruptures. CSF examination can demonstrate minor abnormalities. Diagnosis can be quite challenging.

Similarly, noninfectious inflammatory disorders can affect the CNS—most prominently CNS systemic lupus erythematosus. Again, findings are typically nonfocal; either on exam or imaging, but cerebral edema can be prominent. Since many of these patients are on chronic immunosuppression, one of the greatest diagnostic challenges can be differentiating between insufficiently controlled lupus or a superimposed opportunistic infection in an immunocompromised patient.

### DIAGNOSTIC APPROACH

Given the broad array of disorders, what is the most straightforward approach to the ill patient with altered mental status? As illustrated in Figure 1, the first step is a clinical assessment, focusing on the history. What were the earliest symptoms and how did the disorder evolve? If neurologic involvement is evident from the outset (seizures, persisting focal deficits), the



**Figure 1** Clinical approach to the patient with altered brain function.

possibility of neurologic disease must be assessed simultaneously with the assessment of the patient's overall medical status.

A general examination should initially focus on vital signs—remembering that fever may not be evident at either end of the age spectrum or in those with compromised immunity. The examination must seek evidence of pulmonary, hepatic, or renal compromise. Finally, a limited neurologic assessment, focusing on language, orientation, and cranial nerve function is essential. Key biochemical markers, including glucose, sodium, liver and renal function and, if relevant, blood gases, should similarly be assessed immediately. If none of this reveals significant extra-neurologic disease, focus should shift to the nervous system.

If either the history or examination suggests a primary CNS process, brain imaging (usually, in the interest of timeliness, with computerized tomography) is usually rapidly completed. If this does not demonstrate significant focal mass effect, and the picture does not clearly suggest a noninfectious cause, a lumbar puncture should be performed. Spinal fluid studies should include cell count, differential, protein, glucose (with simultaneous blood glucose!), bacterial culture, and Gram stain. Depending on the context, additional studies may include mycobacterial cultures and PCR, fungal cultures, CSF RPR, paired serum and CSF Lyme serologies, PCR for herpes viruses, serologic and PCR testing for West Nile virus, etc. Blood cultures should normally be obtained as well if there is serious consideration of a nervous system bacterial infection. Initial treatment is often started empirically, depending on context, to cover likely pathogens.

## CONCLUSIONS

Although alterations of nervous system function can arise from a broad range of disorders, a logical clinical approach can lead to rapid diagnosis in most. Fortunately CNS infection is statistically rare. However, when encephalitis does occur, its results can be devastating; generally the earlier the treatment can be initiated the better the likelihood of a favorable outcome.

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# 10 | Severe Community-Acquired Pneumonia in Critical Care

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## INTRODUCTION

Community-acquired pneumonia (CAP) may present as mild, moderate, or severe pneumonia. Patients with severe CAP require hospital admission and usually are admitted to the critical care unit (CCU). Patients with severe CAP in the CCU usually are those with compromised respiratory function requiring ventilatory support. In immunocompetent patients, severe CAP is clinically severe primarily because of the underlying cardiopulmonary status of the patient. While some pathogens are inherently more virulent than others, e.g., *Legionella* is more virulent than *Moraxella catarrhalis*, clinical severity is primarily determined by host rather than microbial factors. A patient with Legionnaire's disease and good cardiopulmonary function may present with severe CAP just as a patient with severe chronic obstructive pulmonary disease (COPD) with *M. catarrhalis* CAP. Patients with various degrees of hyposplenism often present with severe CAP (1–7).

CAP may occur in normal or compromised patients, the clinical approach to determine the cause of severe CAP depends on assessing the cardiopulmonary status, degree of splenic dysfunction, and identifying the disorders associated with specific immune defects. Analysis of host defense defects by history is combined with the chest X Ray (CXR)/CT scan's distribution of infiltrates and degree of hypoxemia (1,8). After noninfectious causes of severe CAP are ruled out (i.e., mimics of CAP), the physician should then consider those patients who might have CAP and a noninfectious disorder (8–10).

Empiric therapy depends upon knowing the usual pathogens associated with specific immune defects. A cardinal principle of empiric antimicrobial therapy is that severe CAP should be treated the same way as non-severe CAP in terms of antibiotic selection. However, patient with severe CAP may have a longer length of stay (LOS), strong clinical course, and may require prolonged antibiotic therapy. Therapy is continued as the diagnostic workup is in progress. If the causative pathogen is identified, there is no rationale for changing the antibiotics to one with a narrower spectrum. Antibiotic resistance potential is related to specific antibiotics and is not related to antibiotic class. Changing to a narrow-spectrum antibiotic has no effect on antibiotic resistance, i.e., with *Streptococcus pneumoniae* CAP, there is no rationale to change from ceftriaxone to penicillin because of a narrower spectrum. Therapy of severe CAP is usually for two to three weeks in total (10–12).

## DETERMINANTS OF SEVERE CAP

### Microbial Virulence

The clinical spectrum of *S. pneumoniae* CAP ranges from mild in young ambulatory adults, to fulminating, overwhelming sepsis in asplenic. Because of advanced lung disease, even low-virulence organisms, e.g., *M. catarrhalis*, may precipitate borderline, already-compromised respiratory function. *M. catarrhalis*, in a patient with severe COPD and may present as severe CAP. More than microbial virulence, host factors are the key determinants of the clinical presentation of severe CAP (Table 1).

Secondary bacteremias associated with CAPs are reflective of the bacteremic potential of the organism, and are not per se a marker of clinical severity. Bacteremia frequently accompanies *S. pneumoniae* or *Hemophilus influenzae* CAP and is part of the clinical presentation and is not related to CAP severity (1,13–20).

**Table 1** Determinants of Severe CAP

Microbial/host factors	Host defense factors
<p>Microbial factors</p> <ul style="list-style-type: none"> <li>• <i>Bacterial virulence</i> <i>Legionella</i> <i>S. pneumoniae</i></li> <li>• <i>Encapsulated organisms</i> <i>S. pneumoniae</i> <i>K. pneumoniae</i></li> <li>• <i>Viral virulence</i> Influenza A Avian influenza (H5N1) Swine influenza (H1N1) SARS HPS</li> </ul> <p>Pulmonary factors</p> <ul style="list-style-type: none"> <li>• <i>Decreased functional lung capacity</i> Emphysema</li> <li>• <i>Advanced lung disease</i> Chronic bronchitis Chronic bronchiectasis Interstitial fibrosis</li> </ul> <p>Cardiac factors</p> <ul style="list-style-type: none"> <li>• <i>CHF</i></li> <li>• <i>Severe valvular disease</i></li> <li>• <i>Severe cardiomyopathy</i></li> <li>• <i>CAD</i></li> </ul> <p>Systemic factors</p> <ul style="list-style-type: none"> <li>• <i>Advanced age (CNS/esophageal dysfunction)</i></li> <li>• <i>Hepatic insufficiency</i></li> <li>• <i>Renal insufficiency</i></li> </ul>	<p><i>Impaired B-lymphocyte function/Hi</i></p> <ul style="list-style-type: none"> <li>• Disorders associated with ↓ HI SLE Multiple myeloma Cirrhosis Hyposplenism Asplenia</li> </ul> <p><i>Impaired T-lymphocyte function CMI</i></p> <ul style="list-style-type: none"> <li>• Disorders associated with ↓ CMI T-cell lymphomas High-dose/chronic steroid therapy Immunosuppressive therapy TNF-<math>\alpha</math> antagonists HIV</li> </ul> <p><i>Impaired combined B-/T-lymphocyte function (HI/CMI)</i></p> <ul style="list-style-type: none"> <li>• Disorders associated with ↓ HI and ↓ CMI CLL SLE with flare SLE with flare/immunosuppressive therapy Advanced age</li> </ul>

*Abbreviations:* SLE, systemic lupus erythematosus; CLL, chronic lymphocytic leukemia; CAP, community-acquired pneumonia; CHF, congestive heart failure; HI, humoral immunity, CAD, coronary artery disease; CNS, central nervous system; CMI, cell-mediated immunity.

### Pulmonary Factors

Elderly adults with decreased lung function have diminished pulmonary reserve, and decompensation of pulmonary function may occur with superimposed CAP. In patients with advanced lung disease/borderline pulmonary function, even relatively avirulent organisms causing CAP may present as severe CAP since lung function is a key determinant of CAP severity (1,2,10–21).

### Cardiac Factors

Cardiac decompensation is common in patients with CAP with borderline cardiac function. The fever from CAP increases the heart rate and alone may be sufficient to precipitate congestive heart failure (CHF) or acute myocardial infarction (MI). The heart rate increases 10 beats per minute for each degree (Fahrenheit) of temperature elevation above normal. Fever often precipitates CHF, increasing the clinical presentation of severe CAP. Cardiac decompensation also results in diminished oxygenation secondary to decreased ejection fraction in patients with CAP, which may exacerbate CHF/precipitate an acute MI (2,10,22–25).

### Cardiopulmonary Factors

The heart and lung are physiologically interrelated and decompensation of one will adversely affect the other. Elderly patients often have advanced lung and heart disease. Elderly patients with CAP, with limited cardiopulmonary reserve, often present clinically as severe CAP (1,2,5,9,10,26).

**CLINICAL APPROACH TO SEVERE CAP**

**Normal Hosts**

Normal hosts presenting with severe CAP are those with impaired cardiac/pulmonary function. The most common cardiopulmonary disorders likely to present as severe CAP are CHF, cardiomyopathies, or severe valvular disease. The most common pulmonary causes associated with a severe CAP presentation are COPD, chronic bronchiectasis, interstitial pulmonary disease/pulmonary fibrosis. These conditions are readily diagnosed by history/physical examination. The CXR appearance/distribution of infiltrates complements the history and physical examination in determining the nature/severity of impaired lung/cardiac function. In patients with good cardiopulmonary function and severe CAP, the clinician should consider immune defects or pathogen virulence to explain CAP severity (1,2,8,10) (Tables 2 to 7).

**Disorders with Associated Immune Defects Determines Probable CAP Pathogens**

Compromised hosts, like normal patients, are most often due to the usual CAP pathogens. However, clinical severity may be increased due to compromised host defenses. Compromised hosts have specific immune defects that predispose to a relative few, not many potential

**Table 2** Diagnostic Approach to Severe CAP with Hypotension/Shock

Infectious causes	Noninfectious with infectious causes
<ul style="list-style-type: none"> <li>● CAP (with hyposplenism)<sup>a</sup></li> <li>● CAP (with asplenia)<sup>b</sup></li> <li>● Zoonotic CAP (tularemia, plague, Q fever)</li> <li>● Human influenza A</li> <li>● Avian influenza (H5N1)</li> <li>● Swine influenza (H1N1)</li> <li>● Severe influenza A (with <i>S. aureus</i> CAP)</li> <li>● SARS</li> <li>● HPS</li> <li>● Adenovirus</li> <li>● CMV<sup>c</sup></li> <li>● PCP</li> </ul>	<ul style="list-style-type: none"> <li>● Acute MI (with CAP)</li> <li>● Acute gastrointestinal bleed (with CAP)</li> <li>● Acute pancreatitis (with CAP)</li> <li>● Advanced lung disease (with CAP)</li> <li>● Severe CAD, severe cardiomyopathy, or severe valvular disease (with CAP)</li> </ul>
Infectious mimics of CAP	Noninfectious mimics of CAP
<ul style="list-style-type: none"> <li>● TV ABE with septic pulmonary emboli</li> <li>● Anthrax hemorrhagic mediastinitis</li> </ul>	<ul style="list-style-type: none"> <li>● ARDS</li> <li>    Due to pegylated interferon-<math>\alpha</math></li> <li>    Due to TNF-<math>\alpha</math> antagonists</li> <li>    Due to acute pancreatitis</li> </ul>

<sup>a</sup>Howell–Jolly bodies on peripheral blood smear. Look for disorders associated with hyposplenism (see Table 3).

<sup>b</sup>Surgically removed or congenitally absent.

<sup>c</sup>In normal hosts.

*Abbreviations:* CAD, coronary artery disease; MI, myocardial infarction; SARS, severe acute respiratory syndrome; CMV, cytomegalovirus; ARDS, acute respiratory distress syndrome; TV, tricuspid valve; ABE, acute bacterial endocarditis; TNF, tumor necrosis factor; HPS, hantavirus pulmonary virus.

**Table 3** Severe CAP Presenting with Hypotension/Shock Disorders Associated with Functional/Anatomic Hyposplenism

Splenic disorders	Extra-splenic disorders
<ul style="list-style-type: none"> <li>● Splenectomy</li> <li>● Congenital asplenia</li> <li>● Splenic atrophy</li> <li>● Impaired splenic blood flow</li> <li>● Amyloidosis</li> <li>● Infiltrative disorders of the spleen</li> </ul>	<ul style="list-style-type: none"> <li>● Sickle cell anemia</li> <li>● Hemoglobin SC disease</li> <li>● Graft-versus-host disease</li> <li>● Rheumatoid arthritis</li> <li>● SLE</li> <li>● Cirrhosis</li> </ul>

*Abbreviation:* SLE, systemic lupus erythematosus.

**Table 4** Clinical Approach to Severe CAP

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I. Presumptive diagnosis of severe CAP
• Initial CXR
• Assess clinical severity
• Sputum/blood cultures
• Ventilatory and vital organ support
II. Consider disorders that mimic severe CAP
• Chest CT scan to r/o CAP and limit differential diagnostic mimics of severe CAP
• Treat medical disorders mimicking severe CAP
III. Consider severe CAP presentation due to noninfectious mimics of CAP superimposed on mild/moderate CAP
• <i>Initiate therapy for treatable medical disorders mimicking severe CAP</i>
• <i>Also, treat underlying mild/moderate CAP</i>
IV. Empiric therapy of severe bacterial CAP
• Initiate empiric antibiotic therapy
• Order additional diagnostic laboratory tests to identify specific CAP pathogens
• Select an agent active against both typical/atypical CAP pathogens
Moxifloxacin or levofloxacin
Tigecycline
Ceftriaxone <i>plus</i> doxycycline or azithromycin
• If influenza A pneumonia with early focal/segmental infiltrates and rapid cavitation <72 hours (MSSA/CA-MRSA CAP)
Linezolid
Tigecycline
• If influenza A pneumonia with improvement after 5–7 days, followed by late focal/segmental infiltrates
Moxifloxacin or levofloxacin
Ceftriaxone

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*Abbreviations:* CAP, community-acquired pneumonia; CXR, chest X ray; CT, computed tomography.

pathogens causing CAP. It is a common clinical misconception that because a patient is immunocompromised, the pathogen range is extensive. Excluding the usual CAP pathogens also seen in normal hosts, the range of pathogens in compromised hosts is defined and limited by the immune defect, i.e., CAP patients with multiple myeloma are prone to CAP due to typical encapsulated bacterial pathogens not viruses, *Rickettsia*, or parasites. If the clinician has determined by history/laboratory tests that the patient has multiple myeloma, then the pathogens are predictable and not extensive or unusual. The clinical approach, therefore, rests on the relationship between the disorders, which is the determinant of the immune defect, which, in turn determines the potential pathogen. The range of potential pathogens determines what constitutes appropriate empiric antimicrobial coverage in normal/immunocompromised patient with severe CAP (1,2,8,9,10).

### **Disorders Associated with Impaired B-Lymphocyte/Humoral Immunity (HI)**

The disorders associated with impaired B-lymphocyte function are those that decrease humoral immunity (HI). The pathogens predisposed to by impaired B-lymphocyte function are the same regardless of the underlying disorder. CAP pathogens associated with impaired HI are the encapsulated pulmonary pathogens, i.e., *S. pneumoniae*, *H. influenzae*. The conditions associated with decreased HI commonly encountered in clinical practice include disorders with hyposplenias/asplenia, multiple myeloma, cirrhosis, systemic lupus erythematosus (SLE), and chronic lymphocytic leukemia (CLL) [a combined B-/T-lymphocyte disorder—HI > CMI (cell-mediated immunity)]. The degree of hyposplenism may be inferred from the CBC by noting the concentration of Howell–Jolly bodies (percentage) in the peripheral smear. The number of Howell–Jolly bodies is inversely proportional to the degree of splenic dysfunction. The most common clinical presentation of CAP associated with hyposplenism is an “apparently normal” host with good cardiopulmonary function that presents as otherwise unexplained severe CAP. Severe CAP always has an underlying cardiopulmonary/virulent pathogens aside, immunologic explanation. Patients presenting with CAP and hypotension/shock have either impaired splenic function, influenza alone or with

superimposed *Staphylococcus aureus* pneumonia, or unrelated systemic disorder causing hypotension/shock, i.e., acute MI, pulmonary embolus, etc. Virulent viral/zoonotic pathogens aside, normal hosts do not present with severe CAP with hypotension/shock (1,8–10,26–30) (Tables 5 to 7).

**Table 5** Epidemiologic Clues to the Etiology of Severe CAP

Epidemiologic clues <sup>a</sup>	CAP pathogen associations
<ul style="list-style-type: none"> <li>● Air travel</li> </ul>	Legionnaire's disease Human influenza A Avian influenza (H5N1) Swine influenza (H1N1)
<ul style="list-style-type: none"> <li>● Rodent exposure</li> </ul>	SARS HPS Plague Tularemia
<ul style="list-style-type: none"> <li>● Deer/rabbit/ticks</li> <li>● Birds/poultry</li> <li>● Closed populations/crowded exposures</li> <li>● Cats</li> </ul>	Avian influenza (H5N1) Adenovirus Q fever Tularemia Plague
<ul style="list-style-type: none"> <li>● Pigs</li> <li>● Construction/water/air conditioning</li> <li>● HIV/organ transplants/immunosuppressive drugs/steroids</li> </ul>	Swine influenza (H1N1) Legionnaire's disease PCP Legionnaire's disease

<sup>a</sup>Recent close contact history.

**Abbreviations:** SARS, severe acute respiratory syndrome; CAP, community-acquired pneumonia; HPS, hantavirus pulmonary syndrome; PCP, *Pneumocystis (carinii) jiroveci* pneumonia.

**Table 6** Clinical Clues to the Causes of Severe CAP

Clinical clues	CAP pathogen associations
<ul style="list-style-type: none"> <li>● Hyperacute onset</li> </ul>	Human influenza A Avian influenza (H5N1) Swine influenza (H1N1) SARS Tularemia
<ul style="list-style-type: none"> <li>● Afebrile</li> <li>● Relative bradycardia</li> </ul>	Plague Legionnaire's disease Q fever
<ul style="list-style-type: none"> <li>● Severe myalgias</li> </ul>	Human influenza A Avian influenza (H5N1) Swine influenza (H1N1)
<ul style="list-style-type: none"> <li>● Mental confusion</li> <li>● Prominent headache</li> </ul>	Legionnaire's disease Tularemia Q fever
<ul style="list-style-type: none"> <li>● Conjunctival suffusion</li> </ul>	Adenovirus Human influenza A
<ul style="list-style-type: none"> <li>● Sore throat</li> </ul>	Avian influenza (H5N1) Swine influenza (H1N1) SARS
<ul style="list-style-type: none"> <li>● <i>H. labialis</i></li> <li>● Chest pain</li> </ul>	<i>S. pneumoniae</i>
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Substernal</li> <li>Pleuritic</li> </ul> </li> </ul>	HPS Human influenza A
<ul style="list-style-type: none"> <li>● Watery diarrhea/abdominal pain</li> </ul>	Legionnaire's disease Swine influenza (H1N1)
<ul style="list-style-type: none"> <li>● Splenomegaly</li> </ul>	Q fever CMV

**Abbreviations:** SARS, severe acute respiratory syndrome; CAP, community-acquired pneumonia; CMV, cytomegalovirus; HPS, hantavirus pulmonary syndrome.

**Table 7** Nonspecific Laboratory Clues to the Etiology of Severe CAP

Nonspecific laboratory test clues	CAP pathogen associations
<ul style="list-style-type: none"> <li>● Leukopenia</li> </ul>	Human influenza A, avian influenza (H5N1), swine influenza (H1N1), SARS, adenovirus, CMV
<ul style="list-style-type: none"> <li>● Relative lymphopenia</li> </ul>	PCP, Legionnaire's disease, adenovirus, CMV, SARS, human influenza A, avian influenza (H5N1), swine influenza, HPS
<ul style="list-style-type: none"> <li>● Acute thrombocytopenia</li> </ul>	Adenovirus, CMV, SARS, HPS, human influenza A, avian influenza (H5N1), swine influenza (H1N1)
<ul style="list-style-type: none"> <li>● Acute thrombocytosis</li> <li>● ↑↑↑ LDH</li> </ul>	Q fever, <i>M. pneumoniae</i> PCP Avian influenza (H5N1)
<ul style="list-style-type: none"> <li>● ↑↑↑ Ferritin levels</li> <li>● ↓ Serum sodium</li> <li>● ↓ Serum phosphorus</li> <li>● ↑ Cold agglutinins</li> </ul>	Legionnaire's disease Legionnaire's disease Legionnaire's disease <i>M. pneumoniae</i> Adenovirus Q fever
<ul style="list-style-type: none"> <li>● ↑ SGOT/SGPT</li> </ul>	Legionnaire's disease, Q Fever, CMV, adenovirus, HPS, SARS, human influenza A, avian influenza (H5N1), swine influenza (H1N1)

Abbreviations: CAP, community-acquired pneumonia, SARS, severe acute respiratory syndrome; PCP, *Pneumocystis (carinii) jirovecii* pneumonia; CMV, cytomegalovirus; HPS, hantavirus pulmonary syndrome.

### Disorders Associated with Impaired T-Lymphocyte Function (CMI)

Patients with impaired T-lymphocyte/macrophage function have decreased CMI. Disorders associated with impaired CMI predispose to CAP due to intracellular pathogens, i.e., viruses, *Rickettsiae*, systemic mycoses, and intracellular bacteria. Impaired CMI does not, per se, predispose to bacterial CAP pathogens. However, all compromised hosts may be infected with the same usual CAP pathogens of normal hosts. Therefore, the intracellular pathogens associated with severe CAP with decreased CMI are predominantly intracellular pathogens, i.e., *Pneumocystis (carinii) jirovecii* (PCP), cytomegalovirus (CMV), and *Legionella*. The most common disorders associated with decreased CMI include chronic/high-dose corticosteroid therapy, immunosuppressive therapy, TNF- $\alpha$  antagonists, organ transplants, and HIV. As mentioned previously, CLL is an example of an acquired combined B-/T-lymphocyte defect with impaired HI greater than CMI (1,8,10,31–35).

### Disorders Associated with Impaired B/T-Lymphocyte Function (HI/CMI)

Excluding CLL, most disorders with combined immune defects are those with underlying B-lymphocyte disorders combined with an immunosuppressant drug which, in addition, decreases CMI, i.e., inflammatory bowel disease treated with monoclonal antibody therapy, steroids, or immunosuppressives, etc. The clinician should appreciate the additive effects of combined immune defects. For example, SLE is a pure B-lymphocyte defect with decreased HI, but SLE patients with flare resemble CLL with predominantly impaired HI and decreased CMI. However, SLE patients with flare on corticosteroids/immunosuppressive therapy add to the "net immunosuppression" further impairing CMI markedly impaired T-lymphocyte function not unlike that of transplant patients (1,4,17,36,37).

### DISORDERS ASSOCIATED WITH DECREASED POLYMORPHONUCLEAR CELL FUNCTION (PMN)

Chemotherapy is often associated with neutropenia. When the peripheral WBC count is less than 1 K/mm<sup>3</sup>, the incidence of infection greatly increases. Neutropenia predisposes to *Pseudomonas aeruginosa* bacteremia or aerobic gram-negative bacilli (GNB) bacteremias. Patients with prolonged neutropenia (>1 week) are predisposed to *Aspergillus* sp. or *Candida* sp. However, even though their WBC counts are very low, neutropenic patients present with bacteremia or fungemia rather than *P. aeruginosa* CAP (2,8,10).

## CLINICAL APPROACH TO SEVERE CAP BY CXR PATTERN AND DEGREE OF HYPOXEMIA

Normal hosts with CAP and without significant preexisting cardiopulmonary disease usually are due to typical pulmonary pathogens and present with segmental/lobar defects with/without pleural effusion. Pleural effusion is pathogen dependent and is most common with CAP due to group A streptococci, less commonly with *H. influenzae*, and very uncommon with *S. pneumoniae*. CAP with ill-defined non-segmental/lobar infiltrates usually due to atypical CAP organisms, i.e., *Mycoplasma pneumoniae*, which may present as severe CAP in compromised hosts. Characteristically, *Legionella* presents radiographically with rapidly progressive bilateral asymmetric infiltrates. Importantly, it is the behavior of the CXR infiltrates rather than the location/description of the infiltrates per se, which suggests the possibility of Legionnaire's disease (1,8,10).

Excluding Legionnaire's disease, CAP patients' bilateral infiltrates, which are primarily perihilar/interstitial, are not a radiographic feature of the usual typical/atypical CAP pulmonary pathogens. Bilateral symmetrical/interstitial infiltrates suggest an intracellular pathogen, e.g., PCP, CMV, influenza A, avian influenza (H5N1), or swine influenza (H1N1) (Tables 8,9). Excluding CAP mimics, bilateral interstitial infiltrates CAP presenting as severe CAP are usually due to intracellular pathogens, i.e., viruses or PCP that are associated with various degrees of hypoxemia. A combination of bilateral perihilar/interstitial infiltrates, hypoxemia, a ↓ DLCO (carbon monoxide diffusing capacity)/↑ A-a gradient indicates an interstitial process, i.e., PCP or viral CAP. There are many noninfectious mimics of CAP that may present with bilateral infiltrates that are not infectious. In critical care, the common mimics of CAP in critical care include acute pulmonary edema (due to fluid overload/acute MI), pulmonary emboli/infarcts, SLE pneumonitis, pulmonary vasculitis, pulmonary drug reactions, bronchiolitis obliterans organizing pneumonia (BOOP), pulmonary leukostasis, pulmonary hemorrhage, and acute respiratory distress syndrome (ARDS). With the exception of viral pneumonias or PCP presenting as severe CAP, bacterial, fungal, or Rickettsial pneumonias may be accompanied by impressive pulmonary infiltrates but are *not* accompanied by severe hypoxemia, i.e., ↓ DLCO/↑ A-a gradient (>30) (1,8,10) (Tables 10–14).

### Severe CAP with Cavitation

Cavitation on the CXR/chest CT scan is an important diagnostic finding in determining the etiology of severe CAP. Acute cavitory CAPs are severe CAPs because cavitation indicates a necrotic/hemorrhagic pneumonia. The different diagnosis of severe CAP with cavitation may be approached clinically by the rapidity of the cavitory process. Cavitation is not a feature of *S. pneumoniae* or *H. influenzae* CAP. *S. pneumoniae* may be severe with cavitation, which may

**Table 8** Swine Influenza (H1N1) Pneumonia: Clinical Case Definitions in Adults<sup>†</sup>

#### Definite Swine Influenza (H1N1) Pneumonia (Laboratory Diagnosis)

ILI with temperature of >102°F and a CXR with no focal/segmental lobar infiltrates **plus one or more of these positive tests:**

- Rapid influenza A test
- Respiratory fluorescent antibody (FA) viral panel
- RT-PCR for swine influenza (H1N1)

#### Probable Swine Influenza (H1N1) Pneumonia (Clinical Diagnosis)

ILI with temperature >102°F and a CXR with no focal/segmental lobar infiltrates *with negative rapid influenza diagnostic tests* (RIDTs) (see above)\* **plus this diagnostic triad:**

- Severe myalgias
- Otherwise unexplained relative lymphopenia
- Elevated CPK

<sup>†</sup>During swine influenza (H1N1) pandemic and requiring hospitalization.

\*Diagnostic tests negative for other viral CAP pathogens (CMV, SARS, HPS, RSV, metapneumoviruses parainfluenza viruses, adenoviruses)

Source: Adapted from Ref. 10.

**Table 9** Swine Influenza (H1N1) Pneumonia: Winthrop-University Hospital Infectious Disease Division's Clinical Diagnostic Point Score System for Adults with Negative Rapid Influenza Diagnostic Tests (RIDTs)

<b>Adults with an ILI with fever &gt;102°F and a CXR with no focal/segmental lobar infiltrates with negative RIDTs plus this Diagnostic Triad<sup>†</sup>:</b>	
• Severe myalgias	+5
• Relative lymphopenia (otherwise unexplained*)	+5
• Elevated CPK (otherwise unexplained)	+5
<b>Consistent but not essential:</b>	
• Elevated serum transaminases (SGOT/SGPT)	+2
• Thrombocytopenia (otherwise unexplained)	+2
<b>Argues against the diagnosis of Swine influenza (H1N1) Pneumonia:</b>	
• Relative bradycardia (otherwise unexplained)	
• Leukopenia (otherwise unexplained)	
• Atypical lymphocytes	
• Highly elevated serum ferritin levels (>2 × n)	
• Hypophosphatemia (otherwise unexplained)	
<b>Swine influenza Diagnostic Point Score Totals:</b>	
Probable swine influenza (H1N1) =	>15
Possible swine influenza (H1N1) =	10–15
Unlikely swine influenza (H1N1) =	<10

<sup>†</sup>Diagnostic tests negative for other viral CAP pathogens (CMV, SARS, HPS, RSV metapneumoviruses, parainfluenza viruses, adenoviruses).

\*Other causes of relative lymphopenia: Infectious causes: CMV, HHV-6, HHV-8, HIV, military TB, Legionella, typhoid fever, Q fever, brucellosis, SARS, malaria, babesiosis, influenza A, avian influenza (H5N1), RMSF, histoplasmosis, dengue fever, chikungunya fever, ehrlichiosis, parvovirus B19, HPS, WNE, viral hepatitis, Noninfectious causes: cytotoxic drugs, steroids, sarcoidosis, SLE, lymphoma, RA, radiation therapy, Wiskott-Aldrich syndrome, Whipple's disease, severe combine immunodeficiency disease (SCID), common variable immune deficiency (CVID), Di George's syndrome, Nezelof's syndrome, intestinal lymphgiectasia, constrictive pericarditis, tricuspid regurgitation, Kawasaki's disease, idiopathic CD<sub>4</sub> cytopenia, Wegener's granulomatosis, acute/chronic renal failure, hemodialysis, myasthenia gravis, celiac disease, alcoholic cirrhosis, coronary bypass, CHF, acute pancreatitis, carcinomas (terminal).

Source: Adapted from Ref. 10.

**Table 10** Clinical Diagnostic Approach to Severe CAP with Bilateral Diffuse Pulmonary Infiltrates

With mild/moderate hypoxemia (↓ P <sub>O<sub>2</sub></sub> /N/↑ A-a gradient)	With severe hypoxemia (↓↓↓ P <sub>O<sub>2</sub></sub> /A-a gradient >35)
<ul style="list-style-type: none"> <li>• Aspiration pneumonia</li> <li>• Acute pulmonary edema</li> <li>• Typical bacterial pneumonias</li> <li>• Atypical bacterial pneumonias</li> <li>• Advanced pulmonary TB</li> <li>• Fungal pneumonias</li> <li>• Rickettsial pneumonias</li> <li>• Parasitic pneumonias<sup>a</sup></li> <li>• Radiation pneumonitis</li> <li>• Pulmonary drug reactions</li> <li>• Noncardiogenic pulmonary edema</li> <li>• Leukostasis</li> </ul>	<ul style="list-style-type: none"> <li>• PCP</li> <li>• CMV</li> <li>• HSV-1</li> <li>• HHV-6</li> <li>• Human seasonal influenza A</li> <li>• Avian influenza (H5N1)</li> <li>• Swine influenza (H1N1)</li> <li>• SARS</li> <li>• BOOP</li> </ul>

<sup>a</sup>excluding PCP.

**Abbreviations:** TB, tuberculosis; Pneumocystis (carinii) jiroveci pneumonia (PCP); CAP, community-acquired pneumonia; CMV, cytomegalovirus; HSV, herpes simplex virus; HHV, human herpes virus; BOOP, bronchiolitis obliterans with organizing pneumonia.

occur with HIV or TNF- $\alpha$  antagonists. Clinically, cavitation <72 hours occurring in a patient with CAP is limited to *S. aureus* or *P. aeruginosa* pneumonias (Table 12).

In adults, human seasonal influenza A may usually present as influenza pneumonia alone and less commonly with superimposed *S. aureus* pneumonia with focal segmental/lobar



**Table 11** Empiric Antibiotic Therapy of Severe CAP<sup>a</sup>

Severe CAP	Usual CAP pulmonary pathogens	Empiric antibiotic therapy
Normal hosts CXR: <i>focal/segmental infiltrates</i>	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i> Atypical CAP pathogens	Respiratory quinolone or ceftriaxone plus either <i>doxycycline</i> or <i>azithromycin</i>
Compromised hosts CXR: <i>focal/segmental infiltrates</i>		Respiratory quinolone or <i>ceftriaxone</i> plus either <i>doxycycline</i> or <i>azithromycin</i>
Disorders with ↓ B-lymphocyte function/HI with mild/moderate hypoxemia A-a gradient <35)	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. calarrhalis</i>	Respiratory quinolone or <i>doxycycline</i> or <i>azithromycin</i>
Disorders with ↓ T-lymphocyte function/CMI with mild/moderate hypoxemia A-a gradient <35)	<i>Legionella</i> Q fever	Respiratory quinolone or <i>doxycycline</i>
CXR: <i>diffuse bilateral symmetrical infiltrates</i> Mild/moderate hypoxemia (A-a gradient <35) Severe hypoxemia (A-a gradient >35)	Human seasonal Influenza <sup>b</sup> Avian influenza (H5N1) Swine influenza (H1N1) Adenovirus RSV HPS SARS CMV PCP	Oseltamivir ± amantadine          Ganciclovir TMP-SMX or pentamidine or atovaqone plus steroids

<sup>a</sup>Treat while r/o mimics of severe CAP.

<sup>b</sup>Influenza pneumonia with focal segmental/lobar infiltrates treat for MSSA/CA-MRSA (see Table 12).

*Abbreviations:* TMP-SMX, trimethoprim-sulfamethoxazole; HPS, hantavirus pulmonary syndrome; SARS, severe acute respiratory syndrome; CMV, cytomegalovirus; *Pneumocystis (carinii) jirovecii* pneumonia (PCP); RSV, respiratory syncytial virus.

**Table 12** Severe CAP with Infiltrates and Cavitation

*Rapid cavitation* (<3 days)<sup>a</sup>

- *S. aureus*<sup>a</sup> (MSSA/CA-MRSA<sup>b</sup>)

*Moderately rapid cavitation* (3 to 5 days)

- *K. pneumoniae*

*Slow cavitation* (>5 days)

- Aspiration pneumonia (oral anaerobes)

<sup>a</sup>only in patients with human seasonal influenza A pneumonia or an influenza-like illness (ILI).

<sup>b</sup>Only *S. aureus* and *P. aeruginosa* cause rapid cavitation in < 3 days. *P. aeruginosa* is not a CAP pathogen except with cystic fibrosis/chronic bronchiectasis.

*Abbreviations:* CAP: community-acquired pneumonia; MSSA, methicillin-susceptible *S. aureus*; CA-MRSA, community acquired methicillin-resistant *S. aureus*.

infiltrates. *S. aureus* (MSSA/CA-MRSA) CAP occurs only with influenza pneumonia and not alone. The third clinical presentation of influenza A pneumonia is that of initial influenza pneumonia followed by a period of improvement (~1 week), followed by *S. pneumoniae* or *H. influenzae* pneumonia with new fevers and focal/segmental infiltrates on CXR. Patients

**Table 13** MRSA Terminology

MRSA strain	Epidemiology and microbiology	Antibiotic therapy
HA-MRSA <sup>a</sup>	Strains <i>originate within the hospital</i> , have SCC <i>mec</i> , I, II < III genes, PVL gene (rare), and elaborate several <i>S. aureus</i> toxins.	Resistant to most antibiotics. Only vancomycin, quinupristin/dalfopristin, minocycline, linezolid, tigecycline, or daptomycin are <i>reliably</i> effective.
CO-MRSA <sup>a</sup>	Strains <i>originate in the hospital and later present (onset) from the community</i> , have SCC <i>mec</i> I, II, III genes, PVL gene (rare), and elaborate several <i>S. aureus</i> toxins.	CO-MRSA has <i>same susceptibility</i> as HA-MRSA and <i>should be treated</i> as HA-MRSA.
CA-MRSA	SCC <i>mec</i> IV, V genes, PVL gene, (common). CA-MRSA PVL-strains are <i>clinically indistinguishable</i> from MSSA or CO-MRSA. Elaborate the usual <i>S. aureus</i> toxins plus 18 other toxins. CA-MRSA (PVL+) present as MRSA pneumonia (with influenza) or severe pyomyositis. <i>Other MRSA from the community should be treated as considered as CO-MRSA.</i>	CA-MRSA susceptible to clindamycin, TMP-SMX, and doxycycline. Antibiotics for CO-MRSA/HA-MRSA are also effective against CA-MRSA, but <i>not vice versa</i> .

<sup>a</sup>Adapted from Refs. 34 and 35.

**Abbreviations:** CA-MRSA, community-acquired MRSA; CO-MRSA, community-onset MRSA; HA-MRSA, hospital-acquired MRSA; PVL, Panton–Valentine leukocidin; SCC, staphylococcal cassette chromosome.

**Table 14** Diagnostic Approach to the Clinical Presentations of Severe Human Seasonal Influenza A Pneumonia

Initial presentation of acute human seasonal influenza A pneumonia	Likely pathogens	Empiric antimicrobial therapy
Severe hypoxemia (A–a gradient >35)		None
<ul style="list-style-type: none"> <li>• <i>No infiltrates (early) or bilateral diffuse infiltrates (later)</i> on CXR/chest CT scan</li> </ul>	Influenza A (human, avian, swine)	Oseltamivir ± amantadine or rimantadine
<ul style="list-style-type: none"> <li>• <i>Focal/segmental infiltrates</i> on CXR/chest CT scan with rapid cavitation (&lt; 72 hours)</li> </ul>	Influenza A ± MSSA/CA-MRSA Avian influenza (H5N1) Swine influenza (H1N1)	if also MSSA/CA-MRSA CAP; tigecycline or linezolid
Initial presentation of human seasonal influenza A pneumonia followed by interval of improvement followed by bacterial CAP (5–7 days)		
Mild/moderate hypoxemia (A–a gradient <35)		
<ul style="list-style-type: none"> <li>• <i>Focal/segmental infiltrates</i> on CXR/chest CT scan</li> </ul>	<i>S. pneumoniae</i>  <i>H. influenzae</i>	Levofloxacin or moxifloxacin or ceftriaxone

**Abbreviations:** CAP, community-acquired pneumonia; CXR, chest X Ray; MSSA, methicillin-susceptible *S. aureus*; CA-MRSA, community-acquired methicillin-resistant *S. aureus*; CT, computed tomography.

presenting with influenza pneumonia A may have an unremarkable CXR early, even with hypoxemia present. Bilateral segmental interstitial infiltrates may appear in 48 hours and are accompanied by severe hypoxemia. *S. pneumoniae* and *H. influenzae* CAP following influenza A pneumonia sequentially after improvement are not, unlike *S. aureus*, accompanied by cavitation. However, if influenza pneumonia A presents simultaneously with focal/segmental infiltrates and rapid cavitation in <72 hours, the likely pathogen is *S. aureus* [methicillin-susceptible *S. aureus* (MSSA) or methicillin-resistant *S. aureus* (MRSA)] (Tables 13 and 14). Avian influenza (H5N1) pneumonia and swine influenza (H1N1) pneumonia have not been complicated by simultaneous subsequent bacterial pneumonia.

Normal hosts do not present with *P. aeruginosa* CAP. *P. aeruginosa* CAP is rare, nearly always fatal, and occurs virtually only in the setting of chronic bronchiectasis/cystic fibrosis (8,10).

With CAP, cavitation occurring after three to five days points to *Klebsiella pneumoniae* as the pathogen. *K. pneumoniae* occurs almost exclusively in patients with chronic alcoholism. Therefore, the clinical history plus the appearance of cavitation points to the diagnosis, easily confirmed by Gram stain/culture of the sputum/blood. *K. pneumoniae* CAP often presents as severe CAP. Acute CAP with cavitation after five to seven days is most often due to aspiration pneumonia. Unless the aspiration is bilateral/massive or if aspiration is superimposed upon already limited pulmonary function, such patients will not present as severe CAP (29,30,38). These patients usually present with CAP that becomes more severe as cavitation becomes apparent after more than one week with bilateral massive aspiration; the initial appearance of pneumonia on CXR of severe CAP is the usual clinical presentation (8,10).

### Empiric Therapy for Severe CAP

Appropriate empiric therapy depends upon identifying the most likely pathogen. The pathogen range is predictable by host factors (8,10,39). Severe CAP may present with focal/segmental infiltrates or bilateral interstitial infiltrates with/without accompanying hypoxemia. The patient's history is important in identifying previously diagnosed disorders associated with specific immune defects. Combined with the CXR, the appearance/distribution and the presence or absence of hypoxemia limits differential diagnostic possibilities (8,10,40,41).

An apparently normal host presenting with severe CAP with focal/segmental infiltrates should be treated for the usual typical and atypical CAP pathogens. Appropriate empiric therapy should be started as soon as the diagnosis of CAP is suspected (2,10,12,42–45).

Apparently, normal hosts presenting with near-normal CXR and profound hypoxemia should be considered as having viral influenza or PCP. If severe pneumonia occurs during influenza season, then influenza is a likely diagnostic possibility. A clue to otherwise-unsuspected HIV is often one or more isolated cytopenias, and PCP is likely if accompanied by an otherwise unexplained, highly elevated serum LDH. PCP is an HIV-defining illness and is not an uncommon cause of CAP in HIV patients. Patients on steroids/immunosuppressive therapy, and organ transplants, when present with acute CAP with focal/segmental infiltration not accompanied by severe hypoxemia should be treated for the usual pathogens affecting normal hosts with CAP. Empiric antibiotic therapy for CAP as in normal hosts should be initiated even when urine/fungal pathogens are suspected while the diagnostic workup proceeds. Because potential viral/fungal pathogens may be clinically indistinguishable, lung biopsy usually is needed for a specific diagnosis to determine optimal specific therapy. Immunosuppressed organ transplants presenting with bilateral symmetrical/interstitial infiltrates may be approached as those with mild/moderate hypoxemia versus those with severe hypoxemia. In such CAP patients, the absence of a significant diffusion defect (A–a gradient <35) suggests pulmonary hemorrhage, pulmonary embolus, or another noninfectious process. In those with bilateral infiltrates accompanied by a profound oxygen diffusion defect (A–a gradient >35) viral pneumonias or PCP are the most likely diagnostic infectious possibilities. The common noninfectious causes of bilateral pulmonary infiltrates with hypoxemia include BOOP and ARDS (1,8,10,47,48).

The clinicians should not use the “shot gun” approach to treating severe CAP cases based on the mistaken notion that there are many potential pathogens. The diagnostic process based on a syndromic approach utilizing history, physical, and laboratory abnormalities, CXR/chest CT appearance, and findings of severity of hypoxemia with limits diagnostic possibilities. Rapid cavitation (<72 hours) with severe CAP points to MSSA/CA-MRSA CAP superimposed on underlying influenza A pneumonia. Treat all such patients for MSSA/CA-MRSA (10,19,35,49–58). Excluding patients with impaired CMI, severe cases of CAP with focal/segmental defects should be treated the same way as normal hosts with antibiotics active against typical/atypical pathogens.

Subacute/chronic CAP with focal/segmental infiltrates (days/weeks) in patients with decreased CMI do not present as severe CAP. Clinicians should be aware of the noninfectious mimics of CAP both in the normal/compromised hosts. The mimics of CAP are common and can usually be easily diagnosed on physical findings, CXR/chest CT appearance, and routine

laboratory tests. In CAP patients unresponsive to apparently appropriate antibiotic therapy, transbronchial or open lung biopsy may be necessary. Compromised hosts respond more slowly than normal hosts to effective therapy. Normal hosts with severe CAP usually show some improvement in three to five days, but in compromised hosts, ~7 to 10 days may be needed before clinical improvement is noted. The duration of antibiotic therapy, IV/PO, for CAP in normal hosts is one to two weeks, whereas in compromised hosts two to three weeks are often necessary because of impaired host defenses (1,8,10).

Obviously, the prognosis in severe CAP is also a function of host factors, i.e., cardiopulmonary reserve/impaired HI/CMI. Inappropriate/delayed empiric therapy lengthens LOS and is associated with a worse prognosis (1,10,59).

### Clinical and Therapeutic Approach to Severe CAP

Patients presenting with severe CAP often require ventilatory, volume, or pressor support. The clinician's first task is to support vital functions and rapidly consider the treatable/reversible causes of severe CAP mimics. The cause of CAP mimics is usually fairly straightforward based on history, physical findings, and routine laboratory tests. The CXR/chest CT scan is helpful in eliminating diagnostic possibilities, limiting diagnostic possibilities, and sometimes in making a specific diagnosis.

If the mimics of severe CAP can be reasonably ruled out, the clinician's next task is to determine the likely pathogen based on history, physical findings, routine laboratory tests, and aspects of the clinical presentation, including assessment of cardiopulmonary function, HI/CMI status, and the degree of hypoxemia (Table 11).

The most common cause of severe CAP in normal hosts is viral pneumonias. The classic severe viral pneumonia in adults is influenza A pneumonia. As mentioned previously, influenza A pneumonia most commonly occurs alone. Alternately, it may be complicated by bacterial CAP, either simultaneously initially (with MSSA/CA-MRSA) or sequentially after a 5–7 day interval of improvement with subsequent CAP due to *S. pneumoniae* or *H. influenzae*. In cases without bacterial superinfection, prognosis is related to degree and duration of hypoxemia. In pandemic influenza A, as in 1918–1919, the majority of the deaths occurred in young, healthy adults without comorbidities and were due to severe hypoxemia uncomplicated by bacterial pneumonia. During the past decade, avian influenza (H5N1) strains have circulated in Asia and Europe. Unlike influenza A, avian influenza (H5N1) is not efficiently transmitted from person-to-person, and for this reason does not, as yet have pandemic potential. However, in contrast to human influenza A, avian influenza (H5N1) is fatal in the majority of cases and affects primarily young healthy adults. Deaths from avian influenza (H5N1) occurs from severe hypoxemia uncomplicated by bacterial pneumonia.

In the spring of 2009, the swine influenza (H1N1) pandemic began in Mexico and quickly spread throughout the world. Although large numbers of the population were affected by swine influenza (H1N1), there were relatively few mortalities. In the fatal cases of swine influenza (H1N1) pneumonia, like avian influenza (H5N1) pneumonia, fatalities died from severe hypoxemia also uncomplicated by bacterial pneumonia. The majority of fatalities with swine influenza (H1N1) pneumonia were young healthy adults without comorbidities (60–65).

Optimal empiric therapy is based on correlating epidemiologic and clinical findings to arrive at a presumptive clinical diagnosis directed at the most likely pulmonary pathogen. Empiric therapy is continued until diagnostic possibilities are eliminated, and if possible, a specific etiologic diagnosis is made. Empiric therapy should be continued if clinically effective.

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# 11 Nosocomial Pneumonia in Critical Care

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## INTRODUCTION

Nosocomial pneumonia or hospital-acquired pneumonia (HAP) is defined as pneumonia that appears 48 hours or more after hospitalization. In this definition, it is assumed that the patient was not incubating the causative microorganism when admitted to the hospital. Patients with HAP may be managed in a ward or, when the illness is severe, in the intensive care unit (ICU). Most cases of HAP occur outside ICUs. However, patients on mechanical ventilation carry the highest risk of HAP, and it is in these patients that the entity has been best studied. Ventilator-associated pneumonia (VAP) refers to pneumonia that begins and develops after endotracheal intubation (1,2). However, a patient who has just undergone tracheotomy and is not yet on a ventilator is similarly susceptible to VAP. Thus, a more appropriate term would be "endotracheal-tube-associated pneumonia." In this chapter, we have, nevertheless, opted for the traditional term.

## Epidemiology

HAP is currently the second most common nosocomial infection in North America and is associated with high rates of morbidity and mortality. Although HAP is not a reportable illness, available data indicate a rate of 5 to 10 cases per 1000 hospital admissions, and this rate is 6 to 20 times higher in patients subjected to mechanical ventilation (3,4). Nevertheless, the incidence density of VAP varies widely depending on the case definition of pneumonia and the hospital population evaluated. Numbers of reported episodes per 1000 days of ventilation are 34.5 after major heart surgery (5), 26 in a burns ICU (6), 18.7 in a pediatric ICU (7), and between 8.0 (8) and 46.3 (9) in mixed medical/surgical ICUs. The most recent report by the Centers for Disease Control National Nosocomial Infection Surveillance (NNIS) System indicates that surgery and trauma ICUs have the highest VAP rates (mean 15.2/1000 ventilator days), followed by medical ICUs (mean VAP rate, 4.9); coronary ICUs (mean VAP rate, 4.4); and surgical ICUs (mean VAP rate, 9.3) (10). Between 10% and 20% of patients receiving >48 hours of mechanical ventilation will develop VAP (11).

The incidence of VAP in mechanically ventilated patients rises as the time of ventilation lengthens. The incidence of VAP is highest early during the course of a hospital stay, with estimates of 3% per day during the first five days of ventilation, 2% per day from days 5 to 10, and 1% per day thereafter (12). Approximately half of all VAP episodes occur within the first four days of mechanical ventilation. The intubation process itself carries a risk of infection, such that when acute respiratory failure is noninvasively managed, the rate of nosocomial pneumonia is lower (13–17).

The overall mortality rate for HAP may be as high as 30% to 70%, but many critically ill patients with HAP die of their underlying disease rather than of pneumonia. VAP-related mortality has been estimated at 33% to 50% in several case-matched studies. Critically ill patients who develop VAP appear twice as likely to die compared with similar patients without VAP (odds ratio, 2.03; 95% confidence interval (CI), 1.16 to 3.56) (11). Increased mortality rates have been attributed to the following factors: bacteremia, especially that caused

by *Pseudomonas aeruginosa* or *Acinetobacter* spp.; medical rather than surgical illnesses; and ineffective antibiotic therapy (18–22).

VAP is the leading cause of both nosocomial mortality and morbidity. Secondary bacteremia and empyema have been reported to occur in 4% to 38% and 5% to 8% of cases, respectively. On an average, the hospital stay of VAP patients is extended for 4 to 13 days (median 7.6 days). Current estimates indicate that this additional length of stay generates a cost of \$20,000 to \$40,000 per case of HAP or VAP in the ICU. In Canada, VAP accounts for approximately 17,000 ICU days per year or around 2% of all ICU days (23); the cost to the health care system is CA \$46 million.

## PATHOGENESIS

The pathogenesis of HAP and VAP is linked to two separate, but related, processes: colonization of the aerodigestive tract with pathogenic bacteria and aspiration of contaminated secretions.

For VAP to occur, the delicate balance between host defenses and microbial invasion has to be upset, allowing pathogens to colonize the lower respiratory tract (24).

In healthy subjects, the oropharynx is colonized by generally nonpathogenic microorganisms, including *Streptococcus viridans*, *Streptococcus pneumoniae*, several anaerobes, and, occasionally, *Haemophilus influenzae*; yet, it is rare to find opportunistic gram-negative rods such as *P. aeruginosa* and *Acinetobacter* spp. Several factors have been proposed to contribute to the pathogenesis of VAP, such as the severity of the underlying disease, prior surgery, exposure to antibiotics, and the use of invasive respiratory equipment (2,25–34). Oropharyngeal and tracheal colonization by *P. aeruginosa* and enteric gram-negative bacilli have been related to length of hospital stay and severity of the underlying disease (30).

The main route of VAP infection is oropharyngeal colonization by normal flora or by exogenous pathogens acquired in the ICU. Typical sources of these pathogens are the hands of medical staff or contaminated respiratory equipment, water, or air.

Once the oropharynx has been invaded, microorganisms may reach the lower respiratory tract and lungs through several mechanisms. The main portals of bacterial entry into the lungs are *oropharyngeal pathogen aspiration* or the leakage of bacteria-containing secretions around the endotracheal cuff. The stomach and sinuses may act as potential reservoirs for nosocomial pathogens colonizing the oropharynx, but their role is largely unknown and could depend on the patient population or the changing natural history and management of VAP.

Microaspiration is common even in healthy individuals. Approximately 45% of healthy subjects aspirate during sleep, and the rate of aspiration is higher in patients with reduced levels of consciousness. Factors promoting aspiration include a generally reduced level of consciousness, a diminished gag reflex, abnormal swallowing for any reason, delayed gastric emptying, or decreased gastrointestinal motility. Reflux and aspiration of non-sterile gastric contents is also a possible mechanism of pathogen entry into the lungs.

The risk of pneumonia is determined by the number and virulence of microorganisms colonizing the oropharynx (35). Hospitalized patients may become colonized with aerobic gram-negative bacteria within several days of admission, and as many as 75% of severely ill patients will be infected within 48 hours (36). In addition, the near sterility of the stomach and upper gastrointestinal tract may be disrupted by alterations in gastric pH due to illness, medication, or enteric feeding. Much attention has, therefore, been paid to the possible detrimental effects of ulcer prophylaxis regimens that raise the gastric pH (33,34).

Orotracheal intubation diminishes the natural defense mechanisms of the respiratory tract, affecting mechanical factors (ciliated epithelium and mucus), humoral factors (antibody and complement), and cell factors (polymorphonuclear leukocytes, macrophages, lymphocytes, and their respective cytokines).

The dorsal decubitus position is more conducive to microaspiration. The use of a nasogastric tube obstructs the ostia of the facial sinuses. The sinuses may then act as an infection reservoir from which organisms may seed the tracheobronchial tree (37–39).

The formation of a biofilm on the endotracheal tube could help sustain tracheal colonization, and this mechanism is also thought to play a role in late-onset VAP caused by resistant organisms.



In summary, most cases of *endemic* VAP are acquired through the aspiration of microorganism-containing oropharyngeal, gastric, or tracheal secretions around the cuffed endotracheal tube into the normally sterile lower respiratory tract.

On the other hand, *epidemic* VAP infection is most commonly contracted via contaminated respiratory treatment equipment, such as bronchoscopes or medical aerosols; water (e.g., *Legionella*); or air (e.g., *Aspergillus*).

**Direct inoculation with pathogens** through ventilation devices is possible if no preventive measures are taken. Bacterial contamination of equipment accounted for several VAP outbreaks in the 1970s, although today's improved hygiene has meant that this route is only responsible for a few isolated outbreaks. Water condensing in the ventilation circuit is a potential source of contamination, and several preventive measures are specifically recommended (see section Prevention) to avoid the risk of contamination via this route (2,26–29,31).

The *inhalation of pathogens*, such as viruses, fungi (*Aspergillus* spp.), or even *Legionella* spp., from the environment (2,16,26) has also been described.

Pneumonia can also be acquired by the *spread* of infection from adjacent infected tissue, such as the pleura or mediastinum, but this occurs very rarely.

*Bacterial translocation* from the gastrointestinal tract is another pathogenic mechanism described for VAP. The intestinal wall of critically ill patients loses its capacity to prevent the systemic absorption of bacteria and toxins. This in turn leads to impaired intestinal function, promoting the invasion of the blood system with intestinal pathogens and thus metastatic infections (40,41). The hematogenous spread of pathogens from intravascular catheters seems to be rare.

An exception to the idea that "pathogenesis always starts with oropharyngeal colonization" is the case of infection by *Pseudomonas* spp. Thus, the findings of several studies have indicated that tracheal colonization by these pathogens may occur without previous oropharyngeal colonization (42–44).

## MICROBIOLOGY

Approximately two-thirds of nosocomial pneumonias are caused by gram-negative bacilli (45), although infections by gram-positive cocci are on the rise (45,46).

There is much paucity of data regarding whether the pathogens that cause VAP differ from those causing HAP in patients who are not mechanically ventilated. One prospective observational study evaluated 158,519 patients admitted to a single center over a four-year period (46). A total of 327 episodes of VAP and 261 episodes of HAP were identified in non-ventilated patients. Pathogens in ventilated patients included gram-negative bacilli (59%—*P. aeruginosa*, 17%; *Stenotrophomonas maltophilia*, 7%; *Acinetobacter* spp., 8%); gram-positive cocci (32%—methicillin-susceptible *Staphylococcus aureus* (MSSA), 9%; methicillin-resistant *S. aureus* (MRSA), 18%); and miscellaneous pathogens (9%). Pathogens in non-ventilated patients were similar, except for non-Enterobacteriaceae bacilli, which were less frequent: gram-positive cocci (43%—MSSA, 13%; MRSA, 20%); gram-negative bacilli (40%—*P. aeruginosa*, 9%; *S. maltophilia*, 1%; *Acinetobacter* spp., 3%); and miscellaneous pathogens (18%).

In a prospective, multicenter, observational study performed in 398 ICU patients with suspected VAP, a similar distribution of pathogens was observed. Major pathogens were identified in 197 patients (49.5%) through either tracheal aspirate or BAL fluid and included primarily MRSA (14.8%), *P. aeruginosa* (14.3%), and other *Staphylococcus* species (8.8%) (47).

Multidrug-resistant (MDR)-related VAP rates have recently undergone a dramatic increase in hospitalized patients. These pathogens are more likely to infect patients with late-onset HAP and VAP. The following risk factors for colonization and infection with MDR pathogens have been identified (2,20,24,48–52):

1. Antimicrobial therapy in the preceding 90 days
2. A length of hospital stay of five days or more
3. An existing high incidence of resistance to antibiotics in the hospital area or unit
4. Risk factors for health care-associated pneumonia:
  - a. Hospitalization for 2 days or more in the preceding 90 days
  - b. Stay in a nursing home or an extended care facility

- c. Home infusion therapy (including antibiotics)
  - d. Chronic dialysis in the previous 30 days
  - e. Home wound care
  - f. Family member with an MDR infection
5. Immunosuppressive disease and/or therapy

Pneumonia due to *S. aureus* is more common in patients with diabetes mellitus and head trauma and in ICU patients (4,53–55). *P. aeruginosa* is a frequent pathogen in patients with severe chronic obstructive pulmonary disease (COPD) and in those with prior hospitalization, prolonged intubation (more than eight days), and prior exposure to antibiotics (56). Infection with *Acinetobacter baumannii* has been related to specific risk factors (57), including neurosurgery, acute respiratory distress syndrome (ARDS), head trauma, and large-volume pulmonary aspiration. Moreover, in some hospitals, *Acinetobacter* spp. are starting to account for a significant number of cases of nosocomial pneumonia (58–60).

Rates of polymicrobial infection are highly variable, although they seem to be on the rise and are particularly high in patients with ARDS (26,27,29,53,61–66).

The detection of an increased load of oropharyngeal commensals (viridans group streptococci, coagulase-negative staphylococci, and *Corynebacterium* spp.) in distal bronchial specimens is difficult to interpret, but it is not generally considered that they could cause pneumonia.

The role of anaerobic bacteria is still under investigation (67). In one report, anaerobes were isolated from 23% of patients with VAP diagnosed by quantitative culture methods (61). The authors of this study highlighted that the anaerobes recovered mirrored the bacteriology of the oropharynx and that only in four patients were they the only microorganisms isolated. No anaerobic bacterium was found in the blood or associated with necrotizing disease. In a more recent study, however, no pathogenic anaerobes could be recovered using the same culture methods in 143 patients strictly followed during 185 episodes of VAP (68). Collectively, these and other findings point to an unlikely role of anaerobes in VAP or late-onset HAP. Their role in patients with poor dentition could, however, be more significant.

Early-onset and late-onset disease can be distinguished using quantitative culture methods of diagnosis. When pneumonia develops within four or five days of admission (or intubation), microorganisms associated with community-acquired pneumonia are isolated with some frequency. In contrast, when disease develops after five days, few pathogens associated with community-acquired pneumonia are recovered, and gram-negative bacilli and *S. aureus* are the main agents detected. Although indicators of late-onset disease, these bacteria can also cause early-onset pneumonia, especially in patients with severe comorbidities under recent antimicrobial treatment, making it more difficult to distinguish between early-onset and late-onset disease. As mentioned above, a longer period of mechanical ventilation and antimicrobial therapy will increase the risk of infection by MDR pathogens.

Fungal or viral pathogens are rarely the causative agents in immunocompetent patients. Nosocomial *Aspergillus* spp. infection should warn of airborne transmission by spores related to an environmental source, such as contaminated hospital air ducts. Recently, a high rate of hospital-acquired *Aspergillus* pneumonia was observed in patients with COPD under therapy with antibiotics and high-dose corticosteroids (69). *Candida albicans* or other *Candida* species are often detected in endotracheal aspirates (EA), but usually indicate airway colonization rather than pneumonia, and antifungal treatment is rarely necessary (70–74).

Outbreaks of HAP and VAP due to viruses, such as influenza, parainfluenza, adenovirus, measles, and respiratory syncytial virus, are usually seasonal. Influenza, parainfluenza, adenovirus, and respiratory syncytial virus account for 70% of all nosocomial viral pneumonias. The diagnosis of these viral infections is often made by rapid antigen testing and viral cultures or serological assays. Influenza A is probably the most common viral cause of HAP in adult patients and predisposes the patient to secondary bacterial infection (2,75–79).

The role of herpes simplex virus (HSV) as a causative agent of VAP is presently under discussion. In a prospective study performed at our center, HSV was isolated from respiratory secretions in 6.4% of all patients not fulfilling VAP criteria and in 13.4% of those who did fulfill these criteria (80). However, the role of HSV in pneumonia is yet far from clear.

**Table 1** Risk Factors for VAP Attributable to a Specific Microorganism

Risk factor	Responsible microorganism
Aspiration	Anaerobic microorganisms
Abdominal surgery	Anaerobic microorganisms
Coma	<i>S. aureus</i>
Iv drug abuse	
Diabetes mellitus	
Chronic renal failure	
Prolonged ICU or hospital stay	<i>Pseudomonas aeruginosa</i>
Antimicrobial therapy	<i>Acinetobacter</i> spp. <i>Stenotrophomonas maltophilia</i> <i>Enterobacter</i> spp. Methicillin-resistant <i>S. aureus</i> <i>Pseudomonas aeruginosa</i>
Chronic obstructive pulmonary disease	
Age >65 years	
Hypoalbuminemia <2.5 g/dL	
Non-resolving pneumonia	
Immunocompromise	<i>Candida</i> spp.
Isolated outbreaks	<i>Aspergillus</i> spp. <i>Mucor</i> spp.

Within the categories described, the causes of nosocomial pneumonia also vary considerably according to geographic, temporal, and intra-hospital factors. The use of up-to-date local epidemiologic ICU data on endemic pathogens can help select the most appropriate empirical antibiotic regimen and infection-control strategies.

Table 1 lists the conditions that may predispose a patient to acquire VAP attributable to a specific pathogen.

## RISK FACTORS

Several risk factors have been linked to nosocomial pneumonia through univariate and multivariate analysis of prospective and retrospective data (12,26,67,81–92). The elderly and moderately to severely ill are especially at risk. In these subjects, respiratory tract function is impaired, lung volume is diminished, and airway clearance may be reduced. Trauma, surgery, medications, and respiratory therapy devices may additionally impair the capacity of the lungs to ward off infection.

Notwithstanding, the most significant risk factor for nosocomial pneumonia is mechanical ventilation. In effect, the terms “nosocomial pneumonia” and “ventilator-associated pneumonia” are often used interchangeably. It has been described that when an endotracheal tube is introduced, many lines of host defense are bypassed, such that microorganisms gain direct access to the lower respiratory tract (26,83,87,89). Further, as the tube is inserted, possible damage to the tracheal mucosa will allow pathogens to achieve a foothold. Table 2 provides additional risk factors listed by category for both VAP and pneumonia occurring in both ventilated and more mixed non-ventilated hospital populations.

The risk factors identified by Croce et al. (115) to predict VAP in a review of admissions to a trauma center over a 28-month period were as follows: penetrating wounds, a high Glasgow Coma Scale score, spinal cord injury, and the coexistence of emergent laparotomy, a high Injury Severity Score, number of blood units transfused in the resuscitation room, and the place of initial intubation.

## PREVENTION

Understanding the pathogenesis of VAP (colonization of the aerodigestive tract with pathogenic bacteria and their subsequent aspiration) has allowed the development of several VAP-prevention strategies. These education-based programs have shown that the occurrence of VAP can be reduced by as much as 50% or more (116) if measures that prevent colonization

**Table 2** Risk Factors for Nosocomial Pneumonia and VAP

Category	Unventilated or wide range of hospital patients	Mechanically ventilated patients
Host related	Advanced age, severe illness, trauma/head injury, poor nutritional status, coma, impaired airway reflexes, neuromuscular disease	Advanced age, chronic lung disease, severe illness, reduced consciousness or coma, organ failure, severe head trauma, shock, blunt trauma, burns, stress ulceration
Device related	Endotracheal intubation, nasogastric tube, bronchoscopy	Prolonged mechanical ventilation, reintubation or self-extubation, ventilator circuit changes at intervals <48 hr, emergent intubation after trauma, PEEP, tracheostomy
Drug related	Immunosuppression therapy	Prior antimicrobial therapy, antacid or H <sub>2</sub> blocker therapy, barbiturate therapy after head trauma
Miscellaneous	Thoracic or upper abdominal surgery, prolonged surgery, prolonged hospitalization, large-volume aspiration	Thoracic or upper abdominal surgery; gross aspiration of gastric contents, supine head position, fall-winter season

*Abbreviations:* H<sub>2</sub>, histamine type 2; PEEP, positive end-expiratory pressure.

*Source:* Data obtained from Refs. 2,12,18,26,32–34,67,82,83,87–114.

and aspiration are implemented. These measures are based on avoiding or improving the specific risk factors identified to promote VAP in studies involving multivariate analysis.

The recently published SHEA/IDSA practice recommendation on “Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals” is a compendium of recommendations sponsored in partnership with the Association for Professionals in Infection Control and Epidemiology (APIC), the Joint Commission, and the American Hospital Association (AHA) (Table 3).

The core recommendations are designed to interrupt the three most common mechanisms whereby VAP develops: aspiration of secretions, colonization of the aerodigestive tract, and use of contaminated equipment.

Key components are (i) ensuring staff education and infection surveillance, (ii) preventing the transmission of microorganisms, and (iii) modifying host risk factors for infection. When fully implemented, guidelines to prevent VAP have been shown to improve patient outcomes and are cost effective (117–121).

Effective infection-control measures, hand hygiene, and patient isolation to reduce cross-infections are routine mandatory practices (2,33,96,112,122). Recommended practices are the surveillance of ICU infections to identify and quantify endemic and new MDR pathogens and the acquiring of recent data on which to base infection monitoring and antimicrobial therapy in patients with suspected HAP or other nosocomial infection (2,32,33,78,96,112,122–125).

The time of invasive ventilatory support and, therefore, the risk of VAP can be reduced by noninvasive ventilatory support (126) and protocol-driven weaning (127). Reintubation also increases the risk of VAP (2,27,33,34,110,128–130).

In high-risk populations, early tracheostomy in patients predicted to require prolonged mechanical ventilation has been proposed as a preventive strategy and shown to reduce the incidence of VAP (131).

The use of orotracheal intubation and orogastric tubes rather than nasotracheal intubation and nasogastric tubes has been reported to prevent nosocomial sinusitis and to reduce the risk of VAP, although a direct link has not been demonstrated (2,33,34,94,112,132).

Good oral hygiene can reduce the load of infective microorganisms in the oropharynx and can be a cost-effective way of preventing VAP (133). The use of oral chlorhexidine has served to avoid ICU-acquired HAP, and at present, the SHEA/IDSA recommendation is to undertake regular oral care with an antiseptic solution (134–139). The optimal frequency for oral care remains unresolved.

**Table 3** Preventing Ventilator-Associated Pneumonia in Acute Care Hospitals—SHEA/IDSA Practice Recommendation

Recommendation	Category
<i>I. Basic practices for preventing and monitoring VAP: Recommended for all acute care hospitals</i>	
A. Education	
1. Teach healthcare personnel who care for patients undergoing ventilation about VAP, including information about the following:	A-II
a. Local epidemiology	
b. Risk factors	
c. Patient outcomes	
2. Teach clinicians who care for patients undergoing ventilation about noninvasive ventilatory strategies	B-III
B. Surveillance of VAP	
1. Perform direct observation of compliance with VAP-specific process measures	B-III
a. VAP-specific process measures include hand hygiene, bed position, daily sedation interruption and assessment of readiness to wean, and regular oral care	
b. Use structured observation tools at regularly scheduled intervals	
2. Conduct active surveillance for VAP and associated process measures in units that care for patients undergoing ventilation who are known or suspected to have a high risk of VAP on the basis of risk assessment	A-II
a. Collect data that will support the identification of patients with VAP and calculation of VAP rates	
C. Practice	
1. Implement policies and practices for disinfection, sterilization and maintenance of respiratory equipment that are aligned with evidence-based standards (see the appendix of the guideline for a list of recommended practices)	A-II
2. Ensure that all patients (except those with medical contraindications) are kept in a semirecumbent position	B-II
3. Perform regular antiseptic oral care in accordance with product guidelines	A-I
4. Provide easy access to noninvasive ventilation equipment and institute protocols to promote the use of noninvasive ventilation	B-III
D. Accountability	
1. The hospital's chief executive officer and senior management are responsible for ensuring that the healthcare system supports an infection prevention and control program to effectively prevent VAP.	
2. Senior management is accountable for ensuring that an adequate number of trained personnel are assigned to the infection prevention and control program	
3. Senior management is accountable for ensuring that healthcare personnel, including licensed and nonlicensed personnel, are competent to perform their job responsibilities.	
4. Direct healthcare providers (physicians, nurses, aides and therapists) and ancillary personnel (house-keeping and equipment-processing personnel) are responsible for ensuring that appropriate infection prevention and control practices are used at all times	
5. Hospital and unit leaders are responsible for holding their personnel accountable for their actions	
6. The person who manages the infection prevention and control program is responsible for ensuring that an active program to identify VAP is implemented, that data on VAP are analyzed and regularly provided to those who can use the information to improve the quality of care, and that evidence-based practices are incorporated into the program	
7. Personnel responsible for healthcare personnel and patient education are accountable for ensuring that appropriate training and education programs to prevent VAP are developed and provided to personnel, patients and families	
8. Personnel from the infection prevention and control program, the laboratory, and information technology departments are responsible for ensuring that systems are in place to support the surveillance program	
<i>II. Special approaches for the prevention of VAP</i>	
Perform a VAP risk assessment. These special approaches are recommended for use in locations and/or populations within the hospital that have unacceptably high VAP rates despite implementation of the basic VAP prevention procedures listed above	

**Table 3** Preventing Ventilator-Associated Pneumonia in Acute Care Hospitals—SHEA/IDSA Practice Recommendation (*Continued*)

Recommendation	Category
1. Use an endotracheal tube with in-line and subglottic suctioning for all eligible patients	B-II
2. Ensure that all ICU beds used for patients undergoing ventilation have a built-in tool to provide continuous monitoring of the angle of incline	B-III
<i>III. Approaches that should not be considered a routine part of VAP prevention</i>	
1. Do not routinely administer intravenous immunoglobulin, white-cell-stimulating factors (filgrastim or sargramostim), enteral glutamine or chest physiotherapy	A-III
2. Do not routinely use rotational therapy with kinetic or continuous lateral rotational therapy beds	B-II
3. Do not routinely administer prophylactic aerosolized or systemic antimicrobials	B-III
<i>IV. Unresolved issues</i>	
1. Avoidance of H <sub>2</sub> antagonist or proton pump inhibitors for patients without a high risk of gastrointestinal bleeding	
2. Selective digestive tract decontamination for all patients undergoing ventilation	
3. Use of antiseptic-impregnated endotracheal tubes	
4. Intensive glycemia control	

Source: Ref. 150.

Selective decontamination of the digestive tract (SDD) using topical antimicrobial agents for oral decontamination and the use of SDD to prevent gastric colonization in critically ill, mechanically ventilated, or ICU patients appear to reduce the incidence of VAP (26,83,135,140–142), although the widespread use of antimicrobial prophylaxis is not recommended, and this issue remains unresolved.

When the pH of the stomach contents is raised, its infective organism load may increase. Thus, H<sub>2</sub> blockers and proton pump inhibitors are risk factors for VAP (143) and unsuitable in patients without a high risk of gastrointestinal bleeding (120). Moreover, the preferential use of sucralfate or H<sub>2</sub>-blocking agents remains an unresolved issue (2). Impairing gastroesophageal reflux reduces the risk of aspiration. Accordingly, a semirecumbent position (95,98–101,144–146) and the use of an inflated esophageal balloon (in patients with a nasogastric tube and enteral feeding tube) during mechanical ventilation (147) can reduce gastroesophageal reflux and, thus, lower the risk of bronchial aspiration of gastric contents.

When used in an individual patient, the breathing circuit (i.e., ventilator tubing and exhalation valve and the attached humidifier) should not be routinely changed. The circuit should be replaced only when visibly soiled or not working properly (2).

Compared with open endotracheal suction systems, closed systems reduce cross-contamination between the bronchial system and gastric juices (148), but increase colonization rates of ventilator tubing with MDR microorganisms (149). There is no increase in VAP frequency (149), however, and closed endotracheal suction systems may be in fact associated with lower rates of VAP relative to open systems (148). The current SHEA/IDSA recommendation is to keep the ventilatory circuit closed during condensate removal (150). Closed suction systems do not have to be changed every day (151,152), and a policy of weekly changes of the in-line suction catheter offers substantial cost savings, with no significant increase in the incidence of VAP (153).

Adequate sputum clearance above the endotracheal cuff is essential if VAP is to be minimized. Subglottic suctioning is effective at removing secretions above the endotracheal cuff (2,39,95,154) and reduces the incidence of VAP nearly by half (risk ratio = 0.51; 95% CI, 0.37 to 0.71) (155), primarily by reducing early-onset pneumonia. Endotracheal tube cuff pressure should be at least 20 cm H<sub>2</sub>O to prevent leakage of bacterial pathogens around the cuff into the lower respiratory tract (156,157).

Good humidification is important for sputum clearance (158), although passive as opposed to active humidification devices have been related to a lower VAP incidence (152,159).

The use of rotational therapy with kinetic or continuous lateral rotational therapy beds is not considered a routine part of VAP prevention in SHEA/IDSA recommendations (2,150,160).

It is difficult to avoid airway contamination from exogenous sources, but changing ventilators only for infection control and not allowing the build up of condensation in the ventilator circuit can minimize contamination (152). Contaminated condensates should be carefully emptied from ventilator circuits, and their entry into the endotracheal tube or in-line medication nebulizer should be avoided (157,161,162).

Silver-coated endotracheal tubes have been reported to reduce the incidence of *Pseudomonas pneumonia* in intubated dogs and to delay airway colonization in intubated patients, although patient subsets likely to benefit from this practice still need to be identified before the system can be applied on a large scale (163–165)]. The use of antiseptic-impregnated endotracheal tubes is described as unresolved in the SHEA/IDSA recommendations (150).

Daily interruption of sedation or its reduction and avoiding agents that could depress the cough reflex have proved effective in the prevention of VAP (128). Making sure that there are adequate numbers of staff in the ICU will reduce length of stay, improve infection-control practices, and reduce the duration of mechanical ventilation (129,130,166,167).

A selective transfusion policy should be adopted for the transfusion of red blood cells or other allogeneic blood products (24). Leukocyte-depleted red blood cell transfusion can help to reduce HAP in some patient populations (168–171).

Intensive insulin therapy to keep serum glucose levels in the range 80 to 100 mg/dl has been explored in ICU patients as a way to reduce nosocomial blood stream infection, duration of mechanical ventilation, ICU stay, morbidity, and mortality, but more studies are required before recommendation for widespread use can be made (172,173).

Preventive measures are ineffective if not put into practice by all medical staff. Accordingly, multidisciplinary educational programs directed toward ICU staff that emphasize preventive strategies have been associated with decreased rates of VAP (152,174). For example, Babcock et al. (175) showed a 46% reduction in the VAP rate following a training program focusing on preventive measures.

Although not mentioned in the healthcare infection control practices advisory committee (HICPAC) guidelines, two further promising preventive measures are the implementation of protocols for ventilator management (176) and the use of antimicrobial agents in the ICU. Indeed, a ventilator management protocol was able to reduce the duration of ventilatory support and the incidence of VAP in a small study (130), and the SHEA/IDSA guideline recommends daily assessments of readiness to wean and the use of weaning protocols (128,150). In a French ICU, the results of a four-year study indicated that the rotation and restricted use of antibiotics reduced the frequency of VAP associated with MDR bacteria, findings that have been subsequently confirmed (177,178). The proportions of VAP caused by MSSA increased from 40% to 60% and those of MDR gram-negative bacilli decreased from 61% to 49%. These findings warrant further investigation.

The program started by the Institute for Healthcare Improvement (IHI), the “100,000 Lives Campaign,” was a voluntary initiative to protect patients from 100,000 incidents of medical harm for a period of two years (December 2006 to December 2008). One of its interventions was the prevention of VAP by implementing a series of interdependent, scientifically grounded steps denoted “the Ventilator Bundle.” Care bundles are sets of best practices for managing a disease process. Individually, these measures improve care, but when applied together, they give rise to a substantial improvement. The scientific basis for each bundle component has been sufficiently established to be considered the care standard. Hence, the IHI’s ventilator bundle is a group of evidence-based practices that, when applied to all patients on mechanical ventilation, leads to a dramatic reduction in the rate of ventilator-associated pneumonia.

The following four measures comprised the ventilator bundle:

1. Elevate the bed headrest (30° to 45°) so that the patient adopts a semirecumbent position
2. Interrupt sedation daily and assess readiness to extubate daily
3. Prophylaxis for peptic ulcer disease
4. Prophylaxis for deep vein thrombosis unless contraindicated

The use of the ventilator bundle in the care of ventilated patients can markedly reduce the incidence of VAP. This reduction was estimated at 45% on an average in a recent ICU collaborative improvement IHI project. The results of this campaign will soon be reported.

## CLINICAL PRESENTATION AND DIAGNOSTIC TESTING

### Establishing a Diagnosis of VAP

There is no single pathognomonic test that ensures or excludes the presence of VAP. Wide spectrum antimicrobial therapy should be started if there is reasonable suspicion, and this can then be adjusted once the results of microbiological tests become available (26,179,180).

The American Thoracic Society and the Infectious Disease Society of America (24) recently defined VAP as the presence of new or progressing lung infiltrates plus clinical evidence that the infiltrates are of an infectious origin. The presence of infection is determined on the basis of two or more of the following data: fever greater than 38°C or hypothermia, leukocytosis or leukopenia, purulent secretions, and reduced oxygenation (181). Diagnosis of VAP requires an abnormal chest radiograph. In the absence of demonstrable pulmonary infiltrates, a diagnosis of infective tracheobronchitis is pursued (182).

Unfortunately, radiographic data from chest X Rays show low sensitivity and specificity for diagnosing VAP (169,183–185). Radiological infiltrates are difficult to define and difficult to distinguish from other frequent conditions in this patient population. Moreover, they correlate poorly with CT data and postmortem criteria. Lung infiltrates are also provoked by other causes such as atelectasis, pulmonary edema, pleural effusion, pulmonary hemorrhage, lung infarction, and ARDS (186). In a study comparing the use of portable chest X Rays and CT scans, 26% of infiltrates detected by CT were missed by the portable chest X Rays, particularly those located in lower lobes (187). This also occurs when we compare any gold standards such as the postmortem examination (181,185) and bronchoscopic examination (185,188–190).

CT has shown a sensitivity and a specificity of 53% and 63%, respectively, for the diagnosis of VAP (191). Ground glass infiltrates appeared to have a higher specificity, but were found in only 45% of patients. Added to these limitations, we find interobserver variability in interpreting radiological observations (192). To date, multi-detector row CT with its excellent contrast resolution is the most sensitive modality for evaluating lung parenchyma infections (193).

The sensitivity of the use of other clinical data increases if only one criterion is considered sufficient, but this occurs at the expense of specificity, leading to significantly more antibiotic treatment (181). For patients with ARDS, suspicion of pneumonia should be high, and even one of the clinical criteria described should prompt further diagnostic testing (194).

When clinical diagnoses of nosocomial pneumonia were compared with histopathologic diagnoses made at autopsy, pneumonia was diagnosed correctly in less than two-thirds of cases (195).

The Clinical Pulmonary Infection Score (CPIS) described by Pugin et al. (196) is a multifactorial system used to make a diagnosis of VAP. This method is based on assigning points to clinical, radiological, and physiological variables. In the original report, a score of  $\geq 6$  points was found to correlate well with a diagnosis of VAP. However, in subsequent studies, the sensitivity and specificity of the CPIS score proved to be not much improved over the subjective clinical approach unless the score included microbiological information (rapid Gram stain or culture results) (Table 4) (197). Nonetheless, a clinical score of  $\leq 6$  is good at identifying a subset of patients who either do not require antimicrobial therapy for VAP or, when antibiotics are prescribed, are amenable to a short course (three days) of treatment, provided the patient remains clinically stable and with a nonincreased score three days later (198).

**Table 4** Modified Clinical Pulmonary Infection Score

Criterion	Points		
	0	1	2
Temperature	$\geq 36.5^{\circ}\text{C}$ – $\leq 38.4^{\circ}\text{C}$	$\geq 38.5^{\circ}\text{C}$ – $\leq 38.9^{\circ}\text{C}$	$\leq 36^{\circ}\text{C}$ – $\geq 39^{\circ}\text{C}$
Blood leukocytes ( $\mu\text{l}$ )	$\geq 4,000$ – $\leq 11,000$	$< 4,000$ or $> 11,000$	$< 4,000$ or $> 11,000$ + bands ( $> 500$ )
Tracheal secretions	Rare	Abundant	Abundant and purulent
Chest X-ray infiltrates	None	Diffuse	Localized
$\text{PaO}_2/\text{FiO}_2$	$> 240$ or ARDS		$< 240$ and no ARDS
Microbiology	Negative		Positive



### Confirming the Etiology

Although the presence of clinical signs should raise a suspicion of VAP, confirming the diagnosis is much more difficult, since clinical variables are of no use for defining the microbiologic etiology of pneumonia. All patients suspected of having VAP should undergo lower respiratory tract sampling, with subsequent microscopic analysis and culture of the specimen (24). For an etiologic diagnosis of VAP, a quantitative or semiquantitative lower respiratory tract culture is needed. The threshold bacterial count depends on the type of specimen collected (more or less dilution of the original respiratory secretions), the collection method, and the sampling time (whether there has been a recent change or not in antimicrobial therapy) (24). Growth below the threshold is assumed to be due to colonization or contamination. This type of information has been used as a basis for decisions about whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (199,200).

Today, the most common methods of sampling the lower respiratory tract are endotracheal aspirates (EA), protected specimen brush (PSB) samples, and bronchoalveolar lavage (BAL). No single method is considered better than any other, including bronchoscopic versus non-bronchoscopic sampling (182,201–207). The evidence indicates that bronchoscopic sampling does not improve mortality, length of hospital stay, duration of mechanical ventilation, or length of ICU stay (208–210). However, it may lead to a narrower antimicrobial regimen or more rapid de-escalation of antimicrobial therapy (208,211–213).

To adequately process a sample and interpret the results, it is essential that the laboratory is informed of the type of sample submitted (24). Nonetheless, in a survey of different sampling techniques, Ruiz et al. (214) found no differences in rates of diagnoses, changing of antimicrobial treatment due to etiologic findings, length of ICU stay and of mechanical ventilation, and crude 30-d- or adjusted mortality.

Quantitative cultures have been found especially useful for diagnosing VAP in patients with a low or equivocal clinical suspicion of infection (206,215). Fagon et al. performed a multicenter, randomized, uncontrolled trial to evaluate the effects on clinical outcome and antibiotic use of the two approaches, “clinical” versus “bacteriological,” to diagnose VAP and select the initial treatment for this condition (211). These authors concluded that the invasive management strategy was significantly associated with fewer deaths at 14 days, earlier improvement of organ dysfunction, and a reduced use of antibiotics.

Blood cultures are not very useful for diagnosing VAP (216,217). Overall, their sensitivity is less than 25%, and, when positive, the organisms detected could largely correspond to an extrapulmonary source, even if VAP is also present (218). Blood cultures are mainly useful for diagnosing extrapulmonary infections or for detecting respiratory pathogens in patients with *borderline* respiratory sample cultures (218–220).

### Value of Rapid Gram Stain

A reliable EA Gram stain can be used to decide upon initial empirical antimicrobial therapy (221) and infrequently gives rise to inappropriate treatment (26,211). In our experience, in patients in whom VAP is suspected, Gram staining of an EA sample and timely reporting of the results is a method of extraordinary value for the etiologic diagnosis of VAP and for early decision making about treatment. At our center, the diagnostic performance of an EA Gram stain when there is suspicion of VAP is as follows: sensitivity, (Sen) 91%; specificity (Spec), 61%; positive predictive value (PPV), 50.5%; negative predictive value (NPV), 94%; accuracy (A), 70%; positive likelihood ratio, 2.3; negative likelihood ratio, 0.14; post-test probability for a negative result, 6%. In other words, a negative result will reasonably exclude a diagnosis of VAP. The medical literature, however, is filled with varying data on the Sen (57% to 95%), Spec (48% to 87%), PPV (47% to 78%), NPV (69% to 96%), and accuracy (60% to 88%) of the Gram stain technique in managing the patient with VAP (200,222–226). Blot et al. (225) assessed the value of the Gram stain in patients with suspected VAP used on respiratory secretions taken both by endotracheal aspiration and using a plugged telescoping catheter. Used on EA, the method showed a high Sen for diagnosing microbiologically proven VAP (91%) and a high NPV (94%) in patients without a recent antibiotic treatment change. On plugged telescoping catheter samples, the Gram stain showed a high Spec (95%) but lower Sen (67%). These authors

claim that a negative Gram stain on an EA sample is of great NPV for a diagnosis of VAP and allows for the decision to not start antibiotic treatment. A positive Gram stain on a plugged telescoping catheter sample indicates VAP is highly probable and treatment should be promptly started. In patients in whom the EA proves positive and the plugged telescoping catheter sample negative, the best therapeutic approach is not as clear, although the clinician should probably make the decision to start antimicrobial treatment pending subsequent adjustment when the culture results are ready. A negative EA culture in a patient without a recent change in antibiotics (within 72 hours) has strong negative predictive value (94%) for VAP (225).

### **Value of Cultures**

The etiologic cause of pneumonia can be determined by culture of an EA with initial microscopic examination (227–229). From a practical standpoint, quantitative culture counts between 100 and 1000 cfu/mL for PSB samples and between 1000 and 10,000 cfu/mL for BAL specimens should be considered probably positive for VAP and are an indication for antibiotic treatment (230). Counts of  $\geq 100,000$  cfu/mL in blind, aspirated, undiluted tracheal secretions suggest infection rather than colonization (227).

Several technical considerations can affect the results of quantitative cultures and may explain why the reported accuracy of invasive methods varies so widely. Methodological issues responsible for the inconsistent results of published studies have been summarized in a meta-analysis (231). One of the most frequent problems is the dilution of BAL, which could minimize bacterial counts. This occurs particularly in patients with severe COPD. Knowledge of the extent of dilution can dramatically increase the value of quantitative cultures. A recently published study has examined the effect of the dilution factor used for the BAL culture on the bacterial count (232). The authors compared the concentration of urea in serum and BAL to determine the dilution factor for the sample and established that 17 additional patients would have reached the cutoff level after correction for the dilution effect, which varied between 1.8- and 130-fold. These findings stress the implications of the dilutions used in cultures for the diagnosis and treatment of these patients.

The recent starting or a change in antibiotic therapy is among the main factors causing false-negative quantitative cultures, especially if the start or change occurs in the preceding 24 to 72 hours (206,233). Thus, all cultures should be obtained prior to treatment. If this is not possible, then a change in the diagnostic threshold could be useful (179,233). For BAL, the use of a threshold 10-fold lower than usual may avoid some false-negative results in patients given antibiotics before testing.

### **Preemptive Rapid Cultures**

The traditional laboratory processing of a respiratory secretion specimen for bacterial isolation usually takes between three and four days to provide the clinician with a result. After plating the sample and incubating for 24 to 48 hours, bacterial counts have to be performed and strains isolated and grown in pure culture. This is followed by microorganism identification and antimicrobial sensitivity testing, which takes a further 24 hours. To this, we would have to add the time taken for transmitting information, writing reports, and making therapeutic decisions. This late information, at least in areas such as blood cultures, clearly helps to improve the prescription of drugs, optimizes their consumption, and reduces costs, but it has not yet been possible to establish its impacts on shortening hospital stay or decreasing mortality (234).

Antibiogram procedures require a standardized inoculum and usually start with isolated bacteria in culture. It is known, however, that antibiograms performed directly on clinical specimens, i.e., omitting the bacterial-isolation step, can provide preliminary information, which generally correlates well with that offered by standard procedures. This is presently undertaken with blood cultures and urine or cerebro spinal fluid (CSF) samples in circumstances in which the urgency demands. A procedure that is not affected by the inoculum is the so-called E-test. This method consists of a strip impregnated with increasing concentrations of an antibiotic. After its diffusion in agar, the strip provides a minimum inhibitory concentration (MIC) for the particular bacterium and antimicrobial agent tested. We compared the results of a direct E-test antibiogram, including six antimicrobials commonly

used in VAP patients, with sensitivities obtained by the usual procedure. The six antibiotics included in the rapid test were oxacilin, cefepime, imipenem, piperacillin-tazobactam, amikacin, and ciprofloxacin. Sensitivity data were comparable to those obtained by the standard procedure in 98% of cases. We have already demonstrated the impact of this method in improving and reducing the use of antimicrobials in patients with VAP (235). Patients with information provided by the direct E-test differed significantly from the second group in terms of the following factors: more days of adequate antibiotic treatment, smaller defined daily doses (DDD) of antibiotics, fewer days of fever, fewer episodes of diarrhea associated with *Clostridium difficile*, and less money spent on antibiotics.

### Assessing the Patient Response

Along with the findings of semiquantitative EA, the patient response should be assessed on day 3 of therapy (236). By this time, fever has resolved, the PaO<sub>2</sub>/FiO<sub>2</sub> is >250 mm Hg, and a normal white blood cell count is found in 73.3%, 74.7%, and 53.3% of patients, respectively (56). Other authors report that infection variables resolve after antimicrobial therapy in patients with VAP by day 6 (237). Resolution of radiologic opacities and clearance of secretions occur at a median time of 14 days and 6 days, respectively (56). However, failure to improve after 48 hours of therapy occurs in 65% of ARDS patients (56). Thus, ARDS significantly delays the clinical response to treatment in critically ill patients with VAP, although temperature is still the earliest resolved factor in this group of patients. Reassessment is necessary in patients who show no clinical improvement by day 3—especially those in whom the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and fever fail to improve—while for those showing a good response, it may be possible to design an abbreviated course of therapy (238,239).

Prompt empirical therapy for all patients suspected of having VAP should be balanced with the need to limit antimicrobial misuse in ICU's. The reassessment of the patient's situation based on culture results is another major principle. In patients with positive cultures, therapy can be tailored in terms of quality and duration. Patients with positive cultures who have not improved probably have VAP, but may be receiving inappropriate antimicrobial therapy; suffer a complication of VAP; have a second source of infection; or have a second diagnosis. The antimicrobial regimen should be adjusted, and, then, complications, other sites of infection, and other pathogens should be sought. In patients with negative cultures, the need to continue treatment with antimicrobial drugs should be promptly reassessed. Discontinuation of antimicrobial agents is presently recommended in patients with a stable condition, although in deteriorating or critically ill patients, it is difficult to make this decision.

### Value of Surveillance

Several research teams have addressed the issue of whether routine systematic surveillance of EA cultures may serve as a predictive diagnostic tool for VAP, although results have been contradictory (5,240–245). In a study performed at our center, the pathogens present in surveillance cultures taken prospectively on a twice-weekly basis did not correlate well with cultures obtained on diagnosis of VAP (5).

Table 5 summarizes the performance of the different culture methods for the diagnosis of VAP.

## ANTIMICROBIAL TREATMENT

### Selecting an Empirical Regimen

When trying to overcome severe infection, cardiovascular support and measures to improve hemodynamics and oxygenation are critical (56). The most important lesson learned in the last decade on the management of VAP is probably that delaying effective antimicrobial therapy in these patients increases mortality (65,122,125,260), length of stay, and costs (261).

As soon as there is clinical suspicion of VAP, adequate antibiotics should be administered to increase the likelihood of an early reduction in the bacterial load.

The first step is to decide whether a patient carries a low or high risk of having an MDR pathogen. The main risk factors for an MDR pathogen are (i) five or more days of prior hospitalization or mechanical ventilation, (ii) exposure to antibiotics in the preceding 90 days, (iii) a high incidence of antimicrobial resistance in the specific hospital unit, and (iv) comorbidities

**Table 5** Performance of the Different Culture Methods for Diagnosing VAP

Diagnostic technique	Cutoff	Sensitivity	Specificity	References
<b>Conventional</b>				
Tracheal aspirates	10 <sup>5</sup> cfu/mL	80% (60–97)	62% (41–74)	(227,246–248)
Tracheal aspirates	10 <sup>6</sup> cfu/mL	66% (38–82)	78% (72–85)	(229,249,250)
BAL	10 <sup>4</sup> cfu/mL	73% (42–93)	82% (45–100)	(203,230,251–255)
Protected specimen brush	10 <sup>3</sup> cfu/mL	66% (33–100)	90% (50–100)	(203,254,255)
Plugged telescoping catheter	10 <sup>3</sup> cfu/mL	72% (54–100)	82% (58–93)	(246,256,257)
<b>Blind</b>				
Tracheal aspirates	10 <sup>5</sup> cfu/mL	94%	50%	(205)
Bronchial suction	10 <sup>3</sup> –10 <sup>4</sup> cfu/mL	74%–97%	74%–100%	(258)
Mini BAL	10 <sup>3</sup> –10 <sup>4</sup> cfu/mL	63%–100%	66%–100%	(205, 258)
Protected specimen brush	10 <sup>3</sup> cfu/mL	66% (54–98)	91% (57–100)	(248,258,259)
Plugged telescoping catheter	10 <sup>3</sup> cfu/mL	65%	83%	(205)

Range given in parenthesis.

Abbreviations: CFU, Colony Forming Units; BAL, Bronchoalveolar Lavage.

such as the use of corticosteroids, head trauma, and lung structural disease among others (24,48,49,51,57,262–266).

Patients with none of these risk factors can be started on therapy with reduced-spectrum drugs such as ceftriaxone; a fluorquinolone (levofloxacin, moxifloxacin); ampicillin/sulbactam; or ertapenem. If the patient has any of the risk factors for an MDR pathogen, then a two- to three-drug regimen should be started, including an anti-*Pseudomonas* beta-lactam agent (cefepime or ceftazidime, or piperacillin/tazobactam or imipenem or meropenem); a second anti-*Pseudomonas* agent (aminoglycoside or an anti-*Pseudomonas* fluoroquinolone such as ciprofloxacin or levofloxacin); and a broad-spectrum agent against gram-positive microorganisms (linezolid or vancomycin) (see Table 6). Treatment should be started immediately after obtaining adequate samples for microbiological diagnosis.

### Treatment Based on Knowledge of the Etiologic Microorganism

A key issue in the antimicrobial treatment of VAP is the de-escalation of treatment once microbiological information becomes available. We have already mentioned that antimicrobial agents should be discontinued when appropriate culture results are negative. Targeted therapy strives to reduce antibiotic use while detecting no evidence of harm in the management of patients with VAP (267).

Once 24 to 48 hours have passed, information on the number and type of microorganisms growing in culture should be available. According to whether gram-negative microorganisms or gram-positive microorganisms are lacking, the specific drug against the corresponding microorganisms can be withdrawn even before the identity and susceptibility of the etiologic agent is known.

Microorganisms that deserve most attention are MRSA, *P. aeruginosa*, and *A. baumannii*.

Vancomycin is presently the standard agent against MRSA, although both industry-sponsored clinical trials and data from individual centers have consistently reported clinical failure rates of 40% or greater, at least using a standard dose. New evidence suggests that vancomycin failure could be related to inadequate dosing (268,269), and some authors argue that trough levels of around 15 to 20 mg/L are needed (270), although the success of this strategy requires confirmation in clinical trials. On the other hand, higher vancomycin MICs themselves may be associated with worse outcomes in patients with VAP due to MRSA. This was suggested in a prospective cohort study of 95 patients with nosocomial MRSA infection

**Table 6** Initial Empirical Antibiotic Treatment of VAP According to the Potential Pathogen

No known risk factors for MDR pathogens, early onset, and any disease severity		
Potential pathogen	Recommended AB	Dosing
<i>S. pneumoniae</i>	Ceftriaxone	2 g/day IV-IM
<i>H. influenzae</i>	or	
MSSA	levofloxacin,	500 mg/day IV-PO
Antibiotic sensitive	moxifloxacin or ciprofloxacin	400 mg/day PO
Gram-negative bacilli	or	750 mg/12 hr PO
( <i>E. coli</i> , <i>K. pneumoniae</i> ,	or	400 mg/12 hr IV
<i>Enterobacter</i> spp.,	ampicillin/sulbactam	
<i>Proteus</i> spp.,	or	1.5-3 g/6 hr IV
<i>S. marcescens</i> )	ertapenem	1g/day IV-IM
Risk factors for MDR pathogens, late-onset, and any disease severity		
Potential pathogen	Combination AB therapy	Dosing
Pathogens above and	Antipseudomonal cephalosporin	
<i>P. aeruginosa</i>	(cefepime,	1-2 g/8-12 hr IV
<i>K. pneumoniae</i> ESBL	ceftazidime)	2 g/8 hr
<i>Acinetobacter</i> spp.	Or	
	Antipseudomonal carbapenem	
	(imipenem,	500 mg/6 hr or 1 g/8 hr IV
	meropenem,	1 g/8 hr
	doripenem)	500 mg/8 hr infused over 4 hr
	or	
	$\beta$ -lactam/ $\beta$ -lactamase inhibitor	4.5 g/6 hr
	(piperacillin-tazobactam)	
	plus	
	Antipseudomonal fluorquinolone	
	(ciprofloxacin,	400 mg/8 hr IV
	levofloxacin)	750 mg/day
	or	
	Aminoglycoside	
	(amikacin,	20 mg/kg/day, single dose
	gentamicin,	7 mg/kg/day, single dose
	tobramycin)	7 mg/kg/day, single dose
MRSA	Linezolid	600 mg/12 hr IV
	or	
	Vancomycin	15 mg/kg/12 hr IV

treated with vancomycin, in which the targeted trough vancomycin concentration was at least four times the MIC (271). Strains of MRSA showing a high MIC of vancomycin ( $\geq 2 \mu\text{g/mL}$ ) were detected in 54% of patients. Despite achieving the target trough concentration, mortality was higher among patients whose MRSA strain had a high MIC than patients whose MRSA strain had a low MIC (24% vs. 10%). The addition of rifampin, aminoglycosides, or other drugs has achieved little improvement (272).

The use of new antimicrobial agents against MRSA has also been explored. Thus, quinupristin-dalfopristin has generated worse results than vancomycin (268). Linezolid, an oxazolidinone antimicrobial agent, is active against MRSA and achieves better tissue penetration than vancomycin, but is bacteriostatic rather than bactericidal (273,274). However, a combined analysis of the results of two randomized trials comparing linezolid with vancomycin for the treatment of nosocomial pneumonia (each in combination with aztreonam for gram-negative coverage) suggests a therapeutic advantage of linezolid (275). In a further analysis of a subset of patients with MRSA VAP, linezolid was associated with a significantly higher probability of bacterial eradication, clinical cure, and hospital survival (276). Despite higher costs, linezolid therapy for MRSA VAP was attributed an absolute mortality benefit of 22%, which translates to five patients as the number-needed-to-treat to save one life (276). On the basis of these findings, linezolid is now recommended as therapy for MRSA VAP (24).

Linezolid might be preferred in patients at risk of or with renal insufficiency in whom vancomycin is often associated with a risk of nephrotoxicity and thus underdosed. In particular, it is preferred in hospitals in which a substantial proportion of MRSA isolates show a vancomycin MIC  $\geq 1$   $\mu\text{g}/\text{mL}$ .

Further agents presently under investigation include tigecycline, a new glycylcycline antimicrobial derived from tetracyclines. Tigecycline has an extremely broad spectrum of action against gram-positive, gram-negative, and anaerobic pathogens, with the exception of *Pseudomonas* (277). Its role in VAP is currently being re-evaluated in a new phase III clinical trial. Still, the need for mechanical ventilation has been associated with lower microbiologic clearance (278), and cancer patients with refractory pneumonia seem to show a relatively low clinical response rate when treated with this drug (51%) (279).

Daptomycin cannot be used to treat pneumonia because it gets inactivated by lung surfactant in the respiratory tract. Investigational glycopeptides, such as telavancin and oritavancin, may eventually play a role in the treatment of nosocomial pneumonia, but a definite date cannot be stated at present.

An anti-MRSA cephalosporin, ceftobiprole, is being evaluated for effectiveness against nosocomial pneumonia in a phase III clinical trial. Pneumonia due to *P. aeruginosa* in ventilated patients is frequently a recurrent disease, caused most of the time by several relapsing infections (280). Frequently, the pathogens are MDR, such that no single antibiotic is active against all isolates. Empirical therapy includes the combination of two drugs active against *P. aeruginosa* to improve the chances of successful early treatment. Once the susceptibility pattern is known, many physicians prefer combination therapy with a beta-lactam agent plus either an aminoglycoside or an anti-*Pseudomonas* fluoroquinolone, based on early findings in patients with bloodstream infections (281).

Despite combination therapy targeted at gram-negative microorganisms being common clinical practice, there is presently no evidence to suggest that combination therapy has any benefit over monotherapy in patients with VAP or other forms of nosocomial pneumonia (282–284).

In select patients with infections caused by MDR strains, aerosolized colistin has proved beneficial as supplemental therapy (285).

The non-fermenting gram-negative rod, *A. baumannii*, has been held responsible for the recent rise in VAP. This bacterium is intrinsically resistant to many antimicrobial agents, and the agents found to be most active against it are carbapenems, sulbactam, and polymyxins (56,58). In effect, intravenous carbapenem is the treatment of choice today for MDR isolates of *A. baumannii* (286). In patients with strains resistant to carbapenems, intravenous colistin has been successfully used (59).

### Adequate Dosing

To ensure the best outcome, it is essential that the dosing of initial antibiotics for suspected MDR pathogens is adequate (274). All too often, agents are initially underdosed. For example, vancomycin should not be routinely given at a dose of 1 g q12h, but rather the dose should be calculated by weight in mg/kg (a dose that needs adjusting for renal impairment). Retrospective pharmacokinetic modeling has suggested that the failures described for vancomycin could be the result of inadequate dosing. Many physicians aim for a trough vancomycin concentration of at least 15 to 20 mg/L, although, as mentioned in the previous section, the success of this strategy has not been prospectively confirmed. Only one matched cohort study exists in which continuous vancomycin infusion was associated with reduced mortality (287).

Some antibiotics penetrate well and achieve high local concentrations in the lungs, while others do not. For example, most beta-lactam antibiotics achieve less than 50% of their serum concentration in the lungs, while fluoroquinolones and linezolid attain equivalent or higher concentrations than blood levels in bronchial secretions. Table 7 shows how to adjust the antibiotic dose in patients with renal impairment.

### Aerosolized Antibiotics

All patients with VAP should initially receive antibiotics intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients. The direct aerosol

**Table 7** Antibiotic Dose Adjustment in Patients with Renal Impairment

Antibiotic	CrCl (mL/min)	Dose adjustment	
Amikacin	≥40	15 mg/kg/24 hr	
	30–39	15 mg/kg/36 hr	
	20–29	15 mg/kg/48 hr	
	<20	7.5 mg/kg × 1 & consult kinetics	
Ampicillin/sulbactam	>30	Normal dose IV q6h	
	15–30	Normal dose IV q12h	
	<15	Normal dose IV q24h	
Cefepime	>60	No adjustment	
	30–60	1–2 g/24 hr	
	11–29	500 mg–1 g/24 hr	
	<11	250–500 mg/24 hr	
Ceftazidime	>50	1–2g/8 hr	
	10–50	1–2g/12 hr	
	<10	1 g/24–48 hr	
Ceftriaxone	Adults with both kidney and liver failure should not receive more than 2g/24 hr		
Ciprofloxacin	>50	750 mg/12 hr PO 400 mg/12 hr IV	
	10–50	250–500 mg/12 hr PO 400 mg/18 hr IV	
	<10	250–500 mg/18h po 400 mg/24h iv	
Doripenem	>50	No adjustment	
	30–50	250 mg/8 hr infused over 1 hr	
	10–30	250 mg/12 hr infused over 1 hr	
Ertapenem	>31	No adjustment	
	≤30	500 mg/24 hr IV–IM	
Gentamicin	≥50	5 mg/kg/24 hr	
	30–49	5 mg/kg/36 hr	
	20–29	5 mg/kg/48 hr	
	<20	2 mg/kg × 1 & consult kinetics	
Imipenem	≥71	≥70 kg: 500 mg/6 hr 60–69 kg: 500 mg/8 hr 50–59 kg: 250 mg/6 hr 40–49 kg: 250 mg/6 hr 30–39 kg: 250 mg/8 hr	
	41–70	≥70 kg: 500 mg/8 hr 60–69 kg: 250 mg/6 hr 50–59 kg: 250 mg/6 hr 40–49 kg: 250 mg/8 hr 30–39 kg 125 mg/6 hr	
	21–40	≥70 kg: 250 mg/6 hr 60–69 kg: 250 mg/8 hr 50–59 kg: 250 mg/8 hr 40–49 kg: 250 mg/12 hr 30–39 kg: 125 mg/8 hr	
	6–20	≥70 kg: 250 mg/12 hr 60–69 kg: 250 mg/12 hr 50–59 kg: 250 mg/12 hr 40–49 kg: 250 mg/12 hr 30–39 kg: 125 mg/12 hr	
		Patients with CrCl ≤5 mL/min should not receive imipenem/cilastatin unless dialysis is programmed within 48 hr. These patients may be at an increased risk of seizures.	
	Levofloxacin	>50	500 mg/24 hr
		20–49	500 mg/48 hr
		<20	500 mg × 1, then 250 mg/48 hr
	Linezolid	No adjustment	
	Meropenem	>50	No adjustment
		26–50	Normal dose q12h
		10–25	50% normal dose q12h
		<10	50% normal dose q24h

**Table 7** Antibiotic Dose Adjustment in Patients with Renal Impairment (*Continued*)

Antibiotic	CrCl (mL/min)	Dose adjustment
Moxifloxacin	No adjustment	
Piperacillin–tazobactam	>40	No adjustment
	20–40	4.5 g/8 hr
	<20	4.5 g/12 hr
Tobramycin	≥50	5 mg/kg/24 hr
	30–49	5 mg/kg/36 hr
	20–29	5 mg/kg/48 hr
	<20	2 mg/kg × 1 & consult kinetics
Vancomycin	>50	15mg/kg/12 hr
	10–50	1g/3–10 day
	<10	1g/5–10 day

CrCl: creatinine clearance calculated using the formula:

Males:  $[(140 - \text{age}) \times \text{IBW}] / [\text{SrCr} \times 72]$

where

Age: age in years

IBW: ideal body weight in kg

IBW in men = 50 kg + 2.3 kg per inch of height over 60 inches

IBW in women = 45.5 kg + 2.3 kg per inch of height over 60 inches

SrCr = serum creatinine in mg/dL

Females = CrCl (males) × 0.85

delivery of antibiotics is not considered standard therapy for either prophylaxis or the treatment of lower respiratory tract infections (288).

In the past, aminoglycosides and polymyxins were the most common agents used in aerosols.

In a prospective randomized trial, the use of intravenous therapy was compared to the same treatment plus aerosolized tobramycin. The results of this trial suggest no better clinical outcome, but bacterial cultures of the lower respiratory tract were more rapidly eradicated (295).

At present, aerosolized antimicrobial therapy is mainly limited to MDR pathogens for which no other treatment exists. Such is the case of MDR *P. aeruginosa* and *A. baumannii*, which are treated with intratracheal colistin (285).

### Monotherapy vs. Combination Therapy

When considering the use of a single antimicrobial agent as opposed to combined therapy, we first need to make the distinction between the use of multiple antimicrobial agents in the initial empirical regimen (to ensure that a highly resistant pathogen is covered by at least one drug) and that of combination therapy continued intentionally after the pathogen is known to be susceptible to both agents. The former use of combination therapy is uniformly recommended, whereas the latter use remains controversial.

The benefits commonly attributed to combination therapy include synergy between drugs and the potential reduction of resistance problems. However, the combined regimen has been even found to fail at avoiding the development of resistance during therapy (283).

Two meta-analyses have recently explored the value of combination antimicrobial therapy in patients with sepsis (284) and gram-negative bacteremia (289). No benefits of combination therapy were shown, and nephrotoxicity in patients with sepsis or bacteremia increased. However, in the subset of bacteremic patients infected with *P. aeruginosa*, combination therapy (usually a beta-lactam and an aminoglycoside) reduced the risk of mortality by half. A trend toward improved survival has been previously observed with aminoglycoside-including, but not quinolone-including, combinations (8). Combination therapy could, therefore, be beneficial in patients with severe antimicrobial-resistant infections. Whether this benefit is due to a more reliable initial coverage or a synergistic effect is unclear (290). The general consensus at present is to opt for combination therapy with an aminoglycoside for the initial five days in patients with VAP caused by gram-negative bacilli (24,178). The nephrotoxicity of aminoglycosides, nevertheless, limits the use of these agents.



### Duration of Therapy

The ideal length of antibiotic therapy is still under debate. In a prospective randomized clinical trial, Chastre et al. (291) demonstrated that an 8-day antibiotic regimen is comparable to a 15-day regimen in terms of mortality, superinfections, and VAP recurrence. A seven-day treatment course was described as safe, effective, and less likely to promote the growth of resistant organisms in patients who are clinically improving. Patients with VAP caused by non-fermenting gram-negative bacilli, including *P. aeruginosa*, given 8 days of antimicrobial therapy had no less favorable outcomes, but had a higher infection-recurrence rate compared with those receiving 15 days of treatment (40.6% vs. 25.4%; difference, 15.2%, 90% CI, 2.9 to 26.6). This was not found in patients with VAP caused by MRSA, in whom infection recurrence was 14.3% and 19% for the 8- and 15-day courses of antibiotics, respectively (90% CI, -9.9 to 0.4). Most authors agree, nevertheless, that the length of treatment should be tailored to suit each patient (264).

Resolution patterns can help optimize the duration of antibiotic therapy. Thus, after 48 to 72 hours of defervescence (apyrexia) and resolution of hypoxemia, antibiotic therapy can be withdrawn (56). In patients with ARDS, fever is the main clinical variable used to evaluate the response to therapy.

### Examining the Causes of Treatment Failure

Treatment failure should be assessed to simultaneously determine both the pulmonary/extrapulmonary and infectious/non-infectious causes of a failed response. The etiology of treatment failure can be ascribed to three possible causes: (a) inadequate antibiotic treatment, (b) concomitant foci of infection, or (c) a noninfectious origin of disease (292). In a study designed to establish the causes of nonresponse to treatment in VAP patients in an ICU performed by Ioanas et al. (293), of a total of 71 patients, 44 (62%) were described as nonresponders. In 64% of these nonresponders, at least one cause of nonresponse was identified: inappropriate treatment (23%), superinfection (14%), concomitant foci of infection (27%), and noninfectious origin (16%). The remaining nonresponding patients experienced septic shock or multiple organ dysfunction or had acute respiratory distress syndrome. In this type of situation, we would recommend the following: when there is clinical worsening and a positive culture result, antimicrobial treatment should be adjusted and resistance assessed; further respiratory sampling should be undertaken, using invasive techniques; central lines should be checked and removed, if necessary, and surveillance cultures taken (294); urine cultures; echocardiography; and ultrasonographic examination of the abdomen. Further possible examinations include CT scans of the sinuses, chest CT (to check for pulmonary embolism or abscess and empyema formation), and abdominal CT.

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# 12 | Intravenous Central Line Infections in Critical Care

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## INTRODUCTION

Intravenous central venous catheters (CVCs) are used for medication, fluid, or nutritional delivery to large vessels. Intravenous CVCs may be inserted centrally, i.e., internal jugular (IJ) vein, subclavian (SC) vein, or femoral vein, or may be inserted peripherally, i.e., peripherally inserted central catheters (PICC) into central veins. Complications of CVCs may be mechanical/infectious. The three most common infectious complications of CVC include line-associated bacteremias, septic thrombophlebitis, and acute bacterial endocarditis (ABE). The most common organisms associated with CVC infections are methicillin-sensitive *Staphylococcus aureus* (MSSA)/methicillin-resistant *S. aureus* (MRSA), *S. epidermitis* also known as coagulase-negative staphylococci (CoNS), and less commonly aerobic gram-negative bacilli (GNBs). Excluding femoral CVC, enterococci are uncommon causes of CVC. Fungal CVC infections may occur with CVCs in place for an extended period of time or when receiving total parental nutrition (TPN). Because most patients in CCUs often have one or more CVCs, clinicians caring for patients with CVCs should be familiar with the differential diagnosis, complications, and therapy of CVC infections (1–10).

There are several factors that predispose to CVC infections. After careful aseptic insertion technique, the most important factors predisposing to CVC infection are duration and location of insertion of CVCs. IV CVC-line infections are also a function of time. CVC-related line infection is uncommon before seven days, but after seven days, there is a gradual increase over time in the incidence of CVC-line infections. The number of CVC lumens may increase the potential for infection. In a patient with otherwise unexplained fever in the CCU, the longer a CVC is in place, the more likely the CVC is the cause of fever. An important determinant of CVC-line infections is the anatomical location of CVC insertion. The best anatomical location with the lowest potential for infection is the SC vein, followed by the IJ vein. From an infectious perspective, the least-desirable location is the femoral vein. Peripheral IV lines rarely result in intravenous line bacteremias. Resultant bacteremia, i.e., intermittent/low blood culture positivity, will not result in ABE. In the unlikely event that peripheral IV lines are the source of any intermittent/low blood culture positivity, bacteremias will not result in ABE subsequently (1–5,11–15) (Tables 1 and 2).

## DIAGNOSIS OF CVC INFECTIONS

The main diagnostic difficulty with CVC infections is that, only 50% of CVC infections have any local indication of infection. When the insertion site is red/painful, the diagnosis of CVC infection is obvious. Differentiating chemical phlebitis /IV line infiltration from cellulitis is usually straightforward. The skin at the IV insertion site with IV infiltration/phlebitis is swollen and painful but not erythematous. IV line infections secondary to CVC should be suspected where the other causes of fever have been ruled out. As mentioned, the likelihood of CVC-related infection increases over time, the longer the CVC has been in place as well as anatomical location of the insertion (1,4,11,16).

In the absence of local signs of infection, CVC infections may be diagnosed by blood cultures and semi-quantitative (SQ) catheter tip cultures. If CVC infection is suspected, the catheter should be removed and the tip sent for an SQ culture. Simultaneously, blood cultures should be drawn from a peripheral vein, not through the CVC. Excluding skin contaminants

**Table 1** Pathogens Associated with CVC Infections

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Most common pathogens
<i>S. aureus</i> (MSSA/MRSA)
<i>S. epidermidis</i> (CoNS)
Enterobacter sp.
<i>K. pneumoniae</i>
Uncommon pathogens <sup>a</sup>
Enterococci <i>E. faecalis</i> (VSE) or <i>E. faecium</i> (VRE)
<i>Burkholderia</i> ( <i>Pseudomonas</i> ) <i>cepacia</i> <sup>b</sup>
<i>Stenotrophomonas</i> ( <i>Xanthomonas</i> ) <i>maltophilia</i> <sup>b</sup>
<i>Citrobacter freundii</i> <sup>b</sup>
<i>Serratia marcescens</i> <sup>b</sup>

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<sup>a</sup>*Pseudomonas aeruginosa* is a rare CVC pathogen.

<sup>b</sup>Often associated with contaminated infusate

**Abbreviations:** CoNS: coagulase-negative staphylococci; MSSA/MRSA, methicillin-sensitive *S. aureus*/methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

**Source:** Adapted from Ref. 1.

**Table 2** Risk Factors Associated with CVC Infections

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Key risk factors for CVC infections
• Aseptic insertion technique
• Duration of catheterization (catheter days)
• Anatomical location of catheter insertion (femoral vein > IJ vein > SC vein)
• CVC maintenance care
Other factors in CVC infections
• Number of catheter lumens (single vs. triple lumen)
• Secondary bacteremias
• CVC junctional disconnects/medication injections
• Contaminated infusate

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**Abbreviations:** CVC, central venous catheters; IJ, internal jugular; SC, subclavian.

**Source:** Adapted from Ref. 1.

acquired during venipuncture, CVC infection is diagnosed if the blood culture isolate is the same organism recovered from the removed CVC SQ tip culture. For the CVC tip culture to be considered positive,  $\geq 15$  colonies should be present. Positive CVC tip cultures without bacteremia indicate the catheter colonization and not CVC infection. Bacteremia without a positive CVC tip culture indicates bacteremia unrelated to the CVC (1,4,11,16).

The empiric therapy of CVC infections is usually two weeks with antibiotics, with MSSA/MSRA, and anti-GNB activity if CVC-related bacteremia is due to MSSA/MRSA and ABE (11). Near the end of the therapy, MSSA/MSRA ABE should be ruled out by transthoracic echocardiography (TTE)/transesophageal echocardiography (TEE). Teichoic acid antibody (TAA) should be obtained. If TAA titers two weeks after bacteremia/CVC removal are elevated (i.e., > 1:8), then anti-MSSA/MRSA therapy should be continued for four weeks. Cardiac echocardiography (TTE/TEE) should be done to rule out ABE in those with high-grade/persistent MSSA/MRSA bacteremia during/following an MSSA/MRSA CVC infection. For ABE screening purposes, a TTE is sufficiently sensitive/specific to detect vegetations on native heart valve. For prosthetic valves, TEE is preferred to detect vegetations (17–39) (Table 3).

## COMPLICATIONS OF CVC INFECTIONS

### Septic Thrombophlebitis

Simple or uncomplicated phlebitis may be associated with low-grade fevers (102°F) but not usually bacteremia. If bacteremia due to skin organisms usually *S. aureus* or CoNS complicates phlebitis, the bacteremia is intermittent/low intensity. Septic thrombophlebitis is an intraluminal infection within the vein. Clinical findings resemble phlebitis except that patients

**Table 3** Diagnosis of CVC Infection

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- I. Epidemiologic diagnosis
- Patients with CVC who develop bacteremias (due to CVC pathogens)
  - No other site of infection with same organisms as in BCs
- II. Clinical diagnosis of CVC infection
- CVC obviously infected CVC (only site erythematous/warm  $\pm$  purulent).
  - If present, culture purulent discharge.
  - Remove CVC and culture tip.
- III. Suspected CVC infection
- Obtain BCs (4) from peripheral vein.
- Do not obtain blood for BCs via the CVC.*
- (Only draw BCs though CVC if no other venous access available)
- remove CVC and end culture tip for SQ catheter tip culture.
  - if venous access still required, replace removed CVC over guidewire while BCs and removed CV tip cultures pending.
    - If CVC tip culture is *negative*, continue to use replaced CVC.
    - If CVC tip culture is *positive* (>15 colonies) and *isolate same as BC isolate taken from peripheral vein*, remove replaced CVC and insert new CVC at another site.
- IV. Therapy of non-CVC infections
- Do not treat non-CVC infections
    - Positive BCs with negative culture of CVC tip.
    - Positive CVC tip culture with negative BCs.
    - Positive BCs with separate CVC catheter tip culture of < 15 colonies.
  - Empiric therapy of CVC
    - Before BC results are known, direct antibiotic therapy against MSSA, aerobic GNBs, and VSE.
    - In institutions where *MSSA more prevalent than MRSA*, begin therapy with meropenem.
    - In institutions where *MRSA are more prevalent than MSSA*, begin therapy with tigacycline or ceftriaxone plus linezolid. If no ABE, treat for 2 wk after CVC removal.
  - If CVC infection due to MSSA, MRSA, or VRE, obtain baseline TTE and at 2 wk to r/o ABE.
    - When BC and CVC tip cultures are known.
    - Continue empiric therapy with meropenem *if isolate is meropenem susceptible*.
    - If isolate is meropenem-resistant*, change therapy to tigacycline or ceftriaxone plus linezolid.
- 

*Abbreviations:* CVC, central venous catheter; BCs, blood cultures; ABE, acute bacterial endocarditis; GNB, gram-negative bacilli; IJ, internal jugular; SC, subclavian; TTE, transthoracic echocardiogram; VSE, vancomycin sensitive enterococci.

are clinically ill with fevers of  $\geq 102^{\circ}\text{F}$  accompanied by rigors. Blood culture positivity is usually of high grade, i.e., 3/4–4/4. The diagnosis of septic thrombophlebitis may be suspected on CT/MRI of the vein/removal of the CVC with pus emanating from the catheter wound. A palpable cord is also often present. Therapy for septic thrombophlebitis is venotomy. After venotomy if ABE is not present, anti-MSSA/MRSA therapy should be continued for two to four weeks (1,7–13).

### ***S. aureus* ABE**

*S. aureus* (MSSA/MRSA) is the commonest cause of ABE. During a prolonged high-grade MSSA/MRSA bacteremia, *S. aureus* can attack normal or native heart valves. In contrast subacute bacterial endocarditis (SBE) due avirulent pathogens, e.g., viridans streptococci require preexisting valvular damage to cause SBE. The key factors that predispose to MSSA/MRSA ABE are prolonged/high-grade MSSA/MRSA bacteremia from a distant focus, e.g., abscess, CVC, pacemaker lead, or an invasive cardiac procedure such as radio frequency ablation (RFA). ABE is not a complication of peripheral IV-line infections (11,13,35,36,39).

The clinical diagnosis of *S. aureus* ABE requires two key diagnostic components. Firstly, the patient must have a continuous/prolonged high grade MSSA/MRSA bacteremia, i.e., 3/4 or 4/4 repeatedly. Secondly, demonstration of a vegetation by TTE/TEE is necessary. *S. aureus* bacteremia that is not high grade/prolonged indicates a transient staphylococcal bacteremia and is not indicative of endocarditis per se. In *S. aureus* endocarditis, the bacteremia characteristically is of high grade and prolonged. Prolonged, high-grade *S. aureus* bacteremia without vegetation on TTE/TEE should suggest intravascular or an extracardiac

focus. Patients with ABE often have no initial murmur or may have a new/rapidly changing cardiac murmur. With lung ABE, often there has been sufficient time for valvular damage to manifest with a cardiac murmur. In patients without bacteremia there is no rationale to get a TTE/TEE to rule out ABE, the vegetation is an incidental finding and not diagnostic of ABE. Sterile vegetations, i.e., marantic endocarditis, may occur in association with malignancy and nonmalignant disorders, e.g., Libman-Saks endocarditis. The diagnosis of MSSA/MRSA is based on demonstrating a continuous/high-grade bacteremia in a patient with vegetation by cardiac. A cardiac murmur may or may not be present. In non-IVDAs, the fever in ABE is usually  $\geq 102^{\circ}\text{F}$  (1,13,36,39) (Tables 4 to 6).

The treatment of MSSA/MRSA ABE is for four to six weeks. For MSSA ABE, treatment is usually with oxacillin, nafcillin, or first-generation cephalosporin, e.g., cephazolin. In penicillin-allergic patients with MSSA ABE/MRSA ABE, quinupristin/dalfopristin, minocycline, linezolid, or daptomycin have been used. Because therapy of MRSA/MSSA is prolonged, i.e., four to six weeks, oral therapy for all or part of the therapy is desirable. The only two oral antibiotics available to treat MRSA ABE orally are minocycline and linezolid (37,39–51) (Tables 7 to 10).

Vancomycin is inferior to  $\beta$ -lactam therapy of MSSA bacteremia/ABE. For MRSA bacteremia/ABE, vancomycin has been associated with acquired resistance/therapeutic failures. Vancomycin serum levels are unhelpful in avoiding nephrotoxicity or optimizing therapeutic outcomes (44–56).

Nafcillin plus gentamicin or rifampin is not more effective than nafcillin alone against MSSA. Combination therapy for MSSA/MRSA has no demonstrated benefit. Vancomycin plus rifampin is often antagonistic (46–51,56). Vancomycin is not nephrotoxic even when combined with aminoglycosides. In terms of pharmacokinetic and pharmacodynamic (PK/PD)

**Table 4** Infectious Complications of CVCs

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I. CVC related bacteremias
A. Diagnostic features
• Bacteremia of intermittent and of variable duration/intensity (1/4, 1/2, 2/4)
• Temperatures usually $\leq 102^{\circ}\text{F}$
B. Therapy
• Remove CVC
• Antibiotic therapy x 2 wk (after CVC removal)
II. Septic thrombophlebitis
A. Diagnostic features
• CVC infection
• High-grade/continuous bacteremia
• Pus from CVC site when CVC removed
• Palpable venous cord often present
• Temperatures usually $\geq 102^{\circ}\text{F}$
• TTE/TEE negative (if no ABE)
B. Therapy
• Remove CVC
• Venotomy preferable
• Antibiotic therapy x 2 to 4 wk (if no ABE)
III. MSSA/MRSA ABE
A. Diagnostic features
• Continuous prolonged/high-grade bacteremia (3/4, 4/4)
• Cardiac vegetation on TTE/TEE
• Cardiac murmur may (not be present early, later new/changing murmur)
• ESR $\uparrow$ ( $\sim 30$ – $50$ mm/h)
• TAA titers usually elevated ( $> 1:4$ )
B. Therapy
• Antibiotic treatment directed against MSSA or MRSA when susceptibility to oxacillin/methicillin known
• Depending on oxacillin/methicillin sensitivity, treat MSSA or MRSA for 4 to 6 wk
• Verify cardiac vegetation regression/resolution of with serial TTEs, serial BCs, $\downarrow$ ESR, $\downarrow$ TAA titers

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*Abbreviations:* BC, blood culture; ESR, erythrocyte sedimentation rate; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TAA, teichoic acid antibody; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.



**Table 5** Classification of MRSA Infections

MRSA Strain	Description	Treatment
HA-MRSA	These strains originate within the hospital environment and have SCC <i>mec</i> I,II,III genes.	Pan-resistant to most antibiotics. Only vancomycin, quinupristin/dalfopristin, minocycline, linezolid, tigecycline, and daptomycin are reliably effective.
CO-MRSA	These strains originate from the hospital environment but later present from the community. They too have SCC <i>mec</i> I,II,III genes (CO-MRSA = HA-MRSA).	Since CO-MRSA strains are in actuality HA-MRSA strains that present from the community, they should be treated as HA-MRSA.
CA-MRSA	<i>Only</i> community MRSA infections presenting with severe pyomyositis or severe/necrotizing community-acquired pneumonia (with influenza) should be considered as CA-MRSA PVL-positive strains (SCC <i>mec</i> IV, V genes). <i>All other MRSA infections presenting from the community should be regarded as CO-MRSA.</i>	CA-MRSA are pauci-resistant, i.e., susceptible to clindamycin, TMP-SMX, and doxycycline. Antibiotics used to treat CO-MRSA/HA-MRSA are effective against CA-MRSA, but <i>not</i> vice versa. Therefore, all MRSA strains can be treated as CO-MRSA/HA-MRSA.

*Abbreviations:* CA-MRSA, community-acquired MRSA; CO-MRSA, community-onset; MRSA HA-MRSA, hospital-acquired MRSA; PVL, Panton-Valentine Leukocidin; SCC, staphylococcal cassette chromosome; TMP-SMX, trimethoprim-sulfamethoxazole.

*Source:* Adapted from Refs. 66 and 67.

**Table 6** Diagnostic Clinical Pathway: MSSA/MRSA ABE

<ul style="list-style-type: none"> <li>• Differentiate <i>S. aureus</i> blood culture positivity (1/2–1/4) from bacteremia (3/4–4/4) positive blood cultures.</li> <li>• With <i>S. aureus</i> bacteremia, differentiate low-intensity/intermittent bacteremia (1/2–2/4) positive blood cultures from continuous/high-intensity bacteremia (3/4–4/4 positive blood cultures).</li> <li>• ABE is <i>not</i> a complication of low-intensity/intermittent <i>S. aureus</i> bacteremia. TTE/TEE unnecessary, but will verify no vegetations.</li> <li>• If continuous/high-grade MSSA/MRSA bacteremia, obtain a TTE or TEE to rule out or document cardiac vegetation and confirm diagnosis of ABE.</li> <li>• Diagnostic criteria for MSSA/MRSA ABE <ul style="list-style-type: none"> <li>• Essential features <ul style="list-style-type: none"> <li>Continuous/high-grade MSSA/MRSA bacteremia</li> <li>Cardiac vegetation on TTE/TEE</li> </ul> </li> <li>• Nonessential features <ul style="list-style-type: none"> <li>Fever <math>\geq 102^{\circ}\text{F}</math> (non-IVDAs)</li> <li>Murmur<sup>a</sup></li> </ul> </li> </ul> </li> </ul>
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<sup>a</sup>With early MSSA/MRSA, a murmur is not present. Later, a new murmur in ABE indicates a vegetation or valvular destruction.

*Abbreviations:* MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; ABE, acute bacterial endocarditis.

*Source:* Ref. 68.

**Table 7** Factors in the Selection of Antimicrobial Therapy for MSSA/MRSA Bacteremias

<ul style="list-style-type: none"> <li>• Select an antibiotic with known clinical efficacy and a high degree of activity against the presumed or known pathogen, e.g., VSE, VRE, MSSA, or MRSA.</li> <li>• If needed, <i>adjust dosage</i> to achieve therapeutic concentrations in serum/tissue.</li> <li>• Select a “low resistance” potential antibiotic, e.g., ertapenem, amikacin, minocycline, moxifloxacin, levofloxacin, meropenem, tigecycline, and etc. Avoid “high resistance” potential antibiotics, e.g., imipenem, ciprofloxacin, gentamicin, tobramycin, and minimize the use of those that select out on resistant organisms, e.g., vancomycin, ceftazidime.</li> <li>• Select an antibiotic with a favorable safety profile and a low <i>C. difficile</i> potential, e.g., daptomycin, tigecycline, linezolid, Q/D, minocycline.</li> <li>• Select an antibiotic that is relatively cost-effective in the clinical context of bacteremia/endocarditis.</li> <li>• If possible, select an oral antibiotic that is the same or equivalent to intravenous therapy for all/or part (IV→PO switch) of the duration of antimicrobial therapy.</li> </ul>
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<sup>a</sup>Bactericidal preferred for therapy of ABE.

*Abbreviations:* IV, intravenous; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; Q/D, quinupristin/dalfopristin; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

*Source:* Adapted from Ref. 69.

**Table 8** Vancomycin Delayed Resolution/Failure in Treating MSSA/MRSA Bacteremias and ABE

	Failure Rates	Duration of Bacteremia	References
● MSSA bacteremia	Nafcillin: 4% Vancomycin: 20%	Nafcillin: 2 days Vancomycin: 7 days (20% > 3 days) (12% > 7 days)	Hackbarth
● MSSA ABE	Nafcillin 1.4%–26% Vancomycin: 37%–50%	Nafcillin: 2 days Vancomycin: 5 days	Gentry Geraci Chang Small
● MRSA ABE		Nafcillin: Not applicable Vancomycin: > 7 days	

*Abbreviations:* ABE, acute bacterial endocarditis; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

*Source:* Adapted from Ref. 56.

**Table 9** Suboptimal Combination Therapy for MSSA and MRSA ABE

Antibiotic Combinations	Comments	References
● MSSA ABE Nafcillin + gentamicin Vancomycin + gentamicin	Outcomes same ± gentamicin	Lee
● MRSA ABE Vancomycin Vancomycin + rifampin	Duration of bacteremia: 7 days Duration of bacteremia: 9 days (antagonistic; <i>not synergistic</i> )	Levine Shelburne

*Abbreviations:* ABE, acute bacterial endocarditis; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

*Source:* Adapted from Ref. 56.

**Table 10** Antibiotic Therapy of MSSA and MRSA Bacteremias

Antibiotics/ Pathogens	Attribute	Disadvantages
<b><i>S. aureus</i> (MSSA)</b>		
Nafcillin	<ul style="list-style-type: none"> <li>● <i>Most active</i> anti-MSSA antibiotic</li> <li>● The only anti-MSSA penicillin with a enterohepatic circulation</li> <li>● Inexpensive</li> <li>● Long experience</li> <li>● No dosing modification in CRF</li> <li>● Low resistance potential</li> <li>● No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>● Short <math>t_{1/2}</math> <i>requires frequent dosing (q4h)</i></li> <li>● Drug fevers (common)</li> <li>● Interstitial nephritis (rare) (avoid oral anti-MSSA PCNs that are <i>not</i> well absorbed instead use oral first-generation cephalosporin, cephalexin)</li> </ul>
Cefazolin	<ul style="list-style-type: none"> <li>● <i>Most active</i> anti-MSSA <i>cephalosporin</i> clinical effectiveness/outcomes nafcillin</li> <li>● Long experience</li> <li>● Inexpensive</li> <li>● Low resistance potential</li> <li>● High <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>● Drug fevers (common)</li> <li>● Avoid in patients with <i>anaphylactic reactions</i> to PCN</li> <li>● No oral formulation (use oral first-generation cephalosporin, cephalexin)</li> </ul>
Ceftriaxone	<ul style="list-style-type: none"> <li>● <i>Less anti-MSSA activity</i> than nafcillin or cefazolin</li> <li>● Low resistance potential</li> <li>● Low <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>● No oral formulation (use oral first-generation cephalosporin, cephalexin)</li> <li>● <i>Non-C. difficile</i> diarrhea (common)</li> <li>● Pseudobiliary lithiasis</li> </ul>

**Table 10** Antibiotic Therapy of MSSA and MRSA Bacteremias (*continued*)

Antibiotics/ Pathogens	Attribute	Disadvantages
Clindamycin	<ul style="list-style-type: none"> <li>• Inexpensive</li> <li>• MSSA excellent for infections (<i>except</i> ABE)</li> <li>• IV/PO formulations</li> <li>• Low resistance potential</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Not</i> active against MRSA</li> <li>• <i>Not</i> useful for MSSA ABE</li> <li>• High <i>C. difficile</i> potential</li> <li>• Alternately, use oral linezolid or minocycline</li> </ul>
<b><i>S. aureus</i> (MRSA)</b>		
Vancomycin	<ul style="list-style-type: none"> <li>• <i>Less</i> active against MSSA than nafcillin</li> <li>• Long experience</li> <li>• <i>Not</i> nephrotoxic</li> </ul>	<ul style="list-style-type: none"> <li>• Permeability mediated resistance during/after therapy (due to cell wall thickening)</li> <li>• No <i>oral</i> formulation for bacteremia/SBE</li> <li>• No <i>oral</i> formulation</li> </ul>
Quinupristin/ dalfopristin	<ul style="list-style-type: none"> <li>• Useful for MSSA/MRSA</li> <li>• Useful in cases of daptomycin-resistant MSSA/MRSA (rare)</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Severe/prolonged myalgias</i></li> <li>• No oral formulation</li> <li>• Leukopenia/thrombocytopenia (uncommon)</li> </ul>
Linezolid	<ul style="list-style-type: none"> <li>• No/low hypersensitivity potential</li> <li>• Active against both MSSA/MRSA</li> <li>• <i>Bacteriostatic</i> but useful to treat MSSA/MRSA ABE</li> <li>• No dosage modification in CRF</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively expensive</li> <li>• Oral formulation (high bioavailability)</li> <li>• Thrombocytopenia (after &gt; 2 wk)</li> <li>• Serotonin syndrome (rare)</li> </ul>
Daptomycin	<ul style="list-style-type: none"> <li>• No dosage reduction in CRF (↑ dosing interval)</li> <li>• For MSSA/MRSA bacteremias/ABE use 6 mg/kg dose</li> <li>• “If MRSA bacteremia persists &gt; 72 hr use “high dose” (12 mg/kg) daptomycin</li> <li>• Not nephrotoxic</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Following vancomycin therapy, resistance may occur during therapy (rarely)</li> <li>• No oral formulation</li> <li>• Alternately, use oral linezolid or minocycline</li> </ul>
Tigecycline	<ul style="list-style-type: none"> <li>• Active against MSSA/MRSA</li> <li>• No dosing modification in CRF</li> <li>• Not nephrotoxic</li> <li>• No/low resistance potential</li> <li>• No <i>C. difficile</i> potential</li> <li>• Useful in PCN/sulfa allergy</li> </ul>	<ul style="list-style-type: none"> <li>• No oral formulation</li> <li>• Alternately, use oral linezolid or minocycline</li> </ul>
Minocycline	<ul style="list-style-type: none"> <li>• Available IV/PO</li> <li>• Limited experience but useful for MSSA/MRSA bacteremias/ABE</li> <li>• Inexpensive</li> <li>• No/low resistance potential</li> <li>• No <i>C. difficile</i> potential</li> <li>• No dosage modifications in CRF</li> </ul>	<ul style="list-style-type: none"> <li>• Skin discoloration (only with <i>prolonged use</i>)</li> <li>• Early/mild transient vestibular symptoms (uncommon)</li> </ul>

*Abbreviations:* ABE, acute bacterial endocarditis IV, intravenous; CRF, chronic renal failure; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; PCN, penicillins.

*Source:* Adapted from Refs. 42 and 44.

considerations, for *S. aureus* isolates with an MIC > 1 mg/mL, vancomycin kills in a concentration-dependent manner, but for isolates with an MIC < 1 mg/mL, killing occurs in a time-dependent fashion. Therefore, measuring vancomycin trough concentrations is clinically irrelevant when MICs are < 1 mg/mL (56–61).

### Clinical Approach to Therapeutic Failure

Therapeutic failure manifested by fever or bacteremia that persists after a week of appropriate therapy should prompt the clinician to reevaluate causes of antibiotic-related therapy. Also,

the nonantibiotic causes of apparent antibiotic failure should also be considered, i.e., myocardial abscess, noncardiac septic foci. The usual dose of daptomycin for bacteremia/ABE is 6 mg/kg (IV) q 24 h (with normal renal function), but the dose of daptomycin may be safely increased if the patient is not responding to daptomycin or other anti-staphylococcal antibiotics. Daptomycin given at a dose of 12 mg/kg (IV) q 24 h (with normal renal function) has been used safely without side effects for over four weeks of therapy. If persistent fever is related to a myocardial/paravalvular abscess, or device related, then surgical drainage/valve replacement may be needed to control/eradicate the infection (62–68).

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# 13 | Infective Endocarditis and Its Mimics in Critical Care

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## INTRODUCTION

Since Osler's landmark clinical description in the 1880s, infective endocarditis (IE) has undergone significant changes as regards its epidemiology, clinical manifestations, and treatment. The availability of antibiotics and the decrease in the prevalence of rheumatic fever in the developed world has significantly altered the profile of IE (1); however, antibiotics have failed to lessen the frequency of embolic complications and mycotic aneurysms in those with subacute IE (2). This is most likely due to the six-week gap between onset of infection and its recognition (3). In this age of intravascular devices, critical care units (CCUs) have become a focal point of concern, both for the treatment and prevention of infective endocarditis. For decades, CCUs have cared for those individuals suffering from the serious effects of IE. The surgical and medical modalities that have been developed to treat these infections actually contribute to both the number and types of cardiac and extracardiac complications of IE. The various intravascular devices that are mainstays of treatment in CCUs have become the most prominent offenders in this regard. The replacement of a damaged valve by a prosthetic one presents a lifetime of infectious risks to the patient. The challenge of IE in the CCU lies with not only treating its life-threatening complications but also preventing its development in this site of care. In many respects, the latter is the much more formidable task. Discussion will focus upon those pathogens that are most frequently encountered in the CCU as well as on the risks of catheter-related bloodstream infections (CRBSI). In addition, the most effective mimics of IE will be discussed.

## MICROBIOLOGY

There is a close association between the type of endocarditis and the infecting organism (Table 1) (4). Gram-positive cocci are clearly the predominant pathogens for all forms of the disease. *Staphylococcus aureus*, both methicillin sensitive (MSSA) and methicillin-resistant (MRSA), cause 32% of cases overall; coagulase-negative staphylococci (CoNS) 10.5%; the *Streptococcus viridans* group 18%; *Streptococcus bovis* 6.5%; other streptococci (*Abiotrophia* spp, formerly known as nutritionally various streptococci) 5.1%; *Enterococcus* spp. 10.6%; other gram-negative anaerobic organisms 2%; fungi 1.8%; polymicrobial 1.3%; other isolates 3.1%, and culture negative 8.1% (5). The data, collected internationally between June 2000 and January 2004, are reflective of cases acquired both in the in community and in health-care facilities (see 'Epidemiology').

The percent of cases of IE caused by the *S. viridans* group has decreased by 35% (Table 2). Overall, these streptococci produce less than 50% of all types of endocarditis compared with greater than 75% in the pre-antibiotic era (6,6a). *S. viridans* remains as the classic organism of subacute IE. It is the major pathogen in cases of IE that are associated with mitral valve prolapse (MVP) (7). For the purposes of this chapter, the term "*S. viridans*" applies to all non-pneumococcal streptococci excluding groups A, B, C and G. *Streptococcus salivarius*, *Streptococcus sanguis I and II*, *Streptococcus mitis*, *Streptococcus intermedius*, *Streptococcus milleri* and *Streptococcus mutans* belong to the *S. viridans* group. These streptococci are commensals of the respiratory and gastrointestinal tracts. With the exception of the *Streptococcus anginosus* group, they generally possess little invasive potential (8). Instead, they are able to adhere to and promote the growth of the fibrin/platelet thrombus. They do so by their ability to stimulate local production of tissue factor by monocytes and to promote platelet aggregation. These bacteria possess microbial surface components recognizing adhesive matrix molecules (MSCRAMMS) on the extracellular matrix molecules of the fibrin platelet thrombus (9,10).

**Table 1** Microbiology of IE in Different Risk Groups

Microorganism recovered (% of cases)	Native valve endocarditis	Intravenous drug users	Prosthetic valve endocarditis	
			Early	Late
<i>Viridans</i> -group streptococci	50	20	7	30
<i>Staphylococcus aureus</i>	19	67	17	12
CoNS	4	9	33	26
Enterococci	8	7	2	6
Miscellaneous	19	7	44	26

**Table 2** Common Causative Organisms of IE in the CCU

Organism	Comments
<i>Staphylococcus aureus</i>	The most common cause of acute IE including PVE, IVDA, and IE related to intravascular infections. Approximately 35% of cases of <i>S. aureus</i> bacteremia are complicated by IE.
Coagulase-negative <i>S. aureus</i>	30% of PVE; currently causes <5% of IE of native valves but increasing frequency; subacute course that is more indolent than that of <i>S. viridans</i> .
<i>Streptococcus viridans</i> group ( <i>S. mitior</i> , <i>S. sanguis</i> , <i>S. mutans</i> , <i>S. salivarius</i> )	70% of cases of subacute IE. Signs and symptoms are immunologically mediated with a very low rate of suppurative complications. Penicillin resistance is a growing problem, especially in patients receiving chemotherapy or bone marrow transplants.
<i>Streptococcus milleri</i> group ( <i>S. anginosus</i> , <i>S. intermedius</i> , <i>S. constellatus</i> )	Up to 20% of streptococcal IE. Unlike other streptococci, they can invade tissue and produce suppurative complications.
<i>Abiotrophia</i> spp. (Nutritionally variant streptococci)	5% of subacute IE. Examples require nutritionally variant streptococci active forms of vitamin B6 for growth. Characteristically produce large valvular vegetations with a high rate of embolization and relapse.
Group D streptococci	Third most common cause of IE. They may produce alpha, beta, or gamma hemolysis. Source is GI or GU tracts; associated with a high rate of relapse. Growing problem of antimicrobial resistance. Most cases are subacute.
Non-enterococcal group D streptococci ( <i>S. bovis</i> )	50% of group D IE; associated with lesions of large bowel.
Group B streptococci	Increasing cause of acute IE in alcoholics, cancer patients, and diabetics as well as in pregnancy. 40% mortality rate. Complications include CHF, thrombi, and metastatic infection. Surgery often required for cure.
Groups A, C, G streptococci	More frequently seen in the elderly (nursing homes) and diabetics. 30%–70% death rate. Commonly cause myocardial abscesses.
<i>Bartonella</i> spp.	<i>Bartonella quintana</i> is the most common isolate. Culture negative subacute IE in a homeless male should suggest the diagnosis. Usually treated with a combination of a β-lactam antibiotic and an aminoglycoside.
HACEK organisms	Most common gram-negative organisms in IE (5% of all cases). Presents as subacute IE. They are part of the normal flora of the GI tract. Intravenous drug abuse is a major risk factor. Complications are arterial macroemboli and congestive heart failure. Cases usually require the combination of ampicillin and gentamicin, with or without surgery, for cure.
<i>Pseudomonas aeruginosa</i>	Most commonly acutely seen in IVDA IE (right-sided disease is subacute) and in PVE.
<i>Serratia marcescens</i>	NIE (acute IE), often requires surgery for cure.
Fungal IE	An increasing problem in the CCU and among IVDA. <i>Candida albicans</i> most common example (especially in PVE) as compared to IVDA IE, in which <i>C. parapsilosis</i> or <i>C. tropicalis</i> predominate. <i>Aspergillus</i> species recovered in 33% of fungal IE. Most cases of fungal IE follow a subacute course.
Polymicrobial IE	Most common organisms are <i>Pseudomonas</i> and enterococci. It occurs frequently in IVDA and cardiac surgery. It may present acutely or subacutely. Mortality is greater than that of single-agent IE.

Abbreviations: GI, gastrointestinal; GU, genitourinary; CCU, critical care unit; IE, infective endocarditis; PVE, Prosthetic valve endocarditis.



The principal MSCRAMM of *S. viridans* is dextran. This carbohydrate promotes its attachment to the fibrin platelet clot. Other MSCRAMMs interact with fibrin and platelets.

*Abiotrophia* spp. (formerly known as nutritionally variant streptococci) requires the presence of cystine or pyridoxine for growth. This type of IE is usually subacute in nature. The organisms may produce massive valvular vegetations that often embolize. Many isolates of *Abiotrophia* are relatively resistant to penicillin. These properties contribute to the greater rate of mortality than that of *S. viridans*, 15% versus less than 5%, (11,12). Accordingly, a greater percentage of these cases would be cared for in a CCU than those due to *S. viridans*.

*S. anginosus*, *S. intermedius* and *Streptococcus constellatus* comprise the *Anginosus* group of *S. viridans*. They are very invasive and abscess producing in both myocardium and valvular structures. Clinically they behave very similar to *S. aureus*. Although they comprise only about 6% of total cases of IE, they are becoming a more frequent cause of health-care associated bloodstream infections (HCBSI) especially among neutropenic cancer patients (13).

Group B streptococci (GBS) are increasingly the cause of acute valvular infection in the elderly suffering from a multiplicity of chronic diseases such as diabetes, renal failure, and cancer. Its mortality rate may be as high as 40% due to metastatic infection, severe valvular damage, and congestive heart failure. The recurrence rate is as high as 4%. The silaic acid component of its capsule is a major virulence factor that inhibits the activation of the alternative complement pathway (14–16, 16a).

Enterococci have classically been classified as group D streptococci. They are now categorized as members of the genus *Enterococcus*. *Enterococcus faecium* and *Enterococcus faecalis* account for 10% to 20% of cases of IE, which is usually subacute in nature. Of these, *E. faecalis* is responsible for 90% of cases. Enterococcal BSI/IE arise from infections of urinary tract, abdominal and pelvic infections, wound infections, biliary tract infections, and intravascular catheters. Up to 40% of these BSI have no definable source. Such a situation is more commonly seen in the immunosuppressed (17,18). Enterococcal BSI are a health-care associated phenomena. Many are polymicrobial. Patients with enterococcal IE are usually debilitated and aged, more often than not male (17).

Enterococci have always been a therapeutic challenge to the clinician. It was recognized early on antibiotic era that enterococcal IE required a synergistic combination of the cell wall antibiotic with an aminoglycoside were. Vancomycin-resistant enterococcal (VRE) bacteremia is on the increase. However, the true incidence of VRE IE is difficult to arrive at because of methodological differences between the criteria used to differentiate VRE BSI from VRE IE. Most of the isolates of VRE represent *E. faecium*; few belong to *E. faecalis*. It appears that the outcome of VRE IE is determined by the overall condition of the patient as much as by the course of the valvular infection itself (19,20).

IE, due to infection with *S. bovis*, clinically is very similar to that produced by *S. viridans*. There is a striking association between *S. bovis* BSI and lesions of and/or manipulation of the gastrointestinal tract. Its connection with chronic liver disease has been more recently appreciated (21) Most isolates are quite sensitive to penicillin (22).

*S. aureus* is overall the most common cause of IE (50% of cases) (5,23). It is especially prominent in acute cases of IE, in prosthetic valve endocarditis (PVE) and intravenous drug abuser (IVDA) IE. More than 50 % of the cases have no known prior valvular disease. The mortality rate of *S. aureus* IE is 40%. In the United States, 78% of *S. aureus* BSI (250,000 cases per year) are associated with intravascular catheters (24). At least, 30% of *S. aureus* BSI progress to IE (25). The ability of *S. aureus* to adhere to the fibrin sheaths of intravascular catheters is its major virulence factor in producing HCBSI (26). *S. aureus* possesses a variety of pathogenic mechanisms. The teichoic acid component of the cell wall facilitates its attachment to the nasal mucosa from which it may set up a "beachhead" on the skin of the patient. Any break in the dermis promotes the entry for the staphylococcus into the microcirculation. Prostatitis and pneumonia are other common portals of entry into the bloodstream. The organisms reach the microcirculation by means of the lymphatic route. They then attach to the venous endothelium, without the need for a preformed thrombus, by means of their MSCRAMMs. Most notable among these are fibronectin-binding proteins and various clumping factors. MSCRAMMs trigger the ingestion of these pathogens by the endothelium (endotheliosis) as well as promoting bacterial aggregation. Staphylococci may remain dormant within the endothelial

cells but are eventually released back into the circulation. *S. aureus* also induces production of tissue factor (TF) by both monocytes and endothelial cells. TF then leads to thrombus on the surface of the endothelial cell by means of the extrinsic clotting system. Once this pathogen is in the bloodstream, it makes effective use of its unique abilities to invade the endothelium and propagate the platelet fibrin thrombus (27–30). When it returns back into the circulation, *S. aureus* is able to infect the valvular endothelium and produce a thrombus de novo in the same fashion as described for the venular endothelium. One should never forget that *S. aureus* is ubiquitous. It resides on the skin of both the healthy and the ill as well as being colonizer of the nares.

*S. aureus* has several defense mechanisms that shield it from the defenses host's phagocytic system. Among these are protein A; catalase; alpha, beta, and gamma toxins; leukocidins and its capsule. After the phagocytes dies, 5% of *S. aureus* remain viable for several minutes within the white cell. It makes use of these circulating cells to travel throughout the body (28). Upon the death of the white cell, the viable staphylococci are deposited into the surrounding tissue or return to the intravascular space. At least 30% of isolates of *S. aureus* from cases of IE are resistant to the  $\beta$ -lactams. The morbidity and mortality for these isolates are significantly greater than the corresponding values for MSSA—63% versus 45% and 55% versus 25%, respectively. (31). The choice of the most appropriate antibiotic in a given patient with MRSA IE can be a daily challenge for the clinician who cares for patients in CCUs.

The term "CoNS" represents at least 15 species of coagulase-negative staphylococci. Similar to *S. aureus*, it is a constant part of our environment. It also possesses a superb ability to infect prosthetic devices of all kinds including intravascular devices/catheters by means of its production of the glycocalix biofilm. This environment protects the organisms from the host's defenses as well as from most antimicrobial agents (32). CoNS currently accounts for 30% of PVE.

There has been in a significant increase in CoNS infections of native valves in recent years. Currently 7.8% of non-IVDA IE of native valves is caused by these organisms, 50% are acquired in the hospital or in other health-care associated venues, and 45% arise from the community. The risk factors are the same as for *S. aureus* IE—hemodialysis fistulas, long-term indwelling central catheters, and pacemakers in implantable defibrillators. Because of its high rate of complications (60% of cases require surgery and 20% die), these patients are often cared for in CCUs (33).

Not all CoNS are species of *Staphylococcus epidermidis*, *Staphylococcus lugdunensis* is much more aggressive than other CoNS with a mortality rate of 70% despite being sensitive to a large variety of antibiotics. It is quite difficult for the clinical laboratory to differentiate them from other coagulase-negative organisms. Because *S. lugdunensis* produces clumping factor and its colonies have a golden hue, it may be confused with *S. aureus* (34).

Gram-negative aerobic organisms account for approximately 5% of cases of IE (23). Although quite commonly involved in spontaneous BSIs, they are unable to adhere as efficiently to valvular endothelium as do the gram-positive cocci. Cirrhotics are particularly at risk of developing gram-negative IE. *Pseudomonas aeruginosa* adheres to the endothelium the most effectively of any of the gram-negative rods. It elaborates several virulence factors, extracellular proteases, elastase alkaline proteases. These produce necrosis in a range of tissues especially in the elastic layer of the lamina propria of all caliber is the blood vessels. Ecthyma gangrenosum is the classic dermatological manifestation of this process. These toxins also disrupt the function of polymorphonuclear leukocytes, K- and T-cells, as well as the structure of complement and immunoglobulins. Exotoxin A disrupts protein synthesis and is the factor that is best correlated with systemic toxicity and mortality. Unlike most gram-negative bacilli, *P. aeruginosa* is resistant to the bactericidal activity of human serum. Its polysaccharide capsule interferes with phagocytosis and the antibacterial effect of the aminoglycosides (35,36). This pathogen is responsible for 4% of IVDA IE (37,38).

The non-HACEK gram-negative rods seldom produce valvular infection. Fifty-seven percent of such cases are acquired in health care facilities (39). *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* spp. constitute the HACEK group. These are genetically unrelated gram-negative bacilli/cocobacilli that share the oropharynx as the primary site of residence. All require incubation in CO<sub>2</sub> for growth. This

group is the most frequent cause of gram-negative endocarditis. They usually produce subacute disease that is notable for its massive arterial emboli (40).

The *Enterobacteriaceae* have demonstrated their ability to resist the entire group of  $\beta$ -lactam antibiotics by their production of extended spectrum  $\beta$ -lactamases (ESBL). ESBL's enable these gram-negative to resist the penicillins, cephalosporins, and monobactams (41). Identification of such organisms is unreliable in many clinical laboratories. An international survey of *Klebsiella pneumoniae* bacteremia in CCU revealed that 43% of isolates produced ESBLs (14). Although this rate may be lower in North America, the possibility of an ESBL-producing organism must always be considered in the CCU patient with gram-negative BSI/IE (42).

Multidrug resistant (MDR), *Acinetobacter baumannii* infections are emerging as an important health-care associated pathogens in CCUs will. Most often, these infections are ventilator or intravascular catheter associated (43). What makes their treatment so difficult is the multiplicity of their defensive mechanisms that make them resistant to many classes of antibiotics. These factors include ESBLs, efflux pumps, altered penicillin binding proteins and mutations of DNA gyrase and topoisomerase IV.

Polymicrobial IE most often occurs in patients with IVDA IE and in those who have undergone cardiac surgery. The most frequently isolated organisms are *P. aeruginosa*, *Streptococcus faecalis*, *S. aureus*, and CoNS. The mortality rate this type of IE is generally twice that of those infected by a single organism (44) Fungal IE has risen by 270% over the last 30 years. Most of this increase is seen individuals cared for in CCUs as well as in those who have undergone cardiac surgery (45).

Fungi cause 1 % of total cases of IE, 5% of IVDA IE, and 13% and 5% of early and late PVE, respectively. Risk factors for its development include exposure to broad-spectrum antibiotics and to cytotoxic agents (46). *Candida* spp. are the most frequent causes of fungal IE. Two-thirds are identified as *Candida albicans*. This organism is also the most frequently recovered from catheter associated IE, especially those devices employed in hyperalimentation. The remainder of fungal IE usually is caused by *Aspergillus* spp., most commonly *Aspergillus fumigatus*. Fungal IVDA is usually caused by *Candida* (*C. albicans*, *C. parapsilosis*, or *C. tropicalis*). They enter the bloodstream from the injection site directly or from contamination of the drug paraphernalia (38). In non-IVDA, IE the gastrointestinal tract or intravascular catheters are the most common sites of entry. Contaminated operating room air is the most common source of *Aspergillus* PVE (47,48).

Approximately 5% of cases of IE have persistently negative blood cultures, culture negative IE (CNIE). This rate may be higher in some areas in the world in which hard to grow organisms, such as *Coxiella burnetti*, are fairly common. Automated blood culture systems are able to readily retrieve organisms that previously had been considered to be fastidious (HACEK group, fungi) Table 3 presents the current causes of CNIE.

In the United States, prior antibiotic usage is the most common cause of CNIE (67% of cases). This is especially true for patients in the CCU. In the author's experience, the injudicious or "knee-jerk" use of broad-spectrum antibiotics in the CCU without full workup of the cause of fever can suppress bacterial growth at the surface but not eradicate it within the valvular thrombus. This can produce the state of "muted IE." These delays in the diagnosis

**Table 3** Causes of Culture Negative IE

Causes	Comments
Prior antibiotic use	Most frequent cause, at least 35%–79% of cases
Sequestration of infection within the thrombus	Surface sterilization phenomena
Fastidious organisms	Fungi, Q-fever, <i>Tropheryma whipplei</i> , <i>Brucella</i> spp., <i>Rickettsiae</i> , <i>Chlamydiae</i> , <i>Legionella</i>
Right-sided endocarditis	Nonvirulent organisms are filtered out by the lungs
Bacteria free stage	Untreated infection for > 3 mo
Mural IE in VSD	–
infection related to pacemaker wires	–

*Abbreviations:* IE, infective endocarditis; VSD, ventricular septal defect.

*Source:* From Ref. 49.

and initiation of appropriate treatment contribute to the high rate of morbidity and mortality of health care IE (HCIE) (50–52). Tables 2 and 3 summarize the microbiology of CCU IE.

## EPIDEMIOLOGY

IE is an infection of the valvular endocardium; rarely of the mural endocardium. The major types of IE are native valve IE (NVIE), prosthetic valve IE (PVIE), pacemaker IE (PMIE), intravenous drug abuser IE (IVDA IE) and HCIE. A major focus of this chapter will be HCIE. The reason for so doing is well expressed by Friedland, “nosocomial endocarditis occurs in a definable subpopulation of hospitalized patients and is potentially preventable.” It is an iatrogenic infection for which caregivers must take responsibility. It is defined as a valvular infection that presents either 48 hours after an individual has been hospitalized or one that is associated with a health-care facility procedure that has been performed within four weeks of the development of symptoms. The typical patient is older with a higher rate of underlying valvular abnormalities. They develop BSIs secondary to a variety of invasive vascular procedures. HCIE accounts for 20% of overall cases of IE and appears to be on the rise. This is mainly due to the increase in staphylococcal BSIs that are associated with intravascular line infections. Type I HCIE is the result of damage to right ventricular structures that is produced by intravascular catheters (Swan–Ganz lines). Type II HCIE involves the left side of the heart. It develops secondary to BSIs of any type. Left-sided HCIE the more common because of greater frequency of abnormalities found on this side of the heart [degenerative valvular disease, mitral valve prolapse (MVP)]s. In addition to *S. aureus* and CoNS, gram-negative organisms and fungi are often isolated from these cases. The mortality rate of HCIE approaches 50% as compared to 11% for community acquired IE. This is attributable in part to the advanced age of patients with HCIE. Sixty-four percent of these are older than 60 years. An important exception to this is that community acquired *S. aureus* IE has a higher rate of death than that which develops in a health care facility. This is probably due to a higher rate of metastatic complications that go unrecognized and to the prolonged untreated bacteremia in the community than occurs in HCIE (53–57).

The incidence of IE throughout the world has not changed over the last 50 years. It ranges from 1.5/100,000 to 6/100,000 per population (58–61). Somewhere between 10,000 and 15,000 IE cases occur yearly in the United States. Because of the difficulties in diagnosis, this figure is at best an estimate. It most likely underestimates the number of cases of HCIE because of the difficulties in making this diagnosis (see below ‘Diagnosis’). The incidence of IE has not significantly decreased in the era of antibiotics (1). The ever-expanding field of cardiovascular surgery and the increasing employment of various intravascular devices accounting great deal for this phenomenon. Significant variations in the rate of IE exist between nations and within a country itself. The incidence, type of cases of IE and pathogens that are cared for in a given health care facility is directly related to the profile of its patients (60,61). Cases of IE are much more frequent in hospitals that serve a large population of IVDA or patients with congenital heart disease or those with prosthetic valves. *S. aureus* is relatively more frequently encountered in community hospitals, whereas enterococcal IE is usually limited to tertiary care institutions (62). In areas of the United States with extremely low rates of IVDA, *S. viridans* remains the most common cause of IE (63).

IE has become a disease of the older population. In a study of patients in the 1990s, the mean age was 50 with 35% more than 60 years of age. Presently, more than 50% of cases occur in those more than 60 years of age (64). This change has been less dramatic in cases of subacute bacterial endocarditis (SBE), with a current median age of 58. In the 1960s, it was 56 years (63), with the elderly more susceptible to developing IE. This vulnerability may be related to nonspecific aging of the immune system (65). Other explanations are based on an increase in calcific valvular disease among this population (66), the use of cardio- invasive techniques, intravascular devices, and the rise nosocomial staphylococcal BSIs. Individuals with congenital heart disease are living longer and frequently require heart surgery (4). In addition, rheumatic heart disease has essentially disappeared from the developed world. The major exception to this “graying” trend is IVDA IE. The median age of these patients is approximately 30 years (67). Table 4 summarizes these trends.

**Table 4** Changing Patterns of IE Since 1966

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Marked increase in the incidence of acute IE

Rise of HCIE, IVDA and prosthetic valve IE

- a. Change in the underlying valvular pathology: rheumatic heart disease <20% of cases
- b. MVP 30% of cases
- c. Prosthetic valve endocarditis 10%–20% of cases
- d. 50% of elderly patients have calcific aortic stenosis

These changes are due to:

- a. The "graying" of patients (excluding cases of IVDA IE, 55% of patients > 60 yr of age)
  - b. The increased numbers of vascular procedures
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*Abbreviations:* IE, infective endocarditis; HCIE, health care associated IE; IVDA, intravenous drug user; MVP, mitral valve prolapse.

IE occurs as at least twice as often in men as in women. This differential increases over the years. The incidence ratio of men to women ranges up to 9/1 at 50 to 60 years of age (68).

There has been a marked increase in cases of HCIE, IVDA IE, and PVE accounting for 22%, 36%, and 16%, respectively, of all cases (5,69). This reflects a significant increase in staphylococcal/HCBSI coupled with a significant decrease in IE caused by *S. viridans* (70,71).

### Cardiac Predisposing Factors

#### *Pathogenesis*

Any discussion of the predisposing factors to the development of IE needs to begin with a basic understanding of the pathogenesis of this disease. Although there are many types of valvular infections, they all share a common developmental pathway. First, there must be a BSI with an organism with the ability to infect the endocardium. Then, the pathogen must adhere to the endocardial surface. Finally, it needs to invade the underlying tissue (72).

In subacute IE, a pre-existing platelet fibrin thrombus (nonbacterial thrombotic endocarditis, NBTE) is the site of attachment for the circulating bacteria. As discussed above, certain organisms, especially *S. aureus*, are able to attach to the endothelium by producing microthrombi. In CCU/HCIE, NBTE develops in one of three possible ways (73):

1. When blood flows over a distorted valve, it loses its laminar characteristics. These rheological changes affect the function of the endocardium (27). Leukocytes adhere more readily to it and platelets become more reactive when in contact with it. The surface of the valve becomes coated with fibrin. Small vegetations result. These increase the degree of turbulence and so accelerate the formation of NBTE.
2. Garrison and Freedman developed a rabbit model of IE (74). First they produced NBTE by scarring the valves of the animal's right ventricle by means of a catheter inserted in the femoral vein. The resultant thrombus was then infected by *S. aureus* that was injected through the catheter. As the infection progressed, the adherent bacteria were covered by successive layers of deposit fibrin. The superficial organisms are metabolically active; those that live deep within the NBTE are quite indolent. Within the thrombus, there is a tremendous concentration of organisms ( $10^9$  colony forming units per gram of tissue) (75). From this safe haven, the bacteria are able to reseed the bloodstream in a continuous manner, the characteristic continuous bacteremia of IE. In the CCU, insertion of a Swan-Ganz catheter reproduces quite closely this experimental model.
3. The Jet and Venturi effects may play an important part in both the development and site of the NBTE (76). When blood flows from a high-pressure area to a lower pressure one, its laminar flow is disrupted and an NBTE develops at the low-pressure sink side of the orifice. For example, in mitral insufficiency, NBTE is found in the atrial surface of the valve and in aortic insufficiency on the ventricular side. In the case of a ventricular septal defect, the NBTE forms on the right ventricular side. An NBTE may also form at the site of the right ventricle that lies directly opposite the septal defect. The endocardium of this area may be damaged by the force of the jet of blood hitting it (Mac Callums patch) (77).

BSIs may occur spontaneously or are secondary to a variety of invasive procedures (78). Transient bacteremias occur in 10% of patients with severe gingival disease (79). Two percent of patients with extensive burns (greater than 60% of body surface area) develop right-sided IE secondary to the BSI's complicating septic thrombophlebitis. *S. aureus* is usually involved (80). Other infections, most commonly pneumonia and pyelonephritis, may give rise to BSIs (66). Table 5 presents the risk of developing of a BSI following a variety of planned invasive procedures (81).

Currently, the chief source of BSIs in the CCU is the non-cuffed, nontunneled, and nonmedicated central venous catheter. The three major determinants of catheter infections are: the type of catheter, the site of insertion, and the duration of the catheter, Table 6 presents the risk of CRBSI of various types of devices (82–84). There are four possible sources of infection of intravascular catheters (85): the insertion site, the hub of the catheter, seeding of the catheter from a BSI, and contamination of the infusate.

Bacterial infection of intravascular catheters depends on the response of the host to the presence of the foreign body, the pathogenic properties of the organisms, and the site of

**Table 5** Risk of Bacteremia Associated with Various Procedures

Low (0%–20%)	Moderate (20%–40%)	High (40%–100%)	Organism
	Tonsillectomy		
Bronchoscopy (rigid)			Streptococcal sp. or <i>S. epidermidis</i> <i>S. epidermidis</i> , streptococci, and diphtheroids
Bronchoscopy (flexible)			
Endoscopy			
Colonoscopy			<i>Escherichia coli</i> and <i>Bacteroides</i> sp. <i>S. epidermidis</i>
Barium enema			Enterococci; and aerobic gram-negative rods
	Transurethral resection of the prostate		Coliforms, enterococci, <i>S. aureus</i>
Cystoscopy		Traumatic dental procedures	Coliforms and gram-negative rods <i>Streptococcus viridans</i>
Liver biopsy (in setting of cholangitis)			Coliforms and enterococci
Sclerotherapy of esophageal varices			<i>S. viridans</i> , gram-negative rods, <i>S. aureus</i>
Esophageal dilatation			<i>S. aureus</i> , <i>S. viridans</i>
Transesophageal echocardiography	Suction abortion		<i>S. viridans</i> and anaerobes Streptococcal sp.

**Table 6** Risk and Rates of Bloodstream Infections Produced by Intravascular Catheters

Types of vascular catheters	Risk For BSI <sup>a</sup> /catheter (%)	Rates of catheter BSI/ 1000 catheter days
Standard CVC <sup>b</sup>	3.3	2.3–2.7
Antibiotic coated CVC <sup>b</sup>	0.2	0.2
Picc <sup>c</sup>	1.2	0.4–1.1
Tunnel and cuffed CVC <sup>b</sup>	20.9	1.2
Swan–Ganz CVC <sup>b</sup>	1.9	3.7–5.5
Hemodialysis catheters	–	2.8
Arterial catheters	–	1.7

<sup>a</sup>Bloodstream infection.

<sup>b</sup>Central venous catheter.

<sup>c</sup>Peripherally inserted central venous catheter.

Source: From Refs. 82–84.

catheter insertion. Within a few days of its placement, a sleeve of biofilm consisting of fibrin and fibronectin, along with platelets, albumin, and fibrinogen is deposited on the extraluminal surface of the catheter. Certain organisms, such as *C. albicans* or CoNS, also may deposit an additional layer of glycocalyx. This composite biofilm protects the pathogens from the host antibodies and white cells as well as administered antibiotics (86).

For catheters that are left in place for less than nine days, contamination of the intracutaneous tracts by the patient's skin flora is the most common source of infection (87). The bacteria migrate all the way from the insertion point to the tip of the catheter. This results in extraluminal infections. For catheters of longer duration of surgically implanted catheters, infection of the hub or lumen of the devices has become the major source of CRBSI (88). By this time, the biofilm has involved the lumen of the catheter. It is the bacterial flora of health care workers hands that contaminate the hubs of the intravascular catheters as they go about their tasks of connecting infusate solutions or various types of measuring devices. The bacteria then migrate down the luminal wall and adhere to the biofilm and/or enter the bloodstream. For long-term catheters (those in place for more than 100 days), the concentration of bacteria that live within the biofilm of the luminal wall of the catheter is twice that of the exterior surface (88).

The major risk factors for hematogenously spread complications of *S. aureus* CRBSI are hemodialysis dependence, MRSA involvement, and duration of symptoms before diagnosis (89).

The infusate may itself be the cause of BSI. Gram-negative aerobes such as *Enterobacter*, *Pseudomonas*, and *Serratia* species are the most likely to be involved because they are able to grow rapidly at room temperature in a variety of solutions.

Because of its hypertonic nature, the solutions of total parenteral nutrition are bactericidal to most microorganisms except *Candida* spp. (90). A wide variety of infused products may be contaminated during their manufacture (intrinsic contamination). These include blood products, especially platelets, intravenous medications, and even povidone-iodine (87,91). Up to 1% to 2% of all parenterally administered solutions are compromised during their administration usually by the hands of the health care workers as they manipulate the system, especially by drawing blood through it. Most of these organisms are not able to grow in these solutions except for the Gram-negative aerobes that may reach a concentration of  $10^3$ /mL (92,93). This concentration of bacteria does not produce "tell-tale" turbidity in the solution. The risk of contamination is directly related to the duration of time that the infusate set is in place.

Arterial catheters have a high rate of CRBSI (greater than 1%). Fifty percent of these are due to their high degree of manipulation (frequent blood drawing) and the high rate of contamination of the saline reservoir of this device. The gram-negative aerobes are most frequently involved (94).

The biofilm of the catheter may be infected during any type of BSI. The infected catheter may then perpetuate the BSI even though the originating infection has been cured (95).

Central venous catheters that are inserted into the femoral vein have a high rate of infection than those placed in the subclavian. Internal jugular catheters are at intermediate risk. More recent data indicates that the infectious complications of hemodialysis catheters may be the same whether placed in the jugular or femoral vein (96). It would be prudent to avoid the femoral route unless absolutely necessary.

More than 50% of cases of acute IE have no definable predisposing cardiac abnormalities (72). Congenital heart disease underlies approximately 15% of all cases of IE. Congenital bicuspid aortic valve disease may account for 20% of cases of IE in those older than 60 years (97). Asymmetric septal hypertrophy accounts for 5% of cases (98). The degree of obstruction is directly proportional to the risk of developing of IE. The greater the pressure gradient, the greater the chance of infection. Interestingly the mitral valve is most frequently involved, rarely the aortic. This is due to displacement of the anterior leaflet to the mitral valve by the abnormal contractions of the septum or by a jet stream affecting the aortic leaflets distal to the obstruction (99). Other underlying congenital conditions include ventriculoseptal defect, patent ductus arteriosus, and tetralogy of Fallot (100). Secundum atrial septal defects and congenital pulmonic stenosis are at negligible risk for the development of IE because of the minor gradients in pressure observed in these conditions.

In the developed world, rheumatic heart disease (RHD) accounts for less than 20% of NVIE. In developing countries, RHD causes 50% of all cases (101,102). Over their lifetimes, 6% of patients with RHD will develop IE usually of the mitral valve.

MVP makes up 30% of NVIE in younger adults. It has taken supplanted RHD as the primary underlying condition for developing IE in this age group (101,103). Patients with the type of MVP that has an insignificant degree of regurgitation, have a quite small risk of developing IE. Additional risk factors for developing IE in MVP are thickened anterior mitral leaflets and male sex greater than 45 years of age (100). Cases of MVP IE generally have relatively lower rates of morbidity and mortality than other types of IE (104,105).

The term “degenerative cardiac lesions” describe a wide variety of abnormalities. These include degenerative valvular disease (DVD) and postmyocardial infarction thrombi. All have in common a roughened endocardium that promotes the development of a fibrin/platelet thrombus. DVD accounts for 20% of all cases and 50% of cases of IE in patients who are older than 60 years (106,107). Calcific aortic stenosis results from the deposition of calcium on either a congenital bicuspid valve correlate previously normal valve damage by the cumulative hemodynamic stresses that occur over a patient’s life span. Because of their age, these patients have a high prevalence of associated illnesses, such as diabetes or chronic renal failure, which contribute to their increased morbidity and mortality. Because the degree of stenosis is not hemodynamically significant, this type of valvular lesion is often neglected for antibiotic prophylaxis (108).

Excluding IVDA IE, 40% of NVIE infects only the mitral valve and 40% the aortic. The right side of the heart is seldom involved except in cases of IVDA IE (109).

PVE accounts for approximately 10% of all cases of valvular infection and up to 26% in those older than 60 years (60,110). The risk of infection is highest during the first three months after implantation. At the end of one year of their placement, 1% to 3.1% had become infected. The rate of infection goes down after this to be about 0.3% per year. Mechanical valves are more susceptible to infection until their first year anniversary. After this, bioprosthetic valves are at greater likelihood of developing IE due to the ongoing calcifications of their leaflets that is caused by degeneration of the valvular tissue (111). The risk of developing PVE is 5% in the 10 years after their placement. Endothelialization of the sewing rings and struts of the valves decreases but does not eliminate the risk of infection.

PMIE and infections of cardioverter–defibrillators and ventricular assist devices are very similar in nature to PVE (112–115). Most cases of PMIE and IE of ventricular assist devices and cardioverter–defibrillators occur within a few months of their placement. The implanted material is “conditioned” by the deposition of fibrinogen, fibronectin laminin, and collagen. This coagulum promotes the appearance of staphylococci. In addition both CoNS and coagulase-positive staphylococci produce a biofilm that protects the infecting bacteria from antibiotics as well as the host’s leukocytes. Unlike the situation in PVE, *S. aureus* predominates in early PMIE and CoNS in later infection (116). Infections of pacemakers most often involve the generator pocket. There may be infection of the proximal leads (intravascular leads). True PMIE is defined as infection of the leads at the point of contact with the endocardium. The lifelong risk for an individual to develop PMIE is 0.5% (117,118).

A previous episode of IE is probably the most important predisposing condition for development of valvular infection (119). The most important risk factor for recurrent IE is IVDAIE, with 40% of these cases recurring. The recurrence rate of non IVDA IE is well less than 10%.

### **Extracardiac Predisposing Factors**

Chronic hemodialysis has become a significant risk factor for the development of IE (120). Various types of infection are second only to coronary artery disease as the most common cause of death in chronic renal failure. This vulnerability is due to the BSIs of infected dialysis catheters, low albumin, excess iron stores that stimulate the growth of bacteria, metabolic acidosis that impairs neutrophil function, accelerated calcification of the cardiac valves, and the immunological dysfunction of chronic renal failure.

In addition, a variety of neoplasms, diabetes mellitus, liver disease, and the administration of corticosteroids are becoming increasingly important predisposing conditions for the



development of IE. All of these diseases share in common an increased frequency of BSIs (72,121).

HIV-positive IVDA patients have a two to eight times greater chance of developing IE than comparable individuals who are HIV-negative. The lower the CD4 count, the greater the chance of valvular infection developing. A CD4 count less than 200 is associated with increased morbidity and mortality in these individuals (122).

## Clinical Presentation

### History

Early in its course, the symptoms of subacute NVIE are marked by a history of quite indolent process that is marked by fever, fatigue, backache, and weight loss (24,123). Because of the relative lack of virulence factors of the organisms that are involved in subacute valvular infections, its manifestations are due primarily to immunological processes, such as focal glomerulonephritis that is secondary to deposition of circulating immune complexes (124). Symptoms of arthritis and arthralgias, especially lumbosacral spine pain, are the result of deposition of immune complexes in the synovium and most likely in the disc space. The dermal, mucocutaneous, musculoskeletal, central nervous system, and renal presentations are produced by the embolic phase that occurs later in the course of this disease. A history of dental or other invasive procedures is found in less than 15% of cases. The incubation time of the disease is not greater than two weeks (3). Subacute NVIE is a very able mimic of many infectious and noninfectious diseases. Because of the nonsuppurative nature of *S. viridans*, the emboli of subacute disease are usually sterile. Up to the point of the development of frank heart failure, the patients symptoms are almost exclusively noncardiac in nature (124) (Table 7).

Acute NVIE begins quite abruptly and dramatically due to the extra and intra-cardiac suppurative complications produced by *S. aureus* as well as other pathogens. Accordingly, this type of IE will most likely be admitted to the CCU. Congestive heart failure is the most common complication of both acute and subacute disease (15%–65% of patients) The leaflets of the infected valve are rapidly destroyed as the organisms multiply within the progressively enlarging, and often quite friable, vegetations. The infected valve may suffer any of the following insults: tearing and fenestration of the leaflets, detachment from its annulus, and rupture of the chordae tendineae and/or papillary muscles (125). The regurgitant jetstream of the incompetent aortic valve can make impact with the mitral and produce erosion of perforation of this valve's leaflets or its chordae tendineae. This may dramatically add to the strain placed on the left ventricle by the insufficient aortic valve (126). Unusually heart failure may be the result of severe valvular stenosis produced by massive vegetations that occurred in IE caused by *S. aureus*, fungi, HACEK organisms, or *Abiotrophia* spp (127). The associated myocarditis of IE may worsen any type of congestive failure. The dyspnea and fatigue of the result of congestive failure appear well within a week. A wide range of neuropsychiatric complications frequently occurring in conjunction with those of congestive heart failure (126,127).

Other intracardiac complications of acute IE include cardiac fistulas, aneurysms of the sinus of Valsalva, and intraventricular abscesses that may lead to perforation or damage to

**Table 7** The Early Nonspecific Signs and Symptoms of Subacute IE<sup>a</sup>

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Low-grade fever (absent in 3%–15% of patients)
Anorexia
Weight loss
Influenza-like syndromes
Polymyalgia-like syndromes with arthralgias, dull sensorium, and headaches resembling typhoid fever
Pleuritic pain
Right upper quadrant pain and right lower quadrant pain
85% of patients present with a detectable murmur; all will eventually develop one
Low-grade fever (absent in 3%–15% of patients)
Anorexia

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<sup>a</sup>The manifestations of SBE are caused by emboli and/or progressive valvular destruction and/or immunologic phenomena.

the conduction system of the heart. Multiple myocardial abscesses are seen primarily in *S. aureus* IE (20% of fatal cases). These may erode into the pericardial sack resulting in fatal cardiac tamponade (128). They may also erode into the intraventricular septum leading to perforation and a left to right shunt. Pericarditis may be the result of erosion of a myocardial or ring abscess into the pericardial space or by deposition of organisms during the BSI. Rarely, it is secondary to a septic coronary artery embolus or rupture of a mycotic aneurysm.

Septic arterial embolization is the second most common complication of IE (35%–50% of cases). Unlike those of subacute disease, they produce metastatic infection. These are more frequently seen younger patients, in left-sided disease and in PVE. *Candida* spp., *S. aureus*, *H. influenzae*, *Aspergillus* spp., and group B streptococci. For example, the right-sided septic emboli of *S. aureus* IVDA IE, produce many small pulmonary abscesses and infarcts. These vegetations may embolize up to 12 months after microbiological care of the valvular infection. Left-sided emboli commonly travel to the spleen, brain, kidneys, coronary arteries, and meninges. Cerebral emboli and have been traditionally estimated to occur in 30% of cases of acute and subacute IE. It appears that when MRI and cerebrospinal fluid analysis were used to study of the rate of cerebrovascular complications in patients with left-sided IE, the incidence of brain damage was much higher than previously appreciated, approximately 65%. Cases were approximately split evenly between symptomatic and asymptomatic (129). The middle cerebral artery is the most frequently involved. Coronary artery emboli are detected at autopsy in 40% to 60% of cases. They are usually clinically unimportant and infrequently produce any significant changes in the patient's electrocardiogram.

Splenic abscesses and infarcts that result from septic emboli may be the source of persistent bacteremia despite successful treatment of the valvular infection itself (130). Abscesses and infarcts of the spleen may have very similar presentations. These include left upper quadrant abdominal pain, back and pleuritic pain, and fever. Despite advanced imaging techniques (MRI, CT scan, and ultrasonography), splenic aspiration may be the only way to distinguish the two.

Table 8 presents, by organ system, the clinical manifestations of NVIE. It is important to note that the distinction between the two types of IE has become blurred because of the use of antibiotics to treat unrecognized IE. Such misdirection of antibiotic therapy suppresses the growth of bacteria with the thrombus and so diminishes many of the clinical abnormalities of IE, the state of "muted endocarditis." Under such circumstances, the diagnosis of IE is often delayed or missed completely.

### Prosthetic Valve Endocarditis

It is clinically useful to describe cases of be the into early, intermediate, and late since the profile of infecting organisms reflects primarily the site and timing of their acquisition (131,132). Early PVE extends through three months past the time of implantation; intermediate 3 to 12 months and late after 12 months. CoNS dominates in the early and intermediate stages. The health care environment (operating world, recovery room, intravascular lines) is the source of the organisms of early PVE that produces infection with diphtheroids, *S. aureus* CoNS, and fungi. The pathogens that are involved in late PVE resemble closely those found in NVIE (Table 2).

The clinical features of PVE generally are quite similar to those of NVIE. There are notable exceptions. If PVE begins within a few weeks of valve placement, its presence may be obscured by the more common surgical infections such as pneumonia or wound infections. Early PVE, due to *S. aureus*, may present as septic shock if an overwhelming paravalvular abscess develops. This deep-seated extension of the valvular infection can lead to calculate incompetence, conduction disturbances, and septic emboli (133). Ten percent of mechanical PVE are complicated by thrombosis of the valve outlet. Forty percent of cases are complicated by arterial emboli. There is a high rate of cerebral emboli within the first three days of *S. aureus* early PVE (134). Because PVE is superimposed on previously damaged hearts, congestive heart failure appears earlier and is more severe than that of NVIE.

Late PVE most frequently follows a subacute or chronic course. There is a high rate of peripheral stigmata of valvular infection such as the skin and changes as well as the presence

**Table 8** Organ Involvement in NVE

Peripheral stigmata (20% of patients)	Musculoskeletal (40%–50% of patients)	Intracardiac
Janeway lesions	Low back pain (presenting symptom)	Valvular vegetations in 15% of patients
Osler's nodes	Diffuse myalgias, especially of legs	CHF
Roth spots	Disc space infection	Myocardial abscess
	Hypertrophic osteoarthropathy	Septal abscess (leading to heart block)
	Splenomegaly	Vascular necrosis
	Arthritis (ankle, knee, wrist)	Aortic cardiac fistula
		Suppurative pericarditis
		Rupture of papillary muscles, chordae tendinae
		Annular abscess
		Mycotic aneurysm of sinus of Valsalva
		Destruction of valvular leaflets
		<i>Staphylococcus aureus</i> responsible for 55%–70% of congestive heart failure
Neurological system	Renal	Mycotic aneurysms
Neurological complications are the presenting symptoms in 50%–70% of patients.	Congestive heart failure and antibiotic toxicity are currently the most common causes of renal failure	Life-threatening in 2.5% of patients
Hemorrhage	Renal abscesses due to highly invasive organisms (i.e., <i>Staphylococcus aureus</i> )	Usually produced by organisms of low invasive capacity (i.e., <i>Streptococcus viridans</i> )
Toxic manifestations (headache, irritability)	Renal infarction (cortical necrosis) occurs in two-thirds of infected patients.	Silent until they leak; seen most commonly in brain
Psychiatric effects (neurosis).	Focal glomerulonephritis occurs in 50% of untreated cases and is associated with renal failure and nephrotic syndrome	Sinus of Valsalva, abdominal aorta and its branches, mesenteric, splenic, coronary, and pulmonary arteries
Psychoses, disorientation, delirium (hallucinations) Stroke	"Flea-bitten" kidney, multiple emboli and hemorrhage	
Meningoencephalitis		
Dyskinesia		
Spinal cord and small nerves (girdle pain, paraplegia, weakness, myalgias, and peripheral neuropathy)		
		Metastatic infections
		Metastatic infections are produced by septic emboli (usually in acute IE) to liver, spleen, gallbladder, coronary arteries (myocardial infarction occurs in 50% of patients), myocardium, lung, and retina

of Janeway lesions, Osler's nodes (20% of cases) (132). The patient may present with symptoms of myocarditis or pericarditis.

It is important to note the susceptibility of prosthetic valves to becoming infected during HCBSI or health care associated fungemia. Sixteen percent of patients with mechanical or bioprosthetic valves in place develop PVE during HCBSI. Sixty-one percent of the BSIs originated from intravascular catheters (33%) or skin and wound (28%) assays infections. Staphylococcal and gram-negative BSI infected 55% and 33%, respectively, of prosthetic valves (135).

### PMIE

PM infections and PMIE may be classified as primary, those infections in which the pacemaker or its pocket is the source of infection or as secondary infections in which the leads (rarely the pacemaker itself or its pocket) are seeded from a BSI (109–113,136). The clinical presentation of PM infections and PMIE is dependent on the site of infection and its origin. Infections within a few months of placement are either acute or subacute infections of the pulse-generator pocket acquired during implantation. There may be associated bacteremia. Thirty-three percent of patients are febrile. Late infections of the pocket are caused by erosion of the overlying skin. They always indicate infection of the generator and possibly of the leads themselves.

Generally PMIE presents with more systemic signs and symptoms than do infections of the pacemaker pocket. Despite the fact that *S. aureus* and CoNS are the most frequent pathogens, PMIE is usually subacute in nature. Fever occurs in 84% 100% of patients. However, absence of fever does not rule out the presence of PMIE. Forty-five percent of cases of PMIE suffer from symptoms of septic pulmonary emboli (dyspnea, pleuritic pain).

### IVDA IE

Approximately 5% to 8% of IVDA who present with fever have IE. The signs and symptoms of IVDA IE are related not only to the nature of the pathogen but also by the particular cardiac valves that are infected. The clinical course of left-sided IVDA is quite similar to that of valvular infections in non-drug users. However there is a high rate of neurological findings (panophthalmitis and cerebral mycotic aneurysms) and persistence of bacteremia when *P. aeruginosa* is involved (38,137,138). Fifty-three percent of cases of IVDA IE present with coughs, pleuritic pain, and hemoptysis due to right-sided involvement. There is low rate of systemic embolization. The pulmonary signs and symptoms may be due to septic emboli, pneumonia and/or empyema. Emboli may also involve the central nervous system, bones, and joints. The high rate of concurrent infection with HIV does not effect the clinical presentation of IVDA IE.

### HCIE

HCIE clinically differs from valvular infection that is acquired in the community. It much more often presents as a nonspecific picture of sepsis with hypotension, metabolic acidosis, and multiple organ failure. Hypotension and pulmonary edema are also more frequent in HCIE (53% vs. 23% and 27% vs. 9%, respectively). It presents itself less often with fever/chills and leukocytosis (55% vs. 25% and 82% vs. 61%, respectively). These features are dependent on the host's mounting an effective inflammatory response. There is a lower rate of the dermatological manifestations of IE such as Osler's nodes and Janeway lesions. The older age and the greater rate of valvular abnormalities of the patient with iatrogenically produced IE may explain these differences (69,139,140).

Although in the recent past, up to 45% of cases of HCIE involved prosthetic valves, in the last 20 years the percentage of native valves infected in health care facilities has been on the increase. It is important to repeat that prosthetic valves are very susceptible to being infected by BSIs. This may occur despite the patients having been given an appropriate antibiotic regimen for more than two weeks at the onset of the bacteremia 34% of these infections were caused by gram-negative and fungi (135). The presentation of fungal HCIE of prosthetic valves is quite indolent and contributes, along with the difficulty in isolating fungi from the bloodstream, to the failure to make an expeditious diagnosis (141).

## DIFFERENTIAL DIAGNOSIS

### History

SBE is a very indolent infection. Its most common symptoms are low-grade fever, fatigue, anorexia, backache (presenting symptom in 15% of cases), and weight loss. Much less frequently, it may present as a stroke or congestive heart failure. Both of these events arise from embolic/and/or immunological processes. They usually occur well into the disease process when diagnosis and therapy has been delayed for several months. Less than 50% of patients have had previously recognized valvular disease. The usual interval between initiating bacteremia and symptoms of subacute disease is two weeks, rarely as long as four (3,123).

The clinical course of acute IV is much more aggressive. It is marked by acute onset of high-grade fever with rapidly progressive valvular destruction often associated with burrowing ring abscesses. These insults to the infected valves can lead to intractable heart failure and sometimes to complete heart block well within a week. The patient should always be questioned about intravenous drug abuse or any recent staphylococcal infections or invasive procedures of any type.

### Physical Examination

Fifteen percent of cases have subacute IE has normal or subnormal temperatures throughout their course (142). This is especially true for the elderly. Acute IE is marked by an extremely high fever. With rare exception, murmurs are consistently present in subacute disease although less than 50% of patients had previously recognized alveolar disease. The characteristics of pre-existing murmurs do not exhibit any change until late in the course of subacute disease. Murmurs are absent in about one-third of patients with left-sided acute IV and two-thirds of those with either right-sided disease or mural endocarditis (143).

The dermal stigmata of valvular infection, Osler's nodes, Janeway lesions, and splinter hemorrhages are currently observed in only about 20% of patients. Of individuals with SBE, 40% develop joint and muscle involvement of various types (144). These include arthritis and synovitis. They represent the immunological phenomena of this type of valvular infection. Septic arthritis may develop from the BSI of staphylococcal IE. Splenomegaly is present in less than 30% of cases, usually acute ones. When candidemia/candidal IE is suspected and ophthalmological consult should be called for evaluation of the patient for the presence of *Candida* emboli and endophthalmitis. Specific eye findings can occur in approximately 30% of patients. Such an examination is helpful both for diagnosis and also length and type of treatment (145). For further physical findings of IE refer to Table 7.

### Laboratory/Imaging Tests

The diagnostic hallmark, of all types of IE, is the presence of a continuous bacteremia. This may be defined as two sets of blood cultures, drawn at least 12 hours apart, that grow out the same organism. At least three out of four blood cultures, positive for the same organism with the first and last sets separated by at least one hour also define a continuous BSI (146). In the case of ABE, the time span for obtaining blood cultures should be shortened to one-half hour because of the imperative in beginning appropriate antibiotic therapy. In the case of *S. aureus* BSI, the time to positivity of the blood culture is also an important parameter. Growth of this organism within 14 hours of culture indicates those patients with an increased likelihood to have valvular infections as the source of the BSI as well as having a greater amount of complications such as metastatic infection (147). In culture positive IE, three sets of blood cultures will detect the pathogen in greater than 99% of cases (148). This figure applies primarily to *S. viridans* IE. When diagnosing possible PVE, five sets of blood cultures should be drawn. The BSI of PVE may not be continuous in up to 10% of cases (149). In addition, multiple blood cultures are helpful in differentiating infection with CoNS from contamination with this organism. At least 64% of patients who have received prior antibiotics will have false negative blood cultures (150). The longer the duration of antibiotic administration, the greater the length of time that the blood cultures remain negative. Under these conditions, the blood cultures should be obtained at least to 48 hours after the antimicrobial agent has been discontinued

in cases of suspected SBE. If these cultures fail to retrieve the organism, then a second set of blood cultures should be obtained between 7 and 10 days after the first. A delay of one or two weeks in beginning treatment for subacute disease does not put the patient at risk from undue complications. However, in patients with acute IE, antibiotic therapy must be begun within one or two hours of the patient's presentation. How frequently antibiotic therapy suppresses the growth of more virulent organisms such as *S. aureus* and gram-negatives is unknown. It is the author's experience that prior antibiotics have a very short-term effect, if any, on the retrieval rate of *S. aureus*. In the individual with persistently negative blood cultures but in whom there remains a high suspicion of valvular infection, more indirect diagnostic means, such as echocardiography, must be employed.

In the past, up to 50% of bacteria isolated in blood cultures represented contamination (151). This figure is improving but not reaching the theoretical minimum of less than 3%. One contaminated blood culture may increase the total hospital bill of the patient by up to 40% by prolonging hospitalization by four days (152–154). Obtaining only one set of blood cultures may be worse than obtaining none at all. A single culture can neither define a contaminant or a continuous bacteremia. Blood cultures should, at a minimum, be obtained in pairs. It is extremely difficult to withhold treatment in an extremely ill patient with a single positive blood culture albeit one that it is suspicious as representing contamination. Conversely, blood cultures are often not obtained in the acutely ill individual since the patient is felt to ill to tolerate even the slightest delay in starting therapy. In such situations it is far better to rapidly draw at least three sets of blood cultures through separate venipunctures than not to obtain any at all. Because the BSI of IE is continuous, there is no reason to wait to draw blood cultures until the patient's temperature is on the rise.

Every precaution should be taken to prevent contamination. The skin should be prepared with 70% isopropyl alcohol followed by application of an iodophor or tincture of iodine. It should be allowed to dry completely for maximum effect (155). Because of the risk of contamination, cultures should never be drawn through intravascular lines except for documenting infection of that line (156). Each set must be drawn through a different venipuncture. Replacement of the needle before inoculating the specimen into the blood culture bottles is unnecessary. Because of the low concentration of bacteria in most BSIs, a 10 mL aliquot should be added to each bottle to produce a 1/10 ratio of blood to broth. This dilution may also inhibit the suppressive effect of both antibiotics and the patient's own antibodies (157). There is no one ideal growth medium for recovering organisms from the blood. Trypticase soy broth is the most commonly used aerobic medium. Thioglycolate is its anaerobic counterpart. The anticoagulant, SPS, is added to the blood culture media because most pathogens do not thrive within blood clots, SPS also interferes with the inhibitory effects of white cells and of several antibiotics (153). *Abiotrophia* spp. requires pyridoxine supplementation for its growth. This substance is present in the broth of automated blood culture systems. These systems make it unnecessary for cultures to be incubated for two to three weeks for recovery of fastidious organisms (i.e., members of the HACEK group, *Brucella* spp. and *Francisella tularensis*). Only 50% of routine blood cultures in the setting of candidal valvular infection are positive (47). *Aspergillus* and *Histoplasma* are rarely recovered from the bloodstream. When specific fungal cultures are employed along with adjunctive tests (serological), the rate of diagnosis of *Candida* IE may increase to 95% (158). A major contributing factor to missing the diagnosis of fungal IE is the failure to even include it in the differential. In one series, only 18% of the cases were suspected at the time of hospitalization (47). This inability to recognize potential cases is increasingly more significant with the ever-increasing numbers of immunosuppressed patients and those who are cared for in CCUs.

There are three major characteristics that the nodes each with positive culture (154):

1. The type of organism recovered. CoNS that is recovered in blood cultures and individual without intravascular catheter or other prosthetic material in place usually represents a contaminant.
2. Multiple specimens that are positive for the same organism.
3. The degree of severity of illness of the patient is directly proportional to the likelihood that a blood culture result does not represent contamination.

Falsely negative blood cultures currently occur in 5% cases of IE. These are most frequently due to the prior administration of antibiotics (159), ranging from 35% to 79% of false negative cultures. The false negative rate is directly related to the frequency of fastidious organisms of (i.e., *Bartonella* spp) in the environment. This figure is most likely higher for patients in CCU because of the multiple courses of antibiotics that are empirically given to treat fevers that are in reality a result of undiagnosed valvular infection. This produces the state of "muted" IE in which the valvular infection goes on while the blood cultures remain negative. Paizin provides a specific example of this phenomenon (160). He demonstrated that the recovery rate of streptococci from blood cultures in patients who had received any antibiotic in the previous two weeks was reduced to 64% is compared with 100% of those patients who had not been given antibiotics. The shorter the course of the antibiotic, the shorter the time it takes the blood cultures to become positive. If the prior course of antibiotics has been prolonged, then it may take up to two weeks of being off of them to be able to detect the pathogen. In the author's experience, antibiotics to be at the suppressive, if at all, the retrieval of *S. aureus* for a few days only (161). Broth may be supplemented with not only sulfopolyanetholsulfonate (SPS) but also resins (BACTEC resin) (162) that theoretically will inactivate whatever antibiotics may be present. This approach has had a moderate amount of success in cases of *S. aureus* BSI and fungemia (163).

In the author's experience, the second most common cause of false negative blood cultures, especially in CCU IE, is produced by a surface sterilization phenomenon. For unknown reasons, the infecting organisms, especially *S. aureus*, leave the surface of the vegetation and penetrate deep within. The BSI stops but the bacteria continue to replicate and to burrow the base of the valve. Paravalvular and/or septal abscesses and ruptured chordae tendinae may be the final result of this process (164). Surface sterilization is most likely becoming more frequent because of the rise in *S. aureus* IE.

Because of the risk of contamination, blood cultures should never be drawn through intravascular lines except for the purpose of documenting line infection. The traditional approach has been the role plate method. This necessitates that the catheter be removed. Only its external surface is cultured. Approximately 80% of intravascular catheters that have been removed because of clinical suspicion of infection have been found to be not infected. Clearly, methods that can diagnose a CRBSI while the catheter is in place are more desirable (165). Paired quantitative blood cultures, drawn through the catheter and peripherally, appear to be the most accurate way to diagnose CRBSI (166). However this technique is expensive and labor-intensive with opportunities for contamination. The differential in time of growth between blood cultures drawn through the intravascular lines and those drawn peripherally is much more practical way to assess the CRBSI. It makes use of the fact that automatic blood cultures systems continuously monitor for and record the time of initial growth. The blood culture, obtained from the intravascular device, becoming positive more than two hours before, which obtained peripherally, reflects a heavier bacterial growth in the catheter. This would indicate that the intravascular catheter is the source of the BSI. Semiquantitative cultures from the hub and skin (superficial cultures) that grew out the same organism is isolated in a venous blood culture provided approximately the same sensitivity and specificity of diagnosing CRBSI as the preceding two methods (167).

The question of how many blood cultures are necessary to diagnose a BSI in the era of automated blood culture systems. In a recent study, one to four sets blood cultures detected cumulatively 73.1%, 87.7%, 96.9%, and 99.7%, respectively. Three sets are the probable optimum number since the difference in yield is essentially insignificant between three and four blood cultures with the possibility of increased contamination as more cultures are drawn (168).

Diagnosis of IE that is caused by pathogens that are challenging to culture in the clinical microbiology laboratory (e.g., *C. burnetii*, *Legionella*) is dependent on the use of serologic studies and various types of DNA amplification techniques (169–171). PCR techniques have been applied directly to explanted valvular tissue obtained at surgery. Limited experience indicates that they are more sensitive and from more specific than standard cultures that have a high rate of contamination (172).

Abnormalities of cardiac conduction are seen in 9% of patients with valvular infection. These are due to septal abscesses or myocarditis (173). During the first two weeks of treatment

of acute IE, electrocardiography should be performed every 48 to 72 hours to help rule out the development of septal abscesses.

Rheumatoid factor is present in 50% of patients and subacute IE. It disappears as successful treatment and may serve as a “poor man’s” substitute for measuring circulating immune complexes (72). The nonspecific findings of elevated sedimentation rate, anemia chronic disease, proteinuria, and hematuria are not helpful in the diagnosis of IE.

Because of the prevalence of false-negative blood cultures, especially HCIE, that are due to the empirical use of antibiotics, several types of imaging techniques have been applied the diagnosis of valvular infection. Radionuclide scans, such as Ga-67 and In-111 tagged white cells and platelets have been used in diagnosing myocardial abscesses. These techniques have been generally been of little help because of their poor resolution and high rate of false negatives (174).

Echocardiography has become the imaging modality of choice for the diagnosis and management of valvular infection. Despite the long-term availability of this technique, there remains a good deal of confusion regarding the indications for its use of as well as the role of transthoracic echocardiography (TTE) versus transesophageal echocardiography in valvular infections. Neither TTE nor TEE should be used in patients with a low clinical probability of IE. Interestingly, pneumonia appears to be the most common alternative diagnoses in these situations (175). Up to 50% of vegetations, demonstrated by either type of echocardiography, represents sterile platelet/fibrin thrombi, or nonbacterial thrombotic endocarditis (NBTE). There are few if any echocardiographic criteria that definitely differentiate infected from noninfected thrombi. Fifty percent of vegetations actually represent leaflet thickening. There is a good deal of interobserver variability in reading either type of echocardiogram. Fifteen percent of cases of IE have no detectable vegetations on echocardiography at any given time (176–179).

Vegetations must be of 3 mm to 6 mm in diameter to be reliably imaged by a transthoracic echocardiography (TTE). A transoesophageal echocardiography TEE may define structures down to 1 mm in diameter. The sensitivity of detecting NVIE ranges up to 95% compared with 68% for TTE. A TTE is ineffective in 15% of patients because of chronic obstructive pulmonary disease (COPD). It has only a 35% sensitivity for detecting PVE as compared with greater than 75% for TEE. TEE is also the superior modality for detecting right-sided vegetations. The negative predictive value of IE by TEE approaches 100% (181).

A TTE should be ordered initially except in the setting of possible PVE, abnormal body habitus, known valvular abnormality, or *S. aureus* bacteremia. If there are no positive findings on TTE, the likelihood of IE is very low, and a TEE should not be performed unless there are persistently positive blood cultures without a definable source or the TTE study was technically unsatisfactory. Table 9 presents the indications for performing echocardiography in NVIE and PVE (182). All cases of proven IE should have an echocardiographic study in order to set the baseline for that individual and so more accurately monitor the therapeutic response and to detect the onset of complications especially aortic regurgitation.

The characteristics of the vegetations are useful in predicting the risk of embolization and abscess formation. Vegetations greater than 10 mm in diameter and those which exhibit significant mobility are three times more likely to embolize than those without these features. Vegetations of the mitral valve, especially those on the anterior leaflet, are more likely to embolize than those located elsewhere. Myocardial abscess formation is positively correlated with aortic valve infection and intravenous drug abuse (183–186).

CT and MRI currently have almost no role in managing cases of IE. The relative “slowness” of current technology is the major limiting factor.

## DIAGNOSIS

### Presumptive Clinical Diagnosis

Whenever there is a BSI with bacteria capable infected in native of prosthetic valve, the possibility of IE must be actively ruled out. IE is a “cannot miss” diagnosis. The presence of the continuous bacteremia, by itself, is adequate for the working diagnosis of IE because no other infection is capable of producing it. A true diagnostic challenge is the clinical scenario in which the patient’s clinical signs and symptoms are consistent with IE but the blood cultures are persistently negative (see ‘Mimics of Endocarditis’).



**Table 9** American College of Cardiology/American Heart Association Guidelines for Echocardiography in Native Valve and Prosthetic Valve Endocarditis

1. Indication	Class <sup>a</sup> (native/prosthetic valve)
2. Detection and characterization of valvular lesions and their hemodynamic severity or degree of ventricular decompensation <sup>b</sup>	I/I
3. Detection of associated abnormalities (e.g., abscesses, shunts etc.) <sup>b</sup>	I/I
4. Reevaluation of complicated endocarditis (e.g., virulent organisms, severe hemodynamic lesion, aortic valve involvement, persistent fever or bacteremia clinical change, or deterioration)	I/I
5. Evaluation of patients with high clinical suspicion of culture-negative endocarditis <sup>b</sup>	I/I
6. Evaluation of persistent bacteremia or fungemia without a known source <sup>b</sup>	Ia/I
7. Risk stratification in established endocarditis <sup>b</sup>	Ila/-
8. Routine reevaluation in uncomplicated endocarditis during antibiotic therapy	Ilb/Ilb
9. Evaluation of fever and nonpathological murmur without evidence of bacteremia <sup>c</sup>	III/Ila

<sup>a</sup>Class I: evidence and/or general agreement that an echocardiography is useful; Ila: conflicting evidence or divergence of opinion about usefulness, but weight of evidence/opinion favor it; lib: usefulness is less well established; 111: evidence or general opinion that echocardiography is not useful.

<sup>b</sup>Transesophageal echocardiography (TEE) may provide incremental value in addition to information obtained by transthoracic echocardiography (TTE). The role of TEE in first-line examination awaits further study.

<sup>c</sup>Prosthetic valves-Ila: for persistent bacteremia; 111: for transient bacteremia.

Source: Adapted from Ref. 180

Definitive pathological diagnosis of IE is derived at by culturing organisms from an endocardial vegetation, an embolized thrombus, or a myocardial abscess. Alternatively, histological examination can confirm the diagnosis. Standard tissues gains have been supplemented by DNA amplification techniques (187).

In 1994, Durack and colleagues developed criteria (The Dukes Criteria) to facilitate the diagnosis of IE. These are based on the combined clinical, microbiological, and echocardiographic findings for a given patient (146).

Major criteria include:

1. The presence of a continuous bacteremia (see above) with organisms typically involved in IE
2. Specific echocardiographic findings of IE
  - a. An oscillating intracardiac mass on a valve or supporting structures or in the path of regurgitant jets or on an iatrogenic device
  - b. Myocardial abscess
  - c. New dehiscence of a prosthetic valve
  - d. New valvular regurgitation

Minor criteria include:

1. Predisposing cardiac conditions or intravenous drug use
2. Fever greater than or equal to 38°C (100.4°F)
3. Vascular phenomena such as arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhages, and Janeway lesions.
4. Immunological phenomena such as glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor.
5. Echocardiographic findings not meeting the above major echocardiographic criteria.
6. Positive blood cultures, not meeting above major criteria, or serological evidence of the presence of an organism typically involved in IE.

The definitive clinical diagnosis of IE is made by the presence of two major criteria or one major and three minor criteria or five-minute criteria.

**Table 10** Differential Diagnoses

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Noninfectious entities
Marantic endocarditis
Antiphospholipid syndrome
Atrial myxoma
Cardiac neoplasms
Polymyalgia rheumatica
Reactive arthritis and Reiter's syndrome
Systemic lupus erythematosus
Thrombotic nonbacterial endocarc
Temporal arteritis and other forms vasculitis
Cholesterol emboli syndrome
Infectious entities
Lyme disease
Viral hepatitis
Disseminated gonococcal infection/gonococcal arthritis

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The presence of a continuous bacteremia differentiates IE from its infectious and noninfectious mimics.

The diagnosis of IE is rejected when:

1. There is a definitive alternative diagnosis.
2. The clinical manifestations of IE resolve after four or less days of antimicrobial therapy.
3. There is no pathological evidence of IE after four or fewer days of antimicrobial therapy.

In general, these criteria are quite useful with certain exceptions. The modified Duke criteria of 2000 include the category of possible IE. This represents findings that are consistent with IE but neither fulfill the definite criteria nor fit the rejected criteria (188). The category of possible IE contributes little to the diagnostic process. In addition, the Duke criteria are more slanted to the diagnosis subacute disease because of the preponderance of immunological phenomena in this variety of valvular infection.

Table 10 presents the differential diagnosis of IE.

### MIMICS OF ENDOCARDITIS

Many disease processes, both infectious and noninfectious, mimic IE especially the subacute variety (189). Echocardiography may readily exclude many of these entities. This discussion will focus on those diseases that mimic IE by damaging cardiac valves, producing valvular vegetations and producing many of the signs and symptoms of IE (immunological phenomena, embolic events, and musculoskeletal complaints). Through a variety of mechanisms, these mimics induce endothelial damage that results in the development of the sterile platelet/fibrin/thrombus. Most of these disease processes are autoimmune in nature. They result in quite friable vegetations that have a high rate of embolization. Blood cultures are sterile in these situations except when the NBTE becomes secondarily infected. IE, which complicates rheumatoid arthritis and systemic lupus erythematosus (SLE), occurs more frequently in the setting of renal failure and in those patients who are receiving prednisone or cyclophosphamide. Many autoimmune disorders such as scleroderma systemic vasculitis lead to valvular damage. However these diseases usually about associated with thromboembolic phenomena in and so should not pose a real diagnostic challenge (190,191).

The most effective mimic of all is atrial myxoma. Upto 50% of left atrial myxomas embolize, most frequently to the central nervous system. Significant fever is documented in 50% of cases. Often the only way to distinguish myxoma from valvular infection is by microscopic examination of tissue that has been recovered from a peripheral artery embolus or at the time of cardiac surgery (192). Tables 11 and 12 present the most diagnostically challenging mimics of endocarditis along with their clinical and laboratory features.

**Table 11** Mimics of Infective Endocarditis

Disease	Type of valvular involvement	Comments
Antiphospholipid syndrome	Stenosis or regurgitation	Patients have thrombotic events and/or recurrent spontaneous abortions. Antibody titers have no direct correlation with disease activity.
Systemic lupus erythematosus	Stenosis or regurgitation occurs in 46% of patients (usually of the mitral valve)	4% of cases of Libman–Sacks endocarditis become secondarily infected usually early in the course of the disease.
Rheumatoid arthritis	Regurgitation occurs in 2% of patients	Valvular infection usually occurs later in the course of the disease.
Atrial Myxoma	Primarily obstruction of the mitral valve due to its "ball valve" effect	It is the most effective mimic due to its valvular involvement, embolic events and constitutional signs and symptoms.

**Table 12** Mimics of Infective Endocarditis: Clinical and Laboratory Features

Mimics of endocarditis	Bacteremia	Cardiac vegetation	Fever	Splenomegaly	Emboli	↑ ESR	Abnormal SPEP <sup>a</sup>
Marantic endocarditis	–	+	–	–	±	–	–
Viral myocarditis	–	–	+	–	±	+	–
SLE (Libman–Sacks endocarditis)	–	+	+	±	–	+	+
Atrial myxoma	–	±	+	–	+	+	+
Infective endocarditis	+	+	+	–	±	+	–

<sup>a</sup>Polyclonal gammopathy on SPEP.

*Abbreviations:* ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus; SPEP, serum protein electrophoresis.

*Source:* From Ref. 189.

## THERAPY

### Nonantibiotic Therapy

An operative approach is eventually required in 25% of cases of IE. Twenty-five percent of these surgeries are performed during the early stages of this disease. The remainder take place later on even after microbiologic cure has been achieved. Surgery has improved outcomes of valvular infection for many. Because of the increase in IE, that is due to *S. aureus*, gram-negatives aerobes and fungi, especially among impaired hosts, overall outcomes have not improved in the last 30 years (193,194).

In both NVIE and PVE, congestive heart failure, that is refractory to standard medical therapy, is the most common indication for surgical intervention. The major indications for operative intervention are: (i) fungal IE (excluding that caused *Histoplasma capsulatum*); (ii) BSI that persists past seven days of appropriate antibiotic therapy and is not determined to originate from an extracardiac source; (iii) recurrent septic emboli occurring after two weeks of appropriate antibiotic therapy; (iv) rupture of an aneurysm of the sinus of Valsalva; (v) conduction disturbances secondary to a septal abscess; and (vi) "kissing" infection of the anterior mitral valve leaflet in cases of aortic valve IE.

Indications for surgery in cases of PVE are the same as above with the addition of the presence of prosthetic valve dehiscence and cases of early acquired PVE. Because of the difficulty in eradicating organisms from prosthetic devices, surgery plays a far more immediate role in the treatment of PVE than in NVIE. Not all cases of PVE require surgery. Characteristics of PVE associated with successful treatment by medical therapy alone include: (i) infection due to susceptible organisms, (ii) late PVE, (iii) mitral valve PVE, and (iv) prompt initiation of antibiotic treatment of BioPVE (195,196).

Certain echocardiographic findings are recognized as being predictive of the need for surgery in IE (197). Among these are: (i) detectable vegetations following a large embolus, (ii) anterior mitral valve vegetations that are greater than 1 cm in diameter, (iii) continued growth vegetations after four weeks of antibiotic therapy, (iv) development of acute mitral insufficiency, (v) rupture or perforation of a valve, and (vi) periannular extension of the valvular infection (198).

The need for and timing of surgery may be divided into three stages. stage 1—the post antibiotic state— surgery that is required for severe aortic regurgitation that begins after bacteriological cure of IE has been achieved; stage 2—elective—surgery during antimicrobial therapy in patients who develop cardiac failure that responds rapidly to medical management; and stage 3—emergent—surgery in patients who suffer from severe complications such as intractable congestive heart failure or persistent BSI (199).

It is extremely important to rule out splenic abscess before surgery is performed for “refractory IE.” These are often clinically occult and produce a continuous BSI (200).

Surgery is often required to eradicate a variety of metastatic infections including aneurysm and cerebral abscesses.

Debridement and the administration of antibiotics may cure an uncomplicated pacemaker infection. Treatment of PMIE requires that the entire system be removed. If the leads have been in place for more than 18 months, their extraction may be extremely difficult. Excimer laser sheaths, by dissolving the fibrotic bands that encase the electrodes, are able to produce complete removal in more than 90% of cases (201).

An increasingly common problem in the CCU in the management of *S. aureus* BSI is the presence of an intravascular catheter. Greater than 25% of these bacteremias represent valvular infection. Correctly differentiating those cases of uncomplicated staphylococcal BSI from endocarditis is essential not only for determining the length of antibiotic therapy but also whether long-term intravascular catheters need to be removed at all. Short-term catheters always need to be removed in the setting of *S. aureus* BSI. When associated with *S. aureus* bacteruria, hematuria may be an indicator of sustained *S. aureus* bacteremia. This type of hematuria may result from either embolic renal infarction or immunologically mediated glomerulonephritis (202). The presence of intracellular bacteria on blood smears that are obtained through intravascular catheters is specific for infection of these devices (203). TEE is the most specific approach of separating a continuous, uncomplicated *S. aureus* bacteremia from IE. At least 23% CRBSI, caused by *S. aureus*, have substantial evidence of valvular infection even in the absence of clinical findings and a negative TTE. Table 13 (204) presents an approach to management of short-term intravascular catheter associated *S. aureus* continuous BSI. It is always essential that infected, short-term intravascular catheters be removed. Cure rates are as low as 20% with antibiotic therapy alone without prompt removal of the catheters (205). Surgically implanted long-term catheters (Broviac, Hickman) do need to be

**Table 13** Management of *S. aureus* Bacteremia in the Presence of an Intravascular Catheter

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1. Prompt removal of the catheter
  2. Institution of appropriate antibiotic therapy
  3. Follow-up blood cultures within 24–48 hr
    - A. If follow-up blood cultures are negative and:
      1. The TEE shows no signs of infective endocarditis.
      2. There is no evidence of metastatic infection.

*Then 2 wk of antibiotic therapy would be appropriate*

- B. If follow-up blood cultures are positive and:
  1. The TEE shows signs of infective endocarditis.

*Then 4 wk of intravenous therapy is appropriate*

- C. If follow-up blood cultures are positive and:
  1. The TEE shows no signs of infective endocarditis.

*Further imaging studies should be performed to rule out other sources of bacteremia (osteomyelitis, mediastinitis, splenic abscess)*

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automatically except in the presence of IE, infection of vascular tunnel, suppurative thrombophlebitis or infection by certain pathogens (*Corynebacterium JK*, *Pseudomonas* spp., fungi, *S. aureus* or mycobacteria) (205). Intraluminal infusions of antibiotics have a cure rate of 30% to 50% against sensitive organisms. Whether the use of thrombolytic agents to dissolve the fibrin sheath of the catheter improves outcomes has not been established (206).

Vascular catheters that are colonized with *S. aureus* may be associated with development of *S. aureus* BSI after their removal. These catheters had no evidence of *S. aureus* BSI up to 24 hours post-removal. Twenty-four percent subsequently developed *S. aureus* bacteremia. The median duration for its development after catheter removal was three days with a range of 2 to 25 days. It appears that the length of placement of the line was a significant risk factor. Administration of an appropriate antibiotic within 24 hours of the catheter's removal reduced the rate of subsequent bacteremia by 83% (207). The delayed appearance of the BSI is probably related to the development of endotheliosis before the extraction of the catheter.

BSI that persists after three days of therapy with an appropriate antibiotic therapy is an independent risk factor for IE as well as for death (208).

### ANTIBIOTIC THERAPY

There are many challenges to sterilizing an infected thrombus. Among these are: (i) the overwhelming density of organisms (10 to 100 billion bacteria/gm of tissue); (ii) the decreased metabolic and replicative activity of the organisms, residing within the vegetation, that results in their being less sensitive to the action of most antibiotics and (iii) the decreased penetration of antibiotics into the platelet/fibrin thrombus. In addition, both the mobility and phagocytic function of white cells is impaired within the fibrin rich vegetation (209–211).

Table 14 presents the basic principles of antibiotic therapy of IE. It is estimated that, in a case of *Escherichia coli* IE, 220 times the minimum bactericidal concentration (MBC) of ceftriaxone is required to sterilize the vegetation (209). Determining the bactericidal titer should be applied only to those patients who are not responding well to therapy or who are infected by an unusual organism.

A maximum daily temperature of greater than 37°C after 10 days of treatment should be of concern to the clinician. It may represent a relatively resistant pathogen, extracardiac infection, pulmonary or systemic emboli, drug fever, *Clostridium difficile* colitis, or an infected intravenous site (212). If the invading organism is sensitive to the administered antibiotic, a thorough search for an extracardiac site should be conducted. Mycotic aneurysms are probably the most difficult source to detect. If the TTE is not helpful, then a TEE should be performed (213,214). Sterile recurrent emboli are usually due to immunological processes and do not necessarily represent antibiotic failure (215). Mortality rates are dependent on the nature of the

**Table 14** Basic Principles of Antibiotic Therapy of the Infective Endocarditis

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The necessity of using bactericidal antibiotics because of the "hostile" environment of the infected vegetation<sup>a</sup>. The MIC and MBC of the administered antibiotic against the isolated pathogen needs to be determined in order to insure adequate dosing of the agent.

Generally, intermittent dosing of an antibiotic provides superior penetration of the thrombus as compared to a continuous infusion. Its penetration into tissue is directly related to its peak level in serum.

All patients with IE should be treated in a health care facility for the first 1–2 wk to monitor their hemodynamic stability.

In cases of potential acute infective endocarditis, antibiotic therapy should be started immediately after three to five sets blood cultures have been drawn. Preferably all of them should be obtained within 1 to 2 hr so as to allow the expeditious commencement of antibiotic therapy. The selection of antibiotic/antibiotics to needs to be made empirically on the basis of physical examination and clinical history.

In cases of potential subacute infective endocarditis, antibiotic treatment should not be started until the final culture and sensitivity data are available. A delay of 1 to 2 wk in doing so does not adversely affect the final outcome. The usual duration of therapy ranges from 4–6 wk. A 4-wk course is appropriate for an uncomplicated case of native valve endocarditis. A shorter course of two weeks may be appropriate in certain cases (see text). Six weeks required for the treatment of prosthetic valve endocarditis and in those infections with large vegetations such as associated with infection by members of the HACEK family.

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<sup>a</sup>Linezolid and quinristin/dalfopristin appear to be exceptions to this principle.

Source: From Ref. 222.

**Table 15** Mortality Rates of Left-sided Native Valve IE Due to Various Organisms

Organism	Mortality Rates
<i>Streptococcus viridans</i> and <i>Streptococcus bovis</i>	4%–16%
Enterococci	15%–25%
<i>Staphylococcus aureus</i>	25%–47%
Groups B, C, G streptococci	13%–50%
<i>Coxiella burnetii</i>	5%–37%
<i>Pseudomonas aeruginosa</i> , <i>Enterobacteriaceae</i> , fungi	>50%

Source: From Ref. 222.

organism, the immune status of the host and age. The four-year mortality rate of individuals successfully treated for non-IVDA IE was 33% (216) (Table 15). There was no difference in survival between patients with NVIE and PVE or between those who underwent surgery in the hospital and those who did not. Mortality was associated with increased age and comorbid diagnoses.

Relapse of IE most frequently occurs within the first two months of cessation of treatment of (215–217). No grave relapse is chiefly dependent on the infecting organism. Well-treated NVIE, due to *S. viridans*, rarely relapses. Four percent of *S. aureus* IE and 30% of enterococcal IE do relapse. Gram-negative organisms, especially *P. aeruginosa*, have higher rates of relapse (218). Untreated IE for greater three months' duration has a significant relapse rate. The greatest risk factor for recurrent IE is a previous valvular infection, especially IVDA IE (219). Forty percent of these cases represent recurrence.

### ORGANISM DIRECTED ANTIBIOTIC THERAPY

The gram-positive organisms have clearly become the major challenge antibiotic therapy of IE. Classically, *S. viridans* has been extremely sensitive to the  $\beta$ -lactam antibiotics and vancomycin [minimum inhibitory concentration (MIC) for penicillin less than 0.12  $\mu\text{g}/\text{mL}$ ]. IE due to the viridans streptococci may be cured by a two-week course of the  $\beta$ -lactam antibiotic combined with gentamicin (220–222). The shortened regimen is appropriate to the following conditions: (i) a sensitive as *S. viridans* (MIC < 0.1  $\mu\text{g}/\text{mL}$ ); (ii) NVIE of less than three months' duration; (iii) vegetation size less than 10 mm in diameter; (iv) no cardiac or extracardiac complications; (v) a low risk for developing aminoglycoside nephrotoxicity; and (vi) a good clinical response during the first week of therapy.

Increasing amounts of *S. viridans* are becoming resistant to penicillin (MIC > 0.1  $\mu\text{g}/\text{mL}$ ). Highly resistant isolates are categorized as having a MIC > 1  $\mu\text{g}/\text{mL}$ . Some 13.4% of *S. viridans*, retrieved from BSIs, are highly resistant. Seventeen percent of these are also highly resistant to ceftriaxone (MIC > 2  $\mu\text{g}/\text{mL}$ ) (223).

All *Abiotrophia* spp. are resistant to penicillin, many highly so. Even the penicillin sensitive strains may be tolerant to the  $\beta$ -lactam compounds (224). Tolerance is a phenomenon in which the MBC of an antibiotic exceeds its MIC by a factor 10 (225). Groups B, C, and G streptococci are less sensitive to penicillin than *S. viridans* or group A streptococci (222).

Penicillin alone can cure most cases of *S. viridans* IE. Because of its pharmacokinetics, ceftriaxone has become antibiotic choice because of its twice-a-day dosing regimen. The combined use of a  $\beta$ -lactam or a glycopeptide with gentamicin is required to eradicate resistant streptococci. Such a combination is beneficial in the treatment of tolerant streptococci as well. Table 16 summarizes the recommendations for the treatment of non-enterococcal streptococci.

Since the beginning of the antibiotic era, enterococci have posed a significant therapeutic challenge because of their ability to raise multiple resistance mechanisms. These organisms are resistant to all cephalosporins and to the penicillinase-resistant penicillins. When used alone, penicillin and ampicillin are ineffective against serious enterococcal infection. Likewise, aminoglycosides fail to treat these infections when used alone because of their inability to penetrate the bacterial cell wall. The combination of a  $\beta$ -lactam agents (with the exception of the cephalosporins) is able to effectively treat severe enterococcal infections. The cell wall active component plus penetration of the aminoglycoside into the interior of the enterococcus in so reach its target, the ribosome. A serum concentration of 3  $\mu\text{g}/\text{mL}$  is necessary is necessary

**Table 16** Guidelines for Antimicrobial Therapy of Nonenterococcal Streptococcal Native Valve IE<sup>b,f</sup>

Antibiotic	Dosage regimen
A. Penicillin-sensitive <i>Streptococcus viridans</i> and <i>Streptococcus bovis</i> <sup>d</sup>	
Penicillin G <sup>a</sup>	Penicillin G 20,000,000 U IV in four divided doses for 4 wk
Penicillin G <sup>a</sup> and gentamicin <sup>c</sup>	Penicillin 20,000,000 U IV in four divided doses for 2 wk gentamicin 3mg/kg given q24h as a single dose or in divided doses q8h for 2 wk (ceftriaxone 2g IV/IM for 4 wk may be used in patients with mild reactions to penicillin)
Or	
Ceftriaxone	Ceftriaxone 2g IV/IM for 4 wk (may be used in patients with mild reactions to penicillin)
B. Penicillin-resistant or tolerant <i>S. viridans</i> and <i>S. bovis</i> <sup>d,e</sup>	
Penicillin G <sup>a</sup> or ceftriaxone	Penicillin G 24,000,000 U IV in four divided doses for 4 wk and ceftriaxone 2g IV/IM for 4 wk
Gentamicin	Gentamicin 3mg/kg given q24h as a single dose or in divided doses q8h for 2 wk
C. <i>Abiotrophia</i> spp. and group B streptococci <sup>d</sup>	
Penicillin G <sup>a</sup> and	Penicillin G 20,000,000 U IV in four divided doses for 6 wk
Gentamicin	Gentamicin 3mg/kg given q24h as a single dose or in divided doses q8h for 2 wk

Drug dosages: <sup>a</sup>Vancomycin 30mg/kg IV q12h in patients highly allergic to penicillin.

<sup>b</sup>For patients with normal renal function.

<sup>c</sup>Short course therapy (see text).

<sup>d</sup>See text for definition.

<sup>e</sup>Regimen is appropriate for treatment of prosthetic valve endocarditis with penicillin sensitive or resistant *S. viridans* or *S. bovis*.

<sup>f</sup>Use of gentamicin is associated with increased risk of renal failure (222a).

Source: From Ref. 222.

to establish synergy. Synergy does not exist if the enterococcus is resistant to the cell wall active antibiotic (226).

Currently 5% of *E. faecalis* and 40% of *E. faecium* exhibit high-grade resistance to gentamicin (> 2000 µg/mL) (227). Some gentamicin-resistant strains may remain sensitive to streptomycin and vice versa (227).

Ampicillin resistance, on the basis of β-lactamase production, has been recognized since the 1980s. This is not usually picked up by routine sensitivity testing and requires the use of a nitrocefin disc for detection.

When the enterococcus is sensitive to the β-lactam antibiotics, vancomycin and the aminoglycosides, the classic combination of a cell wall active antibiotic with an aminoglycoside remains the preferred therapeutic approach (228). Vancomycin is substituted for ampicillin in the treatment of those individuals who are allergic to or whose infecting organism is resistant to ampicillin.

When resistance to both gentamicin streptomycin is present, continuously infused ampicillin to achieve a serum level of 60 µg/mL has had some success. Quinpristin/dalfopristin and linezolid are alternative agents. They have the disadvantage of being bacteriostatic against the enterococcus. Quinpristin/dalfopristin is only active against *E. faecium* but not against the most commonly isolated strain of enterococcus, *E. faecalis* (229–231). Daptomycin is bactericidal against these organisms. Experience with the use of this compound against enterococcus is limited but growing. It is not synergistic with aminoglycosides against enterococcal isolates (232). The combination of ampicillin and ceftriaxone does produce synergy against enterococci both in vitro and in vivo. It appears quite effective in the setting off enterococcal PVE (233). Tables 17 and 18 summarize the antibiotic treatment of enterococcal NVIE.

### **S. Aureus**

The penicillinase-resistant penicillins are the drugs of choice in treating MSSA infections, vancomycin, is significantly less effective. It has a failure rate up to 35% in treating MSSA IE (234). The use of vancomycin in treating MSSA infections in CCU patients should be limited to patients with significant allergies to the penicillins. Cefazolin is used in individuals with mild

**Table 17** Treatment of Enterococcal Native Valve Infective Endocarditis<sup>f</sup>

Type of resistance	Regimen <sup>c</sup>
1) None	Penicillin G (18–30 million units/24 hr IV) <sup>a</sup> or Ampicillin (12 gms/24 hr IV) or Vancomycin (30 mg/kg/24 hr IV) plus Gentamicin (3 mg/kg/24 hr IV/IM)
2) Resistant to penicillins due to β-lactamase production	Ampicillin-sulbactam (12 gms/24 hr IV) <sup>a</sup> or Vancomycin (30 mg/kg/24 hr)
3) Intrinsic penicillin resistance <sup>d,e</sup>	Vancomycin (30 mg/kg/24 hr) plus Gentamicin (3 mg/kg/24 hr)
4) Resistance to penicillins	Aminoglycosides and vancomycin <sup>d,e</sup>
A) <i>Enterococcus faecium</i>	Linezolid (1200 mg/24 hr IV/PO) <sup>b,d</sup> or Quinupristin/dalfopristin (22.5 mg/kg/24 hr IV) <sup>b,d</sup>
B) <i>Enterococcus faecalis</i>	Imipenem (2 gm/24 hr) <sup>b,d</sup> plus Ampicillin (12 gm/24 hr IV)

<sup>a</sup>4 wk duration in symptoms <3 mo; 6 wk if symptoms >3 mo.

<sup>b</sup>Treatment should extend for at least 8 wk.

<sup>c</sup>For adults with normal renal function.

<sup>d</sup>For both native and prosthetic valve endocarditis.

<sup>e</sup>May require emergent valve surgery for cure.

<sup>f</sup>Use of gentamicin is associated with increased risk of renal failure (222a).

Source: From Ref. 222.

**Table 18** Alternative Treatment Regimens for Endocarditis Caused by Highly Resistant Gram-Positive Organisms<sup>a</sup>

Antibiotic and dosage	Undesired effects
Linezolid 600 mg every 12 hr IV or PO <sup>b</sup>	Peripheral neuropathy Optic neuritis Hematological effects Development of resistance
Quipristin/dalfopristin 7.5 mg/kg every 8 hr	Thrombophlebitis Myalgias
Daptomycin 6 or 12 mg/kg every 24 hr <sup>c</sup>	Myositis Increasing resistance
Tigecycline initial dose 100 mg IV; 50 mg IV every 12 hr	Gastrointestinal intolerance

<sup>a</sup>See text for discussion.

<sup>b</sup>Excellent PO absorption is useful for transition therapy.

<sup>c</sup>Higher dosage has been used in relatively resistant organisms.

penicillin allergies. There have been failures of cefazolin in treatment of IE. These are ascribed to the production of type A β-lactamases by the organism (235).

Right-sided, MSSA IVDA IE has been successfully treated with two weeks of intravenous therapy with the combination of nafcillin/oxacillin (2 gms every four hours IV for two weeks and 1 mg/kg of gentamicin every eight hours for five days). Possible explanations for the abbreviated antibiotic course in right-sided disease are greater penetration of antibiotics into right-sided vegetations and the decreased concentration of bacteria compared with left-sided disease because of the low oxygen tension of the right ventricle. Therapy cannot be shortened in those patients with advanced AIDS, left-sided disease, or evidence of metastatic infection (236).

The addition of gentamicin to a penicillin or to vancomycin, in the treatment of MSSA NVE, lessens the duration of bacteremia and fever. In doing so, it may minimize both the intra- and extra-cardiac complications *S. aureus* IE (237). It does not decrease overall mortality but



**Table 19** Antibiotic Therapy of *Staphylococcus aureus* Infective Endocarditis<sup>a,f</sup>

Valve type (IE type)	Antibiotic	Dosage
Native (MSSA)	Oxacillin <sup>d</sup> ± gentamicin	Oxacillin 2g IV q4h for 4–6 wk ± gentamicin 3 mg/kg q 24 h as a single dose or in divided doses q8h for 5 days
	or Vancomycin <sup>b,c</sup> ± gentamicin	Vancomycin 15 mg/kg IV q12h for 4–6 wk ± gentamicin 3 mg/kg q24h as a single dose or in divided doses q8h for 5 days
	or Cefazolin ± Gentamicin	Cefazolin 1.5 g IV q8h for 4–6 weeks (in patients with mild allergies to penicillin) ± Gentamicin 3 mg/kg q24h as a single dose or in divided doses q8h for 5 days
Prosthetic (MSSA)	Oxacillin <sup>d</sup> or	Oxacillin 2 g IV q4h for 4–6 wk or Vancomycin 15 mg/kg IV q12h for 4–6 wk or Cefazolin 1.5 g IV q8h for 4–6 wk in patients with mild allergies to penicillin
	Vancomycin or Cefazolin and Rifampin and Gentamicin	Rifampin 300 mg PO q8h for 6 wk  Gentamicin 3 mg/kg q24h as a single dose or in divided doses q8h for 2 wk
	Native (MRSA) Prosthetic (MRSA) <sup>e</sup>	Vancomycin 15 mg/kg IV q12h for 4–6 wk Vancomycin 15 mg/kg IV q12h for 4–6 wk
	Rifampin and Gentamicin	Rifampin 300 mg PO q8h for 6 wk  Gentamicin 3 mg/kg q24h as a single dose or in divided doses q8h for 2 wk

<sup>a</sup>For patients with normal renal function.

<sup>b</sup>For patients with severe penicillin allergy.

<sup>c</sup>Substitute linezolid in critically ill patients or those with significant renal failure (refer to discussion in text and Table 7).

<sup>d</sup>May substitute nafcillin at equal doses for patients in significant renal failure.

<sup>e</sup>If the isolate is resistant to the aminoglycosides, a quinolone to which it is proven sensitive may be substituted.

<sup>f</sup>Use of gentamicin is associated with increased risk of renal failure (222a).

Source: From Ref. 222.

does significantly increase the rate of renal failure (222). Tables 18 and 19 summarize the antibiotic treatment approaches to *S. aureus* IE.

A triple antibiotic approach is required for treatment of staphylococcal PVE produced either by MSSA, MRSA, or CoNS. Rifampin is the essential component because of its ability to kill both CoNS and coagulase-positive staphylococci that adhere to prosthetic material as well as being able to kill the intracellular phase of these pathogens. The main purpose of the other two agents is to prevent the development of rifampin-resistant organisms (238). For those staphylococci resistant to gentamicin, a fluoroquinolone may be an effective substitute (239).

The role of vancomycin in the treatment of deep-seated *S. aureus* infections needs to be reexamined. The evidence of its inferiority in the treatment of MSSA infections as compared with  $\beta$ -lactam, is approaching the overwhelming point. In patients on hemodialysis, vancomycin was found to be inferior to cefazolin for the treatment of MSSA BSI (240). Of all patients on vancomycin, 36.7 % were considered to be treatment failures (death or recurrence of infection) versus 13% of patients on cefazolin. Cases of IVDA IE that were treated with vancomycin had higher infection-related rates of death than those treated with  $\beta$ -lactam agents even if the patient was switched to the latter compounds when the sensitivity patterns became known (241). The decreasing effectiveness of vancomycin is most likely related to the

increasing prevalence of isolates of *S. aureus* for whom the MIC of vancomycin is greater than 4 µg/mL (242). In addition, it appears that the penetration of vancomycin into target tissues is decreased especially in diabetics (243). Similar concerns exist regarding the efficacy of vancomycin in treating MRSA infections (244). Until sensitivities are known, it is advisable to use high does vancomycin to achieve a trough level of greater than 15 µg/mL (245).

Over the last decade, several antibiotics have come on the market to meet the increasing challenge of severe infections due to resistant gram-positive agents (Table 18). The potential for increasing vancomycin toxicity at higher dose levels is an added reason to consider these agents as both empiric and definitive treatment. Linezolid appears to be superior to vancomycin for many types of MRSA infections including IE (246–248). Therapeutic failures of this agent in treating IE have been documented. Some are due to inadequate serum levels as well as possibly due to the bacteriostatic quality of the drug (249). Linezolid administration is associated with significant hematological side effects including anemia and thrombocytopenia. These are usually reversible upon cessation of treatment. However, the neuropathy occurs at an increasing rate the longer medication is administered. It often is irreversible or partially reversible. This limits its safety period to no more than four to six weeks. The risk of the serotonin syndrome with concurrent SSRI and linezolid therapy does occur. However, the risk–benefit analysis often favors starting linezolid in these patients because of shortcomings of vancomycin. Optic neuritis is an idiosyncratic reaction that can occur at any time. Linezolid’s advantages are that it is extremely well absorbed orally and lends itself to transition therapy. In one series of patients with complicated gram-positive IE who required to mediate cardiac surgery, patients were successfully switched early and successfully to oral linezolid therapy in finish a four- to six-week course of antibiotic (250). The author has had similar success in treating susceptible gram-positive IE in nonsurgical patients.

Daptomycin is a bactericidal drug that has had a good amount of success in treating MSSA and MRSA IE (251). Myositis is a significant side effect especially at higher doses. Resistance to the drug is on the increase. This occurs in association with changes in surface charge, membrane phospholipids, and drug binding of *S. aureus* (252). It appears that prior vancomycin therapy promotes resistance to daptomycin. This is probably due to the decreased penetration of daptomycin secondary to an increase in the thickness of the cell wall of *S. aureus* (253).

Tigecycline is another of the alternative agents for resistant gram-positive organisms. It has relatively few side effects. Experience with this compound is still limited (254). Tables 18, 19, and 20 summarize the antibiotic treatment of staphylococcal IE.

Tables 21, 22, and 23 present the antibiotic regimens for the treatment of other types of the IE that were in the may be encountered in CCU.

## FUNGAL ENDOCARDITIS

Combined medical and surgical treatment is necessary for cure of the vast majority of fungal valvular infections. Amphotericin B has been the mainstay of medical therapy of fungal IE (47).

**Table 20** Therapy for Coagulase-Negative Staphylococcal Infection of Prosthetic Valves or Other Prosthetic Material<sup>a,b</sup>

Antibiotic	Dosage regimen
Vancomycin and Rifampin and Gentamicin	15 mg/kg q12h for 6 wk 300 mg PO q8h for 6 wk 3mg/kg q24h IV as a single dose or in divided doses q12h for 2 wk

<sup>a</sup>80% of isolates recovered within the first year after valve replacement are resistant to the β-lactam antibiotics. After this period, 30% are resistant. Sensitivity to the penicillins must be confirmed because standard sensitivity testing may not detect resistance. If the isolate is sensitive, oxacillin or cefazolin may be substituted.

<sup>b</sup>If the organism is resistant to the aminoglycosides, a quinolone, to which it is proven sensitive, should be substituted.

Source: From Ref. 222.

**Table 21** Suggested Representative Antibiotic Therapy of IE Caused by *Enterobacteriaceae* and the HACEK Organisms

Organism	Antibiotic	Dosage regimen <sup>a,b,c</sup>
<i>Escherichia coli</i> and <i>Proteus mirabilis</i>	Ampicillin	12 grams/day
	± Gentamicin	5 mg/kg/day
	or Ceftriaxone	1–2 g/day
	or Ciprofloxacin	400 mg IV q12h
<i>Enterobacter</i> spp. <i>Klebsiella</i> spp. <i>Citrobacter</i> spp. <sup>d</sup> , <i>Providencia</i> spp.	Ticarcillin/clavulanic acid	6 gm (ticarcillin) IV of q6h
	Meropenem	2 g IV q8h
	or Ceftriaxone	2 g IVq 12h
	or Cefipime	2 g q12h
<i>Serratia marcescens</i> <sup>e</sup>	plus Gentamicin	5 mg/kg/day
	Cefipime	2 g IV q8h
	pr Imipenem	1 g IV q6 h
	or Ciprofloxacin	400 mg IV q12h
<i>Salmonella</i> spp.	plus Amikacin	7.5 mg/kgIV q12h
	Ceftriaxone	2 g IVq12h
	or Ciprofloxacin	400 mg IV q12h

<sup>a</sup>For patients with normal renal function.

<sup>b</sup>Duration of therapy at least 6 wk.

<sup>c</sup>Final selection must be based on sensitivity testing.

<sup>d</sup>*C. freundii* most resistant species of *Citrobacter*.

<sup>e</sup>High frequency of multidrug resistance. Amikacin sensitivity usually preserved. Plasmid-mediated resistant to third and fourth generation cephalosporins and carbapenems. Extended spectrum  $\beta$ -lactamases encountered. Quinolone resistance occurs.

Source: From Ref. 222.

The newer antifungal agents, capsosungin, and voriconazole are less toxic and appear to be effective alternatives to amphotericin (255,256). Table 24 presents the sensitivities of various strains of *Candida*. Table 25 presents an approach to the patient at risk of candidal endocarditis.

### ANTICOAGULATION IN INFECTIVE ENDOCARDITIS

The use of anticoagulation with a variety of agents (warfarin, heparin, and aspirin) has been examined for the treatment of IE since the beginning of an antibiotic therapy. This approach would hopefully decrease the size of the vegetation; however, there is an unacceptably high incidence of cerebral hemorrhage. In patients with PVE of mechanical valves, maintenance anticoagulation should be continued. If hemorrhage does occur, warfarin has to be stopped. A reasonable approach would be to substitute intravenous heparin for Coumadin during the first two weeks of treatment, the time of the greatest risk for embolization. Anticoagulation by this mode can easily and quickly be reversed (193). Even the use of aspirin appears not to be safe and offers no therapeutic benefit (258).

### PROPHYLAXIS OF IE IN THE CCU

Guidelines for the antibiotic prophylaxis of endocarditis have recently been published (259,260). It seems most appropriate that prophylaxis of IE in the CCU should focus on reducing the rate of CRBSI. In 2002, the CDC issued guidelines for the prevention of intravascular catheter-related infections (261). This is a rapidly expanding field of interest. It

**Table 22** Therapy of Various Types of Infective Endocarditis<sup>a</sup>

Organism	Antibiotic regimen	Alternative regimen
Culture-negative	Ampicillin 2 g IV q4h for 4 wk <sup>b</sup> and Gentamicin 5 mg/kg q24h IV given in a single dose or in divided doses q8h for the first 2 wk and Oxacillin 2 g IV q4h for 4 weeks or if MRSA is suspected or prosthetic material is present, vancomycin 30 mg/kg q12h for 4 wk	Culture-negative
<i>Pseudomonas aeruginosa</i>	Ticarcillin 3 g IV q4h for 6 wk <sup>b</sup> and Tobramycin 5 mg/kg q24h IV given in a single dose or in divided doses q8h	Ceftazidime <sup>c</sup> 2 g IV q8h for 6 wk Or Aztreonam <sup>d</sup> 2 g IV q6h for 6 wk  And Tobramycin 5 mg/kg IV q24h given in a single dose or in divided doses q8h
HACEK group	Ampicillin 2 g IV q4h for 4-6 wk <sup>b</sup> and Gentamicin 5 mg/kg q24h as a single dose or in divided doses q8h	Cefotaxime <sup>c</sup> 2 g IV q8h for 4-6 wk And Gentamicin 5 mg/kg q24h given in a single dose or in divided doses

<sup>a</sup>For patients with normal renal function.

<sup>b</sup>Preferred regimen (see text).

<sup>c</sup>In patients with mild penicillin allergy.

<sup>d</sup>In patients with severe penicillin allergy.

Source: From Ref. 222.

**Table 23** Representative Antibiotic Therapy of Various Forms of Infective Endocarditis<sup>a,b</sup>

Organism	Dosage regimen
<i>Corynebacterium jeikium</i>	Vancomycin 1 g q12h IV plus Gentamicin 1 mg/kg q8h
<i>Listeria monocytogenes</i>	Ampicillin 12 g/day plus Gentamicin 1.7 mg/kg q8h
<i>Coxiella burnetii</i>	Doxycycline 100 mg IV/PO b.i.d. plus Chloroquine 200 mg t.i.d. <sup>3</sup>
<i>Brucella</i> spp.	Doxycycline 100 mg b.i.d. PO plus Rifampin 900 mg/day PO plus Trimethoprim-/Sulfamethoxazole 160/800 mg PO t.i.d.
<i>Bartonella</i> spp.	Ceftriaxone 2 g/day for 6 wk, gentamicin 1 mg/kg q8h x14 days plus Doxycycline 100 mg IV x 6 wk

<sup>a</sup>For patients with normal renal function.

<sup>b</sup>Given for at least 6 wk.

<sup>c</sup>See text for duration of therapy.

Source: From Ref. 222.

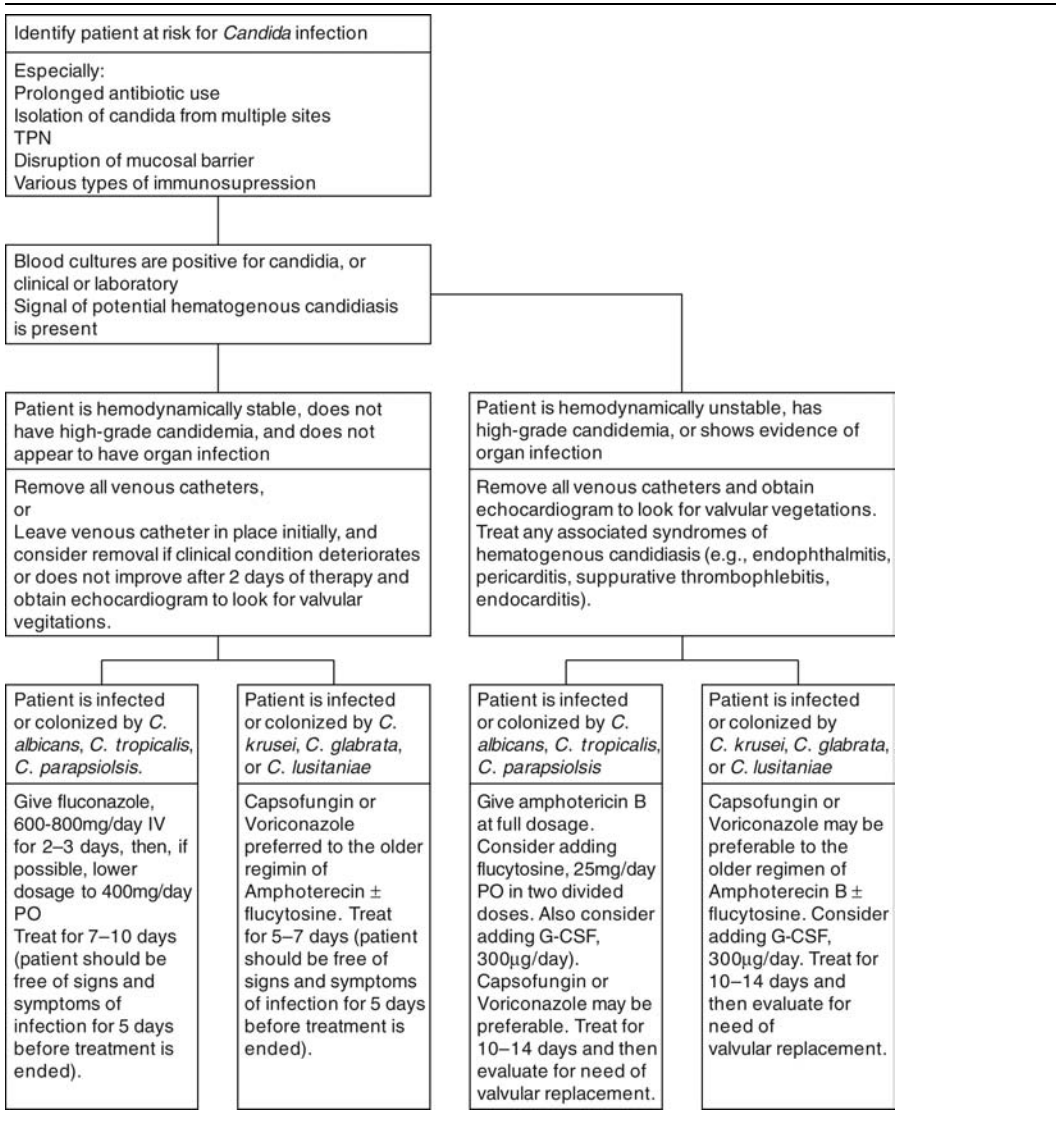
**Table 24** Resistance Patterns of *Candida* spp.

<i>Candida</i> spp.	Sensitivity to antifungals <sup>a</sup>
<i>C. albicans</i>	Sensitive to all classes of antifungals
<i>C. glabrata</i>	Potentially resistant to all azole antifungals and relatively resistant to amphotericin
<i>C. parapsilosis</i>	Sensitive to all classes of antifungals but may be relatively resistant to caspofungin
<i>C. krusei</i>	Resistant to fluconazole. May be relatively resistant to amphotericin
<i>C. lusitaniae</i>	Resistant to amphotericin

<sup>a</sup>Standardization of testing has not been established for echinocandins.

Source: From Ref. 222.

**Table 25** Approach to the Patient at Risk for Candidal Endocarditis



Source: Adapted from Refs. 222 and 257.

**Table 26** The Most Effective Strategies for the Prevention of Infection of Intravascular Catheters

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Development of a comprehensive prevention strategy
100% compliance with hand washing
Insertion of central catheters under strict sterile conditions
Use of chlorhexidine as skin disinfectant
Avoidance of inserting femoral catheters
No routine replacement of intravenous catheters
Removal of catheters as soon as medically feasible
Use of antibiotic impregnated catheters <sup>a</sup>

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<sup>a</sup>Use only under special circumstances (refer to text).

has been thoroughly reviewed in other sources (262). Many innovative approaches to prevention have been developed including heparin bound catheters, antibiotic lock technique, and systemic anticoagulation. These are aimed at preventing either fibrin sleeve formation around the catheter or reducing the risk of bacterial infection of these thrombi. Probably the most effective of this type of approach is the use of antimicrobial-impregnated catheters (263). There has not been a large trial supporting the use. Concern still remains regarding the possibility of allergic reactions to the impregnated material. Use of these devices should probably be employed only when the rate of CRBSI exceeds 4 per 100,000 catheter days despite effective of best practice (264–266).

The largest study of preventing CRBSI, to date, was conducted in Michigan. It was based on 375,000 catheter days involving 103 CCUs of all levels throughout the state. Prevention consisted of using five procedures; handwashing, full barrier precautions during insertion of lines, chlorhexidine for skin antisepsis, removal of catheters as soon as possible, and avoidance of the femoral site of insertion. The use of antibiotic impregnated catheters was not studied. Applying these interventions for 16 to 18 months, the rate of CRBSI per thousand catheter days declined from 7.7 to 1.4. In summary, these outstanding results were based on a comprehensive implementation plan combined with consistently focusing on the important interventions. Success did not necessarily require a dedicated catheter team. Table 26 presents the author's opinion of the most important strategies for prevention of infection of intravascular catheters (264–266).

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# 14 | Intra-abdominal Surgical Infections and Their Mimics in Critical Care

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## INTRODUCTION

Postsurgical patients in the intensive care unit (ICU) often confront a myriad of medical and new surgical complications. Among these, intra-abdominal infections remain the most formidable adversary, affecting an estimated 6% of all critically ill surgical patients. Organ dysfunction continues to be a major manifestation of these infections, resulting in a high mortality of 23% (1). Yet, the literature is relatively sparse in recommendations for diagnosis in management. In updating this chapter, a search of PUBMED for “Intraabdominal infection and ICU” disclosed only 37 articles published between 1989 and 2008, many of which were tangential or simply not relevant. Also, we have not included management of the “open abdomen” in our discussion, focusing instead on specific diseases.

Intra-abdominal infection in the surgical ICU (SICU) patient may occur as a complication of a previous condition or arise *de novo*. In either event, it is evident that the critically ill patient is predisposed to a different set of disease states and pathogens than the clinician might routinely encounter. Moreover, given the complex background of concomitant illnesses in these individuals, physicians must be prepared to interpret a variety of atypical presentations. The burden of the diagnostician in the care of the ICU patient, however, remains not only of sensitivity but also of specificity; accordingly, the physician must be alert to a variety of clinical pictures that may masquerade as abdominal infection in the SICU patient. In this chapter, we review the unique characteristics of intra-abdominal infections in critically ill patients, as well as the challenges faced in their diagnosis and treatment.

## TERTIARY PERITONITIS

With a startling mortality of 20% to 50%, the diagnosis and treatment of tertiary peritonitis has remained a source of intense research for two decades (2). Tertiary peritonitis, or intra-abdominal infection persisting beyond a failed surgical attempt to eradicate secondary peritonitis, represents a blurring of the clinical continuum, often characterized by the lack of typically presenting signs and symptoms. Nevertheless, prompt diagnosis is essential for cure, and given the grim propensity of this complication to strike already critically ill patients—rapidly devolving into multi-organ system failure—the intensivist should be equipped with the necessary knowledge to suspect, confirm, and treat this serious illness.

## Early Recognition

The gradual postoperative transitional period between a diagnosis of secondary and tertiary peritonitis causes the clinical presentation of tertiary peritonitis to be quite subtle. Moreover, because patients are frequently sedated, intubated, or otherwise incapacitated, history and physical exam in the early stages of disease are often an insensitive means to a diagnosis. Therefore, the physician must pay particular attention to those secondary peritonitis patients whose conditions place them at risk, including malnutrition and the several variables detailed under the acute physiological and chronic health evaluation score (APACHE) II scoring system such as age, chronic health conditions, and certain physiologic abnormalities while in the ICU (3). In these individuals, fever, elevated C reactive protein (CRP), and leukocytosis—although admittedly nonspecific in the postsurgical patient—should be addressed quickly and assertively, even when lacking other evidence of infection such as abdominal tenderness and absent bowel sounds (3). As one might reasonably predict, clinical evidence of tertiary peritonitis becomes increasingly more obvious the farther the disease has progressed,

eventually leading to multi-organ system failure. To this end, further scoring systems have been developed to determine the probability that tertiary peritonitis is in fact present postsurgically. Two such systems, the Sepsis-Related Organ Failure Assessment and the Goris scores, attempt to objectively sum the failure of the respiratory, cardiovascular, nervous, renal, hepatic, and coagulation systems. Even though first postoperative day scores are elevated in patients both with and without tertiary peritonitis, subsequent second and third day scores are seen to fall in those without the disease, whereas remaining steady in patients later diagnosed by reoperation with tertiary peritonitis (4). Although these findings may be interesting and statistically significant, their clinical application—in overall terms of mortality avoided—remains to be proven. By pausing for evidence of changing widespread system failure over time, the clinician risks losing the opportunity to avoid medical catastrophe.

Radiologic tools, then, become a mainstay of the physician's investigation. Two such studies, gallium-67 (Ga-67) scintigraphy and computed tomography (CT) scan, are commonly used for the detection of intra-abdominal infection. On the whole, CT is generally the preferred choice. At 97.1% accuracy, it is the more accurate of the two, with an enviable specificity of 100%. Isotope scans suffer in terms of accuracy for the postoperative patient because of false-positive uptake in areas of surgical injury. Moreover, CT has the potential to contribute both diagnostically and therapeutically in the care of patients, as will be discussed later. Finally, CT may be done on demand, whereas Ga-67 scintigraphy requires one to two days for concentration of the isotope at the site of infection. Scintigraphy, however, is not entirely without its own merits.

With a sensitivity of 100% relative to 93.7% for CT, it is superior for uncovering early infection prior to the development of discreet fluid collections. Also, it is worth considering that in centers where indium-111 (In-111) and technetium-99m (Tc-99m) exametazine-labeled leukocyte scans are available, a higher level of scintigraphy accuracy may be attained, albeit at greater expense. Furthermore, as an incidental advantage, nucleotide scanning has been known to reveal extra-abdominal infections such as pneumonia and cellulitis that might imitate tertiary peritonitis (5). Therefore, one might consider this as a second option for the relatively stable patient, in which CT has failed to provide a definitive answer but signs and symptoms persist. Other studies, such as plain film, are impaired by the nonspecific finding of intra-peritoneal free air and other features that might normally be expected in the postoperative patient (6).

### Microbiology and Pathogenesis

The flora of tertiary peritonitis is different from that of secondary peritonitis. Whereas a culture of secondary peritonitis might produce a predominance of *Escherichia coli*, streptococci, and bacteroides—all normal gut flora—tertiary peritonitis is more apt to culture *Pseudomonas*, coagulase-negative *Staphylococcus*, *Enterococcus*, and *Candida* (7,8). The obvious explanation for these differences is the mode of infection: secondary peritonitis is typically community acquired, but tertiary peritonitis occurs in an ICU setting. Time spent in the ICU necessarily implies that the patients affected are critically ill and likely already treated with antimicrobials. Some theorize that disease begins when the gut is weakened by surgical manipulation, hypoperfusion, antibiotic elimination of normal gut flora, and a lack of enteral feeding, thereby creating an opportunity for selected resistant native bacteria to translocate across the mucosal border (9). In fact, independent risk factors for postsurgical enterococcal infection include APACHE II scores greater than 12 and inadequate antibiotic coverage (8). Therefore, empiric antibiotic therapy should be broadly launched to cover the wide range of likely organisms, and later targeted to the specific determined pathogen and sensitivity. Appropriate first agents include, among others, carbapenems or the anti-pseudomonal penicillins, or a regimen of aminoglycosides with either clindamycin or metronidazole for the penicillin-allergic patient (6).

### Treatment

When possible in selected patients, the treatment of tertiary peritonitis may be accomplished by image-guided percutaneous drainage of intra-abdominal abscesses, generally using CT. Percutaneous drainage is not without its inconveniences: complications such as fistulas, cellulitis, and obstructed, displaced, or prematurely removed drains occur in 20% to 40% of

patients (10,11). Nevertheless, the efficacy of this technique is real: Cinat et al. found this method to be 90% successful in postoperative abscess. Abscesses involving the appendix, liver or biliary tract, and colon or rectum were also found to be particularly responsive at rates of 95%, 85%, and 78%, respectively, although pancreatic abscesses and those involving yeast were correlated with poor outcomes by this treatment method (10). Khurram Baig et al. echoed the success of percutaneous drainage in treating abscesses secondary to colorectal surgery, but questioned the applicability of these findings to patients with other than well-defined intra-abdominal abscesses (11).

Other considerations include planned relaparotomy and open management. Data is far from optimal, as these critically ill patients cannot ethically be randomized to different treatment groups. However, it would appear at this time that these strategies still are associated with a high mortality of around 42% (12,13). A study by Schein found a particularly high mortality of 55% in the specific subgroup of diffuse postoperative peritonitis treated by planned relaparotomy, with or without open management. Furthermore, Schein went on to state that open management was associated with over twice the mortality of closed: 58% versus 24% (14). Although necessary flaws in study design make it difficult to say whether these approaches offer an advantage over the more traditional ones, it is nevertheless clear that they are far from ideal.

The hurdles in addressing the challenge of tertiary peritonitis have led to exploration of potential future therapies. Some are in keeping with traditional surgical/mechanical means: Case studies have reported success of laparoscopy, even in the face of diffuse peritonitis and multiple abscesses (15). Other concepts favor a medicine-based approach, rooted in emerging ideas on the disease's basic pathology. As it is believed that bacteria migrate out of the intestinal tract secondary to mucosal ischemia and permeability, strategies that support the mucosa, such as early postoperative enteral feeding or selective elimination of endogenous pathogenic bacteria, have each been tried with mixed results. Likewise, it has been argued that the progression from secondary to tertiary peritonitis represents a crippling of the body's immune system; in support of this belief, granulocyte colony-stimulating factor and interferon- $\gamma$  have each produced limited success in small patient groups, and successfully treated individuals all demonstrated some recovery of immune cell functioning. Another postulate is that a relative lack of corticosteroid exists to fulfill the demands of extreme stress, and it has been suggested that supplying some patients with stress doses of hydrocortisone can improve the vascular effects in early sepsis. Modulation of the inflammatory cascade with activated protein C continues to be investigated, including the associated risk of bleeding. Finally, some researchers have examined the possibility that alleviating the hyper-catabolic state of patients with tertiary peritonitis might decrease mortality. Growth hormone and insulin-like growth factor-1 have both been tried with intermittent positive and negative outcomes (9).

## NEW-ONSET PERITONITIS

### Antibiotic-Associated *Clostridium difficile* Diarrhea in the ICU Patient

#### *Epidemiology, Pathogenesis, and Risk Factors*

The anaerobe *C. difficile* causes twice as many cases of diarrhea as all other bacterial and protozoal causes combined. In hospitalized patients, *C. difficile* is responsible for 30% of diarrhea cases, and in hospitalized patients receiving antibiotic therapy—as is the case for many postsurgical patients—this number rises to an impressive 50% to 70%. *C. difficile*-associated diarrhea (CDAD) is theorized to arise in patients colonized by the pathogen when protective normal gut flora is simultaneously suppressed by broad-coverage antibiotic exposure. Although clindamycin, ampicillin, and the third-generation cephalosporins such as ceftazidime, ceftriaxone, and cefotaxime are the most commonly associated antimicrobials, the newer, broader spectrum quinolones, such as gatifloxacin and moxifloxacin, can also increase risk, and in fact any antibiotic, including, surprisingly, metronidazole and vancomycin, may rarely predispose patients to the disease. Other risk factors for CDAD include age, > 60 years, the winter season, antineoplastic agents (especially methotrexate), recent gastrointestinal surgery, enemas, stool softeners, postpyloric enteric tube feedings (e.g., J-tubes), and even use of proton-pump inhibitors in hospitalized patients (16,17).

### Diagnosis

A CDAD diagnosis is reached based on a number of clinical and laboratory findings such as low-grade fever, median leukocytosis of around 16,000 WBCs/mm<sup>3</sup>, occasional hypoalbuminemia secondary to a protein-losing enteropathy, and, in 5% of patients, even the dramatic presentation of acute abdomen. Sigmoidoscopy, when performed in equivocal cases, will show whitish or yellowish pseudomembranes overlying the mucosa in 41% of cases, and radiologic studies, although nonspecific, will often show signs of inflammation such as cecal dilatation, air-fluid levels, and mucosal thumbprinting. Even though diagnosis is often confirmed using the enzyme-linked immunoassay, it is worth bearing in mind that these tests are only about 85% sensitive. Even polymerase chain reaction (PCR), culture, and the cytotoxicity assay—considered to be the gold-standard in terms of specificity—are likewise imperfect; therefore, a negative test result should not undermine the weight of sound clinical judgment when other likely causes of nosocomial diarrhea have been ruled out (16,17).

### Treatment and Prevention

Therapy for mild cases may consist only of discontinuing the offending antibiotics, or switching to antibiotics less likely to perpetuate CDAD, such as aminoglycosides, macrolides, sulfonamides, or tetracyclines: up to a quarter of cases will resolve following this step alone. For moderate-to-severe cases, metronidazole, either orally or intravenously, is the first line of therapy. In the 20% to 30% of patients who will relapse, a second course of metronidazole is recommended, followed by vancomycin enema for persistent symptomatic infection. Other treatments, such as intravenous immunoglobulin, cholestyramine that binds the bacterial toxin, and probiotics such as *Lactobacillus*, the yeast *Saccharomyces boulardii*, and even donor feces or “stool transplantations” to seed the regrowth of normal gut flora, have all been tried with success but as yet are not commonly done. Of course, prevention remains the most effective means of addressing the *C. difficile* dilemma, and precautions such as contact isolations for known carriers, conscientious handwashing, gloves, and bleach disinfection of hospital surfaces, endoscopes, and other equipment should never be overlooked (16,17).

### Acalculous Cholecystitis

Acalculous cholecystitis, with its difficulty in diagnosis and attendant high mortality, should be a consideration in jaundiced postoperative patients. Although this disease occurs in only about 0.19% of SICU patients, it nevertheless accounts for around 14% of all acute cholecystitis patients, and the mortality ranges from 15% to 41% (18,19). With this in mind, physicians caring for high-risk populations should carefully evaluate the signs and symptoms of this disease, and even a low level of clinical suspicion should prompt more thorough investigation.

### Risk Factors and Pathophysiology

Although the pathogenesis of acalculous cholecystitis has not been entirely elucidated, it is apparent that the critically ill patient is particularly prone. Risk factors include recent trauma, burn injury, or non-biliary tract operations, atherosclerosis, diabetes, hypertension, chronic renal failure, hemodynamic instability such as congestive heart failure or shock, and use of total parenteral nutrition (TPN) (18–21). One patient has been reported in the literature with acalculous cholecystitis secondary to a diaphragmatic hernia mechanically obstructing the cystic duct (19). Only about 13% have a history indicative of gallbladder disease (21). Given these associations, it is likely that there are multiple triggering factors contributing to a common disease state. An experimental form of the disease is produced by a combination of decreased blood flow to the gallbladder, cystic duct obstruction, and bile concentration (21). It can be conjectured that a partially ischemic state, together with the effects of stasis, creates a favorable environment for the growth of enteric bacteria, ultimately leading to inflammation, often with accompanying gangrene, empyema, perforation, and abscess at rates much higher than those seen with calculous cholecystitis (18,20,21). *E. coli* is the organism most commonly isolated (19).

### Presentation and Diagnosis

In addition to having one or more of the above risk factors, acalculous cholecystitis patients frequently present with the classical signs and symptoms of the calculous form, such as right

upper quadrant pain, Murphy's sign, nausea and vomiting, abdominal distention, decreased bowel sounds, fever, jaundice, and abdominal mass (19,21); although patients with mental status changes often lack pain and other symptoms, absence of any one clue should not exclude such a serious possibility (18,22).

Laboratory values suggesting the diagnosis include leukocytosis, hyperamylasemia, and elevated aminotransferases (22). Nevertheless, these findings are nonspecific, and given the likelihood of atypical presentation, the equivocal patient generally warrants radiologic and/or nucleotide (isotope) tests including ultrasound, CT scan, and cholescintigraphy such as hepatobiliary iminodiacetic acid (HIDA) scan. Of these, cholescintigraphy demonstrating an abnormal gallbladder ejection fraction of <40% in 45 minutes has been found most accurate, with a sensitivity of 90% to 100%, and a specificity of 88% (18,23); however, patients receiving TPN for a prolonged period may exhibit delayed gallbladder emptying, producing a false-positive result. CT detects roughly two-thirds of cases (18). Ultrasound, by contrast, when searching for the typical signs of thickened gallbladder wall, sludge, pericholecystic fluid, emphysematous change, and hydrops has recently been shown just 30% sensitive in critically ill trauma patients (23). Finally, diagnostic laparoscopy, although invasive, is nevertheless acceptably safe and allows direct visualization of the organ. In many cases, a combination of studies will be necessary to secure a diagnosis (24).

#### *Treatment*

Cholecystectomy, together with antibiotics, is the definitive treatment for acalculous cholecystitis. Laparoscopic surgery may be possible, and this being minimally invasive, might be considered an attractive option in the critically ill patient. Surgeons, however, must be prepared to encounter many possible complications, including the increased likelihood of gangrene and empyema, both of which are difficult to manage laparoscopically, as well as the tendency to encounter adhesions in any postoperative patient. For poor surgical candidates, another treatment option is percutaneous or laparoscopic cholecystotomy. This procedure is safe and effective in relieving sepsis, but is contraindicated in the cases of gangrene and perforation, and of course, subject to all the limitations of laparoscopy (25). Appropriate antibiotic treatment would center on coverage of gut flora, such as  $\beta$ -lactamase inhibitor penicillin along with an anti-anaerobic agent.

### **Colorectal Anastomotic Leakage**

#### *Risk Factors, Prevalence, and Long-Term Sequelae*

Approximately 3% to 6% of large-bowel surgical anastomoses constructed by experienced surgeons may leak. Anastomotic breakdown is the most common cause of stricture formation and also predisposes to increased local recurrence of cancer, a lower cancer-specific survival, and poor colorectal function. Risk factors for anastomotic leakage include male gender, obesity, malnutrition, cardiovascular disease and other underlying chronic disease states, steroid use, alcohol abuse, smoking, inflammatory bowel disease, and preoperative pelvic irradiation. Specific operations that predispose to the development of a leak include emergency indications for surgery, low anterior resection, colorectal anastomoses, particularly difficult or long surgeries lasting over two hours, intraoperative septic conditions, and perioperative blood transfusions (26).

#### *Diagnosis*

The diagnosis of an anastomotic leak in the postoperative patient is relatively straightforward. A typical triad indicative of infection includes fever, leukocytosis, and pelvic pain. Given these signs and symptoms, together with the appropriate surgical history, anastomotic leakage should be high on the differential diagnosis. Other clues that might prompt clinical suspicion include absence of bowel sounds on postoperative day 4 or diarrhea before day 7, greater than 400 mL of fluid from an abdominal drain by day 3, and renal failure by day 3. Further evidence can be gleaned from CT scan with rectal contrast that will reveal leakage of contrast with a sensitivity of 98%, as well as any abscesses that may be present as a result. CT is reported to be a superior modality to plain film with contrast enema, which in one review was positive in only 54% of patients who were later determined to have anastomotic breakdown (26).

### Treatment

Following intravenous fluid resuscitation and antibiotic therapy to cover gut flora, laparotomy to lavage the abdominal cavity and either place a protecting stoma or an end colostomy is generally indicated for the more severe anastomotic leak. In less severe cases, where rectal contrast is seen to be contained by CT imaging, further surgery is not always necessary. In either event, any abscess formed must be drained, preferably percutaneously with CT guidance when possible (26).

### Perforated Gastroduodenal Ulcer

Although markedly decreased in incidence by improved critical care management, gastro-duodenal ulceration leading to perforation and peritonitis may complicate the course of ICU stays.

### Risk Factors

Perforated ulcer represents yet another potential source of abdominal infection in the postoperative patient. Nonsurgical patients in the ICU are also predisposed to the development of ulcers. Curling's ulcers, or stress ulcers, affect in particular burn patients with septic complications; Cushing's ulcers develop in patients with central nervous system pathology involving midbrain damage, such as occurs after head trauma. In addition, many patients will be treated with nonsteroidal anti-inflammatory drugs and exogenous steroids during their ICU stay, which may contribute to mucosal barrier breakdown and delay recognition of ensuing infection. Risk factors predicting ulcer perforation include smoking, exposure to nonsteroidal anti-inflammatory drugs, cocaine abuse, and *Helicobacter pylori* infection (27,28). Effective, as they are, acid-suppressing drugs do not eliminate the risk entirely (29), and thus the possibility of ulcer perforation should be considered as an explanation of intra-abdominal infection in the ICU patient.

### Presentation and Diagnosis

Perforation most typically presents as an acute abdomen with sudden onset of pain, occasionally accompanied by nausea and vomiting, diffuse abdominal tenderness, rigidity of the abdominal wall, and ileus. As with other illnesses, perforation in the ICU patient may manifest in less obvious ways. Plain abdominal and upright chest films exhibiting signs of free air may detect 85% of free perforations (30) and is often the radiologic modality of first choice. CT scan, although frequently rendered unnecessary in the face of a positive plain film, may nevertheless disclose a remaining few diagnoses: Chen et al. found pneumoperitoneum on CT to be 100% sensitive (31). Moreover, other signs such as fluid collections and soft tissue inflammation also demonstrated by CT may be of further help.

### Treatment

Although there has been debate in recent years with regard to a 12-hour period of observation and supportive treatment before proceeding to surgical intervention for perforation, the poor prognosis associated with delay in definitive treatment and the relatively straightforward surgical procedure has persuaded many surgeons against this approach (28). Currently, direct suture repair, often with omental patch reinforcement, is the usual treatment of choice. Subsequent eradication of *H. pylori*—for example, using ampicillin, metronidazole, and a proton pump inhibitor, otherwise known as “triple therapy”—has been shown to decrease the recurrence of ulcers at one year from 38% to 5% (27).

### Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of intraperitoneal ascitic fluid and resulting peritoneal inflammation that occurs in the absence of other inciting factors, e.g., a perforated viscus. With a 10% to 30% incidence of SBP among random hospital admissions of cirrhotic patients with ascites, and a mortality of 20% to 40% equivalent to that of an esophageal variceal bleed, SBP is a formidable threat to the cirrhotic ICU patient (32,33).

### Risk Factors and Pathogenesis

SBP occurs when enteric bacteria, most commonly *E. coli*, *Klebsiella pneumoniae*, and pneumococcus, translocate across the gut mucosa to mesenteric lymph nodes. From there,

impaired opsonization and phagocytosis in these patients allows bacteria to colonize the ascitic fluid and generate an inflammatory reaction. Hematogenous spread is the possible explanation for gram-positive monoisolates. Complications develop secondary to this inflammation, as intravascular blood volume drops and hepatorenal failure predictably ensues. Renal failure is, in fact, the most sensitive predictor of in-hospital mortality (33).

Although cirrhotic individuals comprise the vast majority of SBP patients, ascites from other etiologies may also become infected, including ascites secondary to fulminant hepatic failure, cardiac etiologies, nephrotic syndrome, and even Budd-Chiari syndrome (33–36). Among patients with ascites, major additional independent risk factors include ongoing gastrointestinal hemorrhage, a previous episode of SBP, high serum bilirubin, and probably ascites protein  $<10$  g/L (32).

#### *Presentation, Diagnosis, and Differential Diagnosis*

SBP generally presents with symptoms typical of peritonitis—e.g., fever, abdominal pain, ileus, diarrhea, vomiting, leukocytosis, and rarely, shock (32). Atypical presentations may consist of acute prerenal renal failure or sudden-onset new hepatic encephalopathy with rapidly declining hepatic function. Given this wide range of potential signs and symptoms, SBP is no longer considered to be a purely clinical diagnosis, but is based principally on laboratory findings. The primary sensitive indicator of SBP is a polymorphonuclear (PMN) count of  $>250/\text{mm}^3$  (in traumatic bloody taps, the total PMN count is corrected by subtracting one PMN per 250 red blood cells) (32). The high incidence of SBP warrants diagnostic paracentesis in cirrhotic patients with ascites and fever or abdominal findings immediately upon hospital admission, and additional paracenteses in any of these patients subsequently developing the signs and symptoms of peritonitis or gastrointestinal bleeding (32).

Although a PMN count  $>250/\text{mm}^3$  may be further supported by positive single organism ascites fluid cultures, this test is only about 60% sensitive even under optimal conditions—bedside aerobic and anaerobic cultures of 10 mL each into blood culture bottles—and requires unacceptable delay as a practical indication of treatment (32). Although recent studies have shown promising results of 100% sensitivity in the diagnosis of SBP using certain urine reagent strips, these findings are not yet supported by sufficient experience to advocate their routine clinical use (37).

Secondary peritonitis is bacterial peritonitis secondary to a viscus perforation, surgery, abdominal wall infection, or any other acute inflammation of intra-abdominal organs. In the postsurgical ICU patient, differentiating SBP from secondary peritonitis is particularly challenging, yet nonetheless pivotal in determining appropriate management. Secondary peritonitis often occurs in the wake of obvious causes, but in settings where underlying issues are subtle, a diagnosis of SBP may be mistakenly seized and acted upon. Thus, a diagnosis of secondary peritonitis should generally be considered when patients fail antibiotic therapy for SBP. Characteristics of ascites fluid strongly favoring secondary peritonitis over SBP include isolation of multiple organisms, isolation of anaerobic or fungal organisms, or an ascites glucose level  $<50$  mg/dL with a protein concentration of  $>10$  g/L and lactic dehydrogenase concentration greater than that of normal serum. These indicators are all very sensitive but nonspecific for a diagnosis of secondary peritonitis, and their presence must be weighed against the remaining clinical picture before any firm diagnoses are reached (32).

#### *Treatment and Prognosis*

Initial empiric treatment for SBP must cover gram-negative aerobic bacteria from the family of Enterobacteriaceae as well as nonenterococcal streptococcal species, and must adequately penetrate into the peritoneal fluid. Low dose, short course cefotaxime—2 g twice a day for five days—is generally considered the first-line therapy, but other cephalosporins such as cefonicid, ceftriaxone, ceftizoxime, and ceftazidime are equally effective, and even oral, lower cost antibiotics such as amoxicillin with clavulanic acid will achieve similar results. For patients with penicillin allergy, oral fluoroquinolones such as ofloxacin are yet another suitable option, except in those with a history of failed quinolone prophylaxis implying probable resistance.

Follow-up paracentesis is recommended after 48 hours of antibiotic therapy to assess response: a fall >25% in the number of ascites PMN cells is considered a success (32). However, antimicrobials are not the only means of management: because renal impairment secondary to decreased intravascular volume is a major cause of mortality in SBP, further management may be aimed at preventing this fluid shift. The addition of albumin to an antibiotic regimen has been shown to decrease in-hospital mortality almost two-thirds from 28% to 10%. It is considered especially beneficial for patients with already impaired renal function and a creatinine >91 mmol/L, or advanced liver disease as evidenced by serum bilirubin >68 mmol/L (33). Nevertheless, the future outlook for patients with SBP is bleak: of those that survive the initial episode 30% to 50% will survive one year further, and only 25% to 30% will live a second year. Given these odds, patients with a history of SBP should be considered for liver transplantation, as well as long-term antibiotic prophylaxis in the interim (33).

### *Prophylaxis*

On weighing the cost of antimicrobials and the threat of inducing antibiotic resistance against the gravity of SBP, prophylaxis is indicated only for patients with the highest risk, namely, those with a previous episode of SBP, ongoing gastrointestinal bleeding, or an ascitic fluid protein <10 g/L. Fluoroquinolones, such as norfloxacin and ciprofloxacin, are the antimicrobials recommended for prophylactic purposes (33). In cirrhotic patients with ascites lacking these risk factors, the one- and three-year incidences of SBP are 0% and 3% respectively, and do not justify regular long-term prophylaxis (32).

## **INFECTIOUS COMPLICATIONS OF PANCREATITIS**

Pancreatitis is a serious but generally self-limited disorder that spontaneously resolves in 48 to 72 hours for the great majority of patients; however, 20% will develop severe acute pancreatitis as defined by the presence of three or more Ranson criteria (38). Among this subset, infected pancreatic necrosis is the leading cause of death (39).

### **Presentation and Diagnosis**

In addition to the typical signs and symptoms of pancreatitis, such as moderate epigastric pain radiating to the back, vomiting, tachycardia, fever, leukocytosis, and elevated amylase and lipase, patients with severe acute pancreatitis present with relatively greater abdominal tenderness, distension, and even symptoms of accompanying multiorgan failure (38). In these patients, the intensivist must maintain a high level of clinical suspicion for necrosis and possibly infection as well. CT scan with intravenous contrast is 80% to 90% sensitive for the detection of necrotic areas as a focal lack of enhancement (40). Infection is estimated to develop in 30% to 70% of patients with necrotic pancreatitis (40). However, necrosis both with and without infection often manifest with similar clinical presentations because necrosis alone causes a systemic inflammatory response, and additional diagnostic data is generally needed to differentiate these (41). Although CT only rarely shows gas bubbles as evidence of necrotic infection, CT-guided percutaneous aspiration of necrotic areas is 90% sensitive in yielding a diagnosis of this complication, and by sampling multiple necrotic areas in a diffusely necrotic pancreas, detection may be higher still (40).

Enterococcus species are the organisms most frequently isolated, although many different pathogens including *Candida* spp. and *Pseudomonas aeruginosa* are frequently seen (38,42).

### **Treatment and Prophylaxis**

The distinction between sterile and infected necrotic pancreatitis is crucial, as the former may be handled medically when necrosis affects less than 30% of the organ, whereas the latter often demands surgical debridement (38). Patients with infected necrotic pancreatitis will return to the operating room for an average of two to three operations as determined necessary by recurrence of clinical signs and symptoms combined with evidence from follow-up postoperative CT scans (41). Recently, several studies have explored the potential of laparoscopy for infectious pancreatic necrosis, but this approach is rarely feasible in instances of extensive necrosis, and data is not yet sufficient to compare the safety and efficacy of



laparoscopic surgery versus laparotomy for this indication (43). Percutaneous drainage has a low success rate of just 32% and is generally insufficient management except in the case of a well-defined abscess, or one remote from the pancreas (41). Runzi et al. recently published a small study in which antimicrobial therapy alone resulted in similar outcomes to antimicrobials combined with surgery (42); however, nonsurgical management is not currently common practice for infectious necrotic pancreatitis.

Abdominal compartment syndrome has been noted in severe acute pancreatitis and decompression has been suggested for patients whose transvesical intra-abdominal pressure reaches 10 to 12 mm Hg (43).

An appropriate antibiotic regimen for infected pancreatic necrosis is the second arm of a successful treatment plan: given the wide range of possible offending organisms, a Gram stain is recommended to tailor specific initial therapies prior to culture results. For gram-negative organisms, a single-agent carbapenem is effective; for gram-positives  $\beta$ -lactamase-resistant drugs, vancomycin, and even linezolid must be considered. When yeast is identified, high-dose fluconazole or caspofungin should be sufficient. In any case, if infection develops despite antibiotic prophylaxis, a different class of drugs must be administered for treatment than was given for prophylaxis (44).

A meta-analysis by Bassi et al. found that antimicrobial prophylaxis for patients with necrotic pancreatitis successfully decreases the incidence of infection by half and triples overall survival (45). Although current literature does not specifically favor any specific antibiotic as prophylaxis, it is nonetheless clear that microbial coverage must be broadly targeted. One- to two-week courses of cefuroxime, imipenem with cilastin, and ofloxacin with metronidazole have each been tried with success (42).

### **MIMICS OF ABDOMINAL INFECTION**

Multiple conditions may mimic a postsurgical abdominal infection and must be considered when searching for diagnosis. An exhaustive list of these is beyond the scope of this chapter; however, the reader should be aware of the general possibilities. Fever, for instance, in the postoperative patient, is not always secondary to infection. Particularly relevant to the postsurgical patient are events such as atelectasis, myocardial infarction, stroke, hematoma formation, and even pulmonary embolism that may occasionally present with a fever component. Other causes that warrant deliberation include drug or transfusion reaction, malignancy, collagen vascular disease, endocrine causes such as hyperthyroidism, and less common etiologies such as disordered heat homeostasis secondary to an ischemic hypothalamic injury or even familial malignant hyperthermia. Pain is yet another symptom that may be misleading: Abadir et al. published a study in which patients with segmental infarction of the omentum or epiploic appendages presented with localized peritonitis, mimicking appendicitis, diverticulitis, and cholecystitis (46). Furthermore, it is important to interpret radiological findings with an open mind. A fluid collection on CT does not necessarily represent an abscess. Again, high on the differential that must be considered is hematoma, and one may explore other diagnoses given the individual patient history. For example, Yu et al. found that the fundus of the excluded stomach following gastric bypass surgery may fill with air, fluid, and contrast material, thus closely resembling a loculated fluid collection (47). Finally, entertain where appropriate the idea of extra-abdominal infections. A myocardial infarction involving the inferior wall of the heart and lower lobe pneumonias, for instance, may present with abdominal pain and fever despite extra-abdominal origins.

### **BLOODSTREAM INFECTION**

Bloodstream infection, defined as a positive blood culture with organisms of intra-abdominal origin, is associated with mortality just over 60% (48). Gram-negative organisms, and *E. coli* in particular, are most common. Approximately 40% of all organisms isolated by DeWaele and colleagues at Ghent University hospital were multidrug resistant. Methicillin-resistant *Staphylococcus aureus* and extended-spectrum  $\beta$ -lactamase-producing (ESBL) organisms are a growing concern. Each ICU will likely have a unique pattern of pathogens with differing antimicrobial susceptibilities; therefore, the clinician should be up-to-date on current antibiograms for resistant flora in the critical care unit.

## DE NOVO COINCIDENTAL INTRA-ABDOMINAL INFECTION

When presenting an overview on the topic of postoperative abdominal infection, it is worth mentioning for the sake of completeness the possibility of coincidental infection. For example, a patient's status post-aneurysm repair has the same likelihood of developing appendicitis as any member of the general population in the same age group. Therefore, the conscientious physician considers all possibilities appropriate for the patient's complete history—not surgical history only—when constructing a thorough differential.

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# 15 | *Clostridium difficile* Infection in Critical Care

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## INTRODUCTION

*Clostridium difficile* was first described in 1935 as a component of the normal intestinal flora in healthy neonates (1). Its role as a pathogen was not clear until 1978 when it was identified as the cause of antibiotic-associated pseudomembranous colitis (PMC) (2). PMC had been recognized as early as 1893 but was a rare entity in the preantibiotic era, primarily associated with colonic, pelvic, or gastric surgery (3). In the 1950s, after antibiotics became available, the incidence of PMC increased and it was linked to antibiotic use. *Staphylococcus aureus* was the suspected pathogen since it was frequently recovered from patients stool culture samples. In 1974, a study showed high rates of PMC among patients treated with clindamycin, and the condition was called "clindamycin colitis" (4). In 1978, the association between cytotoxins released by *C. difficile* and antibiotic-induced PMC was discovered (2,5). Since then, many cases of antibiotic-associated diarrhea (AAD) and the vast majority of PMC cases have been attributed to *C. difficile*. With increased use of cephalosporins in the 1980 to 2000, it became the antibiotic class most commonly associated with *C. difficile* infection (CDI) (6).

Continued research over the last three decades has identified associated risk factors, clinical features, diagnosis, and management of CDI. Until the early 2000, CDI was viewed as an iatrogenic complication, often nosocomial, with low attributable mortality; however, over recent years, there have been marked increases in incidence and severity of illness. There are several plausible explanations: the emergence of a new epidemic, hypervirulent strain (B1/NAP1) that is also resistant to fluoroquinolones, an increasing elderly population, and the expanding use of broad-spectrum antimicrobials including fluoroquinolones. The epidemiology of the disease has also changed with reports of cases of severe community-acquired CDI (CA-CDI) in populations not previously considered to be at risk for the infection (7).

## EPIDEMIOLOGY

### Overview

An analysis of the U.S. hospital discharge data from 2006 showed that CDI rates increased abruptly in 2001, with a doubling of national rates from 2000 to 2003 (8,9).

A review of CDI from Quebec, Canada, of 1771 patients during 1991 to 2003 showed that the incidence of CDI per 100,000 people increased 4-fold for the entire region and 10-fold for persons >65 years of age (10). The incidence among hospitalized patients increased from 3 to 12/1000 persons in 1991 to 2001 to 25 to 43/1000 persons in 2003 to 2004. In addition, there were increased rates of more serious disease that was refractory to therapy.

In a study from 2005 by Pepin et al., patients with CDI were compared with matched controls and the one year cumulative attributable mortality due to CDI was found to be 16.7% (11).

In 2005, data from the Centers for Disease Control (CDC) suggested increasing frequency and severity of CDI also in the United States, including eight hospital outbreaks in six states. This pattern of increased incidence, severity, and more refractory CDI with high rates of relapse was also observed in Europe. The epidemic was confirmed to be caused by a new strain of *C. difficile* named restriction endonuclease analysis group B1/North American pulse

field gel electrophoresis type 1 (B1/NAP1) based on the different techniques of its identification. The new strain B1/NAP1 differs from previous strains of *C. difficile* in several aspects including fluoroquinolone resistance and presence of the binary toxin. In March 2007, B1/NAP1 had been found in 24 U.S. states as well as in the United Kingdom and parts of continental Europe (12).

### **Nosocomial Infection**

CDI is now the leading cause of identified nosocomial infectious diarrhea in the developed world (13,14). U.S. hospital discharges for which CDI was listed as a diagnosis doubled from 82,000 or 31/100,000 population in 1996 to 178,000 or 61/100,000 in 2003 with the steepest increase occurring from 2000 to 2003. The overall rate of acquiring CDI was especially high in persons >65 years of age (228/100,000) compared with the age group with the next highest rate, 45- to 64-year old (40/100,000) (9).

The majority of CDI are acquired nosocomially and most patients remain asymptomatic following acquisition (15). The risk of acquiring *C. difficile* while hospitalized is proportional to the length of hospital stay, with 13% colonization after two weeks and 50% at greater than four weeks of hospitalization (3,16). The carrier rate among healthy adults is approximately 3%. Symptomatic and asymptomatic infected patients are the major reservoirs and sources for environmental contamination. *C. difficile* can persist as spores for many months on environmental surfaces within institutions including commodes, bathing tubs, electronic thermometers as well as hands, clothes, and stethoscopes of personnel (15). Strict adherence to infection control measures is critical in the control of CDI.

A study from 2004 showed that incidence is higher during winter months, which may reflect increased patient census, severity of illness, and antibiotic use due to high rates of respiratory infections (16).

Overall, *C. difficile* incurs more than an estimated \$1 billion in health care costs in the United States annually (17).

### **Community-Acquired Infection**

In 2005, the CDC reported the occurrence of severe CDI, resulting in colectomy and death, affecting several peripartum women and healthy persons living in the community (7). These patient groups had generally been considered at low risk of acquiring CDI. Previous reports of CA-CDI from the United States indicated that it was a very uncommon entity. However, a retrospective Swedish study from 2004 (18) found that as many as 22% of 267 patients had acquired their first episode of CDI in the community. Interestingly, most patients with CA-CDI do not have a history of preceding antibiotic use (8).

### **TRANSMISSION**

*C. difficile* is ubiquitous and has been cultured from soil; swimming pools; and salt, fresh, and tap water (19). It persists as a highly resistant spore that may survive for months in the environment. The gastrointestinal tract of young mammals, including humans, appears to be a reservoir. *C. difficile* is transmitted via the fecal-oral route, either directly [hand carriage by health care workers (HCWs), patient-to-patient contact] or indirectly (from a contaminated environmental source) (16).

In the hospital setting, the bacteria has been cultured from telephones, call buttons, and shoes of HCWs, fingernails, and numerous other objects, and it has been found in infected patients' rooms up to 40 days after discharge (3). Most cases of disease appear to be caused by acquisition of the organism from an exogenous source, rather than from endogenous colonization. In fact, colonization with either toxigenic or nontoxigenic strains appears to protect from clinical disease (20). Fecal carriage among HCWs is rare.

### **RISK FACTORS**

The major risk factors for *C. difficile* are antibiotic exposure, hospitalization, and advanced age (>65 years of age) (Table 1).

**Table 1** Major Risk Factors for Initial Episode of CDI<sup>a</sup>**1. Antibiotic exposure**

- Antibiotics associated with
  - Higher risk of CDI
    - Cephalosporins
    - Clindamycin
    - Fluoroquinolones
    - Penicillins
  - Lower risk of CDI
    - Aminoglycosiodes
    - Aztreonam
    - Piperacillin-tazobactam
    - Tetracycline
    - Trimethoprim-sulfamethoxazole
- Use of combinations of several antibiotics or broad-spectrum antibiotics
- Prolonged duration of antibiotic use

**2. Hospitalization**

- Longer duration of hospitalization
- ICU stay

**3. Advanced age**

- Age >65 years

**4. Impaired immunity**

- Decreased antibody response to clostridial toxins

<sup>a</sup>Community-acquired CDI cases may have none of these risk factors.

Abbreviation: CDI, *Clostridium difficile* infection.

**Antibiotic Exposure**

In healthy adults, the colon contains as many as 10<sup>12</sup> bacteria/g of feces, the majority of which are anaerobic organisms (21). This flora provides an important host defense by inhibiting colonization and overgrowth with *C. difficile* or other potential pathogens. Antibiotics alter this indigenous microflora, thereby allowing *C. difficile* to grow to high concentrations. An animal model (22) showed that agents that disrupt the intestinal flora and lack activity against *C. difficile* (such as ceftriaxone) promoted development of CDI during treatment and during the time that the microflora replenishes after discontinuation of the antibiotics. On the other hand antimicrobial agents without anaerobic activity (e.g., aztreonam) cause minimal disruption of the anaerobic microflora and did not promote CDI in hamsters. Evidence from clinical studies has not consistently supported this theory. Many agents that have minor disruption of the anaerobic microflora have been associated with CDI (e.g., fluoroquinolones). In general, however, antibiotics with significant antianaerobic activity, and to which *C. difficile* has either innate or acquired resistance, pose the highest risk.

Recent observations suggest that antimicrobial resistance in *C. difficile* strains may be playing an important role in the epidemiology of the disease. *C. difficile* strains that are resistant to particular antibiotics may thrive in an environment where other colonic microflora is being suppressed. There have been large outbreaks with clindamycin-resistant CDI strains in the early 1990s that led to a decrease in the use of clindamycin in U.S. hospitals (23).

Nearly all antibiotics have been implicated as a risk factor for CDI. Historically, the antimicrobials most commonly associated with CDI are clindamycin, penicillins, and cephalosporins. Clindamycin was associated with the greatest risk of CDI, while cephalosporins and broad-spectrum penicillins were associated with the greatest numbers of CDI cases due to their extensive use (1). Fluoroquinolones (ciprofloxacin) were approved for use in the United States 1987 and has been frequently used to treat inpatient and outpatient infections. Recently, outbreaks of fluoroquinolone-resistant CDI have been reported including the B1/NAP1. All currently available fluoroquinolones have been implicated in the outbreaks, and switching from one fluoroquinolone to another to avoid CDI is not recommended (21).

The use of combination antibiotic therapy and broad-spectrum antibiotics has been associated with an increased risk of CDI (24). Longer duration of antimicrobial therapy increases the risk of CDI by extending the time that the patients are at risk of acquiring CDI

(21,24). However, even short courses of antimicrobials administered for prophylaxis can cause CDI (25). Parenteral and oral antibiotics appear to present similar levels of risk (26).

The only class of drugs, other than antimicrobials, recognized to induce CDI are antineoplastic agents, primarily methotrexate but also paclitaxel (1). As previously mentioned, CDI has also been reported without known prior antibiotic exposure (21).

### **Hospitalization**

In hospitals and healthcare facilities, the prevalence of *C. difficile* spores in the environment is high. In addition, patient clustering, a greater likelihood of antibiotic use, and a larger proportion of elderly patients may facilitate transfer of the organism (1). The rates of colonization in the feces among hospitalized patients are 10% to 25% and 4% to 20% among residents of long-term facilities as opposed to 2% to 3% among healthy adults in the general population. Stay in an intensive care unit and prolonged hospital stay have been reported as risk factors for CDI (25).

### **Advanced Age**

Patients over the age of 65 years have a 10-fold higher risk of CDI compared with younger patients (1). Other factors that increase the vulnerability of the elderly are underlying severe disease, nonsurgical gastrointestinal procedures, and poor immune response to *C. difficile* toxins (24). In addition, there is a higher likelihood of comorbidities in older patients that may lead to more frequent hospitalizations and exposure to antibiotics compared with the younger population.

### **Immunity**

Host immune response plays an essential role in determining whether patients become colonized with *C. difficile* or develop clinical disease. As mentioned previously, most patients remain asymptomatic following acquisition of *C. difficile* (15). Hospitalized patients who are colonized with *C. difficile* (both toxigenic and nontoxigenic strains) have been shown to have a decreased risk of developing CDI (20) even though the protective effect mediated by the colonization of nontoxigenic *C. difficile* is not completely understood (7).

Patients with a normal immune system who are exposed to toxin A, mount serum IgG antitoxin A antibody in response to *C. difficile* (21). In elderly patients and patients with severe underlying illnesses, the immunologic response may be blunted leading to lower serum antibody response to toxin A. Studies have shown that serum and fecal antitoxin A IgG levels are lower in patients who develop severe, prolonged CDI compared with those with mild disease (27). One study showed that patients who did not develop increased serum antitoxin A IgG titers in response to their first CDI episode were 48 times more likely to develop recurrent CDI than patients who mounted an adequate immune response (28). Elevated serum interleukin (IL)-8 levels also appear to correlate with impaired humoral immune response to *C. difficile* toxin A and increased susceptibility to CDI (29). Another study found fewer macrophages and IgA-producing cells in patients with CDI, particularly in those with PMC, compared with controls with non-*C. difficile* diarrhea (30).

### **Other Risk Factors**

A systematic review of the literature (24) showed that severity of underlying diseases, nonsurgical gastrointestinal procedures, presence of a nasogastric tube, and antiulcer medications were all risk factors associated with CDI. Proton-pump inhibitors (PPIs) neutralized the gastric acid, and even though the gastric acid is unable to affect the spores, it may kill vegetative cells and thereby decrease the inoculum (23). The role of PPIs as a risk factor remains controversial. Some studies have refuted the effect of PPIs in the development of CDI (31), while others (32) have suggested that PPIs are especially important as a risk factor in CA-CDI.

## **MICROBIOLOGY**

*C. difficile* is a large (2–17  $\mu\text{m}$ ), anaerobic, gram-positive, spore-forming, toxin-producing bacillus. It is closely related to *C. sordellii* but not to other toxigenic clostridia, such as *C. perfringens*, *C. botulinum*, and *C. tetani*. *C. difficile* is difficult to isolate in the laboratory (hence

its name) but can be grown on highly selective CCFA (cefoxitin, cycloserine, and fructose agar) media (19). The bacteria can exist in spore and vegetative forms. Outside the colon it survives in the spore form. The spores are resistant to heat, acid, and antibiotics. In the colon, the spores convert to their vegetative, toxin-producing form and become susceptible to killing by antimicrobial agents.

*C. difficile* produces two potent protein exotoxins, toxin A and B, the largest bacterial toxins known (33) and the B1/NAP1 strain also produces a binary toxin. The toxins mediate colitis and diarrhea. Both toxin A and B are optimally expressed at body temperature (19). Purified toxins are capable of causing the full spectrum of disease (17).

Toxin A is a 308-kDa enterotoxin that produces acute inflammation, leading to intestinal fluid secretion and mucosal injury (33). Toxin B is a 270-kDa cytotoxin that is 10 times more potent than toxin A in mediating mucosal damage in vitro. The toxins appear to act synergistically (17). Both toxins act intracellularly by inactivating proteins in the Rho subfamily, which regulate the F-actin cytoskeleton. This results in disaggregation of actin, opening the tight junctions between cells, and resulting in cell retraction and apoptosis manifested as characteristic cell rounding in tissue culture assays and shallow ulceration on the intestine mucosal surface (17,34).

Both toxins are also proinflammatory, inducing release of cytokines, phospholipase A2, platelet-activating factor (33), tumor necrosis factor- $\alpha$ , and substance P. This results in the activation of the enteric nervous system, leading to neutrophil chemotaxis and fluid secretion. *C. difficile* also produces tissue degradation enzymes such as collagenase and hyaluronidase, (3) promoting the development of PMC.

Toxigenic strains of *C. difficile* are not equally virulent; some strains that clearly possess toxin genes demonstrate low levels of gene transcription, resulting in minimal toxin production (35). While most strains produce both toxins, some produce toxin B only but can be equally virulent as strains with both toxins. Rare cases of CDI caused by strains producing neither toxin A nor B have been reported, (34) but nontoxigenic strains are generally considered nonpathogenic.

### Microbiology of the Epidemic Strain, B1/NAP1

The epidemic strain B1/NAP1 is emerging as an important contributor to the current epidemic of CID, but it has been isolated only rarely in the past (6). This strain has had several names, based on the biologic properties tested; NAP1 by pulse field gel electrophoresis, B1 on restriction endonuclease analysis, toxinotype III and ribotype 027 by polymerase chain reaction. Currently, the name B1/NAP1 is favored.

There are several unique features with B1/NAP1, the following five factors have been found in nearly all of the strains (6):

1. The epidemic strain B1/NAP1 produces substantially more toxins A and B in vitro (36).
2. All B1/NAP1 strains are toxinotype III. Toxinotyping is based on analysis of the region of the *C. difficile* genome known as the pathogenicity locus (PaLoc) that includes genes that encode for toxin A (*tcdA*) and toxin B (*tcdB*) and neighboring regulatory genes. More than 80% of non-B1/NAP1 strains are toxinotype 0 (36,37).
3. The epidemic strain B1/NAP1 has a deletion of *tcdC*, which is a gene in the PaLoc responsible for downregulation of toxin production (37).
4. The epidemic strain B1/NAP1 produces a binary toxin in addition to toxin A and B. The binary toxin is an iota-like toxin similar to that produced by *C. perfringens* type E (38). Its role in the pathogenesis of CDI is unclear.
5. The epidemic strain B1/NAP1 is resistant in vitro to fluoroquinolones, which is infrequently observed in strains collected before 2001 (11,37,39).

### CLINICAL PRESENTATION

Most patients exposed to *C. difficile*, even after antibiotic exposure, do not develop clinical disease. Colonization rates of 25% to 80% are seen in healthy infants and neonates but clinical illness is rare (3). For unclear reasons, colonization appears to wane with advancing age, and



**Table 2** Definition of *Clostridium difficile* infection

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1. Presence of symptoms  
>3 unformed stools over 24 hours for at least 2 days in the absence of ileus and
  2. Positive stool test for the presence of toxigenic *Clostridium difficile* or its toxins  
or
  3. Colonoscopy revealing pseudomembranes
- 

only 3% of healthy adults are colonized. Colonization increases to 20% to 30% of hospitalized adults (26), but clinical symptoms develop in only one-third of those who become colonized (34). The immune response of the host plays a role in determining who becomes an asymptomatic carrier and who develops CDI. Colonization has been shown to decrease the risk of developing CDI. However, colonized individuals shed pathogenic organisms and serve as a reservoir for environmental contamination.

CDI ranges over a wide spectrum of disease, and there are no pathognomonic findings on history or physical exam. The definition of CDI includes >3 unformed stools over 24 hours for at least 2 days and either a positive stool test for the presence of toxigenic *C. difficile* or *C. difficile* toxins or a colonoscopy revealing pseudomembranes (Table 2). To date, there is no prospective scoring system for CDI severity that has been validated. The important classification of CDI into mild, moderate, and severe disease is therefore based on criteria that may differ between studies.

The most common clinical presentation of CDI in the hospital is diarrhea associated with a history of antibiotic use. Symptoms can begin as early as the first day of antibiotic use or as late as eight weeks after completion of the precipitating antibiotic course (25). Most commonly, symptoms develop within four to nine days (3).

1. For mild disease, the diarrhea is usually the only symptom, involving <10 episodes a day without systemic symptoms. The diarrhea is frequently watery with a characteristic foul odor, but it can also be mucoid or mushy. It is rarely bloody.
2. Moderate disease, defined as <10 bowel movements per day, leukocytosis <15,000 cells/mL, and creatinine <1.5 times premonitory level, may result in profuse diarrhea, abdominal distention, or abdominal pain located in the lower quadrants, fever, tachycardia, and oliguria, which usually responds readily to volume resuscitation.
3. Severe disease defined as >10 bowel movements per day, leukocytosis >15,000 cells/mL, elevated creatinine (>1.5 times premonitory level), fever (which may be absent in an elderly patient), severe abdominal pain, distention, and partial ileus is present in approximately one-third of patients.
4. Fulminant disease is the most severe form of CDI and develops in 1% to 3% of cases. Defined as severe disease complicated by hypotension or shock, toxic megacolon, perforation, or severe colitis on CT scan, it is associated with high mortality (40). The first warning sign of fulminant colitis may be diminishing diarrhea, due to decreased colonic muscle tone. A study of 44 patients undergoing colectomy for fulminant colitis reported that 5 (11%) presented with frank peritonitis, hypotension, or both (40). Thirty-five percent of patients with fulminant colitis caused by *C. difficile* were diagnosed at autopsy (40), suggesting that a significant number of deaths due to "sepsis" in critically ill patients may be related to *C. difficile*.

Characteristic laboratory findings include leukocytosis that may be severe and hypoalbuminemia. WBC counts as high as 50,000 cells/mL can be seen and band forms are frequently present. One prospective study of 400 inpatients found CDI in 11% of those with WBC of 15 to 19,900 cells/mL, 15% of those with WBC 20 to 29,000 cells/mL, and 34% of those with WBC  $\geq$ 30,000 cells/mL (41). Hypoalbuminemia is the result of large protein losses attributable to leakage of albumin and may occur early in the course of the disease (25).

PMC is seen in moderate to severe cases of CDI. Evidence of colitis includes fever, abdominal cramps, leukocytosis, and presence of leukocytes in the feces. Endoscopic

examination reveals pseudomembranes in the colonic mucosa (see "Diagnosis"). PMC primarily affects the large bowel, although the small intestine may rarely be involved.

The epidemic strain of *C. difficile* B1/NAP1 has similar clinical features compared with other *C. difficile* strains but causes more severe illness. Prominent complications include toxic megacolon requiring colectomy, leukemoid reactions, septic shock, and death (10,11,37).

It is important to note that on rare occasion patients with severe CDI present without diarrhea. This could imply paralytic ileus, which prevents the passage of stool. Symptoms such as fever, leukocytosis, and abdominal pain in a patient with recent antibiotic exposure should raise the suspicion of CDI even in the absence of diarrhea (25).

Extracolonic manifestations of CDI are very rare. The most commonly reported is polyarthrititis involving large joints occurring one to four weeks after infection (34). Case series have described isolation of *C. difficile* from pleural fluid, peritoneal fluid, blood, bone, prosthetic joints, wounds (including necrotizing fasciitis), and splenic, vaginal, and perianal abscesses. Generally, these infections are polymicrobial, making it difficult to ascertain the pathogenic role of *C. difficile*.

Relapsing CDI occurs in approximately 20% to 30% of appropriately treated infections. The clinical presentation is usually very similar to the original presentation (42) and generally occurs one to eight weeks, but usually within two weeks, after completion of anticlostridial therapy.

## DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

AAD is defined as otherwise unexplained diarrhea associated with antibiotic use. The majority of the cases have no established microbial pathogen. A total of 15% to 25% of AAD result from CDI and the likelihood for CDI increases with the severity of the illness. In 2% to 3% of AAD cases pathogens such as *C. perfringens*, *Klebsiella oxytoca*, *S. aureus*, and *Candida albicans* (3,25) have been isolated, but their significance remains questionable. In the remainder of the cases, the etiology is unknown but may be due to osmotic diarrhea resulting from antibiotics disturbing the normal bowel flora and cause failure to catabolize carbohydrates (25). The breakdown of primary bile acids, which are potent colonic secretory agents, may also be affected (26). In addition, certain antibiotics have direct effects on the gastrointestinal system. For example, erythromycin increases the gastric emptying rate, clavulanate stimulates bowel motility, and neomycin causes malabsorption (3).

The differential diagnosis for PMC includes intestinal obstruction, colon cancer, leukemia, severe burns, shock, uremia, heavy metal poisoning, hemolytic-uremic syndrome, Crohn's disease, shigellosis, neonatal necrotizing enterocolitis, ischemic colitis, and Hirschsprung's disease. However, it is extremely uncommon to observe pseudomembranes in any of the conditions listed above, with the exception of rare cases associated with heavy metal poisoning and ischemic colitis. In the right clinical scenario, visualization of pseudomembranes during endoscopy is considered diagnostic of CDI (25).

Other possible alternative diagnoses to CDI are ulcerative colitis, typhlitis in neutropenic patients, or diarrhea induced by medications such as laxatives, antacids, electrolyte supplements (particularly magnesium), proflated nonsteroidal anti-inflammatory drugs (NSAIDs), contrast, products containing lactose or sorbitol, antiarrhythmic or cholinergic medications.

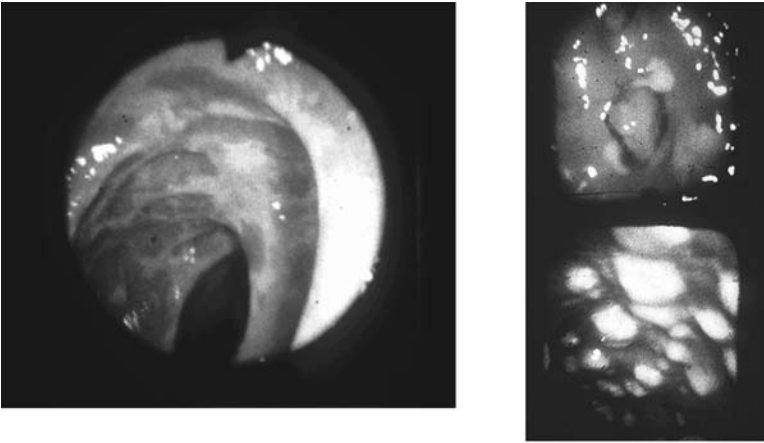
## DIAGNOSIS

### Imaging Studies

Imaging studies have largely been replaced by laboratory testing as a tool for diagnosing CDI (25). Radiologic studies are nonspecific but can support the diagnosis and are useful to monitor for complications such as toxic megacolon and perforation.

*Plain abdominal films* may reveal mucosal edema or paralytic ileus as well as detect free intra-abdominal air and toxic megacolon. The presence of the "fingerprint sign" (showing a patch of elevated and inflamed mucosa next to normal mucosa) is useful to diagnosis CDI.

*Computed tomography (CT)* can be valuable in the diagnosis of PMC or fulminant CDI. Characteristic features include colonic wall thickening, pericolonic stranding, the accordion sign, the double halo sign, and ascites (43). One study of 39 patients with CDI who underwent



**Figure 1** Typical endoscopic findings in pseudomembranous colitis; widely disseminated, punctate yellow plaques with normal intervening mucosa.

CT found that when combined with the clinical scenario all were diagnostic, showing ascites and colonic wall thickening or massive dilatation. Eleven patients had right-sided colitis, while 9 had left-sided colitis and 19 had pancolitis (40). Barium enemas are not recommended due to the risk of perforation (44).

Visualization of pseudomembranes during endoscopy in the right clinical scenario is diagnostic of CDI. Even though there are several other causes of PMC they are exceedingly rare (25). Endoscopy is preferred over sigmoidoscopy since approximately one-third of the patients have involvement of the right colon only. Pseudomembranes found in the colonic mucosa are raised yellow plaques 2 to 10 mm in diameter, frequently with normal intervening mucosa (Fig. 1) (3). Other gross findings include bowel wall edema, erythema, friability, and inflammation. Histologically, a pseudomembrane is composed of sloughed mucus with rare inflammatory cells, fibrin, and cellular debris. The appearance on a biopsy is that of acute nonspecific inflammatory changes with or without crypt abscesses and eruptive “volcano” lesions (45).

In 50% of the cases, however, pseudomembranes are not present, making endoscopy a relatively insensitive test (43). Further, endoscopy should be avoided in patients with severe disease with colonic dilatation due to the risk of perforation.

### **Laboratory Testing**

Analysis of stool samples is the standard diagnostic test for CDI. Laboratory testing for *C. difficile* is recommended for all adults and for children >1 year of age who have otherwise unexplained diarrhea associated with antibiotic use (25).

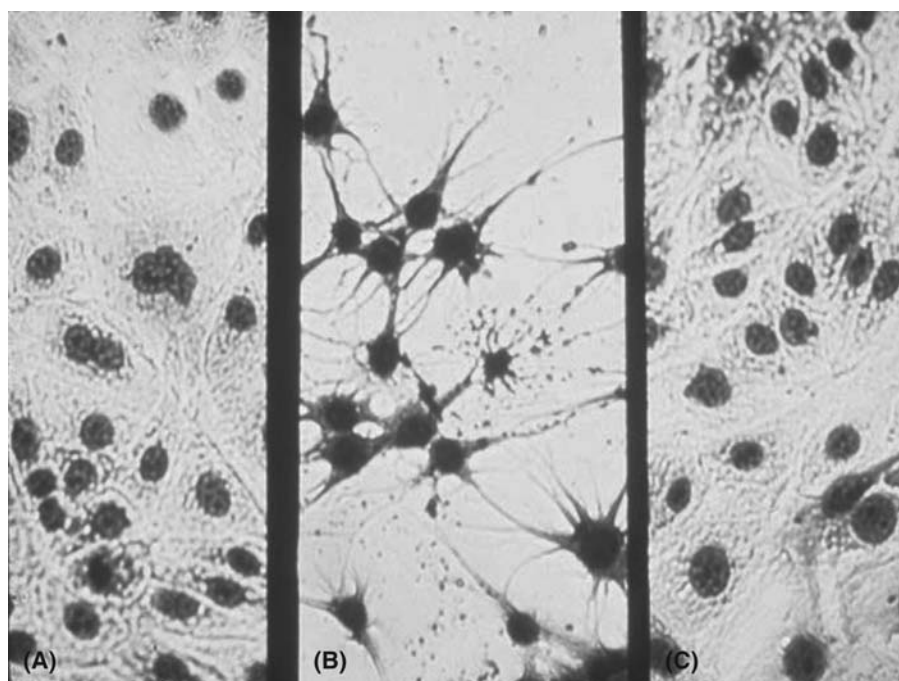
### **Assays Detecting the Organism**

1. *Stool culture* is rarely used for routine diagnosis of *C. difficile* in the United States due to its long turnaround time 24 to 48 hours, and it is labor intensive and not specific for in vivo toxin production (25). Stool cultures are highly sensitive but the specificity is low because non-disease-causing, non-toxicogenic strains of the bacterium would also grow naturally on media. The culture must be accompanied by tissue culture cytotoxin assay or enzyme immunoassay to identify toxigenic strains. As a result, diagnosis may be delayed by three to four days. However, since stool cultures allow for molecular typing it is an essential tool for monitoring molecular epidemiology and antibiotic susceptibility.
2. *The common-antigen test*, also known as the glutamate dehydrogenase (GDH) test, is an EIA for the GDH enzyme. *C. difficile* constitutively produces GDH in easily detectable levels and carries a sensitivity of 96% to 100% (46). However, a positive

culture result only indicates the presence of the organism, not the toxin production. Therefore, the test should be used as a relatively sensitive screening test to detect GDH-positive stool samples that require further testing with tissue culture cytotoxin assay or EIA. Occasionally, other organisms produce GDH, which lowers the specificity. The test is rapid, turnaround time 15 to 45 minutes, and relatively inexpensive.

### Assays Detecting Toxin

1. *Tissue culture cytotoxin assay* was the first test described. It has the highest sensitivity of all the tests and can detect as little as 10 pg of toxin B (26). The assay reveals cytopathic effects on cell culture monolayers characterized by rounding of fibroblasts (Fig. 2). Preincubation with neutralizing antibodies against the toxins demonstrates the specificity of the cytotoxicity. Sensitivity and specificity are high (94–100% and 99%, respectively) (34). It is considered by many experts to be the “gold standard” for demonstrating *C. difficile* toxin the stool. The major disadvantage of the cytotoxin assay is that it is technically demanding and expensive, and many laboratories lack the expertise and equipment to provide rapid turnaround (25).
2. *EIA* allows direct detection of *C. difficile* toxin (15). Commercially available tests can detect toxin A only or both toxin A and B. EIA detecting both toxins is preferred since *C. difficile* strains with toxin B only would otherwise be missed. Although rare *C. difficile* strains producing only toxin B have caused hospital-based cases. Advantages of the EIA include fast turn around time (2 hours), relatively easy to perform, and high specificity (up to 99%). The disadvantage is the low sensitivity (70–80%) linked to the fact that it requires a large amount of toxins (100–1000 pg) for detection. The relatively high false-negative rate can be decreased by 5% to 10% by repeating two to three specimens but this also increases the cost.



**Figure 2** Tissue culture cytotoxin assay for *Clostridium difficile*. (A) Normal primary human amnion cells. (B) Typical changes after application of *C. difficile* toxin. (C) Tissue culture after neutralization with *Clostridium sordellii* antitoxin.

3. *Polymerase chain reaction (PCR)* is very sensitive but requires significant technical expertise. However, a rapid detection method developed in Spain using nested PCR of the toxin B genes has been found to be 96% sensitive and 100% specific, and can be performed in several hours (3). PCR assays are not yet widely available for routine use, but three companies are preparing to release PCR test kits by 2009.

### **Two-Step Protocol**

To improve the laboratory diagnosis of CDI, the Infectious Diseases Society of America (IDSA) and the Society for Hospital Epidemiology of America (SHEA) are recommending a two-step test (45).

The first step uses a test with high sensitivity, such as the common-antigen assay (GDH) or stool culture, as a screening test to exclude *C. difficile* in the 75% to 90% of stool specimens that do not contain *C. difficile*. In the second step, positive specimens are analyzed for the presence of toxins A and B with either tissue culture cytotoxin assay or EIA as a confirmatory test. A study by Ticehurst (46) indicate that this two-step method has good sensitivity, specificity, and cost although there is a 24-to 48-hour delay in reporting results.

The diagnosis of CDI should be based on determination of the presence of toxin A and/or B in stool samples in concert with clinical suspicion for presence of the disease. Stool tests for *C. difficile* toxins should be avoided in cases without clinically compatible picture since toxin positivity without clinical symptoms usually represents mere colonization with a toxigenic strain of *C. difficile*, which does not warrant treatment. Once a stool sample has been demonstrated to contain toxin, repeat testing (e.g., performing a "test of cure" at the end of therapy) is unnecessary because the EIA can remain positive for weeks to months in clinically cured patients (45).

## **TREATMENT**

### **General Treatment Guidelines**

The most important step in the treatment for CDI is the withdrawal of the offending antibiotic as soon as possible. If continued antibiotics are necessary, it is recommended to choose agents with low probability of causing CDI, such as tetracycline, narrow-spectrum  $\beta$ -lactams, piperacillin-tazobactam, macrolides, sulfonamides, aminoglycosides, vancomycin, metronidazole, and trimethoprim-sulfamethoxazole whenever possible. Supportive measures such as intravenous fluid and electrolyte replenishment should be instituted if necessary. Use of antiperistaltic agents, such as narcotics and loperamide, should be avoided as they may promote the development of toxic megacolon (6).

### **Antibiotic Treatment—History**

In the 1950s, when AAD became a well-known complication to antibiotic use, *S. aureus* was the presumed pathogen and oral vancomycin became the standard treatment. *C. difficile* was discovered as the organism causing CDI in 1978 and shortly thereafter oral vancomycin was approved by the U.S. Food and Drug administration (FDA) for treatment of CDI. Vancomycin remains the only drug that has been FDA approved for treatment of CDI. In the 1980s, studies suggested that metronidazole was equally effective compared with vancomycin in the treatment of CDI (47). In addition, metronidazole was less expensive and perhaps less likely to lead to the development of vancomycin-resistant enterococci (VRE). The 1995 guidelines from the Centers for Disease Control and Prevention (CDC), IDSA, and SHEA recommend the use of metronidazole as first-line treatment of CDI. Since then, two prospective randomized trials (48,49) have shown that oral vancomycin is superior to metronidazole in severe CDI while there was a trend of vancomycin being more efficacious in mild and moderate disease. In the 2003 outbreak of the epidemic strain B1/NAP1 in Quebec, initial treatment with oral vancomycin was associated with a 79% lower risk of complicated CDI compared with metronidazole.

### **Vancomycin and Metronidazole-Pharmacology**

CDI, a toxin-mediated disease, is caused when *C. difficile* spores in the colon transform to the vegetative form and produce toxin A and B. To effectively treat the disease the antibiotic needs to reach the colonic lumen.

Oral vancomycin is not absorbed and the colonic levels are very high (500–1000 µg/mL), several hundred-fold higher than the highest measured minimum inhibitory concentration (MIC) for *C. difficile*. Vancomycin, administered via retention enemas, has been shown to be effective in small, uncontrolled case series of patients with severe or fulminant colitis not responding to standard therapy (50). It is important to note that parenteral vancomycin has no activity against CDI. The major drawback with oral vancomycin is the price. The cost per day with standard dosing (125 mg 4 times daily) is approximately \$70 as compared with \$2 with metronidazole. Vancomycin is the drug of choice in pregnant or lactating women. Studies have shown that a regimen of 125-mg oral vancomycin administered four times daily (current standard regimen) is as effective as 500 mg four times a day (older standard) (51). However, for severe/fulminant of CDI the dosing 500 mg four times daily is recommended.

Metronidazole, as opposed to oral vancomycin, is virtually 100% absorbed in the small bowel and reaches the colon through biliary excretion and increased exudation across the intestinal mucosa during diarrhea (52). In healthy volunteers without diarrhea, oral and intravenously administered metronidazole achieve low fecal concentrations but usually exceeds the *C. difficile* MIC (34). Side effects of metronidazole include dose-dependent peripheral neuropathy, nausea, and metallic taste. Metronidazole is typically dosed orally at 500 mg three times daily or 250 mg four times daily.

Resistance to metronidazole has been uncommon. Recently, some strains have shown increasing resistance (“metronidazole creep”) so it is possible to have metronidazole levels in the colon below the MIC for some periods of time. One report from Spain reported 6% rate of resistance to metronidazole (53). Vancomycin resistance has not been reported.

Both vancomycin and metronidazole may promote the development of VRE even though historically vancomycin has been the one most frequently implicated. The relapse rate is approximately the same for each drug (15–30%).

### Indications for Treatment

Treatment for CDI is dependent on the severity of illness and is divided into mild, moderate, severe, and relapsing disease, respectively. First, it must be emphasized that treatment is not indicated in patients who are asymptomatic even with a positive stool toxin assay.

#### *Mild to Moderate Disease*

For very mild disease, discontinuation of the inducing agent may be sufficient therapy and no further antibiotic therapy needed. A Cochrane Library review from 2007 reports uncertainty whether mild CDI needs to be treated (54). This review did not take into account the newly emerging epidemic strain, B1/NAP1, which can start with mild disease and escalate rapidly.

Patients with mild disease (defined according to IDSA Draft guidelines from 2007 as WBC <15,000 cells/mm<sup>3</sup> or rising creatinine <50% higher than prior to CDI), clinical manifestations of CDI (diarrhea, abdominal pain, or nausea and vomiting), and a positive diagnostic assay should receive antibiotics for CDI. Current guidelines recommend oral metronidazole (500 mg 3 times daily or 250 mg 4 times daily) for initial treatment (Table 3). Metronidazole is favored over oral vancomycin in mild to moderate cases due to its lower cost and good efficacy. Empiric therapy is appropriate if clinical suspicion is high and the initial diagnostic assay is pending or negative. One study showed increased mortality among patients who had an initial false-negative toxin (40).

#### *Severe Disease*

Patients with severe CDI (defined according to IDSA Draft guidelines from 2007 as WBC >15,000 cells/mm<sup>3</sup> or rising creatinine >50% higher than prior to CDI) should be treated with withdrawal of the antibiotic implicated to cause CDI, antibiotics, supportive care, and consideration for surgery (see below) if the patient’s clinical status fails to improve.

Two recent prospective randomized trials have shown a statistical significant superiority of oral vancomycin therapy in patients with severe CDI. The recommended dose for severe disease is 125-mg oral vancomycin four times daily. For patients with severe complicated CDI (WBC >15,000 cells/mm<sup>3</sup> or rising creatinine >50% higher than prior to CDI plus hypotension, ileus, toxic megacolon, perforation, need for colectomy, or ICU admission), the recommended

**Table 3** Treatment of CDI as per IDSA Draft Guidelines from 2007

	Clinical definition	Recommended treatment
<b>General measures</b>		
	<ul style="list-style-type: none"> <li>• Stop implicated antibiotic or switch to lower-risk drug</li> <li>• Fluid and electrolytes as needed</li> <li>• Avoid antimotility drugs</li> <li>• Consider surgery if severe colitis and rising lactate (before lactate = 5)</li> </ul>	
Initial episode	Mild to moderate disease (leukocytosis <15,000 and creatinine <1.5 times premorbid level)	Metronidazole 500 mg three times daily for 10–14 days
	Severe (leukocytosis >15,000 or creatinine >1.5 times premorbid level)	Oral vancomycin 125 mg four times a day for 10–14 days
	Fulminant (severe disease complicated by hypotension or shock, megacolon, perforation, severe colitis on CT scan)	<i>Absence of complete ileus</i> Oral vancomycin 500 mg four times a day administered orally or via nasogastric tube and Intravenous metronidazole 500–750 mg every 8 hours <i>Complete ileus</i> Intravenous metronidazole 500–750 mg every 8 hours and if feasible Rectal installation of vancomycin
First recurrence <sup>a</sup>		Same as for initial episode x 14 days
Second recurrence <sup>a</sup>		Oral vancomycin, tapered/pulsed 125 mg 4 times daily x 10–14 days 125 mg twice daily x 7 days 125 mg daily x 7 days 125 mg every 2–3 days for 2–8 weeks A 3-week course of probiotics may be used, first week overlapping with last week of vancomycin

<sup>a</sup>No rigorous trials available—class B recommendations.

Abbreviation: BM, bowel movement.

treatment is oral vancomycin 500 mg four times daily and/or metronidazole 500 to 750 mg intravenously every eight hours. If the patient has complete ileus, the treatment recommendation includes intravenous metronidazole and rectal installation of vancomycin (IDSA, 2007). Colectomy should be performed before serum lactate >5. Anecdotal reports have studied the use of intravenous IgG (IVIG) in severe CDI but the efficacy is unproven (55).

Response to treatment is generally rapid, with decreased fever within one day and improvement of diarrhea in four to five days. Patients who fail to respond may have alternate diagnoses, lack of compliance, or the inability of drug to reach the colon such as with ileus or megacolon (26). Yet, all studies have shown failures with both metronidazole and vancomycin (~15% failure rates in the randomized controlled trials).

Standard duration of treatment is 10 to 14 days, regardless of antibiotic used. Patients requiring prolonged courses of other antibiotics should continue CDI treatment throughout the antibiotic course and for an additional week postcompletion. It is not recommended to check stool *C. difficile* toxin assays after the first positive since a positive result can remain for up to eight weeks.

### Surgery

Overall, a minority of patients (0.39–3.6%) with *C. difficile* colitis require surgery (54). Surgery is indicated for patients with peritoneal signs, systemic toxicity, toxic megacolon, perforation, multiorgan failure, or progression of symptoms despite appropriate antimicrobial therapy and

recommended before serum lactate  $>5$  (54). Total colectomy with end ileostomy is the procedure of choice. Select patients with disease clearly limited to the ascending colon have been treated successfully with right hemicolectomy, but intraoperative colonoscopy should be performed to rule out left-sided disease (40).

A retrospective review with patients infected with the epidemic *C. difficile* strain B1/NAP1 showed that colectomy was most beneficial for immunocompetent patients aged  $>65$  years with a WBC  $>20,000$  cells/ $\mu\text{L}$  and/or a plasma lactate between 2.2 and 4.9 meq/L (56).

Among patients requiring surgery, mortality rates after colectomy have ranged from 38% to 80% in small series (40). In a study of patients with fulminant colitis requiring colectomy, the need for preoperative vasopressor support significantly predicted postoperative mortality (40).

### Other Medications

Alternate agents for the treatment of CDI include teicoplanin, fusidic acid, and bacitracin (34). Teicoplanin may be at least as effective as oral vancomycin or metronidazole but is expensive and not available in the United States. Both fusidic acid, also not available in the United States, and bacitracin have been shown to be less effective than vancomycin (54).

*Anion exchange resins*, such as colestiol and cholestyramine, assert their effect on *C. difficile* toxin by binding toxin in the colon. The anion exchange resins are not as effective as oral vancomycin and metronidazole and should not be used as the single agents. Currently, there is no indication for use of these resins. Resins must be taken at least two hours apart from oral vancomycin since it binds vancomycin as well as toxins.

*Tolevamer*, a new toxin-binding resin developed for use in CDI demonstrated noninferiority to vancomycin in a phase 2 study by Louie et al. (48). However, in the first of two subsequent phase 3 trials, tolevamer demonstrated significantly worse outcomes compared with standard therapy with oral vancomycin and metronidazole (57).

*Rifaximin* is a nonabsorbed, semisynthetic analogue of rifampin, which is FDA approved for treatment of travelers' diarrhea and is useful in managing hepatic encephalopathy. It has wide antibacterial activity and poor absorption, leading to high intraluminal concentrations. In vitro, rifaximin has demonstrated a high degree of activity against most *C. difficile* strains with MIC values similar to rifampin; however, high-level resistance has been demonstrated in 3% or more of *C. difficile* strains and recent reports suggest that resistance is even more widespread (21). Rifaximin should be avoided until it is approved for use by the FDA.

Other investigational agents include nitazoxanide, tinidazole, OPT-80/PAR-101, ramoplanin, human monoclonal antibodies, and toxoid A and B vaccines (58).

### TREATMENT OF RECURRENT CDI

Recurrent CDI occurs in approximately 20% of the cases. Although it usually develops within 15 days after discontinuing the antibiotic, it can develop after as much as two months. Approximately 50% of the recurrences represent reinfection (59).

Risk factors for recurrence include advanced age, marked elevation of WBC count during initial episode, chronic renal insufficiency, CA-CDI, and antimicrobial use between initial treatment and recurrence. The most important risk factor is previous recurrence (8). Patients with at least one recurrence have 50% to 65% risk of experiencing an additional episode. Failure of the immune system to mount antitoxin IgG titers in response to the first episode of CDI may play a role in recurrent CDI. The frequency of relapse is nearly equal for vancomycin and metronidazole (1).

The ultimate goal of treatment of recurrent CDI is to discontinue all antibiotics. It is important to note that not all patients who has recurrent diarrhea after discontinuing metronidazole or vancomycin have recurrent CDI. It is not recommended to repeat stool assays after therapy unless the patients has moderate to severe diarrhea. In cases with minimal symptoms therapy is not warranted (60).

Patients with first recurrence can be treated with the same drug as initial therapy (unless severe CDI in which case oral vancomycin is preferred). Metronidazole should not be used beyond the first recurrence and duration should not be longer than 14 days.

Current recommendations (IDSA, 2007) suggest oral vancomycin taper  $\pm$  pulse dosing beyond the first recurrence (Table 3). Tapered or pulsed dosing of vancomycin allows resistant



spores to develop into vegetative cells between doses, making them susceptible to killing by antibiotics. Patients requiring antibiotics for other indications in the setting of recurrent CDI should continue CDI treatment throughout the antibiotic course and for an additional week postcompletion. Recovery of normal fecal flora may take days to weeks after discontinuation of antibiotics (61).

Aside from cost, repeated courses of anticlostridial therapy have the disadvantage of perpetuating this disruption in intestinal flora. To break this cycle, alternate treatments have been attempted, including probiotics, administration of nontoxigenic *C. difficile* (62), and stool transplantation.

Probiotics, including *Lactobacillus* species and *Saccharomyces boulardii*, are nonpathogenic microorganisms that, when ingested, may benefit the health or physiology of the host. Probiotics have been beneficial in the setting of travelers' diarrhea, rotavirus infection, and in reducing the incidence of simple AAD but their efficacy in preventing CDI is inconsistent (63). They are not effective as solo therapy for active infection but the use of probiotics as an adjunctive therapy in recurrent CDI is widespread.

Stool transplantation, administration of feces or fecal flora via enema, or nasogastric tube has been found effective in small case series of patients with at least two relapses (61); the method remains unpopular for practical and aesthetic reasons.

Because the host immune response to *C. difficile* is thought to play a major role in recurrent CDI, passive immunotherapy with IVIG has been studied in small series of patients with recurrent or refractory CDI (27). Anecdotal reports show that IVIG produce a marked increase in serum antitoxin A/B levels, and resolution of diarrhea (62). Further studies are needed to confirm these results.

## OUTCOME

Pre-epidemic strain B1/NAP1 studies showed that with appropriate treatment, the overall mortality for CDI is <1% in most series but as high as 24% among critically ill patients. Among patients requiring surgery, mortality rates after colectomy have ranged from 38% to 80% in small series (40).

Pepin et al. studied the changes in mortality before and after the emergence of the new epidemic strain (B1/NAP1) and found that the proportion of cases that were complicated increased from 7.1% in 1991–1992 to 18.2% in 2003 and the proportion of patients who died within 30 days after diagnosis increased from 4.7% in 1991–1992 to 13.8% in 2003 (10).

## INFECTION PREVENTION AND CONTROL

Prevention and control of CDI requires restriction in the use of antibiotics and aggressive infection control measures including specific hand washing protocols, isolation of infected patients, and appropriate environmental cleaning strategies (45). (Table 4).

After patients have been diagnosed or strongly suspected to have CDI, patients should be placed on contact precautions in private rooms, if possible. During epidemics or if private rooms are not available it may be necessary to cohort patients to certain designated rooms. Each patient should have a dedicated commode, and privacy curtains should be used to decrease direct contact between beds. As the patient's symptoms resolve, they should be

**Table 4** Infection Control

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### Antimicrobial stewardship

- Restriction of antibiotics associated with increased risk of CDI
- Reducing unnecessary use of antibiotics
- Reducing duration of antibiotic courses
- Switch from oral to parenteral therapy when possible

+

### Infection control

- Proper environmental disinfection
  - Hand hygiene compliance
  - Use designated individual thermometers, blood pressure cuffs and stethoscopes for infected patients
  - Single-room isolation/cohorting
-

moved to another room to avoid reinfection. Mandatory gloving and gowns before entering the room should be initiated. Since *C. difficile* spores can survive for long periods of time on environmental surfaces, it is important to prevent spread to clothing and to use designated portable equipment for patients on precautions. Compliance with hand hygiene should be emphasized. Alcohol-based hand washing agents appear less able than soap and running water to remove spores from the hands. However, no increase in CDI rates has been shown in hospitals using alcohol-based hand washing agents. During the setting of an outbreak, visitors and HCWs should wash their hands with soap and water after caring for patients with CDI. HCWs or asymptomatic patients should not be screened for fecal carriage during CDI outbreaks (45).

Particular emphasis must be given environmental cleaning and disinfection due to the *C. difficile* spores ability to survive on fomites for prolonged periods of time and are only destroyed by high heat or alkaline pH (45). Only chlorine-based disinfectants and high concentrations of vaporized hydrogen peroxide have been shown to be sporicidal (45,64). Generic bleach (containing at least 1000 ppm available chlorine) should be used to address environmental contamination. Horizontal (high touch) surfaces and fomites that commonly harbor *C. difficile* spores (e.g., bed rails, telephones, call buttons) should be thoroughly cleaned and decontaminated. Routine environmental screening for *C. difficile* is not recommended.

Restrictions in the use of antimicrobials are also important in CDI prevention and control. Antimicrobial stewardship programs can help minimize antimicrobial duration and number of agents prescribed to reduce CDI risk. Hospital-wide restrictions of implicated antibiotics (such as clindamycin and cephalosporins) have been shown to effectively reduce the incidence of CDI cases as well as decrease resistance to the implicated antibiotic (45,64).

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# 16 | Urosepsis in Critical Care

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## OVERVIEW

The most common cause of sepsis in patients admitted to the hospital is urosepsis. Urosepsis is bacteremia from a urinary tract source, which is diagnosed by culturing the same organism from urine and blood. It may be community or nosocomially acquired. Community-acquired urosepsis occurs in non-leukopenic compromised hosts, those with preexisting renal disease, or those with anatomical abnormalities of the urinary tract. Nosocomial urosepsis may occur in normal as well as abnormal hosts due to the presence of stones, stents, or nephrostomy tubes (1–5).

## COMMUNITY-ACQUIRED UROSEPSIS

The organisms causing community-acquired urinary tract infections (UTI), i.e., *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, enterococci, *Enterococcus faecalis* [vancomycin-susceptible enterococci (VSE)], group B streptococci, are the organisms isolated from blood as well as from urine in urosepsis. Clinical scenarios that predispose to community-acquired urosepsis include cystitis in non-leukopenic compromised hosts [diabetes mellitus, systemic lupus erythematosus (SLE), alcoholism, multiple myeloma, steroid therapy, etc.], acute pyelonephritis, those with partial/total urinary tract obstruction, preexisting renal disease, or renal/bladder calculi (Table 1).

Urosepsis is accompanied by bacteremia with systemic symptoms with or without hypotension (6–8). Excluding multiple myeloma and chronic lymphatic leukemia (CLL), urosepsis is relatively uncommon in leukopenic compromised hosts (e.g., cancer patients receiving chemotherapy). Immune defects related to malignancy and/or chemotherapy do not diminish mucosal defenses, e.g., secretory IgA that prevent bacterial adherence to uroepithelial cells (4,5).

## UROSEPSIS: NOSOCOMIAL

Nosocomial urosepsis is caused by urinary tract catheterization/instrumentation in non-leukopenic hosts. Catheter-associated bacteriuria in the hospital does not result in urosepsis in normal hosts. Bacteriuria will not result in bacteremia unless the patient has structural abnormalities of the GU tract, i.e., congenital abnormalities of the collecting system, stone disease, or unilateral/bilateral obstruction due to intrinsic/extrinsic causes. Urologic instrumentation/procedures done in the presence of a UTI may result in bacteremia with systemic symptoms/hypotension. Urosepsis from urologic instrumentation/procedures may occur in normal or abnormal hosts (4,5,9–12) (Table 2).

Uropathogens associated with nosocomial urosepsis are aerobic gram-negative bacilli (GNB) or *E. faecalis*. The most common nosocomial uropathogens are *E. coli*, *K. pneumoniae*, *E. faecalis* (VSE), and *E. faecium* [vancomycin-resistant enterococci (VRE)]. Less commonly, *Serratia marcescens*, *Enterobacter sp.*, *Providencia sp.*, *Citrobacter sp.*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, or *Pseudomonas aeruginosa*, are nosocomial *Acinetobacter* uropathogens. Because the uropathogens causing community-acquired versus nosocomially acquired urosepsis are dissimilar, different therapeutic approaches are required for community-acquired and nosocomially acquired urosepsis (5,9,11) (Table 3).

**Table 1** Acute Urosepsis: Community and Nosocomially Acquired

Type of UTI and acquired associated urosepsis	Community-acquired urosepsis	Nosocomially acquired urosepsis
Acute pyelonephritis (normal/abnormal hosts)	+	
Cystitis (normal hosts)	–	–
Cystitis (non-leukopenic compromised hosts)	+	
Acute prostatitis (normal/abnormal hosts)	+	
Prostatic abscess	+	
Urologic instrumentation (with infected urine)		+

Abbreviation: UTI, urinary tract infection.

**Table 2** The Relationship Between Urinary Tract Instrumentation and Nosocomial Urosepsis

Organisms	Bacteriuria	Bacteremia	Bacteremia associated with UT instrumentation
<i>E. coli</i>	1007	72	9
<i>Proteus</i> sp.	301	11	6
<i>K. pneumoniae</i>	243	29	4
<i>P. aeruginosa</i>	296	31	1
<i>Serratia marcescens</i>	166	8	1
<i>Enterococcus</i> sp.	181	20	4
<i>Enterobacter</i> sp.	150	23	3
<i>Citrobacter</i> sp.	15	2	2
Other	242	130	0
Total	2601	326	30

Conditions	Number of cases
Preexisting UT disease alone	23
Preexisting UT disease and diabetes	4
Preexisting UT disease and cirrhosis	2
Preexisting UT disease, diabetes mellitus, cirrhosis	1
No preexisting UT disease	0
Total	30

Abbreviation: UT, urinary tract.

Source: Ref. 12.

## CLINICAL PRESENTATION OF UROSEPSIS

The clinical presentation of urosepsis is not different from sepsis from a non-genitourinary (GU) procedure. The interaction between microorganisms and the host determines the systemic response rather than the origin of the infection. The clinical diagnostic approach is to identify systemic disorders or urinary tract abnormalities that predispose to urosepsis, i.e., a history of preexisting renal disease, recurrent UTIs (relapse variety), recent GU procedures, history of bladder/renal stones, stents/nephrostomy tubes, or history of systemic illnesses predisposing to urosepsis (e.g., diabetes mellitus, SLE), CLL, myeloma (1–5,13).

## DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

The physical exam in urosepsis is unhelpful unless the patient has pyelonephritis, with renal colic stone disease or obstruction, or prostatitis. Gram stain and culture of the urine with urinalysis plus blood cultures are the definitive diagnostic tests. While blood cultures will not

**Table 3** Catheter-Associated Bacteriuria (CAB) and Urosepsis

Clinical CAB setting	GU host factors	Risk of urosepsis	Preferred approach	Comments
● Indwelling (short-term) non-obstructed Foley catheter	Normal	Low	No antibiotics	Remove Foley catheter as soon as possible. No antibiotics.
● Indwelling (short- or long-term) obstructed Foley catheter	Normal	High	Correction of obstruction	IV/PO antibiotics until obstruction relieved.
● Indwelling (short- or long-term non-obstructive) Foley catheter in non-leukopenic compromised hosts (SLE, DM, multiple myeloma, steroids, cirrhosis)	Abnormal	High	If possible, avoid Foley catheter	PO antibiotic prophylaxis.
Not septic	Normal	Low	No antibiotics	PO chronic antibiotic suppressive therapy (optional).
Septic	Abnormal	High	IV/PO antibiotics	First, treat urosepsis IV/PO then follow with PO suppressive therapy.

*Abbreviations:* CAB, catheter-associated bacteriuria; DM, diabetes mellitus; GU, genitourinary; IV/PO, intravenous/by mouth; SLE, systemic lupus erythematosus.

be available for some time, the Gram stain of the urine provides immediate microbiologic information regarding the likely cause of the patient's UTI/urosepsis (1-5,13,14).

Patients with acute pyelonephritis have fever >102°F, pyuria with bacteriuria, and unilateral costovertebral angle (CVA) tenderness or bladder/renal abnormalities. Urosepsis due to cystitis in compromised hosts has no localizing signs (1,4,5) (Table 4).

**Table 4** Differential Diagnosis of Acute Cystitis, Renal Stone, Acute Pyelonephritis

Clinical findings	Acute cystitis	Renal stone	Acute pyelonephritis
● Symptoms			
Abdominal pain	Suprapubic discomfort	Unilateral back pain	Unilateral back pain
Dysuria	+	-	+
● Signs			
Fever >102°F	-	-	+
CVA tenderness	-	-	+
● Laboratory tests			
Leukocytosis	+	+	+
↑ ESR	-	-	+
Urine tests			
Urinalysis			
Pyuria	+	±	+
Microscopic hematuria	-	+	-
Bacteriuria	+	-	+
Blood cultures	- <sup>a</sup>	-	+
● Imaging studies			
Abdominal ultrasound	-	±	±
Abdominal CT scan	-	Hydroureter/hydronephrosis	Cortical abnormalities
		±	Acute pyelonephritis (distorted cortical contour/scarring)
		Hydroureter/hydronephrosis	

<sup>a</sup>Only in compromised hosts with urosepsis, e.g., SLE, systemic lupus erythematosus, DM, diabetes mellitus, MM, multiple myeloma, cirrhosis, etc.

*Abbreviations:* CT, computed tomography; CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate.

Nosocomial urosepsis follows recent urologic instrumentation usually <72 hours. The diagnosis should be considered when a patient becomes septic after a urologic procedure. A patient in the critical care unit (CCU) with an indwelling Foley catheter, with bacteriuria and pyuria, almost never has fever on the basis of urosepsis unless the he or she is a compromised host, i.e., has diabetes mellitus, SLE, cirrhosis, or is on steroids/immunosuppressives (1,3,4,9) (Table 3). In such cases, other sources of fever should be considered in the CCU setting, i.e., IV line infections, *Clostridium difficile* diarrhea/colitis, intraabdominal peritonitis/abscess, or acute pancreatitis (5,9–12,15).

Patients presenting from the community with urosepsis often have stone or structural ureteral, bladder, or renal abnormality, acute prostatitis/prostatic abscess, or acute pyelonephritis. Acute pyelonephritis is diagnosed by a temperature of  $\geq 102^{\circ}\text{F}$ , CVA tenderness, and pyuria with bacteriuria. In acute pyelonephritis, the Gram stain provides a rapid, presumptive, otherwise unexplained microbiologic diagnosis, which should guide antibiotic selection. A Gram stain of the urine in acute pyelonephritis will reveal gram-positive cocci in pairs/chains, group B streptococci or group D enterococci, or GNBs. In acute pyelonephritis GNBs are aerobic since anaerobic GNBs do not cause UTIs/pyelonephritis (3–8).

Patients with acute prostatitis may become septic, but urosepsis often accompanies prostatic abscesses (3–8) (Table 5). Prostatic abscess is a difficult diagnosis in a septic patient without any localizing signs. “Fever everywhere, fever nowhere” suggests an occult subdiaphragmatic abscess. Similarly, in a patient who has a history of prostatitis and no other explanation for fever/hypotension sepsis, a prostatic abscess should be considered in the differential diagnosis. A transrectal ultrasound or an abdominal CT scan are

**Table 5** Mimics of Pyelonephritis

Pyelonephritis mimics	Distinguishing features
<ul style="list-style-type: none"> <li>• Lower lobe community-acquired pneumonia</li> </ul>	<ul style="list-style-type: none"> <li>• No true CVA tenderness</li> <li>• Chest X ray: Lower lobe infiltrate/effusion</li> <li>• UA/UC</li> <li>• Abdominal CT scan</li> <li>• BCs: <math>\pm</math> <i>Streptococcus pneumoniae</i> or <i>Haemophilus influenzae</i></li> </ul>
<ul style="list-style-type: none"> <li>• Hepatic/splenic flexure diverticulitis</li> </ul>	<ul style="list-style-type: none"> <li>• No true CVA tenderness</li> <li>• UA/UC</li> <li>• Abdominal CT scan diverticulitis: <math>\pm</math> peridiverticular abscess</li> <li>• BCs: <math>\pm</math> coliforms/<i>Bacteroides fragilis</i></li> </ul>
<ul style="list-style-type: none"> <li>• Regional enteritis</li> </ul>	<ul style="list-style-type: none"> <li>• No true CVA tenderness</li> <li>• UA: +</li> <li>• UC: –</li> <li>• Abdominal CT scan: ileitis <math>\pm</math> abscess</li> <li>• BCs: –</li> </ul>
<ul style="list-style-type: none"> <li>• Lower rib plasmacytoma</li> </ul>	<ul style="list-style-type: none"> <li>• No true CVA tenderness</li> <li>• Tenderness/mass over rib</li> <li>• UA/UC: –</li> <li>• Abdominal CT scan: –</li> <li>• SPEP: monoclonal gammopathy</li> <li>• BCs: –</li> </ul>
<ul style="list-style-type: none"> <li>• Costochondritis</li> </ul>	<ul style="list-style-type: none"> <li>• No true CVA tenderness</li> <li>• Point tenderness over one/more rib cartilages</li> <li>• UA/UC: –</li> <li>• Abdominal CT scan: –</li> <li>• <math>\uparrow</math> Coxsackie B titers</li> <li>• SPEP: No monoclonal gammopathy</li> <li>• BCs: –</li> </ul>

*Abbreviations:* BCs, blood cultures; CT, computed tomography; CVA, cerebrovascular accident; SPEP: serum protein electrophoresis; UA, urinalysis; UC, urine culture.



diagnostic and surgical drainage may be required. Epididymitis in elderly may occasionally present as urosepsis, and the usual pathogens are aerobic GNBs, particularly *P. aeruginosa* (6,7,13,14).

### EMPIRIC ANTIMICROBIAL THERAPY

Empiric antibiotic therapy of urosepsis depends on the likely pathogen, which is related to whether urosepsis is community or nosocomially acquired. The causative microorganisms in community-acquired urosepsis are aerobic GNBs or group B or D streptococci. The Gram stain of the urine rapidly differentiates gram-positive cocci in pairs/chains from aerobic GNBs, which is sufficient to base initial empiric therapy. Gram-positive cocci in chains are group B or D streptococci, since gram-positive cocci in clusters represent *S. aureus*, not a uropathogen (16,17). In terms of GNBs, coverage should be directed against community-acquired uropathogens. Antibiotics effective against *K. pneumoniae* will almost always also be effective against *E. coli*, *Proteus*, etc. With the exception of epididymitis in the elderly, community-acquired urosepsis does not require *P. aeruginosa* coverage. Antibiotics effective against group D streptococci (VSE/VRE) will also be effective against group B streptococci (5,14,16–21) (Table 6 and 7).

Nosocomial urosepsis is caused by aerobic GNBs and empiric therapy is based on the Gram stain and recent past medical urologic history. Coverage should be directed against *P. aeruginosa*, which will also cover other aerobic nosocomial GNBs. If recent PMH indicated recurrent UTI/procedures due to multidrug resistant (MDR) GNBs, the coverage should be directed against the most recent MDR GNB, i.e., MDR *P. aeruginosa*, MDR *K. pneumoniae*, or MDR *Acinetobacter* species. If urine/blood cultures have grown *S. maltophilia* or *B. cepacia*, treat with trimethoprim-sulfamethoxazole (TMP-SMX) or minocycline respectively (16,21–33).

**Table 6** Community-Acquired Urosepsis: Therapeutic Approach

Urosepsis-associated syndrome	Microorganisms	Urine Gram stain	Empiric coverage
• Acute epididymitis (elderly males)	<i>P. aeruginosa</i>	GNBs	Meropenem Amikacin Antipseudomonal penicillin (APP) Antipseudomonal third-generation cephalosporin (APC) Cefepime Aztreonam
• Acute epididymitis (young males)	<i>C. trachomatis</i>	No bacteria	Quinolone <sup>a</sup> Doxycycline
• Acute prostatitis	Common coliforms Group D enterococci <i>E. faecalis</i> (VSE)	GNBs Gram-positive cocci in pairs/chains	Quinolone <sup>a</sup> Ampicillin Vancomycin Meropenem
• Acute pyelonephritis	<i>E. faecium</i> (VRE) <i>E. coli</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i>	GNBs	Linezolid Meropenem Quinolone <sup>a</sup> Aztreonam Aminoglycoside Third-generation cephalosporin

<sup>a</sup>Levofloxacin or ciprofloxacin.

Abbreviations: GNBs, gram-negative bacilli; Q/D, quinupristin/dalfopristin; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

**Table 7** Nosocomial Urosepsis: Therapeutic Approach

Urosepsis-associated syndrome	Usual uropathogens	Urine Gram stain	Empiric coverage
● Post-urologic instrumentation/procedure	<i>P. aeruginosa</i>	GNBs	Meropenem
	<i>Enterobacter</i> species <i>Serratia</i> species		Amikacin Third-generation cephalosporin Cefepime Aztreonam
● Acute pyelonephritis	MDR GNBs (suspected from recent cultures) MDR <i>P. aeruginosa</i> MDR <i>K. pneumoniae</i> MDR <i>Acinetobacter</i> sp.	GNBs	Colistin or polymyxin B Tigecycline Subactam/ampicillin
	Group D enterococci	Gram-positive cocci in pairs/chains	
	<i>E. faecalis</i> (VSE) <i>E. faecium</i> (VRE)		Piperacillin/tazobactam Meropenem Linezolid Q/D
● CAB in normal hosts (CAB/UTI)		GNBs GPCs	No antibiotic therapy
● CAB (compromised hosts) <sup>a</sup>	Group B streptococci	Gram-positive cocci in pairs/chains	
	Group D streptococci <i>E. faecalis</i> (VSE)		Piperacillin/tazobactam Meropenem Linezolid Q/D
	<i>E. faecium</i> (VRE)		
● CAB (compromised hosts)	Coliforms	GNBs	Piperacillin/tazobactam Meropenem
	MDR GNBs	GNBs	Fosfomycin

<sup>a</sup>Only in abnormal hosts with unilateral/bilateral urinary tract obstruction, preexisting renal disease, or non-leukopenic compromised hosts (DM, SLE, cirrhosis, multiple myeloma, on steroids).

**Abbreviations:** CAB, Catheter-associated bacteriuria; GNB, gram-negative bacilli; CPC, gram-positive cocci in pairs/chain; MDR, multidrug resistant; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

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# 17 | Severe Skin and Soft Tissue Infections in Critical Care

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## INTRODUCTION

Skin and soft tissue infections are common and vary widely in severity from minor pyodermas to severe necrotizing infections. Most of these infections are superficial and treated with regimens of local care and antimicrobial therapy. However, others like necrotizing infections are life-threatening and require a combined medical and surgical intervention. Prompt recognition and treatment is paramount in limiting the morbidity and mortality associated with these infections, and thus a thorough understanding of the various etiologies and presentation is essential in the critical care setting. It is also important to discriminate between infectious and noninfectious causes of skin and soft tissue inflammation. A detailed history and examination are necessary to narrow the possible etiologies of infection. In many instances, surface cultures are unreliable and misleading because surface-colonizing organisms can be mistaken for pathogens. In instances in which the diagnosis is in doubt, aspiration, biopsy, or surgical exploration of the skin can be considered. Typically, soft tissue infections result from disruption of the skin by exogenous factor, extension from subjacent infection, or hematogenous spread from a distant site of infection.

## MICROBIAL FLORA

Normal skin functions as a protective barrier that prevents microorganisms from causing soft tissue infection.

Physiological factors that control the bacterial skin flora include humidity, water content, skin lipids, temperature, and rate of desquamation. The pH of the skin is usually around 5.6. Besides containing secretory immunoglobulin (IgA), sweat also possesses sufficient salt to create a high osmotic pressure, which may be responsible for inhibiting many microbial species. In spite of these barriers to colonization, the skin provides an excellent venue of various microenvironments. Differences in cutaneous microflora may relate to variability in skin surface temperature and moisture content as well as the presence of different concentrations of skin surface lipids that may be inhibitory to various microorganisms. Colonization with organisms sensitive to desiccation, such as gram-negative bacilli, is not favored. The predominant bacterial flora of the skin is the various species of coagulase-negative staphylococci (*Staphylococcus epidermidis*, *S. capitis*, *S. warneri*, *S. hominis*, *S. haemolyticus*, *S. lugdunensis*, and *S. auricularis*), *Corynebacterium* spp. (diphtheroids), and *Propionibacterium* spp. Humans are a natural reservoir for *S. aureus*, and asymptomatic colonization is far more common than infection. Colonization of the anterior nares, perineum, or skin, particularly if the cutaneous barrier has been disrupted or damaged, may occur shortly after birth and may recur anytime thereafter (1–4). The anterior nares are reservoirs for *S. aureus*. Approximately 20% of individuals always carry one type of strain and are called persistent carriers. A large proportion of the population approximately 60% harbors *S. aureus* intermittently, and the strains change with varying frequency. Such persons are called intermittent carriers. Finally, approximately 20% almost never carry *S. aureus* and are called noncarriers (5–7). Carriage rates are higher than in the general population for injection drug users, persons with insulin-dependent diabetes, patients with dermatological conditions, patients with long-term indwelling intravascular catheters, and those with human immunodeficiency virus infection. High nasal carriage rates are found in patients with *S. aureus* skin infections as demonstrated from nasal cultures taken at the time the *S. aureus* infection was present (5). *Micrococcus* spp., *Peptostreptococcus*, *Streptococcus*

*viridans*, and *Enterococcus* spp. can also be isolated. *Acinetobacter* spp. are found in 25% of the populations axillae, toe webs, groin, and antecubital fossa. Other gram-negative bacilli are found more rarely on the skin, and these include *Proteus* and *Pseudomonas* in the toe webs and *Enterobacter* and *Klebsiella* on the hands. Antibiotics disturb the balance within commensal flora and leave the surface vulnerable to colonization by exogenous gram-negative bacilli and fungi. The principal fungal flora is lipophilic yeasts of the genus *Malassezia*, and nonlipophilic yeasts such as *Candida* spp. are also inhabitants of the skin (1,2,4).

Primary skin infections occur in otherwise normal skin and are usually caused by group A streptococci or *S. aureus*. Secondary infections complicate chronic skin conditions (e.g., eczema or atopic dermatitis). A deficiency in the expression of antimicrobial peptides may account for the susceptibility of patients with atopic dermatitis to skin infection with *S. aureus* (8). These underlying disorders act as a portal of entry for virulent bacteria. Other factors predisposing to skin infections include vascular insufficiency, disrupted venous or lymphatic drainage, sensory neuropathies, diabetes mellitus, previous cellulitis, foreign bodies, accidental or surgical trauma, burns, poor hygiene, obesity, and immunodeficiencies.

### CLASSIFICATION OF SKIN AND SOFT TISSUE INFECTIONS

Infections of the skin and soft tissue can be divided on the basis of the depth of penetration and the ability of the organism to produce necrosis. Infection of the outermost layer of skin, the epidermis, is termed impetigo. Extension into the superficial dermis with involvement of lymphatic is typical of erysipelas, whereas cellulitis is an extension into the subcutaneous tissue. In necrotizing fasciitis (NF), there is involvement of fascia, whereas in myonecrosis there is involvement of muscle. A clinically useful distinction with important management implications subdivides soft tissue infections into nonnecrotizing and necrotizing processes (9). The Center for Drug Evaluation and Research for development of antimicrobial drugs has classified skin and soft tissue infection as uncomplicated or complicated. The uncomplicated category included simple abscesses, impetiginous lesions, furuncles, and cellulitis. Complicated category included infection involving the deeper layer or requiring significant surgical intervention. Superficial infection in an anatomical site with a risk of gram-negative pathogen or anaerobes such as the rectal area was also considered to be complicated (10). DiNubile and Lipsky classified skin and soft tissue infections to assist clinician in recognizing uncomplicated and complicated infections (11).

Classification can also be based according to the severity of local and systemic signs and symptoms of infection, and the presence and stability of any comorbidities. Class 1 patients have no signs or symptoms of systemic toxicity without any comorbidities and can be managed in an outpatient setting. Class 2 patients are systemically ill without any unstable comorbidities. Class 3 patients have toxic appearance, one unstable comorbidity, or a limb-threatening infection, whereas class 4 patients have sepsis syndrome or serious

**Table 1** Classification of Skin and Soft Tissue Infection Based on Uncomplicated and Complicated Infections and Systemic Syndromes

Uncomplicated	Complicated	Systemic syndromes
Superficial: impetigo, ecthyma	Secondary infection of diseased skin	Scalded-skin syndrome
Deeper: erysipelas, cellulitis	Acute wound infections:	Toxic shock syndrome
Hair follicle associated:	Traumatic	Purpura fulminans
folliculitis, furunculosis	Bite related	
Abscess: carbuncle,	Post operative	
cutaneous abscess	Chronic wound infections:	
	Diabetic foot infections	
	Venous stasis ulcer	
	Pressure ulcers	
	Perianal infections	
	Necrotizing fasciitis (type 1 and type 2)	
	Myonecrosis (crepitant and noncrepitant)	

Source: Adapted in part from Ref. 11.

life-threatening infections with the majority requiring surgical intervention, such as NF, and are often admitted to intensive care unit (12). Guidelines developed by the Infectious Disease Society of America are written in references to specific disease entities, mechanism of injury, or host factors (13).

Systemic syndromes mediated by toxin and affecting the skin cause staphylococcal scalded skin syndrome (SSSS), toxic shock syndrome (TSS), and purpura fulminans. Classification of skin and soft tissue infections based on uncomplicated and complicated infections, and systemic syndromes is depicted in Table 1.

Here we review causes of skin and soft tissue infection with emphasis on severe skin and soft tissue infection, highlighting the clinical presentation, diagnosis, and approach to management in the critical care setting.

## IMPETIGO

Impetigo is the most common, contagious, superficial skin infection nearly always caused by *S. aureus* or *Streptococcus*. There are two clinical presentations: bullous impetigo and nonbullous impetigo, and both begin as a vesicle (14). Bullous impetigo, like SSSS and the staphylococcal scarlatiniform syndrome, represents a form of cutaneous response to the two extracellular exfoliative toxins produced by *S. aureus* of phage group II (usually type 71). The group A streptococci responsible for impetigo belong to different M serotypes (2,15–21) from those of strains that produce pharyngitis (1,2,4,6,22) (23,24). Crusted impetigo is usually associated with a mixed flora of both *S. aureus* and streptococci. *S. aureus* is known to be the primary pathogen in both bullous and nonbullous impetigo. They are common in exposed areas such as hands, feet, and legs, and are often associated with traumatic events such as minor skin injury or insect bite. Predisposing factors include warm ambient temperature, humidity, poor hygiene, and crowded conditions. Systemic complications are very uncommon. Cutaneous infection with nephritogenic strains (2,15,17–21) of group A streptococci can lead to poststreptococcal glomerular nephritis. For extensive bullous impetigo, treatment with antistaphylococcal agents is selected with consideration of susceptibility testing.

## FURUNCLES AND CARBUNCLES

Furuncle is a deep inflammatory nodule that develops from predisposing folliculitis. A carbuncle is a more extensive process that extends into the subcutaneous fat in areas covered by thick, inelastic skin. Multiple abscesses separated by connective tissue septa develop and drain to the surface along the hair follicle. *S. aureus* is the most common etiological agent. Infections occur in areas that contain hair follicles such as neck, face, axillae and buttocks, sites predisposed to friction, and perspiration. Predisposing factors include obesity, defects in neutrophil dysfunction, and diabetes mellitus. Bacteremia can occur and result in osteomyelitis, endocarditis, or other metastatic foci. Larger furuncles and all carbuncles require incision and drainage. Systemic anti-staphylococcal antibiotics are recommended in the presence of surrounding cellulitis and large abscesses or when there is a systemic inflammatory response present.

## ERYSIPELAS

Erysipelas is a distinctive superficial cellulitis of the skin with prominent lymphatic involvement. In typical erysipelas, the area of inflammation is raised above the surrounding skin, and there is a distinct demarcation between involved and normal skin, the affected area has a classic orange peel (peau d'orange) appearance. The induration and sharp margin distinguish it from the deeper tissue infection of cellulitis in which the margins are not raised and merge smoothly with uninvolved areas of the skin (Fig. 1). Systemic signs of chills and fever are common. Flaccid bullae filled with clear fluid may develop on the second or third day. Occasionally, the infection spreads more deeply and causes cellulitis, abscess, and NF. Desquamation may occur in 5 to 10 days, and scarring is very uncommon. Erysipelas is almost always caused by group A *Streptococcus*, though streptococci of groups G, C, and B and rarely *S. aureus* can also be responsible. Formerly, the face was commonly involved, but now up to 85% of cases occur on the legs and feet largely due to lymphatic venous disruptions (25,26).



**Figure 1** Facial erysipelas involving the right cheek. Sharp demarcation between the erythema and right cheek is evident.

Erysipelas can spread rapidly if not treated promptly. Blood cultures are positive in only about 5% of cases (25).

### Treatment

There has never been a documented report of group A streptococci resistant to penicillin, and thus penicillin remains the drug of choice, intravenous (IV) penicillin G (2 million units every 6 hours). Other alternative agents include first generation cephalosporins or clindamycin. Agents such as erythromycin and the other macrolides are limited by their rates of resistance and the fluoroquinolones are generally less active than the  $\beta$ -lactam antibiotics against  $\beta$ -hemolytic streptococci.

### CELLULITIS

Cellulitis is an acute, spreading pyogenic inflammation of the dermis and subcutaneous tissue (26,27). *S. aureus* and group A  $\beta$ -hemolytic *Streptococcus* spp. are the common organisms (Fig. 2). Cellulitis commonly begins as erythema, edema, and pain and lacks demarcation. It often occurs in the setting of local skin trauma from skin bite, abrasions, surgical wounds, contusions, or other cutaneous lacerations. Edema also predisposes patients to cellulitis. Specific pathogens are suggested when infections follow exposure to seawater (*Vibrio vulnificus*) (28,29), freshwater (*Aeromonas hydrophila*) (30), or aquacultured fish (*S. iniae*) (31). *A. baumannii* is an emerging infection in patients who experience war trauma. *A. baumannii* presented as cellulitis with a "peau d'orange" appearance with overlying vesicles and, when untreated, progressed to necrotizing infection with bullae (hemorrhagic and nonhemorrhagic) (32). Lymphedema may persist after recovery from cellulitis or erysipelas and predisposes patients to recurrences. Recurrent cellulitis is usually due to group A *Streptococcus* and other  $\beta$ -hemolytic streptococci. Recurrent cellulitis in an arm may follow impaired lymphatic drainage secondary to neoplasia, radiation, surgery, or prior infection and recurrence in the lower extremity may follow saphenous venous graft or varicose vein stripping. In addition,



**Figure 2** Cellulitis of the left thigh in an alcoholic patient, blood cultures grew group B *Streptococcus*.

spread to adjacent structures may result in osteomyelitis. Cellulitis infrequently occurs as a result of bacteremia. Uncommonly, pneumococcal cellulitis occurs on the face or limbs in patients with diabetes mellitus, alcohol abuse, systemic lupus erythematosus, nephritic syndrome, or a hematological cancer (22). Meningococcal cellulitis occurs rarely, although it may affect both children and adults (33). Bacteremic cellulitis due to *V. vulnificus* with hemorrhagic bullae may follow the ingestion of raw oysters by patients with cirrhosis, hemochromatosis, or thalassemia. Cellulitis caused by gram-negative organisms usually occurs through a cutaneous source in an immunocompromised patient but can also develop through bacteremia. *Cryptococcus neoformans*, *Fusarium*, *Proteus*, and *Pseudomonas* spp. have been associated with bloodstream infections. Immunosuppressed patients are particularly susceptible to the progression of cellulitis from regional to systemic infections. The distinctive features including the anatomical location and the patient's medical and exposure history should guide appropriate antibiotic therapy. Periorbital cellulitis involves the eyelid and periocular tissue and should be distinguished from orbital cellulitis because of complication of the latter: decreased ocular motility, decreased visual acuity, and cavernous-sinus thrombosis.

A variety of noninfectious etiologies resembling cellulitis in appearance should be distinguished from it. Sweet syndrome associated with malignancy consists of tender erythematous pseudovesiculated plaques, fever, and neutrophilic leukocytosis, which can mimic cellulitis. Cutaneous metastasis (tumor emboli) from solid tumors ranging from 0.7% to 9% can mimic cellulitis (34–36) (Fig. 3).

### Diagnostic Studies

Diagnosis is generally based on clinical and morphological features of the lesion. Culture of a needle aspirate is not generally indicated because of a low yield. Among 284 patients, a likely pathogen was identified in 29%. Of 86 isolates, only 3 represented mixed culture. Gram-positive organisms (mainly *S. aureus*, group A or B streptococci, and *En. faecalis*) accounted for 79% of cases; the remainder was caused by gram-negative bacilli (*Enterobacteriaceae*, *Haemophilus influenzae*, *Pasteurella multocida*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.) (26). Bacteremia is uncommon in cellulitis with only 2% to 4% yielding a pathogen (26). Blood cultures appear to be positive more frequently with cellulitis superimposed on lymphedema. Radiography and computed tomography are of value when the clinical setting suggests a subjective osteomyelitis or there is clinical evidence to suggest adjacent infections such as pyomyositis or deep abscesses. When it is difficult to differentiate cellulitis from NF, a magnetic resonance imaging (MRI) may be helpful, though surgical exploration for a definite diagnosis should not be delayed when the latter condition is suspected.





**Figure 3** Cutaneous metastases from inflammatory breast carcinoma resembling facial cellulitis. Diagnosis was confirmed on biopsy of middle turbinate and nasal septum, which showed vascular tumor emboli.

### Treatment

Since most cases are caused by streptococci and *S. aureus*, therapy should be directed against the pathogen. With the widespread occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) among strains of community-associated *S. aureus* infection, the agents should be active against MRSA. Available oral options for MRSA include trimethoprim/sulfamethoxazole, linezolid, clindamycin, and doxycycline. Specific treatment for bacterial causes is warranted after an unusual exposure (human or animal bite or exposure to fresh or salt water), in patients with certain underlying conditions (neutropenia, splenectomy, or immunocompromised), or in the presence of bullae and is described in Table 2.

### ERYSIPELOID

The localized cutaneous infection caused by *Erysipelothrix rhusiopathiae* presents as a subacute cellulitis (termed "erysipeloid"). It is usually due to contact with fish, shellfish, or infected animals. Contact with this pathogen may occur in recreational settings, domestic exposures, abattoirs, or after lacerations among chefs (37). Between one and seven days after exposure, a red macularpapular lesion develops, usually on hands and finger. Lesions are slightly raised and violaceous. Regional lymphadenopathy occurs in about one-third of cases. Other organisms that cause skin and skin structure infections following exposure to water and aquatic animals include *Aeromonas*, *Plesiomonas*, *Pseudallescheria boydii*, and *V. vulnificus*. *Mycobacterium marinum* can also cause skin infection, but this infection is characterized by a more indolent course. For *Erysipelothrix* bacteremia or endocarditis penicillin G (12–20 million units IV daily) is the drug of choice, alternative antimicrobials include ciprofloxacin, cefotaxime, or imipenem-cilastatin.

### CHANCRIFORM LESIONS: ANTHRAX

A bioterrorism-associated anthrax outbreak occurred suddenly in the United States in 2001. Out of the 22 cases 11 had the cutaneous form (38). After incubation of one to eight days, a painless, sometime pruritic, papule develops on an exposed area. The lesion enlarges and

**Table 2** Antimicrobial Therapy and Pathogens Associated with Specific Risk Factors

Risk factor	Pathogen	Recommended therapy	Optional therapy
Dog and cat bites	<i>Pasteurella multocida</i> and other <i>Pasteurella</i> spp. <i>S. aureus</i> , <i>Capnocytophaga canimorsus</i> , <i>Streptococcus</i> <i>Neisseria canis</i> , <i>Haemophilus felis</i> , <i>Capnocytophaga canimorsus</i> , anaerobes	Ampicillin/sulbactam 1.5–3 g IV every 6 hr	Ciprofloxacin 500 mg PO or 400 mg IV every 12 hr + clindamycin 600–900 mg IV every 8 hr
Human bites	<i>Ei. corrodens</i> , anaerobes, <i>S. aureus</i> , <i>Streptococcus viridans</i>	Ampicillin/sulbactam 1.5–3 g IV every 6 hr	Ciprofloxacin 500 mg PO or 400 mg IV every 12 hr + clindamycin 600–900 mg IV every 8 hr
Salt water	<i>Vibrio vulnificus</i>	Doxycycline 200 mg IV followed by 100–200 mg IV every 12 hr	Cefotaxime 1–2 g IV every 6–8 hr or ciprofloxacin 500 mg PO or 400 mg IV every 12 hr
Freshwater or use of leeches	<i>Aeromonas</i> sp.	Ciprofloxacin 400 mg IV every 12 hr	Imipenem/cilastatin 500 mg–1 g IV every 6–8 hr
Butcher, fish handler, or veterinarian	<i>Erysipelothrix rhusiopathiae</i>	Penicillin G 2–4 mu IV every 4–6 hr	Ciprofloxacin or cefotaxime or imipenem/cilastatin 500 mg–1 g IV every 6–8 hr
Intravenous drug users	MRSA, <i>P. aeruginosa</i>	Vancomycin 15 mg/kg every 12 hr + ceftazidime 1–2 g IV every 8 hr or cefepime 1–2 g IV every 8–12 hr	Linezolid 600 mg PO or IV every 12 hr or daptomycin 4–6 mg/kg IV every 24 hr or trimethoprim/ sulfamethoxazole 320/1600 mg IV or PO 160/800 mg 1–2 tab every 12 hr or tigecycline 100 mg IV then 50 mg every 12 hr or telavancin 10 mg/kg/ every 24 hr + tobramycin 5.0/kg/day <sup>a</sup> or ciprofloxacin

Dose to be adjusted for azotemia except for ceftriaxone, doxycycline, tigecycline, clindamycin and linezolid.

<sup>a</sup>Based on once a day dose of 5.0 mg/kg, however can be given as 1.7 mg/kg IV every 8 hours.

Abbreviation: mu, million unit.

becomes surrounded by a wide zone of brawny, erythematous, gelatinous, nonpitting edema. As the lesion evolves it becomes hemorrhagic, necrotic, and covered by an eschar. Frequently lymphadenopathy is present, if untreated bacteremic dissemination can occur. Incision and debridement should be avoided because it increases the likelihood of bacteremia (39). A skin biopsy after the initiation of antibiotics can be done to confirm the diagnosis by culture, polymerase chain reaction, or immunohistochemical testing. With the concern that strains may have been modified to be resistant to penicillin, treatment with ciprofloxacin or doxycycline has been recommended (40).

## BITES

Each year, several million Americans are bitten by animals, resulting in approximately 10,000 hospitalizations. Ninety percent of the bites are from dogs and cats, and 3% to 18% of dog bites and 28% to 80% of cat bites become infected, with occasional sequelae of meningitis, endocarditis, septic arthritis, and septic shock. Animal or human bites can cause cellulitis due to skin flora of the recipient of the bite or the oral flora of the biter. Severe infections develop after bites as a result of hematogenous spread or undetected penetration of deeper structures. In a prospective multicenter study of infected dog and cat bites, *Pasteurella* spp. was the most common isolate from both dog bites (50%) and cat bites (75%). *Pa. canis* was the most common

isolate of dog bites and *Pa. multocida* subsp. was the most common isolate of cat bites. Other common aerobes include streptococci, staphylococci, *Moraxella*, and *Neisseria*. Common anaerobes include *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Prevotella*. *Capnocytophaga canimorsus* is an invasive organism usually occurring in immunosuppressed patients after a dog bite (41,42). Human bites are usually associated with mixed aerobic and anaerobic organisms including *Str. viridans* and other streptococci, *S. aureus*, *Eikenella corrodens*, *Fusobacterium*, and *Prevotella*. Clenched fist injuries may lead to infection, tendon tear, joint disruption, or fracture (43). Clinicians should ensure that tetanus prophylaxis is current. The local health department should be consulted about the risks and benefits of rabies immunization (for treatment refer to Table 2).

## NECROTIZING INFECTIONS

Necrotizing soft tissue infections are infrequent but highly lethal infections. They can be defined as infections of any of the layers within the soft tissue compartment that are associated with necrotizing changes. A high index of suspicion is necessary to make an early diagnosis of necrotizing skin and soft tissue infections as in early stages distinguishing between a cellulitis that should respond to antimicrobial treatment alone and a necrotizing infection that requires operative intervention may be difficult.

### Necrotizing Cellulitis

Infectious gangrene is a cellulitis that rapidly progresses, with extensive necrosis of subcutaneous tissues and the overlying skin. Pathological changes are those of necrosis and hemorrhage of the skin and subcutaneous tissue. In most instances, necrotizing cellulitis has developed secondary to introduction of the infecting organism at the site of infection. Streptococcal gangrene is a rare form caused by group A streptococci that occurs at the site of trauma, but may occur in the absence of an obvious portal of entry. Cases may follow infection at an abdominal operative wound, around an ileostomy or colostomy, at the exit of a fistulous tract or in proximity to chronic ulceration. The organisms responsible include *Clostridium*, *Bacteroides*, and *Peptostreptococcus*. The diagnosis is suggested when gas is present or when necrosis develops rapidly in an area of cellulitis. Gram-stain and culture of skin drainage, aspirate fluid, or surgical specimens should reveal the pathogenic organisms (44–46).

Treatment consists of immediate surgical exploration beyond the involved gangrenous and undermined tissue. Areas of cutaneous necrosis are excised. Repeat exploration is commonly performed within 24 hours. Antibiotic therapy should be guided by Gram stain results or empirically consist of high-dose IV penicillin G (3–4 million units every 4 hours) or ampicillin (2 g every 4 hours), with the addition of clindamycin.

### Necrotizing Fasciitis

NF is a rapidly spreading infection that involves the fascia and subcutaneous tissue with relative sparing of underlying muscle. The mortality of this disease remains alarmingly high ranging from 6% to 76% (47). Delayed diagnosis and delayed debridement have been shown to increase mortality. Some conditions appear to be more commonly associated with NF; these include injection drug use and chronic debilitating comorbidities (e.g., diabetes mellitus, immune suppression, and obesity). Type 1 NF is polymicrobial with at least one anaerobic species isolated in combination with one or more facultative anaerobic species such as nontypable streptococci and Enterobacteriaceae. Type 1 NFs are postoperative infections and include Fournier gangrene. Type 2 NF is typically monomicrobial, most often caused by group A *Streptococcus* (48) and *Clostridium* spp. There have been increasing case reports of *S. aureus* including community-acquired MRSA (CA-MRSA) being identified as a causative organism. Other organisms that have rarely been implicated in monobacterial infections include *Serratia marcescens*, *Flavobacterium odoratum*, *Ochrobactrum anthropi*, *V. vulnificus*, *Aeromonas* spp., and group G (49). NF presents either as an acute and life-threatening condition usually caused by group A *Streptococcus* or *Clostridium* spp., or as a subacute process, usually caused by mixed aerobic and anaerobic organisms. The primary site is the superficial fascia. Bacteria proliferate within the superficial fascia and elaborate enzymes and toxins. The precise mechanism of



**Figure 4** Necrotizing fasciitis of left leg in a diabetic patient with onset of bullae and tissue necrosis. Patient underwent below the knee amputation.

spread has not been fully elucidated but has been attributed to the expression of hyaluronidase, which degrades the fascia. The key pathological process resulting from this uncontrolled proliferation of bacteria is angiothrombotic microbial invasion and liquefactive necrosis of the superficial fascia. As this process progresses, occlusion of perforating nutrient vessels to the skin causes progressive skin ischemia. This event is responsible for the cutaneous manifestations. As the condition evolves, ischemic necrosis of the skin ensues with gangrene of subcutaneous fat, dermis, and epidermis, manifesting progressively as bullae formation, ulceration, and skin necrosis (Fig. 4).

#### *Clinical Features*

In early stages (stage 1 NF), the disease is indistinguishable from severe soft tissue infection such as cellulitis and erysipelas and presents with only pain, tenderness, and warm skin. Margins of the skin are poorly defined with tenderness extending beyond the apparent area of involvement. Blister or bulla formation is an important diagnostic clue. It signals the onset of skin ischemia (stage 2 NF). The late stage (stage 3 NF) signals the onset of tissue necrosis and is characterized by hemorrhagic bullae, skin anesthesia, and gangrene. Systemic manifestation such as fever, hypotension, and multiorgan failure can occur (50–53). The effects are classically caused by superantigen produced by group A *Streptococcus*. nonsteroidal anti-inflammatory drugs (NSAIDs) are postulated to potentiate tissue damage by decreasing granulocyte adhesion and phagocytosis and increasing cytokine production.

#### *Diagnosis*

NF is a clinical diagnosis with corroborative operative findings that include the presence of grayish necrotic fascia, a lack of resistance of normally adherent superficial fascia, a lack of bleeding of the fascia during dissection, and the presence of foul smelling “dishwater pus.” Wong et al. identified six independent laboratory variables between patients with and without NF. Total white cell count, hemoglobin, sodium, glucose, serum cretonne, and C-reactive protein were selected. The total score had a range from 0 to 13 according to the likelihood of NF (low  $\leq 5$ , intermediate 6–7, high  $\geq 8$ ). In the developmental cohort of 89 patients, only 13 (14.6%) had a diagnosis or suspicion of NF on admission; 80 (89.9%) of these patient had a Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score of  $\geq 6$  (positive predictive value was 92% and negative predictive value was 96%). LRINEC score can be a useful adjunct tool in NF (54,55). In a study by Anaya et al., clostridial infection was an independent predictor for limb loss and mortality and was highly associated with IV drug use and leukocytosis on admission (15).

Features reported to be indicative of NF on the computed tomography scan include deep fascial thickening, enhancement, and fluid and gas in the soft tissue planes. Negative deep fascial involvement on MRI effectively excludes NF. Fine-needle aspiration, frozen section of tissue biopsy, fascial biopsy, and skin biopsy for histopathology are all useful in the diagnosis of NF. The lack of bleeding may be seen or murky dishwasher pus exudates may ooze from the incision site.

Pathognomonic for NF is a positive “finger” test. The finger test can be used to delineate the extent of infection into the adjacent normal appearing skin. A 2-cm incision down to the deep fascia is made under local anesthesia. Probing of the level of the superficial fascia is then performed. The lack of bleeding, foul smelling dishwasher pus, and minimal tissue resistance to finger dissection constitute a positive finger test, which is diagnostic of NF (53,56).

### Treatment

If a diagnosis of NF is made, emergent surgical debridement and/or fasciotomy should be considered (Figs. 5 and 6). Debridement beyond the visible margin of infection is necessary. Repeated debridements may be required and should continue until the subcutaneous tissue can no longer be separated from the deep fascia. Fasciotomy may be performed at the time of debridement. If infection progresses despite serial debridements and antibiotics, amputation may be life saving. Close monitoring of the physiology of the patient as well as serial laboratory data should be performed. Aggressive fluid resuscitation is often required during postoperative period. A combination of broad-spectrum antibiotics, such as penicillin, and an aminoglycoside or a third-generation cephalosporin, and clindamycin or metronidazole can be started depending on the clinical presentation. If *S. aureus* is a consideration vancomycin or linezolid should be included. Once the Gram stain culture and sensitivity results are obtained, the antibiotic regimen can be altered on the basis of these findings. The use of intravenous immunoglobulins (IVIGs) as an adjunctive treatment for patients with streptococcal toxic shock syndrome (STSS) has been used on the basis of retrospective studies and one small prospective randomized trial, but conclusive evidence supporting its use remains limited. IVIG contains many antibodies, which neutralize the exotoxins/superantigens secreted by the *Streptococcus* and are involved in the pathogenesis of STSS. Since STSS and NF are mediated by the streptococcal toxins and inflict their tissue destruction via some of the same cytokines, it was postulated that IVIG would be as effective a treatment in NF as it was in STSS. This has yet to be conclusively demonstrated in a clinical trial. Hyperbaric oxygen has been advocated by



**Figure 5** Necrotizing fasciitis of left arm and shoulder in an IVDU patient who injected in the left arm. Patient underwent disarticulation. One set of blood culture grew *Gemella morbillorum* and second set grew *Streptococcus constellatus*. Operative cultures obtained from left arm grew *Klebsiella oxytoca*, *Peptostreptococcus micros*, and *Peptostreptococcus prevoti*. Abbreviation: IVDU, intravenous drug user.



**Figure 6** Postoperative view in a diabetic patient with necrotizing fasciitis of right leg due to group G *Streptococcus*. Patient underwent debridement and fasciotomy.

some for decreased number of debridements and decreased mortality (16,57). Results are contradictory, with no real epidemiologically based studies performed (for treatment refer to Table 3).

### **Fournier Gangrene**

It originates as a necrotic black area on the scrotum. It is a fulminant, rapidly progressive subcutaneous infection of the scrotum and penis, which spreads along fascial planes and may extend to the abdominal wall. More than 60% of the patients have diabetes mellitus. Fournier gangrene occurs commonly without a predisposing event or after uncomplicated hemorrhoidectomy. Less commonly this can occur after urological manipulation or as a late complication of deep anorectal suppuration. Fournier gangrene is characterized by necrosis of the skin and soft tissues of the scrotum and/or perineum that is associated with a fulminant, painful, and severely toxic infection (58,59). The infection is usually polymicrobial. Successful treatment is again based on early recognition and vigorous surgical debridement. Empiric antibiotic treatment is appropriate until culture results are available. Infection is often polymicrobial. The therapeutic benefit of hyperbaric oxygen treatment remains controversial in this as well as other forms of NF.

### **Clostridial Myonecrosis (Gas Gangrene)**

*Clostridium perfringens* type A is the most common organism. Although initial growth of the organism occurs within the devitalized anaerobic milieu, acute invasion and destruction of healthy, living tissue rapidly ensues. Historically, clostridial myonecrosis was a disease associated with battle injuries, but 60% of cases now occur after trauma. It is a destructive infectious process of muscle associated with infections of the skin and soft tissue. It is often associated with local crepitus and systemic signs of toxemia, which are formed by anaerobic, gas-forming bacilli of the *Clostridium* sp. The infection most often occurs after abdominal operations on the gastrointestinal tract; however, penetrating trauma, and frostbite, can expose muscle, fascia, and subcutaneous tissue to these organisms. Common to all these conditions is an environment containing tissue necrosis, low-oxygen tension, and sufficient nutrients (amino acids and calcium) to allow germination of clostridial spores. The systemic manifestations of gas gangrene are related to the elaboration of potent extracellular protein toxins, especially the  $\alpha$ -toxin, a phospholipase C (PLC), and,  $\theta$ -toxin, a thiol-activated cytolysin (17,18,60,61). Clostridia are gram-positive, spore-forming, obligate anaerobes that are widely found in soil contaminated with animal excreta. They may be isolated from the human gastrointestinal tract and from the skin in the perineal area. *C. perfringens* is the most common isolate (present in

**Table 3** Antimicrobial Therapy and Microbiology Associated with Diabetic Foot Infection and Necrotizing Fasciitis

Clinical syndrome	Pathogen	Recommended therapy	Optional therapy
Diabetic foot infection	<i>S. aureus</i> , <i>Streptococcus</i> , <i>Enterobacteriaceae</i> , <i>P. aeruginosa</i> anaerobes ( <i>Bacteroides</i> , <i>Peptostreptococcus</i> )	Ampicillin/sulbactam 1.5–3 g IV every 6 hr or piperacillin/tazobactam 3.75–4.5 g q.i.d. or ceftriaxone 1–2 g IV every 24 hr + metronidazole 500 mg IV every 8 hr <sup>a</sup>	Carbapenem (imipenem/cilastatin 500 mg–1 g IV every 6–8 hr or meropenem 1 g IV every or ertapenem 1 g IV every 24 hr or doripenem 500 mg IV every 8 hr) or clindamycin 600–900 mg IV every 8 hr + ciprofloxacin (500–750 mg PO or 400 mg IV every 12 hr) or ceftipime 1–2 gm IV every 8–12 hr + metronidazole 500 mg IV or PO every 8 hr
Type 1 NF	Anaerobes ( <i>Bacteroides</i> , <i>Peptostreptococcus</i> ) <i>E. coli</i> , <i>Enterobacteriaceae</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>S. aureus</i>	Vancomycin 15 mg/kg IV every 12 hr <sup>b</sup> + ampicillin/sulbactam 1.5–3 gm IV every 6 hr or piperacillin/tazobactam 3.75–4.5 g IV every 6 hr + clindamycin 900 mg IV every 8 hr ± ciprofloxacin 400 mg IV every 12 hr or Ceftriaxone 1–2 g IV every 24 hr + metronidazole 500 mg IV every 6–8 hr	Carbapenem (imipenem/cilastatin 500 mg–1 g IV every 6–8 hr or meropenem 1 g IV every or ertapenem 1 g IV every 24 hr or doripenem 500 mg IV every 8 hr) or clindamycin 900 mg IV every 8 hr + gentamicin or tobramycin 5 mg <sup>c</sup> or ciprofloxacin
Type 2 NF	Group A <i>Streptococcus</i> <i>S. aureus</i> (MRSA)	Penicillin 2–4 mu IV every 4–6 hr +clindamycin 900 mg IV every 8 hr, ± IVIG Vancomycin 15 mg/kg IV every 12 hr + <sup>d</sup> Clindamycin 900 mg IV every 8 hr	cefazolin 1–2 g every 8 hr or vancomycin 15 mg/kg IV q 12 hr +clindamycin 900 mg IV every 8 hr Daptomycin 4–6 mg/kg IV every 24 hr or linezolid 600 mg IV every 12 hr or tigecycline 100 mg IV then 50 mg every 12 hr telavancin 10 mg/kg IV every 24 hr
	MSSA <i>Clostridium</i> infection	Nafcillin 1–2 gm IV every 4 hr or cefazolin 1–2 g IV every 8 hr + clindamycin 900 mg IV every 8 hr Penicillin 2–4 mu IV every 4–6 hr +clindamycin 900 mg IV every 8 hr	Vancomycin or linezolid or daptomycin or tigecycline or telavancin

Dose adjusted for azotemia except for ceftriaxone, clindamycin and linezolid.

<sup>a</sup>When MRSA suspected use vancomycin, linezolid, daptomycin, or other active agents.

<sup>b</sup>Coverage should include MRSA infection till excluded.

<sup>c</sup>Based on once a day dose of 5.0 mg/kg/day, however can be given as 1.7 mg/kg IV t.i.d.

<sup>d</sup>Clindamycin or linezolid is recommended because of ability to inhibit toxin production.

Abbreviation: mu, million unit.

80% of cases) and is among the fastest-growing clostridial species, with a generation time, under ideal conditions, of approximately eight minutes. This organism produces collagenases and proteases that cause widespread tissue destruction, as well as  $\alpha$ -toxin, which have a role in the high mortality associated with myonecrosis. The  $\alpha$ -toxin causes extensive capillary destruction and hemolysis, leading to necrosis of the muscle and overlying fascia, skin, and subcutaneous tissues. Patients complain of sudden onset of pain at the site of trauma or surgical wounds, which rapidly increases in severity. The skin becomes edematous and tense. Hemorrhagic bullae are common, as is a thin watery, foul smelling discharge. Examination of the wound discharge reveals abundant large, boxcar-shaped gram-positive rods with a paucity of surrounding leukocytes. The usual incubation period between injury and the onset of clostridial myonecrosis is two to three days, but may be as short as six hours. A definitive diagnosis is based on the appearance of the muscle on direct visualization by surgical exposure. Initially, the muscle is pale, edematous, and unresponsive to stimulation. As the disease process continues, the muscle becomes frankly gangrenous, black, and extremely friable. This occurs with septicemia and shock. Nearly 15% of patients have positive blood cultures. Serum creatinine phosphokinase levels are always elevated with muscle involvement. The mortality rate associated with gas gangrene approaches 60%. Among the signs that predict a poor outcome are leukopenia, thrombocytopenia, hemolysis, and severe renal failure. Myoglobinuria is common and can contribute significantly to worsening of renal function. Frank hemorrhage may be present and is a harbinger of disseminated intravascular coagulation. Successful treatment of this life-threatening infection depends on early recognition and debridement of all devitalized and infected tissues. When extremities are involved, amputation is frequently indicated. The role of hyperbaric oxygen therapy has not been established (100% oxygen at 3 atm), but it may have a role early in the treatment of seriously ill patients (19,20). The mainstay of treatment is surgical debridement, and this should not be delayed. A less life-threatening form of this disease is known as clostridial cellulitis. In this process, the bacterial tissue invasion is primarily superficial to the fascial layer, without muscle involvement. *C. septicum* bacteremia is associated with underlying colon cancer or neutropenic enterocolitis (21). *C. sordelli* has been reported to cause rapidly progressive myonecrosis with fulminant shock syndrome, particularly in obstetric patients. Black tar heroin use has resulted in the outbreak of *C. botulism*, *C. tetani*, and *C. sordelli* in IV drug users.

Prompt recognition and treatment, as described earlier, can reduce the associated morbidity and mortality. High dose of penicillin G is the drug of choice. Protein synthesis inhibitors such as clindamycin when combined with penicillin has had considerable better efficacy than penicillin alone.

### Nonclostridial Myonecrosis

Nonclostridial myonecrosis encompasses at least five relatively distinct entities that differ from gas gangrene in their pathogenesis, clinical features, and bacteriology: streptococcal myositis  $\pm$  NF type 2 (see discussion under sect. "Necrotizing Fasciitis"), synergistic nonclostridial anaerobic myonecrosis  $\pm$  NF type 1 (see discussion under sect. "Necrotizing Fasciitis"), anaerobic streptococcal myonecrosis, *Ae. hydrophila* myonecrosis, and infected vascular gangrene.

Anaerobic streptococcal myonecrosis clinically resembles subacute clostridial gas gangrene. The involved muscles are discolored, in contrast to gas gangrene, early cutaneous erythema is prominent. If not treated, the infection progresses to gangrene and shock. The infection is usually mixed; anaerobic streptococci with group A *Streptococcus* or *S. aureus*. Treatment involves the use of high-dose penicillin and antistaphylococcal agent, if indicated, and surgical debridement.

Rapidly progressive myonecrosis resembling clostridial gangrene but caused by *Ae. hydrophila* may occur after injuries sustained in freshwater, or in conjunction with medicinal leech therapy. Cellulitis often develops within 12 to 24 hours, accompanied by excruciating pain, marked edema, and bullae. Bacteremia is often documented. Treatment requires prompt antimicrobial therapy and wide surgical debridement.

Infected vascular gangrene is a focal, usually indolent and primarily ischemic process in the small muscles of a distal lower extremity already gangrenous from arterial insufficiency. Diabetic patients are prone to develop this complication, which usually does not extend



beyond the area of vascular gangrene to involve viable muscle. *Proteus* spp., *Bacteroides* spp., and anaerobic streptococci are among the bacteria found in such lesions (11,62).

### **PYOMYOSITIS**

Pyomyositis is an infection of the skeletal muscle predominantly caused by *S. aureus* and *Streptococcus* spp. (63,64). Other rare organisms include Enterobacteriaceae and anaerobic bacteria. Case reports of *Aspergillus fumigatus*, *Cr. neoformans*, *M. tuberculosis*, and *M. avium-intracellulare* have been reported (65,66). It was originally recognized in patients who acquired the disease in the tropics. Predisposing condition includes diabetes mellitus, cirrhosis, immunosuppressive illness, and HIV, and has been reported in IV drug abusers. Presumed pathogenesis involves a prior bacteremia, commonly transient. Bacterial infection of the muscle usually occurs after a penetrating wound, vascular insufficiency, or a contiguous spread. Common muscle involvement includes deltoid, psoas, biceps, gastrocnemius, gluteal, and quadriceps, though any muscle group can be involved. Patients will typically present with fever, pain, tenderness, and swelling of the involved muscle. Bacteremia is present in 5% to 35% of cases. The diagnosis is best established by computed tomography scan or MRI.

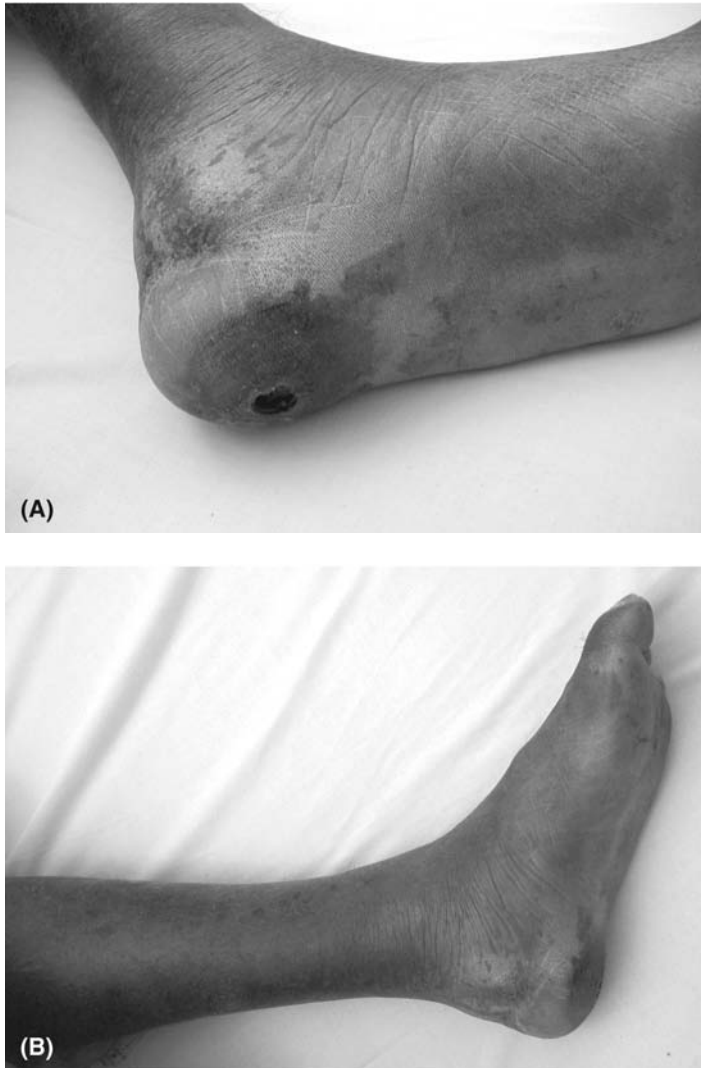
Treatment consists of drainage (percutaneous or open incision). Initial antibiotics today should consist of IV administration of vancomycin, linezolid, or daptomycin since MRSA should be suspected. Early modification of initial antimicrobial therapy is based on Gram stain and culture results.

### **DIABETIC FOOT INFECTION**

Defined as any inframalleolar infection in a person with diabetes mellitus. These include paronychia, cellulitis, myositis, abscesses, NF, septic arthritis, tendonitis, and osteomyelitis. The most common lesion requiring hospitalization is the infected diabetic foot ulcer (Fig. 7). Neuropathy plays a central role, with disturbances of sensory, motor, and autonomic functions leading to ulcerations due to trauma or excessive pressure on a deformed foot. This wound may progress to become actively infected, and by contiguous extension the infection can involve deeper tissues. This sequence can be rapid, especially in an ischemic limb. Various immunological disturbances, especially involving the polymorphonuclear leukocytes, may affect some diabetic patients. *S. aureus* and the  $\beta$ -hemolytic streptococci (groups A, C, G, especially group B) are the most commonly isolated pathogens. Chronic wounds develop a more complex colonizing flora including enterococci; Enterobacteriaceae; obligate anaerobes, *P. aeruginosa*; and other nonfermentative gram-negative rods (67–69). Hospitalization, surgical procedures, and prolonged antibiotics predispose patients to colonization and infection with MRSA or vancomycin-resistant *Enterococcus* (VRE). Community-acquired cases of MRSA are becoming more common. Finally, there have been at least two reported cases of vancomycin-resistant *S. aureus* (VRSA) involved a diabetic patient with a foot infection (70).

### **Therapy**

Initial therapy is empirical and should be based on severity of infection and available microbiological data, such as recent culture results or current smear findings from adequately obtained specimens. The microbiology can be identified by culture only if specimens are collected and processed properly. Deep tissue specimens, obtained aseptically at surgery, contain the true pathogens more often than do samples obtained from superficial lesions. A curettage or tissue scraping with a scalpel from the base of a debrided ulcer provides more accurate results. An antibiotic regimen should always include an agent active against staphylococci and streptococci. Previously treated or severe cases may need extended coverage that also includes commonly isolated gram-negative bacilli and *Enterococcus* spp. Necrotic, gangrenous, deep, or foul smelling wounds usually require antianaerobic therapy. For moderate to severe infection ampicillin/sulbactam or piperacillin/tazobactam can be used. For life-threatening infections imipenem/cilastin may be a consideration. A high prevalence of MRSA may require use of vancomycin or other appropriate agents against these organisms. The duration of treatment for life-threatening infection may be two weeks or longer. Many infections require surgical procedures that range from drainage and excision of infected and necrotic tissues to revascularization or amputation (for treatment refer to Table 3).



**Figure 7** (A) Limb-threatening left diabetic foot ulcer (B) Rapid progression to gas gangrene. Patient underwent below knee amputation. Operative cultures grew group G *Streptococcus*, MRSA, *Streptococcus viridans*, *Enterococcus* spp., and *Bacteroides fragilis*.

### SKIN AND SOFT TISSUE INFECTIONS IN INJECTION DRUG USERS

The mechanism by which infection is established probably relates to tissue trauma, direct effects of drugs, tissue ischemia, and inoculation of bacteria. As a result of repeated injections into a single site, skin and surrounding tissue are damaged, develop local ischemia and necrosis, and become susceptible to infection. Opiates suppress T-cell functions and also inhibit phagocytosis, chemotaxis, and killing by neutrophils and macrophages. Infection ranges from cellulitis to skin and soft tissue abscesses, and occasionally fasciitis and pyomyositis. The most common sites of involvement correspond to injection sites: the upper and lower extremities, the groin and antecubital fossa, with the microbiology being monomicrobial or polymicrobial, involving *S. aureus*, *Str. viridans*, *Str. pyogenes*, *Str. anginosus* group, *Ei. corrodens*; anaerobic organisms like *Clostridium* spp. and *Prevotella*; and gram-negative enteric organisms including *E. coli*, *Klebsiella*, *Proteus mirabilis*, *Pseudomonas*, and *Enterobacter* (71–73). Black tar heroin use has resulted in outbreaks of *C. botulism*, *C. tetani* and *C. sordelli* in IV drug users (74) (for treatment refer to Table 2).

## INFECTIONS IN THE IMMUNOCOMPROMISED HOST

Infections can be caused by either common bacteria or unusual bacteria, viruses, protozoa, helminthes, or fungi. Patients underlying immune status needs to be considered. Neutropenia is frequently associated with mucosal disruption, and the indigenous colonizing flora are responsible for most infections. Pathogens causing initial infections are usually bacterial, including both gram-positive and gram-negative organisms. Pathogens causing subsequent infections are usually antibiotic-resistant bacteria, yeast, or fungi. Acute disseminated candidiasis in neutropenic host can have an erythematous or hemorrhagic palpable rash, which is consistent with small vessel vasculitis (75). *Fusarium* sp. can begin as multiple erythematous macules, papules, and necrotic nodules. Primary cutaneous zygomycosis is seen with disruption of skin in immunocompromised patients and patients with burns or severe soft tissue trauma. It starts as erythema and induration of the skin at a puncture site and progresses to necrosis. In neutropenic patient's local necrosis, tissue infarction, vessel invasion, and dissemination can occur (76,77).

Patients with cellular immune deficiency are at increased risk of infection with *Mycobacterium*, which can manifest as cellulitis, painless nodules, necrotic ulcers, and abscesses. Bacillary angiomatosis (epithelioid angiomatosis), primarily involves the skin and visceral organs in patient with AIDS, is due to *Bartonella henselae* or *Bartonella quintana*. Lesions can occur as red papules or painful cutaneous nodules. Histologically, consist of circumscribed, lobular proliferation of capillaries lined with prominent large endothelial cells. Cutaneous *Nocardia* infection usually represents metastatic infection. Cutaneous *Cryptococcus* infection can appear as papules, nodules, pustules, or necrotic ulcers. Cutaneous manifestation of acute disseminated histoplasmosis are rare, and they appear as nonspecific maculopapular eruptions that may become hemorrhagic. Varicella zoster virus can cause dissemination complicated by secondary bacterial and fungal super infection. Herpes simplex virus lesions frequently coalesce and ulcerate. Skin and soft tissue infection can rarely be infected by parasites (*Strongyloides stercoralis*, *Sarcoptes scabiei*, *Acanthamoeba* sp., and *Balamuthia*).

Biopsy and culture of suspicious lesions frequently are necessary to diagnose these pathogens.

### Ecthyma Gangrenosum

Ecthyma gangrenosum is the classic skin lesion associated with *P. aeruginosa* infection in granulocytopenic patients (78–80) and has been reported in 2% to 28% of patients with *Pseudomonas* bacteremia. Rarely this lesion may be caused by other organisms including *S. aureus*, *Aeromonas*, *Serratia*, *Klebsiella*, *E. coli*, *Capnocytophaga*, *Aspergillus*, and *Candida*. Neutropenic patients with overwhelming septicemia develop a patchy dermal and subcutaneous necrosis. The characteristic skin lesion starts with erythematous macular eruptions that become bullous with central ulceration and necrosis. These are usually multiple occurring in different stages of development, which may concentrate on the extremities or the head and neck. Ecthyma gangrenosum is a cutaneous vasculitis caused by bacterial invasion of the media and adventitia of the vessel wall. Diagnosis of the etiological agent may occur with biopsy of the lesion being cultured or isolated from blood cultures. Treatment is primarily by administration of IV antimicrobial therapy and by debridement of multiple lesions, which may lessen the bacterial burden.

## SURGICAL SITE INFECTIONS

Incisional surgical site infections (SSIs) can be defined according to national nosocomial infection surveillance (NNIS) criteria (81). Superficial SSI involves only skin or subcutaneous tissue of the incision, and in addition SSI includes at least one of the following: (i) purulent drainage; (ii) isolation of an organism from the site; (iii) at least one of the following clinical findings: tenderness, redness, or heat along with incision and drainage by the surgeon; or (iv) diagnosis made by the surgeon or attending physician. Superficial SSI occurs within 30 days following surgery. Deep SSI is defined as infection involving fascial or muscle layers of the incision and accompanied by purulent drainage, spontaneous dehiscence, or intentional opening by a surgeon in a patient with fever, local pain, tenderness, abscess, or diagnosis by a physician. Deep SSI occurs within 30 days of surgery if no implant is left in

place or within one year in the presence of an implant and the infection appears to be related to the surgery.

Pathogenesis of SSI varies with the type of surgical procedure. Implicated pathogen is usually the patient's endogenous flora of patient's skin, mucous membranes, or hollow viscera. Gram-positive cocci (*S. aureus*, coagulase-negative staphylococci) from the patient's skin flora or exogenous environment is the usual pathogen following clean surgical procedure but may include anaerobes and gram-negative when incisions are made around the groin or perineum. Polymicrobial infections are often seen in clean-contaminated, contaminated or dirty wounds. Acute onset within 24 to 48 hours postoperatively or after trauma with systemic manifestation are usually due to *Streptococcus* and *Clostridium* sp. TSS due to *S. aureus* can occur in rare instances. Fever, hypotension, abnormality in renal, and liver function can occur. The primary treatment for most SSI is to open the incision and evacuate the infected material. Antibiotic therapy can be guided by findings of Gram stain and wound cultures (13,39).

## SYSTEMIC SYNDROMES

### Staphylococcal Scalded Skin Syndrome

SSSS, first described in 1956, is a generic term applied to a group of exfoliative dermatopathies caused by an exfoliative (or epidermolytic) exotoxin, produced by various strains of *S. aureus*; mainly of phage group II (usually type 71) (82–84). It primarily affects neonates and young children; although adults with underlying diseases are also susceptible. Two variants of the toxin, the exfoliative toxin A and B have been described. These exotoxins induce pathological changes in the epidermis that closely resemble a scald caused by boiling water, hence the name SSSS (85–87). Histologically, these toxins cause intraepidermal cleavage through the granular layer without damage or alteration of the keratinocytes, bullae formation; and slippage of the upper epidermal layer with the application of gentle pressure (a positive Nikolsky sign). *S. aureus* enterotoxin (A through D) and toxic shock syndrome toxin 1 (TSST-1) are frequently associated with staphylococcal scarlet fever. The clinical response to these exotoxins is varied. Thus, the manifestations of SSSS include several primarily age-dependent presentations: (i) a generalized exfoliative syndrome seen in newborns (Ritter's disease or Pemphigus neonatorum) and children, but can rarely develop in adults; (ii) bullous impetigo, a localized pustulosis in children; and (iii) staphylococcal scarlet fever, form of SSSS that does not progress beyond the initial stage of a generalized erythematous eruption.

SSSS occurs abruptly or few days after a recognized staphylococcal infection with fever, skin tenderness, and scarlatiniform rash. The lesions begin as a vesicle that gradually enlarges into flaccid bullae that rupture, leaving a tender, moist surface that eventually heals. Localized infection occurs usually in the nasopharynx, umbilicus, or urinary tract. Large flaccid clear bullae form over two to three days and result in separation of sheets of skin. Exfoliation exposes large area of bright red skin surface (88,89). Fluid and electrolyte loss can lead to hypovolemia and sepsis syndrome. In adults the mortality rate approaches 60% (90). With appropriate therapy the lesions heal within two weeks. Toxic epidermal necrolysis (TEN) typically occurs as a drug reaction. The lesions are similar to SSSS, however it has more extensive destruction of the epidermis and the stratum corneum layer, recovery is prolonged, and scarring is more frequent. TEN is often fatal and should be treated like a widespread burn. Most cases of SSSS are diagnosed on clinical grounds and are easily treated with antibiotics, which rapidly eliminate the staphylococci producing the toxin. Laboratory investigations are required only if the clinical findings are equivocal or when outbreaks occur. Because the condition is the result of exotoxins that may be produced by staphylococci at a distant site, the blister fluid in generalized SSSS tends to be sterile, whereas the fluid in localized bullous impetigo will contain *S. aureus*. Staphylococci producing ET can usually be cultured from the nares, conjunctiva, or nasopharynx. Biopsy of the blister is one of the most definitive diagnostic tests in SSSS. One study revealed a positive blister biopsy result with intraepidermal cleavage in all 30 adults with SSSS (89). Blood cultures are usually negative because the organisms are frequently noninvasive, particularly in children. In one study, only 3% of children had a positive blood culture, in contrast to 20 (62.5%) of 32 adults (86,89,91–93).

### Treatment

Severe forms require more aggressive treatment with IV antistaphylococcal antibiotics and extra care of denuded skin to prevent secondary infection, fluid losses, and to maintain body temperature, especially in neonates. In methicillin-sensitive strains (methicillin-susceptible *S. aureus*, MSSA), a penicillinase-resistant penicillin nafcillin or oxacillin (2 g IV every 4–6 hours) is the drug of choice. Cefazolin (1–2 g IV every 8 hours) is an alternative treatment that can also be used in patients with histories of delayed-type penicillin allergy. In methicillin-resistant strains (MRSA) vancomycin (1 g or 15 mg/kg IV every 12 hours), trimethoprim/sulfamethoxazole (320/1600 IV every 12 hours), linezolid (600 mg IV or orally every 12 hours), and other agents like daptomycin (4 mg/kg/day IV) for skin and soft tissue infections (6 mg/kg/day IV for severe infections), tigecycline (100 mg IV initial dose followed by 50 mg IV every 12 hours), quinupristin-dalfopristin (7.5 mg/kg IV every 8 hours), and telavancin (10 mg/kg IV every 24 hours) are treatment options (94,95). Telavancin, linezolid, daptomycin, tigecycline, and quinupristin-dalfopristin can be used for vancomycin-intermediate *S. aureus* (VISA). For VRSA strains testing should be performed (96,97). Oritavancin, dalbavancin, ceftobiprole, and ceftaroline are newer agents under development for treatment of resistant strains (97).

### Toxic Shock Syndrome

TSS is a rapid-onset illness causing fever, hypotension, rash, multiple organ system dysfunctions, and desquamation. Infection with *S. aureus* produces classical TSS, whereas *S. pyogenes* causes a modified form of TSS known as either streptococcal TSS or toxic shock-like syndrome (TSLs). TSLs displays many of the typical TSS symptoms with the addition of severe soft tissue necrosis (98). Diagnosis of TSLs caused by streptococci is based on a constellation of clinical and laboratory signs as proposed by the Centers for Disease Control and Prevention (Table 4) (99,100). There are two clinical forms of TSS: menstrual TSS and nonmenstrual TSS. Menstrual TSS starts within three days of the beginning or end of menses and is primarily associated with the use of high absorbency tampons. Clinical signs include high fever, capillary leak syndrome with hypotension and hypoalbuminemia, generalized nonpitting edema, and a morbilliform rash, followed by desquamation after a few days. TSST-1 and

**Table 4** Streptococcal Toxic Shock Syndrome: Clinical Case Definition (CDC)

An illness with the following clinical manifestations occurring within the first 48 hr of hospitalization or, for a nosocomial case, within the first 48 hr of illness:

Hypotension defined by a systolic blood pressure  $\leq 90$  mmHg for adults or less than the fifth percentile by age for children aged  $< 16$  yr. Multiorgan involvement characterized by two or more of the following:

*Renal impairment:* Creatinine  $\geq 2$  mg/dL ( $\geq 177$   $\mu$ mol/L) for adults or greater than or equal to twice the upper limit normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.

*Coagulopathy:* Platelets  $\leq 100,000/\text{mm}^3$  ( $\leq 100 \times 10^6/\text{L}$ ) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products

*Liver involvement:* Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level.

*Acute respiratory distress syndrome:* Defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia

A generalized erythematous macular rash that may desquamate. Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

#### Laboratory criteria for diagnosis

- Isolation of group A *Streptococcus*

#### Case classification

Probable: A case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A *Streptococcus* from a nonsterile site

Confirmed: A case that meets the clinical case definition and with isolation of group A *Streptococcus* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid)

Source: Adapted from Ref. 99.

**Table 5** Toxic Shock Syndrome: Clinical Case Definition (CDC)

An illness with the following clinical manifestations:

*Fever:* Temperature  $\geq 102.0^{\circ}\text{F}$  ( $\geq 38.9^{\circ}\text{C}$ )

*Rash:* Diffuse macular erythroderma

*Desquamation:* 1–2 wk after onset of illness, particularly on the palms and soles

*Hypotension:* Systolic blood pressure  $\leq 90$  mmHg for adults or less than fifth percentile by age for children aged  $< 16$  yr; orthostatic drop in diastolic blood pressure  $\geq 15$  mmHg from lying to sitting, orthostatic syncope, or orthostatic dizziness

*Multisystem involvement* (three or more of the following):

*Gastrointestinal:* Vomiting or diarrhea at onset of illness

*Muscular:* Severe myalgia or creatine phosphokinase level at least twice the upper limit of normal

*Mucous membrane:* Vaginal, oropharyngeal, or conjunctival hyperemia

*Renal:* Blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria ( $\geq 5$  leukocytes per high-power field) in the absence of urinary tract infection

*Hepatic:* Total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory

*Hematological:* Platelets  $< 100,000/\text{mm}^3$

*Central nervous system:* Disorientation or alterations in consciousness without focal neurological signs when fever and hypotension are absent

#### Laboratory criteria

Negative results on the following tests, if obtained:

Blood, throat, or cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*). Rise in titer to Rocky Mountain spotted fever, leptospirosis, or measles

#### Case classification

*Probable:* A case that meets the laboratory criteria and in which four of the five clinical findings described above are present

*Confirmed:* A case that meets the laboratory criteria and in which all five of the clinical findings described above are present, including desquamation, unless the patient dies before desquamation occurs

*Source:* Adapted from Ref. 99.

staphylococcal enterotoxins are the paradigm of a large family of pyrogenic exotoxins called superantigens (SAGs). For nonmenstrual TSS, the offending pathogen can virtually colonize any site in the body (101–104). Recurrent menstrual TSS is a well-described phenomenon (105,106). Two conditions are required for recurrence of TSS: persistent colonization with a toxigenic strain of *S. aureus* and persistent absence of neutralizing antibody. Recurrent TSS develops exclusively among patients who fail to develop a humoral immune response to the implicated staphylococcal toxin (107). Diagnosis of TSS is based on a constellation of clinical and laboratory signs as proposed by the Centers for Disease Control and Prevention (Table 5) (99).

In the late 1980s, a disease similar in appearance to TSS, yet caused by invasive streptococci, was recognized and referred to as “toxic strep,” “streptococcal TSS,” or “STSS”. This condition was found to share many clinical features with TSS. M types 1, 3, 12, and 28 have been the most common isolates from patients with shock and multiorgan failure (108,109). In the majority of cases toxin-producing group A streptococci have been isolated, with streptococcal pyrogenic exotoxin A (Spe-A) production being most closely linked with invasive disease. However, group A streptococci producing streptococcal pyrogenic exotoxin B (Spe-B), streptococcal pyrogenic exotoxin C (Spe-C), streptococcal SAG, and mitogenic factor, as well as non-group A streptococci have been found to be causative in individual cases of STSS as well. Similar to classic TSS, the clinical signs of STSS are postulated to be mediated by massive cytokine release (primarily TNF- $\alpha$ , IL-1b, and IL-6) as a result of toxin/superantigen activity; in addition, streptolysin O, produced by 100% of streptococcal strains associated with STSS, has also been shown to cause TNF- $\alpha$  and IL-1  $\beta$  production and has been demonstrated to act synergistically with Spe-A (110–115). Very young, elderly, diabetic, or immunocompromised persons are more susceptible to the acquisition of invasive streptococcal infection such as STSS. However, the majority of cases of STSS have occurred in young, otherwise healthy persons between 20 and 50 years of age. An absence of protective immunity is postulated as

a potential risk factor in this population. STSS has also been well described as a complication of wounds, varicella, and influenza A. A controversial association of invasive group A streptococcal infections such as STSS with prior NSAIDs use has been suggested (116). The link has been proposed to be depression of the cellular immune response by NSAIDs. Clinically, STSS shares many features with TSS. Fever, hypotension, myalgias, liver abnormalities, diarrhea, emesis, renal dysfunction, and hematological abnormalities may be present in TSS caused by either staphylococci or streptococci. Diffuse macular erythroderma likewise is frequently present in disease caused by both bacteria and is often accompanied by mucous membrane findings, such as conjunctival injection and delayed desquamation of palms and soles.

Nonetheless, certain important differences exist between STSS and TSS. The skin is often the portal of entry in STSS, with soft tissue infections developing in 80% of patients (108). The initial presentation of STSS is often localized pain in an extremity, which rapidly progresses over 48 to 72 hours to manifest both local and systemic signs of STSS. Cutaneous signs may include localized edema and erythema, a bullous and hemorrhagic cellulitis, NF or myositis, and gangrene. Soft tissue involvement of this nature is distinctly uncommon in staphylococcal TSS.

Blood cultures are positive in 60% of patients with STSS (108), compared with less than 3% in TSS. Mortality in streptococcal TSS is between 30% and 80%, whereas in staphylococcal TSS ranges from 3% to 5% (117,118).

#### *Treatment*

Group A *Streptococcus* is susceptible to penicillin and other  $\beta$ -lactam antibiotics in vitro; however clinical treatment failure occurs when penicillin is used alone in severe group A *Streptococcus* infections (119). This may be attributed to the large inoculum size, the so-called Eagle effect (120,121). These large inocula reach the stationary growth phase very quickly. Penicillin and other  $\beta$ -lactam antibiotics are ineffective in the stationary growth phase because of reduced expression of penicillin-binding proteins in this phase. Moreover, toxin production is not inhibited by  $\beta$ -lactam antibiotics during the stationary growth phase. The greater efficacy of clindamycin is multifactorial, it inhibits protein synthesis, and its efficacy is unaffected by inoculum size or the stage of bacterial growth. Clindamycin also suppresses synthesis of penicillin-binding proteins and has a longer post antibiotic effect than  $\beta$ -lactam antibiotics. Lastly, clindamycin causes suppression of LPS-induced monocyte synthesis of TNF (121–124). Prompt antimicrobial therapy with high-dose penicillin and clindamycin should be instituted. Suppression of STSS toxin has been demonstrated in vitro with linezolid (125). Aggressive fluid resuscitation is needed because of intractable hypotension and diffuse capillary leak. Human polyspecific intravenous IgG (IVIG) has been suggested as a potential adjunctive therapy for invasive group A streptococcal diseases mainly because of its ability to neutralize a wide variety of superantigens and to facilitate opsonization of streptococci. An observational cohort study of IVIG in patients with STSS reported decreased mortality rates in patients treated with IVIG compared with controls (67% vs. 34%) (126). A double-blind placebo trial was prematurely terminated because of slow recruitment. Analysis of the primary end point revealed a reduced mortality in IVIG-treated group compared with placebo-treated patients (10% vs. 36%), though statistical significance was not achieved. A significant increase in plasma-neutralizing activity against superantigens expressed by autologous isolates was noted in the IVIG group after treatment (127). If IVIG is to be used, it should be given early and more than one dose should be used, because batches of IVIG have variable neutralizing activity (128). In addition, prompt surgical exploration and debridement of deep-seated streptococcal infection should be performed (see discussion under sect. "Necrotizing Fasciitis").

For management of TSS, antistaphylococcal agents are selected with consideration of susceptibility testing. Supportive care includes aggressive IV fluid resuscitation and vasopressors as needed. The suspected focus of infection requires specific attention. Specifically, management includes the removal of any vaginal device in menstrual cases and the removal of packed dressings in conjunction with drainage and debridement in cases associated with postsurgical wounds.

### Purpura Fulminans

Purpura fulminans is an acute illness most commonly associated with meningococemia but also seen with pneumococcal or staphylococcal disease (129,130). It is typically characterized by disseminated intravascular coagulation (DIC) and purpuric skin lesions. The sharply demarcated purpuric lesions are often symmetrical, often on distal extremities, and evolve into bullae filled with serous fluid, ultimately leading to skin necrosis. Skin changes are thought to result from disseminated intravascular coagulation or due to protein c and s deficiency (131).

There are four primary features of this syndrome: large purpuric skin lesions, fever, hypotension, and DIC. However, five cases associated with *S. aureus* strains have been reported from the Minneapolis-St. Paul, Minnesota metropolitan area. These strains produced high levels of TSST-1, staphylococcal enterotoxin serotype B (SEB), or staphylococcal enterotoxin serotype C (SEC). Only two of the five patients survived (132). Staphylococcal purpura fulminans may be a newly emerging illness associated with superantigen production. There are no specific guidelines for the therapeutic management of this serious manifestation other than assuring that antistaphylococcal agents is selected with consideration of susceptibility testing.

### COMMUNITY-ACQUIRED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

CA-MRSA has become increasingly endemic in many parts of the world (133–135). In the mid-1990s, MRSA began to be detected in the community in persons who did not have contact with the health system. In a study of adult patients with acute, purulent skin and soft tissue infections presenting to 11 university-affiliated emergency departments the overall prevalence of MRSA were 59% (136).

The most common clinical syndrome has been skin and soft tissue infections with abscesses and cellulitis being most frequent (Fig. 8). CA-MRSA may have evolved from community-associated MSSA clones that possessed the genes for Panton-Valentine-leukocidin (PVL) toxin. The organism appears somewhat unique in its characteristics by possessing the MEC IV gene for methicillin resistance and the PVL genes encoding for a toxin presumably responsible for necrosis. In the United States, a single clone of CA-MRSA (USA 300) has become the most prevalent strain (137,138). Several emerging clinical syndromes have been described with CA-MRSA including NF, septic thrombophlebitis, and pyomyositis. CA-MRSA can produce systemic syndromes affecting the skin, such as STSS, Waterhouse-Friderichsen syndrome, and purpura fulminans (139). In a study by Miller et al., 14 patients were identified as CA-MRSA with clinical and intraoperative findings of NF, necrotizing myositis, or



**Figure 8** Right leg abscess, cultures grew MRSA (community acquired).



both (140). Characteristics of CA-MRSA include a lack of hospital-associated risk factors, susceptibility to many non- $\beta$ -lactam antibiotics, distinct genotypes, and distinct genetic determinants of virulence. Numerous reports have suggested the easy transmission CA-MRSA in settings where people are in close contact. These settings include household, day care centers, military installation and jails. Other groups reported to be at increased risk for CA-MRSA infection includes, athletes, Native Americans, Pacific Islanders and men who have sex with men (139,141).

This organism has prompted many clinicians to add vancomycin, linezolid, daptomycin, tigecycline, or other agents effective against MRSA in the empiric treatment of severe skin and soft tissue infections. On November 19, 2008, the FDA advisory board recommended telavancin to be approved for the treatment of skin and soft tissue infections caused by *S. aureus* including MRSA. Telavancin is a lipoglycopeptide (10 mg/kg/day), which is bactericidal against MRSA (142). In phase 3 studies in patients with skin and soft tissue infection it showed noninferiority compared with vancomycin (90% vs. 85%). Most strains of MRSA in this study were MRSA and SCC mec type IV and PVL positive (139,143).

With CA-MRSA there has been increasing use of trimethoprim/sulfamethoxazole, clindamycin, and long-acting tetracyclines. In a randomized control trial for efficacy of trimethoprim/sulfamethoxazole or vancomycin, all patients with *S. aureus* skin infection were cured (95). Clindamycin and linezolid have the ability to inhibit protein synthesis and to turn off toxin production in MRSA. Inducible resistance to clindamycin can be detected by a D-zone test, which some investigators feel should be performed on all isolates of CA-MRSA.

Dalbavancin, oritavancin, ceftobiprole, ceftaroline, and iclaprim are investigational drugs effective against MRSA. Dalbavancin is a semisynthetic bactericidal lipoglycopeptide with a long half-life compatible with weekly doses (1000 mg on day 1 followed by 500 mg on day 8). Oritavancin (1.5–3 mg/kg/day) is a bacteriocidal glycopeptide. In one study cure rates were 74% versus 80% for oritavancin and vancomycin. Ceftobiprole is a broad-spectrum third-generation cephalosporin. In phase 3 study comparing with vancomycin cure rates were 91.8% for ceftobiprole and 90% for vancomycin (144). Iclaprim, a selective dihydrofolate inhibitor, and ceftaroline, a new cephalosporin, are other investigational drugs effective in vitro against MRSA. Surgical drainage is crucial for abscess, and debridement or fasciotomy for necrotizing infections needs to be considered.

## SUMMARY

A wide variety of skin and soft tissue infections can occur in the critical care settings. The rise in immunocompromized patients such as those with AIDS, transplant recipients, and those receiving chemotherapy or prolonged corticosteroid therapy have led to diverse etiologies, clinical manifestations, and severity. *S. aureus* remains the most common pathogen causing infections from minor skin lesions to severe life-threatening illness such as purpura fulminans. CA-MRSA has become increasingly prevalent in many parts of the world. However, a variety of other pathogens may be identified and need to be considered with certain epidemiological clues. Important considerations when evaluating patients include underlying medical conditions; exposure history; presenting signs, symptoms, and radiographic patterns. It is important to discriminate between infectious and noninfectious etiology of skin and soft tissue inflammation. The key to treating serious skin and soft tissue infections successfully is prompt recognition, followed by appropriate antibiotic and surgical intervention as needed to decrease the morbidity and mortality.

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# 18 Tropical Infections in Critical Care

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## INTRODUCTION

It is a familiar and captivating scenario: an exotic infection acquired abroad developing within a returning traveler. Sometimes symptoms begin as early as on the plane ride home, sometimes not until weeks later. In either case, the patient becomes progressively ill, critically so, all the while unknowingly infecting others. The disease spreads, chaos is loosed, and only the timely insight of an awkwardly introverted yet surprisingly attractive physician stands between armageddon and the return of normalcy. In reality, travel medicine is rarely so dramatic. Nonetheless, the likelihood of today's critical care physician having to manage patients with a tropical infection is increasing, as international travel has increased from an estimated 25 million border crossings in 1950 to over 806 million crossings in 2005 (1).

To better prepare travelers prior to their trips abroad, the discipline of travel medicine has been refined over the past 25 years, with an increasing reliance upon evidence-based data and the recent publication of practice guidelines (2). This information assists the physician in determining not only what vaccines or prophylactic regimens may help prevent infection in the traveler, but also stresses the importance of safety awareness and environmental risk avoidance. Unfortunately, the International Society of Travel Medicine (ISTM) suggests that of all travelers, only 8% will seek pretravel medical advice, and recommendations received may be incomplete or inaccurate (3). It is no surprise, then, that each year four million travelers returning from developing countries become ill enough that medical intervention is required either en route or upon return home (4). That is not to say there are four million cases of Ebola or African trypanosomiasis every year, but how can the clinician know what illnesses are being seen, and more importantly, which to consider more likely in their patients? Best available data comes from the GeoSentinel global surveillance network of the ISTM and the Centers for Disease Control (CDC) (5). Established in 1995, it now comprises 41 travel or tropical medicine clinics (16 in the United States, 25 in other countries representing all continents) that not only report what diagnoses are seen in their facilities, but additional invaluable data such as time to presentation of illness, geographic exposures, adherence to prophylactic measures, etc.

With now more than a decade of surveillance information available, it has been shown that febrile illness, dermatologic disorders (especially insect bites), and acute/chronic diarrheal illnesses comprise almost 70% of all travel-related illness (4). An analysis of 6957 travelers with fever revealed that malaria (21%), acute diarrheal disease (15%), respiratory illness (14%), and dengue (6%) were the most commonly identified etiologies (6). In a notable 22% of cases, no etiology was identified. While most patients present within one month of travel, 10% suffer

**Table 1** Fever in a Returned Traveler, Time to Presentation

<2 wk	2–6 wk	>6 wk
Malaria	Malaria	Malaria
Dengue	Typhoid fever	Tuberculosis
Rickettsial illness	Hepatitis A, E	Hepatitis B, E
Leptospirosis	Katayama fever	Visceral leishmaniasis
Typhoid fever	Amebic liver abscess	Lymphatic filariasis
East African trypanosomiasis	Leptospirosis	Schistosomiasis
Acute HIV	Acute HIV	Amebic liver abscess
VHF	East/West African trypanosomiasis	Chronic mycoses
Acute bacteremia		Rabies
Acute diarrheal illness	Viral hemorrhagic fever	West African trypanosomiasis
Rabies	Q fever	
Arboviral encephalitis		
Polio		
Angiostrongyliasis		
Influenza		
Legionellosis		
Histoplasmosis		
Coccidioidomycosis		
Q fever		

*Abbreviations:* HIV, human immunodeficiency virus; VHF, viral hemorrhagic fever.

*Source:* Adapted from Ref. 7.

more indolent processes or infections of longer incubation, and do not present until six months or later. Time to presentation can be helpful to the clinician when generating a differential diagnosis (see Table 1).

It is helpful to realize that the familiar adage “common things are common” applies also to travel medicine. In a review of 25,023 patients within the GeoSentris database, there were no reported cases of travel-related anthrax, yellow fever, primary amebic meningoencephalitis, poliomyelitis, Rift Valley fever, tularemia, murine typhus, tetanus, diphtheria, rabies, Japanese encephalitis, or Ebola (4). In the same report, of 17,353 patients, only one case each of the following infections was identified: *Angiostrongylus cantonensis*, hantavirus, cholera, melioidosis, Ross River virus, legionellosis, meningococcal meningitis, and African trypanosomiasis. If any of these diagnoses is suspected, an infectious diseases consultation is recommended. As malaria is the single most common life-threatening infection in returning travelers (Table 2), it will be emphasized in this chapter. Other critical care infectious disease syndromes to be

**Table 2** General Considerations in Potentially Infected Critically Ill Returning Travelers

Diagnostic consideration	Comments
Make accurate traveler- and itinerary-specific risk assessment.	Obtain detailed history of sites visited, activities, and potential infectious exposures.
Calculate approximate incubation period.	<i>Incubation periods:</i> short (<10 days); intermediate (10–14 days); prolonged (>21 days) A minimum period of 5–7 days before considering malaria. Incubation period exceeding 3 wk rules out arboviral etiologies.
Avoid narrow focus on “tropical infections.”	Avoid becoming so focused on the international travel history that common community-acquired infections such as pneumococcal pneumonia, staphylococcal infections, etc. are not considered.
Use concomitant signs and/or symptoms.	Narrow the differential diagnosis using clinical progression and specific findings (i.e., diarrhea, rash, or respiratory complaints).
Rule out malaria.	Always consider and perform diagnostic testing to evaluate for malaria if a traveler has been in a malarious region with an appropriate incubation period.



discussed include: severe pneumonia or adult respiratory distress syndrome (ARDS), coma and meningoencephalitis, acute abdomen, dysentery and severe gastrointestinal fluid losses, fulminant hepatitis, and tropical fever.

## MALARIA

Malaria is caused by four different species of the plasmodium parasite (*Plasmodium falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*), with *P. falciparum* as the predominant cause of mortality (8). Data from 1997–2002 collected through the GeoSentinel global sentinel surveillance identified malaria in 3.7% of all returning travelers seeking medical care (9). The majority of the cases were caused by *P. falciparum* (60%) followed by *P. vivax* (24%) (9). Patients with falciparum malaria were more likely to have traveled to sub-Saharan Africa (89%), with the majority (80%) presenting within four weeks of their return. Among patients with *P. falciparum* malaria, 60% were hospitalized with 2.4% diagnosed with cerebral malaria and 2.3% with severe complicated noncerebral malaria. There was a 9% case fatality rate among those with severe malaria. The case fatality rate for US travelers with falciparum malaria from 1966–1987 was 3.8% (10), and for 1985–2001 was 1.3% (11). Several important features are noted among those patients who died from their infection. These include: insufficient or inappropriate malaria chemoprophylaxis (90%) and delay in diagnosis and/or effective therapy (40%). Both features highlight the preventable aspect of these deaths (10). In a more recent series, cerebral malaria was the most common complication (48%) followed by renal failure (44%), acute respiratory distress (32%), anemia (21%), disseminated intravascular coagulation (DIC) (11%), and splenic rupture (5%) (11). Deaths were considered preventable in 85% of cases and were commonly attributed to patient-related decisions/actions and/or contributing medical errors (11). In 2006, 1564 cases of malaria diagnosed within the United States were reported to the Centers for Disease Control (CDC) (12). Diagnoses included: *P. falciparum* (39.2%), *P. vivax* (17.6%), *P. malariae* (2.9%), *P. ovale* (3.0%), two or more species (0.6%), and unreported or undetermined (36.6%). Six of the infections were fatal and were caused by *P. falciparum* (5) or *P. malariae* (1).

The current recommendations for malaria prophylaxis take into consideration regional antimalarial drug resistance (13). There is no universally effective regimen, as evidenced by *P. falciparum* mefloquine resistance on the Thai-Burmese and Thai-Cambodian borders, falciparum malaria in US troops in Somalia despite their prophylaxis with doxycycline or mefloquine, and reports of chloroquine-resistant *P. vivax* in Indonesia (14–18). And so, as a result of our population's increasing travel to malaria-endemic areas as well as oftentimes inadequate adherence to prescribed chemoprophylaxis, it is increasingly likely that today's critical care physician will encounter patients with malaria. How then, does one make this critical diagnosis in a timely manner?

Unfortunately, there are no historical or physical findings pathognomonic for malaria. Therefore, malaria cannot be ruled out by history or physical examination alone (11,19,20). Falciparum malaria often presents without the classic features of cyclical fever, chills, and diaphoresis (21). More common, is a nondescript febrile illness without apparent pattern. Other presenting features may include severe anemia, thrombocytopenia, central nervous system (CNS) dysfunction, such as coma or seizures, and pulmonary edema (13,22).

When the diagnosis of malaria is suspected, examination of Giemsa or Wright-stained peripheral blood thick and thin smears should be performed. Thick smears are more sensitive (larger volume of blood), but are also more difficult to interpret. Thin smears aid in species identification, and higher percentage parasitemias may be evident even to the novice. Nonetheless, peripheral smears are best reviewed by experienced microscopists. Because nonimmune persons may be symptomatic even at very low parasitemia levels, CDC guidelines recommend at least three peripheral blood smears (with smears repeated every 12 to 24 hours for a duration of 48 to 72 hours) (23). In 2007, the US Food and Drug Administration (FDA) approved a rapid assay for the diagnosis of malaria (Binax Now<sup>®</sup> Malaria Test, an ELISA-based assay with both global plasmodium and *P. falciparum*-specific antibodies adsorbed to a test card). Venous blood or blood from a peripheral stick is applied to the test card, and within 15 minutes a negative or positive result is apparent. However, serial thick and thin smears are still recommended (although a negative rapid assay, even if falsely negative, likely excludes significant parasitemia). A positive assay should also be followed by examination of the

peripheral smear for confirmation and in order to determine both the species (possibly more than one) and the level of parasitemia. Nonmicroscopic immunochromatographic tests such as the Binax Now<sup>®</sup> Malaria Test assay are rapid and simple to perform. However, they may not detect low parasitemias (<100 parasites/ $\mu$ l), and require microscopic confirmation (24). Parasite density is clinically significant, as a quantitative relationship exists between the level of falciparum parasitemia and mortality (<25,000 parasites/ $\mu$ l = 0.2% mortality; 25,000–100,000 parasites/ $\mu$ l = 1.1% mortality; 100,000–500,000 parasites/ $\mu$ l = 14.8% mortality and >500,000 parasites/ $\mu$ l = 72% mortality) (25). As a frame of reference for the reader, 100,000 parasites/ $\mu$ l = 1% parasitemia.

The successful outcome of the patient with malaria relies upon prompt recognition and initiation of effective therapy with a blood schizonticide to rapidly reduce parasitemia (26). For those patients with *P. falciparum* malaria acquired in Central America, Haiti, the Dominican Republic, and parts of the Middle East, oral or intravenous chloroquine may be sufficient. However, monotherapy should only be used in areas where treatment efficacy has been recently demonstrated and not for severe malaria (15,27). Severe malaria is a medical emergency manifested by prostration, impaired consciousness/coma, respiratory distress (acidotic breathing), convulsions, circulatory collapse, pulmonary edema, acute respiratory distress syndrome, abnormal bleeding, jaundice, severe anemia, acute renal failure, DIC, acidosis, hemoglobinuria, and/or parasitemia >5% (28). Parenteral therapy is recommended due to erratic absorption through the GI tract (29). Currently available treatments include cinchona alkaloids [quinine dihydrochloride (IV/IM) or quinidine gluconate (IV only)] or artemisinin derivatives [artesunate (IV) or artemether (IM)] (26,28).

### Quinidine Gluconate

The only drug licensed in the United States for IV antimalarial therapy is quinidine gluconate, which is typically used in combination with a second blood schizonticide (doxycycline, tetracycline, or clindamycin) for radical cure (30). Unless the patient has received more than 40 mg/kg of quinine in the preceding 48 hours or has received mefloquine within the preceding 12 hours, a loading dose of quinidine is used to rapidly attain effective drug levels (31). Because quinidine use is associated with QRS widening and QTc prolongation, cardiac monitoring is advisable. Hypotension and hypoglycemia are also associated with quinidine use. A transition to oral therapy can be considered once the parasite density is <1% and the patient can tolerate oral medications (quinidine course = seven days if infection was acquired in southeast Asia, three days if infection was acquired in Africa or South America). The second drug (doxycycline/tetracycline/clindamycin) should continue for a total of seven days.

### Artemesinins

This class of drug is not yet approved by the US FDA. However, because of their ability to rapidly reduce levels of parasitemia (artemesinins are active against all of the erythrocytic stages of the malaria parasite, including gametocytes), tolerability, and limited resistance, artemesinins are recommended by the World Health Organization (WHO) as first-line therapy for uncomplicated malaria (32). In the management of severe malaria, artesunate is easier and safer to use than quinine (33). A Cochrane review of the literature comparing artesunate with quinine for the treatment of severe malaria concluded that in adults, treatment with artesunate was associated with reduced parasite clearance time and significantly reduced risk of death (relative risk, 0.62) (34). With evidence accumulating that artesunate may be superior to quinine, the CDC issued guidance for its use by clinicians within the United States under an investigational new drug (IND) protocol. To qualify for the protocol, patients must have severe malaria and one of the following conditions must apply: (1) artesunate is more available than quinidine (if the drugs are equally available, consultation with the CDC will help decide which drug to use); (2) the patient has experienced quinidine failure or intolerance; or (3) use of quinidine is contraindicated. To increase the availability of artesunate, the CDC has stockpiled the drug in depots throughout the country. For details of the protocol, approval for use, and a supply of the investigational drug on a free and emergent basis, health care providers can telephone the CDC Malaria Hotline at 770-488-7788, Monday to Friday, 8 a.m. to 4:30 p.m., eastern time. At other times, clinicians should telephone 770-488-7100 and ask to speak with a

CDC malaria branch clinician. Once approved, four equal doses of artesunate will be provided over a three-day period, with the remainder of the seven-day therapy to be completed with a supplemental antimalaria drug such as doxycycline, clindamycin, mefloquine, or atovaquone-proguanil (35).

Although there is no randomized controlled trial demonstrating efficacy or survival benefit over chemotherapy alone, exchange transfusion is occasionally used for severe malaria when parasitemia levels exceed 10% or if the patient has altered mental status, non-volume overload pulmonary edema or renal complications (36,37). It is usually continued until the parasite load is <1% (usually 8 to 10 units). IV quinidine or artesunate should not be delayed for an exchange transfusion and can be given concurrently. Controlled trials of adjunctive corticosteroid use has shown not only a lack of efficacy, but deleterious effects in patients with severe malaria (38). Renal failure and/or lactic acidosis can contribute to life-threatening metabolic acidosis in patients with severe malaria, and hemofiltration is associated with lower mortality than peritoneal dialysis in these patients (39).

Early recognition and prompt therapy of patients with complicated malaria is critical to successful outcome. All patients with severe or complicated malaria should be managed in an intensive care setting. Proposed criteria for ICU admission include: base excess < -8, high-level parasitemia (non-endemic area > 10% and endemic area > 20%), Glasgow Coma Score < 8, blood glucose < 2.2 mmol/L, urine output < 0.5 mL/kg/h, or pulmonary edema (29). Close clinical monitoring with special attention to the following is recommended: (1) clinical improvement within 48 to 72 hours; (2) thick and thin smears prepared every 12 hours; (3) parasitemia reduced by 75% within 48 hours. Failure to show clinical or microscopic resolution suggests one or more of the following: (1) secondary complications such as bacterial superinfection [observed in 14% of returning travelers with severe malaria (40)]; (2) problems with medication administration; and (3) antimalarial resistance.

## CRITICAL CARE INFECTIOUS DISEASE SYNDROMES

### Severe pneumonia or ARDS

Among travelers, respiratory tract infections comprised only 8% of all infections reported to GeoSentinel from 1997–2001 (41). For severe pneumonia or infection-related ARDS acquired within the United States, the most common etiologies are community-acquired respiratory pathogens such as *Streptococcus pneumoniae* and *Legionella pneumophila* or as a complication of bacterial sepsis with other pathogens (42,43). However, the differential diagnosis of potential pathogens is broader if the patient is a returned traveler.

The WHO estimates that one-third of the world's population is currently infected with TB, and that prevalence increases by greater than 85,000 new infections each day (44). It is not clear how many travelers acquire this infection abroad. One Dutch study that evaluated travelers to countries where the population faces at least a 1% risk of TB infection annually, found the overall incidence of new TB infection was 3.5 per 1000 person-months of travel (approaching that of the local populations in endemic areas) (45).

It is helpful for the critical care physician to recall not only the high prevalence of TB world-wide, but the variable presentation of this infection, which may include pulmonary infiltrate with hypoxia and hemoptysis, exudative pleural effusion, miliary, even disseminated disease (46–48). A fulminant presentation of miliary TB may occur in both adults and in children, with as many as two-thirds of the latter cases complicated by meningeal involvement (46,47). The clinical presentation of severe tuberculous pneumonia may be indistinguishable from other causes of bacterial pneumonia. Miliary TB has a nonspecific presentation, including fever, tachypnea, rales, and altered mental status and, less commonly, ARDS and DIC.

With mortality rates of miliary TB as high as 21%, airborne precautions, aggressive diagnostic evaluation (acid-fast staining of sputum, bronchial washings, etc.), and early initiation of an empiric multidrug antituberculous regimen (e.g., isoniazid, rifampin, pyrazinamide, and ethambutol/streptomycin) (49,50) should be considered whenever miliary TB is suspected. However, with drug-resistant TB increasingly prevalent (44), choosing the most tolerable empiric drug regimen with the highest likelihood of success can be challenging. Multidrug-resistant (MDR) TB has been defined as an isolate resistant to isoniazid and rifampin; while extensive drug-resistant (XDR) TB defines an isolate resistant to isoniazid,

rifampin, any fluoroquinolone, and at least one of the injectable second-line, anti-TB drugs (i.e., capreomycin, kanamycin, and amikacin). Some clues that the patient may harbor drug-resistant TB include prior treatment of latent or active TB (51), exposure to a person with known resistant TB, and possibly, travel abroad. XDR-TB has been identified in at least 41 countries (44), including the United States. Soberingly, an analysis of TB patients in California from 1993–2006 revealed 424 were infected with MDR TB, 18 of whom were infected with XDR-TB (52). Consultation with a specialist experienced in TB management is recommended if the diagnosis of MDR or XDR-TB is suspected.

*S. pneumoniae* is a common cause of life-threatening bacterial pneumonia worldwide, and the commonest cause in the United States (43). The presence of known risk factors such as chronic lung disease, HIV, and asplenia should increase the suspicion of pneumococcal disease, but their absence does not exclude the diagnosis since pneumococcal pneumonia is also common in previously healthy people. Penicillin-resistant *S. pneumoniae* (PRSP) is increasingly problematic worldwide with an overall prevalence in the United States of approximately 21% (53). Treatment options of PRSP infections include a respiratory fluoroquinolone or an advanced macrolide plus a beta-lactam antibiotic (such as cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem). Vancomycin should also be considered for CNS involvement or severe infections (54).

The CDC estimates that within the United States, 8000–18,000 persons are hospitalized each year with Legionnaires disease, 20% of whom have recently traveled (55). *L. pneumophila* has been documented as a cause of severe pneumonia among travelers using whirlpool spas on cruise ships (56). In one outbreak involving 50 cruise ship passengers, the risk of acquiring Legionnaire's disease increased by 64% for every hour spent in the whirlpool (56). The diagnosis of *L. pneumophila* can be difficult and respiratory specimens must be cultured on selective media (57). Urine antigen testing can provide a more rapid diagnosis of *L. pneumophila* serogroup 1 (which comprises 80% of *L. pneumophila* isolates) with a sensitivity of 80% and specificity >99% (57). Recommended treatment of severe Legionnaire's disease includes azithromycin or a respiratory fluoroquinolone for at least 10 days ± rifampin 300 mg IV.

It is helpful to recall that no matter what time of the year it is, somewhere around the globe there is an active influenza epidemic. With this thought in mind, a good travel history can be essential to help determine the likelihood of influenza in the returned traveler. Epidemic influenza varies in seasonality based on the geographic region, with outbreaks typically occurring in the northern hemisphere from December through April, in the southern hemisphere from May through September, and in tropical regions year long. Focal outbreaks have also been documented among returning travelers and their contacts (58). Complicated influenza disease may be anticipated in patients with advanced age, respiratory comorbidity, and compromised immunity. It has also been suggested that those taking trips >30 days and those who travel to visit family/friends are at greater risk as well (41). Although the northern and southern hemisphere influenza vaccines differ somewhat in their viral component composition, there are currently no recommendations for travelers to obtain the local influenza vaccine upon arrival to their destination (59). The diagnosis of influenza is based on a compatible clinical presentation during the appropriate season (abrupt onset, high fevers, myalgias, and respiratory symptoms), isolation or detection of virus, and/or serology. Antiviral therapies with the neuraminidase inhibitors (oseltamivir, zanamavir) have documented efficacy against influenza A and B. Because of increasing rates of resistance, the CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza (60). If after several days of improvement, signs of relapse arise (new fever, cough, sputum production, new infiltrate on chest radiography), consideration should be given for a potential secondary bacterial pneumonia with organisms, such as *Staphylococcus aureus* or *S. pneumoniae*, and initiation of appropriate antibiotics.

Other less common respiratory infections among travelers include hantaviral pulmonary syndrome (HPS), *Pseudomonas pseudomallei* infection (melioidosis), plague, histoplasmosis and atypical manifestations of malaria, typhoid fever, leptospirosis, rickettsial diseases as well as some protozoal (amebiasis), and helminthic (schistosomiasis, fascioliasis) infections (48). In 1993, an outbreak of the first described HPS cases within the United States occurred (61).

Hantaviruses have a global distribution and patients typically present with hemorrhagic (petechiae, mucosal bleeding diathesis, capillary leak) and/or renal disease. Other variably present clinical features that may help to distinguish HPS from more common causes of severe respiratory infections include the absence of sore throat and cough (as seen with influenza) and radiographic evidence of lobar infiltrates (as seen with bacterial pneumonia) (61). Dizziness, nausea or vomiting, absence of cough, thrombocytopenia, decreased serum bicarbonate, and hemoconcentration were present among all HPS patients described in one case series (61). Several recent studies have confirmed these findings as clinical predictors of HPS (62). In one study, ribavirin given at a loading dose of 33 mg/kg (maximum 2 g), followed by either 16 mg/kg (maximum 1 g) every six hours for four days or 8 mg/kg (maximum 0.5 g) every eight hours for three days reduced mortality sevenfold in patients with hantaviral hemorrhagic fever with renal syndrome (HFRS). However, efficacy was not demonstrated in a randomized controlled trial for HPS (63,64). *Burkholderia pseudomallei* (melioidosis) has rarely been reported as a cause of fulminant disease in travelers from Southeast Asia and Australia and more commonly presents as a chronic granulomatous illness resembling tuberculosis (65). The spectrum of disease in melioidosis ranges from asymptomatic infection to chronic debilitating illness to fulminant septicemia. The recommended treatment for melioidosis is intravenous ceftazidime (or imipenem) followed by a prolonged course of oral cotrimoxazole plus doxycycline to prevent relapse (66,67). Plague may present in either a bubonic (i.e., tender, fluctuant adenopathy with systemic illness), septicemic, or pneumonic form. Although there are no recently documented reports of plague in international travelers, one needs to consider this diagnosis among travelers with a compatible clinical syndrome returning from endemic areas (e.g., India, Vietnam, Myanmar, Zaire, and Madagascar) (68,69). Patients with plague can present with symptoms ranging from a mild febrile illness with a bubo to fulminant sepsis. Given the potential for rapid deterioration as well as contagious spread by respiratory droplets, prompt institution of appropriate therapy (e.g., gentamicin 2 mg/kg loading dose then 1.7 mg/kg every eight hours) is critical. A large outbreak of acute pulmonary histoplasmosis recently occurred among students returning from Mexico (70). Their exposure to *Histoplasma capsulatum* apparently occurred at a hotel where maintenance projects were underway. Other endemic mycoses, such as coccidioidomycosis and penicilliosis (especially within HIV patients), are also considerations in the differential diagnosis of a febrile respiratory illness in a returning traveler (71).

Severe acute respiratory syndrome (SARS), caused by a newly identified coronavirus, should be considered in travelers returning from Far East destinations or areas with known prior SARS transmission (72,73). However, the last reported cases occurred in China in 2004 [CDC SARS situation report]. SARS generally presents as a severe atypical pneumonia. However, one proposed diagnostic algorithm among cases confirmed with RT-PCR was associated with 90% sensitivity and 62% specificity (74). Predictors of SARS included: (1) potential contact with a SARS patient; (2) an illness consisting of fever, myalgias, and malaise; (3) an abnormal chest radiograph (diffuse haziness or consolidation); and (4) lymphopenia and thrombocytopenia. Age >65 years or <18 years, sputum production, abdominal pain, sore throat, rhinorrhea, and leukocytosis were not predictive of SARS. This tool was applied in one epidemic setting and requires further validation (74–76).

The highly pathogenic avian influenza A (H5N1) has become the subject of much international attention. The first reports of human disease appeared in 1997 and the incidence has subsequently increased. The WHO reports that from 2003–2008 a total of 387 human cases (245 fatal) were documented (77). Thus far, human to human transmission is exceedingly rare. However, concerns for a viral mutation that would promote more effective transmission among humans has prompted reassessment of pandemic influenza response plans and the stockpiling of antiviral therapy as well as a recently FDA-approved H5N1 vaccine (78). Optimal treatment of H5N1 influenza has yet to be determined. However, the WHO currently recommends weight-based oseltamivir (75 mg po bid if >40 kg) for five days (79).

### **Coma and Meningoencephalitis**

Infections may result in CNS dysfunction either indirectly as a systemic infection as in typhoid fever or directly through CNS invasion. A returning traveler presenting with one or more of

the following signs/symptoms with or without fever must be evaluated for CNS infection: meningismus, altered mental status (delirium, lethargy, obtundation, or coma), seizures, severe headache, photophobia, or focal neurologic findings (80). Common tropical infections such as malaria (cerebral malaria), typhoid, and TB should remain high on the differential diagnosis. The diagnostic approach including CNS imaging studies (CT or MRI scans) with cerebrospinal fluid (CSF) analysis will be similar to the approach used in nontravelers. The incubation period is particularly important when trying to decide if certain etiologic agents need be considered. Travelers presenting within two to three weeks post-travel from developing regions may have acquired regional arboviruses causing meningoencephalitis or meningococcal disease whereas incubation periods exceeding two to three weeks require inclusion of TB, African trypanosomiasis, and rabies.

Endemic or sporadic meningococcal disease varies between 1 to 3 and 10 to 25 cases per 100,000 persons in developed and developing regions respectively (81). In addition to this increased endemic risk for travelers, there is also the potential of epidemic meningococcal disease (primarily serogroup A) with attack rates as high as 1000/100,000 as seen in the meningococcal belt of sub-Saharan Africa (81). Rapid diagnosis using CSF analysis (neutrophilic pleocytosis, elevated protein, low glucose, and gram-negative diplococci) with prompt institution of antibiotic therapy is critical since treated meningococcal meningitis carries mortality rates in the range of 5% to 15% (82).

Herpes simplex (HSV-1) encephalitis is the most common cause of sporadic viral encephalitis seen by clinicians in the United States; however, endemic arboviruses such as California group bunyaviral encephalitis are also not uncommon (83). Additionally, international travel into developing regions with potential mosquito exposure further broadens the differential diagnosis. Knowledge of the regional arboviral threats, such as Japanese encephalitis in rural areas of eastern Asia and the Indian subcontinent and Rift Valley fever in Egypt and central/southern Africa, will allow appropriate inclusion/exclusion of arboviral threats (84–86). Flavivirus encephalitis occurs in both developed and developing countries with regional threats such as Japanese encephalitis in South and Southeast Asia, Murray Valley encephalitis in Australia and New Guinea, West Nile encephalitis across many areas including Africa, Southwest Asia, Europe, and North America, and St. Louis encephalitis throughout the Americas (87). These viral encephalitides have much higher rates of asymptomatic infection as compared to CNS illness and may present with a meningitis syndrome rather than encephalitis. Human rabies is often transmitted in developing urban areas through contact with rabid dogs and cats unlike the wild animal reservoir in the United States (88). Patients presenting with a compatible clinical syndrome for rabies (respiratory and/or GI prodromal symptoms followed by acute neurologic symptoms, furious or paralytic, leading to coma) should have a thorough travel history focusing on any animal contact. Diagnostic testing, virus-specific fluorescent material in skin biopsy, serum or CSF antirabies antibodies, and/or virus isolation in saliva, should be used in appropriate settings with prompt initiation of isolation precautions and postexposure immunoprophylaxis (88). Emergent threats such as the Nipah virus in Malaysia in 1998–1999 further add to the differential diagnosis for returning travelers with encephalitis (89). An open-label trial reported a 36% reduction in mortality for acute Nipah virus encephalitis when treated with intravenous ribavirin (90). Eosinophilic meningoencephalitis (CSF leukocytosis with >10% eosinophils) is a clinical syndrome with relatively limited etiologies including parasites (*Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, migrating ascarids, and schistosomiasis), coccidiomycosis, and hypersensitivity reaction (drug-related) (91). The travel and exposure history will greatly assist in the inclusion/exclusion of parasitic etiologies.

### Acute Abdomen

Returning travelers presenting with an acute abdomen are most likely to have common conditions seen in nontravelers such as appendicitis, cholecystitis, diverticulitis, or peptic ulcer with perforated viscus (92). Two common diseases in indigenous populations, enteric fever and amebic liver abscess, occur occasionally in immigrants and less commonly in naive travelers (92–94). Both of these diseases may present with an acute abdomen secondary to severe abdominal pain from uncomplicated disease or as a result of complicated disease such as cyst rupture in

amebiasis or bowel perforation in enteric fever. Risk factors for intestinal perforation in typhoid fever were a short duration of symptoms (within 2 weeks of illness onset), inadequate antibiotic therapy, male gender, and leukopenia in a case-control study in Turkey (95). Enteric fever is most commonly due to *Salmonella typhi*, but also can be caused by *S. paratyphi* or *Brucella* species (96,97). In the United States, the total number of typhoid fever cases has decreased. A larger proportion (69%) has been imported during foreign travel especially from Mexico and India (98). Typhoid fever may also present with other clinical syndromes requiring ICU admission including ARDS, lower gastrointestinal bleeding, splenic rupture, and coma (95,97,99,100). Confirmatory diagnosis of typhoid fever requires blood culture isolation that is positive in approximately 80% of cases or approximately 90% with bone marrow culture (97,101). Stool and urine cultures are occasionally positive, 37% and 7%, respectively, but do not constitute definitive evidence of systemic infection. Widespread multidrug-resistant *S. typhi* (resistant to ampicillin, chloramphenicol, and TMP/SMX) has been documented in many areas of Asia, Africa, and the Middle East requiring the use of fluoroquinolones, as first-line therapy, or alternatives such as third-generation cephalosporins or azithromycin (94,97,102,103). Adjunctive therapy with high-dose corticosteroids has been shown to decrease mortality in severely ill typhoid fever patients with delirium, obtundation, coma, or shock (104). The majority (95%) of amebic liver abscesses will present within the first two to five years after leaving the endemic region (93,105,106). Diarrhea is present in less than half with amebic trophozoites or cysts in <30%. The differential diagnosis must also include bacterial liver abscess, echinococcal cyst, and hepatoma. Ultrasound and CT imaging will assist in defining the hepatic lesions and highly sensitive and specific serology will often confirm extraintestinal amebiasis (often negative in the first seven days) (93). Therapy with parenteral metronidazole results in mortality rates of <1% in uncomplicated liver abscesses (93). However, complicated amebic liver abscesses with extension into the thoracic cavity, peritoneum, or pericardium have case-fatality rates of 6.2%, 18.4%, and 29.6%, respectively (105).

### **Dysentery and Severe Gastrointestinal Fluid Losses**

Dysentery is characterized by a toxic appearance, fever, lower abdominal pain, tenesmus, and frequent small-volume loose stools containing blood and/or mucus with large numbers of fecal leukocytes on microscopic exam. Etiologies of dysentery can be divided into amebic (*Entamoeba histolytica*) versus bacillary [*Shigella* spp. especially *S. dysenteriae* and *S. flexneri*, *Campylobacter jejuni*, nontyphoidal *Salmonella* spp., *Yersinia enterocolitica*, enteroinvasive *Escherichia coli* and enterohemorrhagic *E. coli* (EHEC)] (106). Shigellosis is the most common etiology and is associated with fatality rates as high as 9% in indigenous populations in endemic regions and 20% during *S. dysenteriae* epidemics (107). Complications can include bacteremia, intestinal perforation, dehydration, toxic megacolon, ileus, rectal prolapse, hemolytic uremic syndrome (also well documented with EHEC strains such as O157:H7), altered consciousness, and seizures. Predictive factors associated with increased risk of death in shigellosis (age older than one year, diminished serum total protein, thrombocytopenia, and altered consciousness) reflect the importance of sepsis in shigellosis-related deaths (108). Diarrhea-related mortality in noninflammatory diarrhea has been significantly reduced globally with the institution of oral rehydration therapy. Dysentery-related deaths have not been significantly reduced and require antimicrobial therapy and supportive intensive care in addition to appropriate rehydration (106,107,109,110). The majority of noninflammatory diarrhea cases in returning travelers present as mild or moderate illness due to bacterial agents such as ETEC, *Campylobacter jejuni*, and, less commonly, protozoal agents such as *Giardia lamblia*. Noninflammatory diarrhea due to cholera may present in a returning traveler with life-threatening dehydrating illness with profound fluid and electrolyte deficits (111). Imported *Vibrio cholerae* is rare in the United States; however, an appreciation of regional risks of epidemic strains (El Tor in South/Central America and Africa, non-O1 *V. cholerae* O139 in Southeast Asia and the Indian subcontinent) is important (111).

### **Fulminant Hepatitis**

Fulminant hepatitis manifests as severe acute liver failure with jaundice and hepatic encephalopathy (112). Viral hepatitis accounts for the majority (approx. 75%) of fulminant

hepatitis and may be either early-onset (within first eight weeks) or late-onset (8 to 12 weeks) after jaundice develops (112–115). Hepatitis B accounts for 30% to 60% with coinfection with delta virus in 30% to 40% that has been demonstrated to increase disease severity (116). Hepatitis A only accounts for <0.1% of causes of fulminant hepatitis, although overall Hepatitis A represents the most commonly acquired agent of viral hepatitis (50% to 60% in most series) (113). Hepatitis C association with fulminant non-A, non-B hepatitis has been reported in Japan but is very uncommon in Western countries (117,118). Hepatitis E, a virus transmitted via an enteric route, has an increased fatality rate in pregnant women (119). Early indicators of a poor prognosis and the potential need for liver transplantation in viral hepatitis include age <11 years or >40 years, duration of jaundice before onset of encephalopathy less than seven days, serum bilirubin >300  $\mu\text{mol/L}$ , and prothrombin time >50 seconds (120). Early diagnosis of acute hepatitis is important, given evidence of specific benefit from antiviral therapies including lamivudine in acute Hepatitis B and interferon therapy for Hepatitis C (121–125). Other less common causes of fulminant hepatitis include Yellow fever virus and leptospirosis. Yellow fever virus–endemic zones are updated on a regular basis and available (as are cholera- and plague-endemic zones) through the weekly CDC publication (the *Blue Sheet*). A resurgence in yellow fever in Africa and South America emphasize the continued threat from this agent for unvaccinated travelers (126). Severe yellow fever is fatal in >50% of cases and continues to be a cause of deaths in returning travelers (127–130). Leptospirosis has widespread distribution and is usually transmitted to humans through contact with surface water contaminated with urine from infected animals (131). Travelers returning with leptospirosis typically present with a mild or moderate illness. The spectrum of disease includes fulminant hepatitis, meningoencephalitis, hemorrhagic manifestations, pulmonary manifestations including ARDS, and renal failure (131–136). Leptospirosis should be considered in most severely ill returning travelers. A recent randomized controlled trial demonstrated equal efficacy of seven-day intravenous therapy with ceftriaxone (1 g daily) and penicillin G (1.5 million U every six hours) in severe leptospirosis (137). However, case fatality was 5.8% with 10% requiring dialysis and 22% experiencing respiratory failure.

### Fever with Eosinophilia

Eosinophilia in the returning traveler is not uncommon and requires an initial assessment of the absolute eosinophil count (eosinophilia  $>450/\text{mm}^3$ ), consideration if travel-related (i.e., check pretravel differential white blood cell counts) and the most likely parasite based on travel destination, duration of stay, and exposure history (138). Critically important is a determination of whether the eosinophilia is related to the patient's current symptoms since most causes of eosinophilia in travelers result in either asymptomatic or mild disease; although the predictive value of peripheral eosinophilia has limitations (139). A tenet of tropical infectious diseases is that patients may present with multiple infections, an acutely ill traveler with moderate eosinophilia may have malaria as the cause of the symptoms and asymptomatic hookworm infection as the etiology of the eosinophilia. Infectious etiologies of fever and eosinophilia that may present with potentially life-threatening illnesses include acute schistosomiasis (acute serum sickness-like disease termed Katayama fever or acute neurologic sequelae of myelitis or encephalitis), visceral larva migrans, tropical pulmonary eosinophilia, acute fascioliasis, and acute trichinosis (138). Schistosomiasis is the most common of these infections with reported high infection rates (mean 77%) in groups of travelers exposed to fresh water in endemic regions occasionally resulting in severe acute infection approximately four to eight weeks postexposure (140–142). Definitive diagnosis of schistosomiasis requires identification of the ova in stool, urine, or tissue specimens. The acute hypersensitivity syndromes of schistosomiasis occurring prior to ova deposition or ectopic distribution of the schistosome ova (such as in the CNS) necessitate the use of sensitive serologic methods for diagnosis (143). Specific therapy with praziquantel is highly efficacious in the low worm density infections seen in travelers (143). The acute hypersensitivity syndromes often require adjunctive corticosteroid therapy.



### Toxic Appearance and Fever

Patients with a toxic appearance with fever often present difficult diagnostic dilemmas. As has already been discussed, malaria must be ruled out. Other potential diagnoses already discussed such as typhoid fever, early shigellosis, leptospirosis, and anicteric hepatitis remain in the differential diagnosis. This group of conditions can be further subdivided into the presence or absence of a rash. The presence of a hemorrhagic rash is somewhat helpful in narrowing the differential to arboviral, rickettsial, and meningococcal etiologies but even this is not completely reliable. Maculopapular rashes can be either the common exanthem of that illness (i.e., measles) or an earlier stage in an evolving exanthem (i.e., rickettsial or meningococcal disease). Rickettsial diseases are usually in the differential for critically ill patients with fever and rash. There has been increasing recognition of rickettsial infections as etiologies of serious travel-associated infections (144,145). The majority of imported rickettsial disease in travelers is due to *R. africae*, the spotted fever group agent of African tick bite fever, and less commonly, *R. conorii*, the spotted fever group agent of boutonneuse fever, both of which typically present as mild and self-limited illnesses (144,146–149). Scrub typhus has reported case fatality rates in indigenous populations of 15% and rarely has caused life-threatening disease in returning travelers (150). These reports highlight the importance of including rickettsial agents in the differential diagnosis and consideration of empiric therapy with doxycycline. Rapid responses to doxycycline therapy within 24 hours support the diagnosis and the lack of response should prompt alternative diagnoses. Sexually transmitted diseases such as secondary syphilis, disseminated gonococcal infection, or acute retroviral syndrome may rarely present in this manner and need consideration. Measles has significant morbidity with the most common complication, pneumonitis, resulting in mortality rates of 2% to 15% in children and <1% in adults (151,152). A study of hospitalized adults with complications of typical measles revealed pneumonitis rates of approximately 50% with respiratory failure and mechanical ventilation in 18% (153).

Dengue fever is, by far, the most common arboviral etiology of nonspecific febrile illness in returning travelers (126,154,155). Global estimates of 150 million cases of classic dengue fever and 250,000 cases of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), continued regional spread in the western hemisphere, and the urban peridomestic transmission from infected *Aedes aegypti* (also *A. albopictus*) mosquito vectors make dengue fever a prominent consideration in returning travelers with fever (156). As with other arboviral etiologic agents of viral hemorrhagic fever (VHF), illness onset with an elapsed time exceeding three weeks (two weeks with dengue) from the potential exposure effectively rules out these agents (157). Dengue fever may be caused by any one of the four serotypes with the relative risk of severe disease (DHF/DSS) 100-fold higher during the second dengue infection than with the first (156). Dengue fever rarely presents with life-threatening infection in US travelers probably due to the lack of prior dengue infections. In West Africa, Lassa fever is endemic, causing 100,000–300,000 human infections and approximately 5000 deaths each year (158). Other than in regions where it is endemic, Lassa fever is encountered rarely. To date, approximately 20 cases of imported Lassa fever have been reported worldwide with one death in the United States in 2004 after travel to West Africa (158). Etiologies of VHF that have been known to cause person-to-person transmission [Lassa virus, Ebola virus, Marburg virus, and Crimean-Congo hemorrhagic fever (CCHF) virus] are particularly important since specific recommendations are available for patient management and proper containment of these potentially deadly viruses (157,159,160). VHF is characterized by fever, nonspecific symptoms (i.e., pharyngitis, myalgias, respiratory symptoms, headache, and malaise), and in severe cases, shock and hemorrhagic manifestations (157,159–162). These viruses have distinct geographic distributions, variable case fatality rates, and potential therapeutic options as detailed on Table 3. Nosocomial transmission has been documented for each of these agents and is primarily transmitted through direct contact or aerosolization of blood or body fluids from often terminally ill infected patients (157,162). Table 4 summarizes the general concepts from the CDC in properly managing a suspected VHF patient. Recent interim CDC guidance provides updates on VHF transmission and infection control precautions with specific focus on patient care practices, environmental procedures, reporting, specimen handling, human remains handling, and postexposure management (163) (Table 5). Consideration should also be given to postexposure

**Table 3** Severe Malaria Treatment Options

	Adult dose	Pediatric dose
Severe malaria <sup>a,b,c,d</sup>		
All regions	<p>Quinidine gluconate<sup>b</sup> plus one of the following:                      Doxycycline, Tetracycline, or Clindamycin</p> <p>Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1–2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hrs. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hrs, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hrs every 8 hrs, starting 8 hours after the loading dose (see package insert). Once parasite density &lt;1% and patient can take oral medication, complete treatment with oral quinine, dose as above.</p> <p>Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America.</p> <p>Doxycycline: Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hrs and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.</p> <p>Tetracycline: Treatment as above</p> <p>Clindamycin: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hrs. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.</p>	<p>Quinidine gluconate<sup>b</sup> plus one of the following:                      Doxycycline<sup>e</sup>, Tetracycline<sup>e</sup>, or Clindamycin</p> <p>Quinidine gluconate: Same mg/kg dosing and recommendations as for adults.</p> <p>Doxycycline: Treatment as above. If patient not able to take oral medication, may give IV. For children &lt;45 kg, give 2.2 mg/kg IV every 12 hrs and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days.</p> <p>Tetracycline: Treatment as above.</p> <p>Clindamycin: Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hrs. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.</p> <p><i>Investigational new drug (contact CDC for information):</i>                      Artesunate followed by one of the following:                      Atovaquone-proguanil (Malarone<sup>TM</sup>),<sup>f</sup>                      Clindamycin, or Mefloquine</p>

(Continued)

**Table 3** Severe Malaria Treatment Options (Continued)

Adult dose	Pediatric dose
<p data-bbox="234 807 278 1209"><i>Investigational new drug (contact CDC for information):</i></p> <p data-bbox="284 794 302 1209">Artesunate Followed by one of the following:</p> <p data-bbox="307 836 326 1209">Atovaquone-proguanil (Malarone™),†</p> <p data-bbox="331 736 379 1209">Doxycycline (Clindamycin in pregnant women), or Mefloquine</p>	<p data-bbox="402 156 500 1794"><sup>a</sup>Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of &gt; 5%) are considered to have manifestations of more severe disease. Severe malaria is practically always due to <i>P. falciparum</i>.</p> <p data-bbox="505 156 652 1794"><sup>b</sup>Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hrs or if they have received mefloquine within the preceding 12 hrs. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.</p> <p data-bbox="658 156 779 1794"><sup>c</sup>Consider exchange transfusion if the parasite density (i.e. parasitemia) is &gt; 10% OR if the patient has altered mental status, non-volume overload pulmonary edema, or renal complications. The parasite density can be estimated by examining a monolayer of red blood cells (RBCs) on the thin smear under oil immersion magnification. The slide should be examined where the RBCs are more or less touching (approximately 400 RBCs per field). The parasite density can then be estimated from the percentage of infected RBCs and should be monitored every 12 hrs. Exchange transfusion should be continued until the parasite density is &lt; 1% (usually requires 8–10 units). IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout the exchange transfusion.</p> <p data-bbox="784 683 802 1794"><sup>d</sup>Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.</p> <p data-bbox="808 156 926 1794"><sup>e</sup>Doxycycline and tetracycline are not indicated for use in children less than 8 yrs old. For children less than 8 years old with chloroquine-resistant <i>P. falciparum</i>, quinine (given alone for 7 days or given in combination with clindamycin) and atovaquone-proguanil are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 yrs old with chloroquine-resistant <i>P. vivax</i>, quinine (given alone for 7 days) or mefloquine are recommended treatment options. If none of these treatment options are available or are not being tolerated and if the treatment benefits outweigh the risks, doxycycline or tetracycline may be given to children less than 8 years old.</p> <p data-bbox="931 653 950 1794"><sup>f</sup>Give atovaquone-proguanil with food. If patient vomits within 30 min of taking a dose, then they should repeat the dose.</p>

Source: Adapted from Ref. 31.

**Table 4** VHF Etiologies Associated with Nosocomial Spread

Virus	Geographic Region	Case Fatality Rate	Therapeutic Options
Lassa	West Africa	1%–2%	Ribavirin (efficacy in clinical trial) <sup>a</sup>
Ebola	Zaire, Sudan	65%–88%	Supportive care
Marburg	East and Central Africa	23%	Supportive care
CCHF	Eastern Europe, eastern Mediterranean, Asia, and Africa	15%–70%	Ribavirin (in vitro evidence/no controlled trial)

<sup>a</sup>Ribavirin dosing regimen—30 mg/kg loading dose IV (max. 2 g) then 16 mg/kg (max. 1 g/dose) q6h × 4 days, then 8 mg/kg (max. 500 mg) q8h × 6 days; ribavirin prophylaxis in close contacts—(unproven regimen) 5 mg/kg t.i.d. × 2–3 weeks.

**Abbreviations:** CCHF, Crimean-Congo hemorrhagic fever; VHF, viral hemorrhagic fever.

**Table 5** General Considerations in the Management of Suspected VHF

Steps	Action
1	Rapid assessment to determine if VHF suspect (fever within 3 wks of exposure plus travel to endemic region or direct contact with potentially infected blood or body fluids)
2	Isolate immediately (main focus is avoidance of blood/body fluid exposure—refer to CDC guidelines for specific details)
3	Rule out more common illness such as malaria and typhoid fever (refer to guidelines for proper specimen handling)
4	Contact local/state health department and the CDC [tel: (404) 639-1510 during normal working hours; after hours (404) 639-2888]
5	If clinical syndrome/exposure history supportive of Lassa fever or CCHF, consider ribavirin therapy (also consider prophylaxis for high-risk contacts)

All suspected cases of VHF should be reported immediately to local and state health departments and to CDC (Special Pathogens Branch, 404 639-2888). Consult the Special Pathogens Branch before obtaining or sending specimens to CDC for confirmatory testing. State health departments should also be notified before sending specimens to CDC. For links to state health departments visit the “Information Networks and Other Information Sources” page on the CDC Web site <http://www.cdc.gov/other.htm>

**Abbreviations:** CCHG, Crimean-Congo hemorrhagic fever; CDC, Centers for Disease Control; VHF, viral hemorrhagic fever.

prophylaxis based on the infectious agent such as ribavirin in imported Lassa fever cases (161). In the event this situation was to arise, the medical personnel must obtain the CDC references in the *Morbidity and Mortality Weekly Report* in order to have all specific guidelines.

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# 19 Infections in Cirrhosis in Critical Care

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## INTRODUCTION

Cirrhosis is characterized by fibrosis of the hepatic parenchyma with regenerative nodules surrounded by scar tissue. It can result from a variety of chronic, progressive liver diseases. The clinical manifestations vary widely from asymptomatic disease (up to 40% of patients) to fulminant liver failure. Cirrhosis is a major cause of morbidity worldwide. In the United States cirrhosis has an estimated prevalence of 360 per 100,000 population and accounts for approximately 30,000 deaths annually. The majority of cases in the United States are a result of alcoholic liver disease or chronic infection with hepatitis B or C viruses.

Infection is a common complication of cirrhosis (reviewed in Refs. 1–4). A Danish death registry study (5) examined long-term survival and cause-specific mortality in 10,154 patients with cirrhosis between 1982 and 1993. The results revealed an increased risk of dying from respiratory infection (fivefold), from tuberculosis (15-fold) and other infectious diseases (22-fold) when compared to the general population. In a prospective study (6) 20% of cirrhotic patients admitted to the hospital developed an infection while hospitalized. The mortality among patients with infection was 20% compared with 4% mortality in those who remained uninfected. Of patients admitted to the critical care unit, 41% became infected. The most common bacterial infections seen in cirrhotic patients are urinary tract infections (12% to 29%), spontaneous bacterial peritonitis (7% to 23%), respiratory tract infections (6% to 10%), and primary bacteremia (4% to 11%) (7). The increased susceptibility to bacterial infections among cirrhotic patients is related to impaired hepatocyte and phagocytic cell function as well as the consequences of parenchymal destruction (portal hypertension, ascites, and gastroesophageal varices).

It should be noted that the usual signs and symptoms of infection may be subtle or absent in individuals who have advanced liver disease. Thus a high index of suspicion is required to ensure that infections are not overlooked in this patient population, especially in those who are hospitalized. Occasionally fever may be due to cirrhosis itself (8), but this must be a diagnosis of exclusion made only when appropriate diagnostic tests, including cultures, have been unrevealing.

## ROLE OF THE LIVER IN HOST DEFENSE AGAINST INFECTION

The liver plays an important role in host defense against infection. Cirrhosis can adversely affect a number of these host defenses. The mechanisms identified in human and experimental animal studies include depression of reticuloendothelial system clearance of organisms from the bloodstream (9); impairment of chemotaxis, phagocytosis, and intracellular killing by polymorphonuclear leukocytes (PMNL) and monocytes (10–12); reduction in serum bactericidal activity and opsonic activity (13,14); depression of serum complement (15–17); dysregulation of cytokine synthesis and metabolism (18), and reduced protective efficacy of type-specific antibody (19) and granulocyte colony-stimulating factor (20).

## CLASSIFICATION OF LIVER DISEASE SEVERITY

Patients who have cirrhosis are at increased risk for both community-acquired and nosocomial infections, the majority of which are bacterial. The incidence of infection is highest for patients with the most severe liver disease (6,21–23). Accurate assessment for risk of infection is dependent upon proper classification of the extent of liver disease. The Child–Pugh scoring system of liver disease severity (24) is based upon five parameters: (i) serum bilirubin, (ii) serum albumin, (iii) prothrombin time, (iv) ascites, and (v) encephalopathy. A total score is

**Table 1** Modified Child–Pugh Classification of Liver Disease Severity

Parameter	Points Assigned		
	1	2	3
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Grade 1–2	Grade 3–4
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (mg/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds increased)	1–3	4–6	>6.0
	Total score	Child–Pugh Class	
	5–6	A	
	7–9	B	
	10–15	C	

derived from the sum of the points for each of these five parameters. Patients with chronic liver disease are placed in one of three classes (A, B, or C). Despite having some limitations the modified Child–Pugh scoring system continues to be used by many clinicians to assess the risk of mortality in patients with cirrhosis (Table 1).

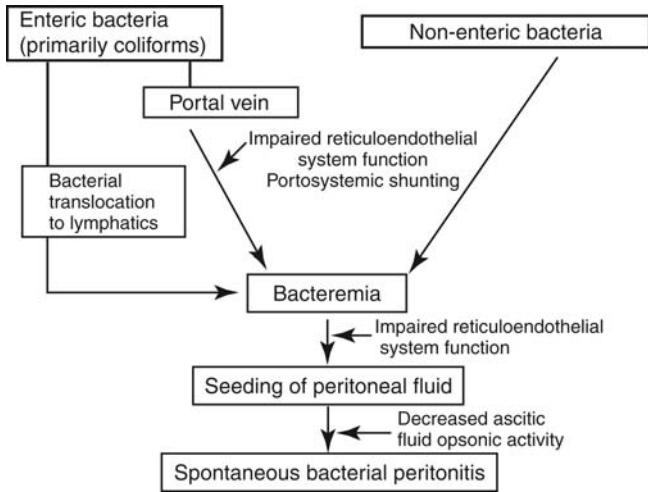
## SPONTANEOUS BACTERIAL PERITONITIS

### Pathogenesis

Spontaneous bacterial peritonitis (SBP) is the infection of ascitic fluid with no identifiable abdominal source for the infection. SBP is perhaps the most characteristic bacterial infection in cirrhosis, occurring in as many as 20% to 30% of cirrhotic patients who are admitted to the hospital with ascites (6,21,23). SBP occurs when normally sterile ascitic fluid is colonized following an episode of transient bacteremia. Aerobic gram-negative bacilli, especially *Escherichia coli*, cause approximately 75% of SBP infections. Aerobic gram-positive cocci, including *Streptococcus pneumoniae*, *Enterococcus faecalis*, other streptococci, and *Staphylococcus aureus*, are responsible for most other SBP cases (25,26). Because enteric bacteria predominate in SBP, it is thought that the gut is the major source of organisms for this infection. Several mechanisms have been proposed to explain the movement of organisms from the intestinal lumen to the systemic circulation (reviewed in Ref. 1). Cirrhosis-induced depression of the hepatic reticuloendothelial system impairs the liver's filtering function, allowing bacteria to pass from the bowel lumen to the bloodstream via the portal vein. Cirrhosis also is associated with a relative increase in aerobic gram-negative bacilli in the jejunum. A decrease in mucosal blood flow due to acute hypovolemia or drug-induced splanchnic vasoconstriction may compromise the intestinal barrier to enteric flora, thereby increasing the risk of bacteremia. Finally, bacterial translocation may occur with movement of enteric organisms from the gut lumen through the mucosa to the intestinal lymphatics. From there bacteria can travel through the lymphatic system and enter the bloodstream via the thoracic duct. It is assumed that SBP caused by non-enteric organisms also is due to bacteremia secondary to another site of infection with subsequent seeding of the peritoneum and ascitic fluid (Fig. 1).

Decreased opsonic activity of ascitic fluid also increases the risk of SBP in patients with cirrhosis. Immunoglobulin, complement, and fibronectin are important opsonins in ascitic fluid, and patients with low protein concentrations in their ascitic fluid are especially predisposed to SBP (27,28). Patients with ascitic fluid protein concentrations below 1 g/dL have a sevenfold increase in the incidence of SBP when compared to patients with higher protein concentrations in ascities (27).

Other risk factors have been associated with SBP, including gastrointestinal bleeding, fulminant hepatic failure, and invasive procedures such as the placement of peritoneovenous shunts for the treatment of ascites. An elevated bilirubin level also is correlated with a high risk of peritonitis in patient with cirrhosis (28).



**Figure 1** Pathogenic mechanisms underlying spontaneous bacterial peritonitis. *Source:* Adapted from Ref. 1.

## Diagnosis

Classic signs and symptoms of peritonitis, including fever, chills, abdominal pain, and increasing ascites may or may not be present in cirrhotic patients who have SBP. Abdominal symptoms may be absent in up to one-third of cases. Patients with SBP may present with encephalopathy, gastrointestinal bleeding, or increasing renal insufficiency. Therefore a high index of suspicion must be maintained in all cases of cirrhotic patients who have ascites and are acutely ill.

A diagnostic paracentesis must be performed on all patients suspected to have SBP. A PMNL count in ascitic fluid of greater than 250 cells/mm<sup>3</sup> is highly suggestive of infection. Gram-stain of centrifuged ascitic fluid will reveal organisms in approximately 30% of cases. The fluid should be cultured both aerobically and anaerobically. Inoculating some fluid directly into blood culture bottles increases the yield of positive cultures. But this nonquantitative culture technique also increases the risk of false-positives if any skin flora contaminant is introduced into the blood culture bottle at the bedside.

As indicated previously, aerobic gram-negative enteric bacilli are the most frequent isolates from ascitic fluid cultures in SBP. Anaerobes are uncommon causes of SBP, and their presence in ascitic fluid should raise suspicions for bowel perforation. If ascitic fluid cultures yield polymicrobial flora, *Candida albicans* (or other yeast), or *Bacteroides fragilis* one should suspect a secondary peritonitis caused by an acute abdominal infection.

## Treatment

Historically SBP has been a severe, frequently fatal infection. In the past few decades mortality rates have dropped from over 90% in the 1970s to the current 20% to 40% mortality for patients who have their first diagnosis of SBP. Earlier detection and treatment and the use of non-nephrotoxic antibiotics has contributed to the increased short-term survival. The most common causes of death in patients with SBP are liver failure, gastrointestinal bleeding, and renal failure. One of the greatest threats to long-term survival is recurrence of SBP, which can occur in 70% of patients (29).

Previously aminoglycosides, alone or in combination with beta-lactam antibiotics, were widely used to treat SBP. However the risk of aminoglycoside nephrotoxicity in cirrhotic patients has limited the usefulness of this class of agents (30). Expanded-spectrum cephalosporins are active against most of the strains of enteric gram-negative pathogens that cause SBP. Cefotaxime has been shown effective in a number of trials with regimens of 2 g administered every 8 hours for five days (26) or 2 g every 12 hours for a mean of nine days (31). In a more recent study (32) 24/33 (73%) of cirrhotic patients with SBP had clinical and bacteriologic cures after receiving one gram of ceftriaxone every 12 hours for 5 days. With

prolonged treatment using ceftriaxone or with a change to another antibiotic according to susceptibility, SBP resolved in seven of the nine patients who had not responded by day 5 of therapy. Study patients had an overall hospital mortality of only 12%. The authors concluded that antibiotic therapy for SBP can be discontinued if the polymorphonuclear differential count in ascitic fluid is less than 250 cells/mm<sup>3</sup> on day five of treatment (32).

Other parenteral antibiotics that have been reported effective for the treatment of SBP include aztreonam (500 mg every 8 hours) (33), cefonicid (2 g every 12 hours) (34), and amoxicillin–clavulanic acid (35). Several small trials have involved the use of oral antibiotics. These included intravenous followed by oral therapy with amoxicillin–clavulanic acid (36) or ciprofloxacin (37) and oral ofloxacin (38). While some experts recommend that patients with moderate symptoms and a positive response to a short course of intravenous antibiotics could benefit from therapy with oral fluoroquinolones (39), others have found the supporting evidence to be inconclusive (40).

Deterioration of renal function is the most sensitive predictor of in-hospital mortality in patients with SBP (41). In a randomized, multicenter comparative study, patients with SBP who received intravenous albumin for plasma volume expansion plus cefotaxime had less renal impairment and significantly lower mortality (22%) than those receiving cefotaxime alone (41%) (42). The dose of albumin used in this study was 1.5 g/kg of body weight at the time of diagnosis followed by 1 g/kg on day 3.

### Prophylaxis

The use of prophylactic antibiotics decreases the incidence and mortality of bacterial infections, including SBP, in patients who are hospitalized with cirrhosis and ascites (7). Cirrhotic patients who recover from SBP also are at increased risk of subsequent episodes. The one-year probability of recurrence of SBP in this population has been estimated to approach 70% (43). Antibiotics reported effective in preventing SBP have included trimethoprim/sulfamethoxazole (44) and, more commonly, fluoroquinolones such as norfloxacin, ofloxacin and ciprofloxacin (7,45–47). A major concern regarding repeated or prolonged courses of antibiotic prophylaxis is selection for resistant bacterial pathogens. There are a growing number of reports of the development of SBP or other infections caused by fluoroquinolone-resistant organisms, including *E. coli*, *Pseudomonas* species, and methicillin-resistant *S. aureus*, in cirrhotic patients on fluoroquinolone prophylaxis (7,48,49). Thus the use of prophylactic antibiotics should be restricted to patients at greatest risk of SBP, weighing the increased risk of inducing resistant bacteria against the benefits of preventing infection.

### URINARY TRACT INFECTIONS

Urinary tract infections account for 25% to 40% of infections in hospitalized cirrhotic patients (21,23,50). The majority of these patients have asymptomatic bacteriuria, but approximately one-third have symptomatic infections (23). The incidence of significant bacteriuria (>10<sup>5</sup> colony-forming units/mL) is higher in women than in men and does not correlate with the severity of the underlying liver disease or with the age of the patient (50). The presence of an indwelling urinary catheter increases the risk of infection. The most common pathogens are *E. coli* and other aerobic gram-negative coliforms. Asymptomatic bacteriuria does not require treatment, particularly in patients with an indwelling urinary catheter. A urine culture should be obtained on any cirrhotic patient suspected to have a urinary tract infection. Antibiotic therapy, when indicated, should be guided by microbiologic susceptibility testing of the urinary isolate. Antibiotic options for empiric therapy of symptomatic infections include fluoroquinolones or expanded-spectrum penicillins or cephalosporins. Indwelling urinary catheters should be removed as soon as possible to reduce the risk of infection.

### BACTEREMIA AND SEPSIS

Cirrhosis predisposes patients to systemic bloodstream infections due to intrahepatic blood shunting and impaired bacterial clearance from the portal blood. Bacteremia has been reported to occur in approximately 9% of hospitalized cirrhotic patients (51) and accounts for 20% of the infections diagnosed during their hospital stay (23). The incidence of bacteremia increases with

the severity of liver disease, and individuals with cirrhosis are more likely to have a diagnosis of sepsis when compared with patients without a diagnosis of cirrhosis (52). The most commonly identified sources of bacteremia have been spontaneous bacterial peritonitis, urinary tract infections, pneumonia, soft tissue infections, and biliary tract infections (51,53). The pathogens identified in blood cultures from bacteremic patients mirror those responsible for the primary source infections. *E. coli*, *Klebsiella pneumoniae*, *Aeromonas hydrophila* and other enteric gram-negative aerobes are common causes of bacteremic infections. Most gram-positive bacteremias are due to *S. aureus*, *S. pneumoniae*, or other aerobic streptococcal species. Bloodstream infection is associated with a poor prognosis despite appropriate antibiotic therapy. Mortality rates commonly exceed 50% (51,54). Poor outcome is independent of the type of bacteremia (54), but in-hospital mortality has been correlated with the absence of fever, an elevated serum creatinine, and marked leukocytosis (53). Cirrhotic patients with suspected bacteremia should receive empiric therapy directed against the most common gram-negative and gram-positive pathogens in this setting. Antibiotic selection should take into consideration local microbial susceptibility patterns. Usual therapeutic options would include expanded-spectrum cephalosporins, piperacillin/tazobactam, or a fluoroquinolone such as levofloxacin or moxifloxacin.

Cirrhotic patients who undergo endoscopic procedures for gastrointestinal hemorrhage or transhepatic procedures are at increased risk of bacteremia. Endoscopic variceal sclerotherapy or band ligation for bleeding esophageal varices is associated with a reported risk of bacteremia ranging from 5% to 30% (55–57). Although the bacteremia associated with these procedures may be brief, cirrhotic patients are susceptible to infections from transient bacteremia. Gastrointestinal hemorrhage itself is an independent risk factor for bacteremia and other infections in cirrhotic patients. Antibiotic administration has been shown to reduce infectious complications and mortality in cirrhotic patients who are hospitalized for gastrointestinal hemorrhage (58–61). Antibiotic prophylaxis is recommended for all cirrhotic inpatients with gastrointestinal bleeding (62,63). Fluoroquinolone antibiotics were used in most trials with a median treatment duration of seven days.

## PNEUMONIA

Respiratory tract infections account for approximately 20% of the infectious diseases that are diagnosed in hospitalized cirrhotic patients (21,23,64). *S. pneumoniae* continues to rank first among bacterial pathogens causing community-acquired pneumonia (CAP) in adults (65). Chronic liver disease has long been recognized as a risk factor for bacteremic pneumococcal pneumonia (66). The mortality rate for pneumococcal bacteremia in cirrhotic patients may exceed 50% despite appropriate antibiotic therapy (67). Other organisms commonly responsible for CAP include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Haemophilus influenzae*. Cirrhosis has been associated with an increased risk of severe CAP caused by *Acinetobacter baumannii* (68). Sputum and blood samples should be obtained for appropriate diagnostic studies, including gram-stain (sputum) and cultures (sputum and blood). Chronic severe liver disease and/or admission to the intensive care unit are clinical indications for pneumococcal urinary antigen testing in patients suspected to have CAP (69). Appropriate empiric therapy while awaiting the results of cultures and other tests would include an expanded-spectrum cephalosporin plus a macrolide or a beta-lactam/betalactamase-inhibitor plus a macrolide or a fluoroquinolone (69).

Health care-associated and hospital-acquired pneumonia may be caused by a wide variety of bacteria. Common pathogens include aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, *E. coli*, *K. pneumoniae*, *Serratia marcescens*, *Enterobacter* species, *Proteus* species, and *Acinetobacter* species. *S. aureus* and *S. pneumoniae* predominate among gram-positive pathogens, and the incidence of methicillin-resistant *S. aureus* (MRSA) nosocomial pneumonia is increasing. A number of risk factors have been identified for nosocomial pneumonia caused by multidrug-resistant bacteria (70) (Table 2).

Recommended initial empiric antibiotic therapy for nosocomial pneumonia in patients with no risk factors for multidrug-resistant pathogens or *P. aeruginosa* would be ceftriaxone or a fluoroquinolone or ampicillin/sulbactam or ertapenem. Patients with any risk factors listed in Table 2 or with onset of nosocomial pneumonia after four days of hospitalization are more

**Table 2** Risk Factors for Nosocomial Pneumonia Due to Resistant Bacteria

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Antimicrobial therapy in preceding 90 days
Current hospital stay $\geq$ 5 days
High frequency of antibiotic resistance in the community or hospital unit
Hospitalization $\geq$ 2 days in preceding 90 days
Residence in nursing home or extended care facility
Home infusion therapy (including antibiotics)
Chronic dialysis within 30 days
Home wound care
Family member with multi-drug resistant pathogen
Immunosuppressive disease and/or therapy

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Source: Adapted from Ref. 70.

likely to have infection due to multidrug-resistant pathogens. Initial empiric therapy in such cases should include an antipseudomonal cephalosporin (e.g., cefepime) or antipseudomonal carbapenem (e.g., imipenem) or piperacillin/tazobactam plus an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) plus vancomycin or linezolid if MRSA risk factors are present or there is a high incidence locally (70). Because of increased risks of aminoglycoside-induced nephrotoxicity and ototoxicity, the use of these agents should be avoided in cirrhotic patients if possible (30).

## OTHER INFECTIONS

### ***Vibrio* Infections**

*Vibrio* bacteria are gram-negative halophilic inhabitants of marine and estuarine environments. Typical infections caused by these organisms include gastroenteritis, wound infections, and septicemia. Infection usually occurs following consumption of contaminated food or water or by cutaneous inoculation through wounds. The most common pathogens include *V. cholerae*, *V. parahaemolyticus*, and *V. vulnificus*. Preexisting liver disease is a major risk factor for *Vibrio* infections and has been associated with a fatal outcome in both wound infections and primary septicemia (71). *V. vulnificus*, the most virulent of the noncholera vibrios, can rapidly invade the bloodstream from the gastrointestinal tract. Classic clinical features of *V. vulnificus* sepsis include the abrupt onset of chills and fever followed by hypotension with subsequent development of disseminated skin lesions within 36 hours of onset. The skin lesions progress to hemorrhagic vesicles or bullae and then to necrotic ulcers (72). This syndrome is highly associated with a history of consuming raw oysters. The mortality rate exceeds 50%. Recommended antibiotic therapy includes using an expanded-spectrum cephalosporin plus a tetracycline (e.g., cefotaxime or ceftazidime plus doxycycline) or a fluoroquinolone (e.g., ciprofloxacin) (72).

### **Endocarditis**

Infective endocarditis is a relatively unusual complication of cirrhosis. In the past *E. coli* and *S. pneumoniae* were commonly implicated in these infections. More recent studies have identified *S. aureus* as the most common pathogen along with other gram-positive bacteria such as the *Viridans* streptococci and *Enterococcus* species (73,74). *Streptococcus bovis* biotypes [recently reclassified as *Streptococcus gallolyticus* (*S. bovis* I), *Streptococcus lutetiensis* (*S. bovis* II/1) and *Streptococcus pasteurianus* (*S. bovis* II/2)] are emerging as another important cause of bacteremia and endocarditis in patients with chronic liver disease (75,76). Endocarditis caused by *S. bovis* is commonly associated with bivalvular involvement and a high rate of embolic events.

### **Spontaneous Bacterial Empyema**

Spontaneous bacterial empyema is an infection of a preexisting hydrothorax in cirrhotic patients. Although the majority of these patients have ascites, the presence of ascites is not a prerequisite for spontaneous bacterial empyema. Spontaneous bacterial peritonitis is present in approximately half of patients who develop empyema. The most common causes of

spontaneous bacterial empyema include *E. coli*, *K. pneumoniae*, and streptococci, including *Enterococcus* species, and *S. bovis*. A diagnostic thoracentesis is recommended in patients with cirrhosis who develop pleural effusions and signs and symptoms of infection (77).

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# 20 | Severe Infections in Asplenic Patients in Critical Care

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## INTRODUCTION

The spleen is the largest lymphoid organ in the body, at a crossroads between arterial blood supply and venous return. It acts as a mechanical filter for particulate antigens and microorganisms. As a part of the immune system, the spleen is involved in production of immune mediators like opsonins. A decrease in the level of factors responsible for opsonization, such as properdin and tuftsin, occurs in splenectomized patients (1,2). Complement levels are generally normal after splenectomy, but defective activation of alternate pathway has been reported. In addition, neutrophil and natural killer cell function and cytokine production are impaired (3). The ability of the spleen to remove encapsulated bacteria is especially significant, because these organisms evade antibody and complement binding (4). The antibody response to capsular polysaccharide (in encapsulated bacteria) in normal adults consists of IgM and IgG<sub>2</sub>. In patients with asplenia, IgM production is impaired, recognition of carbohydrate antigens and removal of opsonized particles containing encapsulated organisms are defective. There is no compensatory mechanism within the immune system to overcome these defects in patients with asplenia or suboptimal splenic function. Consequently asplenic and hyposplenic patients are susceptible to fulminant infections, e.g., overwhelming postsplenectomy infections (OPSIs) (4,5).

An extensive review concluded that the incidence of sepsis in adult asplenic is equal to that of the general population, but the mortality rate from sepsis is 58-fold higher (6). A meta-analysis showed that incidence of sepsis after splenectomy done for hematologic disorders, such as thalassemia, hereditary spherocytosis, congenitally acquired anemia, and lymphomas, is as high as 25% (7,8). Most of the infectious complications (50% to 70%) occur within two years of splenectomy (6–10). However the risk of overwhelming infection is lifelong, and postsplenectomy sepsis has been reported more than 40 years after surgery (10–14).

The precise incidence of postsplenectomy infections remains controversial. In one retrospective review of 5902 postsplenectomy patients studied between 1952 and 1987, the incidence of infection was 4.4% in children <16 years and 0.9% in adults (7). A Danish study found that the incidence of pneumococcal infection in splenectomized children decreased dramatically following the introduction of the pneumococcal vaccine and the promotion of early penicillin therapy (15). In another study the overall rate of first, second, and third severe infections in postsplenectomy patients were reported as 7, 45, and 109 per 100 person-years respectively. Second (42% to 76%) and third (61% to 84%) episodes of severe infections occurred within 6 months after the first severe infection. The susceptibility to severe infection was highest in older age groups (5.5 per 100 person-years in those aged >50 years) and in patients splenectomized for hematologic malignancy (9.2 per 100 person-years). Between 50% and 80% of all severe infections or deaths occurred within one to three years after splenectomy; males had a shorter survival compared with females after splenectomy (16).

## MECHANISM OF SEPSIS SYNDROME

In brief, endotoxins released from the breakdown of lipopolysaccharides in the bacterial cell wall initiate the cytokine cascade leading to sepsis syndrome. The host macrophages, plasma cells, endothelial cells, and neutrophils produce reactive products such as tumor necrosis

factor (TNF), interleukins (IL) 1,2,6, and 8, platelet-activating factor (PAF), endorphins, and endothelial-derived relaxin factor. Other reactants in the cascade are arachidonic acid metabolites, prostaglandins, cyclooxygenase lipoxygenase, complement C5a, leukotrienes, bradykinins, and kinins. The bacterial products bind to CD14 molecules on leukocytes, endothelial cells, and other cells leading to release of inflammatory mediators like interleukins, TNF nitric oxide, leading to fever and production of acute-phase reactants. Later during the course it causes vasodilatation and thrombosis with tissue injury. If the cascade is not interrupted, it leads to DIC (disseminated intravascular coagulation), decreased myocardial function, adult respiratory distress syndrome, acute renal failure, shock, multiorgan failure, and ultimately death (17,18). Waterhouse–Friderichsen syndrome and bilateral adrenal hemorrhage may be found at autopsy (19). The mechanism of sepsis syndrome in asplenic patients is the same as in the general population. However, the course is rapid and fulminant.

### CAUSES OF ASPLENIA

There are various conditions that require surgical removal of spleen, but also there are nonsurgical equivalents of splenectomy like congenital asplenia and functional hyposplenism, i.e., anatomically present but poorly performing organ. Functional hyposplenism is associated with various disorders. Although most severe infections are seen in splenectomized patients, they may also occur in functional hyposplenism as well. Functional hyposplenism is associated with the following: *hematologic diseases* such as sickle cell hemoglobinopathies, hemophilia; *neoplasms* such as chronic myeloid leukemia, non-Hodgkin's lymphoma, and following bone marrow transplantation; *gastrointestinal disorders* such as Crohn's disease, ulcerative colitis, and Whipple's disease, the degree of hyposplenism appears to be less in Crohn's disease than ulcerative colitis; *autoimmune disorders* such as chronic active hepatitis, rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus; *infiltrative diseases* such as amyloidosis and sarcoidosis. Alcoholism and splenic irradiation can also lead to hyposplenism (20).

### Epidemiology

The significance of postsplenectomy infections is in its excessive morbidity and mortality despite low incidence. The indications for splenectomy have been reevaluated and there is more conservative approach to splenic resection. Overall numbers are decreasing as well as the percentage of cases for particular indications. This has been the case primarily in two areas: splenic trauma and hematologic malignancies. The growing awareness of potential long-term complications continues to lead to more caution in the use of splenectomy with greater effort in surgery to preserve some splenic tissue (21–26).

### Microbiology

Infections in asplenic or hyposplenic patients can occur with any organism, be it bacteria, virus, fungus, or protozoan. Acute and short-term complications in the perioperative period, such as subphrenic abscess, are high when multiple other procedures are performed. The etiology of these infections is primarily staphylococci and enteric gram-negative bacilli, not the conventional bacteria involved in OPSIs. Delayed and long-term major risks include recurrent bacterial infections with encapsulated bacteria (10). The three most common encapsulated organisms that cause OPSIs are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* (6,10).

#### *Streptococcus pneumoniae*

*S. pneumoniae* is the most common organism involved in postsplenectomy sepsis, it is the causative agent in 50% to 90% of cases (6,10). Age appears to be an important factor; the percentage of pneumococcal OPSIs tends to increase with age (27). There is neither a predominant pneumococcal capsular serotype nor anything to suggest that the distribution of pneumococcal serotypes involved in OPSI is different than in the general population.

*Haemophilus influenzae*

*H. influenzae* type b is the second most common organism related to OPSI and accounts for 32% of the mortality. Most cases (86%) occur in children younger than 15 years, but the overall incidence has decreased due to wide usage of conjugated *H. influenzae* type b vaccine (7).

*Neisseria meningitidis*

*N. meningitidis* is cited as the third most common cause of OPSI. Even though there is no conclusive evidence, many investigators feel that splenectomized patients are at high risk for fulminant meningococemia (7).

*Capnocytophaga canimorsus*

It is a fastidious gram-negative bacillus, previously referred to as CDC group DF-2 (dysgonic fermentor-2), and part of normal oral flora of dogs and cats. The organism is transmitted to humans by exposure to an animal, usually via bite or scratch, and can lead to fulminant sepsis (28). Infection in asplenic or hyposplenic settings can be associated with an eschar at the bite site and can produce intraleukocytic gram-negative bacilli in the Buffy coat or peripheral blood smear. The illness tends to manifest one to seven days after animal exposure (29–31).

**Other Bacteria**

*Salmonella* species do not play a large role in OPSIs, although *salmonella* is a prominent pathogen in children with sickle cell anemia and splenic dysfunction. Non-typhoid *Salmonella* species, which normally cause gastroenteritis, may cause disseminated infection in asplenic patients. Infections with gram-negative bacteria, notably *Escherichia coli* and *Pseudomonas aeruginosa*, also occur with increased frequency in splenectomized patients and are often associated with high mortality. *Enterococcus* species, *Bacteroides* species, *Bartonella*, *Plesiomonas shigelloides*, *Eubacterium plautii*, and *P. pseudomallei* also are reported. Both *Salmonella* and *Bartonella* infection has been linked to reticuloendothelial blockade (32,33). *Streptococcus suis*, a zoonotic gram-positive bacteria, has been reported in several cases of bacteremias in asplenic individuals and is associated with swine exposure (34). Human granulocytic ehrlichiosis may be more severe, recurrent, with a prolonged course in individuals who are asplenic (35).

**NONBACTERIAL PATHOGENS**

The splenectomized host also appears to be more susceptible to serious infections with certain protozoa. Babesiosis caused by an *intraerythrocytic protozoan*, *Babesia microti* in North America and *Babesia bovis* in Europe has been reported to cause significant morbidity and mortality in asplenic hosts. In a review of 22 cases of babesiosis in splenectomized individuals, the infection was more severe and more likely associated with hemolytic anemia, high-grade and persistent parasitemia, and in some cases required exchange transfusion (36). In a recent study splenectomized patients secondary to trauma were twice as likely to have *Plasmodium falciparum* parasitemia and it was more likely to be associated with febrile symptoms. Mature parasites were seen more often in the peripheral blood in asplenic individuals (37).

**HIV INFECTION AND SPLENECTOMY**

Splenectomy may be required in refractory thrombocytopenia associated with HIV. It is not clear however, if the risk of postsplenectomy sepsis in the HIV-infected individual is different from that in the non-HIV-infected person or whether low CD4 cell level contributes to the risk. Following removal of the spleen, CD4 and CD8 lymphocytes will rise, as it does in a non-HIV-infected individual (38). Thus the absolute CD4 count may not be helpful in therapeutic decision making in splenectomized patients, however the CD4 to CD8 ratio remains low and becomes more relevant to decisions on antiretroviral therapy (39).

**OVERWHELMING POSTSPLENECTOMY INFECTIONS****Clinical Presentation**

Time to diagnosis and management is a key factor in OPSIs, with 68% of the deaths occurring within 24 hours and 80% within 48 hours from the initial symptoms (20). OPSIs have a short prodrome and early consideration is vital to facilitate an aggressive and prompt intervention.

A high index of clinical suspicion must be maintained for febrile presentations in the asplenic patient or one with a chronic disease that can produce a dysfunctional spleen. Patients may present with nonspecific symptoms like, low-grade fever, chills, rigors, pharyngitis, muscle aches, and vomiting and diarrhea that might have been present for one to two days prior to clinical deterioration (10). In the setting of known asplenia or splenic dysfunction any febrile illness with or without focal symptoms must be suspected to be postsplenectomy sepsis. Usually no clinically demonstrable site of infection is found in adults. In children younger than five years, however focal infections, particularly meningitis are more prominent. Following the prodrome, deterioration can be very rapid, with progression to hypotension, DIC, diffuse purpura, respiratory distress, and coma can occur in hours rather than in days. Peripheral gangrene requiring amputations has been reported in survivors. Adrenal hemorrhage has frequently been described in cases that come to autopsy. Bacteria can be seen on microscopic examination of peripheral blood and in multiple organ systems in autopsied cases (40-44). Other sequelae include, deafness associated with meningitis and mastoid osteomyelitis, and aortic insufficiency following endocarditis (45,46).

### Diagnosis and Management

The management of OPSIs includes initial aggressive management of the acute illness followed by combination of immunization, antibiotic prophylaxis, and patient education. Diagnostic workup should never delay the presumptive antibiotic therapy. Bacteria can be visualized on Gram stain or Wright stain of the peripheral blood Buffy coat, and if seen on peripheral blood smear it suggests a quantitative bacteremia of  $>10^6$ /mL, which is four logs or greater than that of usual bacteremia. Because of this degree of bacteremia, blood cultures are positive in 12 to 24 hours. Any bullous lesions should be aspirated for Gram stain and culture. A CSF examination may be needed based on clinical symptoms, particularly in children because of the high incidence of meningococcal meningitis with sepsis. Standard lab tests like complete blood count, serum chemistries, and appropriate radiologic studies should be done. In a patient who is postoperative day 5 after splenectomy for trauma, WBC greater than  $15 \times 10^3$ /microl and platelet to WBC ratio less than 20 are reliable marker of infection (47). Further tests, including the peripheral smear for malaria or babesiosis, should be guided by the patient's history. Ascitic and pleural fluid should be examined, if indicated. Furthermore, Howell-Jolly bodies or other evidence of hyposplenism should be sought, especially in an individual with a history of an illness predisposing to hyposplenism.

### Antimicrobial Therapy

Currently there is no proof that early treatment will prevent incipient bacteremia from progressing to full-blown OPSI. However, the literature does support that an aggressive approach improves survival (48). Despite the absence of any controlled studies, self-administration of an antibiotic at first sign of suspicious illness in the asplenic or hyposplenic person is advised, this should be specially instituted if delivery of medical care is not immediately available. In an outpatient setting, a patient suspected to have postsplenectomy sepsis should receive an appropriate broad-spectrum antimicrobial such as ceftriaxone parenterally prior to hospital transfer, whether or not blood cultures are obtained. Local resistance patterns should be taken into account when selecting an initial presumptive regimen, with consideration of antibiotic, such as ceftriaxone and cefotaxime, which are active against penicillin-resistant pneumococci, as well as beta-lactamase producers such as *H. influenzae* and *C. canimorsus*. Some penicillin-resistant pneumococcal isolates are also resistant or only intermediately susceptible to cephalosporins. If such resistance is suspected, the use of vancomycin combined with gram-negative antibiotic coverage for organisms such as meningococcus must be considered. High-level penicillin-resistant pneumococci will definitely require vancomycin with or without rifampin. Other choices include an anti-pneumococcal quinolone, such as levofloxacin, amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, or a newer macrolide (clarithromycin, azithromycin). Levofloxacin has activity against penicillin-resistant *S. pneumoniae*, as well as gram-negative organisms including *H. influenzae*, *N. meningitidis*, and *C. canimorsus*. Amoxicillin/clavulanic acid has activity against beta-lactamase-producing *H. influenzae* and *C. canimorsus* but not against penicillin-resistant

pneumococci. Trimethoprim/sulfamethoxazole and the macrolides do not have consistent activity against penicillin-resistant pneumococci (PRP). The decision to broaden the gram-negative coverage to other gram negatives including *P. aeruginosa* should be based on Gram stain results. In patients with known or suspected central nervous system infections, vancomycin with or without rifampin plus a third-generation cephalosporin is the most optimal initial therapy. Intravenous immunoglobulin is another intervention that has been shown to decrease mortality in asplenic animals (49,50). Granulocyte-macrophage colony-stimulating factor has increased macrophage bactericidal activity in eusplenic and asplenic mice. Treated animals have had improved survival after pneumococcal challenge (51). Babesiosis in the asplenic host is best treated with a combination of clindamycin and quinine. Exchange transfusions to lower high levels of parasitemia also have been used (52,53).

Intravascular volume deficits should be corrected aggressively. Other therapeutic modalities, such as vasopressors, may be warranted in selected cases. The use of high-dose steroid has not been demonstrated to be beneficial.

### Prevention

Preventive strategies fall into three major categories: education, immunoprophylaxis, and chemoprophylaxis (33,54).

### Education

It represents a mandatory strategy in attempting to prevent OPSI. A low level of knowledge regarding OPSI risk can exist at the patient, family, and even the health care worker level. Most patients with asplenia (11% to 50%) remain unaware of their increased risk of serious infection or the appropriate health precautions that should be undertaken (55,56). Asplenic patients should be encouraged to wear a Medi-Alert bracelet or necklace and carry a wallet explaining their lack of spleen and other medical details (33). Patients should be explained regarding the potential seriousness of postsplenectomy sepsis and rapid time course of progression. Patients should be instructed to notify their physician in the event of any acute febrile illness and proceed to nearest emergency department. They should inform any new health care provider, including their dentist, of their asplenic or hyposplenic status. Patients should also be educated regarding travel-related infections such as malaria and babesiosis. Malaria chemoprophylaxis relevant to the local pattern of infestation should be prescribed and preventive measures implemented to reduce mosquito bites (33,54). They should also be educated regarding prompt treatment of even minor dog or other animal bites.

### Immunoprophylaxis

Vaccination is a very important strategy in preventing OPSI. Asplenia or hyposplenism itself is not a contradiction for routine immunization including live vaccines. Vaccination significantly reduces the risk of bacteremia of any cause beyond the postoperative period, and vaccinated patients carry a lower risk of infection than non-vaccinated ones (57).

#### *Pneumococcal Vaccine*

Efficacy of pneumococcal polysaccharide vaccine in preventing postsplenectomy infections has not been determined. Most virulent pneumococcal serotypes tend to be the least immunogenic, and the efficacy of vaccine is poorest in younger patients who would be at the highest risk (58,59). Studies indicate that 30% to 60% postsplenectomy patients never receive the pneumococcal vaccine (55,56). Pneumococcal vaccination should be performed at least two weeks before an elective splenectomy (60). If this could not be done then patients should be vaccinated as soon as possible after surgical recovery and before discharge from hospital. Unimmunized patients who are splenectomized should be immunized at the first opportunity. The immunogenicity of the vaccine is reduced if it is given after splenectomy or while the patient is receiving cancer therapy (58). For this reason the manufacturer recommends that the immunization be delayed for at least six months following immunosuppressive chemotherapy or radiotherapy. Revaccination is recommended for persons two years of age or older who are at highest risk for serious pneumococcal infections. Revaccination in three years may be

considered in asplenic individuals two years or older. Pneumococcal conjugate vaccine is used for routine vaccination of children younger than 24 months and children 24 to 59 months with high-risk medical conditions including asplenia (61). In order to expand the spectrum of protection against pneumococcal disease, consideration should be given to use of both vaccines in all age groups.

#### *Haemophilus Influenzae type B Vaccine*

The *Haemophilus* vaccine has been shown to be immunogenic in patients with impaired splenic function associated with sickle cell anemia (62). The specific concentration of antibody required in patients lacking a spleen is not known. In general, *H. influenzae type B* (HiB) vaccination of persons older than 59 months of age is not recommended. Previously non-vaccinated persons older than 59 months having high-risk condition like functional or anatomic asplenia should be given at least one pediatric dose of a HiB conjugate vaccine (63). The requirement for reimmunization is not defined.

#### *Meningococcal Vaccine*

The quadrivalent, unconjugated capsular meningococcal vaccine (type A, C, Y, and W135) is immunogenic in the asplenic patient but less so in those patients who are also treated with chemotherapy and radiotherapy (64). Vaccine is recommended for persons with increased risk of meningococcal disease, including persons with functional or anatomical asplenia. The efficacy and importance of meningococcal vaccination in splenectomized individuals is unknown. The antibody levels rapidly decline in two to three years and postsplenectomy patients will always be at risk, revaccination may be considered five years after receipt of the first dose. The quadrivalent conjugated meningococcal vaccine is used for routine immunization of adolescents and persons 2 to 55 years of age who are at increased risk of meningococcal disease, which includes asplenia (65). The exact duration of protection is unknown but is longer than polysaccharide vaccine.

#### *Influenza Vaccine*

Annual administration of influenza virus vaccine is recommended in asplenic or hyposplenic individuals to prevent the primary disease as well as complications of secondary bacterial infections (33).

### **Chemoprophylaxis**

The first one to three years after splenectomy is the most important time for the risk of infection and mortality. Therefore, the institution of antibiotic prophylaxis in this period is likely to reduce morbidity and mortality. The risk of infection declines significantly beyond that time, and continuing antibiotic prophylaxis would provide lesser benefits. Since most patients are unwilling to take antibiotics lifelong, they should be persuaded to take antibiotics for at least three years, in addition to vaccines as described above. The likelihood of a second or third infection is high in the first six months after a first infection and antibiotic prophylaxis could offer the most benefit in this period for patients who have had a first severe infection (66). Some guidelines advocate continuing the antibiotic prophylaxis in children for five years or until the age of 21. Such approach in adults has never been evaluated. Compliance is a problem in long-term prophylaxis in adults as is the inevitable selection for colonization with nonsusceptible pathogens. A single daily dose of penicillin or amoxicillin is the regimen of choice, but these antibiotics will not protect against organisms resistant to penicillin. Cefotaxime or ceftriaxone have been recommended as presumptive treatment for symptomatic patients who have been taking antibiotic prophylaxis or those with strains known to show intermediate resistance to penicillin (33,67).

### **Self-treatment**

The other strategy is the provision of standby antipneumococcal antibiotics, i.e., the patient retains a personal supply of antibiotics to be taken at first sign of respiratory illness, fever, or



rigors. If there is likely to be a delay in medical evaluation, most authorities support this strategy, but there is no proof that such early self-treatment will lower the incidence of OPSI. The use of prophylactic measures should never be allowed to engender a false sense of security, because OPSIs involving pneumococcal infection have been reported in patients receiving penicillin prophylaxis and vaccinated patients (68).

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# 21 Infections in Burns in Critical Care

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## INTRODUCTION

Over one million people are burned in the United States every year, most of whom have minor injuries and are treated as outpatients. However, approximately 60,000 per year have burns severe enough to require hospitalization. Roughly 3000 of these die (1). Burns requiring hospitalization typically include burns of greater than 10% of the total body surface area (TBSA), and significant burns of the hands, face, perineum, or feet.

Between 1971 and 1991, burn deaths from all causes decreased by 40%, with a concomitant 12% decrease in deaths associated with inhalation injury (2). Since 1991, burn deaths per capita have decreased another 25% according to the Centers for Disease Control (Fig. 1) (3). The graph shows burn deaths have been decreasing by approximately 124 per 100,000 population per year on a linear basis for the last 20 years ( $r^2 = 0.99$ ), which has been most pronounced in the African-American population. These improvements were likely due to effective prevention strategies resulting in fewer burns and burns of lesser severity, as well as significant progress in treatment techniques.

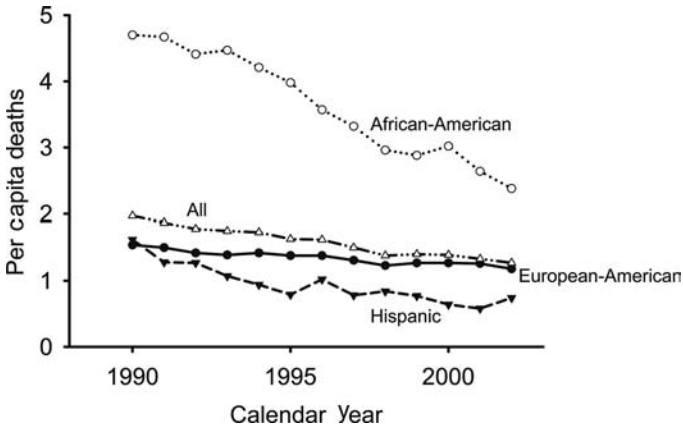
Improved patient care of the severely burned has undoubtedly improved survival. Bull and Fisher first reported in 1949 the expected 50% mortality rate for burn sizes in several age groups (LA<sub>50</sub>). They reported that the LA<sub>50</sub> burn was 49% TBSA for children aged 0 to 14, 46% TBSA for patients aged 15 to 44, 27% TBSA for patients aged 45 and 64, and 10% TBSA for patients 65 years and older (4). These dismal statistics have dramatically improved, with the latest reports indicating 50% mortality for 98% TBSA burns in children 14 and under, and 75% TBSA burns in other young age groups (5,6). Therefore, a healthy young patient with any size burn might be expected to survive (7). The same cannot be said, however, for those aged 45 years or more, where improvements have been much more modest, especially in the elderly (8).

Reasons for these dramatic improvements in mortality after massive burn that are related to treatment generally include better understanding of resuscitation, improvements in wound coverage, improved support of the hypermetabolic response to injury, enhanced treatment of inhalation injuries, and perhaps most importantly, control of infection.

Burn mortality can generally be divided into four causes:

1. Immolation and overwhelming damage at the site of injury, with relatively immediate death
2. Death in the first few hours/days due to overwhelming organ dysfunction associated with burn shock
3. Death due to medical error at some time during the hospital course
4. Development of progressive multiple organ failure with or without overwhelming infectious sepsis, highlighted by the development of the acute respiratory distress syndrome and cardiovascular collapse

The first cause is generally unavoidable other than by primary prevention of the injury. The second cause is unusual in modern burn centers with the advent of monitored resuscitation as advocated by Pruitt et al. (9) and Baxter and Shires (10). The third cause is minimized by appropriate medical care, and is being rectified to some extent by the institution



**Figure 1** Per capita mortality from burns in the United States. The rate has been decreasing yearly at approximately 124 deaths/100,000 persons per year ( $r = 0.99$ ).

of evidence-based clinical guidelines and quality improvement programs, which are becoming the standard in intensive care units around the world. The last is the most common cause of death for those who are treated at a burn center, and it is that which is linked to the development of infection to the burn wound.

### PREVENTION OF BURN WOUND INFECTION

Two practices have revolutionized burn care to improve outcomes by decreasing invasive wound infections. Early excision and closure of the burn wound prevents infection by eliminating the eschar that harbors microorganisms and providing a barrier to microorganism growth and invasion. The other is the timely and effective use of antimicrobials both topical and systemic. The infected burn wound filled with invasive organisms is uncommon in most burn units due to wound care techniques and the effective use of antibiotics.

Early excision and an aggressive surgical approach to deep wounds have achieved mortality reduction in patients with extensive burns. Early removal of devitalized tissue prevents wound infections and decreases inflammation associated with the wound. In addition, it eliminates foci of microbial proliferation, which may be a source of transient bacteremia. Those transient bacteremias, most common during surgical manipulations, may prime immune cells to react in an exaggerated fashion to subsequent insults leading to whole body inflammation—the systemic inflammatory response syndrome (SIRS), and remote organ damage (multisystem organ failure). We recommend complete early excision of clearly full-thickness wounds within 48 hours of the injury, and coverage of the wound with autograft or allograft skin when autograft skin is not available. Within days, this treatment will provide a stable antimicrobial barrier to the development of wound infections. Barret and Herndon described a study in which they enrolled 20 subjects, 12 of whom underwent early excision (within 48 hours of injury) and 8 of whom underwent delayed excision (>6 days after injury). Quantitative cultures from the wound excision showed that early excision subjects had less than 10 bacteria/g of tissue, while those who underwent delayed excision had greater than  $10^5$  organisms, and three of these patients (37.5%) developed histologically proven burn wound infection compared to none in the early excision group (11). In another study from the same center, it was found that delayed excision was associated with a higher incidence of wound contamination, invasive wound infection, and sepsis with bacteremia compared with the early group when the rest of the hospitalization was considered (12). These two studies show that the best control of the burn wound is obtained with early excision.

Before or after excision, control of microorganism growth is obtained by the use of topical antibiotics. Available topical antibiotics can be divided into two classes, salves and soaks. Salves are generally applied directly to the wound and left exposed or covered with cotton dressings, and soaks are generally poured into cotton dressings on the wound. Each of these classes of antimicrobials has advantages and disadvantages. Salves may be applied once or twice a day, but may lose effectiveness between dressing changes. More frequent dressing

**Table 1** Topical Antimicrobials Commonly Used in Burn Care

Salves	Advantages	Disadvantages
Silver sulfadiazine (Silvadene 1%)	<ul style="list-style-type: none"> <li>• Broad-spectrum</li> <li>• Relatively painless on application</li> </ul>	<ul style="list-style-type: none"> <li>• Transient leucopenia</li> <li>• Does not penetrate eschar</li> <li>• May tattoo dermis with black flecks</li> </ul>
Mafenide acetate (Sulfamylon 11%)	<ul style="list-style-type: none"> <li>• Broad-spectrum</li> <li>• Penetration of eschar</li> </ul>	<ul style="list-style-type: none"> <li>• Transient pain upon application to partial thickness burns</li> <li>• May cause an allergic rash</li> <li>• Carbonic anhydrase inhibition</li> </ul>
Polymyxin B/neomycin/bacitracin	<ul style="list-style-type: none"> <li>• Wide spectrum</li> <li>• Painless on application</li> <li>• Colorless allowing direct inspection of the wound</li> </ul>	<ul style="list-style-type: none"> <li>• Antimicrobial coverage less than alternatives</li> </ul>
Mupirocin (Bactroban)	<ul style="list-style-type: none"> <li>• Broad-spectrum (especially <i>Staphylococcus</i> species)</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive</li> </ul>
Nystatin	<ul style="list-style-type: none"> <li>• Broad antifungal coverage</li> </ul>	<ul style="list-style-type: none"> <li>• May inactivate other antimicrobials (Sulfamylon)</li> </ul>
<i>Soaks</i>		
Silver nitrate (0.5%)	<ul style="list-style-type: none"> <li>• Complete antimicrobial coverage</li> <li>• Painless</li> </ul>	<ul style="list-style-type: none"> <li>• Black staining when exposed to light</li> <li>• Electrolyte leaching</li> <li>• Methemoglobinemia</li> </ul>
Mafenide acetate (Sulfamylon 5%)	<ul style="list-style-type: none"> <li>• Same as salve</li> </ul>	<ul style="list-style-type: none"> <li>• Same as salve</li> </ul>
Sodium hypochlorite (Dakin's 0.05%)	<ul style="list-style-type: none"> <li>• Broad-spectrum coverage</li> </ul>	<ul style="list-style-type: none"> <li>• Inactivated with protein contact</li> <li>• Cytotoxic</li> </ul>
Acetic acid	<ul style="list-style-type: none"> <li>• Broad-spectrum coverage (especially <i>Pseudomonas</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• Cytotoxic</li> </ul>

changes increase the risk of shearing with loss of grafts or underlying healing cells. Soaks will remain effective because antibiotic solution can be added without removing the dressing, however, the underlying wound and skin can become macerated. Topical antibiotic salves include 11.1% mafenide acetate (Sulfamylon), 1% silver sulfadiazine (Silvadene), polymyxin B, neomycin, bacitracin, mupirocin, and the antifungal agent nystatin (Table 1). No single agent is completely effective, and each has advantages and disadvantages.

Silver sulfadiazine is the most commonly used topical agent. It has a broad spectrum of activity from its silver and sulfa moieties covering gram-positives, most gram-negatives, and some fungal forms. Some *Pseudomonas* species possess plasmid-mediated resistance. It is relatively painless upon application, has a high patient acceptance, and is easy to use. Occasionally, patients will complain of some burning sensation after it is applied, and a substantial number of patients will develop a transient leukopenia three to five days following its continued use. This leukopenia is generally harmless, and resolves with or without cessation of treatment.

Mafenide acetate 11.1% cream, which also has a broad spectrum of activity particularly against resistant *Pseudomonas* and *Enterococcus* species and readily diffuses into eschar, can control, and even reduce the density of bacteria in a burn wound in which delayed initiation of topical antimicrobial therapy has permitted intraeschar proliferation of microorganisms. Control of the microbial density in the burn wound by topical therapy not only decreases the occurrence of burn wound infection per se but also permits burn wound excision to be carried out with marked reduction of intraoperative bacteremia and endotoxemia. These two conditions formerly compromised the effectiveness of burn wound excision performed on other than the day of injury. Disadvantages include transient pain following application to skin with sensation,

such as second-degree wounds. It also can cause an allergic skin rash and has carbonic anhydrase inhibitory characteristics that can result in a metabolic acidosis when applied over large surfaces. For these reasons, mafenide acetate is typically reserved for small full-thickness injuries, wounds with obvious bacterial overgrowth, or in those full-thickness wounds that cannot be rapidly excised, such as in patients with concomitant devastating head injuries.

Petroleum-based antimicrobial ointments with polymyxin B, neomycin, and bacitracin are clear on application, painless, and allow for easy wound observation. These agents are commonly used for treatment of facial burns, graft sites, healing donor sites, and small, partial-thickness burns. Mupirocin is another petroleum-based ointment that has improved activity against gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* and selected gram-negative bacteria. Nystatin, either in a salve or powder form, can be applied to wounds to control fungal growth. Nystatin-containing ointments can be combined with other topical agents to decrease colonization of both bacteria and fungus. The exception is the combination of nystatin and mafenide acetate because each will inactivate the other.

Available agents for application as a soak include 0.5% silver nitrate solution, 0.025% sodium hypochlorite (Dakin's), 5% acetic acid (Domburo's), and most recently mafenide acetate as a 5% solution. Silver nitrate has the advantage of painless application, and almost complete antimicrobial coverage. The disadvantages include its staining of surfaces to a dull gray or black when the solution dries. This can become problematic in deciphering wound depth during burn excisions and in keeping the patient and surroundings clean of the black staining with exposure to light. The solution is hypotonic as well, and continuous use can cause electrolyte leaching, with rare methemoglobinemia as another complication. Dakin's is a basic solution with effectiveness against most microbes; however, it also has cytotoxic effects on the patients wounds, thus inhibiting healing. Low concentrations of sodium hypochlorite have less cytotoxic effects while maintaining the antimicrobial effects in vitro. In addition, hypochlorite ion is inactivated by contact with protein, so the solution must be continually changed either with frequent application of new solution or continuous irrigation. The same is true for acetic acid solutions; however, this solution may be more effective against *Pseudomonas*, although this may only be a discoloration of pyocyanine released by this organism without effect on its viability. Mafenide acetate soaks have the same characteristics of the mafenide acetate salve but are not recommended for primary treatment of intact eschar.

It must be stated that all topical agents inhibit epithelialization of the wound to some extent, presumably due to toxicity of the agents to keratinocytes and/or fibroblasts, polymorphonuclear cells, and macrophages. Therefore, these agents should be used with this in mind. The alternative of wound infection occurring in an untreated wound, however, justifies the routine use of topical agents.

The use of perioperative systemic antimicrobials also has a role in decreasing burn wound sepsis until the burn wound is closed. Common organisms that must be considered when choosing a perioperative regimen include *Staphylococcus* and *Pseudomonas* species, which are prevalent in wounds. After massive excisions, gut flora are often found in the wounds, mandating consideration of these species as well, particularly *Klebsiella pneumoniae*. Perioperative antibiotics clearly benefit patients with injuries greater than 40% TBSA burns, as described below.

The use of perioperative antibiotics has been linked to the development of multiple resistant strains of bacteria and the emergence of fungi in several types of critical care units. Considering this and other data, we recommend that systemic antibiotics should be used short term (24 hours) routinely as perioperative treatment during excision and grafting because the benefits outweigh the risks. We use a combination of vancomycin and amikacin for this purpose, covering the two most common pathogens on the burn wound, i.e., *Staphylococcus* and *Pseudomonas*. The preferred perioperative regimen includes 1 g of vancomycin given intravenously one hour prior to surgery, and another gram 12 hours after the surgical procedure, and a dose of amikacin (based on patient weight, age, and estimated creatinine clearance) given 30 minutes prior to surgery and again eight hours after surgery. Next, systemic antibiotics should be used for identified infections of the burn wound, pneumonia, etc. The antibiotics chosen should be directed presumptively at multiply resistant *Staphylococcus* and *Pseudomonas* and other gram-negatives. The antibiotic regimen is modified if necessary on the basis of culture and sensitivity results.

The most common sources of sepsis are the wound and/or the tracheobronchial tree; efforts to identify causative agents should be concentrated there. Another potential source, however, is the gastrointestinal tract, which is a natural reservoir for bacteria. Starvation and hypovolemia shunt blood from the splanchnic bed and promote mucosal atrophy and failure of the gut barrier. Early enteral feeding has been shown to reduce morbidity and potentially prevent failure of the gut barrier (13). At our institution, patients are fed immediately during resuscitation through a nasogastric tube. Early enteral feedings are tolerated in burn patients, preserve the mucosal integrity, and may reduce the magnitude of the hypermetabolic response to injury. Support of the gut goes along with carefully monitored hemodynamic resuscitation. Enteral feedings can and should be continued throughout the perioperative and operative periods.

Selective decontamination of the gut has been reported to be of use in preventing sepsis in the severely burned. de La Cal et al. showed a significant reduction in mortality in severe burns treated with selective gut decontamination that was associated with a decreased incidence of pneumonia. This study analyzed 107 patients randomized to placebo or treatment (14). This is refuted by another smaller study that showed no benefit to selective gut decontamination, but only an increase in the incidence of diarrhea (15).

### BURN WOUND INFECTION

Before the development of effective topical antibacterial chemotherapy, burn wound infections were the most common infections in burn patients, and invasive burn wound sepsis was the most common cause of death in patients who died in burn centers (16). Destruction of the blood vessels in the burned tissue renders it ischemic. The denatured protein comprising the eschar presents a rich pabulum for microorganisms. Both of these conditions conspire to make the burn wound a *locus minoris resistentiae* in the setting of burn-induced immunosuppression. Effective antimicrobial chemotherapy, achieved by the use of topical agents such as mafenide acetate and silver sulfadiazine burn creams and silver nitrate soaks or silver-impregnated materials, impedes colonization and reduces proliferation of bacteria and fungus on the burn wound.

The combined effect of topical therapy and early burn wound excision decreased the incidence of invasive burn wound sepsis as the cause of death in patients at burn centers from 60% in the 1960s to only 6% in the 1980s. An historical study of the use of mafenide acetate in burned combatants during the Vietnam War demonstrated a 10% reduction in mortality in those with severe burns treated with mafenide versus those without topical treatment (17). In the past 14 years, invasive burn wound infection, both bacterial and fungal, has occurred in only 2.3% of 3,876 patients admitted to the U.S. Army Burn Center in San Antonio (18) who were treated with early excision and topical/systemic antibiotics as described above.

The organisms causing burn wound infections change over time and have anticipated, by approximately a one decade lead time, the predominant organisms causing infections in other surgical ICUs. Prior to the availability of penicillin, beta-hemolytic streptococcal infections were the most common infections in burn patients. Soon after penicillin became available, *Staphylococci* became the principal offenders. The subsequent development of anti-staphylococcal agents resulted in the emergence of gram-negative organisms, principally *Pseudomonas aeruginosa*, as the predominant bacteria causing invasive burn wound infections. Topical burn wound antimicrobial therapy, early excision, and the availability of antibiotics effective against gram-negative organisms was associated with a recrudescence of staphylococcal infections in the late 1970s and 1980s, which has been followed by the reemergence of infections caused by gram-negative organisms in the past 15 years. During this time period, it was also noted that hospital costs and mortality are increased in those patients from whom *Pseudomonas* organisms were isolated (19).

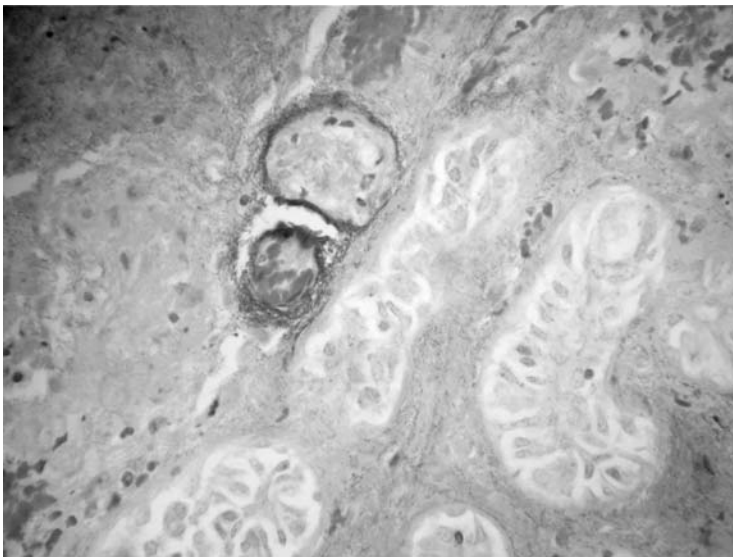
Assessment of the microbial ecology in burn centers is common. Recent data in the literature indicate that coagulase-negative *Staphylococcus* and *S. aureus* are the most common organisms recovered from the burn wound on admission. In the following weeks, these organisms were superseded by *Pseudomonas*, indicating that these organisms are the most common found on burn wounds later in the course, and are therefore the most likely organisms to cause infection (20). In another burn center, it was again found that late isolates are dominated by *Pseudomonas*, which was shown to be resistant to most antibiotics save amikacin and tetracycline (21). Of late, common isolates in the burn wound are those of the *Acinetobacter* species, which are often resistant to most known antibiotics. Currently at the U.S.



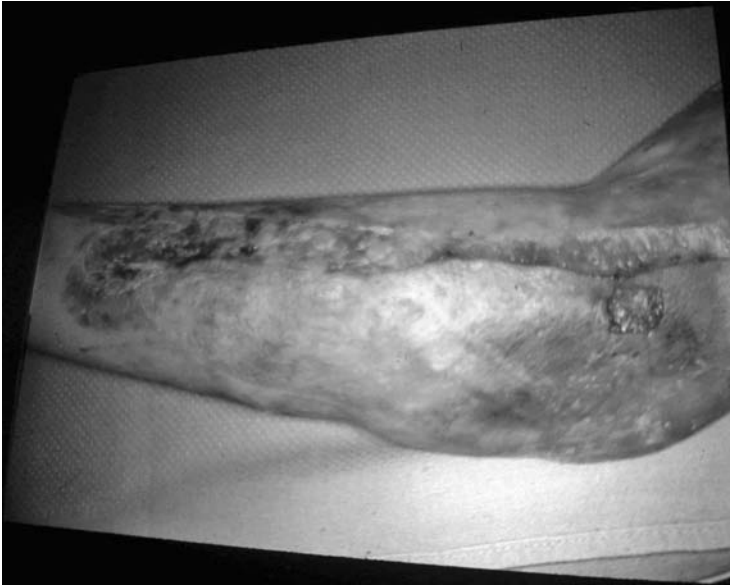
Army Burn Center (2003–2008), approximately 25% of the isolates from patients newly admitted are of this type. However, in no case were these organisms found to be invasive, and in those who died, infection with this organism was not found to be the most likely cause of death (22). Instead, it was the finding of invasive fungus or *K. pneumoniae*, which were the likely cause of death in those who succumbed to burn wound infection. This is in congruence with the findings of Wong et al in Singapore, who showed that acquisition of *Acinetobacter* was not associated with mortality. They did note, however, that acquisition of *Acinetobacter* was associated with the number of intravenous lines placed and length of hospital stay (23), which increased hospital costs (24). If treatment is deemed necessary, oftentimes this will require intravenous colistin, which has a high toxicity profile. It was recently shown to have a 79% response rate when used in the severely burned with *Acinetobacter* infection, however, 14% of these developed renal insufficiency (25). Of other historical note, the isolation of vancomycin-resistant *Enterococcus* species was common in burn centers in the 1990s, but again, these organisms were not found to cause invasive wound infection and were at best associative with burn death, which was much more likely to be due to other causes and other organisms.

### DIAGNOSIS OF BURN WOUND INFECTION

It is essential to identify microbial invasion of the burn wound at the earliest possible time to prevent extensive microvascular involvement and hematogenous dissemination of the infecting organisms to remote tissues and organs. The entirety of the wound should be examined at the time of the daily wound cleansing to record any change in the appearance of the burn wound. The most frequent clinical sign of burn wound infection is the appearance of focal dark brown or black discoloration of the wound, but such change may occur as a consequence of focal hemorrhage into the wound due to minor local trauma. The most reliable sign of burn wound infection is the conversion of an area of partial thickness injury to full thickness necrosis. Other clinical signs that should alert one to the possibility of burn wound infection include unexpectedly rapid eschar separation, degeneration of a previously excised wound with neoeschar formation, hemorrhagic discoloration of the subeschar fat, and erythematous or violaceous discoloration of an edematous wound margin. Pathognomonic of invasive *Pseudomonas* infection are metastatic septic lesions in unburned tissue (ecthyma gangrenosum) (Fig. 2) and green discoloration of the subcutaneous fat by the pyocyanin produced by the invading organisms (Fig. 3).



**Figure 2** Ecthyma gangrenosum. The dark staining viable organisms shown as a “cuff” around the vessel can readily enter the circulation and spread hematogenously to form nodular foci of infection in remote tissues and organs.

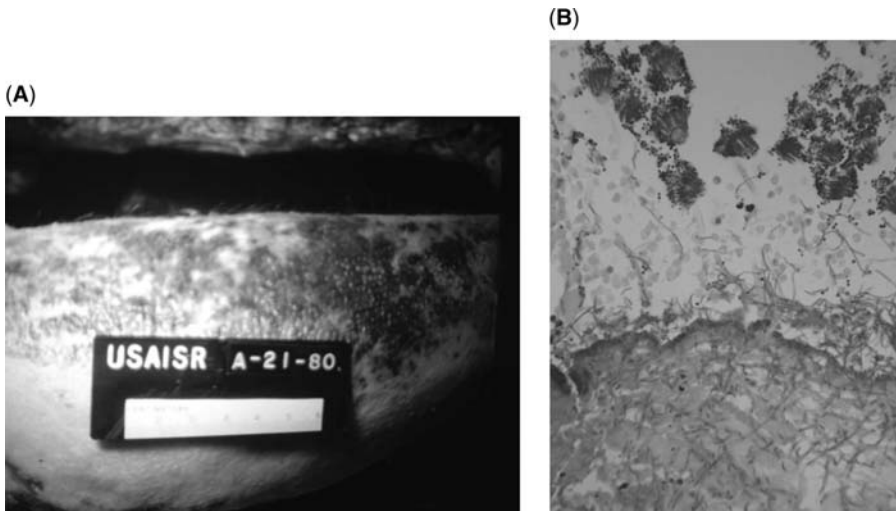


**Figure 3** Gross appearance of invasive *Pseudomonas* infection in the burn wound. Note the focal areas of dark green discoloration distributed unevenly in the burn eschar and exposed subcutaneous tissue in the base of the escharotomy incision.

As early as 1971, it was noted that with the introduction of topical mafenide acetate, wound infections caused by *Phycomycetes* and *Aspergillus* increased 10-fold (26), and further measures such as patient isolation, wound excision, and other topical chemotherapy decreased bacterial infections dramatically while having no effect on the fungi (27). In recent years, as a perverse consequence of the effectiveness of current wound care, fungi have become the most common causative agents (72%) of invasive burn wound infection. Fungal burn wound infections typically occur relatively late in the hospital course (fifth to seventh postburn week) of patients with extensive burns who have undergone successive excision and grafting procedures, but have persistent open wounds. The perioperative antibiotics, which those patients receive for each grafting procedure, suppress the bacterial members of the burn wound flora thereby creating an ecological niche for the fungi. The most common nonbacterial colonizers are *Candida* species, which fortunately seldom invade underlying unburned tissues and rarely cross tissue planes. Isolation of this organism in two sites has been associated with longer wound healing and length of hospital stay, use of artificial dermis, and use of imipenem for bacterial infection (28).

*Aspergillus* and *Fusarium* species, in that order, are the most common filamentous fungi that cause invasive burn wound infection, and these organisms may cross tissue planes and invade unburned tissues (Fig. 4). The most aggressive fungi are the *Phycomycetes*, which readily traverse fascia and produce ischemic necrosis as a consequence of the propensity of their broad nonseptate hyphae to invade and thrombose dermal and subdermal vessels. Rapidly progressing ischemic changes in an unexcised or even excised burn wound should alert the practitioner to the possibility of invasive phycomycotic infection as should proptosis of the globe of an eye. One should be particularly alert to the possibility of invasive phycomycotic infection in patients with persistent or recurrent acidosis. The comorbid effect of a positive fungal culture or fungal infection has been recently reported to be equal to an additional 33% body surface area burn (29). Further work from this group reported that fungal elements were found in 44% of all those who died and underwent an autopsy and death was attributed to fungal wound infection in one-third of these (30).

The appearance of any of those changes mandates immediate assessment of the microbial status of the burn wound. Because of the nature of the wound, bacteria and fungi will be found, some commensals and others opportunists. The mere presence of an organism,



**Figure 4** (A) Gross appearance and histologic finding of invasive *Aspergillus* infection on the arm in a patient who succumbed to infection. Note the discolored, dark, hemorrhagic appearance of the skin. Note organisms present in viable tissue surrounding blood vessels. (B) The photomicrograph shows the presence of hyphae in viable tissue (Stage II B).

however, does not imply infection. It is only with invasion of organisms into viable tissue that they gain access to the bloodstream and spread to other tissues where they release toxins and induce the severe inflammatory response that characterizes burn wound sepsis. Surface swabs and even quantitative cultures, therefore, do not reliably differentiate colonization from invasion (31,32). Histologic examination of a biopsy specimen is the only means of accurately identifying and staging invasive burn wound infection (33). Using a scalpel, a 500 mg lenticular tissue sample is obtained from the area of the wound showing changes indicative of invasive infection. The biopsy must include not only eschar, but also underlying, unburned subcutaneous tissues as histologic diagnosis of invasive infection requires identification of microorganisms that have crossed the viable–nonviable tissue interface to take residence and proliferate in viable tissue. A local anesthetic agent if used should be injected at the periphery of the biopsy site to avoid or minimize distortion of the tissue to be examined histologically. One-half of the biopsy specimen is processed for histologic examination to determine the depth of microbial penetration and identify microvascular invasion. The other half of the biopsy is quantitatively cultured to determine the specific microorganisms causing the invasive infection. The culture results are used to guide systemic antibiotic therapy. In the case of fungal invasion, firm identification of the causative organism is problematic even with both histology and culture, since histology results do not necessarily correlate with culture results (34). Therefore, antifungal coverage should be such that all organisms identified are covered to maximize outcomes.

The biopsy specimen is customarily prepared for histologic examination by a rapid section technique that affords diagnosis in three to four hours. Burn wound infection, if present, can then be staged on the basis of microbial density and depth of penetration to guide treatment. Alternatively, the specimen can be processed by frozen section technique that yields a diagnosis within 30 minutes, but is associated with a 0.6% falsely positive diagnosis rate and a 3.6% falsely negative diagnosis rate (35). If the frozen section technique is utilized, permanent sections must be subsequently examined to confirm the frozen section diagnosis and exclude false negatives. The microbial status of the burn wound is classified according to the staging schema detailed in Table 2. In stage I (colonization), the bacteria are limited to the surface and nonviable tissue of the eschar. Stage I consists of three subdivisions (A, B, and C) defined by depth of eschar penetration and proliferation of microorganisms. Stage II (invasion) also consists of three subdivisions (A, B, and C) defined by extent of invasion of microorganisms into nonviable tissue and involvement of lymphatics and microvasculature. Subsequent

**Table 2** Histologic Staging of Microbial Status of the Burn Wound

## Stage I: Colonization

- A. Superficial: microorganisms present only on burn wound surface
- B. Penetrating: variable depth of microbial penetration of eschar
- C. Proliferating: variable level of microbial proliferation at the nonviable–viable tissue interface (subeschar space)

## Stage II: Invasion

- A. Microinvasion: microorganisms present in viable tissue immediately subjacent to subeschar space
- B. Deep invasion: penetration of microorganisms to variable depth and extent within viable subcutaneous tissue
- C. Microvascular involvement: microorganisms within small blood vessels and lymphatics (thrombosis of vessels common)

mortality increases as the histologic staging increases from IA to IIC with a marked increase in mortality between stages IC and IIA and a further increase with stages IIB and IIC. Microvascular involvement connotes the likelihood of systemic spread and the development of burn wound sepsis, i.e., an invasive burn wound infection associated with systemic sepsis and progressive organ dysfunction.

A negative biopsy in association with progressive clinical deterioration mandates repeat biopsy from other areas of the wound showing changes indicative of infection. Successive biopsies that show progressive penetration and proliferation of microorganisms within the eschar indicate the need for a change in topical agent, i.e., institution of mafenide acetate that can diffuse into the eschar and limit proliferation of the colonizing bacteria. The high mortality associated with microvascular involvement and the recovery of positive blood cultures emphasizes the importance of early diagnosis prior to hematogenous dissemination of the invading microorganisms to remote tissues and organs or rapid proliferation locally with production of toxins.

An immediate change in wound care is called for if a diagnosis of invasive burn wound infection (stage II) is made. Systemic antimicrobial therapy in full dosage should be initiated (amphotericin B or one of the newer agents in the case of fungal infections). The patient should be prepared for surgery and taken to the operating theater as soon as possible to excise the infected tissue, which in the case of invasive fungal infection may necessitate major amputation to encompass extensive subcutaneous transfascial spread. Before excision of a wound harboring an invasive bacterial infection, one-half of the daily dose of a broad-spectrum penicillin (e.g., piperacillin/tazobactam) should be suspended in 150 to 1000 mL of saline and injected by clysis into the subcutaneous tissues beneath the area of infection. A second clysis should be performed immediately before operation if more than six hours have elapsed from the initial clysis. The clysis therapy will prevent further proliferation of the invading organisms and reduce the number of viable bacteria and their metabolic byproducts disseminated by operative manipulation of the infected tissue. In the case of invasive fungal infection, clotrimazole cream or powder should be applied to the infected area as soon as the diagnosis is made and prior to excision.

Following excision of an area of invasive bacterial burn wound infection, the excised wound should be dressed with 5% mafenide acetate soaks. The patient should be returned to the operating room 24 to 48 hours later for thorough wound inspection and further excision of residual infected tissue if necessary. That process is repeated until the infection is controlled and no further infected tissue is evident at the time of re-examination. If the wound infection was caused by a fungus, mafenide acetate soaks should not be used since they may promote further fungal growth; Dakin's soaks or a silver containing dressing should be used.

Successful treatment of patients with extensive burns involving the head and neck has been associated with an increased occurrence of superficial staphylococcal infections in healed and grafted wounds of the scalp and other hair-bearing areas. Those focal areas of suppuration have been termed "burn wound impetigo," which, if uncontrolled, can cause extensive epidermal lysis of the healed and grafted burns. Daily cleansing and twice daily topical application of mupirocin ointment typically controls the process and permits spontaneous healing of the superficial ulcerations. If not controlled with mupirocin, control may be

obtained with frequent irrigation with Dakin's (sodium hypochlorite) or Domburo's (acetic acid) solution.

## BACTEREMIA

The topical antimicrobial chemotherapeutic agents commonly applied to burn wounds are bacteriostatic. They do not sterilize the burn wound but limit bacterial proliferation in the eschar and maintain microbial density at levels that do not overwhelm host defenses and invade viable tissue. Even so, manipulation of the wound by cleansing or surgical excision can result in bacteremia. In the 1970s, before early excision became commonplace, wound manipulation was associated with an overall 21% incidence of transient bacteremia (36). The incidence of bacteremia, which increased in proportion to the extent of burn and the vigor of the manipulation, provided the rationale for perioperative antibiotic administration as described above.

The previously noted decrease in invasive bacterial burn wound infection stimulated Mozingo et al. to reassess the incidence of bacteremia associated with burn wound cleansing and excision procedures. In 19 burn patients, those authors found only a 12.5% overall incidence of manipulation induced bacteremia. The incidence of bacteremia was related to both the extent of burn and the time that had elapsed after the burn injury. Wound manipulation in patients with burns of less than 40% of the total body surface did not elicit bacteremia. In patients with more extensive burns, the incidence of bacteremia was 30% overall when wound manipulation occurred on or after the 10th post-burn day and rose to 100% in patients whose burns involved more than 80% of the total body surface (37). Those findings can justify omission of perioperative antibiotics for patients with burns of less than 40% of the total body surface, and perhaps even for those with more extensive burns who undergo excision prior to the 10th day after burn.

Bacteremia may also occur in association with uncontrolled infection in other sites. In a critically ill burn patient with life threatening complications, recovery of multiple organisms from a single blood culture, or different organisms from successive blood cultures, indicate severe compromise of host resistance and should not be interpreted as contamination of the cultures. An antibiotic or antibiotics effective against all of the recovered organisms should be administered to such a patient at maximum dosage levels and the septic source of the blood-borne organisms should be identified and controlled. The comorbid effect of septicemia is organism-specific. Historically, gram-negative septicemia and candidemia significantly increased mortality above that predicted on the basis of the extent of burn, but gram-positive septicemia had no demonstrable effect upon predicted mortality (38). Current techniques of wound care and improvements in general care of the burn patient have not only reduced the incidence of bacteremia but have also significantly ameliorated the comorbid effect of gram-negative septicemia (39).

Anaerobes are very rarely isolated from the blood of burned patients. In a nine-year study, investigators compared 4059 paired aerobic and anaerobic cultures from burned patients and found only four anaerobic isolates (all *Propionibacterium*), none of which were associated with infection. However, they noted that 46 cultures with isolated bacteria, or 13% of those with identified bacteria, were found only in the anaerobic bottle. All of these were obligate or facultative anaerobes. They concluded that detection of significant anaerobic bacteremia in burned patients is very rare, and anaerobic cultures are not needed for this purpose. However, anaerobic culture systems are also able to detect facultative and obligate bacteria; deletion of anaerobic culture medium may have deleterious clinical impact.

## SEPSIS

The diagnosis of sepsis based on clinical criteria is made commonly in the severely burned, but the screening for the diagnosis is at times difficult. In fact, traditional signs of infection such as elevation of white blood cells, increasing neutrophil content, or temperature elevation are not reliable (40). Other signs such as enteral feeding intolerance, thrombocytopenia, and increasing insulin resistance may be better signs of sepsis (41). Once the diagnosis of sepsis is secure, a clear source of infection from the burn wound, pneumonia, or bacteremia may still be elusive. This is usually associated with progression of multiple organ failure when a source is not

identified and controlled. In fact, investigators have shown that 17% of burned patients who develop sepsis associated with multiple organ failure will not have a preceding diagnosis of infection (42). In this condition, a thorough search should be made for an infectious source, including careful and repeated examination of the wound. Other potential sources include the urinary tract, endocarditis, catheter related sepsis, and meningitis. A perirectal abscess must also be considered. If a source is still not found, it is conceivable that an overwhelming signal of inflammation from the wound could be the cause. It must be emphasized that this is a diagnosis of exclusion, and even after the diagnosis is made, the search for a source of infection must continue. Such patients are often treated with presumptive wide-spectrum antibiotics. In this case, anti-fungal medications might also be considered.

Of late, investigators have been in search of genetic markers that herald the development of sepsis, which could be related to the condition described earlier. Barber et al. recently described two single nucleotide polymorphisms (SNPs) in the DNA of patients who were more susceptible to the development of severe sepsis defined as signs of sepsis such as fever and high white blood cell count, and organ dysfunction or septic shock. The first, TLR4 +896 G-allele, imparted a 1.8-fold increased risk of developing severe sepsis following burn relative to AA homozygotes. The second, tumor necrosis factor-alpha -308 A-allele, imparted a 1.7-fold increase in risk compared to GG homozygotes. However, these alleles were not associated with mortality (43). This early work signifies that slight genetic differences are likely to result in different responses to injury such as a burn. Identification of these alleles may eventually assist practitioners in the care of these patients who are at risk and even mandate treatment modifications.

## VIRUSES

On occasion, fevers will develop in the burned patient in association with the development of herpetic lesions. These initially present as papules with or without an erythematous rash that progress to vesicles and pustules. These lesions commonly rupture and develop crusts on the denuded base. Crusted, shallow, serrated lesions at the margin of a healing or recently healed partial thickness burn, particularly in the nasolabial area, are typical of herpes simplex virus-1 infections. Cytomegalovirus infections have also been reported in burned patients. Titers for antibodies to cytomegalovirus and herpes simplex virus-1 may be found to increase, and intranuclear inclusion bodies in a biopsy specimen from the lesion may also be found.

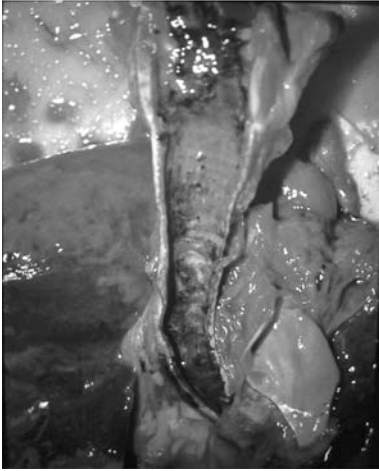
Excision is not required for the treatment of herpetic burn wound infections unless secondary invasive bacterial infection occurs in the herpetic ulcers, in fact, no changes in mortality or length of stay was found in those with viral infections and those without (44). The cutaneous ulcerations of herpetic infections should be treated with twice-a-day application of a 5% acyclovir ointment to decrease symptoms. Identified viral infection is usually self-limited, but in severe cases, consideration can be given to systemic or topical treatment with acyclovir or ganciclovir. Systemic herpes simplex virus-1 infections involving the liver, lung, adrenal gland, and bone marrow, though rare, are typically fatal and justify systemic acyclovir treatment.

## PNEUMONIA

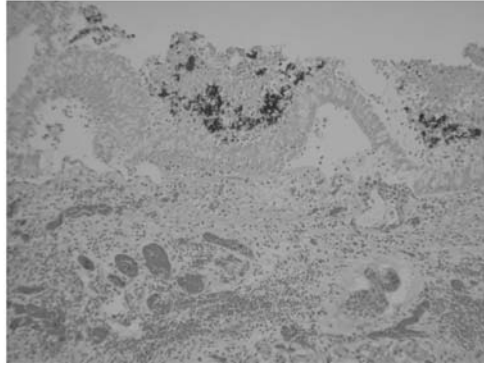
Pneumonia is now the most common infection in burn patients. The burn injury makes the patient fivefold more susceptible to the development of pneumonia because of mucociliary dysfunction associated with inhalation injury, atelectasis associated with mechanical ventilation, and impairment of innate immune responses (45) (Fig. 5). However, with better microbial control of the burn wound, the route of pulmonary infection has changed from hematogenous to airborne, and the predominant radiographic pattern has changed from nodular to that of bronchopneumonia (46). Nonetheless, some investigators still report a pneumonia rate of 48% in severely burned patients treated in a burn center (47,48). Others have observed much lower rates (49–51).

The diagnosis of pneumonia in the burned patient is difficult, as the traditional harbingers of pneumonia such as fever, high white blood cell count, and purulent sputum are common in the absence of infection in the severely burned, who have inflammation associated with burn induced SIRS. They are also often intubated for airway control because of inhalation

(A)



(B)



**Figure 5** (A) Gross appearance and histology of inhalation injury. Note the denudation and hemorrhagic change in the trachea wall with erythema and soot. (B) The photomicrograph shows loss of epithelium and soot, which can lead to tracheobronchitis. Similar inflammatory changes and edema in the distal airway predispose the patient to pneumonia.

injury causing airway edema and unhealed lesions and purulence in the tracheobronchial tree (Fig. 5). This provides a portal of entry for microbes into the airway and the lung itself. For this reason, we recommend that pneumonia in the severely burned must be confirmed with the presence of three conditions, signs of systemic inflammation, radiographic evidence of pneumonia, and isolation of a pathogen on quantitative culture of a bronchoalveolar lavage specimen of 10 mL with greater than  $10^4$  organisms/mL of the return. Those patients with signs of sepsis and isolation of high colony counts of an organism on bronchoalveolar lavage without radiographic evidence of pneumonia are considered to have tracheobronchitis, which can become invasive with subsequent demise. These patients are then documented separately from those with pneumonia, but are treated similarly with systemic antibiotics directed at the organism isolated on culture.

Organisms commonly encountered in the tracheobronchial tree include the gram-negatives, such as *Pseudomonas* and *Escherichia coli*, and on occasion the gram-positives such as *S. aureus*. When the diagnosis of pneumonia or tracheobronchitis is entertained, empiric antibiotic choice should include one that will cover both these types of organisms. We recommend imipenem and vancomycin given systemically until the isolates from the bronchoalveolar lavage are returned. The caveat to this is the finding of gram-negative organisms on routine surveillance cultures of the wound. Generally, microbes found on the wound do not reliably predict the causative agent of pneumonia, which requires separate microbial identification. This is certainly true for gram-positive organisms, but recent data from the U.S. Army Institute of Surgical Research indicates that identification of gram-negative organisms, particularly *Pseudomonas* and *Klebsiella* on the wound of a patient with pneumonia warrant presumptive antimicrobial coverage until the causative organism is determined. If sensitivities of the wound organisms are known, the antimicrobial therapy should at the very least include agents to which the organisms are sensitive.

Although no such infections have been encountered in our burn patients to date, there is concern over the recently described necrotizing pneumonias caused by community-acquired MRSA producing the Panton-Valentine leukocidin (52). Those organisms can activate neutrophils within the lung parenchyma, which may then cause rapidly progressing necrosis associated with a forbiddingly high mortality. Recovery of MRSA, from the bronchus of a patient with rapidly progressing pneumonia, mandates prompt institution of maximum dose intravenous vancomycin therapy. The cultured MRSA should be assayed for the leukocidin.

## LINE SEPSIS

As in other critically ill populations, the presence of indwelling catheters for infusion treatments provides a potential source of infection. Because of the relative frequency of bacteremia associated with wound treatment, relative immunosuppression, and the high concentrations of organisms on the skin often surrounding the access site for the intravascular device, line sepsis is common in the burned patient. Santucci et al. reported an incidence of 34 catheter-related bloodstream infections per 1000 central line days in burn patients (51). It has been well documented in other critically ill patients that the most likely portal of entry is the skin puncture site. Ramos et al. did show a significant reduction in catheter-related infection if the site of insertion was at least 25 cm from a burn wound (53). To date, no definitive prospective studies have been done to determine the true incidence of catheter-related infections related to the duration of catheterization. For this reason, most burn centers have a policy to change catheter sites on a routine basis, every three to seven days. Vigilant and scheduled replacement of intravascular devices presumably minimizes the incidence of catheter-related sepsis. The first can be done over a wire using sterile Seldinger technique, but the second change requires a new site. This protocol should be maintained as long as intravenous access is required. Whenever possible, peripheral veins should be used for cannulation even if the cannula is to pass through burned tissue. The saphenous vein, however, should be avoided because of the high risk of suppurative thrombophlebitis. Should this complication occur in any peripheral vein, the entirety of the vein must be excised under general anesthesia with appropriate systemic therapy.

## OTHER INFECTIONS

Aside from the burn wound and catheter-related infections, burn patients are also susceptible to other infections similar to other critically ill patients (Table 3). The third most common site would be the urinary tract because of the common presence of indwelling bladder catheters for monitoring urine output. However, ascending infections and sepsis are uncommon because of the use of antibiotics for other infections and prophylaxis against infection that are commonly concentrated in the urine and thereby reduce the risk of urinary tract infection. The exception to this is the development of funguria, most commonly from *Candida* species. When *Candida* is found in the urine, systemic infection should be considered, as the organisms may be filtered and sequestered in the tubules as a result of fungemia. The same holds true for the other fungi. For this reason, blood cultures are indicated in the presence of funguria to determine the source. If the infection is determined to be local, treatment with bladder irrigation of anti-fungals is indicated. Otherwise, systemic treatment should be initiated.

Because of the relative frequency of bacteremia/fungemia in the severely burned, sequestration of organisms around the heart valves (endocarditis) can be found on occasion. In most large burn centers, at least one case per year of infectious endocarditis will be found on a search for a source of infection. In fact, about 1% of severely burned patients develop this complication. The diagnosis is generally made by the persistent finding of pathogens in the blood, most often *Staphylococcus* or *Pseudomonas* in the presence of valvular vegetations identified by echocardiography (54). This should generally be confirmed with transesophageal echocardiography if lesions are found on transthoracic echocardiography. If such a lesion is found, routine blood cultures should be performed to identify the offending organism. Treatment is primarily long-term intravenous antibiotics (12 weeks) aimed at the isolate. In the presence of a hemodynamically significant valvular lesion, excision and valve replacement

**Table 3** Infections in Burned Patients

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Burn wound infection
Pneumonia
Catheter-related infection
Urinary tract infection
Sinusitis
Endocarditis
Infected thrombophlebitis
Infected chondritis of the burned ear

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should be considered. In these cases even with appropriate treatment, mortality approaches 100% as a reflection of the severity of the burn injury.

Sinusitis is a concern in burn patients because of the need for prolonged intubation of one or both nostrils with feeding tubes or an endotracheal tube (55). Headache, facial pain, or a purulent discharge suggests this diagnosis. Computed tomography of the head and face is used to confirm the diagnosis. Treatment is generally focused on removal of the tubes if possible, and topical decongestants. Sinus puncture for a specimen should be considered if the infection is thought to be life-threatening, with systemic antibiotic treatment of the isolate.

Meningitis is an uncommon infection in the burned patient, but has been found in patients with deep scalp burns involving the calvarial bone and in those with indwelling intraventricular catheters for monitoring of intracranial pressures when there are concomitant head injuries. Only in these cases should this diagnosis be considered, which can be confirmed with computed tomography of the head with intravenous contrast, or lumbar puncture. The diagnosis and treatment of meningitis is covered in depth in other chapters.

An infection that is unique to burned patients is the development of infected chondritis of the ear cartilage. When the skin of the ear is damaged by a burn, this leaves a portal of entry for microorganisms to invade the cartilage of the ear, which is relatively privileged because of a lack of vascularization. This complication occurs two to three times per year in busy burn centers and can be minimized by the use of mafenide acetate cream for treatment of ear burns. This compound diffuses into the cartilage, making it a forbidding environment for bacteria. When the complication occurs, it is characterized by a red, painful, swollen ear that has been burned with open or recently healed wounds. Treatment is surgical with debridement of necrotic and infected cartilage. Adequate drainage of the area must be established with incisions along the outer edge of the pinna or posterior pinna to 'bivalve' the ear if necessary. Following debridement, the wound should be treated with topical mafenide acetate cream.

Lastly, another infection that is common in burned patients is the development of scalp folliculitis (Fig. 6). Burns to the scalp that heal secondarily are susceptible to chronic growth of organisms in remaining hair follicles that result in ulceration and open wounds. Donor sites taken from the scalp because of limited donor sites in other areas can also result in this problem. Initial therapy is aimed at topical treatment to eradicate organisms and allow healing. Because gram-positive organisms predominate, mupirocin is commonly used; alternatively, acetic acid washes are employed. After a reasonable course of treatment (two to three weeks), if the wound does not heal, split thickness grafting may be required.



**Figure 6** Photograph of folliculitis of the scalp. Note the chronic nature and ulceration.

## SUMMARY

Infectious complications have decreased in the severely burned due to effective strategies for prevention and treatment. Nonetheless, infections in the severely burned are still common and can be lethal, highlighted by burn wound infection and pneumonia. Infections common to other critically ill patients are also seen in burn patients and require similar therapeutic interventions. Further strategies to prevent and treat infections in burned patients are still needed and are being actively researched.

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# 22 | Infections Related to Steroids in Immunosuppressive/Immunomodulating Agents in Critical Care

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## INTRODUCTION

This chapter will discuss considerations necessary in the management of the critical care patient taking exogenous glucocorticoids and/or biologic agents for chronic autoimmune or inflammatory disease. Discussion will focus on complications of therapy in relation mainly to serious infections—defined as infection that is fatal, life threatening, or causing prolonged hospitalization. The use of biologic agents as they are newer therapies will be highlighted in the discussion.

## GLUCOCORTICOIDS

Glucocorticoid therapy is the central therapeutic agent for the immediate control of active inflammatory and autoimmune disease due to its blanket and immediate effects on the immune system. However, its use is fraught with a catalogue of damaging and disabling complications that will not be listed here. For this reason, it has been used as a bridge therapy during the time it takes for other less harmful therapeutics to take effect. The hospital-based physician needs to be aware of two potentially devastating complications in the management of the in-patient receiving exogenous corticosteroids: (i) hypothalamic suppression leading to adrenal insufficiency and (ii) risk of serious infection.

Consensus in defining levels of immune suppression with glucocorticoid use is difficult to reach due to immunologic complexities inherent in underlying diseases being treated with corticosteroids as well as variances in patient sensitivity based on genetic make-up. But it is generally accepted that the degree of immune suppression increases with level of dosing and observation of physical changes such as cushingoid features, striae, and vascular friability.

Level of dosing effecting immune response has been suggested through vaccine response studies and studies ascertaining infections as follows:

- Daily prednisone of 10 mg (or its equivalent) or a greater or cumulative dose of 700 mg carried an increased relative risk of 1.6 versus placebo (1)
- Daily prednisone of 10 mg (or its equivalent) or greater carried 1.5 increased risk of infection (2)
- Daily prednisone greater than 40 mg or greater carried an eightfold increased risk of infection (2)

From the above and other studies we glean a tentative definition of prednisone in relation to immunologic suppression as:

- Low dose: less than 10 mg daily
- Moderate dose: 10 to 40 mg daily
- High dose: greater than 40 mg daily

Unlike the other therapeutic agents discussed in this chapter that need to be stopped immediately upon signs of serious infection, abruptly discontinuing glucocorticoids may be detrimental to the patient taking exogenous steroids. Depending on the severity of the illness, glucocorticoids may indeed need to be supplemented to address hypothalamic stress caused by the illness itself. Decisions of hypothalamic support should be made on a case-by-case basis with decision-making between the critical care specialist, rheumatologist, infectious diseases specialist, and perhaps an endocrinologist.

Virtually all cells have glucocorticoid cell membrane and cytoplasmic receptors. The effects of glucocorticoids on the immune system are several:

- The appearance of increased white blood cell count is due to de-margination of leukocytes from the vascular endothelium.
- De-margination of white cells results in decreased leukocyte entry, and thus activity, into areas of inflammation and infection.
- Decreased macrophage and neutrophilic phagocytosis interfere with microbial killing and antigen presentation.
- The steroid/receptor interaction ultimately interferes with the genetic expression of cytokines, chemokines, and adhesion molecules central to initiating and maintaining an inflammatory response. Nuclear factor kappa beta (key transcription factor) is prevented from attaching to the promoter regions of the genes expressing the above inflammatory agents.

The risk of serious infection in the patient receiving exogenous corticosteroids is a real one. Due to steroid effects on innate and adaptive immunity, these patients may present in a very atypical manner with normal signals of the inflammatory response such as fever, itching, rash, or discrete pulmonary lesions, for example, being muted. Corticosteroids act further upstream in the body's immune response and more widely than most of the biologics listed below. Therefore, patients receiving moderate-to-high-dose steroids have been reported to be vulnerable to each of the microbial entities that are listed in the following section for biologic therapy. It is important to maintain a high level of suspicion and conduct a thorough investigation for the unusual suspects and have a low threshold to begin empiric therapy.

## **BIOLOGIC AGENTS**

The introduction of biologic agents has produced an astounding transformation by halting or slowing the progression of diseases, such as rheumatoid arthritis (RA), psoriatic arthritis, spondyloarthropathy, collagen vascular disease, inflammatory bowel disease, and multiple sclerosis resulting in marked decrease of disability and improvement in quality of life and health outcomes. Anti-tumor necrosis factor (TNF) therapy is associated with the development of serious life-threatening infections in addition to other documented effects such as immunogenicity, heart failure, malignancy, and demyelinating disease. Interestingly, we have not seen a similar incidence of serious infections in the newer non-TNF-mediating therapies. This may be due to lessons learned from the postmarketing experience of TNF inhibitors with resultant cautionary measures taken. Further susceptibility to infection is likely conferred by concomitant use of other immunosuppressive therapies, such as glucocorticoids and disease-modifying agents such as methotrexate, coexistent morbidities (3), age (4), and underlying immune dysfunction inherent to many autoimmune diseases (5). It is important to recognize that the patient numbers reflected here are small in comparison to the vast number of patients receiving biologic therapy. Until we understand better infectious disease patterns with the use of these agents, it is important to maintain a high index of suspicion for serious infection with both the usual and the unusual suspects presenting in usual and unusual ways. *Very importantly, with signs or symptoms of potentially serious infection, biologic agents must be discontinued.* We also advocate that with the exceptions of hydroxychloroquine and the presence of transplantation, all other immunosuppressants, such as methotrexate, mycophenolate, cyclosporine etc., be discontinued in the presence of serious infection.

Biologic agents currently in use or under investigation can roughly be divided into:

1. Anti-cytokine [anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), anti-interleukin (IL)-1, anti-IL-6, anti-ILs-12 and -23]
2. Transcription factor interference [anti-Janus kinase 3 (JAK3)]
3. Interference of immune cell migration and entry into sites of inflammation (alefacept, natalizumab)
4. B-cell depletion (rituximab)
5. T-cell interference (abatacept)

### Therapeutic Targets

TNF- $\alpha$  is a multifunctional cytokine that is a chief mediator of inflammation and an integral component to a healthy immune response against infection and malignancy. It is a protein secreted by T cells, natural killer cells, and mast cells but mainly from activated mononuclear phagocytes in response to antigen presentation. Most cells possess TNF receptors. Receptors are either membrane bound or freely circulating. The soluble form acts to neutralize excess circulating TNF. TNF- $\alpha$  has profound pathologic complexity mediating both systemic effects and local damage present in serious systemic complications of infection like sepsis and the destruction seen in many auto-inflammatory diseases. Its effects are as follows (6–9):

- On the hypothalamus causing fever
- On muscle to produce catabolism with resultant weight loss and malaise
- On liver to synthesize acute-phase reactants
- Macrophage recruitment to site of infection
- Stimulation of granulocyte colony-stimulating factor
- Production of nitric oxide in macrophages needed for killing organisms
- Induction of IL-1, another key component in the inflammatory cascade
- Activation of inflammatory and coagulation processes of endothelial cells
- Apoptosis of various tumor cells

There are several approved anti-TNF therapies in use and under investigation (Table 1) for a wide spectrum of disease: amyloidosis, ankylosing spondylitis, Behcet's disease, inflammatory bowel disease, periodic fever syndromes, psoriasis, psoriatic arthritis, RA, and uveitis.

IL-1 is a key cytokine in the inflammatory cascade that mediates fever, systemic and local inflammation, as well as being associated with bone and cartilage destruction. It is recognized as important in stimulating macrophages, fibroblasts, and hematopoiesis in bone marrow. The IL-1 receptor blocker, anakinra, is used in RA, Still's disease, periodic fever syndromes, and Behcet's disease. It appears that there is no increased risk of infection over placebo (10,11).

IL-6 is a key pro-inflammatory cytokine that is important in the mediation of fever and acute-phase responses. It is secreted by T cells, macrophages, and fibroblasts in response to tissue damage and presence of antigenic material. It is required for resistance against *Streptococcus pneumoniae*. The IL-6 receptor blocker, tocilizumab, is under investigation for use in RA and Castleman's disease, which is a lymphoproliferative disorder.

ILs-12 and -23 are pro-inflammatory targets of combined inhibition by the drug ustekinumab. This is in use and under investigation for inflammatory bowel diseases, multiple sclerosis, psoriasis, and psoriatic arthritis.

JAK3 is a tyrosine kinase responsible for intracellular signaling of hematopoietic cells especially lymphocytes, natural killer cells, and monocytes. This signaling lies upstream of major cytokine expression and adaptive immunity mechanisms such as T- and B-cell proliferation and signaling. Mutations for JAK3 result in severe combined immunodeficiency syndrome (SCID) rendering severe defects in T- and B-cell function. JAK3 is currently under investigation, alone, and in combination with anti-TNF therapy, as a target for several autoimmune and auto-inflammatory diseases of which RA is the most common.

**Table 1** Biologic Agents

Biologic agent	Mechanism of action	Half-life	Administration
Anakinra ( <i>Kineret</i> )	IL-1 receptor antagonist	4 to 6 hours	Daily subcutaneous
Adalimumab ( <i>Humira</i> )	TNF reduction via antibody to TNF- $\alpha$ ; prevents its binding to TNF- $\alpha$ receptor	2 weeks	Subcutaneous injection every 2 wk
Certolizumab pegol ( <i>Cimzia</i> )	A pegylated mAb under investigation conferring a longer half-life	2 weeks	Subcutaneous injection weekly
Etanercept ( <i>Enbrel</i> )	Reduction of circulating TNF via soluble receptor; partial blockade	4 days	Subcutaneous injection twice weekly
Golimumab	A mAb with activity targeting circulating and membrane-bound TNF pending approval	7–20 days	Subcutaneous or intravenous monthly injection
Infliximab ( <i>Remicade</i> )	Antibody inactivates TNF- $\alpha$ ; biologic activity documented at 2 months	9 days	Intravenous infusion at weeks 0, 2, 6, then every 8 wk
Abatacept ( <i>Orencia</i> )	Protein mimics natural CTLA-4; binds CD80 and CD86 on APC blocking CD28 on T cell and thus co-stimulation and activation	8–25 days	Intravenous infusion at weeks 0, 2, 4 then, every 4 wk
Alefacept ( <i>Amevive</i> )	Inhibits T-lymphocyte activation by binding to lymphocyte receptor CD2, blocking interaction with LFA-3	11–12 days (for IV)	Intravenous infusion or intramuscular injection weekly for 12 wk; regimen may be repeated with 12-wk interval
Efalizumab ( <i>Raptiva</i> )	Binds to CD11a of LFA-1 on leukocytes interfering with multiple aspects of T-cell activation and migration	5–8 days	Subcutaneous injection weekly
Rituximab ( <i>Rituxin</i> )	B-cell lysis via chimeric antibody to CD20	Approximately 17 days	Two intravenous infusions, 2 wk apart for RA
Natalizumab ( <i>Tysabri</i> )	Antibody to $\alpha$ -4 integrin molecules blocking T-cell migration into extravascular tissue	7–15 days	Intravenous infusion every 4 wk
Tocilizumab	Antibody to IL-6 receptor	10 days	Intravenous infusion every 4 wk
Anti-JAK3	Inhibits activity of tyrosine kinase required for JAK3 for transcription	Unknown at this time	Daily oral
Ustekinumab	Inhibits activity of IL-12 and IL-23	20–39 days	Subcutaneous injection every 8–12 wk

*Abbreviations:* APC, antigen-presenting cell; IL, interleukin; JAK3, janus kinase 3; LFA, leukocyte function-associated antigen; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

*B-cell depletion* via targeting of the anti-CD20 B-cell surface marker is the anticipated mechanism of action of rituximab. It is in use or under investigation for several disease entities: lymphoma, multiple sclerosis, RA, systemic lupus erythematosus, thrombocytopenic thrombotic purpura, and life-threatening vasculitides. Peripheral measurement of CD19+ B cells can provide insight to immune reconstitution. Lymphocytes may show repletion three weeks after therapy; however, depletion may last as long as one year.

*T-Cell activation and migration* are targeted under several therapies with very different mechanisms of action. Such therapies include abatacept for RA, alefacept, and efalizumab for psoriasis and psoriatic arthritis, and natalizumab for multiple sclerosis.

Abatacept inhibits the activation of T cells by mimicking the naturally inducible CTLA-4. Endogenous CTLA-4 and exogenous abatacept both down-regulate T-cell activity through higher affinity binding to CD80/CD86 on an antigen-presenting cell (APC), which prevents the co-stimulatory binding of CD28 of lesser affinity on the T cell. This co-stimulatory binding is



necessary for activation of T cells that directly impacts cytokine activation and B-cell proliferation. Abatacept is used in the treatment of adult and juvenile RA.

### **Mycobacterium**

Biologic agents, specifically, anti-TNF- $\alpha$  inhibitors, generated great concern when postmarketing surveillance revealed a preponderance of tuberculosis (TB) infection associated with infliximab use (12). Greater than 50% of these cases were disseminated extrapulmonary disease with involvement of bone, bladder, meninges, and lymphoid tissue (12–14). With TNF- $\alpha$  inhibition, the normal mechanisms of immunity are suppressed and unable to mount an effective inflammatory response that would normally wall off the site of TB infection by forming a granuloma, therefore predisposing the immune suppressed patient to disseminated extrapulmonary disease (15). Patients often present atypically without the warning signs of fever, night sweats, respiratory symptoms to which we are familiar (12,16,17). Non-TB mycobacterium, such as *Mycobacterium avium* and *M. leprae* as well as disseminated *M. marinum*, have been rarely described in association with anti-TNF therapy.

It now appears that TB cases associated with anti-TNF- $\alpha$  tend to be reactivations of latent tuberculosis infection (LTBI), occur in the first six months after initiation of therapy, and is more likely to occur with infliximab (14,18–21). Also, 90% of new TB infections would normally be contained; however, with anti-TNF use a high proportion of new infections progress to active disease (20). Regardless of the results of screening tests, it is important to maintain a high suspicion of disseminated mycobacterial infection in patients, receiving biologic agents with collection of appropriate stains and cultures while maintaining a low threshold for empiric treatment.

### **Bacterium**

Adjusted risk of hospitalization for serious infection with an identified bacterial organism appears to be two times greater overall and four times greater in the first three to six months in RA patients on anti-TNF therapy than on methotrexate alone (22,23). Again, a high index of suspicion for both the usual and unusual suspects should be maintained with signs of infection in patients receiving biologic therapy especially in the early months of treatment. Inability to identify the bacterial pathogen in serious infections is at least 15% with the most commonly unidentified infections being pulmonary (23,24). Empiric antibiotic coverage for the organisms discussed subsequently is appropriate in a patient on biologic agents who presents with signs of serious infection.

*Listeria* carries a general mortality rate as high as 25% (25) causing meningitis, encephalitis, and sepsis in vulnerable populations such as newborns, elderly, and patients with immune dysfunction. TNF- $\alpha$  appears to be an important cytokine in effecting macrophage bactericidal ability against *Listeria* (6,7,26,27). Patients on biologic agents with *Listeria* infection may present with severe flu-like, gastrointestinal, or neurological symptoms. Empiric therapy in patients on biologic agents should include ampicillin for *Listeria* coverage.

*Streptococcus pneumoniae* has been described as leading to sudden and severe pneumonia and sepsis, meningitis, necrotizing fasciitis, and peritonitis in patients receiving biologics. TNF- $\alpha$  prevents bacteremia and death in mouse models. TNF- $\alpha$  levels increase proportionally to bacterial burden (28) with TNF- $\alpha$  inhibition conferring impaired clearance of bacteria and early mortality (29) because of pneumococcal pneumonia and fatal peritonitis (30).

*Legionella* pneumonitis, contracted via inhalation from a humid source, usually manifests in people who are elderly or immunosuppressed and has been described in case reports in patients receiving anti-TNF therapy. Depletion of TNF- $\alpha$  impairs pulmonary host immune response to *Legionella* with persistent pneumonitis in rats (31).

*Salmonella* has been described as septicemia and septic arthritis in several case reports in patients receiving anti-TNF therapy (32,33). *Bartonella* and *Brucella* have been recorded in patients receiving anti-TNF therapy with *Nocardia* occurring 4.85-fold higher in infliximab than etanercept (14).

### **Mycoses and Parasites**

The Food and Drug Administration (FDA) has recently required stronger warnings for invasive fungal infection, having declared patients receiving anti-TNF therapy as “at risk for

**Table 2** Overview of Mycoses

Organism	Region	Transmission	Investigation	Presentation in Active Disease
<i>Coccidioides</i> sp.	US southwest desert and Mexico	Disruption of soil or dust with bat/bird droppings Inhalation of mold spores	History: <ul style="list-style-type: none"> <li>• Travel</li> <li>• Residential</li> <li>• Hobbies</li> <li>• Prior CNS infections</li> <li>• <i>Coccidioides</i> prior infection</li> </ul> Serology Chest X Ray	Cough Fever Headache Rash Mucosal ulcers Myalgias Neurological
<i>Histoplasma capsulatum</i>	Ohio, Mississippi, St Lawrence, Rio Grande, river valleys	As above	History: <ul style="list-style-type: none"> <li>• Travel</li> <li>• Residential</li> <li>• Hobbies</li> </ul> Urine histoplasmin	Fever Arthritis Pulmonary Rash Gastrointestinal Hematological Neurological
<i>Cryptococcus</i> sp.	Ubiquitous	As above	History: <ul style="list-style-type: none"> <li>• Hobbies</li> <li>• Work environment</li> </ul> <i>Cryptococcus</i> infection	Pulmonary Neurological

Abbreviation: CNS, central nervous system.

developing invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections” (34). The FDA has alerted the medical community that infection due *Histoplasma* infection in patients on anti-TNF therapy is inconsistently recognized by physicians causing increased mortality due to delayed investigation and treatment (34). Effective investigation consists of travel and residential history with subsequent serology or urine testing. Chest radiograph for patients with possible exposure may offer insight to previous exposure (Table 2). If active disease is suspected, biologic therapy should be stopped and appropriate anti-fungal treatment administered. In severely and acutely ill patients with positive geographic history, empiric therapy should include coverage for these entities until mycotic infection is excluded.

#### Endemic Mycoses

Along with inciting early apoptosis of infected macrophages thus foiling human adaptive immunity’s ability to protect against life-threatening disseminated disease, TNF inhibition creates a similar dilemma in endemic mycotic infection as in TB infection: derangement of granuloma formation resulting in invasive fungal infection. Again, as with TB, most declarations of infection occurred within three to six months of starting therapy indicating likelihood of reactivation versus new infection and the importance of effective screening. Infliximab was significantly more likely to be the associative anti-TNF therapy in these granulomatous infections (14,20). TNF- $\alpha$  potentiates antifungicidal capability of human monocytes (35). As with TB, in mycotic infection, TNF inhibition interferes with granuloma formation and apoptosis of infected macrophages occurs, which undermines the host’s ability to protect against disseminated infection.

The most important pathogens are *Coccidioides* sp. and *Histoplasma capsulatum*. Coccidioidomycosis may have a greater than sixfold increased risk in patients receiving anti-TNF agents (14,36). Proper investigation includes residential, travel, and recreational history, prior history of CNS infection, and serology testing. Histoplasmosis, one of the most prevalent mycoses in the United States, need be considered in patients on biologic therapy presenting with fever, malaise, cough, pneumonitis, pulmonary nodules, or hematological

derangement (34,37–40). Investigation should not preclude empiric therapy and should be conducted as for coccidioidomycosis including assay for urine histoplasmin (39).

### Opportunistic Mycoses and Parasites

*Aspergillus* sp. is a ubiquitous mycoses usually presenting as a mild allergic nuisance. However, in immune-compromised populations, it is cause of concern for fatal invasive disease. In the four years following FDA approval of anti-TNF therapy, 30 cases of aspergillosis were identified (14). There have been serious and fatal cases reported with anti-TNF therapy whereby diagnosis was revealed only after bronchoscopy or on autopsy thus making fluid cultures possibly insufficient for diagnosis. High index of suspicion should be maintained (34).

*Cryptococcus* sp. may confer mortality and permanent neurological damage in the immune-suppressed patients in whom disease is not recognized and treated early in disease course. In the handful of years after FDA approval, 24 cases associated with anti-TNF agents have been identified (14,41–45). Invasive disease has been reported to occur in absence of positive CSF or serum serology in patients receiving anti-TNF therapy (42,43). Patients on biologic therapy, who have a prior history of infection and have not been on suppressive therapy with an anti-fungal agent, are at risk and should be treated empirically for disseminated infection if serious infection is being considered.

*Pneumocystis jiroveci* had demonstrated cause for concern in RA patients receiving anti-TNF therapy when there appeared to be more cases (15 cases) of *P. jiroveci* having been reported in the first couple of years with anti-TNF therapy than in all the years with methotrexate since it has been available (12 cases) (46,47). After five years, 84 cases of *P. jiroveci* had been reported to FDA in association with infliximab therapy alone with a fatality rate of 27% (48).

*Candida* sp. has been inconsistently described in the literature, though a statistically significant increase of 2.3-fold with anti-TNF therapy has been calculated from cases reported to the FDA with a fivefold increase in systemic infection with infliximab versus etanercept (14).

### Viruses

TNF inhibition has variable effects on virus pathology. In some instances, as in certain stages of hepatitis C and HIV, viral pathology may in fact be dependent on TNF- $\alpha$  for pathological progression and anti-TNF therapy may interrupt viral pathology, whereby other viral entities, such as influenza or hepatitis B in association with TNF- $\alpha$  suppression are opportunities for potential devastation.

*Influenza* is the serious infection that is most likely to occur in patients receiving TNF inhibition. Ideally, patients should have received influenza vaccine two weeks before initiation of treatment and then annually while on therapy. However, history of vaccination does not preclude the possibility of serious illness due to influenza.

*Varicella zoster* is not uncommonly seen in patients receiving biologic therapy (21). *Herpes simplex* virus pathology, as examined in animal models, may be inhibited by the presence of TNF- $\alpha$  in both primary and reactivation phases (49,50). It is reasonable to pay close attention to history of such lesions, specially to lesion recurrence.

*JC virus*, a virus that is latent in up to 80% of adults, and resultant progressive multifocal leukoencephalopathy (PML) has been identified in one RA patient, two cases of SLE and 23 cases of non-Hodgkin's lymphoma being treated with rituximab (34). There have been few cases of PML in SLE patients receiving other immunosuppressant agents prior to these cases. Whether these fatalities are a direct result of specific immunosuppression with rituximab is not resolved. It is worth noting that off label use of rituximab for SLE is a fairly new treatment with much fewer patients exposed. Similarly, natalizumab, for treatment of multiple sclerosis and Crohn's disease, was temporarily taken off the market with labeling now containing a black box warning as its use "increases the risk of PML" after three patients with multiple sclerosis developed PML (34). It is now administered only through a special program whereby prior to initiation of treatment an MRI of the brain is recommended and treatment be stopped at signs of neurological symptoms. Anti-TNF therapy has been associated with demyelinating disease clinically similar to multiple sclerosis; however an association with the JC virus has not been established (47).

*Hepatitis A* has made little appearance in the literature in relation to biologic use. *Hepatitis B* in patients being treated with anti-TNF or rituximab therapy is quite clearly associated with potentially devastating disease. Ascertainment of *Hepatitis B* status is now standard of care prior to biologic treatment with positivity warranting co-administration of a nucleoside analogue like lamivudine with subsequent evaluation of aminotransferases.

## In Consideration of Surgery

### *Glucocorticoids*

There are three important considerations with regard to surgical intervention in a patient taking exogenous glucocorticoids:

1. Integrity of the hypothalamic axis
2. Risk of infection
3. Effects on wound healing and bleeding

For this reason, careful attention to development of infection, hematoma, dehiscence, and hemodynamic decompensation are important constellations in postsurgical care. Again, the decision for supplemental steroid use to compensate for the stress of surgery is based on individual cases with consideration of degree of hypothalamic suppression and the intensity of the surgery.

### *Biologic Agents*

Uncertainty surrounds the perioperative use of anti-TNF agents. Limited information culled from bowel surgeries for Crohn's disease and rheumatoid foot surgeries initially suggested perioperative use of biologics had little adverse effect on healing with small studies (51–53). Larger patient samples suggested that continuation of anti-TNF therapy increased risk of postoperative infection (54,55), the most important risk factor for infection being previous history of surgical site infection (56). All published studies on this topic contain major limitations making a clear conclusion elusive.

The controversy of continuation of biologic agents in the setting of surgical intervention lies within the benefits on wound healing, vascular integrity, and general wellness associated with control of underlying inflammatory disease versus the potential increased risk of infection. The British registry that tries to maintain information on all patients receiving anti-TNF agents found a significantly increased risk of skin and soft tissue infections—this however was not defined within the context of surgery (57). Interestingly, a large retrospective study identified previous history of joint surgery as the single risk factor for serious infection in patients receiving anti-TNF therapy (56). Studies defined within the surgical setting identified the most important risk factor being that of prior history of either surgical site or skin infection (54).

The general consensus for when to discontinue agents in the perioperative period is quite varied and somewhat arbitrary. The British Society of Rheumatology supports discontinuation two to four weeks prior to surgery (58) while both the Dutch and French Societies of Rheumatology both support discontinuation for the quadrupled half-life of the agent before surgery. Most common practice in the States is to withhold anti-TNF therapy by at least one dosing interval. For example, a patient would be scheduled for surgery at least one week after discontinuing an anti-TNF agent that is given weekly.

Currently, studies regarding perioperative infection and abatacept (interruption of T-cell co-stimulation with APC) are not available. Caution would suggest withholding infusion for one dosing interval in nonemergent surgical procedures. Regarding, B-cell-depleting therapy such as rituximab, it may take up to one year for repletion of circulating B cells. Measurement of peripheral CD19+ positive B cells are thought to be a good estimation of returned humoral immunity. Though it is important to bear in mind that B-cell depletion potentially incites other B-cell-related mechanisms of immune suppression other than pure B-cell lysis, which is not quantifiable at this time. Close observation for the development of infection is warranted in these patients.

Again, in emergent situations, withholding biologics may not be possible. Therefore, the physicians' best judgment weighing benefits and risks of delaying surgery on morbidity and mortality is crucial.

### Mimics of Sepsis in Diseases of Immune Dysregulation

*Macrophage activation syndrome (MAS) or hemophagocytic syndrome* is a rare syndrome of aberrant T-cell activation, resulting in diffuse phagocytosis of blood cells that occurs in patients with autoimmune disease especially systemic-onset juvenile RA, Still's disease, some immune deficiencies, and systemic lupus erythematosus. MAS is fatal if not recognized and may mimic a severe disease flare or sepsis or septic-disseminated intravascular coagulation. Presenting signs may include persistent fever, neurologic symptoms such as mental status changes or irritability suggestive of meningitis, splenomegaly, and rash. Laboratory values may show pancytopenia, transaminase elevation, and coagulopathy with hypofibrinogenemia. Often present is the discerning clue of a plummeting erythrocyte sedimentation rate (ESR) due to consumption of coagulation proteins. Marked elevation of serum ferritin is often present. Accepted treatment for MAS, in contrast to sepsis, includes high-dose glucocorticoids and cyclosporine and may require intravenous immunoglobulin or plasmapheresis.

*Thrombotic thrombocytopenic purpura (TTP)* may occur as a secondary phenomenon to autoimmune diseases such as systemic lupus erythematosus as well as to immunosuppressant medications such as cyclosporine. It may mimic complications related to sepsis in a patient on immunosuppressant medications. Diagnostic, clinical features, and treatment of secondary TTP are the same as that for primary TTP.

### Adverse Event Reporting

This chapter is built on systematic reviews of biologic agents and is reliant on data from limited trials and through adverse event reporting systems (AERS) in the United States and abroad (59). It is important to understand the shortcomings of passive reporting systems such as in the States (60,61). Underreporting of adverse events is caused by an unrecognized association resulting from transfer of care, length of time interval from treatment to event, and lack of familiarity with these agents. Also, commonly acquired pathogens are less likely to be reported (37). Clinicians may not be aware of reporting systems or how to access them. They may not perceive reporting as a responsibility, or find the reporting system too cumbersome. It is presumed that data presented here are incomplete in numbers and that serious infections are of more relevance and far-reaching than this chapter would suggest (62). It is the inherent responsibility of at least one treating physician to file a report and should be discussed with the prescribing physician.

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# 23 Infections in Organ Transplants in Critical Care

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## INTRODUCTION

Solid-organ transplant (SOT) recipients may require intensive care unit (ICU) admissions for different reasons in different moments of their evolution, and infection is one of the most important of them. Between 5% and 50% transplantation candidates must await transplantation in an ICU and, after the procedure, most of them spend there a mean of four to seven days for life support (1–6). If the ICU stay is prolonged due to postsurgical complications, the probability of acquiring a nosocomial infection increases significantly.

Most ICU stays will take place during the period of deepest immunosuppression (7), but transplant recipients may require readmission to the ICU at any time due to infectious and noninfectious complications such as severe organ rejection, bleeding, organ dysfunction, etc. In fact, infections are the most common indication for admissions of transplant recipients in emergency departments (35%), and severe sepsis (11.7%) is the most common reason for ICU utilization (8). Figures regarding infections and ICU admissions show that one-half of all febrile days of liver recipients occur in the ICU, and 87% of these are caused by infections (9).

Antimetabolite immunosuppressive drugs such as mycophenolate mofetil and azathioprine are associated with significantly lower maximum temperatures and leukocyte counts (10). However, in general, the immunosuppression caused by transplantation does not abolish the inflammatory response, so most transplant recipients with a significant infection will have fever and most fevers will have an infectious etiology in this setting.

In a multicentric study in Italy, it was shown that most centers are not supported by an ICU exclusively dedicated to transplantation (11). Accordingly, many of these patients will be cared by physicians not always familiar with the specific problems posed by the transplant population. Our aim is to provide information and guidelines regarding most frequently encountered clinical scenarios relevant to critically ill infected SOT recipients. This chapter deals with the etiology, approach, and outcome of most common infectious complications intensive care specialists may find when taking care of SOT recipients. Where no solid data were available, perspectives based on our own experience and opinion are presented.

## INFLUENCE OF THE TYPE OF TRANSPLANTATION AND OF THE TIME AFTER TRANSPLANTATION

The incidence of infection after a heart transplantation (HT) ranges from 30% to 60% (with a related mortality of 4–15%) and the rate of infectious episodes per patient is 1.73 in a recent series (12). Infections are more frequent and severe than those occurring in renal transplant recipients, but less frequent than those occurring after a liver or a lung transplantation. The type of SOT and the time after transplantation may be useful clues to the clinician since, unless unexpected exposure has occurred, there is a timetable according to which different infections occur post organ transplantation (13,14). According to it, although pneumonia can occur at any



**Table 1** Chronology of Most Common Infections or Causative Microorganisms in Severely Ill Solid Organ Transplant Recipients

Chronology of infection	Most common syndromes
Early infection (1st month)	Bacterial infections Pneumonia Surgical wound infection Deep infections near the surgical area Intra-abdominal abscesses Urinary tract infection Catheter related infection Bloodstream infection Antibiotic associated diarrhea  Viral infections <i>Herpes simplex</i> stomatitis HHV-6 infections Primary CMV disease  Infections transmitted with the allograft Invasive aspergillosis or candidiasis
Intermediate infections (2–6 months)	Opportunistic infections: bacterial, tuberculosis, nocardiosis, invasive aspergillosis, other fungal infections, viral diseases, toxoplasmosis
Late infections (after 6th month)	Common community-acquired infections Respiratory tract infections Urinary tract infections Varicella-zoster infections CMV, adenovirus Other opportunistic microorganisms: listeriosis, <i>Cryptococcus</i> , <i>P. jiroveci</i>

point in the posttransplant course, the etiology will be very different at different points in time (Table 1).

### Importance of the Underlying Disease and Type of Transplantation

The type of organ transplanted, the degree of immunosuppression, the need for additional antirejection therapy, and the occurrence of technical or surgical complications, all impact on the incidence of infection posttransplant.

In each type of transplantation, there are patients in which the risk of infection is greater. In HT, patients with prior ischemic cardiomyopathy experience more surgical complications, need longer postoperative mechanical assistance, and are more susceptible to *Pneumocystis jiroveci* pneumonia (15,16). Incidence of infection is higher in thoracic transplantation pediatric population than that in adult (17).

After orthotopic liver transplantation (OLT), patients with prior fulminant liver disease fared the worst ICU course and cirrhotics the best (18). Thrombocytopenia of  $<50 \times 10^9/L$  for three days is frequent after liver transplantation and as such was not found to be an important contributor to bleeding. The unique associated event identified for significant bleeding was sepsis (HR 34.80; 95% CI 1.5–153.4) (19). If severely ill patients with end-stage liver disease are selected appropriately, liver transplant outcomes are similar to those observed among subjects who are less ill and are transplanted electively from home (20).

Following lung transplantation, patients with obstructive lung disease, double-lung transplant, or cystic fibrosis have a longer stay in the ICU and a higher risk of infection (2,21,22).

The type of SOT also determines the complexity of the surgery, the intensity of immunosuppression, and the most likely sites of infection. Lung and HT recipients are especially susceptible to thoracic infections, whereas intra-abdominal complications predominate in OLT or pancreas recipients. Patients receiving alemtuzumab for the treatment of allograft rejection are more prone to suffer opportunistic infections (23,24).

Certain infections are characteristic of a particular type of transplantation, for example, infections related to circulatory support devices (intra-aortic balloon pumps, ventricular

assistance devices, and total artificial hearts) in HT recipients (25–28) or endotipsitis in cirrhotic patients (29). Infections such as insertion site sepsis, endocarditis, pneumonia, candidiasis, or sternal infection may complicate 38% of support courses. Lung transplant recipients are admitted to the ICU most commonly due to respiratory deterioration requiring mechanical ventilation (59%) or due to suspicion of sepsis (35%) (30).

The use of extended donors does not seem to increase the risk of poor outcome (31). Some characteristics, such as elderly donor, with hypertension combined with the presence of metabolic acidosis, or a prolonged ICU donor stay, have been found to have a negative impact on liver graft survival (32).

### Time of Appearance of Infection After Transplantation

All SOT recipients share a number of conditions (end-stage organ failure, surgery, immunosuppressive regimens, etc.) that bring along a predictable timeline of posttransplant infectious complications. The time of appearance of infection after transplantation is an essential component of the evaluation of the etiology of infection. Early infections occurring in transplant patients within the first month after transplantation are generally similar to that in nontransplant patients who have undergone major surgery in the same body area. Reactivation of latent infections and early fungal and viral infections account for a smaller proportion of febrile episodes during this period. Intermediate infections (2–6 months) are usually caused by opportunistic microorganisms such as cytomegalovirus (CMV), fungi, and multiresistant bacteria. Finally, late infections (after 6 months) may be caused either by common community pathogens in healthy patients or by opportunistic microorganisms in patients with chronic rejection.

#### Early Infections

In the first month after SOT, patients are very susceptible to ventilator-associated pneumonia, IV catheter-related infections, surgical wound infection, or urinary tract infection (UTI) usually due to bacterial or candidal infections (33,34). Some of these may not be evident during the initial examination, which should be frequently repeated. If the patient is still intubated and the chest X ray does not reveal infiltrates, the possibility of tracheobronchitis or bacterial sinusitis should be considered. Staphylococci or *Enterobacteriaceae* will cause most early infections. Gram-positives predominate if quinolone prophylaxis is given. Herpetic stomatitis and infections transmitted with the allograft or present in the recipient may also appear at this time.

Bleeding or anastomosis dehiscences may require a new surgical intervention. Prolonged ICU stay due to CNS lesions or organ failure usually implies involvement of more resistant species such as vancomycin-resistant enterococci (VRE), *Acinetobacter*, *Pseudomonas*, methicillin-resistant *Staphylococcus aureus* (MRSA), or *Candida* (35). *Aspergillus* may also cause early infection in patients requiring prolonged stay in the ICU and who are especially difficult to diagnose (36,37).

#### Intermediate Period

From the second to the sixth month, patients are susceptible to opportunistic pathogens that take advantage of the immunosuppressive therapy. In this period, we may expect infection with immunomodulatory viruses and with opportunistic pathogens (*P. jiroveci*, *Listeria monocytogenes*, and *Aspergillus* spp.). Most life-threatening infections occur within the first three months. CMV is the most common pathogen after SOT. When no prophylaxis is given, 30% to 90% of patients will show laboratory data of “CMV infection” and 10% to 50% may develop associated clinical manifestations (CMV disease). However, CMV disease is readily diagnosed at present and seldom requires ICU admission. In our experience, only gastrointestinal and respiratory CMV diseases have required ICU admission. Cultures for human herpesvirus-6 (HHV)-6 should be advised in patients with leukopenia. Some bacterial infections such as listeriosis may appear at this time as primary sepsis or meningitis. Tuberculosis and nocardiosis are also characteristics of this second period (38). Aspergillosis may be encountered in patients with risk factors or massive exposure (39) and toxoplasmosis in seronegative recipients of a seropositive allograft (40).

### Late Period

From the sixth month onward SOT patients are susceptible to community-acquired infections if chronic rejection is not present. Herpes zoster virus, bacterial pneumonia, and UTI predominate. At this time, fever of unknown origin should be managed almost as in immunocompetent hosts. However, the aforementioned opportunistic infections may complicate this late period in patients with chronic viral infection such as hepatitis B or C, which may progress to end-stage organ dysfunction and/or cancer. Patients requiring chronic hemodialysis or with malignancy or late rejection are also susceptible to opportunistic infections (*Cryptococcus neoformans*, *P. jiroveci*, *L. monocytogenes*, etc.) in this time frame (41).

### Anamnesis and Physical Examination

Risk factors for infection should be carefully sought in all SOT patients admitted to the ICU, since they may suggest an etiology and a clinical syndrome. The pretransplantation history, for example, serological status against microorganisms such as CMV, hepatitis virus, *Toxoplasma*, etc., may yield valuable information. Previous infections or colonization, exposure to tuberculosis, contact with animals, raw food ingestion, gardening, prior antimicrobial therapy or prophylaxis, vaccines or immunosuppressors, and contact with contaminated environment or persons should be recorded (42,43). History of residence or travel to endemic areas of regional mycosis (44) or *Strongyloides stercoralis* may be essential to recognize these diseases (45). Exposure to ticks may be essential to diagnose entities such as human monocytic ehrlichiosis, which may be potentially lethal in immunosuppressed patients (46). Diagnosis may be confirmed by polymerase chain reaction (PCR) for *Ehrlichia chaffeensis*, serology, and by in vitro cultivation of *E. chaffeensis* from peripheral blood.

Certain complications may increase the risk of bacterial and fungal infections in the early posttransplant period (Table 2). They include long operation (over 8 hours), blood transfusion in excess of 3 L, allograft dysfunction, pulmonary or neurological problems, diaphragmatic dysfunction, renal failure, hyperglycemia, poor nutritional state, and thrombocytopenia (18,47–50). Intraoperative hypothermia has increased the incidence of early CMV infection in liver transplant recipients (51). Blood cell transfusions have been associated to an increased risk of ventilator-associated pneumonia (52), and leukocyte reduction of all administered blood products during OLT is associated to an improved outcome demonstrated by both a decreased incidence of acute cellular rejection and length of hospital stay (53). Critically ill OLT patients with kidney failure managed with a conservative anticoagulation policy and continuous veno-venous hemofiltration (CVVH) have a much better outcome than patients with acute renal failure (ARF) without OLT (54).

Fever in critically ill transplant recipients should be considered an emergency. In our opinion, a basic tenet of the management of an SOT with fever is that physical examination data should be directly obtained by the ID consultant, not relying on second-hand information. This may be more useful than many expensive and time-consuming tests.

**Table 2** Risk Factors for Infection in Heart Transplant Patients

Preoperative period	Intraoperative period	Postoperative period
<ul style="list-style-type: none"> <li>• Pulmonary hypertension not responsive to vasodilators</li> <li>• Critically ill status and mechanically ventilated patients at time of transplantation</li> <li>• Renal insufficiency</li> <li>• Cardiac cachexia</li> <li>• Prior sternotomy</li> <li>• Donor's CMV positive serology</li> <li>• Older age</li> <li>• Repeated hospital admissions</li> <li>• Lack of pathogen-specific immunity</li> <li>• Latent infections in the donor or the recipient</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged operative time</li> <li>• Complicated surgical procedure</li> <li>• Need for large number of blood transfusions</li> <li>• Need for ventricular assist devices</li> <li>• Presence of pathogens in the transplant allograft</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged stay in intensive care unit</li> <li>• Mediastinal complications and need for reintervention</li> <li>• Prolonged hospitalization</li> <li>• Prolonged antibiotic use</li> <li>• Renal insufficiency</li> <li>• Induction therapy with OKT3</li> <li>• Immunosuppressive drugs and treatment of allograft rejection</li> <li>• Immunosuppression due to concomitant viral infections</li> <li>• Retransplantation</li> </ul>

The oral cavity is frequently forgotten and may disclose previously unnoticed herpetic gingivo-stomatitis or ulcers. Within the exploration of the thoracic area, the consultant should visualize the entry sites of all intravascular devices, even if they "have just been cleansed." It should be remembered that the presence of inflammatory signs is suggestive of infection, although their absence does not exclude infection. Sepsis, without local signs, may be the initial sign of postsurgical mediastinitis. When the sternal wound remains closed, a positive epicardial pacer wire culture may be a clue to sternal osteomyelitis (55). Although unusual after SOT, cardiac auscultation and echography may help detect endocarditis (56) and physical examination may occasionally disclose the existence of pneumonia or empyema before abnormal radiological signs become evident.

The abdominal examination is always essential, especially in OLT recipients. The surgical wound is also a common site of infection and a cause of fever. Its presence requires rapid debridement and effective antimicrobial therapy and should prompt the exclusion of adjacent cavities or organ infection. If ascites is present, it should be immediately analyzed and properly cultured to exclude peritonitis. We recommend bedside inoculation in blood-culture bottles due to its higher yield of positive results. Examination of the iliac fossa is particularly important after kidney transplantation (KT). Tenderness, erythema, fluctuance, or increase in the allograft size may indicate the presence of a deep infection or rejection. Ultrasound or CT-guided aspiration may facilitate the diagnosis. The possibility of colonic perforation in steroid-treated patients or gastrointestinal CMV disease should always be considered in intra-abdominal infections. It is important to remember that even very severe intestinal CMV disease may occur in patients with negative antigenemia, especially in patients on mycophenolate mofetil at a high dose (3 mg/day) (57,58).

Finally, skin and retinal examinations are "windows" at which the physician may look in and obtain quite useful information on the possible etiology of a previously unexplained febrile episode. We have analyzed the value of ocular lesions in the diagnosis and prognosis of patients with tuberculosis, bacteremia, and sepsis (59,60). Cutaneous or subcutaneous lesions are a valuable source of information and frequently allow a rapid diagnosis. Viral and fungal infections are the leading causes of skin lesions in this setting. The entire skin surface should be inspected and palpated in SOT recipient with unexplained fever. The biopsy of nodules, subcutaneous lesions, or collections may lead to the immediate diagnosis of invasive mycoses and infections caused by *Nocardia* or mycobacteria, among others.

An aggressive diagnostic approach is necessary when dealing with febrile compromised ICU hosts since it has been shown or documented that many infectious complications remain undiagnosed. In a recent study, complete agreement between pre- and postmortem diagnoses took place in only 58% of a total 149 patients. Two-thirds of all missed diagnoses were infectious and disagreement was particularly prominent in the transplant population (complete agreement 17% and major error in 61%) in comparison with trauma patients (complete agreement 86%) or cardiac surgery group (69%). The majority of the missed diagnoses were fungal infections. Longer ICU stays increased the rate of error (37,61,62).

Approximately 25% of febrile episodes do not present with an evident focal origin and do not permit a straight syndromic approach (63). Therefore, the patient's antecedents, type of transplantation, and time after surgery are essential. We systematically recommend to our residents to go over the viral, bacterial, fungal, and parasitic etiologies that should be excluded.

## **MOST COMMON CLINICAL SYNDROMES**

### **Pneumonia**

Pneumonia accounts for 30% to 80% of infections suffered by SOT recipients and for a great majority of episodes of fever in the ICU (41% of all febrile infections during the first 7 days of ICU stay and 14% of those after 7 days) (9). Pneumonia is among the leading causes of infectious mortality in this population. Pneumonias occur predominantly in the early postoperative period, especially in the patients who require prolonged ventilation or are colonized or infected before transplantation. Up to 95% of posttransplant pneumonias occur within the first six months (64). The net state of immunosuppression is the main risk factor in

late-onset pneumonias. The crude mortality of bacterial pneumonia in solid-organ transplantation has exceeded 40% in most series (65,66). The clinical presentation and the differential diagnosis are similar to those in other critical patients.

The incidence of bacterial pneumonia is highest in recipients of heart-lung (22%) and liver transplants (17%), intermediate in recipients of heart transplants (5%), and lowest in renal transplant patients (1–2%) (67–69). The crude mortality of bacterial pneumonia in solid-organ transplantation has exceeded 40% in most series (66).

Pneumonias occur in 13% to 34% of liver transplant recipients. Singh has recently analyzed 40 OLT patients who developed lung infiltrates in the ICU (41). The etiology was pulmonary edema 40%, pneumonia 38%, atelectasias 10%, acute respiratory distress syndrome (ARDS) 8%, contusion 3%, and unknown 3%. The signs that suggest an infectious origin were Clinical Pulmonary Infection Score (CPIS) >6 (73% vs. 6%), abnormal temperature (73% vs. 28%), and creatinine level >1.5 mg/dL (80% vs. 50%) (41). MRSA, *P. aeruginosa*, and *Aspergillus* caused 70% of all pneumonias in the ICU (9). All *Aspergillus* and 75% of MRSA pneumonias but only 14% of the gram-negative pneumonias occurred within 30 days of transplantation. *Legionella*, *Toxoplasma gondii*, and CMV may also cause pneumonia in this setting (7,70).

Pneumonia is the most common infection following HT. It occurs in 15% to 30% of patients, with an attributable mortality of 23%. Risk factors include prolonged intubation, CMV infection, and preoperative lung infarction. Gram-negative pneumonia in the early posttransplant period is associated with significant mortality. In a recent multicentric prospective study performed in Spain, the incidence of pneumonia after HT was 15.6 episodes/100 HT (65). Most cases occurred in the first month after transplantation. Etiology could be established in 61% of the cases. Bacteria caused 91% of the cases, fungi 9%, and virus 6%. In another study, opportunistic microorganisms caused 60% of the pneumonias, nosocomial pathogens 25%, and community-acquired bacteria and mycobacteria 15% (64). Gram-negative rods caused early pneumonias (median 9 days), and gram-negative cocci, fungi, *Mycobacterium tuberculosis* and *Nocardia* spp. and virus caused pneumonias in 11, 80, 145, and 230 days, respectively. *Legionella* should always be included in the differential diagnosis (71–74). Pneumonia increases the risk of mortality after HT (OR 3.7; 95% CI 1.5–8.1;  $p < 0.01$ ).

Lung infections are very common in lung and heart-lung transplant recipients. These patients have particular predisposing factors, since the allograft is in contact with the outside environment, and have an impaired mucociliary clearance, ischemic lymphatic interruption, and abolition of the cough reflex distal to the tracheal or bronchial anastomoses. In fact, the anastomosis is especially vulnerable to invasion with opportunistic pathogens including gram-negative bacilli (*Pseudomonas*), staphylococci, or fungus. Lung transplant recipients with underlying cystic fibrosis may be prone to suffer infections caused by multiresistant microorganisms such as *Burkholderia cepacia*. In this group of patients perioperative antimicrobials are chosen on the basis of surveillance cultures. Pathogens transmitted from the donor may also cause pneumonia in this setting, though it is not very frequent (75).

Pneumonia is less common after renal transplantation (8–16%), although it remains a significant cause of morbidity (67–69).

#### *Most Common Pathogens in Transplant Patients with Pneumonia*

We have already mentioned some data on the etiology of pneumonia in SOT recipients, but we will now review some of the most common pathogens in more detail.

**Bacteria.** Although bacterial pneumonia may occur any time after transplantation, the period of greater risk is the first month after the procedure. Need for mechanical ventilation and intensive care in this period are among the causes. The etiology will depend on the moment after transplantation, length of previous hospital stay, the days on ventilation, previous use of antimicrobial agents, and clinical and radiological manifestations (Table 3). Gram-negative rods predominate (*P. aeruginosa*, *Acinetobacter* spp., *Enterobacteriaceae*) but gram-positive cocci (*S. aureus*, *Streptococcus pneumoniae*) account for a significant proportion of cases, as we mentioned before.

**Table 3** Probable Etiology of Pneumonia in Relation to the Type and Progression of the Infiltrates

Radiological pattern	Probable etiology in relation to the type and progression of the infiltrates	
	Acute <sup>a</sup>	Subacute
Consolidation	Bacteria ( <i>S. Pneumoniae</i> gram-negative rods, <i>Legionella</i> , <i>S. aureus</i> ) (1–2 wk) Embolism, atelectasis Hemorrhage Acute graft rejection in lung transplant recipients CMV (2–3 m or later if prophylaxis)	<i>Aspergillus</i> (30 days), <i>Nocardia</i> , tuberculosis (9–23 mo), drugs <i>P. jiroveci</i> , <i>Legionella</i> , HSV, VZV, <i>Toxoplasma</i> Bronchiolitis obliterans
Interstitial	Edema Transfusions (Bacteria)	Virus (CMV, influenza, parainfluenza, RSV, EBV), <i>P. jiroveci</i> , drugs (Fungi, <i>Nocardia</i> , tuberculosis)
Nodular	(Bacteria, edema)	Fungi, <i>Nocardia</i> , <i>R. equi</i> , tuberculosis ( <i>P. jiroveci</i> , CMV)

<sup>a</sup>Requires attention in <24 hours. Less common possibilities are among brackets.

*Legionella* has been reported in 2% to 27% of SOT recipients with pneumonia (76–78). Most common species implicated are *Legionella pneumophila* and *L. micdadei* (79,80). A prodrome of influenza-like symptoms is followed by a sometimes “explosive” pneumonia with patchy lobular or interstitial infiltrates on chest radiograph. High fever, hypothermia, abdominal pain, and mental status changes are sometimes seen. Pneumonia is the most common presentation, but some patients have just fever (74). Other manifestations have also been described such as liver abscesses, pericarditis, cellulitis, peritonitis, or hemodialysis fistula infections (81). Infiltrate is usually lobar, but *Legionella* has to be included in the differential diagnosis of lung nodules, cavitating pneumonia, and lung abscess (71). *Legionella* infections can be overlooked unless specialized laboratory methodologies (cultured on selective media, urinary antigen test) are applied routinely on all cases of pneumonia (72). Routine culture for *Legionella* in the water supply is recommended in all transplant centers and ICUs with cases of legionellosis (82). The use of impregnated filter systems may help prevent nosocomial legionellosis in high-risk patient care areas (83). Late community-acquired bacterial pneumonias are 10-fold more frequent in cardiac transplant recipients than in the general population (2.6 cases/100 cardiac transplants) (64). The etiological agents are similar to those of the general population (*S. pneumoniae*, *Haemophilus influenzae*, etc.), with the exception of lung transplant patients who may suffer recurrent pneumonias caused by *P. aeruginosa* or *B. cepacia* (84).

The frequency of *M. tuberculosis* disease in receptors of solid-organ transplantation in most developed countries ranges from 1.2% to 6.4%, but in transplant patients living in areas of high-level endemicity it might reach up to 15% (38,85–87). Although there is a huge regional variability, in general, SOT incidence is 20 to 74 times higher than in the general population, with a mortality rate of up to 30%. The most frequent form of acquisition of tuberculosis after transplantation is the reactivation of latent tuberculosis in patients with previous exposure. Tuberculosis develops a mean of 9 months after transplantation (0.5–13 months). Risk factors for early onset are nonrenal transplant, allograft rejection, immunosuppressive therapy with OKT3 or anti-T cell antibodies, and previous exposure to *M. tuberculosis*. Clinical presentation is frequently atypical and diverse, with unsuspected and elusive sites of involvement. A large series of tuberculosis in transplant recipients described pulmonary involvement in 51% of patients, extrapulmonary tuberculosis in 16%, and disseminated infection in 33% (38). In lungs, radiographic appearance may vary between focal or diffuse interstitial infiltrates, nodules, pleural effusion, or cavitory lesions. Manifestations include fever of unknown origin, allograft dysfunction, gastrointestinal bleeding, peritonitis, or ulcers. In transplant patients, *M. tuberculosis* infection was also described in skin, muscle, osteoarticular system, CNS, genitourinary tract, lymph nodes, larynx, adrenal glands, and thyroid (38,88). Ocular lesions may be an early way to detect dissemination (59). Coinfection with other pathogens is not

uncommon. Treatment requires control of interactions between antituberculous drugs and immunosuppressive therapy. A high index of suspicion is recommended. If diagnosis of pneumonia is uncertain in the first 24 to 48 hours, specific cultures and PCR for *M. tuberculosis* should be considered.

*Rhodococcus equi* (89) and *Nocardia* (90–94) are well-known causes of respiratory tract infection in transplant recipients. However, they usually present in a subacute form and rarely require ICU admission. These infections usually occur more than three months posttransplantation. Radiologically, they may appear as multiple and bilateral nodules, possibly due to their long-term silent presentation. The incidence of nocardiosis has been significantly reduced since the widespread use of cotrimoxazole prophylaxis. *Nocardia farcinica* may be resistant to cotrimoxazole prophylaxis and cause particularly aggressive disease (90). In a retrospective cohort study among 577 lung transplant recipients from 1991 to 2007, nocardiosis occurred in 1.9% of patients and was associated with a mean of nearly two weeks to diagnosis and frequent adverse effects on therapy (95).

*R. equi* is an opportunistic pathogen that usually causes cavitated pneumonia in HIV-positive patients, but SOT recipients may be affected as well. Infection occur usually late (median of 49 months after transplantation) and the lungs are primarily involved in most cases. Infection presents as a lung nodule in half of the patients. Clinicians should consider *R. equi* when evaluating a solid-organ recipient with an asymptomatic lung nodule, particularly when cultures fail to identify mycobacteria, *Nocardia*, or fungal organisms. Clinical microbiology laboratories should be alerted when an *R. equi* infection is suspected, since it could be mistaken for a contaminant diphtheroid and will not respond to the standard empirical therapy.

**Fungi.** Fungal infections have been reported to occur in 5% to 20% of SOT recipients, and although they are decreasing proportionally, they increase in absolute figures as more transplantation procedures are performed each year. Rates vary according to the type of transplant recipient and are greatly influenced by the degree of immunosuppression, the use of prophylaxis, the rate of surgical complications and of renal failure among the transplant population. Fungal pathogens more likely to cause pneumonia in this population are *Aspergillus*, *P. jiroveci*, *Candida* spp., and *Cryptococcus* spp.

Different types of transplantations imply differences in fungal infections (96). A recent series prospectively collected in Spain reported incidence of invasive aspergillosis (IA) in SOT recipients, which ranged from 0.3% in KT to 3.9% in pancreas recipients (97). In lung and heart-lung transplantation, the incidence of fungal infections, most notably aspergillosis, ranges from 14% to 35% if no prophylaxis is provided, but has significantly decreased since aerosolized amphotericin B is provided to these patients (98,99). In single-lung transplant patients, IA more commonly affects the native lung than the transplanted lung and may arise immediately postoperatively due to preexistent disease in pretransplant immunosuppressed patients. In lung and heart-lung transplant recipients, the types of disease presentation include bronchial anastomosis dehiscence, vascular anastomosis erosion, bronchitis, tracheobronchitis, invasive lung disease, aspergilloma, empyema, disseminated disease, endobronchial stent obstruction, and mucoid bronchial impaction. Kramer et al. have described a distinct form of IA after lung transplantation: ulcerative tracheobronchitis, a semi-invasive disease involving the anastomosis site and the large airways (100). Risk factors include CMV infection, obliterative bronchitis, rejection, and increased immunosuppression.

In HT, *Aspergillus* is the predominant fungal isolate and accounts for 38% of all lung nodular lesions (101). It appears as a median of  $50 \pm 63$  days after HT (102). We found that postoperative hemodialysis, CMV disease, reoperation, and other episodes of aspergillosis in the ward close to the transplantation date are the major risk factors for IA in this population. The use of oral itraconazole is an effective way of preventing this infection.

In liver transplantation, *Aspergillus* infection is less common when compared with lung or heart-lung transplant recipients and is more commonly found than in KT recipients. In liver transplant recipients, IA usually is an early event and most patients were still in the ICU with evidence of organ dysfunction when the disease was diagnosed (87,103). Retransplantation is also an independent risk factor (103,104), although aspergillosis may happen in low-risk

patients if an overload exposure has occurred (39). Accordingly, ICUs caring for transplant patients should maintain a good quality of air control (105). *Aspergillus* may appear late after transplantation, mainly in patients with a neoplastic disease (106).

Pulmonary involvement is described in 90% of the cases, but CNS or disseminated manifestations may predominate (107). The isolation of *Aspergillus* from any SOT recipient sample is always a warning clue. Although the lung is the primary site of infection, other presentations have also been described (surgical wound, primary cutaneous infection, infection of a biloma, endocarditis, endophthalmitis, etc.). Voriconazole is the mainstay of therapy; although combined therapy may be indicated in especially severe cases (108).

*Scedosporium* spp. are increasingly recognized as significant pathogens, particularly in immunocompromised hosts. These fungi now account for ~25% of all non-*Aspergillus* mould infections in organ transplant recipients (109). *Scedosporium* spp. are generally resistant to amphotericin B. *S. prolificans* in particular is also resistant to most currently available antifungal agents. We found that 46% of *Scedosporium* infections in organ transplant recipients were disseminated, and patients may occasionally present with shock and sepsis-like syndrome (110). Fungemia is especially frequent when *S. prolificans* is involved. Overall, mortality rate for *Scedosporium* infections in transplant recipients in our study was 58%. When adjusted for disseminated infection, voriconazole as compared with amphotericin B was associated with a lower mortality rate that approached statistical significance ( $p = 0.06$ ).

*P. jiroveci* (former *P. carinii*) is now rarely seen in SOT receiving prophylaxis. Before prophylaxis, incidence was around 5%, although it has been described to reach up to 80% in lung transplant recipients. PCP was diagnosed a median of 75 days after transplant (range, 37–781 days). Clinical presentation was acute (less than 48 hours) with fever (89%), shortness of breath (84%), dry cough (74%), and hypoxia (63%). CMV was also isolated from lung or blood in 74% of patients. Chest X ray usually showed interstitial pneumonia (84%). Some patients required ventilatory support. Mortality was 26%. Older age was the only significant poor prognostic factor (61 vs. 49 years;  $p < 0.03$ ) (111). Week-end prophylaxis (1 double-strength tablet, 160/800 mg, every 12 hours on Saturdays and Sundays) has shown practically universal efficacy, also eliminating the risk for *Listeria* infections and most cases of *Nocardia* infections (95,112).

*C. neoformans* affects the lung in 55% of SOTs with cryptococcosis (113). However, the disease is uncommon and appears a median of 24 months after transplantation (1 month to 17 years). An immune reconstitution syndrome-like entity may occur in organ transplant recipients with *C. neoformans* infection. This entity may be interpreted as failure of therapy. Immunomodulatory agents may have a role as adjunctive therapy in such cases (114).

Although *Candida* is frequently recovered from the lower respiratory tract (LRT) of ventilated patients, *Candida* pneumonia is exceedingly rare (115). It has been reported in lung transplant recipients and the diagnosis requires histological confirmation, since the recovery of *Candida* may represent colonization. In these patients, infection with *Candida* may be associated with very severe complications such as the necrosis of bronchial anastomoses (116–119).

**Virus.** CMV was the most common organism infecting the lungs in solid transplant recipients, but the incidence has significantly decreased with the widespread use of prophylaxis. CMV may be the sole causative agent of pneumonia after SOT or appear as a copathogen when other microorganisms are isolated (73). CMV pneumonitis commonly adopts a diffuse interstitial radiological appearance, but focal and even nodular infiltrates are described in up to one-third of patients. CMV may cause severe pneumonia with ARDS requiring ICU admission. In a recent study, in KT recipients, including 21 patients in this situation, it was found that among 13 surviving patients, the numbers of CD4+ and CD8+ T cells and their ratio increased as the patients recovered. In eight nonsurviving patients, the numbers of CD4+ and CD8+ T cells and their ratio was similar to day 0. The authors conclude that the variations of CD4+ and CD8+ T lymphocytes and their ratio are useful indicators of the severity of disease and the outcome of patients with CMV infections accompanying ARDS after renal transplantation. Nevertheless, it may be helpful to evaluate the efficiency of ongoing treatment methods in these patients (120). Herpes simplex (121,122) and Varicella zoster virus (VZV) may also cause pneumonia in the transplant population. HHV-6 has been



reported to cause diverse clinical symptoms including fever, skin rash, pneumonia, bone marrow suppression, encephalitis, and rejection.

The respiratory viruses, particularly respiratory syncytial virus, influenza, parainfluenza, adenovirus, and picornavirus, are increasingly recognized as significant pathogens in these populations. Adenovirus may also cause pneumonia, occasionally with dysfunction of the allograft (123). Respiratory syncytial virus and influenza have been found to be the most common of the respiratory viruses causing severe infections in transplant recipients (124–130). New antiviral medications may bring improved outcomes of picornavirus infections in this population. Finally, a new virus, the human metapneumovirus, has recently been described and may be a significant respiratory pathogen in immunocompromised transplant recipients, particularly lung recipients. In this population, human metapneumovirus is a leading cause of acute respiratory tract illness. The incidence and clinical spectrum at presentation are similar to RSV, although the latter seems to be associated with a higher risk of chronic rejection (131,132). Respiratory viruses may be associated with high morbidity, particularly in lung transplant recipients and may appear as “culture-negative” pneumonia. Molecular methods, such as reverse transcription-PCR assays allow the identification of respiratory viruses in bronchoalveolar lavage (BAL) specimens (133). Advances in prevention, particularly with regard to infection control practices, and to a lesser extent treatment have had a substantial impact on the frequency and outcomes of this infection.

Considering the high mortality that some of these pathogens condition, the prompt detection of the etiology is of the utmost importance. As with other critical patients, differentiating pneumonia from other etiologies of pulmonary infiltrates can be extremely difficult. In liver transplant patients, a CPIS score >6, abnormal temperature, and renal failure (serum creatinine >1.5 mg/dL) were significant predictors of pneumonia (41). It is important to bear in mind that some drugs, such as sirolimus, may cause pulmonary infiltrates (134). Patients may develop dyspnea, cough, fatigue, and sometimes fever. Characteristic radiological changes are bilateral lower-zone haziness. The presentation ranges from insidious to fulminant, and usually there is a rapid response to sirolimus withdrawal.

Chest X rays predominantly show alveolar or interstitial infiltrates of variable extension. However, nodular lesions are not uncommon. The differential diagnosis of a lung nodule in a normal host includes many malignant and benign processes. However, in immunosuppressed patients the most common causes are potentially life-threatening opportunistic infections that may be treated and prevented. We have detected single or multiple lung nodules on the chest radiograph in 10% of our HT patients (101). *Aspergillus* infection was detected early after transplantation (median 38 days, range 23–158), whereas *N. asteroides* and *Rhodococcus* infections developed only later (median 100 days, range 89–100). Nodules due to CMV occurred 16 to 89 days after HT (median 27 days). Patients with *Aspergillus* were, overall, more symptomatic and were the only ones in our series to present neurological manifestations and hemoptysis. CT is more sensitive than standard chest X ray in identifying the number of lesions and may assist guided biopsy.

Etiological diagnosis is mandatory considering that only 50% of the empirical treatments of pneumonia in HT patients are appropriate (64). For this reason, fast diagnostic procedures that guide antimicrobial treatment are necessary. Etiological diagnosis may be performed by using different techniques, so this requires careful tailoring to each single patient. Once pneumonia is identified, blood cultures, respiratory samples for culture of bacteria, mycobacteria, fungi, and viruses and urine for *Legionella* and *S. pneumoniae* antigen detection must be sent to the laboratory (if possible, before starting antimicrobials). The rate of expected bacteremia in patients with pneumonia is 16% to 29% (135). Demonstration of pathogenic microorganisms (*M. tuberculosis*, *Legionella*, *Cryptococcus*, *R. equi*, or *P. jiroveci*) in a sputum sample is diagnostic. PCR techniques may help improving diagnostic sensitivity (85). A bronchoscopic sample with bronchial biopsy is preferable for CMV, *Aspergillus*, *P. jiroveci*, or *Legionella* pneumonia. If pleural fluid is present it should also be analyzed. In our series of nodular lesions in HT patients, etiological diagnosis was established within a median of eight days (0–24) (Table 3). A median of 1.8 invasive techniques per patient was necessary to achieve the diagnosis. Overall diagnostic yield was 60% for transtracheal aspiration, 70% for BAL, and 75% for transthoracic aspiration. BAL was the first positive technique in 58% of the patients.

The only complications were a minor pneumothorax after a transbronchial biopsy and minor hemoptysis after a transthoracic needle aspiration. Direct microscopic examination of the respiratory samples (Gram stain, potassium hydroxide, or cotton blue preparations) were positive in 3/5 cases of aspergillosis and in 3/4 cases of nocardiosis (101). A serum sample should also be submitted. Pneumonia is the infection with the highest related mortality rate, and this can also be maintained for SOT recipients, so prompt empirical therapy is highly recommended for patients in critical conditions after obtaining adequate samples. The selection of the empirical therapy will be guided by the characteristics of the patient and the clinical situation.

### Postsurgical Infections

Complications in the proximity of the surgical area must always be investigated. Surgical problems leading to devitalized tissue, anastomotic disruption, or fluid collections markedly predispose the patient to potentially lethal infection. In the early posttransplantation period, renal and pancreas transplant recipients may develop surgical site infection (SSI), perigraft hematomas, lymphoceles, and urinary fistula (136). Incisional SSIs were detected in 55 of 1400 consecutive renal transplants in Spain a median of 20 days after transplantation. The most frequently isolated pathogens were *Escherichia coli* (31.7%), *P. aeruginosa* (13.3%), *Enterococcus faecalis* (11.6%), *Enterobacter* spp. (10%), and coagulase-negative staphylococci (8.3%). Risk factors were diabetes, and use of sirolimus (137). In another study, risk factors for SSI in KT recipients included reoperation, chronic glomerulonephritis, acute graft rejection, delayed graft function, diabetes, and high body mass index (138). SSI requires rapid debridement and effective antimicrobial therapy and should prompt the exclusion of adjacent cavities or organ involvement. Liver transplant recipients are at risk for portal vein thrombosis, hepatic vein occlusion, hepatic artery thrombosis, and biliary stricture formation and leaks. Heart transplant recipients are at risk for mediastinitis and infection at the aortic suture line, with resultant mycotic aneurysm, and lung transplantation recipients are at risk for disruption of the bronchial anastomosis. In intestinal transplant recipients, abdominal wall closure with mesh should be avoided because of the high rate of infectious complications (139).

### Intra-abdominal Infection

In OLT recipients intra-abdominal infections may be responsible for 50% of bacterial complications and cause significant morbidity (140); they include intra-abdominal abscesses, biliary tree infections, and peritonitis (141). In nonabdominal transplantations, intra-abdominal infections may be caused by preexisting problems such as biliary tract litiasis, diverticulitis, CMV disease, etc.

Risk factors for intra-abdominal complications after OLT include prolonged duration of surgery, transfusion of large volumes of blood products, use of a choledochojejunostomy (Roux-en-Y) instead of a choledochostomy (duct-to-duct) for biliary anastomosis, repeat abdominal surgery, biliary-tract dehiscence or obstruction, intra-abdominal hematomas, vascular problems of the allograft (e.g., the thrombosis of the hepatic artery or the ischemia of the biliary tract may condition the apparition of cholangitis and liver abscesses), previous antibiotic administration, and CMV infection (142). Occasionally, the complications will appear after the performance of some procedure such as a liver biopsy or a cholangiography. These infections may be bacteremic and, in fact, OLT recipients show the highest rate of secondary bloodstream infections (143). Most common microorganisms include *Enterobacteriaceae* bacilli, enterococci, anaerobes, and *Candida*.

In a series published by Singh et al., the biliary tree was the origin of 9% of infections associated with fever in the ICU (9). Biliary anastomosis leaks may result in peritonitis or perihepatic collections, cholangitis, or liver abscesses (144–146). OLT recipients are especially predisposed to suffer cholangitis. Recent data suggest that duct-to-duct biliary anastomosis stented with a T tube tends to be associated with more postoperative complications (147). A percutaneous aspirate with culture of the fluid is required to confirm infection. Culture of T tube is unreliable, since it may only reflect colonization.

Hepatic abscess is frequently associated with hepatic artery thrombosis, which occurs in up to 7% of patients (148). In one series, median time from transplant to hepatic abscess was 386 days (range 25–4198). Clinical presentation of hepatic abscess was similar to that described in nonimmunosuppressed patients. Occasionally, the only manifestations are unexplained fever and relapsing subacute bacteremia. In fact 40% to 45% of the liver abscesses are associated with bacteremia. Prolonged antibiotic therapy, drainage, and even retransplantation may be required to improve the outcome in these patients. Catheter drainage was successful in 70% of cases. Mortality rate was 42% (149). Ultrasonography or CT of the abdomen is the normal technique to identify intra-abdominal or biliary infections. However, sterile fluid collections are exceedingly common after liver transplantation, so an aspirate is necessary to establish infection.

### *Mediastinitis*

In heart and lung transplant recipients, the possibility of mediastinitis (2–9%) should be considered. HT patients have a higher risk of postsurgical mediastinitis and sternal osteomyelitis than other heart surgical patients (150). It may initially appear merely as fever or bacteremia of unknown origin. Inflammatory signs in the sternal wound, sternal dehiscence, and purulent drainage may appear later. The most commonly involved microorganisms are staphylococci but gram-negative rods represent at least a third of our cases. *Mycoplasma*, mycobacteria, and other less common pathogens should be suspected in culture-negative wound infections (151,152). A bacteremia of unknown origin during the first month after HT should always suggest the possibility of mediastinitis (153). Risk factors are prolonged hospitalization before surgery, early chest reexploration, low output syndrome in adults and the immature state of immune response in infants. Therapy consists of surgical debridement and repair, and antimicrobial therapy given for three to six weeks.

### **Urinary Tract Infections**

UTIs are the most common form of bacterial complication affecting renal transplant recipients (154–156). The incidence in patients not receiving prophylaxis has been reported to vary from 5% to 36% in recent series (157,158). Pretransplant history of UTI increases the risk of infection after transplantation (159). Some authors have found a cumulative incidence of acute pyelonephritis (APN) after KT of 18.7%. The risk of developing APN was higher in female (64%) than in male recipients, and correlated with the frequency of recurrent UTI and rejection episodes. Multivariate analysis revealed that APN represents an independent risk factor associated with the decline of renal function ( $p = 0.034$ ) (160).

UTI, however, is not a common cause of ICU admission. The most common pathogens include *Enterobacteriaceae*, enterococci, staphylococci, and *Pseudomonas* (161). Other less frequent microorganisms like *Salmonella*, *Candida*, or *Corynebacterium urealyticum* pose specific management problems in this population (162). It is also important to remember the possibility of infection caused by unusual pathogens like *Mycoplasma hominis*, *M. tuberculosis*, or BK and JC viruses. Unless another source of fever is readily apparent, any febrile KT patient with an abrupt deterioration of renal function should be treated with empiric antibacterial therapy aimed at gram-negative bacteria, including *P. aeruginosa*, after first obtaining blood and urine cultures, especially in the first three months after transplantation (163). Examination of the iliac fossa is particularly important after KT. Tenderness, erythema, fluctuance, or increase in the allograft size may indicate the presence of a deep infection or rejection. Ultrasound or CT-guided aspiration may facilitate the diagnosis. Prolonged administration of broad-spectrum antimicrobial therapy has been classically recommended for the treatment of early infections, although no double-blind, comparative study is available (155). Antimicrobial resistance to drugs commonly used, such as cotrimoxazole or quinolones, is common, so they should not be selected for empirical therapy of severe UTI (164,165).

### **Gastrointestinal Infections**

Abdominal pain and/or diarrhea are detected in up to 20% of organ transplant recipients (135). Gastrointestinal symptoms are present in up to 51% of HT patients in recent series,

although only 15% are significant enough to warrant endoscopic, radiological, or surgical procedures. Possible manifestations include gastrointestinal bleeding, diarrhea, abdominal pain, jaundice, nausea or vomiting,odynophagia, dysphagia, or just weight loss (166). Hepatobiliary, peptic ulcer, and pancreatic complications are the most prevalent. Peritonitis, intra-abdominal infections, and *Clostridium difficile* colitis accounted for 5% of all febrile episodes in OLT in the ICU (9). CMV and *C. difficile* are the most common causes of infectious diarrhea in SOT patients. A particular gastric lymphoma called mucosa-associated lymphoid tissue (MALT) lymphoma may develop in renal transplant patients. It usually responds to the eradication of *Helicobacter pylori* (167).

CMV may involve the whole gastrointestinal tract, although duodenum and stomach are the most frequent sites involved (168). Infection of the upper gastrointestinal tract with CMV used to be a major cause of morbidity in transplant patients (169). In one series 53/201 HT patients had persistent upper gastrointestinal symptoms (abdominal pain, nausea, and vomiting). Of these 53 patients, 16 (30.2%) had diffuse erythema or ulceration of the gastric mucosa (14), esophagus (1), and duodenum (1) with biopsy results that were positive for CMV on viral cultures (incidence, 8%). All patients with positive biopsy results were treated with IV ganciclovir. Recurrence developed in 6 patients (37.5%) and required repeated therapy with ganciclovir. None of the 16 patients died as a result of gastrointestinal CMV infection. Other possible presentation symptoms are fever and gastrointestinal bleeding. Differential diagnosis should include diverticulitis, intestinal ischemia, cancer, and Epstein-Barr virus (EBV)-associated lymphoproliferative disorders. Practically all patients with gastrointestinal CMV will have a positive PCR in blood. However, occasionally, severe intestinal CMV disease may occur in patients with negative antigenemia, especially in patients on mycophenolate mofetil (58). PCR is also an accurate method for the detection of CMV in the mucosa of the GI tract (170).

The natural history of CMV disease associated with solid-organ transplantation has been modified as a result of the widespread use of potent immunosuppressants and antiviral prophylaxis and late severe forms are now detected (171). Hypogammaglobulinemia may also justify severe or relapsing forms of CMV after solid-organ transplantation (172).

*Clostridium difficile* should be suspected in patients who present with nosocomial or community-acquired diarrhea. It is more common in transplant population who frequently receive antimicrobial agents, and up to 20% to 25% of patients may experience a relapse (173–175). Incidence of *C. difficile* infection is increasing, even taking into account improved diagnosis and increased awareness. Most infections occur early after transplantation (174). The most important factor in the pathogenesis of disease is exposure to antibiotics that disturb the homeostasis of the colonic flora. Nosocomial transmission has also been described. SOT recipients have many risk factors for developing *C. difficile* associated diarrhea (CDAD): surgery, frequent hospital admissions, antimicrobials exposure, and immunosuppression.

Most common clinical presentation is diarrhea, but clinical presentation may be unusually severe (176,177). In a recent series, 5.7% of the kidney or pancreas transplant recipients developed fulminant CDAD that presented with toxic megacolon, and underwent colectomy. One of them died; the other patient survived after colectomy (178). Absence of diarrhea is a poor prognostic factor. In these cases significant leukocytosis may be a very useful clue. The infection may be demonstrated with a rectal swab. Occasionally, patients present with an acute abdomen (179) or inflammatory pseudotumor (180).

Fresh stool samples should be analyzed for the presence of toxin producer *C. difficile*. The reference method for diagnosis is the cell culture cytotoxin test that detects toxin B in a cellular culture of human fibroblasts (181). Culture in specific media is also recommended since it allows resistance study, molecular analysis of the strains, and the performance of a “second-look” cell culture assay that enhances the potential for diagnosis (182). Toxigenic culture tests *C. difficile* isolates for toxin production and has higher sensitivity and equivalent specificity compared with the cytotoxicity assay (183). *C. difficile* colitis may occur in coincidence with CMV gastrointestinal infection (173,184).

The first step in managing diarrhea and colitis caused by *C. difficile* is discontinuation of the antibiotic therapy that precipitated the disease, whenever possible. About 15% to 25% of patients respond within a few days. Patients with severe disease should be treated with oral

metronidazole or vancomycin. Oral metronidazole (500 mg t.i.d. or 250 mg every 6 hours) and oral vancomycin (125 mg every 6 hours) administered for 10 to 14 days have similar therapeutic efficacy, with response rates near 90% to 97%. When oral administration is not feasible, IV metronidazole should be used, since IV vancomycin is not effective. Nearly, all patients respond to treatment in about five days. Comparison of metronidazole's activity with that of vancomycin in patients with moderately severe disease shows similar response rates. The former is preferred because of its reduced risk of vancomycin-resistance induction and lower cost. However, recent reports of severe clinical forms suggest that vancomycin may be preferable for these especially virulent strains.

*C. difficile* strains resistant to metronidazole and with intermediate resistance to vancomycin have been described. The administration of probiotics such as *Saccharomyces boulardii* or *Lactobacillus* spp. for prophylaxis of CDAD remains controversial, and we do not recommend it in critical patients since the occurrence of severe invasive disease by *S. boulardii* has been described (185).

As mentioned, a substantial proportion of patients (10–25%) have a relapse usually 3–10 days after treatment has been discontinued, even with no further antibiotic therapy. Relapse usually results from either a failure to eradicate *C. difficile* spores from the colon or due to reinfection from the environment. Nearly all patients respond to another course of antibiotics if given early. The frequency of relapses does not seem to be affected by the antibiotic selected for treatment, the dose of these drugs, or the duration of treatment.

Multiple relapses may be difficult to manage. Several measures have been suggested: gradual tapering of the dosage of vancomycin over one to two months, administration of "pulse-dose" vancomycin, use of anion-exchange resins to absorb *C. difficile* toxin A, administration of vancomycin plus rifampin or administration of immunoglobulins.

Infectious enteritis is especially frequent in intestinal transplant recipients (39%). Viral agents are the cause in two-thirds of the cases. In a recent series, there were 14 viral enteritis (one CMV, 8 rotavirus, 4 adenovirus, 1 EBV), 3 bacterial (*C. difficile*), and 3 protozoal infections (1 *Giardia lamblia*, 2 *Cryptosporidium*). The bacterial infections tended to present earlier than the viral infections, and the most frequent presenting symptom was diarrhea (186).

Immunosuppressive drugs such as mycophenolate mofetil, cyclosporine A, tacrolimus, and sirolimus are all known to be associated with diarrhea. The incidence of diarrhea ranged from 13% to 38% for regimens containing CSA and MMF and 29% to 64% for regimens with tacrolimus and MMF (187). Rarely, graft-versus-host disease (GVHD), lymphoproliferative disorder, de novo inflammatory bowel disease (IBD), or colon cancer may present as diarrhea. Flare-up of preexisting IBD is also not uncommon after liver transplantation.

CMV and *C. difficile* are the most common causes of proven infectious diarrhea in SOT patients in the developed world (178,188–190). Accordingly, the first step of the management of a patient with fever and diarrhea or abdominal pain should be directed to exclude these pathogens. If clinical manifestations persist despite exclusion of these, a wider differential diagnosis and more sophisticated diagnostic techniques should be considered since there are reports of SOT recipients with infections caused by Norwalk virus (191), rotavirus (192), adenovirus (193), EBV (194), *Cryptosporidium parvum* (195), *Isospora belli* (196,197), etc. However, the cause of acute diarrhea remains unidentified in one of three patients (188).

### Neurological Focality

The detection of CNS symptoms in an SOT recipient should immediately arise the suspicion of an infection (198). Fever, headache, altered mental status, seizures, focal neurological deficit, or a combination of them should prompt a neuroimaging study (135). Noninfectious causes include immunosuppressive-associated leukoencephalopathy (199), toxic and metabolic etiologies, stroke, and malignancies (200). Therapy with OKT3 monoclonal antibody has been related to the production of acute aseptic meningitis (CSF pleocytosis with negative cultures, fever, and transient cognitive dysfunction). Infectious progressive dementia has been related to JC virus, herpes simplex, CMV, and EBV.

Most common cause of meningoencephalitis in organ transplant recipients are herpes viruses, followed by *L. monocytogenes*, *C. neoformans*, and *T. gondii*. HHV-6 is a neurotropic

ubiquitous virus known to cause febrile syndromes and exanthema subitum in children. Less commonly, and particularly in organ transplant recipients, it may cause hepatitis, bone marrow suppression, interstitial pneumonitis, and meningoencephalitis (201–207). In a recent review, HHV-6 encephalitis occurs a median of 45 days (range 10 days to 15 months) after transplantation. Mental status changes ranging from confusion to coma (92%), seizures (25%), and headache (25%) were the predominant clinical presentations. Focal neurological findings were present in only 17% of the patients. Twenty-five percent of the patients had fever, occasionally reaching 40°C. Cerebrospinal fluid pleocytosis was generally lacking. Magnetic resonance images of the brain may reveal multiple bilateral foci of signal abnormality (nonenhancing involving both gray and white matter). HHV-6 can be detected in cerebrospinal fluid by PCR or by viral isolation. HHV-6 viremia was documented in 78% of the patients. Overall mortality in patients with HHV-6 encephalitis was 58% (7 of 12); 42% (5 of 12) of the deaths were caused by HHV-6. Cure was documented in 7 of 8 patients who received ganciclovir or foscarnet for  $\geq 7$  days, compared with 0% (0 of 4) in those who did not receive these drugs or received them for  $< 7$  days ( $p = 0.01$ ) (203). A growing body of evidence suggests that the more important effect of HHV-6 and HHV-7 reactivation on the outcomes of liver transplantation may be mediated indirectly by their interactions with CMV (204). HHV-6 viremia is an independent predictor of invasive fungal infection (208).

CMV infection of the CNS is quite uncommon in SOT recipients. It may affect the brain (diffuse encephalitis, ventriculoencephalitis, cerebral mass lesions) or the spinal cord (transverse myelitis, polyradiculomyelitis). Diagnosis is very difficult and should be based on clinical presentation, results of imaging, and virological markers. The most specific diagnostic tool is the detection of CMV DNA by PCR in the CSF. Treatment should be initiated promptly if CMV infection is suspected. Antiviral therapy consists of IV ganciclovir, IV foscarnet, or a combination of both. Cidofovir is the treatment of second choice. Patients who experience clinical improvement or stabilization during induction therapy should be given maintenance therapy (209). Encephalitis caused by HSV has also been described (210,211).

Among causes of encephalitis, West Nile virus (WNV) has emerged as an important cause of several outbreaks of febrile illness and encephalitis in North America over the past few years. In a recent report, 11 transplant recipients with naturally acquired WNV encephalitis were identified (4 kidney, 2 stem cell, 2 liver, 1 lung, and 2 kidney/pancreas). Ten patients developed meningoencephalitis, which in three cases was associated with acute flaccid paralysis. All patients had cerebrospinal fluid pleocytosis and WNV-specific IgM in the cerebrospinal fluid and/or serum. Magnetic resonance images of the brain were abnormal in seven of eight tested patients, and electroencephalograms were abnormal in seven of seven, with two showing periodic lateralized epileptiform discharges. Nine of 11 patients survived infection, but 3 had significant residual deficits. This viral infection should be considered in all transplant recipients who present with a febrile illness associated with neurological symptoms (212–214).

*L. monocytogenes* infections can occur at almost any time, although the most common occurrence is two to six months posttransplant (215). The incidence has significantly been reduced since prophylaxis with cotrimoxazole is used (111). *Listeria* infections may present as isolated bacteremia or with associated meningitis (216,217). OLT recipients may present with acute hepatitis (218). Brainstem encephalitis or rhomboencephalitis have been characteristically described in patients with listeriosis in which cranial nerve palsies or pontomedullary signs may be observed. Cerebritis/abscess due to *L. monocytogenes*, without meningeal involvement, is less common (219).

Incidence of cryptococcosis after organ transplantation is 2.6% to 5% and CNS is involved in 25% to 72% of the patients (220–223). *Cryptococcus* is mostly a cause of meningitis, pneumonia, and skin lesions (224–227). Cryptococcomas are rare (228). However, more uncommon sites of infection have been also described in immunocompromised patients such as hepatic cryptococcosis in an HT recipient (229). The patient developed fever, dyspnea, and signs of liver damage. Diagnosis was made with liver biopsy and with cryptococcal antigen in serum (229). Cryptococcosis is usually a late disease after transplantation, although rare fulminant early cases have been reported (230). CSF analysis usually reveals moderate

pleocytosis. CSF cryptococcal antigen is positive in most patients. In a recent series, 83 transplant recipients with cryptococcosis were analyzed. Patients with CNS infection (69% vs. 16%,  $p < 0.001$ ), disseminated infection (82.7% vs. 20%,  $p < 0.001$ ), and fungemia (29% vs. 8%,  $p = 0.046$ ) were more likely to receive regimens containing amphotericin B than fluconazole as primary therapy. Survival at six months tended to be lower in patients whose CSF cultures at two weeks were positive compared with those whose CSF cultures were negative (50% vs. 91%,  $p = 0.06$ ) (113). No correlation was found between CSF or serum cryptococcal antigen titer and evolution or CSF sterilization at two weeks (231).

Focal brain infection (seizures or focal neurological abnormalities) may be caused by *Listeria*, *T. gondii*, fungi (*Aspergillus*, mucorales, phaeohyphomycetes, or dematiaceous fungi), posttransplantation lymphoproliferative disease or *Nocardia*. Brain abscesses are relatively uncommon (0.6%) in SOT patients and most of them (78%) are caused by *Aspergillus* (232), followed by *T. gondii* and *N. asteroides*. Fever is not common and was documented in only 45% of the liver transplant recipients with brain abscesses. As discussed herein, the characteristics that may help in the differential diagnosis are the time of appearance of the lesion and the presence of concomitant extraneural disease (predominantly pulmonary), which is very frequent in patients with fungal brain abscesses (70%). Such lesions usually provide an early clue to the diagnosis. If extraneural involvement is not documented, a brain biopsy should be performed to establish the etiological diagnosis. Empiric therapy of brain abscesses in SOT recipients should include antifungal, and not antibacterial or antiviral therapy.

*Aspergillus* brain abscesses usually occur in the early posttransplantation period. Most of the patients present with simultaneous lung lesions that allow an easier diagnostic way. Overall, disseminated *Aspergillus* disease has been described in 9% to 36% of kidney recipients, 15% to 20% of lung recipients, 20% to 35% of heart recipients, and 50% to 60% of liver recipients with IA (107,233,234). Disseminated infection with CNS involvement occurred in 17% of the cases studied in Spain. Clinical manifestations of CNS aspergillosis include alteration of mental status, diffuse CNS depression, seizures, evolving cerebrovascular accidents, and headache (107,235). The CSF fluid is almost always sterile.

*Scedosporium*, zygomycetes, and other uncommon fungi are being increasingly detected as significant CNS pathogens in transplant recipients (110,236–238). Brain abscesses due to dematiaceous fungi are described a median of three months posttransplantation, but may occur as late as two years later (239). Infections due to the agents of zygomycosis seem to be increasing in the transplant population and nearly 50% are of the rhinocerebral form (240–242).

Toxoplasmosis was more prevalent when prophylaxis with cotrimoxazole was not provided (40,243). The incidence is higher in HT recipients. The disease usually occurred within three months posttransplantation, with fever, neurological disturbances, and pneumonia as the main clinical features. Chorioretinitis may also be found (244,245). Diagnosis was established by serology and by direct examination, culture, or PCR of biological samples. In HT recipients, the diagnosis may be provided by the endomyocardial biopsy (246). The lesions of *T. gondii* are usually multiple, have preferential periventricular localization, and demonstrate ring enhancement. The donor was the likely source of transmission to most recipients (247). The mortality rate was high (around 60%). Obstructive urinary tract lithiasis involving sulfadiazine crystals have been described (248). Disseminated toxoplasmosis should be considered in the differential diagnosis of immunocompromised patients with culture-negative sepsis syndrome, particularly if combined with neurological, respiratory, or unexplained skin lesion (249).

Other parasitic infections such as Chagas disease, neurocysticercosis, schistosomiasis, and strongyloidiasis are exceedingly less common (250).

Nocardiosis is usually observed between one and six months posttransplantation. The clinical presentation of nocardiosis includes pneumonia, CNS focal lesions, and cutaneous involvement (198,251–254). Brain abscesses due to *Nocardia* are multiple in up to 40% of the cases and may demonstrate ring enhancement. Diagnosis may be reached by direct observation of biological samples using modified Ziehl-Neelsen staining or Gram stain. The mainstays of treatment are sulphonamides or cotrimoxazole, although some authorities recommend induction therapy with a combination of drugs including carbapenem derivatives.

### Bloodstream Infections, Catheter-Related Infections, and Infective Endocarditis

As other patients requiring intensive care, catheter-related bloodstream infections (CRBSIs) are a potential threat for severe infection after SOT. In a recent study performed by our group in HT recipients, CRBSI accounted for 16% of BSI in this population (34). In HT recipients, the incidence of bloodstream infection is 15.8%. BSI episodes were detected a median of 51 days after transplantation. The main BSI origins were lower respiratory tract (23%), urinary tract (20%), and CRBSI (16%). Gram-negative organisms predominated (55.3%), followed by gram-positive organisms (44.6%). We found a clear relationship between time of onset and some characteristics of the BSI. During the first month after transplantation, 95% of BSIs were nosocomially acquired and the main origins were IV catheter (32%), surgical site, and LRT (18% each). From month 2 to month 6, 70% of the BSIs were nosocomially acquired and the main origins were UTI and LRT (25% each). After the sixth month, only 22% of the BSI episodes were nosocomial and the most common portals of entry were LRT (33%), primary bacteremia (22%), and UTI (17%) ( $p = 0.1$ ). Mortality was 59.2%, with 12.2% directly attributable to BSI. Independent risk factors for BSI after HT were hemodialysis (OR 6.5; 95% CI 3.2–13), prolonged ICU stay (OR 3.6; 95% CI 1.6–8.1), and viral infection (OR 2.1; 95% CI 1.1–4). BSI was a risk factor for mortality (OR 1.8; 95% CI 1.2–2.8) (34).

CRBSI caused 15% of the febrile episodes of liver transplant recipients in the ICU (9). Although only 37% of the bacterial infections after liver transplantation occur more than 100 days after transplant, 60% of the cases of primary bacteremia after liver transplantation occur late (255). The incidence of BSI after OLT is 0.28 episodes/patient. BSI accounted for 36% of all major infections. Intravascular catheters were the most frequent source and MRSA was the most frequent pathogen causing BSI. In recent years, a shift toward a higher importance of gram-negative microorganisms causing bacteremia has been observed (34,256). Gram-negative CRBSI, mainly if more than one case is detected, should always prompt exclusion of a nosocomial hazard, such as contamination of the infusate or transmission by health care workers (257,258).

Seventy percent of catheter-related and all bacteremias due to intra-abdominal infections occurred  $\leq 90$  days, whereas 75% of the bacteremias due to biliary source occurred  $> 90$  days after transplantation. Length of initial posttransplant ICU stay ( $p = 0.014$ ) and readmission to the ICU ( $p = 0.003$ ) were independently significant predictors of bloodstream infections. Up to 40% of the candidemias occurred within 30 days of transplantation and were of unknown origin, whereas the portal of entry in all candidemias occurring  $> 30$  days posttransplant was known (catheter, hepatic abscess, urinary tract). Mortality in patients with bloodstream infections was 52% (15/29) vs. 9% (9/101) in patients without bloodstream infections ( $p < 0.001$ ). In conclusion, intravascular catheters (and not intra-abdominal infections) have emerged as the most common source of BSI after OLT (259).

In another study, primary (catheter-related) bacteremia (31%; 9 of 29 patients), pneumonia (24%; 7 of 29 patients), abdominal and/or biliary infections (14%; 4 of 29 patients), and wound infections (10%; 3 of 29 patients) were the predominant sources of bacteremia (260).

The most important risk factor for CRBSI is the length of catheterization. Most catheters used in critically ill SOT patients are short termed. These include central venous catheters, temporary hemodialysis catheters, peripheral venous catheters, and arterial cannulas. The site of central venous catheterization (internal jugular vein vs. the subclavian vein) does not seem to have an impact on the incidence of related infections, as long as catheterization is performed by experienced personnel (261). *S. aureus* nasal carriage is associated with a higher risk of bacteremia (63). Active surveillance cultures to detect colonization and implementation of targeted infection control interventions have proved to be effective in curtailing new acquisition of *S. aureus* colonization and in decreasing the rate of *S. aureus* infection in this population (262). Strict adherence to hand hygiene and to prophylactic guidelines may help reduce the incidence of these infections.

*Prototheca* spp. are unicellular algae of low virulence that are rarely associated with human infections. Of nine cases reported in the literature, five had a localized infection and four had disseminated protothecosis (263). Seven cases were due to *P. wickerhamii*, and two were due to *P. zopfii*. Overall mortality in transplant recipients with *Prototheca* infections was 88% (7/8). All four cases of disseminated protothecosis died despite therapy with amphotericin B.



*Infective endocarditis* is a rare event in SOT population (1.7–6%), but it may be an underappreciated sequela of hospital-acquired infection in transplant patients (56). The spectrum of organisms causing infective endocarditis was clearly different in transplant recipients than in the general population; 50% of the infections were due to *Aspergillus fumigatus* or *S. aureus*, but only 4% were due to viridans streptococci. Fungal infections predominated early (accounting for 6 of 10 cases of endocarditis within 30 days of transplantation), while bacterial infections caused most cases (80%) after this time. In 80% (37) of the 46 cases in transplant recipients, there was no underlying valvular disease. Seventy-four percent (34) of the 46 cases were associated with previous hospital-acquired infection, notably venous access device and wound infections. Three patients with *S. aureus* endocarditis had had an episode of *S. aureus* bacteremia more than three weeks prior to the diagnosis of endocarditis and had received treatment for the initial bacteremia of less than 14 days' duration. The overall mortality rate was 57% (26 of 46 patients died), with 58% (15) of the 26 fatal cases not being suspected during life (56). CMV, *Toxoplasma*, and parvovirus B19 may cause myocarditis in this population. Therapy of established infections is similar to that of other immunosuppressed patients.

### Fever of Unknown Origin

Undoubtedly, the most common alarm sign suggesting infection is fever. In transplant recipients, fever has been defined as an oral temperature of 37.8°C on at least two occasions during a 24-hour period (9). Antimetabolite immunosuppressive drugs, mycophenolate mofetil and azathioprine, are associated with significantly lower maximum temperatures and leukocyte counts (10). However, it is important to remember that fever and infections do not always come together. The absence of fever does not exclude infection. In fact, 40% of the liver recipients with documented infection (mainly fungal) were afebrile in a recent series (41). In fact, absence of febrile response has been found to be a predictor of poor outcome in liver transplant recipients with bacteremia (260). In that series, the independent factors predictive of greater mortality were ICU stay at the time of bacteremia (100% vs. 47%;  $p = 0.005$ ), absence of chills (0% vs. 53%;  $p = 0.005$ ), lower temperature at the onset of bacteremia (99.2°F vs. 101.5°F;  $p = 0.009$ ), lower maximum temperature during the course of bacteremia (99.3°F vs. 102°F,  $p = 0.008$ ), greater serum bilirubin level (7.6 vs. 1.5 mg/dL;  $p = 0.024$ ), abnormal blood pressure (80% vs. 16%;  $p = 0.001$ ), and greater prothrombin time (15.6 vs. 13.3 seconds;  $p = 0.013$ ).

A major difference with immunocompetent critical patients is that the list of potential etiological agents is much longer and is influenced by time elapsed from transplantation. CMV (as main offender or as copathogen) should be considered in practically all-infectious complications in this population. Accordingly, a sample for CMV antigenemia (or PCR if available) should always be obtained. Other viruses such as adenovirus, influenza A, or HHV-6 may also cause severe infections after SOT and can be recovered from respiratory samples or blood. If indicated, invasive diagnostic procedures should be performed rapidly and a serum sample stored.

Bacterial infections must always be considered and urine and blood cultures obtained before starting therapy. Diagnosis of catheter-related infections without removing the devices may be attempted in stable patients. Lysis centrifugation blood cultures as well as hub and skin cultures have a high negative predictive value (264). The first steps for diagnosis of pneumonia should include a chest X ray and culture of expectorated sputum or bronchoaspirate (submitted for virus, bacteria, mycobacteria, and fungus). A CT scan or ultrasonography may also be ordered to exclude the presence of collections in the proximity of the surgical area. Lumbar puncture and cranial CT (including the paranasal sinus) must be performed if neurological symptoms or signs are detected. In case of diarrhea, *C. difficile* should be investigated. Cultures and PCR for detection of *M. tuberculosis* should be ordered for all transplant recipients with suspicion of infection.

Fungal infections should be aggressively pursued in colonized patients and in patients with risk factors. Early stages of fungal infection may be very difficult to detect (107,265). Isolation of *Candida* or *Aspergillus* from superficial sites may indicate infection. Fundus examination, blood and respiratory cultures, and *Aspergillus* and *Cryptococcus* antigen detection tests must be performed.

Parasitic infections are uncommon, but toxoplasmosis and leishmaniasis should be considered if diagnosis remains elusive. Serology or bone marrow cultures usually provide the diagnosis. The possibility of a *Toxoplasma* primary infection should be considered when a seronegative recipient receives an allograft from a seropositive donor. HT recipients are more susceptible to toxoplasmosis, which may be transmitted with the allograft and occasionally requires ICU admission. The risk of primary toxoplasmosis (R-D+) is over 50% in HT, 20% after liver transplantation, and <1% after KT. Patients with toxoplasmosis have fever, altered mental status, focal neurological signs, myalgias, myocarditis, and lung infiltrates. Allograft-transmitted toxoplasmosis is more often associated with acute disease (61%) than with reactivation of latent infection (7%). Lethal cases associated to hemophagocytic syndrome have been described (266). Leishmaniasis is another parasitic infection that should be excluded, though it is exceedingly uncommon after SOT. It may present as fever, pancytopenia, and splenomegaly.

Multimodality imaging with the use of combined indium-labeled WBC scintigraphy and CT allowed the detection of infection within a retained left ventricular assist device tubing in an HT recipient with a diagnosis of fever of unknown origin (267).

### **Noninfectious Causes of Fever**

Both infectious and noninfectious causes of fever should be considered when approaching a febrile SOT patient. In a recent series, 87% of the febrile episodes detected in OLT in the ICU were due to infections and 13% were noninfectious (9). Rejection, malignancy, adrenal insufficiency, and drug fever were the most common noninfectious causes.

Fever is common in the first 48 hours after surgery and after certain procedures. If it is not persistent or accompanied by other signs or symptoms, it should not trigger any diagnostic action. Acute rejection accounts for 4% to 17% of noninfectious febrile episodes (268). It is usually related to an impairment of the allograft function and requires histological confirmation. It is more common in the first six months, especially in the first 16 days after transplantation in one study (269). It is important to remember that severe graft rejection and increased immunosuppression could stimulate cooperatively active CMV infections (270,271).

Malignancy, mainly lymphoproliferative disease, is relatively common after SOT and may initially present as a febrile episode (80%) (272–274). It usually occurs longer after transplantation (268). Acute adrenal insufficiency should be excluded in SOT patients admitted to an ICU because of sepsis or surgery, mainly when corticosteroids have been withdrawn and drugs that accelerate the degradation of cortisol (phenytoin, rifampin) are administered (275). However, although analytical adrenal insufficiency is frequent in SOT patients, prospective studies suggest that supplemental steroids are not needed in most cases even under stress (276–278). Another setting of potential adrenal insufficiency is in renal transplants that return to dialysis (279,280). Occasionally, lymphoproliferative disease may present with adrenal insufficiency after liver transplantation (281).

Drugs such as OKT3, ATG, everolimus, antimicrobials, interferon, anticonvulsants, etc. may also cause fever in this population (282). The temporal relationship with the drug is usually a diagnostic clue. New induction therapies such as basiliximab are related to fewer side effects and fewer CMV infections (283).

Other causes of noninfectious fever include thromboembolic disease, hematoma reabsorption, pericardial effusions, tissue infarction, hemolytic uremic syndrome, and transfusion reaction. Noncardiogenic pulmonary edema (pulmonary reimplantation response) is a common finding after lung transplantation (50–60%) and may occasionally lead to a differential diagnosis with pneumonia. It conditions prolonged mechanical ventilation and ICU stay but does not affect survival (284).

## **MANAGEMENT**

### **Diagnostic Approach**

As mentioned before, the diagnostic approach to a critically ill SOT with suspected infection should take into account the time onward transplantation (Table 1) and previous complications such as episodes of rejection, surgical or technical problems, reactivation of a latent infection, etc.

The findings provided by the anamnesis and physical examination (see preceding text) may suggest a focus causative of the fever (pneumonia, wound infection, etc.). In this situation, a list of possible pathogens as well as necessary samples and tests for diagnosis should be elaborated. In most cases, analytical and imaging studies will also be ordered. Samples for culture should be obtained before starting empirical antimicrobial therapy.

In a recent study, 79% of the infections associated with fever in the liver recipients in the ICU were bacterial, 9% viral, and 9% fungal. Accordingly, blood cultures are practically always needed. Bacteremia is present in 45% of the febrile critical SOT patients and its origin must always be investigated. In liver recipients, the most common sources are IV devices, lung, biliary tree, and wound infections. Accordingly, the entry site of the catheters must be examined. MRSA and *P. aeruginosa* caused 65% of the bacteremias in ICU patients (7). Lack of febrile response in bacteremic OLT recipients portended a poorer outcome (255).

In HT recipients, the main BSI origins were lower respiratory tract, urinary tract, and CR-BSI that should always be investigated (34). If focal signs of infections are present, appropriate samples must be sent to the laboratory (catheter tips, wound exudate, CSF, etc.) as in any other critical patient. When a collection of fluid or pus is to be sampled, aspirated material provides more valuable information than samples obtained by means of a swab. Skin lesions must be biopsied and sampled.

Length of stay in the ICU is also a determinant factor that may help find the origin of the infection: pneumonia is more common in the first seven days of ICU stay, while CR-BSI incidence tripled after the first week.

Information on some of the most severe infections may be obtained rapidly when the clinician and the microbiology laboratory communicate effectively and the best specimen type and test are selected. Antigen detection tests for adenovirus, HSV, influenza A and B, RSV, and rotavirus are available. Most common herpesviruses can be easily cultured and detected. Gram stain requires expertise but may provide valuable rapid information (5 minutes) on the quality of the specimen and whether gram-negative or gram-positive rods or cocci are present. It may reveal yeast and occasionally molds, parasites, *Nocardia*, and even mycobacteria. The amount of material and the number of organisms limit detection sensitivity. Continuous agitation blood cultures have significantly reduced the detection time to less than 24 hours for bacterial isolates.

Direct testing of specimens with antigen assays are mainly used for CSF samples (*N. meningitidis*, *S. pneumoniae*, *H. influenzae*, *C. neoformans*). Group A streptococci, *C. difficile*, and *C. trachomatis* antigen detection tests are also available. Specific stains for *Legionella* direct fluorescent-antibody testing (DFA) and *Bordetella pertussis* are offered by most laboratories. *Legionella* urinary antigen test will be very useful in pneumonias caused by *L. pneumophila* serotype 1, and *S. pneumoniae* antigenuria can also be rapidly investigated. HIV infection, *Brucella*, and syphilis are some of the infections that can be rapidly diagnosed serologically.

Acid-fast stain and fluorochrome stains for mycobacteria or *Nocardia* require a more prolonged laboratory procedure (30–60 minutes). New techniques, such as PCR and quantification of interferon- $\gamma$ , have been developed to achieve more rapid and accurate diagnoses. *M. tuberculosis* complex PCR is very effective in smear-positive specimens. In smear-negative samples its sensitivity is ~70% (85).

Fungal elements may be rapidly detected in wet mounts with potassium hydroxide or immunofluorescent calcofluor white stain. An India ink preparation allows the identification of encapsulated *C. neoformans*, particularly in CSF in approximately 50% of patients. The latex agglutination test or EIA cryptococcal antigen have greater sensitivity. Fluorescent antibody stains or toluidine blue O permits the detection of *P. jiroveci*. Antigen detection for *Histoplasma capsulatum* is quite sensitive and the detection of *Aspergillus* antigen is useful, although its efficiency is lower than that in hematological patients (285–287).

## Management

Fever is not harmful by itself, and accordingly it should not be systematically eliminated. In fact, it has been demonstrated that fever enhance several host defense mechanisms (chemotaxis, phagocytosis, and opsonization) (135). Besides, antibiotics may be more active at higher body temperatures. If provided, antipyretic drugs should be administered at regular intervals to avoid recurrent shivering and an associated increase in metabolic demand.

After obtaining the previously mentioned samples, empiric antibiotics should be promptly started in all transplant patients with suspicion of infection and toxic or unstable situation. They are also recommended if a focus of infection is apparent, in the early posttransplant setting in which nosocomial infection is very common, or when there has been a recent increase of immunosuppression. In a stable patient without a clear source of infections, further diagnostic testing should be carried out and noninfectious causes be considered.

We have recently demonstrated that only 58.5% of patients with BSI received appropriate empirical antimicrobial therapy. Inadequate treatment was related to a longer hospital stay, a higher mean risk of CDAD, a higher mean overall mortality rate, and a higher risk of infection-related mortality (288). So once blood cultures are obtained, empirical broad-spectrum antimicrobials guided by the clinical condition of the patient and the presumed origin should be promptly started. When results of blood cultures are available, antibiotics should be adjusted according to susceptibility patterns of the isolates. This antibacterial de-escalation strategy attempts to balance the need to provide appropriate, initial antibacterial treatment while limiting the emergence of antibacterial resistance.

The selection of the antimicrobial should be based on the likely origin of the infection, prevalent bacterial flora, rate of antimicrobial resistance, and previous use of antimicrobials by the patient. In our series of bacteremia in HT recipients, gram-negative microorganisms predominated (55.3%), followed by gram-positive microorganisms (44.6%). Gram-negatives accounted for 54% of infections in the first month, 50% during months 2 to 6, and 72% of infections occurring afterward ( $p = 0.3$ ) (34).

The possibility of drug interactions, mainly with cyclosporine and tacrolimus, is very real and impacts significantly on the choice of antimicrobial. There are three categories of antimicrobial interaction with cyclosporine and tacrolimus. First, the antimicrobial agent (e.g., rifampin, isoniazid, and nafcillin) upregulates the metabolism of the immunosuppressive drugs, resulting in decreased blood levels and an increased possibility of allograft rejection. Second, the antimicrobial agents (e.g., the macrolides erythromycin, clarithromycin, and to a lesser extent azithromycin or the azoles ketoconazole, itraconazole, and to a lesser extent fluconazole) downregulate the metabolism of the immunosuppressive drugs, resulting in increased blood levels and an increased possibility of nephrotoxicity and overimmunosuppression. And finally, there may be synergistic nephrotoxicity, when therapeutic levels of the immunosuppressive agents are combined with therapeutic levels of aminoglycosides, amphotericin, and vancomycin, and high therapeutic doses of cotrimoxazole and fluoroquinolones.

### Outcome of Febrile Processes of SOT Recipients in the ICU

SOT patients have higher risk of dying after an ICU admission than the general population, and in most series it is a poor prognostic factor (289,290). However, the overall prognosis is better than that of bone marrow recipients (291–293). The overall ICU mortality of SOT patients was 18% in a recent series and infection was the major cause of death (disseminated mycoses, HCV, multiorgan failure, hepatic artery thrombosis with sepsis, and primary nonfunction of the graft).

Mortality of febrile liver recipients at 14 days (24% vs. 0%,  $p = 0.001$ ) and at 30 days (34% vs. 5%,  $p = 0.001$ ) was significantly higher in the ICU, as compared with non-ICU patients (9). Mortality of OLT with lung infiltrates in the ICU was 28%. Pneumonia, creatinine level  $>1.5$  mg/dL, higher blood urea nitrogen, and worse APACHE (Acute Physiology and Chronic Health Evaluation) neurological score were predictors of poor outcome (41). The need for mechanical ventilation was an independently significant predictor of mortality (7). Infection was a risk factor for early renal dysfunction (294). Need for preoperative ICU care was predictive of an increased risk of death in OLT patients waiting for retransplantation (290).

Infection is also a leading cause of death in heart recipients (30% of early deaths, 45% of deaths from 1 to 3 m, and 9.7% thereafter) (295). Overall, 31% of the patients with pneumonia died (*Aspergillus* 62%; CMV 13%; nosocomial bacteria 26%). Mortality was 100% in patients requiring mechanical ventilation (7/13 *Aspergillus*, 5/11 *P. jiroveci*, 1/8 CMV) (64). Infectious complications including pneumonia, bacteremia, and sepsis are significant predictors of overall mortality in extended criteria HT recipients [pneumonia hazard ratio (HR) 4.2 (95% CI 2.5–7.0), bacteremia HR 3.0 (95% CI 1.9–4.9), sepsis HR 6.0 (95% CI 3.6–10.2)] (296).

From 51 lung transplant recipients who required admission to the ICU at the Duke University Medical Center, 53% required mechanical ventilation and 37% died (59% of those requiring mechanical ventilation) (297). In other series, mortality of lung transplant recipients requiring admission to a medical ICU was 37%. A preadmission diagnosis of bronchiolitis obliterans syndrome, APACHE II score, nonpulmonary organ system dysfunction, initial serum albumin level, and duration of mechanical ventilation are important prognostic factors (30). Mortality of renal transplant recipients in the ICU was 11% in a recent series and infection caused 6/7 deaths (298).

### Prevention

Organ transplant patients admitted to the ICU should receive all measures available to prevent nosocomial infection. The first one could be to avoid the admission to the unit itself, which has been demonstrated to be a very stress-inducing situation for transplant recipients (299). In one recent study, the proportion of liver transplant patients who could be extubated immediately after surgery and transferred to the surgical ward without intervening ICU care was determined. Of 147 patients, patients did not meet postsurgical criteria for early extubation and 111 patients were successfully extubated. Eighty-three extubated patients were transferred to the surgical ward after a routine admission to the postoperative care unit. Only three patients who were transferred to the surgical ward experienced complications that required a greater intensity of nursing care. A learning curve detected during the three-year study period showed that attempts to extubate increased from 73% to 96% and triage to the surgical ward increased from 52% to 82% without compromising patient safety. The protocol resulted in a one-day reduction in ICU use in 75.5% of study subjects (300). The same approach can be extended to the use of IV catheters or indwelling bladder catheters, which should be withdrawn as soon as possible.

Other measures such as selective gastrointestinal decontamination (301), use of gowns, or HEPA filters have not demonstrated so clearly an impact on the reduction of mortality or even nosocomial infections.

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# 24 | Miliary Tuberculosis in Critical Care

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## INTRODUCTION

In the developing world tuberculosis (TB) continues to be a major cause of morbidity and mortality. In industrialized countries TB has essentially become a public health issue. While diagnostic and therapeutic issues remain, disease in most cases is not threatening enough to warrant admission to the critical care unit. Miliary TB, however, is often rapidly fatal, providing a diagnostic and therapeutic challenge to even the most skilled intensivists.

The term miliary was first introduced by John Jacobus Manget in 1700, when he likened the multiple small white nodules scattered over the surface of the lungs of affected patients to millet seeds (Fig. 1). While miliary TB was initially an anatomic and later a radiologic term, it now denotes all forms of progressive, widely disseminated TB. Synonyms include hematogenous TB, generalized TB, disseminated TB, septic TB, and Landouzy sepsis. As a disease entity, miliary TB is not due to infection with particularly virulent pathogens but is generally precipitated by host issues. Affected patients are typically predisposed by a weakened immune system, most notably defects in cellular immunity, resulting in the unchecked lymphohematogenous dissemination of *Mycobacterium tuberculosis*. The development and widespread use of more potent immunosuppressive agents, as well as the emergence of HIV/AIDS in recent years, have resulted in an increased proportion of TB cases presenting with disseminated disease.

## EPIDEMIOLOGY

Estimates for incidence and prevalence rates are often based on convenience samples, as population-based data are not available. Autopsy- and hospital-based case series, however, generally suffer from selection and allocation bias.

A large Boston City Hospital series collected in the pre-antibiotic era found that 20% of all patients with TB had evidence of disseminated infection at autopsy (1). In the 1970s, another study from Boston City Hospital found that only 0.4% of patients with TB had a miliary disease pattern (2). Since the advent of the HIV epidemic, most case series have reported that miliary TB accounted for approximately 1% to 2% of all cases of TB and 8% of all cases of extrapulmonary TB (3). Rates as high as 38%, however, have been reported in case series from hospitals with high HIV case rates (4). In the 2006 surveillance report from the Centers for Disease Control and Prevention (CDC), 1.8% of all cases of TB were classified as miliary (5). In general, the incidence of miliary TB in a given institution is going to depend on the rate of TB in the population served and the proportion of patients with increased risk for dissemination.

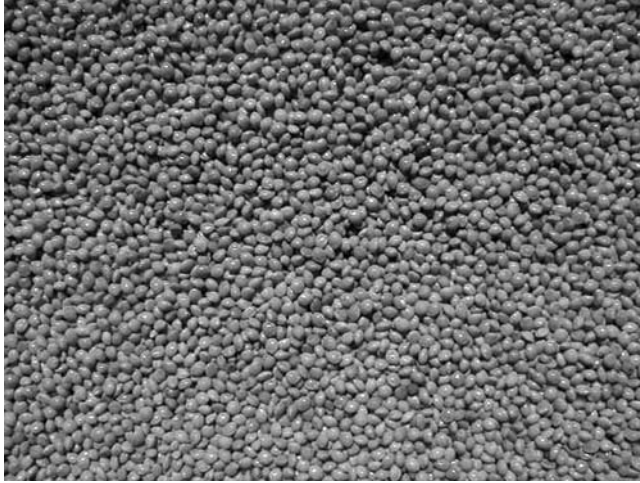
## PATHOPHYSIOLOGY

### Predisposing Conditions

Age and predisposing medical conditions (Table 1) are the most significant risk factors for the development of miliary TB. Miliary TB, however, should never be excluded from the differential diagnosis merely because a patient has no underlying medical illness. In all large case series, a significant percentage of patients have no demonstrable high-risk condition for dissemination. Race, ethnicity, and gender can affect TB demographics, but appear to have little effect on the proportion of patients presenting with miliary TB.

### Age

In the pre-antibiotic era, miliary TB was predominantly a disease of infants, children, and adolescents (1,3). Due to the delayed development of the cellular immune system, children under the age of three years are at highest risk for progressive disease (6). While TB nowadays



**Figure 1** Millet seeds.

**Table 1** Underlying Medical Conditions

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Concurrent childhood infections (measles, tonsillitis)
Malnutrition
HIV/AIDS
Gastrectomy
Alcohol abuse
Malignancy
Corticosteroids or other iatrogenic immunosuppression
Connective tissue disorders (with or without iatrogenic immunosuppression)
End-stage renal disease
Diabetes
Solid organ or bone marrow transplantation
Silicosis
Pregnancy

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is rare in infants, the proportion of TB patients presenting with disseminated disease is still higher than in any other age group. In a series from South Africa, miliary TB accounted for 8% of hospital admissions for TB in children compared with 1% in adults. More than 50% of such cases occurred in children under the age of one year (7).

Reports from the early 1970s indicated a progressive shift of the epidemiology to adult populations (8,9). In an autopsy study conducted at a hospital in Northern Ireland, 54% of patients diagnosed with miliary TB between 1946 and 1949 were less than 20 years of age; in a latter era (1966–1969), all patients with miliary TB were aged over 30 years (8). The widespread use of BCG vaccination has resulted in substantial reductions in miliary TB among young vaccines. The increasing uses of modern radiologic and invasive diagnostic methods have also contributed to the demographic shift. While infants remain at high risk for the development of miliary TB, the majority of cases now occur in adults. In accordance with the current population distribution of TB and the growing population of older adults presenting with age-related waning or iatrogenic impairment of cellular immunity, the elderly have now become the most common group to develop miliary disease (2,10). In a study from Scotland, the mean age of patients with miliary TB was 59.3 years during 1954–1967 but was 73.5 years during 1984–1992 (10). The HIV/AIDS pandemic and an increasing number of patients with iatrogenic impairments of cellular immunity have led to an additional peak of miliary TB among younger adults, resulting in a biphasic epidemiologic curve.

### Underlying Medical Conditions

Mycobacterial virulence factors and host immune defenses determine the risk of dissemination. In large studies, 30% to 80% of patients with miliary TB had underlying medical conditions (Table 1).

Tumor necrosis factor alpha (TNF- $\alpha$ ) plays an important role in the host immune response to TB. Not surprisingly, the increasing use of anti-TNF agents like infliximab and etanercept has resulted in a disturbing numbers of reports of patients suffering from pulmonary and disseminated TB.

### Immunology

Adequate containment of tubercle bacilli requires an intricate interplay of different components of the innate and the adaptive immune system. Macrophages generally represent the first line of defense. Binding to surface toll-like receptors (TLRs) initiates a robust innate immune response. TLR-mediated signals influence cytokine production and homing of effector T cells to the site of infection. Engulfed bacteria are eliminated by reactive nitrogen and oxygen intermediates. Infected macrophages process and present antigens to various T-cell subsets, including MHC class II-restricted CD4+ T-helper lymphocytes and MHC class I-restricted cytolytic CD8+ T-suppressor lymphocytes. Processed peptides and secreted cytokines, including interleukin (IL)-12, trigger TH1 cells to secrete cytokines including IL-2 and TNF- $\alpha$ , which in a feedback loop further activate the macrophages. Dominance of TH2-type cytokines (IL-4, IL-5, IL-10) increases the risk of dissemination by cross-inhibiting protective responses such as granuloma formation.

Additional molecular defects also contribute to an increased risk of developing disseminated TB. These mechanisms include impaired expansion of  $\gamma\delta$  T cells, inadequate CD4 cell function or quantity, the presence or absence of certain HLA-phenotypes, impaired MHC class II-restricted target cell lysis, and premature lysis of target cell macrophages.

### CLINICAL PRESENTATION

Miliary TB can arise as a result of progressive primary infection, from reactivation of a latent focus with subsequent spread, or rarely even following iatrogenic infection. Disseminated TB has, for instance, been reported after extracorporeal shock wave lithotripsy (11,12), homograft cardiac valve placement (13), and even catheterization of the urethra (14). Transplantation of a solid organ not previously recognized and infected with *M. tuberculosis* can also result in miliary TB (15,16).

The clinical manifestations of miliary TB are highly variable and often nonspecific. In immunocompromised patients or when miliary TB develops during primary infection, the disease tends to have a more acute onset and follow a more rapid clinical course. Fulminant disease with Landouzy sepsis, a systemic inflammatory response syndrome with refractory shock (17,18), potentially including multiorgan system failure (19), and acute respiratory distress syndrome (ARDS) (20–23) may ensue. The “cytokine storm” can be quite dramatic and result in a clinical picture resembling gram-negative septic shock. These complicated cases are typically the patients encountered by critical care providers.

Reactivation miliary TB can present as an acute illness as well, but is more likely to be subacute or chronic. Reinfection may have a role in highly endemic areas. At the chronic end of the spectrum, presentation with prolonged fever of unknown origin, anorexia, weight loss, lassitude, night sweats, and cough are frequent. In one series of 38 patients, the median duration of illness reported was two months (24). Rarely, especially among older people, apyrexial presentations with progressive wasting strongly mimicking a metastatic carcinoma are seen (25,26). This is occasionally described as cryptic miliary TB (26). Rigors are unusual but have been described (27,28).

Paradoxical worsening of lesions during effective TB therapy is known as immune reconstitution disease (IRD). While IRD is distinctly rare in HIV-negative individuals, almost one-third of patients with HIV/TB coinfection experience some form of IRD within days to weeks of the initiation of highly active antiretroviral therapy (HAART). Manifestations include fever, appearance or worsening of lymphadenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions, and new or expanding CNS tuberculomas (29).

Atypical presentations and the nonspecific symptomatology can delay the diagnosis and account for the fact that this diagnosis is frequently missed, even in the current era of improved diagnostics. In a recent review, approximately 20% of reported cases of miliary TB in the United States were diagnosed postmortem (30).

### Organ Manifestations

At autopsy, organs with high blood flow, including lungs, spleen, liver, bone marrow, kidneys, and adrenals, are frequently affected. Most organ system afflictions remain subclinical.

Concurrent, clinically apparent pulmonary disease is present in more than 50% of patients with miliary TB. Respiratory symptoms (cough, dyspnea, pleuritic chest pain) are present in 30% to 70% of patients. Hypoxemia, when looked for, is common and may progress to acute respiratory failure and ARDS.

Gastrointestinal tract involvement is seen in 10% to 30% of patients with miliary TB. Commonly reported symptoms include abdominal pain (diffuse or localizing to the right upper quadrant), nausea, vomiting, and diarrhea. Liver function tests are frequently abnormal and typically suggest a cholestatic pattern. Frank jaundice, ascites, cholecystitis (31), and pancreatitis (32) are rare, but elevations of alkaline phosphatase and transaminases were reported in 83% and 42% of patients in one series (33). Fulminant hepatic failure has been reported (34).

Cutaneous disease is rare except for in patients with underlying HIV infection (28,35–37). The skin manifestations are as protean as the clinical manifestations of miliary TB. The most typical skin lesions, termed “tuberculosis cutis miliaris disseminata” or “tuberculosis cutis acuta generalisata”, are described as small papules or vesiculopapules (37). Rarely lichenoid, macular, purpuric lesions, indurated ulcerating plaques, and subcutaneous abscesses have been reported (35,37).

Adrenal gland involvement has been found in as many as 42% of autopsy-based case series (38). A recent study using computed tomography (CT) found adrenal gland enlargement in 91% of patients with miliary TB (39). Interestingly, overt adrenal insufficiency remains rare, occurring in less than 1% of reported cases of miliary TB (33).

Central nervous system (CNS) disease, typically presenting as meningitis or brain tuberculomas, is clinically evident in 15% to 30% of patients. Conversely, about one-third of patients presenting with TB meningitis have underlying miliary TB (40). In a small series from India, magnetic resonance imaging (MRI) with gadolinium enhancement revealed asymptomatic brain lesions in all patients (41).

At autopsy, seeding of every organ in the body has been reported. Osteomyelitis, discitis, and arthritis may be clinically evident. Eye disease is usually asymptomatic but can be diagnostically important. Laryngitis may increase risk of transmission. Even in autopsy series, cardiovascular involvement, with the exception of pericarditis, is distinctly rare. Mycotic aortic aneurysms are unusual but can be the cause of fatal ruptures.

### DIAGNOSIS

The issue with diagnosing miliary TB is generally not how and where to find the pathogens as they tend to be everywhere in this disease. The problem is to consider the diagnosis in time and to initiate diagnostic work up and therapeutic interventions without delay, as the host is generally not able to control *M. tuberculosis* without help. As miliary TB can be rapidly fatal, useful diagnostic tests will have to have a short turnaround.

Previously, cryptic miliary TB was often diagnosed only at autopsy. However, with the availability of high-resolution computed tomography (HRCT) scans, these patients can now be diagnosed during life. Although miliary TB involves almost all organs, most often the involvement is asymptomatic.

### Laboratory

Laboratory abnormalities are common in patients with miliary TB, however, no specific patterns of abnormal hematological and biochemical markers have been identified (24,25,33,38).

A typically normocytic, normochromic anemia is seen in approximately 50% of the patients. Most patients have a normal white blood cell count, but leukopenia and leukocytosis

occur in an approximately equal minority of patients. A leukemoid reaction simulating acute leukemia can occur (42). Thrombocytopenia and thrombocytosis have been reported. Pancytopenia due to bone marrow infiltration or a hemophagocytic syndrome has been described.

Disseminated intravascular coagulation may accompany septic TB and is associated with a poor outcome. Hyponatremia, the most common biochemical abnormality, often indicates inappropriate antidiuretic hormone secretion. Hypercalcemia and polyclonal hypergammaglobulinemia have been reported in several cases. Bronchoalveolar lavage tends to reveal absolute and relative lymphocytosis, but mostly due to conflicting results no other useful markers have been identified. As HIV infection is so common in patients with TB, all persons suspected of having active TB should undergo HIV testing.

#### *Detection of Latent TB Infection*

Tuberculin purified protein derivative (PPD) anergy is more common in patients with miliary TB compared to other TB manifestations. Less than half of all patients with miliary TB will have a positive PPD. In some patients, tuberculin conversion may occur following successful treatment.

Newer in-vitro assays have become available that detect latent TB infection based on measurement of interferon-gamma release by T cells following exposure to specific MTB antigens. These assays are now commercially available and have been automated. Sensitivity and specificity of these assays appears to be higher than that of the tuberculin skin test, but it is not at all clear how they will perform in miliary TB. Early case reports appear to indicate that these tests may not always be able to confirm latent infection in patients with disseminated disease (43)

### **Imaging**

#### *Chest Radiograph*

The diagnosis of miliary TB is often based on the presence of a "classic" miliary pattern on chest X Ray, which, according to the recommendations of the Nomenclature Committee of the Fleischner Society, is defined as a collection of tiny, discrete pulmonary opacities that are generally uniform in size and widespread in distribution, each of which measures 2 mm or less in diameter (44) Fig. 2. If present, the faint, reticulonodular infiltrate is usually indeed characteristic enough to alert astute clinicians to consider the diagnosis of miliary TB. There are, however, several problems with relying too much on the radiologic diagnosis of disseminated TB. The typical miliary pattern may only become apparent days or weeks after



**Figure 2** CT scan with miliary disease pattern.

the onset of clinical symptoms (24,33,45,46). The initial nodular interstitial spread occurs without significant alveolar involvement. In order to be large enough to be appreciated on a plain chest radiograph, however, some spread to the adjacent alveoli will have to have occurred (47). Furthermore, while many studies report extraordinary high rates of classic radiologic findings; this usually is a self-fulfilling prophecy as the radiologic findings were often used as an inclusion criterion as well. Recent studies that did not rely on radiologic criteria for inclusion found the classic X-Ray presentation in less than 50% of patients with miliary TB (24,33). An additional 10% to 30% of patients have larger or atypical lesions. Asymmetrical nodular pattern, coalescing nodules, mottled appearance, snowstorm appearance, ground-glass appearance, and air-space consolidation have been described (3). Conversely, other conditions that typically present with larger nodules such as alveolar hemorrhage, lymphangitic cancers, or inhalational diseases can appear as early small nodules. While most of the nodules observed in these diseases tend to be larger and more heterogeneous than classic miliary TB, the overlap may be significant (48). Approximately 5% of patients have additional findings that may provide additional clues to the diagnosis. Such findings include evidence of intrathoracic lymphadenopathy, pleural effusion, parenchymal lesions and cavitations, thickening of interlobular septa, pneumothorax, pericardial effusion, or other evidence of active or healed parenchymal TB.

Subtle miliary lesions are best appreciated in slightly underpenetrated films, but in many cases visualization requires a high index of suspicion and review with an experienced chest radiologist.

### CT Scanning

CT scanning, especially with HRCT is more sensitive for miliary TB than plain chest radiography. Numerous small (1–3 mm) nodules, distributed throughout both lungs, are easily visualized. However, while sensitive, these findings are not necessarily specific. In series correlating clinical and pathologic findings with HRCT, disseminated nodules were also found in many other infections (*Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Candida albicans*) and noninfectious diseases (sarcoidosis, metastatic adenocarcinoma, lymphoma, amyloidosis, hypersensitivity pneumonitis, and pneumoconiosis) (49–51). CT-guided needle biopsies may help elucidate the diagnosis, but no data on the sensitivity of CT-guided invasive techniques are available.

## Microbiology

### Smear and Culture

Smear and culture examination of expectorated or induced sputum, gastric lavage, pleural, peritoneal, or pericardial fluid, cerebrospinal fluid, urine, pus, bronchoscopic secretions, peripheral blood, bone marrow, liver biopsies, lymph node material, and transbronchial lung biopsy specimens have all been used to confirm the diagnosis of miliary TB, but with varying results.

A recent review, however, came to the conclusion that “in the published reports, no systematic pattern of diagnostic approach could be identified and invasive diagnostic sampling appeared to be arbitrary and individualized, especially in the pediatric series” (3). While it is indeed difficult to generate evidence-based recommendations for testing, recent studies have helped establish several important testing paradigms (24,33).

Smears for acid-fast bacilli are generally not sensitive enough to rule out miliary TB as samples at any site were only positive in a minority of patients (Table 2). However, the probability of a positive smear increased with the number of sites sampled. Thus, when present, samples of sputum, gastric aspirate, urine, pleural fluid, pericardial fluid, and ascites should all be rapidly examined for the presence of acid-fast bacilli. Fluorochrome dye-based stains may be more sensitive than conventional Ziehl–Nielsen staining (52). It should be noted that neither of these traditional stains allows for distinction between tuberculous and nontuberculous mycobacteria, but direct probes have been developed that allow for species detection in smear-positive samples (53).

**Table 2** Frequency of Positive Smear or Culture Results in Patients with Miliary TB

Specimen	Percentage of positive tests			
	Maartens, 1990 (33)		Kim, 1990 (24)	
	Smear	Culture	Smear	Culture
Sputum	33	62	36	76
BAL	27	55	9	54
CSF	8	60	0	0
Urine	14	33	7	59
Gastric aspirate	43	100	0	55
Serosal	6	44	0	14

*Abbreviations:* BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; TB, tuberculosis.

Cultures tend to be more sensitive, but the turnaround time of several weeks significantly diminishes their usefulness in the critical care setting. However, even if the results may not be available in time before treatment decisions have to be made, it is extremely important to procure tissue/fluids as positive cultures are prerequisite for later drug-susceptibility testing.

Although blood cultures in miliary TB are most likely to be positive in HIV-infected patients, mycobacterial blood cultures are a rapid and minimally invasive method of diagnosis.

All specimens should be inoculated into an automated radiometric detection system, preferably using lysis centrifugation techniques, which is both more rapid and more sensitive than standard techniques using solid medium for the isolation of *M. tuberculosis*. Nucleic acid probes have been developed that can differentiate *M. tuberculosis* from commonly isolated nontuberculous mycobacteria directly from liquid culture media.

### Rapid Testing

Enzyme-linked immunosorbent assays (ELISA) capable of detecting mycobacterial antigens, antibodies, and immune complexes have been used for diagnosis of miliary TB, but the true usefulness of serodiagnostic tests remains to be established.

The United States Food and Drug Administration (FDA) has approved several nucleic acid amplification tests (NAATs) for the rapid identification of *M. tuberculosis* in respiratory samples. These tests produce results within two to seven hours after sputum processing and are therefore of interest in critically ill patients. NAATs should be performed in biosafety level II or III laboratories. False-positive or false-negative results occur more frequently when technician proficiency is suboptimal. While sensitivity and specificity are somewhat dependent on pretest probability, all available tests perform better in smear-positive samples than in smear-negative patients. Not a single study has evaluated the usefulness of NAATs for the diagnosis of patients with miliary TB.

Target amplification using the polymerase chain reaction (PCR) has been more sensitive than standard techniques in some series examining respiratory specimens, bone marrow or liver biopsy specimens, CSF, or blood (54–57).

Molecular rapid tests have generally replaced adenosine deaminase and interferon-gamma-based tests that have mostly been evaluated in resource-limited settings with high pretest probabilities. Although molecular diagnostic tests can support the diagnosis of miliary TB in the appropriate clinical setting, a negative test cannot rule out miliary TB and treatment or additional diagnostic tests should not be delayed because of negative results.

### Histopathology of Tissue Samples

Histopathologic examination of tissues continues to play an important role in the rapid diagnosis of miliary TB. Liver biopsies have the highest yield. In the two modern case series, granulomas were demonstrated in up to 100% of liver biopsies, 82% of bone marrow biopsies, and 72% of transbronchial biopsies (24,33). Lymph nodes and serosal biopsies also had high yields in these series. If biopsies were guided by clinical or laboratory abnormalities specific to

the organ system being sampled, the yield was generally higher. Specific target amplification can be performed on fresh and even processed samples. While this appears highly promising, data for its use in miliary TB are to be generated.

### Other Tests

If present, choroidal tubercles are pathognomonic of miliary TB. A dilated ophthalmoscopic examination may offer a valuable clue to the diagnosis of miliary TB. Positron emission tomographic (PET) can help distinguish infection from malignant lesions but it should be noted that 1 to 3 mm lesions may be too small to generate a positive signal. Pulmonary function tests often show abnormalities, but no characteristic pattern have been identified that would increase the diagnostic yield of other studies.

### Differential Diagnosis

The differential diagnosis of febrile illnesses with miliary chest X-Ray infiltrates is broad and includes infectious and noninfectious entities. Infectious diseases include other nontuberculous mycobacterial infections. Fungal infection mostly due to endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis) can mimic miliary TB. Appropriate exposure and travel history may provide important clues. Bacterial infections described in the literature include legionella infection, nocardiosis, pyogenic bacteria (*Staphylococcus aureus*, *H. influenzae*), psittacosis, tularemia, bartonellosis, brucellosis, and melioidosis. Viral infections (varicella, cytomegalovirus, influenza, measles) and parasitic infections (toxoplasmosis, strongyloidiasis, schistosomiasis) can produce similar patterns.

Neoplastic diseases, including lymphoma, lymphangitic spread of various cancers, or mesothelioma, are in the differential diagnosis as are other diseases including sarcoidosis, amyloidosis, hypersensitivity pneumonitis, alveolar hemorrhage, storage disorders, pneumoconioses, and foreign-body-induced vasculitis related to injection drug use.

### TREATMENT

While many patients control TB even without therapy, miliary TB is uniformly fatal if not treated. Even when treated, the mortality related to miliary TB remains about 10% to 20% in children and 20% to 30% in adults. Delay in the diagnosis or initiation of treatment contributes to the high mortality. Currently, there are no randomized trials evaluating the efficacy of different regimens for the treatment of miliary TB.

### Antituberculous Chemotherapy

The American Thoracic Society, CDC, and the Infectious Diseases Society of America have issued joint guidelines for the treatment of TB, which address treatment of miliary TB (58). Based on a number of clinical trials, the guidelines recommend four basic regimens for treating patients with TB caused by drug-susceptible organisms. These regimens are applicable to most patients with TB, although modifications are made for specific populations. Each regimen has an initial phase of two months followed by a choice of several options for the continuation phase of either four or seven months. The choice of treatment in the initial phase is empiric as susceptibility data are usually not available or only available at the end of the initial phase of treatment. Susceptibility data should be available at the beginning of the continuation phase and should be used to direct therapy if drug-resistance is identified.

The initial drug regimen is based on knowledge of the likely drug susceptibility, and four drugs are used in the initial phase of treatment when the total duration of treatment is six months. The treatment regimen for most adults with previously untreated TB consists of a two-month initial phase of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). In the continuation phase treatment is given for either four or seven months and consists, in most cases, of INH and RIF alone. Most patients will be treated with the four-month continuation therapy for a total duration of treatment of six months.

The recommendations for disseminated TB are essentially the same as for pulmonary TB. Since extrapulmonary TB is less common than pulmonary TB, these recommendations are based upon retrospective review of a relatively small number of patients with extrapulmonary TB.



While the data suggest that this approach is successful in the era of potent bactericidal regimens, it is important to individualize the regimens in specific circumstances. Longer therapy should, for instance, be considered in certain patients with miliary TB, including children and immunocompromised hosts. The American Academy of Pediatrics advocates nine months of treatment in their guidelines (59). In the presence of associated TB meningitis, treatment duration needs to be extended to at least 12 months. In view of the high frequency of TB meningitis in patients with miliary TB, the British Thoracic Society suggests that all patients with miliary TB undergo a lumbar puncture in order to determine the optimal duration of treatment (60). Patients with lymphadenitis, a large organism burden, and those with a slow microbiologic or clinical response also tend to have a higher relapse rate and may benefit from prolonged therapy but no evidence-based recommendations are available for such circumstances.

The guidelines clearly recommend directly observed therapy (DOT) as the best way to assure completion of appropriate therapy (58).

Close monitoring of patients in the intensive care unit is more important than in other inpatient or outpatient settings. Especially in nonresponsive patients in critical care it is important to coadminister vitamin B<sub>6</sub> (pyridoxine) with INH therapy in order to avoid INH neuropathy. INH can also cause liver toxicity and cytopenias, which may be synergistic with other toxicities or comorbidities in critically ill patients. Rifampin is a strong inducer of cytochrome P450 metabolism. It is imperative to review all other drugs in patients on RIF in order to anticipate potentially serious drug–drug interactions. Hypersensitivity reactions (fever, rash) and liver toxicity are other important side effects that require constant monitoring, especially in critically ill patients. Ethambutol can cause irreversible optic neuritis.

## **Adjunctive Therapy**

### *Corticosteroids*

Several randomized controlled trials and reviews have addressed the role of corticosteroids in patients with various forms of extrapulmonary TB, such as TB meningitis, pericardial TB, and pleural TB. No study has specifically evaluated the role of adjunct corticosteroid treatment in patients with miliary TB. Current recommendations are based on limited evidence, further hampered by conflicting results. A beneficial response was observed in some studies, but not in others (61,62).

Presence of associated adrenal insufficiency is an absolute indication for corticosteroid use. Adjunctive corticosteroid treatment may be beneficial in miliary TB with TB meningitis, large pericardial or pleural effusion, IRD, ARDS, immune complex nephritis, and histiocytic phagocytosis. Recent reviews have summarized the evidence for adjunctive corticosteroids in the treatment of tuberculous pericarditis, meningitis, and pleural effusion. These reviews have shown improved mortality for patients with pericarditis and meningitis. While clinical parameters improved more rapidly in patients with pleural effusion, steroids were not associated with any lasting improved outcomes for such patients (63,64).

### *Drotrecogin Alfa*

Only one case report using activated drotrecogin alfa in miliary TB is available in the literature (65). Decisions to use this compound will have to be based on generally approved indications for this treatment adjunct.

### *Supportive Therapy*

Patients with miliary TB often behave like patients in septic shock. Treatment can further paradoxically worsen the intense cytokine release and the associated multiorgan failure either through release of intracellular antigens from dying tubercle bacteria or reversal of TB-induced immunosuppression causing IRD. Treatment-induced side effects can aggravate comorbidities or drug effects commonly encountered in critically ill patients. Drug–drug interactions can be difficult to manage in patients on rifampin-containing regimen. Collectively, these patients tend to be complicated, at high risk for mortality, and therefore require intensive multidisciplinary supportive therapy.

### Prevention/Infection Control

Any significant suspicion of active pulmonary TB should prompt placement in an AII room with negative pressure isolation. Patients should be educated about the purpose of such isolation and instructed to cover their nose and mouth when coughing or sneezing, even when in the room. If the patient must leave the room, a surgical mask must be worn. All other persons entering the room must use respiratory protection, usually an N95 mask (66).

Doors must be kept closed and negative pressure should be verified daily. Anterooms are desirable, but not required; when present, the door to the anteroom and the door to the AII room should not be opened simultaneously. There must be at least 6 air exchanges per hour; 12 or more exchanges per hour are preferred and are required for any renovation or new construction. Air should be exhausted to the exterior, removed from any intake vents; if recirculation to general ventilation is unavoidable, HEPA filters must be installed in the exhaust ducts (66).

A patient may be transferred from an AII room to another hospital room when he/she is being effectively treated for TB, is improving clinically, and three consecutive sputum samples, obtained on different days, are smear-negative for AFB. For patients with initially negative AFB smears, at least two weeks of TB treatment should be administered before isolation is discontinued. If three additional specimens can be obtained at this time, they should all be AFB negative. Maintaining AII isolation throughout hospitalization is strongly recommended for patients with MDR-TB, cavitory lesions, or laryngeal TB (66). Most health care facilities have hospital-specific guidelines that should be consulted and followed.

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# 25 | Bioterrorism Infections in Critical Care

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*Half a league, half a league, Half a league onward, All in the valley of Death Rode the six hundred.*

—Alfred, Lord Tennyson (August 6, 1809–October 6, 1892), from *The Charge of the Light Brigade*

## BASICS BEFORE THE INTRODUCTION

The critical care team is entrusted with patients with the severest pathology. Victims of bioterrorism are often not immediately recognized, and present special and daunting challenges. However, before these challenges can be addressed, basic precepts must be followed. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) *Handbook for the Management of Biological Casualties* (1) recommends the following:

1. *Maintain an index of suspicion.*
2. *Protect yourself.*
3. *Assess the patient.*
4. *Decontaminate as appropriate.*
5. *Establish a diagnosis.*
6. *Render prompt treatment.*
7. *Practice good infection control.*
8. *Alert the proper authorities.*
9. *Assist in the epidemiologic investigation and manage the psychological consequences.*
10. *Maintain proficiency and spread the word* (1).

These 10 steps intended for battlefield conditions are applicable to our own battlefield—the intensive care unit. To this, we add that *the clinician-in-charge must put himself into the mind of the enemy*. By the application of each of these steps, the intensivist can lead his clinical team to safely, efficiently, and competently diagnose and deliver the essential care to the victims of a bioterrorism, and at the same time participate in the overall ongoing defensive response to these attacks upon ourselves and society.

## INTRODUCTION: DEFINITION, HISTORY OF BIOLOGICAL WEAPONS, AND USAMRIID STEPS FOR THE MANAGEMENT OF BIOLOGICAL CASUALTIES

*It is a mistake to try to look too far ahead. The chain of destiny can only be grasped one link at a time.*

—Sir Winston Churchill (November 30, 1874–January 4, 1965)

DA Bray of The National Center for Infectious Diseases, The Centers for Disease Control and Prevention (CDC) in 2003 defined bioterrorism as “[t]he use or threatened use of biological

agents or toxins against civilians, with the objective of causing fear, illness, or death" (2,3). The CDC has classified the most likely agents according to their cumulative properties and threat (Table 1) (1,4–8). This definition has been expanded to include attacks against animals and plants (2). In fact, animals may likely act as early warning "sentinels" (9).

Between 1900 and 1999, there were 415 incidents (278 cases between 1960 and 1999) of the use or attempted use of chemical, biological, or radiological materials by criminals or terrorists. In recent years, investigations into these threats, especially biological threats, have dramatically increased (10). Awareness of the history of the use of biological weapons will help the clinician better appreciate future epidemiologic threats. We present this abbreviated history in Table 2 (1,2,5,11).

### **Maintain an Index of Suspicion**

Specific epidemiologic characteristics should raise the clinician's index of suspicion that he is dealing with a bioterrorism event. These are listed in Table 3 (1,2,5,12).

### **Protect Yourself (and Your Patients)**

Intensive care units render care to a relatively small proportion of hospitalized patients, but nationally account for <20% of health care-associated infections (13). "Hand hygiene..." overall, is the most important element in preventing nosocomial infections (13). A review of infection control is essential in order to effectively apply isolation principles in the event of a bioterrorist attack.

The two-tier system for preventing nosocomial infections consists of (i) standard precautions, and (ii) transmission-based precautions (TBP). Standard precautions (the combination of universal precautions and body substance isolation precautions) apply to all patients, and presumes that "ALL blood, body fluids, secretions, excretions except sweat, non-intact skin, and mucous membranes" may transmit infectious agents. Standard precautions include hand hygiene, safe injection practices and handling of sharps, personal barrier precautions and supplies, and addressing the risk of contamination of the patient environment. Newer elements such as respiratory hygiene/cough etiquette, safe injection practices, and the use of masks for inserting catheters or procedures involving a lumbar puncture have been added (13).

TBP are employed when contagion cannot be contained by standard precautions. For the agents most likely to be encountered in a bioterrorist attack, TBP are needed to safely render care. The three categories of TBP are contact precautions, droplet precautions, and airborne precautions. These precautions are always applied together with standard precautions, and may be used in combination with one another. (See Ref. 13 for details.)

In brief, *contact precautions* require personnel to don personal protective equipment prior to entering the patient's room, and remove it before leaving (preferably in the anteroom of the patient's isolation room). Single rooms are always preferred, but where cohorting is the only option, there must be greater than 3 ft distance between beds (13). *Droplet precautions* do not require rooms with special air handling or ventilation. In addition to other protective garments, all those entering the room must wear a mask. A respiratory mask is not necessary. Patients must also wear a mask when they are transported from the room (13).

*Airborne precautions* are required for infectious agents that are a threat over long distances (i.e., rubeola virus, varicella virus, *Mycobacteria tuberculosis*, SARS-CoV, smallpox). Patients suspected of infection with these agents should be placed in a single room designated as an airborne infection isolation room (AIIR) (14,15). Guidelines for these rooms include monitored negative pressure, 12 air exchanges per hour for new construction or renovation, 6 air exchanges for existing facilities, and air exhausted directly outside or through high efficiency particulate air (HEPA) filtration before return. It is mandatory to implement a respiratory protection program that includes the use of respirators, fit testing, and user seal checks. Where this cannot be accomplished, an N95 or higher-level respirator must be worn (13).

TBP should be instituted as soon as the patient arrives at the hospital. As identification of the pathogen may take one or more days, decisions must be made based upon clinical presentation (syndromic application—see Table 4) (13,16). Table 5 lists the recommended isolation precautions for each of the organisms by class (13,16–22).

**Table 1** Classification of Bioterrorism Agents

Category and agents	Characteristics
<i>Category A</i>	“High-priority agents include organisms that pose a risk to national security because they:
Anthrax ( <i>B. anthracis</i> ) Botulism ( <i>Clostridium botulinum</i> toxin)	can be easily disseminated or transmitted from person to person;
Plague ( <i>Yersinia pestis</i> ) Smallpox ( <i>V. major</i> )	result in high mortality rates and have the potential for major public health impact;
Tularemia ( <i>Francisella tularensis</i> ) Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)]	might cause public panic and social disruption; and require special action for public health preparedness.”
Rabies (see discussion in “Selected Pathogens” section)	
<i>Category B</i>	“Second highest priority agents include those that:
Brucellosis ( <i>Brucella</i> spp.) Epsilon toxin of <i>C. perfringens</i>	are moderately easy to disseminate; result in moderate morbidity rates and low mortality rates; and require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance.”
Food safety threats (e.g., <i>Salmonella</i> species, <i>Escherichia coli</i> O157:H7, <i>Shigella</i> , <i>Vibrio</i> spp., <i>Listeria monocytogenes</i> , <i>C. jejuni</i> , <i>Y. enterocolitica</i> ) Glanders ( <i>Burkholderia mallei</i> ) Meliodosis ( <i>Bk. pseudomallei</i> ) Psittacosis ( <i>Chlamydomphila psittaci</i> ) Q fever ( <i>Coxiella burnetii</i> ) Ricin toxin from <i>Ricinus communis</i> (castor beans) Staphylococcal enterotoxin B Typhus fever ( <i>Rickettsia prowazekii</i> ) Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis]) Viruses (noroviruses, hepatitis A virus) Water safety threats (e.g., <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i> ) Protozoa ( <i>Cyclospora cayatanensis</i> , <i>Giardia lamblia</i> , <i>Enamoeba. histolytica</i> , <i>Toxoplasma</i> spp., <i>Microsporidia</i> )	
<i>Category C</i>	“Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of:
Emerging infectious diseases such as Nipah virus and hantavirus, yellow fever virus, tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus.	availability;
Tick-borne hemorrhagic fever viruses [Crimean-Congo hemorrhagic fever ( <i>Nairovirus</i> -a Bunyaviridae), Omsk hemorrhagic fever, Kyasanur forest disease and Alkhurma viruses].	ease of production and dissemination; and
Multidrug-resistant <i>M. tuberculosis</i>	potential for high morbidity and mortality rates and major health impact.”
SARS virus (SARS-associated coronavirus) West Nile virus (a Flaviviridae) Pandemic and avian influenza (H5N1 influenza) Monkeypox virus ( <i>Orthopoxvirus</i> of the Poxviridae family) Genetically engineered biological weapons	

Source: From Refs. 1, 4–8.

**Table 2** A Brief History of Biological Warfare and Bioterrorism

Dates	Biological agent(s)	Method of delivery	Comments
12th to 15th centuries BC	Diseased animals and prisoners	Hittites herd diseased animals and people into enemy territory.	
6th century BC	Rye ergot	Assyrians poison enemy wells.	
300 BC to the 19th century	Rotting animal carcasses	Contaminating wells and drinking water supplies.	Utilized by Greek city-states against their enemies. Similar methods used in later times by the Romans, Persians, and in Europe during the Medieval and Renaissance times, and during the siege of Vicksburg during the American Civil War.
184 BC	"Serpents" probably snakes	Hurling snakes in pots onto the decks of warships.	Hannibal the Carthaginian attacking King Eumeneus of Pergarum.
1346 (Kaffa); 1422 (Carolstein); and 1710 (Revat)	<i>Y. pestis</i>	Catapulting plague victims over the wall of the besieged city of Kaffa. The Russians repeated this with plague victims while battling the Swedes at Revat.	Tartars used the bodies of their own soldiers who died of the plague to defeat the Genoese. This event and similar events accelerated the plague pandemic of the middle ages.
1532–1533	Smallpox	Pizzaro gave smallpox-laden clothing to the Incas.	
1754–1767 French and Indian Wars	Smallpox	Blankets from smallpox patients were sent to the Indians fighting for the French by the British by Lord Jeffrey Amherst.	Epidemic killed up to 50% of targeted tribes. Amherst the town and college named in Lord Jeffrey's honor. Cultures were confiscated.
1915	<i>V. cholera</i> , <i>Y. pestis</i> , <i>B. Anthracis</i> , and <i>Bk. mallei</i>	Germany intended to infect Romanian sheep for export to Russia with <i>B. anthracis</i> and <i>Bk. mallei</i> , and introduce cholera into Italy and plague into St. Petersburg.	
WWI	<i>B. pseudomallei</i>	German agents infect horses and mules on the eastern front.	Human cases increase during and after WWI.
1920s	Russia initiates its biological warfare programs	The Vector facility in Koltsovo is known to work with smallpox and hemorrhagic fever viruses.	
1932–1945	<i>B. anthracis</i> , <i>Y. pestis</i> , <i>Neisseria meningitidis</i> , <i>Shigella</i> spp., <i>V. cholera</i> , <i>Salmonella</i> spp.	Japan's Unit 732: sprayed cultures, contaminated water supplies, and dropped plague-infected fleas over Chinese cities.	10,000 prisoners died as a result of experimentation; 210,000 Chinese in 11 cities died because of contaminated water and food supplies, some from spraying of <i>B. anthracis</i> , <i>V. cholerae</i> , <i>Shigella</i> spp., and <i>Salmonella</i> spp. cultures; 1700 Japanese troops died in 1942 mostly from cholera contracted from their own bioweapons.

(Continued)



**Table 2** A Brief History of Biological Warfare and Bioterrorism (Continued)

Dates	Biological agent(s)	Method of delivery	Comments
WWII	Killed <i>Proteus</i> OX19	Polish physicians, Dr Eugeniusz Lazowski (1913–2006) and Dr Stanislaw Matulewicz, inject the people of Rozvadow and Zbydniowie in Poland with dead <i>Proteus</i> OX19.	When blood samples from these individuals were sent for testing, they were interpreted as "positive" for antibodies indicating typhus infection. German officials became convinced that a typhus epidemic was raging and the Wehrmacht would not enter the town.
WWII	<i>R. prowazekii</i> , <i>R. mooseri</i> , hepatitis A, <i>Plasmodium</i> spp.	German experiments on prisoners in concentration camps.	
WWII	<i>B. anthracis</i>	England conducts animal and environmental experiments on Gruinard Island off the coast of Scotland.	The spores were found to be long-lived and the island was quarantined. In 1986, 280 tons of formaldehyde was sprayed. The quarantine was lifted in 1990.
WWII	<i>B. anthracis</i> , <i>Botulinum</i> toxin, <i>F. tularensis</i> , <i>Brucella suis</i> , <i>C. burnetti</i> , <i>Staphylococcus</i> enterotoxin B, Venezuelan equine encephalitis, rice blast, rye stem rust, wheat stem rust	U.S. Offensive Biological Program (War Reserve Service) stockpiles agents but does not weaponize them.	Programs are terminated in 1969 and 1970 by President Nixon's two executive orders.
1960s	Pungi sticks smeared with feces	Traps or pits.	Utilized by the Vietcong during the Vietnam War.
1970 1972	<i>Salmonella typhi</i> , diphtheria, dysentery, meningitis	Reports of Weather Underground attempting to obtain agents from R.I.S.E. radical organization stockpiles cultures	Fort Detrick. Not confirmed. Cultures discovered. No attack
September 7, 1978 at Waterloo Bridge, London	Ricin	The Darzhavna Sigurnost and the KGB use an umbrella gun with a ricin-containing pellet to assassinate Bulgarian defector Georgi Markov. He dies September 11.	It was not raining. It was not an accident. The first time ricin was used as a biological weapon.

1979	<i>B. anthracis</i>	Accidental release of spores (airborne) from weapons plant in Sverdlovsk, USSR.	77 anthrax cases with 66 deaths.
1984	<i>S. typhimurium</i>	Rajneesh Cult contaminated salad bars in 10 restaurants in Dalles, Oregon.	Outbreak involves 751 patients, and 45 hospitalization. Significant economic harm is suffered by individual businesses and the community. Attack aborted by the FBI.
1991	Ricin	Deliver ricin by application through the skin with contaminated skin products (aloe and dimethyl sulfoxide).	Attack aborted by the FBI.
1995	<i>B. anthracis</i> and <i>Botulinum</i> toxin	Iraq confirms it has produced offensive weapons utilizing these agents.	
1995	<i>B. anthracis</i> , <i>Botulinum</i> toxin, Q fever, Ebola virus in aerosol form	Aum Shinrikyo employed biological, chemical, and nerve gas agents.	Biological weapons attacks failed but sarin gas attack killed 12 and sickened 5500 in the Tokyo subway.
1997	<i>Shigella dysenteriae</i>	Laboratory employee.	Contaminated muffins and donuts sickening 45 laboratory employees with 4 requiring hospitalization.
2001	<i>B. anthracis</i>	Spores sent through U.S. mail to multiple states and Washington DC.	5 deaths, 22 infections and closing of a major postal facility in Hamilton, New Jersey.
July 31, 2008		Bruce E. Ivins, an employee of the US biodefense laboratories at Fort Detrick, Maryland, committed suicide after learning of the impending indictment against him for the 2001 anthrax attacks in the United States. Steven Hatfill, whose name was leaked as a "person of interest" settled his lawsuit against Attorney General John Ashcroft and the Department of Justice for a one-time payment of \$2.825 million and a \$150,000 annuity.	

Source: From Refs. 1, 2, 5, and 11.

**Table 3** Epidemiologic Characteristics of a Bioterrorist Attack

Epidemiologic characteristic	Comments and special considerations in a civilian attack
Epidemic of similar disease in a limited population	The combination of prolonged incubation periods and the release of an airborne pathogen at a transportation hub (subway, train, or bus station, or airport) may allow infected individuals to travel considerable distances before becoming ill.
Incubation periods	Casualties occurring within hours of one another suggest chemical or toxin. Casualties presenting over days suggests a biologic agent.
Characteristics in epidemic curve	A sudden rise and fall in the number of cases or a steady increase in the number of casualties suggests a biologic agent.
Unexplained increases in morbidity and mortality	This may not become apparent early after an attack, especially in an individual institution. Variations in the cross section of those exposed to the pathogen: the most severely affected will be the elderly and those with common chronic diseases (cardiac and pulmonary diseases)—those most commonly admitted to intensive care units.
More severe disease than expected from the isolated pathogen and failure to respond to standard recommended therapy	This is often the case with compromised patients who are admitted to the intensive care unit.
Disease that is unusual for a geographic area or season	Travel and contact history may be difficult to obtain from patients <i>in extremis</i> .
Vector-transmitted disease occurring in an area devoid of the vector	
Multiple simultaneous cases of different infectious diseases in the same population	In a single institution, this may only become apparent sometime after the initial cases of each disease present themselves.
A single case of an uncommon disease	Examples: All category A pathogens, smallpox ( <i>V. major</i> and <i>V. minor</i> ), monkeypox, viral hemorrhagic fevers, plague, tularemia, or anthrax in any form, brucellosis, <i>Bk. mallei</i> (glanders), <i>B. pseudomallei</i> (melioidosis), Hanta virus, Nipa virus, and other emerging infections.
Disease unusual for an age group	
Unusual strains, variants or antimicrobial resistance patterns	We have become so accustomed to seeing multidrug resistance, that this may not arouse suspicion.
Similar or genetically identical organisms isolated from different sources at different times, especially those that do not appear to have an epidemiologic link	This will not be initially apparent and will require a high enough index of suspicion for the clinician to order the appropriate genetic testing.
Markedly different attack rates between persons indoors and outdoors.	This will not be initially apparent to the clinician.
Disease outbreaks in places not connected by geography or epidemiology.	
Disease outbreak that is both human and zoonotic; an increase is noted in dying or dead animals	Unless there is a history of the patients' pets or livestock becoming ill, this will not be apparent to the clinician, especially in an inner city hospital.
Intelligence about or threats from terrorists.	

Source: From Refs. 1, 2, 5, and 12.

### Assess the Patient

Many if not most of the likely agents to be used for bioterrorism have overlapping incubation periods and clinical presentations. Where under normal circumstances we could depend on epidemiology to assist us in narrowing our differential diagnosis, for the initial cases, we must rely exclusively on a syndromic approach prior to laboratory confirmation. Table 6 (1,5,23–30) provides a comparison of clinical presentations for Class A agents. Selected Class B and C agents are discussed in Table 7 (7,8,31–42).

**Table 4** Abbreviated Syndromic-Based Isolation Precautions

Clinical presentation or syndrome	Transmission-based precautions in addition to standard precautions	Comments
Diarrhea	Contact precautions	
Meningitis	Droplet precautions	No pulmonary infiltrates.
Meningitis	Airborne precautions	Pulmonary infiltrates.
Meningitis	Airborne and contact precautions	Draining lesions.
Neurologic symptoms	Airborne and contact precautions	Suspect rabies. See “Selected Pathogens” discussion.
Petechial rash	Droplet precautions and contact precautions with face/eye protection, barrier precautions, sharps safety, and use of a N95 or higher respirator when aerosol generation is a risk	<i>N. meningitidis</i> , Ebola virus, Lassa virus, and Marburg virus.
Vesicular rash	Airborne and contact precautions.	Varicella-zoster, herpes simplex, variola, monkeypox, vaccinia viruses.
Variola—smallpox	Type C facility should be utilized for (i) persons with laboratory-confirmed disease; (ii) compatible illness following suspected or confirmed exposure; or, (iii) persons referred by a consultant with atypical but suspected disease	Type C facility is a dedicated isolation medical facility with heating, air conditioning, and ventilation that exhausts 100% to the outside through HEPA filters or is located at least 100 yards from any other occupied building or area.
Variola—smallpox: vaccinated contacts under surveillance who become febrile ( $\geq 101^{\circ}\text{F}$ ) on two readings but without a rash	Type C or type X facility.	Type X facility is the same as a type C facility except it need only supply basic medical monitoring (vital signs).
Variola—Smallpox: afebrile vaccinated contacts: afebrile vaccinated contacts who were with the index case 10–18 days prior to the rash (because of possible common exposure and contacts refusing vaccination)	Type R facility	A patient’s home.
Maculopapular rash with cough, coryza, and fever	Airborne precautions	Rubeola virus.
Respiratory infections	Airborne and contact precautions	Use eye/face protection if aerosol-generating procedure or contact with respiratory secretions.
Skin and wound Infection	Droplet and contact precautions	

Source: From Refs. 13 and 16.

### The Chest Radiograph

The chest X ray is one of the most important tools of the intensivist. Chest radiographic findings for selected pathogens are described in Table 8 (33,43–55).

To date, *inhalational anthrax* represents the most significant bioterrorist threat to challenge the intensivist. Community-acquired pneumonia (CAP) is the most likely alternative diagnosis to inhalational anthrax. Although there are differences in the chest X-ray findings between inhalational anthrax and CAP, none can be used to differentiate the two entities. Kyriacou, et al. have proposed applying an algorithm for distinguishing inhalational anthrax from CAP that utilizes both clinical and radiographic findings (43). Their algorithm has 100% sensitivity for inhalational anthrax and 98.3% specificity for CAP. Patients presenting with respiratory complaints of cough, congestion, and shortness of breath consistent with CAP are first divided

**Table 5** Recommended Transmission-Based Isolation Precautions

Pathogen	Recommended isolation precautions	Comments
<i>Class A pathogens</i>		
Anthrax ( <i>B. anthracis</i> )		
Cutaneous	Standard, contact.	Direct contact with skin lesions can result in cutaneous disease.
Pulmonary	Standard.	
Gastrointestinal	Standard, contact.	
Environmental: aerosolizable spore- containing or other substances	Standard, contact, droplet, airborne.	Until decontamination, wear respirator (N95 or powered air-purifying respirator, protective clothing, and decontaminate those in contact with substance. Postexposure prophylaxis following environmental exposure with 60 days of either doxycycline, ciprofloxacin, or levofloxacin: postexposure vaccination under investigation. Antibiotic prophylaxis with active immunization may hold promise. Minimize aerosol-generating procedures.
Botulism ( <i>C. botulinum</i> toxin)	Standard.	Not transmitted person-to-person.
Plague ( <i>Y. pestis</i> )		
Bubonic	Standard, contact (with draining lesions)	
Pneumonic	Standard, droplet, airborne (respiratory).	Chemoprophylaxis for health care workers with close-contact exposure. Antibiotic treatment rapidly reduces contagion. Minimize aerosol-generating procedures.
Smallpox ( <i>V. major</i> )	Standard, contact, droplet, airborne.	See Table 4. Postexposure vaccination and vaccination of health care providers at-risk is essential for controlling outbreak. Nonvaccinated health care workers should not provide care when vaccinated health care workers are available. Minimize aerosol-generating procedures.
Tularemia ( <i>F. tularensis</i> )	Standard.	Transmitted by inhalation of aerosolized bacteria or ingestion. Person-to-person spread is rare. <i>Microbiology laboratory personnel at particular risk.</i> Minimize aerosol-generating procedures.
Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)]	Standard, contact, droplet, and airborne.	Single-patient room preferred. Emphasize sharps safety, hand hygiene, barrier protection, impermeable gowns, face/eye protection with masks, goggles, or face shields, and waste handling. Use of N95 respirator for any aerosol-generating procedures. Double gloves, leg, and shoe coverings also recommended. Minimize aerosol-generating procedures.
Rabies	Standard, contact, droplet, and airborne. <i>All   caregivers in   contact with the   patient should   receive   postexposure   rabies prophylaxis   with vaccine and   rabies immune   globulin.</i>	Single-patient room preferred. Emphasize sharps safety, hand hygiene, barrier protection, impermeable gowns, face/eye protection with masks, goggles, or face shields, and waste handling. Use of N95 respirator for any aerosol-generating procedures. Double gloves, leg and shoe coverings also recommended. Minimize aerosol-generating procedures.

**Table 5** Recommended Transmission-Based Isolation Precautions (*Continued*)

Pathogen	Recommended isolation precautions	Comments
<i>Class B pathogens</i>		
Brucellosis ( <i>Brucella</i> species)	Standard	Person-to-person transmission infrequent (Mesner O, Riesenberg K, Biliar N, et al. The many faces of human-to-human transmission of brucellosis: congenital infection and outbreak of nosocomial disease related to an unrecognized clinical case. Clin Infect Dis 2007; 45:e135–e140). Antibiotic prophylaxis after laboratory exposure.
Epsilon toxin of <i>C. perfringens</i>	Standard	
Food safety threats (e.g., <i>Salmonella</i> sp., <i>E. coli</i> O157:H7, <i>Shigella</i> , <i>Vibrio</i> spp., <i>L. monocytogenes</i> , <i>C. jejuni</i> , <i>Y. enterocolitica</i> )	Standard, contact	
Glanders ( <i>Bk. mallei</i> )	Standard, contact	Not transmitted person-to-person.
Melioidosis ( <i>Bk. pseudomallei</i> )	Standard, contact	Not transmitted person-to-person.
Psittacosis ( <i>C. psittaci</i> )	Standard	Not usually transmitted from person-to-person. Very rare cases have been reported and resulted in more severe disease.
Q fever ( <i>C. burnetii</i> )	Standard	Very rare cases of human-to-human transmission among family members living together.
Ricin toxin from <i>R. communis</i> (castor beans)	Standard	
Staphylococcal enterotoxin B	Standard	
Typhus fever ( <i>R. prowazekii</i> )	Standard, contact	Transmitted person-to-person by close personal contact. Minimize aerosol-generating procedures.
Viral encephalitis [alphaviruses (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis)]	Standard	Not transmitted person-to-person. Rarely transmitted by transfusion.
Viruses (noroviruses, hepatitis A virus)	Standard, contact	Postexposure hepatitis A vaccine recommended.
Water safety threats (e.g., <i>V. cholerae</i> , <i>C. parvum</i> )	Standard, contact	
Protozoa ( <i>C. cayatanensis</i> , <i>G. lamblia</i> , <i>E. histolytica</i> , <i>Toxoplasma</i> spp., <i>Microsporidia</i> )	Standard, contact	
<i>Class C pathogens</i>		
Emerging infectious diseases, such as Nipah virus and hantavirus, yellow fever virus; Tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus	Standard, contact	

(Continued)

**Table 5** Recommended Transmission-Based Isolation Precautions (*Continued*)

Pathogen	Recommended isolation precautions	Comments
Tick-borne hemorrhagic fever viruses (Crimean-Congo hemorrhagic fever ( <i>Nairovirus</i> -a Bunyaviridae), Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhurma viruses)	Standard, contact	
Multidrug-resistant <i>M. tuberculosis</i>	Standard, contact, droplet, airborne	
Extrapulmonary tuberculosis with draining lesion	Standard, contact, airborne	Examine for pulmonary tuberculosis.
Extrapulmonary tuberculosis, meningitis, no draining lesion	Standard, contact, airborne	Examine for pulmonary tuberculosis.
Extrapulmonary tuberculosis, laryngeal disease suspected or confirmed	Standard, contact, droplet, airborne	Laryngeal disease is highly contagious and always accompanied by pulmonary disease.
SARS virus (SARS-associated coronavirus)	Standard, contact, droplet, airborne	Minimize aerosol-generating procedures. Airborne precautions preferred; N95 respiratory protection, eye protection, "vigilant environmental disinfection (see <a href="http://www.cdc.gov/ncidod/sars">www.cdc.gov/ncidod/sars</a> ). (See Ref. 96 for complete recommendations.) Minimize aerosol-generating procedures.
West Nile virus (a Flaviviridae)	Standard, contact	
Pandemic and avian influenza (H5N1 influenza)	Standard, contact, droplet, airborne	Minimize aerosol-generating procedures.
Monkeypox virus ( <i>Orthopoxvirus</i> of the Poxviridae family)	Standard, contact, airborne: airborne precautions must be taken until smallpox excluded	See <a href="http://www.cdc.gov/ncidod/monkeypox/">www.cdc.gov/ncidod/monkeypox/</a> for most current recommendations. Person-to-person transmission well documented. Minimize aerosol-generating procedures.
Hantavirus pulmonary syndrome	Standard	Not transmitted person-to-person.
Genetically engineered biological weapons	Standard, contact, droplet, airborne	Unknown potential.

*Abbreviation:* SARS, severe acute respiratory syndrome.

*Source:* From Refs. 13, 16–22.

by whether or not there is widening of the mediastinum (with or without other radiographic findings). Those *with* that finding and a hematocrit of >45% are diagnosed as having inhalational anthrax as opposed to CAP. Patients on the other arm of the algorithm (patients *without mediastinal widening*, but with altered mental status) are diagnosed with inhalational anthrax. The limitations to this diagnostic scheme are that it was not derived prospectively, and its application is limited to previously healthy individuals (43).

Kyiacou et al. have developed another algorithm for differentiating CAP from influenza-like illness utilizing temperature (>100.4°F), heart rate (>110 beats/min) and room air pulse oximetry (<96% saturation). No single characteristic was sufficiently sensitive or specific, but the algorithm produced a result that was 70.8% sensitive and 79.1% specific for the diagnosis of CAP (44).

(text continues on page 466)

**Table 6** Assessing the Patient for Category A Agents

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Inhalation anthrax</i> (1–6 days most common; up to 6 wk reported). In monkey experiments, spores germinated as late as 58–98 days after exposure.	Malaise, fever, fatigue, myalgia, substernal discomfort, headache, abdominal pain, and vomiting in the first phase before transient improvement.	Hemorrhagic meningitis may develop in up to 50% of patients.	<i>Class A pathogens</i> <i>Anthrax (B. anthracis)</i> Nonproductive cough, followed by stridor and respiratory failure. Chest X ray may reveal a widened mediastinum in second phase of disease.			Biphasic disease is well described. Improvement may be seen 1–3 days after initial symptoms followed by rapid respiratory failure and shock. No person-to-person spread. Up to 86% mortality reported after accidental release in Sverdlovsk, USSR.
<i>Cutaneous anthrax</i> (1–12 days: most commonly the incubation from a cut, abrasion, or insect bite is 2–3 days but varies from 12 hr to 19 days.)	Usually none. Dissemination has been reported.				Pruritis followed by a painless papular lesion that evolves to vesicles (24–36 hr) and into an eschar (1–3 days) with surrounding edema. 10% have multiple lesions.	Can be spread person-to-person by contact with skin lesions. Lesions are found most commonly on the head and neck and upper extremity. Untreated, there is up to 20% mortality. With treatment, 80–90% of lesions resolve without scarring.
<i>Oropharyngeal anthrax</i> . (1–2 days) after consuming (usually) contaminated meat.			Many patients develop respiratory distress and sepsis.	Local edema and lesions appear on the base of the tongue, tonsils, posterior pharynx, or hard palate.		

(Continued)



**Table 6** Assessing the Patient for Category A Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Gastrointestinal anthrax</i> (1–7 days although commonly 3–7 days)				Nausea, vomiting, anorexia, fever, abdominal pain, hematemesis, bloody diarrhea.		An eschar forms on the wall of the intestine, usually the terminal ileum or caecum. Untreated, death in 2–5 days, (25–60% mortality). Rare patients succumb within hours.
<i>Anthrax meningitis</i>		5% of anthrax cases involve meningitis or hemorrhagic meningoencephalitis. CT and MRI reveal focal intracerebral hemorrhage with leptomeningeal enhancement.	25% of cases develop from inhalation anthrax.		The majority of anthrax meningitis cases developed from cutaneous disease.	No primary focus can be found in 10% of cases.
<p><i>An anthrax bioterrorist attack may result in all five forms of anthrax in a single patient or any permutation or combination of disease presenting in patients appearing simultaneously or sequentially to a single institution or area institutions!</i></p>						
<p><b>Botulism (<i>C. botulinum</i> toxin)</b></p>						
<i>C. botulinum</i> , <i>C. baratii</i> , <i>C. butyricum</i> , <i>C. argentinense</i> toxins	Patients are afebrile and fatigue is common (77%). Typically causes cranial nerve paralysis (facial paralysis (63%); gaze paralysis (65%); tongue weakness (58%); decreased gag (65%)] without affection sensation.	Double vision (91%); blurred vision (65%); pupils fixed and dilated pupils (40%); nystagmus (22%); ptosis (73%); slurred speech, dizziness (51%); weakness (69–73%); unsteady gait, descending weakness, flaccid paralysis with full consciousness (90%) until respiratory failure; paresthesias (14%); ataxia (17%).	Dyspnea (60%); sensation of a sore throat (54%).	Dysphagia (96%); constipation (73%); nausea (64%); vomiting 59%; abdominal cramps (42%); diarrhea (19%).	Increased mucous production in mouth and throat and/or dry mouth (93%) and throat.	
A–G. (12–80 hr by inhalation; immediate to 12–72 hr—range 2–8 days by ingestion). Most naturally occurring human disease is caused by types A, B, and E (E associated with fish; type C and D often cause disease in mammals and birds).						

<p><b>Hematogenous</b></p>	<p>Less than 50% of naturally occurring disease has lymphadenopathy.</p>	<p><i>Plague (Y. pestis)</i></p>	
<p><i>Plague Pneumonia</i> (24–60 hr)</p>	<p>Contagious and rapidly fatal. May present simply as fever with cough and dyspnea.</p>	<p>Patients present with fever, cough, chest pain, dyspnea, and hemoptysis.</p>	<p>70% have GI symptoms with secondary plague pneumonia.</p>
<p><i>Inhalation plague pneumonia</i> (incubation depends on inoculum: 24–60 hr).</p>		<p>Sore throat may be an initial presenting symptom. X ray reveals a patchy bronchopneumonia.</p>	<p>Nausea, vomiting, abdominal pain, and diarrhea may be seen.</p>
<p>Expectation after an aerosol biologic attack: 1–6 days.</p>		<p>Sputum is thin, watery, and blood tinged.</p>	
<p><i>Bubonic plague</i> (24–60 hr)</p>	<p>75% of naturally occurring cases. Sudden onset of fever, rigors, malaise, headache, and weakness with simultaneous (or next day) painless localized lymphadenopathy</p>	<p>Tachycardia, tachypnea, hypotension.</p>	<p>25% develop pustules, vesicles, eschars, or papules near bubo or flea bite. Cellulitis, abscesses, ulcerations, and ecthyma gangrenosum are rare. Untreated, some develop a generalized papular rash of the hands, feet, and pectoral areas, which, if the patient survive, evolve from papules to vesicles to pustules resembling smallpox.</p>
	<p>Insomnia, delirium, stupor, weakness, staggering gait, vertigo, slurred speech, memory loss.</p>	<p>Hepatomegaly present, elevated liver enzymes and hypoglycemia may suggest Reye's syndrome.</p>	

**Table 6** Assessing the Patient for Category A Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Subclinical plague</i>	In endemic areas, the prevalence of positive serology rises by 10 fold in asymptomatic individuals during periods of increased disease activity.					
<i>Plague pharyngitis</i>	Plague bacillus has been isolated from throat swabs of asymptomatic persons, but long-term carriage has not been documented.		Disease resembles acute tonsillitis accompanied by inflamed anterior cervical nodes.			
<i>Pestis minor</i>	Mild febrile illness with local lymphadenopathy.					
<i>Septicemic plague (Pestis siderans)</i>	Occurs in 26% of cases of bubonic plague. Rapidly developing disease and deterioration.			70% have GI symptoms with secondary septicemic plague.		
<i>Plague meningitis</i> (appears between the 9th and 17th day of bubonic plague)	Caused by spread from septicemic disease. Patients with axillary buboes are at increased risk of developing meningitis, but may present without lymph-adenopathy.	Kernig's sign, seizures, vestibulocerebellar symptoms, coma.				

<p><i>Smallpox (V. major)</i></p>	<p>Nausea, vomiting, abdominal pain, and diarrhea; less frequent in prodrome.</p>	<p>Transient erythematous or petechial rash lasting 12 hr may be confused for measles.</p>	<p>Discrete or confluent rash.</p>	<p>Nonimmune individuals: 20–50% mortality.</p>
<p>Headache in prodromal period. Delirium less frequent in prodrome.</p>	<p>Delirium (15%).</p>	<p>Most patients complain of spitting headaches and spinal pain; some develop hallucinations, delirium, depression, and manic depression. This may persist into convalescence.</p>	<p>Abdominal pain more frequent.</p>	<p>Vaccine-modified disease: Rare deaths. Death occurs between 7th and 15th day from encephalitis or hemorrhage. Mortality: 85% Discrete-immunized: 45% Confluent unimmunized: 99%.</p>
<p>48–72 hour prodrome although it may be as long as 5 days. Sudden onset of fever, chills, lumbar pain.</p>	<p>Prodrome prolonged and severe. Patients are toxic and restless and fevers are high.</p>	<p>Pharyngeal form: Spotty enanthema over soft palate, uvula and pharynx.</p>	<p>Dusky erythema to pleomorphic or petechial rash. Papules not well formed. Rash may be discrete or confluent.</p>	<p>Mortality in immunized patients: 98%. Mortality in unimmunized patients: 96%.</p>
<p>Fever, rigors, prostration, headache.</p>	<p>Less severe symptoms. More severe symptoms, persistent fever.</p>	<p>Pulmonary disease: severe symptoms, cyanosis, bilateral infiltrates.</p>	<p>Dusky rash appears on chest followed by diffuse petechiae and bleeding from mucous membranes. Those who survive after 10 days develop a confluent hemorrhagic vesiculation.</p>	<p>Low or no immunity. Mortality rates not available.</p>
<p>Modified smallpox</p>	<p>Flat (malignant) smallpox</p>	<p>Pharyngeal form: Spotty enanthema over soft palate, uvula and pharynx.</p>	<p>Dusky erythema to pleomorphic or petechial rash. Papules not well formed. Rash may be discrete or confluent.</p>	<p>Mortality in immunized patients: 0% mortality</p>
<p>Average incubation: 10–12 days; range: 6–22 days. Incubation period dependent on inoculum.</p>	<p>Ordinary smallpox</p>	<p>Pharyngeal form: Spotty enanthema over soft palate, uvula and pharynx.</p>	<p>Dusky rash appears on chest followed by diffuse petechiae and bleeding from mucous membranes. Those who survive after 10 days develop a confluent hemorrhagic vesiculation.</p>	<p>Mortality in immunized patients: 0% mortality</p>
<p>48–72 hour prodrome although it may be as long as 5 days. Sudden onset of fever, chills, lumbar pain.</p>	<p>Fever, rigors, prostration, headache.</p>	<p>Pulmonary disease: severe symptoms, cyanosis, bilateral infiltrates.</p>	<p>Dusky rash appears on chest followed by diffuse petechiae and bleeding from mucous membranes. Those who survive after 10 days develop a confluent hemorrhagic vesiculation.</p>	<p>Mortality in immunized patients: 0% mortality</p>
<p>Modified smallpox</p>	<p>Flat (malignant) smallpox</p>	<p>Pharyngeal form: Spotty enanthema over soft palate, uvula and pharynx.</p>	<p>Dusky rash appears on chest followed by diffuse petechiae and bleeding from mucous membranes. Those who survive after 10 days develop a confluent hemorrhagic vesiculation.</p>	<p>Mortality in immunized patients: 0% mortality</p>
<p>Average incubation: 10–12 days; range: 6–22 days. Incubation period dependent on inoculum.</p>	<p>Ordinary smallpox</p>	<p>Pharyngeal form: Spotty enanthema over soft palate, uvula and pharynx.</p>	<p>Dusky rash appears on chest followed by diffuse petechiae and bleeding from mucous membranes. Those who survive after 10 days develop a confluent hemorrhagic vesiculation.</p>	<p>Mortality in immunized patients: 0% mortality</p>

(Continued)

**Table 6** Assessing the Patient for Category A Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Tularemia (F. tularensis)</i> incubation: average 3–6 days (range hours to 2–3 wk) for all forms of disease.						
<i>Ulceroglandular or glandular tularemia</i> from direct contact with infected animals (hands) or vector-borne disease (legs).	Sudden onset of fever, chills, myalgias, headache, dry cough. Pathologic changes in the lung include necrotizing bronchopneumonia and caseous necrosis.		30% develop pneumonia.		In the ulceroglandular form, patients present with fever, chills, and skin lesions accompanied by regional adenopathy.	Portal of entry through skin where a papule develops to a slow-healing ulcer with a crust. Several enlarged axillary or inguinal nodes develop.
<i>Oropharyngeal tularemia</i> from ingestion of contaminated food or water.			Ulcerative pharyngitis or tonsillitis, most often unilateral with lymphadenopathy.			From contaminated food or water supply.
<i>Oculoglandular tularemia</i>						A form of ulceroglandular disease with primary lesion in conjunctiva.
<i>Typhoidal tularemia.</i> May be contracted through inhalation or ingestion of contaminated food. Untreated mortality: 30%.			Prolonged high-grade fever with relative bradycardia. Pulmonary infiltrates common.	Gastrointestinal symptoms are common.	Papular lesions and erythema nodosum may be seen in all forms.	No focal disease. Life-threatening sepsis may develop. Known complications: meningitis, endocarditis, rhabdomyolysis.
<i>Respiratory or pneumonic tularemia</i> contracted through inhalation or hematogenous spread.			Severe respiratory insufficiency or necrotizing pneumonia. <i>F. tularensis</i> subspecies <i>holarctica</i> may cause discrete infiltrates (24).			X ray may show necrotizing pneumonia, infiltrates similar to plague pneumonia, hilar adenopathy, and pleural effusion.

*Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)]*

*Arenaviridae*

*Lassa fever* (7–14 days; range 5 days–3 wk)      Gradual onset of malaise, fever, and myalgia.      30% develop permanent late sensorineural deafness. Sudden onset of deafness has been noted and no correlation with severity of illness.      Cough and chest pain. 60% of children have cough.      Abdominal pain, nausea, and vomiting. 60% of children have vomiting.      Conjunctival injection, pharyngitis with white and yellow exudates or ulcers.      Mild disease improves in 10 days.

High fever poor prognostic sign.      Other neurologic complications (tremors, confusion, seizures, and coma associated with death).      Patients with severe disease develop facial and laryngeal edema, cyanosis, bleeding, and shock.      Complications include pleural and pericardial effusions.      Tachypnea poor prognostic sign.      Bloody diarrhea poor prognostic sign.      Pharyngitis poor prognostic sign.      Overall mortality 1–2%. Pregnant women have the highest mortality (16%).

*Guanarito virus:*  
*Venezuelan hemorrhagic fever* (7–14 days)

(Continued)

**Table 6** Assessing the Patient for Category A Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Junin virus: Argentine hemorrhagic fever</i> (7–14 days)	Presents with fever, thrombocytopenia, and neurologic symptoms.	Neurologic symptoms are common and begin with the onset on hemorrhage on the 4th day of illness. Patients are irritable, lethargic, and have muscular hypotonia, hyporeflexia, areflexia, proprioceptive disturbances, tremors of the tongue and hands, changes in levels of consciousness, and inability to walk.				3–4 days after a nonspecific illness, patients develop hypotension and petechiae in the soft palate, axilla, and gingiva. Untreated: 15–30% mortality.
<i>Rift valley fever</i> (2–6 days)	Sudden onset of fever, headache, joint and muscle pains, conjunctivitis, and photophobia.	5–10% develop retinal disease 1–3 wk after onset of fever (macular exudates, retinal hemorrhages, and vasculitis). 1–5% develop neurologic complications.	<i>Bunyaviridae</i>			Commonly causes abortions in livestock. Patients experience a partial recovery and then symptoms return for a protracted course. 1% mortality
Crimean-Congo hemorrhagic fever (1–3 days after tick bite and 5–6 days after transfusion)	Sudden onset of fever, chills, dizziness, neck pain, and myalgia.	Neuropsychiatric symptoms.	Cardiovascular symptoms.	Lymphadenopathy and hepatomegaly. Nausea, vomiting, and diarrhea, diffuse gastrointestinal bleeding.		Nosocomial transmission documented. Hemorrhage and flushing is seen. DIC, renal, hepatic, and respiratory failure may ensue with a 30% mortality.

<p><i>Hemorrhagic fever with renal syndrome</i> (2–3 wk; range 2 days–2 mo)</p>	<p>Febrile phase.</p>	<p><i>Hantavirus</i> genus</p>	<p>Conjunctival and pharyngeal injection from vascular dilatation. Petechiae may develop.</p>	<p>Flu-like illness with low back pain from retroperitoneal edema, flushing.</p>
	<p>Hypotensive phase.</p>	<p>Mild hypotension to shock and hemorrhage lasting 1–2 days. Pulmonary edema.</p>	<p>Massive gastrointestinal bleeding in some patients.</p>	<p>Hypertension and renal failure. Untreated: 50% mortality. May last several months</p>
	<p>Oliguric phase.</p>	<p>Change in mental status.</p>		
	<p>Diuretic phase.</p>			
	<p>Convalescent phase.</p>			
<p><i>Hanta virus pulmonary syndrome: Sin Nombre virus</i> (1–2 wk; range 1–4 wk)</p>	<p>Prodromal phase 3–5 days (range 1–10 days). Abrupt onset of fever, myalgia, malaise, chills, anorexia, and headache.</p>	<p>Shortness of breath and pulmonary edema, productive and nonproductive cough, tachypnea, fever, hypotension, and hypoxia.</p>	<p>As patient worsens, there is nausea, vomiting, abdominal pain, and diarrhea.</p>	<p>Chest X ray may be initially normal but progresses to pulmonary edema and acute respiratory distress syndrome. Most deaths in 48 hr. 33% recover (those that survive the first 2–3 days). Evidence of person-to-person spread. This is another virus as a bioterrorists weapon.</p>
<p><i>Andes virus</i> (A south American hantavirus)</p>				
<p><i>Ebola virus: Ebola hemorrhagic fever</i> (4–10 days; range 2–21 days)</p>	<p>Abrupt onset of fever, severe headaches, myalgia, abdominal pain, diarrhea, and pharyngitis.</p>	<p><i>Filoviridae</i></p>	<p>Hematemesis, bloody diarrhea, and generalized mucosal bleeding.</p>	<p>Shock, metabolic acidosis, diffuse coagulopathy. Patients die by day 10 (60–90% mortality).</p>
	<p>Hemiplegia, psychosis, coma, and seizures are common.</p>		<p>Herpes-like lesions on the mouth and pharynx. Severe conjunctival injection and gingival bleeding. There is a prominent maculopapular rash that evolves into petechiae, ecchymosis, and bleeding from venepuncture sites and mucosa.</p>	

(Continued)



Table 6 Assessing the Patient for Category A Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin and mucous membranes	Miscellaneous
<i>Marburg virus:</i> <i>Marburg hemorrhagic fever</i> (3–10 days)	Sudden onset of fever, chills, headache, myalgia.	Delirium develops late in the disease with shock, massive bleeding, and multi-organ failure. Uveitis reported.	Rash is followed by nausea, vomiting, chest and abdominal pain. Jaundice, weight loss, pancreatitis, liver failure. <i>Flaviviridae</i>	Some patients develop a maculopapular rash beginning on the 5th day of illness.	After 6–8 days, patients progress to severe hemorrhagic fever.	Mortality recorded at 25–90% (more often 25–30%)
<i>Dengue and dengue hemorrhagic fever</i> (2–7 days)	Nonspecific febrile illness, Dengue fever	Sudden onset of (break bone fever) severe muscle pains, headache, prostration. Retro-orbital pain. Anorexic and restless 4–6 days.			Facial flushing, conjunctival injection. 50% of patients have an early transient erythematous rash. As fever rapidly resolves, a morbilliform or scarlatini-form rash appears on extremities with petechiae on the legs and generalized lymphadenopathy.	Fever, arthralgia, and rash. Positive tourniquet test, epistaxis, petechiae, or purpura.  There is a 2nd febrile phase lasting 2–3 days with rash desquamation. Convalescence is long and patients remain debilitated and depressed. 10% mortality may be reduced to < 1% mortality with fluid resuscitation.
<i>Yellow fever virus and yellow fever</i> (3–6 days)	Dengue hemorrhagic fever  Most infections mild and patients recover in 48 hr.	Begins day 2–5 after dengue fever. Restlessness, diaphoresis. Encephalopathy may complicate clinical condition  Minority have severe headache.	Shock, hypotension, hemorrhagic manifestations, respiratory failure (alveolar hemorrhage and fluid accumulation, renal failure). Relative bradycardia for degree of fever.	Petechiae, purpura, spontaneous bleeding from gums and gastro-intestinal tract, tender hepatomegaly.		Minority have low back pain and proteinuria with headache.

<p><i>Yellow fever severe disease</i></p>	<p>Abrupt onset of high fever, severe headache</p>	<p>Severe headache.</p>	<p>Hypotension, heart failure, prolongation of the PR and QT intervals.</p>	<p>Nausea, vomiting, abdominal, back loin, and limb pain. Dehydration, jaundice, epigastric pain, vomiting, and gastrointestinal bleeding develop.</p>	<p>Bleeding from nose and gums.</p>	<p>Patients may recover after 3 days or temporarily improve for 24 hr before deteriorating. Recovery in 3–4 days to 2 wk or death on the 7th–10th day.</p>
<p><i>Rabies</i> (4 days to 19 yrs. Most cases present in 1–2 mo. 75% present in 20–90 days after exposure).</p>	<p>Prodrome (1–10 days): anxiety, depression, gastro-intestinal symptoms, pain, and/or paresthesia at site of inoculation.</p>	<p>Symptomatic (furious) rabies—80% of patients: agitation, hallucination, mixed with lucid periods, autonomic dysfunction, hydrophobia, aerophobia, cranial nerve abnormalities, coma.</p>	<p>Myocarditis, cardiac arrhythmia, congestive heart failure</p>	<p>Nausea, vomiting, diarrhea, ileus, gastrointestinal bleeding.</p>		

Source: From Refs. 1, 5, 6, and 23–30.

**Table 7** Assessing the Patient for Selected Category B and C Agents

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin, joints, and mucous membranes	Miscellaneous
<i>Brucellosis (Brucella species)</i> (10 days–3 mo)	Fever (sometimes intermittent), malaise, headache, myalgias, back arthralgias, back pain, malodorous diaphoresis, chills, weight loss.	Depression is common; change in mental status. Other complications: acute and chronic meningitis, encephalitis, myelitis, radiculoneuritis, brain abscess, epidural abscess, demyelination, and vasculitis, cerebral aneurysms/subarachnoidal hemorrhage  Uveitis is a late complication. 7.9% and 0.7% of patients with chronic or acute disease respectively have eye complications.	<i>Category B pathogens</i> Endocarditis.	Anorexia, nausea, vomiting, diarrhea, or constipation in majority of patients. Bad taste in mouth.	Sacroiliitis, spondylitis, and large joint effusions. Skin lesions are unusual (rashes, papules, ulcers, erythema nodosum, petechiae, purpura, vasculitis), cellulitis and abscesses, osteomyelitis.	Recurrent and persistent disease occurs.
				Hepatosplenomegaly (20–30%), lymphadenopathy (10%), severe pharyngitis, panniculitis.		Other complications: mixed cryo-globulinemia, orchididymitis, pancreatitis, Coombs-positive autoimmune hemolytic anemia, cold agglutinin-associated hemolytic anemia, pancytopenia and capillary leak syndrome, acquired progressive spastic paraparesis, subacute thyroiditis.

<p><b>Epsilon toxin of <i>C. perfringens</i></b> (incubation in humans unknown)</p>	<p>Microvascular endothelial injury and diffuse vasogenic cerebral edema.</p>	<p>In animals, in gastrointestinal tract, causes wasting, diarrhea, and enterocolitis.</p>
<p><b>Food safety threats</b> (e.g., <i>Salmonella</i> sp., <i>E. Coli</i> O157:H7, <i>Shigella</i>, <i>Vibrio</i> spp., <i>L. monocytogenes</i>, <i>C. jejuni</i>, <i>Y. enterocolitica</i>):</p>	<p>These organisms may present with gastrointestinal and/or systemic disease. <i>L. monocytogenes</i> has a propensity to cause meningitis in the compromised host and rhombencephalitis in the normal host. <i>E. coli</i> O157:H7 hemolytic uremic syndrome. <i>S. typhi</i> causes typhoid fever, which may be protracted, and patients may present with relative bradycardia and occasionally rose spots on the trunk. <i>Shigella</i> species causes bloody diarrhea.</p>	<p>These organisms may present with relative bradycardia and occasionally rose spots</p>
<p><b>Disease presentation of Melioidosis (<i>Bk. pseudomallei</i>)</b></p>	<p>Most disease subclinical although fulminant rapidly fatal disease in immune compromised patients. May present as sepsis. Chronic infection may manifest as multiple abscesses of the skin, soft tissue and viscera.</p>	<p>Jaundice, hepatomegaly, splenomegaly.</p>
<p><b><i>Melioidosis</i> (<i>Bk. pseudomallei</i>)</b> (1–21 days; 1–5 days for sepsis; hours for inhalation; incubation period may be extended over months to years). Weaponized disease may appear in 1–4 days.</p>	<p>Sepsis patients may present with confusion, headache, photophobia, myalgias, flushing, cyanosis, jaundice.</p>	<p>Pulmonary lesions on chest X ray most common site of localized disease. Cyanosis with severe disease.</p>
<p><b><i>Glanders</i> (<i>Bk. mallei</i>)</b> (1–21 days; 1–5 days for sepsis; hours for inhalation). Weaponized disease may appear in 1–4 days.</p>	<p>Presents abruptly with swollen nodes, weight loss, and subcutaneous abscesses. Chronic infection may manifest as multiple abscesses of the skin, soft tissue, and viscera.</p>	<p>Chronic localized abscesses in liver, lung, brain, lymphadenitis, osteomyelitis, septic arthritis and spleen. Ulcerating nodules in gastrointestinal tract.</p>
<p>Weaponized disease may appear in 1–4 days.</p>	<p>Mucocutaneous exposure may result in headache, fever, myalgia, localized nodular or erosive infection. Photophobia, severe headache, lacrimation, ocular exudates and ulceration, erosion of the nasal septum.</p>	<p>Tends to form abscesses. Cutaneous and subcutaneous pustules. Erythroderma, lymphadenopathy.</p>
<p>Recrudescence of infection occurs especially in times of stress. Parotid abscesses in children.</p>	<p>Mortality 19–50% even with treatment. Mortality &gt;90% in 24–48 hr without treatment in septicemic form.</p>	<p>Recrudescence of infection occurs especially in times of stress. Parotid abscesses in children.</p>

(Continued)

Table 7 Assessing the Patient for Selected Category B and C Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin, joints, and mucous membranes	Miscellaneous
<i>Psittacosis (C. psittaci)</i> (1–2 wk)	Asymptomatic disease to severe pneumonia.		Pneumonia during recovery, thrombophlebitis and pulmonary embolism reported.	May be accompanied by splenomegaly. Early, mild transaminase elevations.		Mortality: 15–20% untreated; <1% treated patients.
<i>Q fever (C. burnetii)</i> (10–21 days)	Usually asymptomatic or self-limited mild flu-like illness.	May present as meningoencephalitis.	May present as pneumonia (most common). Varying radiologic appearances. Endocarditis can complicate disease. Rare fatal cases from myocarditis.	May present as granulomatous hepatitis especially in younger patients.		Malaise and fever may last for months. Some patients develop chronic fatigue-like syndrome.
	Has rarely presented as severe multiorgan failure, or fever and severe cholera-like diarrhea.			May be accompanied by splenomegaly. Early, mild transaminase elevations. Has mimicked peritonitis.		
<i>Ricin toxin</i> from <i>R. communis</i> (castor beans) (sublethal exposures—onset 4–8 hr)	Human sublethal exposure: fever, chest tightness, cough, shortness of breath, nausea, and joint pain.	Sublethal doses in animals resulted in ataxia and weight loss in addition to inflammatory infiltrates in the lungs.	Causes immediate acute lung injury and adult respiratory distress syndrome. Rapidly fatal necrotizing airway disease in animals.	Oral intake causes bloody diarrhea.		Lethal doses resulted in deposition of fibrin and glomerular leukocytosis.
<i>Staphylococcal enterotoxin B</i> (3–12 hr)	Sudden onset of fever, chills, headache, and myalgia. Fever for 2–5 days.		Nonproductive cough (may persist up to 4 wk). Occasional retrosternal chest pain and shortness of breath.	Nausea, vomiting, diarrhea. If swallowed, gastrointestinal symptoms more severe.		Can result in toxic shock and death with intense exposure or ingestion.

**Typhus fever** (*R. prowazekii*) (8–16 days for louse-borne disease)

Prodrome 2 days. Onset abrupt with fever, chills, myalgias.

Headache progresses to delirium without treatment.

Rales. Chest X ray: interstitial infiltrates. Cough becomes severe without treatment.

Gangrene a rare complication seen in untreated patients.

80% develop rash (erythematous 2–6 mm macules) in 4 days sparing the face, palms, and soles; conjunctival injection. Rash becomes hemorrhagic without treatment.

Brill–Zinsser disease (recrudescence typhus).

**Viral encephalitis** [alphaviruses (e.g., Venezuelan equine encephalitis 1–6 days), EEE (5–7 days), WEE (5–10 days)]

Most disease self-limited, flu-like illness.

Venezuelan: 1% of adults and 4% of children develop encephalitis with 20% mortality. EEE >50% mortality with clinical disease. WEE 3–4% mortality.

**Viruses (noroviruses, hepatitis A virus):** common cause of gastroenteritis (norovirus) and hepatitis A.

**Water safety threats** [e.g., *V. cholerae*, *C. parvum* (1–14 day incubation)]

**Protozoa** [*C. cayatanensis*, *G. lamblia* (12–20 day incubation), *E. histolytica* (3 wk incubation)]. Usually cause gastroenteritis.

*Category C pathogens*

**Emerging infectious diseases** such as Nipah virus and hantavirus; yellow fever virus, Tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus. See Table 6 for hantavirus and yellow fever virus.

**Tick-borne hemorrhagic fever viruses** [Crimean-Congo hemorrhagic fever (*Nairovirus*-a Bunyaviridae)], Omsk hemorrhagic fever, Kyasanur forest disease and Alkhurma viruses. See Table 6.

(Continued)

**Table 7** Assessing the Patient for Selected Category B and C Agents (Continued)

Pathogen (incubation period)	Systemic symptoms	Central nervous system	Cardiorespiratory	Gastrointestinal	Skin, joints, and mucous membranes	Miscellaneous
<p><i>Multidrug-resistant M. tuberculosis</i>. Usually pulmonary, can be disseminated.</p> <p>SARS-associated coronavirus (2–14 days)</p>	<p>Nonrespiratory prodrome 2–7 days: fever, headache, malaise, myalgia, diarrhea.</p>		<p>Respiratory phase begins 2–7 days after prodrome: nonproductive cough, shortness of breath. Physical findings minimal. Chest X ray: ground-glass opacities, focal consolidations especially in periphery and subpleural regions of lower lobes. By 2nd wk, shifting X-ray picture and progression to both lungs.</p>			<p>Human-to-human transmission through droplets, direct and indirect contact with patients or fomites contaminated by respiratory secretions, feces, urine, and tears; airborne transmission has occurred. Fatality rate 9.6%.</p>
<p><i>West Nile virus</i> (a Flaviviridae) (5–14 days)</p>	<p>Mild flu-like prodrome. Significant risk for older adults and compromised patients.</p>	<p>Hyponatremia, tremor, acute asymmetric flaccid paralysis or single-limb weakness, myoclonus, dyskinesias, Parkinsonism, with encephalitis have poor prognosis. No sensory disturbances.</p>				<p>Encephalopathic patients (without metabolic abnormalities) have generalized slow-wave abnormalities and in some cases triphasic waves.</p>

<p><i>Pandemic and avian influenza</i> (H5N1 influenza) (2–5 days after exposure to poultry; 2–8 days range; median: 3.5 days)</p>	<p>Rapidly progresses to adult respiratory distress syndrome, multiorgan failure, and death in 6–10 days.</p>	<p>Acute respiratory symptoms: fever &gt;38°C, cough, shortness of breath, sore throat (less common).</p>	<p>Diarrhea, vomiting, abdominal, and pleuritic pain progresses rapidly to respiratory failure within 1st wk.</p>
<p>Majority of cases have abnormal chest X rays: bronchopneumonia or lobar pneumonia. Some autopsies revealed hemorrhagic pneumonia similar to 1918 pandemic influenza. Fatality rate 62.7%.</p>	<p>Most infectious before illness and in 1st 2 days of illness. Sore throat, cough, rhinitis, cough, pneumonia, or respiratory complications 12%. Upper respiratory tract lymphadenitis with dysphagia and airway obstruction.</p>	<p>Majority of cases have abnormal chest X rays: bronchopneumonia or lobar pneumonia. Some autopsies revealed hemorrhagic pneumonia similar to 1918 pandemic influenza. Fatality rate 62.7%.</p>	<p>Bacterial skin infection most common complication.</p>
<p><i>Monkeypox virus</i> (<i>Orthopoxvirus</i> of the Poxviridae family) (9–21 days)</p>	<p>2–3 day febrile prodrome (sometimes with lymphadenopathy, chills, back pain, and headache) typical preceding rash.</p>	<p>Encephalitis.</p>	<p>Gastrointestinal complaints (nausea, vomiting, abdominal pain, diarrhea)</p>
<p>Rash: papular or vesicular pustular rash. Fever may develop without rash and vice versa.</p>	<p>&lt;25 lesions—7.5%: not incapacitated; 25–90 lesions: incapacitated; &gt;100 lesions: required intensive nursing.</p>	<p>Incubation period and symptoms differ for those with noninvasive versus complex exposures (see Ref. 30).</p>	<p>Genetically engineered biological weapons. <i>Expect the unexpected!</i></p>

Abbreviations: EEE, eastern equine encephalitis; WEE, western equine encephalitis.

Source: From Refs. 7, 8, and 31–42.



**Table 8** Radiographic Findings

Pathogen	Chest radiographic findings	Comments and other radiologic findings
<p>Anthrax (<i>B. anthracis</i>) Inhalation anthrax (36)]</p>	<p style="text-align: center;"><i>Category A pathogens</i></p> <p><i>Radiographic findings</i> (comparing inhalational anthrax and CAP)</p> <p>Mediastinal widening only Pleural effusion only Infiltrate* only (* = focal density, opacity, or consolidation) Mediastinal widening and pleural effusion Mediastinal widening and infiltrate* Pleural effusion and infiltrate* Mediastinal widening, pleural effusion, and infiltrate* Nonspecific findings Normal Pneumonia complicating fatal cases. Aspiration pneumonia. 10% of patients with bubonic plague develop secondary pneumonia.</p>	<p>Inhalational anthrax (N = 22)</p> <p>CAP (N = 188)</p> <p>9.1% 0% 0% 18.2% 9.1% 18.2% 45.5% 0% 0%</p> <p>1.1% 0% 41.5% 1.1% 4.3% 19.1% 1.6% 15.4% 14.9%</p>
<p>Botulism (<i>C. botulinum</i> toxin) Plague (<i>Y. pestis</i>)</p>	<p>In septicemic plague, bilateral infiltrates may represent secondary plague pneumonia or diffuse alveolar damage from sepsis. Secondary plague pneumonia appears as bilateral parenchymal infiltrates that may be initially nodular. Cavitation occurs but is uncommon. Pneumonic plague is caused either by hematogenous disease or direct inhalation. Viral and/or bacterial pneumonia has been reported in some patients. Pulmonary edema is a common complication of flat and hemorrhagic smallpox.</p>	<p>Extensive bilateral secondary opacities cannot be distinguished from primary plague pneumonia or acute respiratory distress syndrome. Mediastinal, cervical, and hilar adenopathy may not be consistently present in bubonic and secondary pneumonic plague. Also described a multilobar air-space disease without extensive hilar or mediastinal node enlargement.</p>
<p>Pneumonic plague from inhalation has a 4-day incubation period.</p>	<p>Patients present 9–12 days with fever. Radiographs show ill-defined nodular opacities in the upper lung fields that may persist for months. These nodules calcify after several years.</p>	<p>The skin rash usually appears before pulmonary disease, thus the diagnosis is almost never in doubt. Bones and joints may become involved with periostitis of the diaphyses of long bones, and patchy destruction of the metaphyses involving the joints (especially the elbow). Occurs in vaccinated patients who are in contact with smallpox patients, especially health care workers.</p>
<p>Smallpox (<i>V. major</i>)</p>	<p>“Smallpox handlers disease” (incubation: 9–12 days after contact)</p>	<p>Extensive bilateral secondary opacities cannot be distinguished from primary plague pneumonia or acute respiratory distress syndrome. Mediastinal, cervical, and hilar adenopathy may not be consistently present in bubonic and secondary pneumonic plague. Also described a multilobar air-space disease without extensive hilar or mediastinal node enlargement.</p>

Tularemia ( <i>F. tularensis</i> )	<p>Bronchopneumonia that is usually bilateral and may cavitate. Early papers suggest ulceroglandular form more often involves mediastinal lymph nodes and typhoidal form involves the lungs. Later reports suggest the two forms are radiologically indistinguishable.</p> <p>Chest X rays in individuals who developed diseases from aerosolized organisms were initially normal. They progressed to multifocal segmental or lobar infiltrates. Mediastinal adenopathy was not seen but hilar adenopathy developed in some cases.</p> <p>Early in the disease, there is interstitial edema. Kerley B lines, and subpleural edema (even though the patients are usually hypovolemic). This progresses to bilateral alveolar infiltrates in 48 hours. These patients have 50% mortality.</p> <p>Lobar consolidation is seen in 20% of patients with bacterial superinfection.</p>	<p>Pneumonia occurs in most cases of typhoidal disease and 30% of patients with ulceroglandular disease.</p> <p>A tularemia outbreak caused by aerosolized organisms occurred on Martha's Vineyard in 2000. Initial chest X rays were normal.</p>
Hanta virus pulmonary syndrome: Sin Nombre virus	<p>Some patients with less severe disease do not progress to the stage of interstitial edema.</p>	
Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)]	<p>Chest X rays in patients with Argentine hemorrhagic fever are often normal. Encephalitis common but MR imaging often negative.</p>	
Rabies	<p>Rift Valley fever encephalitis: CT revealed multiple cortical infarcts most prominent in occipital area.</p> <p>MRIs are similar in patients with furious and dumb rabies (non-enhancing, ill-defined, mild hyperintensity in the brain stem, hippocampus, hypothalamus, deep and subcortical white matter, and deep and cortical gray matter in the conscious patient).</p> <p>In comatose patients, gadolinium enhances the hypothalamus, brain stem nuclei, spinal cord, gray matter, and intradural cervical nerve roots.</p>	
Brucellosis ( <i>Brucella</i> species)	<p>Rabies after a bite to the arm: MRI will reveal enhancement of the brachial plexus</p> <p>Extensive pulmonary edema usually represents excessive fluid therapy.</p> <p>Bronchopneumonia on chest X ray. CT reveals non-enhancing symmetrical hypodensities of the basal ganglia.</p> <p>Pediatric cases: lobar pneumonia or non-resolving pneumonia. Fatal disease with multifocal liver and lung nodules.</p> <p><i>Category B pathogens</i></p>	<p>23% complain of cough, but practically none have physical or radiographic findings. Flare cases of air-space pneumonia, bronchopneumonia, lung abscess, pleural effusion, and empyema reported.</p>

(Continued)

Table 8 Radiographic Findings (Continued)

Pathogen	Chest radiographic findings	Comments and other radiologic findings
Epsilon toxin of <i>C. perfringens</i>	In calves severe acute pulmonary edema that was particularly marked in the interlobular septa. The histological lesions consisted of intra-alveolar and interstitial edema of the lung and variable degrees of perivascular proteinaceous edema in the internal capsule, thalamus, and cerebellar white matter.	In sheep experiments histological changes consisted of severe edema of pleura and interlobular septa and around blood vessels and airways and acidophilic, homogeneous, proteinaceous, perivascular edema in the brain.
Food safety threats (e.g., <i>Salmonella</i> sp., <i>E. coli</i> O157:H7, <i>Shigella</i> , <i>Vibrio</i> spp., <i>L. monocytogenes</i> , <i>C. jejuni</i> , <i>Y. enterocolitica</i> )	<i>Salmonella</i> sp.: Pneumonia, empyema, and lung abscess.  <i>E. coli</i> : Severe confluent bronchopneumonia, empyema, abscess. <i>L. monocytogenes</i> : Pneumonia is rare. <i>C. jejuni</i> : Food aspiration has caused lung abscess, lobar pneumonia in splenectomized patients. <i>Y. enterocolitica</i> : Pneumonia, interstitial pneumonia, empyema (child), cavitary disease, lung abscess, nodular infiltrates, and necrotizing pneumonia especially but not exclusively in compromised patients Acute pneumonia, abscess formation frequent, empyema, and hilar adenopathy. Chronic granulomatous disease imitates tuberculosis.	
Glanders ( <i>Bk. mallei</i> )	Acute disease: irregular nodular opacities 3–15 mm, disseminated bilaterally or segmental or lobar consolidation (one or more segments may be involved), Nodules enlarge, coalesce, and cavitate (40–60% of patients). 15% have pleural effusion at or near presentation. Chronic disease: nodular, irregular, linear opacities, consolidation and cavitation predominantly or exclusively involving the upper lobe but not the apex-like tuberculosis.	Majority of infected patients are asymptomatic.  Acute disease: CT frequently demonstrates liver and spleen abscesses.
Melioidosis ( <i>Bk. pseudomallei</i> )	The chest X ray often abnormal (72%): homogeneous ground-glass opacity sometimes with small radiolucent areas, patchy reticular pattern radiating from the hilum, or nonsegmental consolidation with or without atelectasis. Enlarged hilar node not uncommon. Rare miliary pattern seen.	Chronic disease seldom associated with retraction of the hila and rarely calcifies.  Takes many weeks (average 6 wk, range 1–20 wk) for X ray to clear after treatment.
Psittacosis ( <i>C. psittaci</i> )		

**Q fever (*C. burnetii*)**  
 Pneumonia is the most common clinical presentation (50% of patients). Appearance is nonspecific on chest X ray and chest CT. May appear as segmental, patchy, or lobar consolidation with or without pleural effusions. A sublethal dose of intratracheal instilled ricin (2 µg/100 g body weight) induced a similar response in lungs but did not cause detectable damage in other organs. Lungs of mice that recovered from a sublethal dose of ricin displayed evidence of fibrosis and residual damage. Airways exposure to SEB (7.5–250 ng/trachea) caused a dose- and time-dependent neutrophil accumulation in BAL fluid, the maximal effects of which were observed at 4 hr post-SEB exposure (250 ng/trachea). Eosinophils were virtually absent in BAL fluid, whereas mononuclear cell counts increased only at 24 hr post-SEB. Significant elevations of granulocytes in bone marrow (mature and immature forms) and peripheral blood have also been detected. Interstitial pneumonia.

**SEB**  
 Mice developed interstitial pneumonia, with consolidation of the alveoli, hemorrhages in lungs, multifocal granulomas in liver, and hemorrhages in brain, as seen in humans. MR more sensitive than CT for encephalitis. For EEE, abnormalities are seen in the basal ganglia and thalamus. T2-weighted images show increased intensity in basal ganglia that represents inflammation, ischemia, and edema rather than necrosis. Abnormalities regress with clinical improvement. *Basal ganglia rather than temporal lobe abnormalities differentiates this from herpes encephalitis.*

**Typhus fever (*R. prowazekii*)**  
 Norovirus commonly causes gastroenteritis. Hepatitis A has been associated with bacterial pneumonia. Cryptosporidia usually causes diarrhea that may be severe. It has caused respiratory distress as part of disseminated disease in immune compromised infants. Non-01 strains of *V. cholerae* has caused lobar pneumonia. *E. histolytica*: pneumonia, lung abscess, pleurisy, hepatobronchial fistulization, and more infrequently pulmonary embolism. The preferential localization is the right hemithorax related to abscess in the right lobe of the liver. Left lobe abscesses lead to left-sided pleuropulmonary complications with the risk of rupture into the pericardium.

**Viral encephalitis [alphaviruses (e.g., Venezuelan equine encephalitis, EEE,WEE)]**  
 Viruses (noroviruses, hepatitis A virus)  
 Water safety threats (e.g., *V. cholerae*, *C. parvum*)

**Protozoa (*C. cayatanensis*, *G. lambia*, *Entamoeba histolytica*, *Toxoplasma* spp., *Microsporidia*)**  
*E. histolytica*: Pleuropulmonary complications almost always occur in patients with a liver abscess, the intrathoracic contamination via transphrenic dissemination predominating.

**CT** may detect mild lymphadenopathy not seen on chest X ray but this is not specific for Q fever.

**Intratracheal instillation of a lethal dose of ricin (20 µg/100 g body weight)** resulted in a hemorrhagic inflammatory response in multiple organs.

(Continued)

**Table 8** Radiographic Findings (Continued)

Pathogen	Chest radiographic findings	Comments and other radiologic findings
Emerging infectious diseases such as Nipah virus and hantavirus; yellow fever virus, tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus.	<i>Toxoplasma</i> pneumonia may be severe, even in the normal host with bilateral interstitial infiltrates. Usually there is a focal reticular pattern similar to viral pneumonia, poorly defined ground-glass opacities, and hilar nodes are usually enlarged. In compromised (AIDS) patients, bilateral coarse nodular pattern or a diffuse reticuloalveolar pattern without lymphadenopathy, pleural effusions have been reported. <i>Microsporidia</i> may cause tracheobronchitis or bronchiolitis.	
Nipah virus	generating interstitial pneumonia or encephalitis.	Category C pathogens
Tick-borne hemorrhagic fever viruses (Crimean-Congo hemorrhagic fever (Nairovirus-a Bunyaviridae), Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhurma viruses.	Tick-borne encephalitis complex: atypical pneumonia syndrome. Crimean-Congo hemorrhagic fever: manifested in the hemorrhagic period with blood-spitting pulmonary hemorrhage and bleeding into the pleural cavity. Alkhurma viruses: acute febrile, flu-like illness with hepatitis (100%), hemorrhagic manifestations (55%), and encephalitis (20%).	

- Multidrug-resistant *M. tuberculosis*: See tuberculosis in Ref. 46.
- SARS virus (SARS-associated coronavirus)  
 Unilateral or bilateral infiltrates; multiple patchy opacities with bilateral distribution. The opacities are usually ground-glass in appearance, sometimes with air-space consolidation, progressively evolving. The evolution is very rapid in some cases, resulting in the confluence of lesions and large areas of opacification in a short time.
- West Nile virus (a Flaviviridae)  
 Has caused pneumonia in a transplant patient and pneumonia has been one of the admitting diagnosis for patients with West Nile virus infection.
- Pandemic and avian influenza (H5N1 influenza)  
 Interstitial infiltrates, lobar infiltration
- Monkeypox virus (*Orthopoxvirus* of the Poxviridae family)  
 Consolidation, pneumothorax (on mechanical ventilation) Unknown. The Brighton strain of cowpox virus causes lethal bronchopneumonia when delivered as a small-particle (1 µm) aerosol to weanling BALB/c mice.
- Genetically engineered biological weapons

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Abbreviations: BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; SWEB, staphylococcal enterotoxin B; EEE, eastern equine encephalitis; MR, magnetic resonance; WEE, western equine encephalitis.

Source: From Refs. 33, 43-55.

### Decontaminate as Appropriate

Under most circumstances, victims of a bioterrorist attack will present hours or days later. Patients will be triaged and screened in the emergency department where all clothing will be removed and preserved for testing and as evidence. Decontamination of the patient is critical in the case of a chemical, biologic, or radiologic attack and should take place in a designated decontamination area, usually outside or adjacent to the emergency department. For most agents, removal and securing of all clothing and a five- to six-minute shower with soap and water is sufficient (56). Use of caustic solutions will harm the patient by damaging the skin and mucous membranes, complicate care, without realizing any advantage in decontaminating the patient (1). Standard solutions of hypochlorite are adequate to clean any surfaces contaminated with any potential pathogen, *but should never be applied to the patient* (1,57).

### Establish a Diagnosis

The most definitive diagnostic test for each pathogen is listed in Table 9 (1,6,11,58–71). It is important to consider the possibility that the victim of bioterrorism may be infected or poisoned by more than one agent. Combinations of bacterial and viral agents, and/or agents with widely different incubation periods may be purposely employed to add confusion and increase the lethality of the attack. Incubation periods in some cases are dose dependent (72–74). Exposure concentrations will vary according to whether the pathogens are released indoors or outdoors, air flow [status of a building's heating ventilation air-conditioning (HVAC) system] or wind, weather (sunlight, rain, relative humidity), distance from the point of release, and, time when entering or remaining in a contaminated area or atmosphere after release. In the case of the use of two or more agents, their individual physical properties may allow for different distribution properties, and even organisms with similar incubation periods may present at widely different times. Relapses may be part of the disease course or the presentation of a second disease or intoxication.

### Render Prompt Treatment

Table 10 outlines the recommended treatments for each of the pathogens (1,6,11,23,29,58–60, 75–98). Presumptive therapy and precautions must be initiated as soon as possible. As was our experience during the Trenton-anthrax threat of 2001, definitive recommendations will come from public health authorities once the pathogens are identified with sufficient certainty.

### Practice Good Infection Control

Standard precautions are usually adequate to manage most patients with anthrax, tularemia, brucellosis, Q fever, Venezuelan equine encephalitis, and toxin-mediated diseases. Table 4 lists isolation precautions for potential threats.

Hand washing is the most basic and key component to infection control. A study utilizing *Bacillus atrophaeus* as a surrogate for *B. anthracis* spores found that hand washing using a nonantimicrobial soap under running water or antibacterial (2% chlorhexidine gluconate) agents was far superior to waterless hand hygiene agents containing alcohol. After 10 seconds of washing, there was no difference in reducing the spore count between the antimicrobial soap and plain soap. There was also no difference between either soap by increasing washing from 10 to 60 seconds. Chlorine-containing microfiber towels were inferior to hand washing at 10 seconds duration, but superior at 60 seconds duration (56).

### Alert the Proper Authorities

The hospital administration should notify local, municipal, state, and federal health and law enforcement authorities. Bypassing the institutional chain-of-command and protocol will lead to confusion, misinformation, and delay in responding appropriately. The first line of notification in most if not all institutions is infection control or the designated institutional individual for any suspected cases of a contagious disease, whether or not bioterrorism is suspected. All personnel on *all shifts* should be familiar with the institution's individual protocol.

(text continues on page 473)

**Table 9** Definitive Diagnostics

Pathogen	Diagnostic test
	<i>Category A pathogens</i>
Anthrax ( <i>B. anthracis</i> )	Culture of blood, sputum, pleural fluid, cerebrospinal fluid, or skin lesions. PCR may be used to speciate.
Botulism ( <i>C. botulinum</i> toxin)	Mouse bioassay (may be negative in wound and infant botulism). Confirmatory testing (bioassay and stool cultures) for toxin may be time consuming. Optical immunoassay for toxins A, B, E, and F is rapid. Other assays: a vertical-flow strip immunochromatography and a small disposable immunoaffinity column for type A toxin.
Plague ( <i>Y. pestis</i> )	Culture of sputum or blood or other tissue. Real time PCR of sputum can rapidly detect organism in the experimental setting. Direct fluorescent antibody testing of tissue or fluids.
Smallpox ( <i>V. major</i> )	Viral culture from skin lesions with real-time PCR to differentiate from other poxviridae (monkeypox)—only performed by the CDC or WHO.
Tularemia ( <i>F. tularensis</i> )	Difficult to grow on laboratory media. Serology (enzyme-linked immunosorbent assay) or histologic examination of involved tissue may be needed. PCR is of value in examining samples from primary lesions. Culture and lymphocyte stimulation have also been used.
Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg)] and arenaviruses (e.g., Lassa, Machupo]	Antigen testing by enzyme-linked immunoabsorbent assay or viral culture—only performed by the CDC.
Rabies	Nuchal biopsy specimen and saliva sample will reveal the presence of viral antigen and viral RNA by DFA test and RT-PCR, respectively.
	<i>Category B pathogens</i>
Brucellosis ( <i>Brucella</i> species)	Culture (confirmatory), blood culture immunofluorescence, agglutination titers, ELISA, other serologies, and real-time PCR.
Epsilon toxin of <i>C. perfringens</i>	Detection of anti-epsilon toxin serum antibodies and real-time PCR for detection and toxin-typing organisms.
Food safety threats (e.g., <i>Salmonella</i> spp., <i>E. coli</i> O157:H7, <i>Shigella</i> , <i>Vibrio</i> spp., <i>L. monocytogenes</i> , <i>C. jejuni</i> , <i>Y. enterocolitica</i> )	Culture.
Glanders ( <i>Bk. mallei</i> )	Culture from sputum, blood, urine, pus, or swabs of skin lesions: PCR used to identify organisms; various serologic tests (polysaccharide microarray serology; ELISA, agglutination, and complement fixation).
Melioidosis ( <i>Bk. pseudomallei</i> )	Culture: PCR used to identify organisms; polysaccharide microarray serology; IHA titer.
Psittacosis ( <i>C. psittaci</i> )	Culture: isolation in cell culture, identifying by immunofluorescence staining, PCR identification in clinical samples; serology (ELISA, MIF, nested PCR-EIA).
Q fever ( <i>C. burnetii</i> )	Serology gold standard for diagnosis but antibodies take 2–3 wk to detect. Cell culture sensitivity maybe low. Real-time PCR rapidly detects organism.
Ricin toxin from <i>R. communis</i> (castor beans)	Serum antigen detection by ELISA, assay configurations use monoclonal capture antibody coupled with either a polyclonal or monoclonal detector antibody for detection of toxin in foods.
Staphylococcal enterotoxin B	Capture ELISA serum assay; mass spectrometry (availability limited), PCR, latex agglutination assay, LAMP assay targeting the toxin genes, measurement of toxin-neutralizing antibodies (may be absent in immune-compromised patients).

(Continued)



**Table 9** Definitive Diagnostics (*Continued*)

Pathogen	Diagnostic test
Typhus fever ( <i>R. prowazekii</i> )	Serology: indirect microimmunofluorescence assay is the most sensitive and specific, but is not usually positive when the patient is acutely ill. PCR specific but not sensitive. Real-time PCR both sensitive and specific.
Viral encephalitis [alphaviruses (e.g., Venezuelan equine encephalitis, EEE, WEE)]	Direct detection (nucleic acid or virus isolation from acute-phase serum or CSF); serologic assay (specific IgM in CSF using capture ELISA or monoclonal antibody antigen capture ELISA) at time of clinical encephalitis. Plaque reduction neutralization test and ELISA can differentiate the alphaviruses.
Viruses (noroviruses, hepatitis A virus)	Norovirus: reverse transcription PCR, ELISA on stool samples. Hepatitis A: serology.
Water safety threats (e.g., <i>V. cholerae</i> , <i>C. parvum</i> )	<i>V. cholerae</i> : culture. <i>C. parvum</i> : nested PCR on stool; modified acid-fast stain, antibody staining, and other staining techniques on direct stool smears; serum antibody response.
Protozoa ( <i>C. cayatanensis</i> , <i>G. lamblia</i> , <i>Entameba histolytica</i> , <i>Toxoplasma</i> spp., <i>Microsporidia</i> )	Direct microscopy of stool (wet mounts, stained specimens, and formal-ether concentrations), PCR; ELISA used to detect <i>E. histolytica</i> antigen in stool.
<i>Category C pathogens</i>	
Emerging infectious diseases such as Nipah virus and hantavirus; yellow fever virus, tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus.	Viral culture, PCR, and serology. Yellow fever: virus may be isolated from blood during the first 3 days of illness. Other methods of identification include antigen-capture enzyme immunoassay, probe hybridization, and immunofluorescence assay.
Tick-borne hemorrhagic fever viruses (Crimean-Congo hemorrhagic fever ( <i>Nairovirus</i> -a Bunyaviridae), Omsk hemorrhagic fever, Kyasanur forest disease and Alkhurma viruses.	Viral culture, PCR, serology (ELISA). Quantitative real-time reverse transcription-PCR to measure viral load.
Multidrug-resistant <i>M. tuberculosis</i>	Culture and DNA probe. IFN-gamma-release assay that measures the release of interferon after stimulation in vitro by <i>M. tuberculosis</i> antigens for latent tuberculosis and disease in immune compromised.
SARS virus (SARS-associated coronavirus)	Viral detection via real-time PCR from respiratory samples—only performed by the CDC, serology.
West Nile virus (a Flaviviridae)	
Pandemic and avian influenza (H5N1 influenza)	Viral detection from oropharyngeal aspirate, swab, or lower-respiratory sample. Viral subtyping by PCR by public health laboratories. Rapid immunofluorescence or enzyme immunoassay can differentiate between influenza A and B strains.
Monkeypox virus ( <i>Orthopoxvirus</i> of the Poxviridae family)	Viral culture from skin lesions with real-time PCR to differentiate from other poxviridae (smallpox)—only performed by the CDC or WHO.
Genetically engineered biological weapons	

*Abbreviations:* CDC, Centers for Disease Control; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EEE, eastern equine encephalitis; ELISA, enzyme-linked immunosorbent assay; IHA, indirect hemagglutination assay; LAMP, loop-mediated isothermal amplification; MIF, microimmuno-fluorescent test; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; PCR-EIA, PCR-enzyme immunoassay; WEE, western equine encephalitis; WHO, World Health Organization.

*Source:* From Refs. 1, 6, 11, and 58–71.

**Table 10** Treatment for Adults

Pathogen	Initial treatment prior to availability of susceptibility
<p>Anthrax (<i>B. anthracis</i>)</p> <p style="text-align: center;"><i>Category A pathogens</i></p> <p>Adults, including pregnant patients, with cutaneous disease (also including pregnant patients). Adults including pregnant patients with inhalation, gastrointestinal, oropharyngeal, fulminant bacteremia, or severe systemic or life-threatening disease.</p> <p>Adults including pregnant women with anthrax meningitis.</p>	<p>Ciprofloxacin (400 mg PO b.i.d.) or Levofloxacin (500 mg PO daily) for 60 days. Ciprofloxacin (500 mg IV q12h) is preferred as meningeal is likely, with systemic disease plus one or two other agents (rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin). The addition of clindamycin (900 mg IV q8h) and rifampin (300 mg IV q12h) is recommended. Treat for 60 days. Adjust therapy according to clinical condition. Same as above. Treat for 60 days. Use of steroids may be of benefit, but there are no studies supporting this recommendation.</p>
<p>Botulism (<i>C. botulinum</i> toxin) Plague (<i>Y. pestis</i>)</p>	<p>In case of ingestion, if no contraindication, clear gastrointestinal tract. Trivalent or pentavalent antitoxin. First choice: Streptomycin 30 mg/kg/day (max dose 1 g q12h IM); Alternative agents: Gentamicin 5 mg/kg IM or IV daily or 2 mg/kg loading dose followed by 1.7 mg/kg q8h IV or IM; Doxycycline has been added to gentamicin therapy; or Doxycycline 100 mg IV q12h or 200 mg IV daily; or Chloramphenicol 25 mg/kg q6h IV only; or Ciprofloxacin 400 mg IV daily or 500 mg PO daily. For pregnant patients: Gentamicin 5 mg/kg IM or IV daily or 2 mg/kg loading dose followed by 1.7 mg/kg q8h IV or IM. Cidofovir has been used to treat other poxviridae. Other promising therapy: imatinib mesylate (Gleevec) and other acyclic nucleoside phosphonates analogues.</p>
<p>Smallpox (<i>V. major</i>)  Tularemia (<i>F. tularensis</i>)</p>	<p>In order of preference: Streptomycin 15 mg/kg IV q12h for 10 days; Gentamicin 5 mg/kg IV daily for 10 days; Doxycycline 100 mg IV or PO q12h for 14–21 days (release rate higher); Ciprofloxacin 400 mg IV q12h or 500 mg PO q12h for 14–21 days. Third-generation cephalosporins, clindamycin, cotrimoxazole, and chloramphenicol <i>not</i> recommended.</p>

(Continued)

**Table 10** Treatment for Adults (*Continued*)

Pathogen	Initial treatment prior to availability of susceptibility
Viral hemorrhagic fevers [filoviruses (e.g., Ebola, Marburg) and arenaviruses (e.g., Lassa, Machupo)] Rabies	Supportive therapy and ribavirin.
Brucellosis ( <i>Brucella</i> species)	Supportive care. The "Milwaukee Protocol" (see "Selected Pathogens"). <i>Category B pathogens</i> Doxycycline 100 mg PO b.i.d. (6 wk) plus gentamicin (7 days) or doxycycline as above plus streptomycin 1 g IM daily for 2–3 wk. Alternative therapy: doxycycline as above plus rifampin 600–900 mg PO daily for 6 wk or doxycycline plus cotrimoxazole (160 mg trimethoprim) po qid for 6 wk. Meningitis has been treated with trimethoprim-sulfamethoxazole, rifampin, and doxycycline. Alternative therapy or treatment for pregnant patients: Trimethoprim (6–8 mg/kg/day/sulfamethoxazole (40 mg/kg/day) IV in one or two divided doses followed by the same dose PO plus rifampin 10–15 mg/kg/day in one or two doses followed by 600–900 mg PO daily for 6 wk. Supportive care. Specific antimicrobial therapy as outlined in standard texts.
Epsilon toxin of <i>C. perfringens</i> Food safety threats (e.g., <i>Salmonella</i> spp., <i>E. coli</i> O157:H7, <i>Shigella</i> , <i>Vibrio</i> spp., <i>L. monocytogenes</i> , <i>C. jejuni</i> , <i>Y. enterocolitica</i> ) Glanders ( <i>Bk. mallei</i> )	Supportive care.
Melioidosis ( <i>Bk. pseudomallei</i> )	Septicemic disease is treated intravenously for 2 wk followed by oral therapy for a total of at least 6 mo. Pulmonary disease requires 6–12 mo total therapy. Other severe disease requires 20 wk therapy combining IV and oral medications. Doxycycline plus imipenem recommended for the treatment of severe cases. Consistently susceptible to imipenem. Good in vitro activity for doxycycline and minocycline. Ceftazidime effective but rare isolates have been resistant. Meropenem also recommended for treatment. Amoxicillin/clavulanate, piperacillin, and piperacillin/tazobactam probably effective. All isolates resistant to aminoglycosides, clindamycin, and erythromycin. Intermediate or highly resistant to amoxicillin, ticarcillin, cefoxitin, cefoperazone, cefsulodin, aztreonam, cotrimoxazole, azithromycin, chloramphenicol. 50% of isolates intermediate or resistant to ciprofloxacin, pefloxacin, ofloxacin, and norfloxacin. Quinolones demonstrate poor efficacies for preventing relapses and are not recommended for treatment or prophylaxis.
It should be noted there is a disparity between MICs and susceptibility testing by disc diffusion and clinical response. Time-kill studies, animal response, and clinical experience necessary to validate the use of other antibiotics that show susceptibility. Psittacosis ( <i>C. psittaci</i> )	Doxycycline 100 mg PO b.i.d. for 10–21 days. Azithromycin, chloramphenicol, and selected quinolones may be alternatives.

Q fever (*C. burnetii*)

Susceptible to tetracyclines, macrolides, rifampin, and quinolones. Long-term cotrimoxazole treatment should be used to treat pregnant women with Q fever (320 mg of trimethoprim and 1600 mg of sulfamethoxazole for at least 5 wk of pregnancy. After delivery, patients with "chronic" serologic profiles were treated with a combination of doxycycline; resistant to  $\beta$ -lactams and aminoglycosides.

Clarithromycin and moxifloxacin are adequate alternatives to doxycycline monotherapy. Monotherapy associated with relapses. The addition of rifampin problematic in patients taking anticoagulation. Fluoroquinolone-doxycycline or doxycycline-hydroxychloroquine are two combination therapies that may be superior to monotherapy.

Meningitis: fluoroquinolone.

Endocarditis: doxycycline plus hydroxychloroquine or monotherapy.

Supportive care. In case of ingestion, if no contraindication, clear gastrointestinal tract (gastric lavage and charcoal instillation). Postexposure passive antibody therapy and vaccine in animal experimentation.

Supportive care. In case of ingestion, activated charcoal should be used to bind remaining toxin in gastrointestinal tract.

Underdevelopment: single immunoglobulin-like domain of the T-cell receptor (variable region, V $\beta$ ) protein-binding agent. Doxycycline 200 mg/day for 5–10 days as soon as this diagnosis is suspected.

Supportive therapy. Chloroquine has been shown to inhibit another alphavirus, chikungunya virus. Vaccines have not been approved yet, and monoclonal antibodies have undergone animal studies.

Supportive therapy. Vaccination for hepatitis A. Specific antimicrobial therapy and supportive care.

Category C pathogens

Ricin toxin from *R. communis* (castor beans)

Staphylococcal enterotoxin B

Typhus fever (*R. prowazekii*)

Viral encephalitis [alphaviruses (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis)]

Viruses (noroviruses, hepatitis A virus)

Water safety threats (e.g., *V. cholerae*, *C. parvum*)

Protozoa (*C. cayatanensis*, *G. lamblia*, *E. histolytica*, *Toxoplasma* spp., *Microsporidia*)

Emerging infectious diseases such as Nipah virus and hantavirus; yellow fever virus, tick-borne encephalitis complex (Flaviviridae). Other viruses within the same group are louping ill virus, Langat virus, and Powassan virus.

(Continued)

**Table 10** Treatment for Adults (*Continued*)

Pathogen	Initial treatment prior to availability of susceptibility
Tick-borne hemorrhagic fever viruses (Crimean-Congo hemorrhagic fever), <i>Nairovirus</i> -a Bunyaviridae, Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhurma viruses. Multidrug-resistant <i>M. tuberculosis</i> SARS virus (SARS-associated coronavirus)	Ribavirin.
West Nile virus (a <i>Flaviviridae</i> ) Pandemic and avian influenza (H5N1 influenza)	See Ref. 97. Supportive care. Interferon alpha, pegylated interferon alpha in small series. Steroids may or may not be of benefit. No randomized controlled trials with a specific anti-coronavirus agent have been conducted. Reports using historical matched controls have suggested that treatment with protease inhibitors together with ribavirin, or convalescent plasma-containing neutralizing antibody, could be useful. Ribavirin alone does not appear effective. Presently, no antiviral therapy has proven effective. Supportive therapy. Animal trials with monoclonal antibody appear promising. Minocycline has some <i>in vitro</i> antiviral activity. Vaccination when vaccine becomes available for control. Oseltamivir 75 mg/kg bid for 5 days or Zanamivir two inhalations bid (5 mg) b.i.d. for 5 days. Intravenous formulation of zanamivir 10 mg/kg and at 20 mg/kg in the combined prophylactic and therapeutic groups with both prophylaxis (commencing 12 hr before infection) and therapy (commencing 4 hr after infection) showing similar reductions in viral load in cynomolgus macaque model. Tissue culture studies with chloroquine and IM peramivir in mice appear promising.
Monkeypox virus ( <i>Orthopoxvirus</i> of the Poxviridae family) Genetically engineered biological weapons	Supportive therapy. Cidofovir in animal models. See smallpox.

Abbreviation: MIC, minimum inhibitory concentration.

Source: From Refs. 1, 6, 11, 23, 26, 28, 29, 58–60, and 75–98.

**Assist in the Epidemiologic Investigation and Manage the Psychological Consequences**

The intensive care team will likely be the first caregivers with an opportunity to obtain detailed information from the patient and/or family. Accurate history-taking (food and water sources, occupation, place of employment, travel, modes of travel and commuting, human and animal contacts, etc.) is essential. A comprehensive list of hospital personnel, caregiver, and visitor contacts in the intensive care unit must be compiled as soon as the patient arrives at the institution. Data on ambulance personnel or individuals transporting the patient should be gathered upon the patient's arrival. Protocol should exist detailing the regular and frequent updating of this data, at least for every hospital shift. The number of different caregivers and visitors for the suspect patient should be limited as much as is practical until an etiologic diagnosis is established.

The intensive care unit team must consider the distinct possibility that an early casualty may be one of the perpetrators. Clinical specimens should be clearly labeled and preserved for laboratory examination. Establishment and implementation of protocols for *chain-of-evidence* should be undertaken (99). Usually, the most difficult aspect of chain-of-evidence is identification of the evidence by the individual who collected it.

Clothing and personal items may have already been collected from the patient elsewhere. All clothing and personal items must (i) be considered contaminated, and (ii) must be preserved as possible evidence. Patient specimens for culture and analysis should be treated as evidence. They need to be clearly labeled and initialed by the individual collecting them. Transportation to the laboratory should not be through the routine messenger service, but by a person who is familiar with the chain-of-evidence protocol, and is prepared to document the hand-off to the laboratory personnel. Methods of dealing with the psychological effects of a bioterrorist threat is discussed elsewhere (100).

**Maintain Proficiency and Spread the Word**

Participation in disaster planning and drills is essential for effective and safe treatment of victims of bioterrorism. Your institution's disaster plan should be at hand (1). USAMRIDD's *Medical Management of Biological Casualties Handbook*, 6<sup>th</sup> edition is both concise and a sufficiently comprehensive reference manual that can easily be kept on-hand in clinical areas. It is available online from any computer in the institution with Internet access.

**SELECTED PATHOGENS (58)**

*A single death is a tragedy; a million deaths is a statistic.*  
—Joseph Stalin (December 18, 1878–March 5, 1953)

The illnesses that are most likely to result in the need for "mass" critical care are influenza, severe acute respiratory syndrome (SARS), viral hemorrhagic fevers, smallpox, plague, tularemia, and anthrax. To this list, we add rabies, a pathogen that appears to be little appreciated as a possible bioterrorist's weapon. The virus should be classified as a Category A agent: it is well known to the public, feared, widespread through nature, can be spread person-to-person, may be disseminated by airborne means and through the gastrointestinal tract, has practically a 100% mortality, and rabies vaccination is viewed by the public with great apprehension.

**Influenza and (H5N1) Avian Influenza (37,54,101,102)**

H5N1 avian influenza virus is a single-stranded minus-sense RNA virus of the Orthomyxoviridae genus. Free-ranging waterfowl are the natural reservoir. Most naturally occurring cases involved individuals with direct or indirect contact with poultry. The first cases occurred in Hong Kong in 1997 (18 cases). A second wave of infection occurred in 2001 in poultry, while human cases again occurred in February 2003 (37,101). Human-to-human transmission of this wild-type virus does occur, but very inefficiently (54).

*Incubation period:* The incubation period after contact with a sick or dead bird is two to eight days (54). Patients were ill an average of four days ( $\pm 2.9$  days) before seeking medical care (37).

*Contagious period:* : Duration of illness. The World Health Organization (WHO) and the CDC recommend contact and airborne precautions for all suspected cases (54). Respiratory

protection should be worn and an impermeable gown, face shield, and gloves utilized. Patients should be placed in a negative pressure room with 6 (old standard) to 12 (standard for new construction) air exchanges per hour. Antiviral chemoprophylaxis should be made available to caregivers and family members (54).

*Clinical disease:* There are no clinical or laboratory findings that distinguish avian influenza from other influenza-like illnesses, severe CAP, or ARDS. In naturally occurring disease, only epidemiology hints at the diagnosis (101).

Upon presentation, the mean temperature was 37.8°C (35.8°C to 40°C). Patients were frequently hypotensive and tachypneic (average 35/min: range 15–60/min). Over 90% of patients had either bronchopneumonia or lobar pneumonia. Approximately 15% of patients had pleural effusions. Most patients were young adults. Mortality was approximately 60% to 80% (37,54,101,102). Patients succumb between 4 and 30 days after the onset of symptoms (median: 8 to 23 days) (101). Aerosol-generating procedures should be minimized.

Postmortem examinations reveal disseminated intravascular coagulation (DIC), lymphoid necrosis and atrophy, and diffuse alveolar and multiorgan damage.

*Diagnosis:* Rapid diagnosis by antigen detection or reverse-transcription polymerase chain reaction can be performed on throat swabs or nasopharyngeal aspirates in viral transport media. Antigen detection is accomplished by indirect immunofluorescence, enzyme immunoassays, or rapid immunochromatographic assays. Sensitivity of kits appears to be 33.3% to 85.7% (54).

*Differential diagnosis:* Other forms of CAP.

*Treatment:* Oseltamivir is the drug of choice (75 mg PO b.i.d.) (37,101).

### **SARS and SARS-Associated Coronavirus (103–117)**

SARS is caused by a coronavirus (a large enveloped positive-stranded RNA virus) that has been isolated from live animal market Himalayan palm civets and raccoon dogs, bats, and other animals (Chinese ferret bagger, domestic cats, and pigs). Rats have been experimentally infected and may have been responsible for an outbreak in an apartment complex (103).

From November 1, 2002, through July 31, 2003, there were 8098 SARS cases reported from 29 countries, with 774 deaths (9.6%). Of those cases, 1701 health care workers were infected (21% of cases) (104).

*Incubation period:* Incubation periods have varied depending upon the site of the outbreak (2–16 days, 2–11 days, 3–10 days) (105).

*Contagious period:* Historically, health care settings were important in the early spread of SARS. The risk posed by individual patients is variable. Unrecognized SARS patients were the primary source of contagion (106). Isolation (in a negative-pressure room) should be maintained throughout the course of the patient's illness. Infection control recommendations are complex and outlined by Levy et al. (107). SARS coronavirus may be detected in stools for as long as nine weeks (108).

*Clinical disease:* The severity of clinical disease appears to be related to age and genetic factors (IL-12 RB1 variants, manose-binding lectin polymorphisms, OAS1, MxA gene, interferon gamma gene, RANTES gene, and ICAAM3 gene) (109).

Fever of more than 38°C lasting more than 24 hours is the most frequently encountered symptom. In general, the clinical presentation is varied and nonspecific. At presentation, of five medical centers in Hong Kong and Canada, four reported chills and/or rigors (55–90% of patients); all reported cough (46–100% of patients); four reported sputum production (10–20%); two reported sore throat (20–30%); four reported dyspnea (10–80%); four reported gastrointestinal symptoms (15–50%—most commonly diarrhea); three reported headache (11–70%); all reported myalgia (20–60.9%); and one reported pleurisy (30%) (105). Gastrointestinal symptoms were prominent in U.S. cases (110).

Chest X rays may be normal early in the disease, but abnormal radiographs were present in 78% to 100% of patients. These abnormalities consisted of unilateral disease (54.6%) or multifocal or bilateral disease (45.4%). At one center, the 13% that had normal chest X rays, had abnormal chest CT examinations (105).

Chest X rays in pediatric cases revealed nonspecific findings. In addition to the findings above, peribronchial thickening, and (infrequently) pleural effusion were noted (111).

On presentation, laboratory abnormalities found in some but not all patients include elevated liver enzymes (uncommon to 80%), prolonged APTT, lymphopenia, hyponatremia (20–60%), hypokalemia, thrombocytopenia (33–50%), and hypoxia (104).

From 23% to 34% of patients were admitted to intensive care units. Predictors of mortality were age over 60 years and elevated neutrophil count on presentation. Two institutions reported mortality rates of 12% and 15.7% (105). Mortality rates for SARS patients admitted to an intensive care unit are 34% to 53% at 28 days (112). In the United States, eight cases were identified in 2003, two were admitted to intensive care units, one required mechanical ventilation, and there were no deaths (110).

*Diagnosis:* Immunoswab (monoclonal antibody-based) assay; ELISA, Western Blot, immunodot, immunofluorescent antibody, viral culture and viral neutralization—for confirmation of serology (biosafety level III laboratory required), and reverse transcriptase polymerase chain reaction. Electron microscopy and viral culture are low-sensitivity tests (113).

*Differential diagnosis:* Other bacterial and viral pneumonias, tickborne relapsing fever with ARDS, antiphospholipid syndrome (114,115). SARS should be suspected in patients with no response to therapy in the first 72 hours, especially in the presence of lymphopenia or an absolute low neutrophil count.

*Treatment:* Supportive. It has been recommended that those patients requiring mechanical ventilation should receive lung protective, low tidal volume therapy (116).

There is a higher incidence of pneumothorax in mechanically ventilated SARS patients (20–34%), but the study by Kao et al. found no statistical difference in pneumothorax risk in respirator settings (117).

Steroids may be detrimental and available antivirals have not proven of benefit (107).

### **Viral Hemorrhagic Fevers (6)**

The viral hemorrhagic fever agents principally fall into four families of RNA viruses: the *Arenaviridae* (Argentine, Bolivian, Brazilian, and Venezuelan hemorrhagic fevers and Lassa fever); the *Bunyaviridae* (Hantavirus genus, Crimean-Congo hemorrhagic fever from the *Nairovirus* genus, and Rift Valley fever virus from the *Phlebovirus* genus); the *Filoviridae* (Ebola and Marburg viruses); and the *Flaviviridae* (dengue and yellow fever viruses).

*Incubation period:* Incubation periods for most pathogens are from 7 to 14 days, with various ranges (Lassa fever: 5–21 days; Rift Valley fever: 2–6 days; Crimean-Congo hemorrhagic fever after tick bite: 1–3 days; contact with contaminated blood: 5–6 days); Hantavirus hemorrhagic fever with renal syndrome: 2 to 3 weeks (range: 2 days–2 months); Hantavirus pulmonary syndrome (Sin Nombre virus): 1 to 2 weeks (range: 1–4 weeks); Ebola virus: 4 to 10 days (range 2–21 days); Marburg virus: 3 to 10 days; dengue hemorrhagic fever: 2 to 5 days; yellow fever: 3 to 6 days; Kyasanur forest hemorrhagic fever: 3 to 8 days; Omsk hemorrhagic fever: 3 to 8 days; Alkhumra hemorrhagic fever: not determined. These incubation periods are documented for the pathogens' traditional modes of transmission (mosquito tick bite, direct contact with infected animals or contaminated blood, or aerosolized rodent excreta).

*Contagious period:* Patients should be considered contagious throughout the illness.

*Clinical disease:* Most diseases present with several days of nonspecific illness followed by hypotension, petechiae in the soft palate, axilla, and gingiva. Some patients develop neurologic complications. Patients with *Lassa fever* develop conjunctival injection, pharyngitis (with white and yellow exudates), nausea, vomiting, and abdominal pain. Severely ill patients have facial and laryngeal edema, cyanosis, bleeding, and shock.

Livestock affected by *Rift Valley fever virus* commonly abort and have 10% to 30% mortality. There is 1% mortality in humans with 10% of patients developing retinal disease one to three weeks after their febrile illness.

Patients with *Crimean-Congo hemorrhagic fever* present with sudden onset of fever, chills, headache, dizziness, neck pain, and myalgia. Lymphadenopathy and tender hepatomegaly is present. Some patients develop nausea, vomiting, diarrhea, flushing, hemorrhage, and gastrointestinal bleeding.

Patients with *Hantavirus hemorrhagic fever with renal syndrome* go through five phases of illness: (i) febrile (flu-like illness, back pain, retroperitoneal edema, flushing, conjunctival, and



pharyngeal injection); (ii) hypotensive phase (may range from mild hypotension to shock and hemorrhage lasting for one to two days); (iii) oliguric phase (associated with hypertension, renal failure, pulmonary edema, confusion); (iv) diuretic phase (may last several months); and (v) convalescence. Patients typically have thrombocytopenia, leukocytosis, hemoconcentration, abnormal clotting profile, and proteinuria. Mortality is from 1% to 15%.

*Hantavirus pulmonary syndrome* presents with a prodromal stage (three to five days—range: 1–10 days) followed by a sudden onset of fever, myalgia, malaise, chills, anorexia, and headache. Patients go on to develop prostration, nausea, vomiting, abdominal pain, and diarrhea. This progresses to cardiopulmonary compromise with a nonproductive cough, tachypnea, fever, mild hypotension, and hypoxia. Chest X rays are initially normal but progress to pulmonary edema and acute respiratory distress syndrome. Patients have thrombocytopenia, leukocytosis, elevated partial thromboplastin times, and serum lactic acid and lactate dehydrogenase. Few patients develop DIC.

Patients infected with *Ebola virus* have a sudden onset of fever, headache, myalgia, abdominal pain, diarrhea, pharyngitis, herpetic lesions of the mouth and pharynx, conjunctival injection, and bleeding from the gums. The initial faint maculopapular rash that may be missed in dark-skinned individuals evolves into petechiae, ecchymosis, and bleeding from venepuncture sites and mucosa. Hemiplegia, psychosis, coma, and seizures are common. Mortality rates are 60% to 90%.

*Marburg hemorrhagic fever* is similar with a sudden onset of symptoms progressing to multiorgan failure and hemorrhagic fever syndrome. Some but not all of these patients may present with a maculopapular rash. Mortality is 25% to 90% (average 25% to 30%).

Half of the patients with *dengue hemorrhagic fever* and classical dengue have a transient rash. Two to five days after classical dengue fever, patients go into shock, develop hepatomegaly, liver enzyme elevations, and hemorrhagic manifestations. Patients develop respiratory and renal failure. Mortality is 10% but may be reduced to <1% with aggressive supportive care.

*Differential diagnosis:* Malaria, typhoid, gastroenteritis, meningococemia, etc.

*Treatment* is supportive for all infections. Ribavirin has been used for prophylaxis and treatment of Lassa fever, Sabia virus hemorrhagic fever, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, and Venezuelan hemorrhagic fever. Convalescent serum therapy has been used for Venezuelan hemorrhagic fever. Ribavirin has been used to treat Hantavirus hemorrhagic fever with renal syndrome but does not appear effective in treating Hantavirus pulmonary syndrome. There is no specific therapy for yellow fever, Ebola, or Marburg virus infections. Ribavirin has not shown promise in nonhuman primates (118). Ampligen (polyI:polyC12U) induces interferon production and is being investigated as a treatment modality for dengue, chronic fatigue syndrome, HIV, Epstein-Barr virus-positive Hodgkin's lymphoma, and other entities.

Intravenous ribavirin is twice as effective as oral medication. The intravenous regimen recommended for the viral hemorrhagic fevers is as follows: 2 g loading dose, followed by 1 g every six hours for four days, followed by 0.5 g every eight hours for six days. Another intravenous regimen: 30 mg/kg loading dose, followed by 15 mg/kg every six hours for four days; followed by 7.5 mg/kg every eight hours for six days. Oral regimen: 2 g loading dose, followed by 4 g/day in four divided doses for four days; followed by 2 g/day for six days.

### Smallpox (11)

Humans are the only natural reservoir for smallpox virus (*Poxvirus variolae*, genus *Orthopoxvirus*—a linear, double-stranded DNA virus). Infection is naturally acquired by inhalation. Aerosolized virus is inactivated in 48 hours, but may remain viable in house dust for up to two years. Exposure to contaminated materials, clothing, and blankets can spread infection, and although rare, infection over long distances has been reported.

*Incubation period:* 10 to 12 days; range: 6 to 22 days.

*Contagious period:* Patients are not contagious during the incubation period but one to two days before the onset of symptoms or when the oral enanthema appears (24 hours prior to the rash). Viral shedding is greatest during the first 10 days of the rash, but persists until all scabs and crusts are shed. Infection rates for close contacts are 37% to 88%.

*Clinical disease:* The prodrome begins with the sudden onset of fever, chills, back pain, headache, malaise, and sometimes nausea, vomiting, abdominal pain, and confusion. Diarrhea is less frequent. Children sometimes have seizures. The prodrome usually last two to three days but may be as long as five days. Some patients display a short-lived (12 hours) erythematous or petechial rash.

The typical patient develops a centrifugal rash two to three days after the onset of symptoms or very quickly after the enanthem. *Typical or ordinary smallpox (Variola major)* occurs in the majority of patients. A maculopapular rash first appears on the face, hands, and forearms. Early lesions are shotty and within 24 to 48 hours become vesicular then pustular. The lesions then involve the palms, soles, trunk, and upper thighs. In survivors, the rash crusts and scabs fall off in eight to nine days. Mortality for this form of the disease is 15% to 50%.

*Flat malignant smallpox* (10% to 20% of patients, usually unvaccinated children) present with a severe prodrome, poorly formed papules, and dusky erythema of the face followed by arms, back, and upper chest. The rash may progress to petechiae. Death (45% to 99% of patients) occurs in 7 to 15 days from encephalitis or hemorrhage. Hemorrhagic fulminate smallpox mimics hemorrhagic fever with most patients succumbing in seven days. Mortality rate is 95% regardless of vaccination status. Those who survive to 10 days develop a maculopapular rash.

*Modified smallpox (vaccino-modified, V. minor, alastrim, amaas)* is seen in partially immune patients and patients infected with a less virulent virus. The disease is mild and influenza-like until the rash appears. The rash appears usually three to five days after the prodrome, but may appear later. The course is short, mild, complications are rare, and mortality is very low. Other mild forms of disease include an influenza-like illness and pharyngeal disease that is mild and presents without rash (*variola sine eruptione, variola sine exanthemata*).

*Complications* include encephalopathy, eye complications (10–20% of patients), smallpox (viral) osteomyelitis (*osteomyelitis variolosa*), hemorrhagic disease particularly in pregnant women, fetal death, and premature delivery.

*Differential diagnosis:* Includes acne, chickenpox, drug eruptions, generalized vaccinia or eczema vaccinatum, insect bites, monkeypox, secondary syphilis, vaccine reactions, and viral hemorrhagic fever.

*Treatment* is supportive. Parenteral cidofovir and imatinib mesylate (Gleevec) may have a role in severe cases.

## **Plague (25,26,29)**

*Incubation period:* Bubonic plague (from a fleabite or direct contact of the skin or mucous membrane): two to six days. Primary plague pneumonia from inhalation of infected droplets: one to three days. Septicemic plague may be primary or secondary. Incubation periods for gastrointestinal or pneumonic plague are variable.

*Contagious period:* Antibiotic treatment rapidly reduces contagion.

*Clinical disease:* Patients present with one or more of five clinical syndromes: (i) classic bubonic plague; (ii) septicemic plague; (iii) upper respiratory infections; (iv) nonspecific febrile illnesses, and (v) gastrointestinal or urinary tract infections (95).

### *Bubonic Plague*

Patients present with sudden onset of fever, chills, headache, and malaise. A papule, vesicle, pustule, ulcer, or eschar may be present at the inoculation site. Regional nodes enlarge within 24 hours (1 to 10 cm), are tender, inflamed, and become fluctuant.

### *Septicemic Plague*

The symptoms (fever, chills, malaise, headache, and gastrointestinal symptoms) and signs (tachycardia, tachypnea, and hypotension) of septicemic plague are similar to those of other forms of gram-negative septicemia. One-half of the patients have abdominal pain. Generally, there is a paucity of specific findings. Primary septicemic disease occurs from cutaneous exposure, but without regional lymphadenopathy. Gangrene in the extremities and tip of the nose from small vessel thrombosis occurs (The Black Death).

*Primary pneumonic plague* from inhalation of infected droplets manifests itself with sudden onset of fever, chills, headache, chest pain, shortness of breath, hypoxia, and hemoptysis. Death can occur in the first 24 hours of disease.

*Pharyngitis* from inhalation or ingestion may be asymptomatic (colonization in contacts of patients with plague pneumonia) or present with swollen tonsils and/or inflamed cervical nodes.

*Diagnosis:* Blood and site-specific cultures and direct fluorescent antibody (DFA) testing of tissue or fluids. Real time polymerase chain reaction (PCR) of sputum can rapidly detect organism in the experimental setting.

*Differential diagnosis:* Plague must be differentiated from other forms of sepsis. The differential diagnosis for plague pneumonia includes all causes of bilateral pneumonia, tularemia, Q fever, mycoplasma, Legionnaires' disease (especially in the presence of diarrhea), tuberculosis, fungal infections, and viral pneumonias.

*Treatment:* Streptomycin is the drug of choice. Gentamicin, doxycycline, chloramphenicol, and ciprofloxacin are alternate agents. Treatment is for at least 10 days.

*Prophylaxis (adult dosing):* Prophylaxis should be administered for seven days after the last exposure. The preferred agents are doxycycline (100 mg PO b.i.d.) or ciprofloxacin (500 mg PO b.i.d.).

### **Tularemia (1,30)**

*Incubation period:* The average incubation period after any of the exposures is three to six days (range a few hours to three weeks).

*Contagious period:* Natural infection is acquired by contact with infected animals, especially rodents and rabbits, arthropod, insect and tick bites, inhalation, and ingestion. The organism is not transmitted from person-to-person. Clinical specimens represent a risk. The laboratory must be notified so that no procedures are carried out at an open bench.

*Clinical disease:* Patients present with an abrupt onset of fever, chills, myalgia, headache, and often a dry cough in all forms of the disease. A papular rash or erythema nodosum is common.

#### *Ulceroglandular or Glandular Tularemia*

Papule at site of entry progresses to a slow-healing crusting ulcer with the development of tender regional lymphadenopathy. Glandular tularemia lacks the ulcer.

#### *Oropharyngeal Tularemia*

Occurs after ingestion of contaminated food or water. Patients present with ulcerative tonsillitis or pharyngitis, often unilateral, with regional lymphadenopathy.

#### *Oculoglandular Tularemia*

This is similar to ulceroglandular disease except the primary lesion is in the conjunctivae. There is usually severe unilateral conjunctivitis with enlargement of the preauricular nodes.

#### *Typhoidal Tularemia*

Patients present with the same general symptoms, high fever with relative bradycardia, gastrointestinal symptoms, and pneumonia. There are no focal signs. The disease may be self-limited or a life-threatening sepsis.

#### *Pneumonic Tularemia*

Contracted through inhalation or secondary to sepsis. Patients may have infiltrates, hilar adenopathy, pleural effusions, or necrotizing pneumonia.

*Diagnosis:* Diagnosis is usually confirmed by acute and convalescent serology. PCR, culture, and lymphocyte stimulation testing have also been used to confirm the diagnosis where serology has failed.

*Differential diagnosis:* Pneumonia must be differentiated from CAPs, atypical pneumonias, tuberculosis, psittacosis, Q fever, pneumonic plague, inhalation anthrax, and SARS. Typhoidal disease, especially if prolonged, must be differentiated from other forms of sepsis, including typhoid fever, enteric fever, brucellosis, Legionella, Q fever, disseminated mycobacterial or fungal disease, rickettsial disease, malaria, and endocarditis.

Ulceroglandular disease may be mistaken for *Mycobacterium marinum* or sporotrichosis infections. Because lymphadenopathy may be present without the skin lesion and persist for long periods of time, bacterial infection, cat scratch disease, syphilis, chancroid, lymphogranuloma venereum, tuberculosis, nontuberculous mycobacteria, toxoplasmosis, sporotrichosis, rat-bite fever, anthrax, plague, and herpes simplex must be included in the differential diagnosis.

Oculoglandular disease with predominantly tender preauricular, submandibular, and cervical nodes may be mistaken for mumps.

Pharyngeal tularemia may mimic other forms of exudative tonsillitis (streptococcal, infectious mononucleosis, adenovirus), and diphtheria.

*Treatment:* Streptomycin or gentamicin for 7 to 14 days. Treatment with doxycycline 200 mg PO daily for 14 days is often used in Europe, but the risk of relapse is higher. Fluoroquinolones appear to be efficacious for the subspecies *holarctica* (limited experience). Third-generation cephalosporins clinically fail in spite of in vitro susceptibility testing results. Chloramphenicol is not recommended because of the risk of relapse and hematologic toxicity. The bacterium appears to be resistant to clindamycin and co-trimoxazole.

### **Anthrax (23,27)**

*Incubation period:* *Cutaneous anthrax:* five days (range: 1 to 10 days). Gastrointestinal disease: The precise incubation period is unknown. In one case, symptoms developed 48 hours after consumption of well-cooked meat from an infected cow.

*Contagious period:* Direct contact with skin lesions represents a risk.

*Clinical disease:* *Inhalation anthrax:* In addition to pulmonary symptoms patients more frequently have nausea, vomiting, pallor or cyanosis, diaphoresis, confusion, tachycardia >110 beats/min, temperature >100.9° F, and hemoconcentration. Patients with fulminant disease had 97% mortality. Hemorrhagic meningoencephalitis was present in 50% of autopsy deaths after the accidental release of anthrax in Sverdlovsk.

#### *Hemorrhagic Meningoencephalitis*

Neurologic spread of infection may occur with inhalation disease, cutaneous disease, or gastrointestinal disease. Patients also develop cerebral edema, intracerebral hemorrhages, vasculitis, and subarachnoid hemorrhages. There is 95% mortality *with* treatment.

#### *Cutaneous Anthrax (Also Known as Malignant Pustule)*

This is the most common form of anthrax. It is a consequence of skin contact with anthrax spores. There is localized edema that evolves into a pruritic macule and papule. In 24 hours, this ulcerates and is surrounded by small (1 to 3 mm) vesicles. A painless black eschar with local edema is seen, which eventually dries and falls off in one to two weeks. Sometimes there is lymphangitis and painful local lymphadenopathy. *There is 20% mortality without treatment.*

#### *Gastrointestinal Anthrax*

Presents with severe gastrointestinal symptoms. Patients may succumb from necrotizing enterocolitis with hemorrhagic ascitic fluid.

*Differential diagnosis:* Cutaneous anthrax: plague, tularemia, scrub typhus, rickettsial spotted fevers, rat-bite fever, ecthyma gangrenosum, arachnid bites, and vasculitis.

*Diagnosis:* Blood cultures before antibiotics (growth in 6 to 24 hours). Antibiotics will rapidly sterilize blood cultures. Confirmatory tests by special laboratories are available (special staining, ELISA for protective antigen, gamma-phage lysis, PCR, and real-time PCR).

*Treatment:* Ciprofloxacin or doxycycline for the initial intravenous therapy until susceptibility is reported. Prophylaxis is necessary for those exposed to the spores (usually

for 60 days). Delay in initiating antibiotics in patients with pulmonary disease resulted in a 40% to 75% mortality. Cutaneous disease is usually treated for 60 days.

### **Rabies (119–126)**

*Virology:* Rabies virus is a negative-stranded enveloped lyssavirus (lyssavirus type 1). Classical rabies virus is the only naturally occurring lyssavirus in the western hemisphere. There are seven genotypes and seven serotypes. With the exception of the Lagos bat virus, all have caused human disease. The virus is stable between pH 3 and 11 and will survive for years at  $-70^{\circ}\text{C}$  or when freeze-dried and stored at  $0^{\circ}\text{C}$  to  $4^{\circ}\text{C}$ . Phenol, detergents, and formalin disinfectants inactivate the virus.

*Risk of transmission:* Rabies is commonly transmitted by a bite or lick of a rabid animal. Airborne transmission has been documented in caves and in laboratory incidents. Corneal transplants have been responsible for a number of human-to-human infections. Rabies virus may be transmitted from human to human as the virus has been isolated from saliva, respiratory secretions, sputum, nasal swabs, pharyngeal swabs, eye swabs, tears, cerebrospinal fluid, urine, blood, and serum. Anecdotal reports of rabies transmission by lactation, kissing, a bite, intercourse, providing health care, and transplacental (human) have been reported. Bait laced with attenuated rabies virus has transmitted the infection to animals and the consumption of dying or dead vampire bats has transmitted the infection to foxes and skunks.

Cryptogenic rabies (no evidence or history of an animal bite) represents the largest group of human rabies cases in the United States. Two strains of rabies virus associated with two species of bats rarely found among humans were responsible for the majority of cases. These two strains of rabies virus (*i*) replicate at lower temperatures, (*ii*) easily infect skin because of their ability to infect fibroblasts and epithelial cells, (*iii*) grow in higher titers in epithelial and muscle tissue as compared to dog or coyote street rabies virus, and (*iv*) have changes in the antigenic sites that increases infectivity.

*Incubation period:* The average incubation period (Stage I) is one to two months (range: 4 days to 19 years). Seventy-five percent of symptoms develop 20 to 90 days after exposure.

*Clinical disease: The prodromal period (Stage II) lasts for 10 days.* Patients display anxiety and/or depression. Half the patients have fever and chills and in some patients, gastrointestinal symptoms predominate including nausea, vomiting, diarrhea, and abdominal pain. At the bite site or proximally along the nerve radiation, there is itching, pain, or paresthesia. *Myoedema* (mounding of a part of the muscle when hit with the reflex hammer) may be demonstrated. If present, this sign persists throughout the course of disease.

#### *Symptomatic Rabies (Stage III)*

Symptomatic rabies (stage III) (2–14 days—average survival 5–7 days) manifests itself as furious rabies in 80% of cases. Patients are agitated, hyperactive, waxing and waning alertness, bizarre behavior, hallucinations, aggression, with intermittent lucid periods. There is piloerection, excessive salivation, sweating, priapism, repeated ejaculations, and neurogenic pulmonary edema. *Hydrophobia* begins with difficulty swallowing liquids resulting in pharyngeal and laryngeal spasms and aspiration. As it becomes more severe, the sight of water triggers spasms. *Aerophobia* (spasms triggered by gently fanning the face) is often present. Seizures occur near death.

Presenting symptoms may mimic schizophrenia or delirium tremors.

*Symptomatic dumb or paralytic rabies* patients have a longer average survival (13 days). Patients present with weakness or paralysis in a single limb or may present with quadriplegia. There is pain and fasciculation in the affected muscle groups, and sensory abnormalities in some patients. Some patients have meningeal signs but normal mentation. Cranial nerve abnormalities develop and patients appear expressionless. Twenty percent of patients develop Guillain-Barre syndrome. Some patients survive as long as a month without respiratory support but eventually die with paralysis of respiratory and swallowing muscles.

#### *Coma (Stage IV)*

Coma (stage IV) may occur immediately after symptoms appear or up to two weeks later.

*Recovery or Death (Stage V)*

On average, death occurs 18 days after the onset of symptoms. Patients cared for in intensive care units have survived from 25 days to months with respiratory support. Death in these patients is often from myocarditis with arrhythmia or congestive heart failure.

*Diagnosis:* Nuchal biopsy and saliva—viral antigen and viral RNA can be detected by DFA test and reverse transcription polymerase chain reaction (RT-PCR), respectively (121).

*Differential diagnosis:* Other causes of viral encephalitis, tetanus (when opisthotonos is present), acute inflammatory polyneuropathy, transverse myelitis, and poliomyelitis. When there is a prolonged incubation period, clinical disease may suggest progressive multifocal leukoencephalopathy. Spongiform changes in the brain may resemble prion disease.

*Treatment* in an intensive care unit should be considered if (i) the patient received rabies vaccine before the onset of symptoms, (ii) the patient presents at a very early stage of disease (i.e., paresthesias), (iii) the patient is generally in good health, (iv) the acceptance of the high probability of death or significant neurologic deficits, and (v) availability of adequate resources. Some authors disagree about limiting therapy to cases strictly in the earliest stages (122).

All patients should receive rabies vaccine (human diploid vaccine) and rabies immune globulin (RIG). *All individuals potentially exposed to the virus (including caregivers) should receive both the vaccine and RIG as soon as possible. There is no time limit after exposure that the vaccine and RIG cannot be given! Pregnancy is not a contraindication.* Contacts should be traced to at least one week prior to the onset of neurologic symptoms in order to provide them with prophylaxis.

*Postexposure prophylaxis:* People previously vaccinated against rabies within two years and who have evidence of immunity: 1.0 mL intramuscularly (IM) on days 0 and 3; no human RIG. People not previously vaccinated against rabies 1.0 mL IM (deltoid in adults, anterior lateral thigh in children) on days 0, 3, 7, 14, and 28, plus human RIG (20 IU/kg) within seven days of first vaccine dose. In the absence of documented immunity, the full schedule of postexposure prophylaxis is indicated.

A patient survived rabies without vaccine or RIG after treatment with antiviral agents and induced coma (ketamine, midazolam, ribavirin, and amatadine—the Milwaukee Protocol). She was discharged alert, but with choreoathetosis, dysarthria, and unsteady gait (123). Ketamine-induced coma and ribavirin therapy has failed in other patients (121,124).

Ketamine was administered to one rabies survivor. In the mouse model, ketamine showed no benefit. Minocycline has been suggested as therapy. But, in the mouse model, minocycline appeared to aggravate the disease (125).

A rabies survivor was found to have deficiencies of tetrahydrobiopterin (BH4) and related neurotransmitters. Based upon this finding, investigators monitored flow velocities, and resistive and pulsatility indices of the middle cerebral arteries by transcranial Doppler. Patients with vasoconstriction were treated with nitroprusside, BH4, BH4 and L-arginine (126).

**CONCLUSION**

*Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.*

—Sir Winston Churchill, *Speech in November 1942*

The intensivists participate in all disaster planning and is thoroughly familiar with hospital protocols. What is simultaneously considered after the initial recognition that the patient may be a victim of bioterrorism includes the most likely diagnosis and differential diagnosis, the broadest emergent treatment, identification and prophylaxis of contacts where indicated, and isolation and safety precautions. Other scenarios include: (i) the patient being infected with two or more agents, especially with differing incubation periods; (ii) additional victims presenting similarly but infected with a different pathogen or pathogens as a result of a second simultaneous attack; (iii) a second attack at a later time with the same or different agents; and (iv) genetically altered agents that renders them more resistant to treatment and/or more difficult to identify. An even more sinister possibility is that the hospital (building, buildings, or campus) becomes one of the primary or secondary targets.

Clinicians confronted with the first victims must put themselves into the mind of the enemy. Diagnostic, therapeutic, and infection control decisions must be quickly implemented, and often based upon inadequate data. They should take into account the possibility of a second pathogen in the same patient or different pathogens in subsequent patients early in the outbreak before there is an alteration in the initial and usually most stringent isolation precautions.

Epidemiologic, clinical, laboratory, and historical data on the first patients will often be the key to identifying the pathogen(s), means of distribution, and the culprits responsible. Again, the terrorists may be among the first and most critically ill patients presenting to the intensive care unit.

*Cannon to right of them, Cannon to left of them, Cannon behind them Volley'd and thunder'd;  
Storm'd at with shot and shell, While horse and hero fell, They that had fought so well Came thro' the jaws of Death Back from the mouth of Hell, All that was left of them, Left of six hundred. When can their glory fade? O the wild charge they made! All the world wondered. Honor the charge they made, Honor the Light Brigade, Noble six hundred.*

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*The superior man, when resting in safety, does not forget that danger may come. When in a state of security he does not forget the possibility of ruin. When all is orderly, he does not forget that disorder may come. Thus his person is not endangered, and his States and all their clans are preserved.*

—Confucius (孔夫子:Kǒng Fūzǐ in Hanyu Pinyin)(551–479 BC), from *The Confucian Analects*

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# 26 | Selection of Antibiotics in Critical Care

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## INTRODUCTION

In most hospitals the numbers of immune compromised and acutely ill patients requiring admission to the intensive care unit (ICU) continue to increase. A portion of these patients present with life-threatening community-acquired infections, but all of them are susceptible to hospital-acquired infections on account of such necessary interventions as multiple vascular access lines, hemodynamic monitoring devices, mechanical ventilation, urethral catheterization, surgery, and trauma management. Most ICU patients exhibit at least some manifestations of the systemic inflammatory response syndrome (SIRS), and a fraction of these will have infection (sepsis). Aggressive empiric antimicrobial therapy necessarily becomes an almost routine aspect of ICU care, and indeed has been shown to improve survival. The familiar downsides include adverse drug reactions, colonization, and superinfection by opportunistic pathogens, cost, and—of global importance—emergence of increasingly difficult-to-treat drug-resistant strains. The purpose of this chapter is to review some principles pertaining to antibiotic selection.

## A MULTIDISCIPLINARY TEAM APPROACH

Two organizational trends impact favorably on the potential to make empiric antimicrobial therapy in the ICU more “rational” than it has been in the past. The first of these, encouraged by leaders of the patient safety movement including the Leapfrog Group (a consortium of Fortune 500 companies representing health care purchasers and federal and state agencies), is the trend for ICU patients to be managed by full-time intensivists—that is, physicians with special training and experience in ICU care (1). The second trend, likewise encouraged by the patient safety movement and endorsed by the Infectious Diseases Society of America (IDSA), consists of the increasing role of multidisciplinary teams in various aspects of health care delivery. Such teams enhance the likelihood that the major principles for setting guidelines for antimicrobial use, which have been recognized for several decades, will indeed be honored in practice (2).

The IDSA guidelines for such a multidisciplinary core team call for an infectious diseases (ID) physician, an ID pharmacist, a clinical microbiologist, an information systems specialist, an infection control practitioner, an epidemiologist, and an intensivist, where ICUs are concerned (3). At some institutions, interested ID pharmacists will assume team leadership and at others, it may be the ID physicians or the intensivists themselves (4). Independent of institution setting, endorsement from hospital administration is essential to ensure sufficient authority, define program outcomes, and obtain necessary infrastructure, but the overarching desideratum is to achieve “buy-in” among all prescribing physicians. A multidisciplinary team should focus especially on (i) the evolving medical literature on effective approaches to antimicrobial therapy in the ICU, including new drug developments; (ii) local experience pertaining to ICU pathogens and their antimicrobial susceptibility patterns; and (iii) methods for improving and streamlining prescribing practices. Such methods include computer-based surveillance, formulary restriction and preauthorization, prospective audit with intervention and feedback, and continuing medical education (3,5).

## AGGRESSIVE INITIAL EMPIRIC ANTIMICROBIAL THERAPY

Today's mantra for antimicrobial prescribing in the ICU reads: "Hit early, hit hard, and then de-escalate." Aggressive initial therapy correlates with survival. Limiting the duration of broad-spectrum therapy reduces the likelihood of drug-resistant pathogens not only for the patient being treated but also for the ICU, the hospital, and even for society as a whole.

Numerous studies over the past two decades demonstrate that inadequate antimicrobial therapy leads to increased mortality, prolonged lengths of stay, and poorer outcomes (6–9). Results of a study involving more than 600 patients indicated that the survival rate decreased by 7.6% for every one-hour delay in treatment (8). Prior to the year 2000, investigations of the effect of initial "appropriate" antimicrobial therapy [usually defined by the use of agents to which the eventual pathogen(s) were determined to be susceptible] focused mainly on bloodstream infections, which allow easy retrospective analysis based on "clean" bacteriologic specimens. Such studies amply confirmed lower mortality rates for patients who received appropriate initial antimicrobial therapy (10,11). More recent data extend these observations to patients with ventilator-associated pneumonia (VAP) and sepsis. The Monoclonal Anti-TNF: A Randomized Clinical Sepsis (MONARCS) trial was conducted in 157 centers across North America to assess the safety and efficacy of afelimomab (a TNF- $\alpha$  blocker) in sepsis. Out of a total of 2634 patients enrolled, 91% got adequate antibiotics. The most common gram-positive organisms were *Staphylococcus* spp. and *S. pneumoniae*, and the most common gram-negative pathogens were *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*. Overall mortality rate was 34%; the breakdown was 33% and 43% for patients who got adequate and inadequate antibiotics, respectively (12). Another Sepsis trial from Spain found excess in-hospital mortality of 39% with inadequate initial treatment. There was also an increase in ICU and hospital length of stay (9).

Factors to consider when prescribing initial empiric antimicrobial therapy include the following (Table 1):

1. *The duration of hospitalization and recent antimicrobial exposure:* Patients who have been hospitalized for less than 48 hours and who have not had recent exposure to antibiotics are more likely to have typical "community-acquired" pathogens. Common examples include *Streptococcus pneumoniae* and *Haemophilus influenzae* in pneumonia, *E. coli* in urinary tract infection (urosepsis), and *S. aureus* [both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) *S. aureus*] in endocarditis or undifferentiated sepsis syndrome. Patients who have been hospitalized for longer durations and who have received multiple prior antibiotics should receive appropriate treatment for drug-resistant gram-negative bacilli, MRSA, and—if the clinical setting "fits"—anaerobic pathogens. The guidelines of the American Thoracic Society and the IDSA for the management of health care-associated pneumonia (HCAP) suggest that risk factors for multidrug-resistant (MDR) pathogens are antimicrobial therapy within the last three months, current hospitalization for more than five days, immune suppression, local epidemiological data suggesting a high frequency of antibiotic resistance in the community, and risk factors for HCAP (13). The recommended regimens include an aminoglycoside or an antipseudomonal fluoroquinolone and an appropriate  $\beta$ -lactam—if extended-spectrum  $\beta$ -lactamase (ESBL) or MDR pathogens are suspected, then a carbapenem—and treatment for MRSA if the latter is suspected. Critically ill patients are also at risk for yeast infections, with reported rates of 1% to 2% of invasive candidiasis, although it still remains unclear whether to prescribe empiric antifungal drugs in the nonneutropenic patient (14). In a recent study of 270 adult ICU patients with fever despite broad-spectrum antibiotic therapy, empiric use of fluconazole did not improve the stated outcome compared with placebo, but reduced the incidence of candidemia in the treated population (15).
2. *The clinical syndrome:* Pneumonia in patients who have been hospitalized for more than 48 hours is most often due to gram-negative bacilli including *P. aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, but can also involve gram-positive pathogens including MRSA. Urosepsis in patients with prolonged hospitalization is commonly due to gram-negative bacilli. Patients who lack an obvious source of infection are classified as having "primary bacteremia (or fungemia)," which is most

**Table 1** Empiric Antibiotic Selections in ICU

Site	Abdomen		Blood	Central nervous system		Lung		Skin	Urine
	Peritonitis	Sepsis ± shock		Bacterial meningitis <sup>a</sup>	Posttrauma	CAP	HCAP		
Potential pathogens	<i>S. pneumoniae</i> Enterococcus Enterobacteriaceae <sup>b</sup> <i>P. aeruginosa</i> <sup>f</sup>	<i>S. aureus</i> Coag (-) <i>Staphylococcus</i> <i>S. pneumoniae</i> <i>E. coli</i> <i>P. aeruginosa</i> Other gram (-)	<i>S. pneumoniae</i> <i>N. meningitidis</i>	<i>S. pneumoniae</i> <i>S. aureus</i> <i>P. aeruginosa</i> Coag (-) <i>Staphylococcus</i>	<i>S. pneumoniae</i> <i>H. influenzae</i> Atypical	<i>S. aureus</i> <i>P. aeruginosa</i> Other gram (-) <i>S. pneumoniae</i>	Grp. A <i>Streptococcus</i> <i>S. aureus</i> <i>C. perfringens</i> Gram (-) Polymicrobial	<i>Enterococcus</i> Enterobacteriaceae <sup>b</sup> <i>Staphylococcus</i> <i>P. aeruginosa</i>	
Piperacillin/tazobactam <sup>\$\$</sup>						Add vancomycin or linezolid for MRSA	Add clindamycin <sup>d</sup> for toxin production		
Carbapenems <sup>e, f, \$\$-\$\$\$</sup>			Add vancomycin for <i>S. pneumoniae</i>	Add vancomycin for MRSA		Add vancomycin or linezolid for MRSA	Add clindamycin <sup>d</sup> for toxin production		
Fluoroquinolones <sup>g, \$</sup>	Add metronidazole unless moxi used	In combination with gram (+) agent			Except ciprofloxacin	Combination <sup>h</sup>		Except moxifloxacin	
Aminoglycosides <sup>g</sup>	Combination <sup>h, i</sup>	Combination <sup>h, i</sup>				Combination <sup>h, i</sup>		Combination <sup>h, i</sup>	
Ceftriaxone <sup>g</sup>			Add vancomycin for <i>S. pneumoniae</i>		Add azithromycin				

(Continued)

**Table 1** Empiric Antibiotic Selections in ICU (Continued)

Site	Abdomen	Blood	Central nervous system		Lung		Skin	Urine
	Peritonitis	Sepsis ± shock	Bacterial meningitis <sup>a</sup>	Posttrauma	CAP	HCAP	cSSTI	Complicated UTI
Cefepime <sup>\$</sup>				Ceftazidime may be substituted for cefepime add vancomycin for MRSA		Add vancomycin or linezolid for MRSA		
Tigecycline <sup>\$\$</sup>								
The following drugs have effective gram-positive coverage only and should be combined with an agent appropriate for the clinical setting								
								If MRSA is suspected

Shaded boxes represent approved/recommended indications.

<sup>a</sup>Add ampicillin if *Listeria monocytogenes* meningitis is suspected.

<sup>b</sup>Enterobacteriaceae include *Escherichia coli*, *Klebsiella* sp., *Proteus* sp., and *Enterobacter* sp.

<sup>c</sup>*Pseudomonas aeruginosa* is a potential pathogen in secondary peritonitis.

<sup>d</sup>Rationale for clindamycin is suppression of toxin production in *Streptococcus pyogenes* infection.

<sup>e</sup>Imipenem and meropenem are interchangeable; however, imipenem has a slightly increased risk for precipitating seizures.

<sup>f</sup>Doripenem is an emerging carbapenem with activity similar to meropenem, but currently is only approved for complicated UTI and intra-abdominal infections.

<sup>g</sup>Ciprofloxacin is inadequate monotherapy for *Staphylococcus pneumoniae*, but maintains a more favorable AUC/MIC ratio for *P. aeruginosa*.

<sup>h</sup>Use in combination with agent appropriate for clinical setting.

<sup>i</sup>Combination therapy with aminoglycosides, although potentially nephrotoxic, remains controversial but may be useful in empiric treatment in critically ill.

<sup>j</sup>Use when resistant gram-positive pathogen(s) suspected.

**Abbreviations:** ICU, intensive care unit; CAP, community-acquired pneumonia; HCAP, health care-associated pneumonia; cSSTI, complicated skin and soft tissue infection; UTI, urinary tract infection; moxi, moxifloxacin; MRSA, methicillin-resistant *S. aureus*. \$, \$\$, \$\$\$, approximate relative cost, ranging from least expensive (\$) to most expensive (\$\$\$).

- commonly due to vascular access lines. Gram-positive cocci including methicillin-resistant coagulase-negative staphylococci (MRSE), MRSA, gram-negative rods, and yeasts (notably, *Candida* spp.) are the usual culprits.
3. *The severity of the patient's underlying illness*: Studies in the older literature classified patients' underlying illnesses as "rapidly fatal" (that is, likely to result in death during the present hospitalization), "ultimately fatal" (that is, likely to result in death within 5 years), and "nonfatal." Dating to the landmark 1962 paper by McCabe and Jackson, such studies demonstrated a powerful effect of underlying illness on mortality rates, especially from sepsis due to gram-negative bacilli (16). More recent studies extend those observations using newer tools, notably the APACHE II and SOFA scoring systems for disease severity (17). The take-home point is that one should err toward broader-spectrum empiric therapy for patients with serious underlying diseases on account of the smaller margin for error.
  4. *Local epidemiology and antibiotic susceptibility data*: There are data to indicate that prescribing by an "on-call" infectious diseases specialist correlates with appropriate prescribing (in one study, 78% vs. 54% for other physicians) and improved survival (18). Infectious diseases specialists presumably performed better by dint of greater awareness of the most likely pathogens and their susceptibilities. The question arises whether this benefit might likewise be achieved through greater awareness of local epidemiology and antimicrobial susceptibility data, informed by knowledge of the most likely pathogens for this or that disease syndrome. Such local data on resistant pathogens is now being taken into account in computer-based prescribing tools tailored to individual hospitals and ICUs. Even traditional workhorses such as piperacillin/tazobactam and to some extent the carbapenems are now facing resistant bacteria. In a recent article from France, 16% of *E. coli* isolates from clinically relevant specimens were resistant or intermediate to pip/tazo (10). High-level penicillinase production was the main mechanism of resistance, and prior amoxicillin therapy was a risk factor.

Trouillet et al. identified the following significant independent factors for piperacillin-resistant VAP: presence of an underlying fatal medical condition, previous fluoroquinolone use, and initial disease severity (19). The antimicrobial resistance rates among gram-negative bacilli in ICUs across the United States were evaluated in a Merck-sponsored database. During the 12-year period from 1993 to 2004, 74,394 gram-negative bacillus isolates were evaluated. The organisms most frequently isolated were *P. aeruginosa* (22.2%), *E. coli* (18.8%), *Enterobacter cloacae* (9.1%), *Acinetobacter* spp. (6.2%), and *Serratia* (5.5%). The investigators found a greater than fourfold increase in the prevalence of multidrug resistance (defined as resistance to at least one extended-spectrum cephalosporin, one aminoglycoside and ciprofloxacin) for *P. aeruginosa* and *Acinetobacter* spp. (20).

5. *Cost*: Cost becomes a relatively minor consideration when a patient's life is at stake. Moreover, the cost of antimicrobial agents is relatively minor compared to the cost of other modalities (including newer biological agents such as activated protein C) and the total cost of ICU stay. Nevertheless, the cost of antimicrobial therapy is far from trivial and, moreover, newer agents can be extremely expensive compared with the tried-and-true old standbys. Examples include the cost of linezolid or daptomycin versus generic vancomycin for MRSA and MRSE infections and the cost of lipid formulations of amphotericin B versus amphotericin B deoxycholate. It therefore behooves prescribing physicians to be broadly familiar with which agents are the most cost-effective. Many hospitals provide this information in a general way (e.g., \$, \$\$, \$\$\$, or \$\$\$\$), since indicating the exact cost presents problems for both the hospital and the prescriber.

#### **DE-ESCALATION: LIMITING THE DURATION OF BROAD-SPECTRUM THERAPY**

Except in the direst emergencies, appropriate specimens should be obtained for cultures before instituting empiric antimicrobial therapy. While a thorough discussion of appropriate



microbiologic specimens is beyond the scope of this brief chapter, the following should be mentioned:

- *Suspected line sepsis*: A decision must be made whether to remove one or more vascular access devices or to rely on clinical observation combined with “through-the-line” blood cultures obtained simultaneously with blood cultures drawn by venepuncture.
- *Suspected ventilator-associated pneumonia*: Data based on specimens obtained by bronchoscopy, using either bronchoalveolar lavage or bronchial brushing, have added enormously to our understanding and treatment of VAP. Whether such specimens should be part and parcel of routine ICU practice remains controversial.
- *The obtunded patient*: One should remember the possibility of meningitis and/or encephalitis, and the old adage “if you think of a lumbar puncture then do one” still remains true.
- *Blood cultures*: Scrupulous collection technique is required especially to avoid unnecessary treatment of contaminating microorganisms, most commonly coagulase-negative staphylococci (usually, MRSE). Through-the-line cultures are to be discouraged except for diagnosis of line sepsis, as mentioned above. At least two cultures should be obtained.

Pretreatment cultures provide much of the basis for subsequent simplification.

In 1977, Lowell Young and his colleagues proposed “the rules of three” for bloodstream infections (21). They pointed out that if three blood cultures have been obtained and that if at the end of all three days these specimens remain sterile, it becomes progressively unlikely that bloodstream infection will be documented by those specimens. This rule takes advantage of the relatively rapid isolation of most aerobic pathogens. With only rare exceptions, such as the “HACEK” organisms (certain fastidious gram-negative rods that occasionally cause infective endocarditis) and *Brucella* spp., this rule applies to most organisms likely to be encountered in the ICU, including yeasts. Numerous studies confirm this clinical insight. Indeed, one can argue that improvements in microbiologic techniques now mandate a revision to “the rules of two.” One could make a case for “a rule of one,” and it is certainly conceivable that, at some point during the 21st century, molecular techniques will make it possible to rule in or out various pathogens within a matter of minutes.

De-escalation therapy has been best studied in the case of VAP. VAP, discussed at length elsewhere in this volume, constitutes the single-most common cause of death from hospital-acquired infection. Serial studies of respiratory secretions from patients on ventilators commonly reveal an all-too-familiar “parade of pathogens” whereby increasingly difficult-to-treat bacteria emerge during therapy, prompting “spiraling empiricism” in the use of increasingly broad-spectrum and potentially toxic agents. For effecting what amounts to a revolution in our approach to VAP, due credit must be given to the French workers who championed the use of bronchoscopy to obtain specimens for bronchoalveolar lavage (BAL) or the protected specimen brush (22).

Mention will be made here of two studies from the substantial and growing literature on de-escalation therapy for VAP, based, at least in part, on specimens obtained by bronchoscopy. Singh and colleagues conducted a study whereby patients with less extensive evidence of pulmonary infection were randomized to receive standard care (antibiotics for 10–21 days) or to be reevaluated after three days. Patients who were reevaluated at three days experienced similar mortality but were less likely to develop colonization or superinfection by resistant organisms (15% vs. 35%,  $p = 0.017$ ) (23). Rello and colleagues made a practice of reevaluating patients after two days of therapy, taking into account clinical improvement and culture results. Approximately 40% of their 115 patients were on a trauma service. More than one-half (56%) of their patients had their therapy modified, and the ICU mortality rate was significantly lower (18% vs. 43%,  $p < 0.05$ ) in patients whose therapy was modified (24).

The concept of de-escalation and also of limiting the duration of antibiotic therapy to seven or eight days for uncomplicated VAP (and other HCAPs) has now been endorsed by the American Thoracic Society (13). Current and future investigators will no doubt take advantage of evolving diagnostic techniques to refine and extend these recommendations to most, if not all, ICU infections.

## DOSE OPTIMIZATION

A working knowledge of antimicrobial pharmacokinetics and pharmacodynamics is required for appropriate antimicrobial selection and dosing within an ICU. Simply put, pharmacokinetics may be defined as “how the body affects the administered drug” and pharmacodynamics can be viewed as “how the administered drug affects the body.”

Pharmacokinetic analysis involves four elements: absorption, distribution, metabolism, and elimination (ADME), each of which is typically altered in the critically ill. Collectively, such alterations influence serum and tissue drug concentrations, time to maximum concentrations, volumes of distribution, and serum half-lives. Impaired gastrointestinal motility and incompatibilities with enteral nutrition result in unreliable drug bioavailability following oral administration, and therefore intravenous (IV) routes for antibiotic administration should be used initially. Studies demonstrate that timely and appropriate conversion to oral route of administration can reduce length of stay, costs, and potential complications due to IV access (25–27). Changes in drug distribution may be observed as a consequence of fluid shifts, shifts in blood flow, and altered protein binding. Shifts in blood flow may also interfere with drug metabolism and renal function. Renal elimination serves as the primary route of elimination for many antibiotics, and renal insufficiency is often observed in the critically ill; therefore, dose adjustments should be performed and reassessed periodically in this patient population. Careful attention to dosing is crucial during continuous renal replacement therapy (CRRT) and hemodialysis (28).

From the minimum inhibitory concentration (MIC) against a specified microorganism, the peak serum level after a dose ( $C_{\max}$ ), and the magnitude and duration of serum levels over time after a dose (area under the curve, or AUC), we can derive three key relationships:  $C_{\max}/\text{MIC}$  (the “kill ratio”);  $T > \text{MIC}$  (the amount of time during which the serum level exceeds the MIC after a dose); and  $\text{AUC}/\text{MIC}$  (the relationship between the magnitude and duration of serum levels and the MIC). These relationships, and also tissue distributions at target sites, affect dosing strategies.

Two important pharmacodynamic factors influencing antimicrobial efficacy include (i) the duration of time that target sites are exposed to the administered antimicrobial and (ii) the drug concentration achieved at these sites. On the basis of these factors, patterns of antimicrobial activity are defined as “time dependent” or “concentration dependent.” For example, the  $\beta$ -lactam class exhibits time-dependent bacterial killing, and as a result, many clinicians use continuous or prolonged infusions in an effort to decrease peak concentrations and maintain appropriate drug concentrations for longer durations of time. A study investigated the impact of infusion times of doripenem on target attainment ( $T > \text{MIC}$  40% for carbapenems) for various MIC values. Prolonged infusions, using the same daily dose, were effective in achieving target attainment in organisms with increased MICs (29).

For concentration-dependent agents, dosing strategies can be optimized by administering increased doses such that increases in  $C_{\max}$  and AUC are achieved. The aminoglycosides are concentration-dependent killers ( $C_{\max}/\text{MIC}$  ratio of 8 to 10) and dose optimization can be achieved with extended-interval dosing of these agents while reducing potential for nephrotoxicity (30,31). More recently, the standard dose of levofloxacin, for most indications, has increased from 500 to 750 mg once daily in an effort to elevate  $C_{\max}$  and AUC values with this concentration-dependent anti-infective.

An understanding of pharmacokinetic and pharmacodynamic (PK/PD) parameters, the importance of target attainment, and awareness of the changes among PK/PD parameters in the critically ill are crucial for dose optimization and should be incorporated into antimicrobial guideline development in ICUs.

## DRUG THERAPY

Vancomycin is a bactericidal glycopeptide that treats most gram-positive pathogens including MRSA. In spite of tons of vancomycin being used in clinical settings, there are only seven reported cases of vancomycin-resistant *S. aureus* (VRSA). However, over the last few years there have been accumulating data that the usefulness of this drug is steadily decreasing. In a recent practice statement in Clinical Infectious Diseases, the authors even go so far as to say that vancomycin is obsolete, although most clinicians feel this is a premature generalization (32). The steadily increasing MICs (the “MIC creep”) for MRSA and clinical failure with MIC

values greater than 4 µg/mL have led the Clinical and Laboratory Standards Institute to lower the MRSA vancomycin susceptibility breakpoint MIC to 2 µg/mL. Although vancomycin penetrates into the CSF, lung tissue, as well as other body tissues, the levels achieved are variable and therefore higher troughs of 15 to 20 µg/mL are recommended in serious infections like endocarditis and meningitis. Overall incidence of nephrotoxicity from vancomycin alone remains low, and occurs in 1% to 5% of patients, but is clearly augmented by other concomitant nephrotoxic agents.

Linezolid is a bacteriostatic oxazolidinone that exhibits activity against a number of gram-positive pathogens including MRSA, coagulase-negative staphylococci, and vancomycin-resistant *Enterococcus faecium*. It has shown superiority over vancomycin in pneumonia due to MRSA (33). Nausea, headache, and thrombocytopenia are the major side effects, the latter usually occurring about two weeks into therapy. There are increasing reports of linezolid resistance emerging during therapy in *E. faecium*, *S. aureus*, and coagulase-negative staphylococcus infections (34,35).

Daptomycin is a bactericidal lipopeptide whose spectrum of activity includes most aerobic gram-positive organisms including MRSA and VRE. It is comparable to vancomycin for *S. aureus* bacteremia, including that associated with right-sided endocarditis (36). There is, however, concern about increasing MICs while on prolonged treatment, and subsequent potential for development of resistance. The recommended dose for skin and soft tissue infections (SSTIs) is 4 mg/kg/day and 6 mg/kg/day in bacteremia. The dose should be administered every 48 hours if the creatinine clearance is <30 mL/min. Daptomycin's adverse event profile involves an elevation in the serum creatine phosphokinase, and levels should be monitored weekly during therapy.

The carbapenems are β-lactam agents with broad antimicrobial activity including *Pseudomonas* spp., MSSA, ESBL-producing strains of *Klebsiella*, and anaerobes. Meropenem and imipenem are more or less equivalent; however, ertapenem lacks activity against *Enterococcus* and *Pseudomonas*, and none of the carbapenems cover MRSA or VRE. Doripenem is a newer agent that apparently has better activity against *Pseudomonas*. There are reports of carbapenem resistance among *Klebsiella* spp., especially as these drugs are being used with increasing frequency as empirical treatment in the critically ill patient.

Piperacillin/tazobactam is a penicillin derivative with an antimicrobial spectrum similar to the broad-spectrum carbapenems and can be used as empirical treatment for HCAP, sepsis, intra-abdominal infections, and SSTIs. As it is a time-dependent killer, prolonged infusions over four hours can overcome intermediate MICs.

The fluoroquinolones are agents with a broad range of activity. However, there are important interclass differences including decreased activity of ciprofloxacin against *S. pneumoniae* and enhanced anaerobic activity of moxifloxacin. In general, the fluoroquinolones should not be used as monotherapy for serious staphylococcal infections.

Cefepime is a fourth generation cephalosporin that may be used in HCAP, sepsis, meningitis, and febrile neutropenia. Ceftobiprole, a "fifth" generation cephalosporin, has an increased affinity to penicillin-binding proteins in MRSA and penicillin-resistant *Str. pneumoniae* strains, resulting in bactericidal activity against both these pathogens. In addition, ceftobiprole demonstrates activity against vancomycin-intermediate and vancomycin-resistant *S. aureus*. Ceftobiprole has good in vitro activity against Enterobacteriaceae. The main adverse effects associated with ceftobiprole are nausea and taste disturbance, and currently it is only approved for complicated skin and soft tissue infections (cSSTIs).

Aminoglycosides like gentamicin and tobramycin are agents with gram-negative coverage and may be used as combination therapy for the "septic" patient until the susceptibility patterns are available for therapy de-escalation. The main side effect is nephrotoxicity, which can be diminished by extended-interval dosing as described above (except when used for synergistic dosing in enterococcal and staphylococcal infections, burns, pregnancy, or pediatric patients).

Tigecycline is a tetracycline derivative that has activity against MRSA, VRE, gram-negative pathogens including *Klebsiella* spp. and *Acinetobacter* and anaerobes. However, it lacks activity against *Pseudomonas*, is a bacteriostatic drug, and is currently only approved as

monotherapy for cSSTI and intra-abdominal infections. There are also concerns about emerging resistance.

Colistin use is seeing a reemergence as ICUs battle increasingly resistant *Acinetobacter* and *Pseudomonas*. Its utility is limited by its significant risk of nephrotoxicity.

### ANTIBIOTIC CYCLING

We will make only brief mention of the concept of antibiotic cycling, since this practice continues to be of unproven merit at the time of this writing. Antibiotic cycling involves rotating the standard empiric therapy regimens in an ICU, usually every several months, with the aim of reducing the emergence of drug-resistant pathogens. Several studies conducted around the turn of the 21st century suggested great promise to this approach. In 2001, Raymond and colleagues reported that rotating empiric regimens even at one-year intervals might be beneficial (37). However, questions remained, and it was currently felt that the evidence is insufficient to recommend this practice as a routine measure (8,38).

### SUMMARY

In light of the continuous evolution of drug-resistant and MDR pathogens, limited numbers of anti-infectives in the pipeline, and an increasing severity of illness among the ICU patient population, special attention toward appropriate antibiotic selection is of utmost importance. As we discussed in this chapter, prompt empirical therapy based on host factors and local epidemiological data reduces morbidity and mortality; however, clinicians must be mindful that their duty as stewards of our antimicrobial armamentarium does not end with the initial selection. Providers must reassess antibiotic regimens on a regular basis for early de-escalation to definitive therapy, dose optimization, compatibilities, untoward drug events, intravenous to oral conversions, and importantly, therapy duration.

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# 27 | Antimicrobial Therapy of VRE and MRSA in Critical Care

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## INTRODUCTION

### Group D Enterococci

Aerobic streptococci are classified via the Lancefield typing system, i.e., group A, B, C, G, or D streptococci. Group D streptococci may be further subdivided as enterococcal or non-enterococcal group D streptococci. The most important non-enterococcal group D streptococcus is *Streptococcus gallolyticus* (*S. bovis*), which is ordinarily not an important pathogen in the critical care setting. Group D enterococci, however, are the predominant streptococcal pathogens encountered in critical care. Group D enterococci reside in the hepatobiliary and gastrointestinal tracts. Group D enterococci are relatively noninvasive with a pathogenicity that is intermediate between methicillin-sensitive *Staphylococcus aureus*/methicillin-resistant *Staphylococcus aureus* (MSSA/MRSA) and coagulase-negative staphylococci (CoNS). Because group D streptococci colonize the terminal colon, they are frequent colonizers of the urinary tract. Group D enterococci primarily colonize the hepatobiliary/gastrointestinal tract and are frequent secondary colonizers of bile, wounds, and urine (1).

The two most important group D enterococcal pathogens are *Enterococcus faecalis* and *Enterococcus faecium*. *E. faecalis* almost always is susceptible to vancomycin and so may also be termed vancomycin-sensitive enterococci (VSE). In contrast, *E. faecium* is uniformly resistant to vancomycin and may be termed vancomycin-resistant enterococci (VRE). As with MSSA/MRSA, VSE/VRE isolates are equally virulent and have the same clinical spectrum of infection. The only difference between VSE and VRE, as with MSSA and MRSA, is antibiotic susceptibility. Unlike with MRSA, in vitro susceptibility to VSE/VRE as with MSSA correlate with in vivo effectiveness. The clinical spectra of VSE/VRE infections include catheter-associated bacteriuria (CAB), urinary tract infections (UTIs; cystitis, pyelonephritis), biliary tract infections (cholecystitis, cholangitis), hepatic infections (copathogen in liver abscesses), intra-abdominal/pelvic pathogens (copathogen in peritonitis, abscess), central venous catheter (CVC) infections, and subacute bacterial endocarditis (SBE). Ordinarily VSE/VRE are not pathogens in CNS infections, pneumonias, skin/soft tissue infections, or bone/joint infections. Isolation of VSE or VRE as a single pathogen in blood cultures should suggest biliary tract infection, UTI, or SBE. Group D streptococci, occurring in blood cultures as part of a polymicrobial infection should suggest a gastrointestinal source. Excluding intravascular and intra-abdominal infections between the gallbladder and the urinary bladder, group D enterococci should be regarded as "permissive pathogens." As mentioned above, VSE/VRE may be pathogenic alone in infections of the biliary tract, urinary tract, or intravascular infections. Excluding CVC infections, unlike staphylococci, group D enterococci are rarely, if ever, associated with device-related infections (1).

Selection of antimicrobial therapy of VSE/VRE infections depends on the susceptibility of the isolate host factors (allergy history, renal/hepatic function, site of infection, etc.). The duration of therapy depends on the type/site of infection and varies from one to two weeks for hepatobiliary or intra-abdominal infections to four to six weeks for SBE. Because group D enterococci are copathogens in intra-abdominal/pelvic abscesses, surgical drainage is the most important therapeutic intervention in these infections (1).

## Staphylococci

The most important gram-positive coccal pathogens in critical care are staphylococci and group D enterococci. For clinical purposes, staphylococci may be subdivided into MSSA, MRSA, or *S. epidermidis*, also known as CoNS. *S. epidermidis* (CoNS) are relatively avirulent pathogens and are common colonizers of the nares/skin. Because of their lack of invasive potential, CoNS are associated only with infections that are device related, i.e., prosthetic joint infections, CVC infections, pacemaker/pacemaker generator/pacemaker-lead infections, intracardiac prosthetic materials, prosthetic joints, or prosthetic heart valves.

*S. aureus*, either of the MSSA or MRSA variety, are common colonizers of the skin, but have invasive capability and are highly virulent organisms if treated early and with appropriate antibiotics, the clinical spectrum of infection and virulence potential and outcomes are the same for MSSA and MRSA. Some clinicians have difficulty in determining what is appropriate/effective antimicrobial therapy for MRSA infections if antibiotic selection is based on *in vitro* susceptibility testing. Unlike MSSA, *in vitro* susceptibility testing for MRSA does not correlate well with *in vivo* clinical effectiveness. MRSA isolates are often reported as susceptible to fluoroquinolones or cephalosporins, but these agents are ineffective against MRSA *in vivo*. The spectra of staphylococcal infections due to MSSA/MRSA are skin/soft tissue infections, device-associated infections (as with CoNS *vide supra*), acute bacterial endocarditis (ABE), and community-acquired pneumonia (CAP) only if superimposed on underlying influenza/influenza-like illnesses (ILIs). An intravascular source of staphylococci may metastatically spread to body sites, such as the CNS (brain abscess, meningitis), the kidneys (renal abscess, perinephric abscess), or lungs (abscess), that are not normally infected by staphylococci. Staphylococci are not usual hepatobiliary, gastrointestinal, or urinary tract pathogens (1).

Antimicrobial therapy of staphylococcal infections depends on the isolate susceptibility (CoNS, MSSA, but not MRSA) and host factors (allergy history, renal/hepatic function, site of infection, etc.). Duration of therapy depends on the type/site of infection ranging from one to two weeks of therapy for skin/soft tissue infections to four to six weeks for ABE or osteomyelitis. Clinically, in addition to appropriate/effective antimicrobial therapy, device-associated infections due to CoNS or MSSA/MRSA usually require removal of the device for cure (1).

## ***Enterococcus faecalis* (VSE) and *Enterococcus faecium* (VRE)**

### *Clinically Relevant Microbiology of VSE/VRE*

Group D streptococci are classified either as enterococcal group D streptococci or non-enterococcal group D streptococci. Non-enterococcal group D streptococci are differentiated from enterococcal group D streptococci microbiologically on the basis of penicillin susceptibility, bile esculin hydrolysis, and growth in 0.9% sodium chloride. Non-enterococcal group D streptococci are penicillin sensitive and do not ferment bile esculin or grow in 0.9% sodium chloride, whereas group D enterococci are resistant to penicillin and do hydrolyze esculin and grow in 0.9% sodium chloride. The most important non-enterococcal group D streptococci encountered in clinical practice is *S. gallolyticus* (*S. bovis*). Clinically, the most important enterococcal group D streptococci are *E. faecalis* and *E. faecium*.

Group D enterococci are also classified on the basis of their susceptibility to vancomycin. Because nearly all strains of *E. faecalis* are susceptible to vancomycin, *E. faecalis*, for practical purposes, are termed vancomycin-sensitive enterococci (VSE). Similarly, nearly all isolates of *E. faecium* are resistant to vancomycin and for clinical purposes are termed vancomycin-resistant enterococci (VRE). Presumptively, VRE may be differentiated from VSE isolates on the basis of vancomycin susceptibility. Isolates that are vancomycin susceptible are invariably ampicillin susceptible as well. Although *in vivo* susceptibility testing often reports VSE as susceptible to penicillin, penicillin alone has no anti-group D enterococcal activity. Penicillin combined with gentamicin has anti-VSE activity. Group D enterococci constitute a small part of the normal gastrointestinal tract flora in the colon, ~75% of the bacteria are anaerobic, e.g., *Bacteroides fragilis*. The next most common organism making up the colonic microflora are aerobic gram-negative bacilli (GNBs) that constitute ~20% of the colon's flora. The remaining

portion of the colonic flora is made up of miscellaneous organisms and less than 5% of the group D enterococcal colonic flora, ~95% is *E. faecalis* (VSE), and the remaining ~5% is *E. faecium* (VRE) (1,2).

#### *Epidemiology of VSE/VRE*

All group D enterococci, i.e., VSE and VRE, are normal inhabitants of the human colon. The carriage of VSE and VRE is intermittent but persistent of long duration. VRE colonization of patients is determined by positive VRE rectal cultures. VRE does not normally inhabit the skin but may transiently be present on the skin. VRE is an occasional contaminant of blood cultures introduced during venipuncture from fecal contamination of the antecubital fossa. Fecal colonization contamination of skin is not uncommon in hospitalized patients from the mid-chest to the lower extremities. The recovery of VRE in blood cultures (1 out of 4) unaccompanied by other signs of VRE infection represents colonization and should be regarded as a contaminant of no clinical significance. Patients colonized with VRE remain on VRE precautions for the duration of hospitalization because VRE in feces is intermittent and discontinuation of precautions sets the stage for the spread of VRE when the fecal flora again contains VRE (1,3-9).

#### *Clinical Spectrum of VSE/VRE Infections*

VSE/VRE intra-abdominal/pelvic infections. VSE and VRE differ only in their susceptibility to antibiotics. The types of infection and spectrum of clinical severity is the same for VSE and VRE. VSE and VRE are relatively avirulent pathogens with little inherent invasive ability. VRE should be regarded as an innocent bystander or permissive pathogen in intra-abdominal/pelvic infections. VSE or VRE are important single pathogens in gallbladder/biliary and UTIs. In intra-abdominal infections, VSE or VRE are permissive pathogens and require other organisms to initiate/maintain infection. Experimentally, VSE or VRE injected intraperitoneally will not cause infection unless other organisms, aerobic or anaerobic, are present. This is independent of inoculum size or location within the intra-abdominal cavity (1,2).

VSE/VRE CAB and UTIs. The second most common isolates in CAB are VSE and VRE that are of no clinical consequence in normal hosts. In compromised hosts, i.e., diabetes mellitus, systemic lupus erythematosus, myeloma, etc., CAB may be treated with oral or parenteral antibiotics. VSE/VRE UTIs may present as cystitis or acute pyelonephritis in normal hosts. Urosepsis due to VSE/VRE may occur in normal hosts with preexisting renal disease, partial/total urinary tract obstructions, or in nonleukopenic hosts, i.e., diabetes mellitus, systemic lupus erythematosus, or myeloma.

VSE/VRE Bacteremia/SBE. Group D enterococci also are the sole pathogens in infective endocarditis. When causing infective endocarditis, VSE or VRE presents clinically as a syndrome of intermediate severity between SBE and ABE (10). The clinical expression of an "intermediate" and intensity of endocarditis with enterococcal group D streptococci also pertains to non-enterococcal group D streptococci, i.e., *S. gallolyticus* (*S. bovis*) (1).

Therefore, the major clinical manifestations of infections due to VRE are infective endocarditis, wound infections, biliary, hepatic of lower intra-abdominal infections, UTIs, and uncommonly CVC infections (10-13). Group D enterococci may also be pathogens in ventriculoperitoneal (VP) shunt infections if the intra-abdominal catheter perforates an abdominal viscus. Group D enterococci are ordinarily unimportant causes of acute bacterial meningitis, CAP, nosocomial pneumonia, or bone/joint infections (Table 1) (1,13,14).

#### *Antimicrobial Therapy of VSE/VRE*

It is a common misconception that group D enterococci are becoming more resistant to antibiotics. Rather, excessive use of some antibiotics, i.e., metronidazole for *Clostridium difficile* and vancomycin (IV, not PO) for empiric medical/surgical prophylaxis/therapy has resulted in decrease in the concentration of VSE in the colonic flora and commensurate increase in



**Table 1** Enterococcal Bacteremia: Diagnostic and Therapeutic Approach

## Diagnostic approach:

- Differentiate enterococcal blood culture positivity (1/4–1/2 positive blood cultures) from bacteremia
- Consider the source of enterococcal bacteremia
  - Intra-abdominal/pelvic infection
  - Urinary tract infection
  - Endocarditis
- Determine the source of enterococcal bacteremia
  - Urinary tract source
    - Urine analysis/culture
  - Abdominal/pelvic source
    - Abdominal/pelvic CT scan to diagnose or r/o abdominal/pelvic abscesses, cholecystitis, or diverticulitis
    - Abdominal/pelvic CT scan to diagnose or r/o renal obstruction, stones, intrarenal/perinephric abscesses
  - Cardiac source
    - TTE/TEE to diagnose or r/o endocarditis

## Therapeutic approach:

- Empiric therapy of VSE
  - Non-penicillin-allergic patients
    - Ampicillin
  - Penicillin-allergic patients
    - Vancomycin
    - Linezolid
    - Daptomycin
    - Tigecycline
- Empiric therapy of VRE
  - Penicillin- and non-penicillin-allergic patients
    - Linezolid
    - Daptomycin
    - Quinupristin/dalfopristin
    - Tigecycline

Source: Adapted “Diagnostic approach” from Ref. 26 and “Therapeutic approach” from Ref. 13.

intrinsically resistant VRE component. This results in increased resistant group D enterococci, i.e., VRE in hospitals. However, this does not represent an increase in group D enterococcal resistance, but rather indicates an increase in the prevalence of intrinsically more resistant VSE.

As mentioned previously, VSE are usually susceptible to vancomycin as well as ampicillin. In contrast, VRE isolates are uniformly resistant to vancomycin and ampicillin. Relatively few antibiotics have anti-VRE activity. Antibiotics useful to treat serious systemic infections due to VRE include quinupristin/dalfopristin, linezolid, daptomycin, tigecycline, chloramphenicol, and minocycline. For VRE CAB or cystitis, nitrofurantoin is useful. For VRE endocarditis, which is rare, preferably a bactericidal anti-VRE drug should be used, i.e., quinupristin/dalfopristin (1,15) (Table 2).

The route of administration of the antibiotic depends on the severity of the infection and gastrointestinal absorption. In general, all non-critically ill patients capable of gastrointestinal absorption may be treated equally. The duration of treatment for VRE infections depends on location. VRE CAB does not require treatment in normal hosts. In compromised hosts, after urinary catheter change/removal, one week of therapy is usually sufficient.

If SBE is not present, the treatment of VRE CVC infections after IV line removal is for two weeks. Such patients must be followed to be sure that VRE bacteremia from the CVC line infection does not result in infective endocarditis (10–13). Serial blood cultures and echocardiography will differentiate VRE bacteremia from VRE endocarditis. The duration of therapy for VRE endocarditis depends on the duration of symptoms prior to clinical presentation. Patients with a history of  $\leq 3$  months of symptoms are treated for 4 weeks and those with  $> 3$  months are treated for 6 weeks preferably with a bactericidal anti-VRE antibiotic (1,16–20).

**Table 2** Anti-enterococcal Group D Streptococcal Antibiotics for Serious Systemic Infections

Preferred antibiotics	Usual dose <sup>a</sup>	Same/oral equivalent antibiotic
<i>S. faecalis</i> (VSE)		
Ampicillin	2 g (IV) q4h	Amoxicillin 500 mg (PO) q24h
Vancomycin + gentamicin	1 g (IV) q12h + 120 mg (IV) q24h (synergy dose)	600 mg (PO) q12h None
Meropenem	1 g (IV) q8h	Moxifloxacin 400 mg (PO) q24h
<i>S. faecium</i> (VRE)		
Daptomycin	12 mg/kg (IV) q24h <sup>b</sup>	Linezolid 600 mg (PO) q12h
Tigecycline	200 mg (IV) 1 dose, then 100 mg (IV) q24h	Minocycline 100 mg (PO) q12h or linezolid 600 mg (PO) q12h
Linezolid	600 mg (IV/PO) q12h	600 mg (PO) 12h
Minocycline	100 mg (IV/PO) q12h	100 mg (PO) q12h
Quinupristin/dalfopristin	7.5 mg (IV) q8h	Linezolid 600 mg (PO) q12h
Chloramphenicol	500 mg (IV/PO) q6h	500 mg (PO) q6h

<sup>a</sup>Normal renal function.

<sup>b</sup>If repeat blood cultures are negative and no vegetation on TTE/TEE, treat enterococcal bacteremia for two weeks. Treat native valve enterococcal SBE for 4 weeks in patients with symptoms of <3 months and for 6 weeks in patients with symptoms of >3 months.

Abbreviation: SBE, subacute bacterial endocarditis.

Source: Adapted from Ref. 1.

## METHICILLIN-SENSITIVE STAPHYLOCOCCUS AUREUS (MSSA) & METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

### Clinically Relevant Microbiology of MSSA/MRSA

Staphylococci are normal colonizers of the skin and may be classified on the basis of coagulase production. The predominant CoNS of the skin is *S. epidermidis* whereas *S. aureus* is the predominant coagulase-positive staphylococcus. *S. aureus* may be further classified on the basis of susceptibility or to methicillin. Since methicillin is no longer used for in vitro susceptibility testing, oxacillin is used in its place. Therefore, MSSA are reported as oxacillin-susceptible. MRSA are reported as resistant to oxacillin. *S. aureus* (MSSA/MRSA) are common colonizers of the nares/skin (19,20). Staphylococci are not part of the normal flora of the mouth, GI tract, urine, or respiratory tract (1,21,22).

MRSA may be further subdivided on the basis of the site of origin or acquisition of the infection. Strains of MRSA that originated in the hospital are termed hospital-acquired MRSA (HA-MRSA). Strains of HA-MRSA which colonize/infect patients who are discharged to the community and later return to the hospital with MRSA originally acquired in the hospital have community-onset MRSA (CO-MRSA). CO-MRSA infections are those that have an onset in the community but originate in the hospital and are clinically and microbiologically indistinguishable from HA-MRSA strains. In the past few years, a new strain of *S. aureus* emerged from the community without prior exposure to the hospital setting. These strains of MRSA have been termed based on the location of acquisition as community-acquired MRSA (CA-MRSA). In patients presenting with MRSA from the community, it is of critical importance to differentiate those of community onset (CO-MRSA) from those acquired in the community (CA-MRSA). CA-MRSA is genetically distinctive, i.e., HA-MRSA. CA-MRSA strains have different staphylococcal chromosomal cassettes (SCC) than the HA-MRSA strains. HA- and CO-MRSA genetically are characterized by SCC<sub>mec</sub> I, II, III, and elaborate several *S. aureus* toxins. Another virulence factor for staphylococci is the presence of the Pantone-Valentine leukocidin gene that is rare in HA- and CO-MRSA. In contrast, CA-MRSA strains are characterized genetically by the SCC<sub>mec</sub> IV and V genes and the PVL gene, which is common. CA-MRSA strains that are PVL positive are highly virulent and present almost exclusively with severe pyodermas or necrotizing soft tissue infections or as MRSA, CAP in patients with ILIs. CA-MRSA strains that are PVL negative clinically resemble CO- and HA-MRSA strains in terms of their pathogenicity

and clinical presentation. In addition to PVL toxin, PVL-positive HA-MRSA strains also produce other toxins that are virulence factors (21,22).

CA-MRSA strains also are susceptible to antibiotics that are usually ineffective against CO- or HA-MRSA strains. CA-MRSA strains are usually susceptible to clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), or doxycycline. These antibiotics are not uniformly effective against CO- or HA-MRSA strains. Clinicians must be careful not to assume that all patients with MRSA being admitted *from* the community have CA-MRSA strains. Unless the patient presents with severe pyoderma/necrotizing soft tissue infections or necrotizing MRSA CAP with influenza, all patients coming *from* the community should be considered as CO-MRSA until proven otherwise. Therapeutically, this is important since the antibiotics that are effective against HA- and CO-MRSA strains, i.e., vancomycin, quinupristin/dalfopristin, minocycline, linezolid, daptomycin, or tigecycline are reliably effective against all MRSA strains including HA-MRSA. Therefore, patients severely ill with MRSA infections coming *from* the community should be treated as HA- or CO-MRSA because these antibiotics are effective against *all* MRSA strains. Conversely, it is not prudent to assume that all MRSA strains *from* the community are CA-MRSA because nearly all excluding those mentioned above are of the CO-MRSA variety and will not respond to empiric treatment with clindamycin, TMP-SMX, or doxycycline (21–23).

#### *Epidemiology of MSSA/MRSA*

Staphylococci colonize the skin/nares. Unlike colonization with VRE, colonization with MRSA is episodic and not continuous. Unlike VRE, MSSA/MRSA has more inherent invasive potential/virulence. Because MSSA/MRSA commonly colonize the skin, it is predictable that nearly all staphylococcal infections originate from the skin and are the result of breaching the integrity of the skin as a protective antimicrobial barrier. Unlike aerobic GNBs, staphylococci may be transmitted from person to person. Staphylococci do not colonize the urine, but urine cultures may be contaminated by staphylococci from the skin of distal urethra during urine specimen collection. HA- and CO-MRSA occur in all age groups and are related to either skin trauma or invasive procedures that traverse the skin. In contrast, CA-MRSA occurs primarily in young adults in the community who experience skin abrasion/trauma. In some cases, CA-MRSA may also complicate influenza pneumonia (Table 3) (1,22).

**Table 3** Classification of MRSA Infections

MRSA strain	Description	Treatment
• Hospital-acquired MRSA (HA-MRSA)	These strains originate within the hospital environment and have <i>SCCmec</i> I, II, III genes	Pan resistant to most antibiotics. Only vancomycin, quinupristin/dalfopristin, minocycline, linezolid, tigecycline, and daptomycin are reliably effective
• Community-onset MRSA (CO-MRSA)	These strains originate from the hospital environment but later present from the community. They too have <i>SCCmec</i> I, II, III genes (CO-MRSA = HA-MRSA)	Since CO-MRSA strains are in actuality HA-MRSA strains that present from the community, they should be treated as HA-MRSA
• Community-acquired MRSA (CA-MRSA)	<i>Only</i> community MRSA infections presenting with severe pyomyositis or severe/necrotizing community-acquired pneumonia (with influenza) should be considered as CA-MRSA PVL-positive strains ( <i>SCCmec</i> IV, V genes). <i>All other MRSA infections presenting from the community should be regarded as CO-MRSA</i>	CA-MRSA are pauci-resistant, i.e., susceptible to clindamycin, TMP-SMX, and doxycycline. Antibiotics used to treat CO-MRSA/HA-MRSA are effective against CA-MRSA, but <i>not</i> vice versa. Therefore, all MRSA strains can be treated as CO-MRSA/HA-MRSA

*Abbreviation:* PVL, Pantón–Valentine leukocidin.

*Source:* Adapted from Refs. 21 and 22.

*Clinical Spectrum of MSSA/MRSA Infection*

**MSSA/MRSA skin/soft tissue infections.** As mentioned previously, staphylococcal infections originate from trauma or procedures done through the skin. Hence, staphylococci are the most common pathogen implicated in skin/soft tissue infections and are important pathogens in CVC-associated infections (1,11,12). Staphylococcal abscesses may complicate any invasive procedure done penetrating the skin.

**MSSA/MRSA Bacteremia/ABE.** MSSA/MRSA are the most common causative organisms responsible for nosocomial ABE. *S. aureus* ABE is also the most frequent pathogen in intravenous drug abusers (IVDAs) who have right-sided ABE. Nonnosocomial MSSA/MRSA ABE may complicate prolonged high-grade/continuous bacteremia from a distant source, i.e., a staphylococcal abscess, a CVC-related infection. The most common nosocomial ABE are associated with CVCs (temporary or semipermanent), invasive cardiac procedures, i.e., radio frequency ablation or implanted devices, i.e., defibrillator/pacemaker-lead/generator-associated infections (10,12,21). Staphylococcal ABE is not a complication of cardiac catheterization and is an extremely rare complication following coronary stent placement. Right-sided ABE may be differentiated clinically from left-sided ABE by the presence or absence of pulmonary involvement (10). Patients with right-sided ABE have a clinical presentation similar to those with left-sided ABE except that septic pulmonary emboli invariably complicate right-sided staphylococcal ABE. The presence of bilateral cavitory infiltrates some of which may be wedge-shaped/pleural-based with temperatures  $\geq 102^{\circ}\text{F}$  is diagnostic of septic pulmonary emboli in a patient with right-sided ABE. Bilateral septic pulmonary emboli may be differentiated from bland pulmonary emboli by fever, i.e., septic pulmonary emboli are associated with temperatures  $\geq 102^{\circ}\text{F}$ , whereas with bland pulmonary emboli, fevers are  $\leq 102^{\circ}\text{F}$  (1,10). Also, with bland pulmonary emboli, there are one or very few lesions, whereas in septic pulmonary emboli, there are multiple lesions that rapidly cavitate. Whereas pulmonary infarcts may cavitate, later and without fever  $> 102^{\circ}\text{F}$ , they should not be easily confused with the massive bilateral multiple acutely cavitating lesions of septic pulmonary emboli from right-sided MSSA/MRSA ABE (10,11,24–26).

Unlike the relatively avirulent pathogens, i.e., viridans streptococci that cause SBE, MSSA/MRSA are capable of attacking normal native heart valves and do not require preexisting valvular damage to initiate the infectious process. Therefore, non-IVDAs in patients with ABE present with fever  $\geq 102^{\circ}\text{F}$  with a continuous high-grade MSSA/MRSA bacteremia that may not be accompanied by a murmur. The presence of a murmur indicates valvular dysfunction. If a patient with ABE presents early there will be no cardiac murmur. However, subsequently, the patient will develop a new/changing murmur typical of ABE (10,25,26). In contrast, patients with SBE present with a cardiac murmur that remains unchanged during the subacute course of SBE. Whereas CoNS are the most common pathogens associated with prosthetic valve endocarditis (PVE), MSSA/MRSA may also cause PVE (10).

A common problem faced by clinicians in critical care is to assess the clinical significance of positive blood cultures, particularly those containing gram-positive cocci. Preliminary blood culture results are usually presented as gram-positive cocci in clusters growing in blood culture bottles. Since CoNS and MSSA/MRSA all appear the same on Gram stain, the clinician must await speciation to be sure which staphylococcal species the initial report represents. However, the clinician may fairly accurately predict the clinical significance of the isolate based on the degree of blood culture positivity (1).

Clinicians must differentiate between positive blood cultures contaminated during the venipuncture/blood culture processing from true bacteremias. Gram-positive cocci in 1/4–2/4 blood cultures most frequently are indicative of skin contamination during venipuncture (11,25). Blood cultures should be obtained from peripheral veins and unless there is no alternative should not be drawn from arterial lines or peripheral/central venous lines. Staphylococcal bacteremias are likely with high blood culture positivity, i.e., 3/4–4/4 positive blood cultures. If a patient with high degree of blood culture positivity is later identified as CoNS then the clinician should search for a device-associated source. Most commonly, CoNS bacteremias, when not blood culture contaminants, are associated with CVC

temporary/semipermanent catheters. Alternately, in patients with prosthetic devices, i.e., artificial joints, heart valves, plastic shunts, etc, CoNS bacteremias are often the only indication of device-associated infection (10). The treatment of CoNS CVC infections is CVC removal (1,10). The device related CVC CoNS infections are subacute/chronic and are not usually a diagnostic or therapeutic problem in the critical care setting.

If the isolate from continuous/high culture positivity blood cultures is subsequently identified as *S. aureus*, the clinician should look for a source, i.e., osteomyelitis, abscess, CVC or device-associated infection, or ABE. If not readily apparent from the past medical history, physician examination, and routine laboratory tests, the abscesses may be detected by imaging studies, i.e., CT/MRI or gallium/indium scans. ABE may be ruled out by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Patients with vegetations without bacteremia, i.e., marantic endocarditis, do not have ABE, and patients with positive blood cultures without a vegetation have bacteremia without ABE (10,12,25).

**MSSA/MRSA CVC Infections.** CVC-associated infections may be diagnosed by removing the catheter and sending the CVC tip for semiquantitative culture. If the removed CVC tip grows  $\geq 15$  colonies of the same organism, i.e., MSSA/MRSA from a peripherally drawn blood culture, then the diagnosis of CVC line infection is confirmed. Patients with positive CVC tip cultures without bacteremia have CVC colonization, but not CVC infection. Those with positive blood cultures and negative removed catheter tip cultures have bacteremia but not IV line infection. The preferred therapy of CVC infections is catheter removal since prolonged high-level bacteremia may result in metastatic seeding through other organs or may result in ABE (1,11,25,26).

In general, without hematogenous seeding/contiguous spread MSSA/MRSA do not cause CNS infections (1,21). The important exceptions are CNS shunt-related infections secondary to ventriculo-atrial (VA) or VP shunts or secondary to implant-associated infection materials, i.e., plate/mesh or ventriculostomy drainage tubes. MSSA/MRSA acute purulent meningitis is a recognized complication of ABE. MSSA/MRSA rarely, if ever, is associated with oral infections. Excluding dental implant infections, neither biliary infections nor UTIs are caused by MSSA/MRSA. *S. saprophyticus* is the only staphylococcal uropathogen that occurs as community-acquired cystitis in young females and does not cause pyelonephritis/urosepsis and is not an issue in critical care (1,21).

Renal MSSA/MRSA abscesses may complicate renal surgery or may occur as a result of contagious/hematogenous spread. Staphylococcal renal abscesses are cortical in contrast to medullary abscesses that are due to, in the main, aerobic GNBs (1,21).

MSSA/MRSA may cause septic arthritis, either by hematogenous spread or by direct inoculation into the joint during aspiration/steroid injections. MSSA/MRSA is the most common cause of acute osteomyelitis, but is also a common pathogen in chronic osteomyelitis particularly in patients with diabetes mellitus/peripheral vascular disease (1,21,25).

Besides culture of blood, infected materials or purulent materials, serious systemic MSSA/MRSA infections may be indirectly diagnosed by demonstrating an elevation in teichoic acid antibody (TAAb) titers. TAAb titers  $\geq 1:4$  indicate a deep-seated underlying infection, i.e., osteomyelitis, abscess, or ABE. All patients with these infections do not have positive TAAb titers and a negative TAAb titer does not rule out a deep-seated/systemic MSSA/MRSA infection. TAAb titers are unhelpful in diagnosing CoNS infections. TAAb titers are particularly helpful in determining the duration of therapy in CVC line infections in determining the duration of therapy. Patients with MSSA/MRSA bacteremia due to CVC catheters should have a TAAb titer drawn at two weeks. If the titer is negative, two weeks of anti-MSSA/MRSA therapy is sufficient. However, patients with MSSA/MRSA bacteremia due to a CVC catheter and an elevated TAAb titer at two weeks should be treated as if they have ABE for four weeks after CVC removal (Table 4) (1,10,11,26,27).

Staphylococci rarely, if ever, cause pneumonia in normal hosts. IVDAs with tricuspid valve ABE have septic pulmonary emboli that may mimic pneumonia. Even diabetics who are frequently colonized with MSSA/MRSA are not predisposed to develop *S. aureus* CAP (28). CA-MSSA/MRSA pneumonia occurs virtually only in patients with influenza pneumonia (27,29–35). MSSA/MRSA rarely, if ever, causes NP/VAP (1,27). *S. aureus* CAP complicating

**Table 4** Diagnostic Clinical Pathway: MSSA/MRSA Bacteremias/ABE

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- Differentiate *S. aureus* blood culture positivity (1/2–1/4) from MSSA/MRSA bacteremia (3/4–4/4 positive blood cultures)
  - With *S. aureus* bacteremia, differentiate low intensity/intermittent bacteremia (1/2–2/4 positive blood cultures) from continuous/high intensity bacteremia (3/4–4/4 positive blood cultures)
  - ABE is not a complication of low intensity/intermittent *S. aureus* bacteremia. TTE/TEE is unnecessary, but will verify no vegetations
  - If continuous/high-grade MSSA/MRSA bacteremia, obtain a TTE or TEE to rule out or document cardiac vegetation and confirm diagnosis of ABE
  - Diagnostic criteria for MSSA/MRSA ABE
    - Essential features
      - Continuous/high-grade MSSA/MRSA bacteremia
      - Cardiac vegetation on TTE/TEE
    - Nonessential features
      - Fever  $\geq 102^{\circ}\text{F}$  (non-IVDAs)
      - Heart murmur
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influenza pneumonia may be due to MSSA, CO/CA-MRSA. The virulence of MSSA/MRSA CAP is the same if the MRSA strain is CA-MRSA (PVL–) (21,22). Excluding CA-MRSA (PVL+) strains, the virulence of MSSA, HA-MRSA, CO-MRSA, and CA-MRSA (PVL–) strains is the same (36–42).

#### *Antimicrobial Therapy of MSSA/MRSA*

Outcomes of MSSA/MRSA (PVL–) strains are the same if treated appropriately and early. The therapy of MRSA depends on the nature/severity and location of the infection. Selection of an anti-MRSA antibiotic should be based on clinical experience and not in vitro susceptibility testing (21,23). MRSA is an organism where in vitro susceptibility does not necessarily correlate with in vivo effectiveness (21,23). In the 1970s when MRSA first became widespread in the United States, there was no experience in treating this organism. Patients infected with MRSA were treated according to susceptibility testing often using betalactam antibiotics to which MRSA was reportedly susceptible. Over time, clinicians noted the discrepancy between susceptibility testing results and clinical outcomes, which led to the realization that only certain antibiotics were effective against MRSA regardless of in vitro susceptibility testing (23). It has been shown over time that the antibiotics with demonstrated clinical efficacy against MRSA infections are limited to vancomycin, minocycline, quinupristin/dalfopristin, linezolid, daptomycin, tigecycline, and ceftibiprole (18,43–61). Other antibiotics have invariably been effective clinically against MRSA, i.e., TMP-SMX and doxycycline. Other antibiotics should not be used in spite of susceptibility testing, i.e., quinolones and cephalosporins (1,21). If a tetracycline is selected to treat CA-MRSA, use minocycline, not doxycycline.

As mentioned previously, CA-MRSA has different susceptibilities than HA/CO-MRSA. HA-MRSA is susceptible to TMP-SMX, doxycycline, and chloramphenicol whereas HA/CO-MRSA strains are not. Since nearly all strains presenting to the hospital from the community are CO-MRSA rather than CA-MRSA, it is prudent to treat all MRSA as HA-MRSA or CA-MRSA. HA/CO-MRSA antibiotics will also be effective against CA-MRSA (PVL+/PVL– strains) as well (Table 5) (1,22).

There are only two clinically effective anti-MRSA antibiotics available as oral formulations, i.e., minocycline and linezolid (1,16,21,26,43). All of the other clinically effective anti-MRSA antibiotics are only available parenterally (1,21). As with other infectious diseases, the preferred treatment for MRSA abscesses is surgical drainage. Similarly, MRSA line infections should be treated primarily by removal of CVC lines. Unless there is associated ABE, antimicrobial therapy for MRSA CVC line infections is ordinarily two weeks (1,21). Complicated skin/soft tissue infections are usually treated with an IV/PO anti-MRSA antibiotic for one to two weeks (1,21). MRSA PVE is treated with valve removal and antimicrobial therapy. Native valve MRSA ABE is treated for four to six weeks of IV/PO

**Table 5** Factors in the Selection of Antimicrobial Therapy for Staphylococcal Bacteremias

<ul style="list-style-type: none"> <li>• Select an antibiotic with known clinical efficacy and a high degree of activity against the presumed/known pathogen, e.g., VSE, VRE, MSSA, or MRSA.</li> <li>• If needed, <i>adjust dosage</i> to achieve therapeutic concentrations in serum/tissue.</li> <li>• Select a “low-resistance” potential antibiotic, e.g., ertapenem, amikacin, minocycline, moxifloxacin, levofloxacin, meropenem, tigecycline, and etc. Avoid “high-resistance” potential antibiotics, e.g., imipenem, ciprofloxacin, gentamicin, tobramycin, and minimize the use of those that select out on resistant organisms, e.g., vancomycin and ceftazidime</li> <li>• Select an antibiotic with a favorable safety profile and a low <i>C. difficile</i> potential e.g., daptomycin, tigecycline, linezolid, Q/D, minocycline.</li> <li>• Select an antibiotic that is relatively cost-effective in the clinical context of bacteremia/endocarditis.</li> <li>• If possible, select an oral antibiotic that is the same or equivalent to intravenous therapy for all/or part (IV → PO switch) of the duration of antimicrobial therapy.</li> </ul>
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Bactericidal antibiotics preferred for ABE.

Source: Adapted from Ref. 26.

therapy (1,10,26). While bactericidal drugs are preferable in the treatment of MRSA ABE, linezolid and minocycline have been clinically as effective as bactericidal agents. MRSA bone or joint infections are treated for four to six weeks or two weeks, respectively, with an IV/PO anti-MRSA antibiotic (1,21). In addition to antimicrobial therapy, septic arthritis due to MRSA requires joint aspiration/lavage. MRSA CNS shunt infections are treated primarily by VA/VP shunt removal together with antimicrobial therapy that penetrates the CSF (1,21,62,63). The anti-MRSA antibiotics that have excellent CNS penetration are linezolid and minocycline. There is no evidence that “double drug” therapy to treat MRSA infections offers any advantage over monotherapy. In particular, the addition of rifampin to an MRSA antibiotic does not enhance anti-MRSA killing or improve outcomes and may be antagonistic (Table 6) (1,21,64).

Because of the relatively limited number of agents that are useful and detrimental against MRSA, there is concern about the eventual loss of effectiveness of these agents due to

**Table 6** Anti-MSSA and Anti-MRSA Antibiotics for Serious Systemic Infections

Antibiotics/pathogens	Attributes	Disadvantages
<i>S. aureus</i> (MSSA)		
Nafcillin	<ul style="list-style-type: none"> <li>• Most active anti-MSSA antibiotic</li> <li>• The only anti-MSSA penicillin with an enterohepatic circulation</li> <li>• Inexpensive</li> <li>• Long experience</li> <li>• No dosing modification in CRF</li> <li>• Low resistance potential</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Short <math>t_{1/2}</math> requires frequent dosing</li> <li>• Drug fevers (common)</li> <li>• Interstitial nephritis (rare)</li> <li>• No oral formulation (avoid oral anti-MSSA PCNs which are <i>not</i> well absorbed instead use oral 1st generation cephalosporin, e.g., cephalexin)</li> </ul>
Cefazolin	<ul style="list-style-type: none"> <li>• Most active anti-MSSA cephalosporin → clinical effectiveness/outcomes ~ nafcillin</li> <li>• Long experience</li> <li>• Inexpensive</li> <li>• Low resistance potential</li> <li>• High <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Drug fevers (common)</li> <li>• Avoid in patients with <i>anaphylactic reactions</i> to PCN</li> <li>• No oral formulation (use oral 1st generation cephalosporin, cephalexin)</li> </ul>
Ceftriaxone	<ul style="list-style-type: none"> <li>• Less anti-MSSA activity than nafcillin or cefazolin</li> <li>• Low resistance potential</li> <li>• Low <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• No oral formulation (use oral 1st generation cephalosporin, e.g., cephalexin)</li> <li>• Non-<i>C. difficile</i> diarrhea (common)</li> </ul>
Clindamycin	<ul style="list-style-type: none"> <li>• Inexpensive</li> <li>• MSSA excellent for infections <i>except</i> ABE</li> <li>• IV/PO formulations</li> <li>• Low resistance potential</li> </ul>	<ul style="list-style-type: none"> <li>• Not active against MRSA</li> <li>• Not useful for MSSA ABE</li> <li>• <i>C. difficile</i> (common) alternately, use oral linezolid or minocycline</li> </ul>

(Continued)

**Table 6** Anti-MSSA and Anti-MRSA Antibiotics for Serious Systemic Infections (*Continued*)

Antibiotics/pathogens	Attributes	Disadvantages
<i>S. aureus</i> (MRSA) Vancomycin	<ul style="list-style-type: none"> <li>• Less active against MSSA than nafcillin</li> <li>• Long experience</li> <li>• <i>Not</i> nephrotoxic</li> <li>• Drug fevers uncommon</li> </ul>	<ul style="list-style-type: none"> <li>• No oral formulation for bacteremia/SBE, alternately use minocycline or linezolid</li> </ul>
Quinupristin/dalfopristin	<ul style="list-style-type: none"> <li>• Useful for MSSA/MRSA</li> <li>• Useful in rare cases of daptomycin-resistant MSSA/MRSA</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Severe/prolonged myalgias</i> (rare, but serious)</li> <li>• No oral formulation, alternately use minocycline or linezolid</li> </ul>
Linezolid	<ul style="list-style-type: none"> <li>• No hypersensitivity reactions</li> <li>• Active against both MSSA/MRSA</li> <li>• <i>Bacteriostatic</i> but useful to treat MSSA/MRSA ABE</li> <li>• No dosage modification in CRF</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively expensive</li> <li>• Oral formulation (high bioavailability)</li> <li>• Thrombocytopenia after &gt; 2 wk</li> <li>• Serotonin syndrome (rare)</li> </ul>
Daptomycin	<ul style="list-style-type: none"> <li>• No dosage reduction in CRF</li> <li>• For MSSA/MRSA bacteremias/ABE use 6 mg/kg dose</li> <li>• If bacteremia persists &gt;72 hours use "high-dose" (12 mg/kg) daptomycin (well tolerated)</li> <li>• Not nephrotoxic</li> <li>• No hypersensitivity reactions</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Following vancomycin therapy, resistance may occur during therapy (rarely).</li> <li>• No oral formulation</li> <li>• Alternately, use oral linezolid or minocycline</li> </ul>
Tigecycline	<ul style="list-style-type: none"> <li>• Active against MSSA/MRSA</li> <li>• No dosing modification in CRF</li> <li>• Not nephrotoxic</li> <li>• No resistance potential</li> <li>• Highly active against <i>C. difficile</i> (No <i>C. difficile</i> potential)</li> </ul>	<ul style="list-style-type: none"> <li>• No oral formulation</li> <li>• Alternately, use oral linezolid or minocycline</li> </ul>
Minocycline <sup>a</sup>	<ul style="list-style-type: none"> <li>• Available IV/PO</li> <li>• Limited experience, but useful for MSSA/MRSA bacteremias/ABE</li> <li>• Inexpensive</li> <li>• No resistance potential</li> <li>• No <i>C. difficile</i> potential</li> </ul>	<ul style="list-style-type: none"> <li>• Skin discoloration (with <i>prolonged use</i>)</li> <li>• <i>Early/mild</i> transient vestibular symptoms (uncommon)</li> </ul>

<sup>a</sup>For CA-MRSA/CO-MRSA use minocycline instead of doxycycline.

*Abbreviations:* MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ABE, acute bacterial endocarditis; PCN, penicillin; CRF, chronic renal failure.

*Source:* Adapted from Ref. 1.

resistance. There has been no clinically important resistance that has developed to any of the anti-MRSA drugs except vancomycin (1,21,65–67). Additionally, there are concerns about emerging resistance to daptomycin during therapy. Vancomycin therapy selects out heteroresistant strains of MRSA that are relatively resistant to vancomycin. These isolates are termed vancomycin intermediate susceptible *S. aureus* (hVISA). These strains of hVISA are relatively resistant to vancomycin and are difficult to detect with conventional susceptibility testing. MRSA isolates with vancomycin minimum inhibitory concentrations (MICs) between 1 and 2 µg/mL should be further tested to detect hVISA strains. Vancomycin resistance may be mediated by staphylococcal cell wall thickening, which results in a "permeability-mediated" resistance. Exposure to vancomycin over several days often results in thickened staphylococcal cell walls. Thickened staphylococcal cell wall results in a "penetration barrier" to vancomycin as well as other anti-staphylococcal antibiotics. Clinically, this is manifested as an increase in MICs, which may represent either relative or high-level resistance. Strains of MRSA with extremely high MICs are known as vancomycin-resistant *S. aureus* (VRSA) strains. Fortunately, these MRSA isolates remain extremely rare. Because of the widespread use of vancomycin, cell



**Table 7** Causes of Antibiotic Failure (Apparent or Actual)

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- In vitro susceptibility but clinically ineffective in vivo (MRSA: doxycycline vs. minocycline)
  - Antibiotic “tolerance” with gram-positive cocci
  - Inadequate coverage/spectrum
  - Inadequate antibiotic blood levels
  - Inadequate antibiotic tissue levels
  - Undrained abscess
  - Foreign body–related infection
  - Protected focus (e.g., cerebrospinal fluid abscess, device associated, etc)
  - Organ hypoperfusion/diminished blood supply (e.g., chronic osteomyelitis in diabetics)
  - Drug interactions
    - Antibiotic inactivation
    - Antibiotic antagonism
  - Decreased antibiotic activity in tissue (pH, local hypoxia, cellular debris)
  - Fungal superinfection
  - Treating colonization (not infection)
  - Noninfectious diseases
    - Medical disorders mimicking infection (e.g., SLE)
    - Drug fever
  - Antibiotic-unresponsive infectious diseases
    - Viral infections
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*Source:* Adapted from Ref. 1.

wall thickening/permeability-mediated resistance increases, resulting in the loss of vancomycin usefulness (1,68,69). As mentioned, the extensive use of vancomycin has also resulted in resistance to other agents, i.e., daptomycin.

There have been reports of daptomycin resistance in treating MRSA infections that have occurred during therapy. A review, to date, of all the cases of daptomycin resistance occurring during therapy have occurred in patients who previously received vancomycin (70–74). The best way to preserve the activity of daptomycin for MRSA infections is to minimize/avoid parenteral vancomycin use whenever possible and instead preferentially use another anti-MRSA antibiotic, linezolid, minocycline, quinupristin/dalfopristin, or tigecycline (55). In cases of vancomycin or daptomycin resistance, quinupristin/dalfopristin or tigecycline may be effective.

There have been reports of linezolid “tolerance” with both VRE and MRSA infections (75–77). The phenomenon of “tolerance” refers to isolates that have a minimal bactericidal concentration (MBC)  $\geq 32 \times$  MIC. Such isolates appear susceptible with in vitro susceptibility testing. Clinicians assume that if using antibiotics is reported as susceptible with a predictable serum concentration, the organism should be eliminated. However, with “tolerant strains,” unless the MBC of the isolate is determined, patient isolated with susceptible MICs will appear susceptible but not respond to therapy. In the differential diagnosis of apparent/actual therapeutic failure, antibiotic “tolerance” needs to be considered (Table 7) (75–78). In treating MRSA infections, “tolerance” is an uncommon occurrence but is most likely with vancomycin or linezolid. Because of concerns of antibiotic “tolerance” and antibiotic resistance, linezolid, should be used sparingly to preserve its ability to treat infections for which there are few other therapeutic alternatives, i.e., MRSA CNS infections.

For CA-MRSA infections use minocycline in place of doxycycline. Doxycycline ineffectiveness for MRSA may be due to less intrinsic anti-MRSA activity/efflux mediated resistance (doxycycline, but not minocycline) (1,79).

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# 28 | Antibiotic Therapy of Multidrug-Resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* in Critical Care

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## INTRODUCTION

### Multidrug-Resistant *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*

Therapeutically, the most problematic microorganisms encountered in daily practice in critical care are *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*. The aerobic gram-negative bacilli (GNBs) are usually sensitive to a variety of antibiotics, but some strains may become resistant to multiple antibiotics from different classes and are then considered to be multidrug resistant (MDR) isolates. Antibiotic resistance among these three species may be related to a mutation that causes resistance or may be induced by certain antibiotics-mediated resistance, or may be clonally spread throughout the critical care unit (CCU) or the ward hospital or even the region. The clonal dissemination of MDR GNBs in the CCU and beyond is not caused or related to antibiotic use. Clonally derived MDR GNB isolates may be spread extensively if not limited by effective infection-control containment measures. Clonal spread of MDR GNBs may result in a widespread resistance within an institution and not related to antibiotic usage patterns. Although problematic for individual patients colonized/infected with MDR/GNBs, containment of the clonally derived isolate to a single patient limits the magnitude of potential resistance problems in the CCU and institution.

The other type of resistance which is not caused by mutation and spread by dissemination of MDR clonal isolates is that associated with antibiotic use. It is a common clinical misconception that antibiotics have the same resistance potential or that the resistance potential is related to antibiotic class. Antibiotic resistance is not related to volume of use, i.e., "antibiotic tonnage," antibiotic class, or duration of time that the drug has been on the market or the duration of postmarket exposure, i.e., years available for general use. Attempts have been made to correlate structure-activity relationships with antibiotic resistance with different classes of antibiotics. This approach applies to relatively few antibiotic aminoglycosides, but not to the majority of antibiotics in other antibiotic classes. A historical approach to understanding antibiotic-associated resistance from a clinical standpoint indicates that some antibiotics are more likely to cause resistance than others. These antibiotics may be termed "high-resistance potential" antibiotics indicating the resistance potential is not necessarily high in terms of percentage but relatively higher than those with a "low-resistance potential." Antibiotics referred to as low-resistance potential antibiotics are those which when used in high volume over extended periods of time have not been associated with acquired resistance to various microorganisms. While antibiotics should not be used thoughtlessly, all other things being equal, it is always preferable to use an antibiotic with a low resistance potential, in preference to one with a high resistance potential. Common examples of low-resistance potential antibiotics are amikacin among the aminoglycosides; meropenem, ertapenem, and doripenem among the carbapenems; doxycycline and minocycline among the tetracyclines; cefazolin, cephalexin, and cefprozil among the first-generation cephalosporins; ceftazidime and ceftiofur among the second-generation cephalosporins; ceftazidime, ceftiofur, and ceftiofur among the third-generation cephalosporins; ceftiofur among the fourth-generation cephalosporins; aztreonam among the monobactams; piperacillin among the anti-pseudomonal penicillins; levofloxacin and moxifloxacin among the quinolones;

chloramphenicol, polymyxin B, colistin, and tigecycline. High-resistance potential antibiotics used for GNBs include imipenem, ciprofloxacin, ceftazidime, TMP-SMX, and gentamicin. There is no good explanation for why within each antibiotic class there are one or more antibiotics that have high resistance potential while the others in the group with a similar structure and pattern/volume of use have not been associated with significant resistance problems. Low-resistance potential antibiotics have been used for decades without causing widespread resistance, i.e., doxycycline, minocycline, amikacin, ceftriaxone, nitrofurantoin, fosfomycin, and amphetamine salts (1–5).

Antibiotic-induced resistance, therefore, is not related to antibiotic class, volume, or duration of antibiotic use, but rather is an attribute of one or more antibiotics in each antibiotic class that may be considered as high-resistance potential antibiotics whereas the other antibiotics in the class may be termed low-resistance potential antibiotics. This distinction is clinically useful and has practical applications. However, it should be remembered that if an institution has a resistance problem with a particular organism, i.e., *P. aeruginosa*, MDR *P. aeruginosa* strains may not be eliminated by single substitutions in an antibiotic formulary. For example, if an institution has a problem with MDR *P. aeruginosa*, that appears to be related to gentamicin usage, the mere substitution of amikacin for gentamicin may not eliminate the resistance problem. All antibiotics with anti-pseudomonal activity in the institution must also be changed substituting anti-pseudomonal, low-resistance potential antibiotics for those on formulary that have a high antibiotic resistance potential. Therefore, in this case, not only should amikacin be substituted for gentamicin but meropenem must be substituted for imipenem, cefepime should be substituted ceftazidime, and levofloxacin substituted for ciprofloxacin. By implementing formulary changes that address the problem in the total microbiological milieu of the institution, recognizing that the resistance problem cannot be eliminated without making appropriate formulary substitutions for all antibiotics that have activity against the problematic MDR pathogen, for example, MDR *P. aeruginosa*. If multiple formulary substitutions are not implemented, the antibiogram of the institution will show increasing resistance among the low-resistance potential anti-pseudomonal antibiotics that have not replaced their high-resistance potential counterparts. In this setting, if amikacin is substituted for gentamicin but imipenem, ciprofloxacin, and ceftazidime usage continues, resistance problems will be manifested by the worsening susceptibility patterns of meropenem, levofloxacin, and cefepime. This may be manifested in individual isolates by slowly increasing minimal inhibitory concentrations (MICs), i.e., “MIC creep.” In an institution to eliminate a widespread MDR resistance effectively due to GNBs requires preferential use of all low-resistance potential antibiotics that have activity against the resistant strain and by eliminating or limiting the use of the high-resistance potential antibiotics that have activity against the MDR species (1,4,5).

There are other considerations in dealing with MDR GNBs. Antibiotic resistance may be classified as intrinsic or natural. Intrinsic resistance refers to the lack of activity of an antibiotic against an isolate, e.g., *P. aeruginosa* is intrinsically resistant to chloramphenicol. In contrast, acquired antibiotic resistance refers to isolates that were once formally sensitive to an antibiotic that have subsequently become resistant and the resistance is related to antibiotic use not mutation, i.e., ampicillin was formerly highly effective against *E. coli* but is now much less effective. Acquired antibiotic resistance may be further subdivided into relative resistance and absolute or high-level resistance. High-level resistance refers to an MIC of isolate that is far in excess of achievable serum/tissue levels when using an antibiotic at the usual or even at higher than usual doses, i.e., an isolate of *P. aeruginosa* with an MIC of  $>200 \mu\text{g/mL}$  to gentamicin (susceptible MIC  $< 4 \mu\text{g/mL}$ /resistant  $> 16 \mu\text{g/mL}$ ). “Relative resistance” refers to isolate MICs somewhat above the susceptibility break point for an antibiotic. Although reported as “resistant,” such an isolate may in fact be susceptible in body sites that concentrate the antibiotic to greater than serum levels, i.e., bile or urine or by using the usual or higher doses of antibiotics that achieve site concentrations above isolate-resistant MICs reported. For example, if a *P. aeruginosa* isolate is reported as “resistant” to meropenem (susceptible breakpoint MIC  $< 4 \mu\text{g/mL}$ /resistant  $> 16 \mu\text{g/mL}$ ). A higher than usual dose of meropenem, i.e., 2 g IV will be effective in most body sites. After a 2 g dose of IV, serum concentrations of meropenem are  $\sim 100 \mu\text{g/mL}$ , well in excess of the concentration (MIC) necessary to eradicate most “relatively

resistant" isolates. When using antibiotics with a wide "toxic/therapeutic ratio," i.e., beta-lactams, many "relatively resistant" or resistant GNBs may be effectively eradicated at most body sites with usual or higher doses. An infectious disease consultation can be useful in properly interpreting the subtleties of susceptibility testing vis-a-vis achievable antibiotic optimizing antibiotic therapy dosing to assess the probability of eradication of MDR GNB isolates at infected sites (1-6).

## THE MAJOR PROBLEMATIC MDR GRAM-NEGATIVE BACILLI (GNBs) IN CRITICAL CARE

### MDR *P. aeruginosa*

#### *Epidemiological Considerations*

*P. aeruginosa* is a water-borne aerobic GNB. In the CCU environment, it is a common colonizer of body fluids, i.e., respiratory secretions, wounds, irrigation solutions, and urine. *P. aeruginosa* in the CCU commonly colonizes fluids used in the CCU, i.e., intravenous fluids, irrigation fluids, nebulizer fluids; therefore, *P. aeruginosa* is prevalent in the CCU aquatic environment. With the exception of nosocomial pneumonia (NP), *P. aeruginosa* is a highly virulent organism; it has limited invasive ability in non-immunocompromised hosts. Excluding NP, also known as hospital-acquired pneumonia (HAP) or in ventilated patients known as ventilator-associated pneumonia (VAP), *P. aeruginosa* only causes infection in neutropenic patients, those with chronic bronchiectasis/cystic fibrosis, and those with extensive burn wounds. *P. aeruginosa* nosocomial urosepsis not uncommonly is a complication of urological procedures/instrumentation. *P. aeruginosa* is not a common cause of IV line infections, skin/soft tissue infections, central nervous system (CNS) infections, gastrointestinal/pelvic infections, bone/joint infections. *Pseudomonas* is not an infrequent colonizer of the urine in patients with indwelling urinary catheters, i.e., *P. aeruginosa* catheter-associated bacteriuria (CAB). CAB is an example of colonization of the urinary tract and is not a urinary tract infection (UTI) per se. *Pseudomonas* may colonize body fluids or other fluids used in the CCU by person-to-person or fomite transmission. *P. aeruginosa* strains that colonize the CCU may be of the sensitive or MDR variety (1,2).

Non-MDR *P. aeruginosa* isolates are usually susceptible to one or more aminoglycosides, anti-pseudomonal penicillins, anti-pseudomonal cephalosporins (cefoperazone or cefepime), aztreonam, anti-pseudomonal penicillins, and meropenem and carbapenems, excluding ertapenem. MDR *P. aeruginosa* may be defined as a *P. aeruginosa* isolate resistant to three or more different classes of antibiotics to which it is normally susceptible. MDR *P. aeruginosa* strains may occur as the result of mutation and be spread clonally within the unit. These strains should be identified as such and their spread limited by effective infection-control containment measures. Ultimately, MDR resistance may be antibiotic mediated using "high resistance" potential anti-pseudomonal antibiotics extensively in the CCU, i.e., imipenem, ciprofloxacin, ceftazidime. The therapeutic approach for non-MDR *P. aeruginosa* usually can be treated effectively with various "low resistance" potential anti-*P. aeruginosa* antibiotics. In contrast, MDR *P. aeruginosa* is a definite problem because, by definition, there are few antibiotics effective against such pan-resistant strains (1,2).

Aside from preferentially using "low-resistance" potential anti-*P. aeruginosa* antibiotics in preference to "high-resistance" potential anti-*P. aeruginosa* antibiotics, the next most important therapeutic consideration is to avoid using antibiotics to treat antibiotic colonization. Colonization is more difficult to eradicate than infection. The reason for this is that colonizing strains exist in sites where the concentration of antibiotics may be subtherapeutic. All other things being equal, subtherapeutic concentrations of antibiotics are more likely to predispose to resistance than our supra therapeutic concentrations. If at all possible, avoid treating colonization versus infection. It is important to differentiate colonization from infection to avoid needless antibiotic use (3-6).

#### *Nosocomial Pneumonia (NP)/Ventilator Associated Pneumonia (VAP)*

The typical CCU dilemma is in evaluating the clinical significance of *P. aeruginosa* isolates in respiratory secretions of ventilated patients. Because it is well known that the single most

important but not most frequent cause of NP/HAP/VAP is *P. aeruginosa*, there is a tendency to “cover” isolates cultured from respiratory secretions of intubated patients. The incorrect clinical assumption is that the isolate in the respiratory secretions is reflective of the pathological process in the parenchyma of the lung. Respiratory secretions and parenchyma of the lung are rarely related and nearly always represent colonization rather than infection.

*P. aeruginosa* NP/VAP has a distinctive clinical presentation characterized by precipitous clinical deterioration, cyanosis, dramatically decreased lung function, and rapid cavitation (<72 hours) on the chest X Ray (CXR)/chest CT scan. In ventilated patients with fever and leukocytosis with a shift to the left and pulmonary infiltrates, it is well known that the cause of such patients’ pulmonary infiltrates is more commonly noninfectious than infectious. There are many disorders that can present with these findings, i.e., congestive heart failure (CHF), pulmonary hemorrhage, pulmonary drug effects, bronchiolitis obliterans organizing pneumonia (BOOP), adult respiratory distress syndrome (ARDS), interstitial lung disease, lymphangitic spread of malignancies, etc. Therefore, the clinician should not conclude pulmonary infiltrates in a febrile patient with leukocytosis, and a left shift are diagnostic of NP. Isolates recovered from respiratory secretions in such patients should not be considered as potential pathogen even if NP is present. *P. aeruginosa* NP/HAP/VAP should be considered only if the patient has clinical presentation characteristic of *P. aeruginosa* pneumonia (*vide supra*) whether or not *P. aeruginosa* is cultured from respiratory secretions (7–9).

Therefore, until proven otherwise, the recovery of *P. aeruginosa* respiratory secretions in a ventilated patient with fever, leukocytosis/shift to the left, and pulmonary infiltrates should not be considered diagnostic of *P. aeruginosa*. Patients with *bona fide P. aeruginosa* NP/VAP have atypical infiltrates, i.e., necrotizing pneumonia, which is responsible for the bilateral rapid cavitory lesions seen on CXR/chest CT. The necrotic/invasive nature of this fulminating/necrotic pneumonia is manifested by demonstrating elastin fibers using an elastin stain in respiratory secretions. Unless occurring in the characteristic clinical context, it is prudent not to treat possible NP/VAP based solely on respiratory secretions isolates. Since *P. aeruginosa* NP/VAP is not the most frequent but is the most virulent pathogen, it is prudent in the absence of a definitive diagnosis to empirically treat for *P. aeruginosa* in NP/VAP patients realizing that many such patients will, in fact, not have *bona fide P. aeruginosa* NP/VAP. Given the nature/virulence of *P. aeruginosa* NP/VAP, empiric coverage with an anti-*P. aeruginosa* antibiotic with a low-resistance potential should be selected. For empiric coverage where *P. aeruginosa* is a potential pathogen, empiric monotherapy is as efficacious as double drug antibiotic therapy, but for proven *P. aeruginosa* NP/VAP, double drug therapy is preferred.

Empiric therapy for NP/VAP is continued for two weeks. If the pulmonary infiltrates remain unchanged after two weeks, the diagnosis of NP/VAP should be questioned and a lung biopsy should be obtained to arrive at a definitive diagnosis (7,8).

#### *Catheter Associated Bacteriuria (CAB)*

In the urine, *P. aeruginosa* commonly colonizes the urine of patients with indwelling urinary catheters, i.e., CAB. In normal hosts, CAB need not be treated since it represents colonization and not a *bona fide* UTI. CAB has important infection control, but not clinical importance. Before treating CAB, it is important to remove/change the indwelling urinary catheter to avoid trying to eradicate strains embedded in catheter biofilm. If the physician elects to treat *P. aeruginosa* CAB after Foley removal/change, there are relatively few oral antibiotics available that are effective against *P. aeruginosa* (3–5).

#### *Antibiotic Therapy of MDR P. aeruginosa Infections*

To treat susceptible strains of *P. aeruginosa* in the CCU setting, the clinician should select an antibiotic based upon resistance potential of the antibiotic as well as the site of infection. Aminoglycosides concentrate the high concentration in the urine and are ideal agents to use in *P. aeruginosa* urosepsis. If the *P. aeruginosa* strain is quinolone-sensitive, then levofloxacin is as effective or more effective against *P. aeruginosa* than ciprofloxacin. For *P. aeruginosa* CAB, single-dose amikacin therapy may be effective depending upon renal function. Alternately, the only oral antimicrobial regularly effective against MDR *P. aeruginosa* CAB/UTIs is fosfomycin.



Patients with MDR *P. aeruginosa* urosepsis following urological instrumentation/procedures may be effectively treated with colistin, polymyxin B, or doripenem (6–10).

For the empiric treatment of NP/VAP where *P. aeruginosa* is the most important therapeutic consideration, a variety of anti-pseudomonal antibiotics may be used with susceptible strains. Piperacillin/tazobactam plus amikacin, meropenem, or ceftipime may be used for the empiric treatment of MDR *P. aeruginosa* presumed NP/VAP. There are relatively few anti-pseudomonal antibiotics that are effective and reach therapeutic concentrations in the lung. Empiric treatment of potential MDR *P. aeruginosa* NP/VAP may be initially with meropenem. If the MDR *P. aeruginosa* isolate is meropenem resistant, then doripenem, colistin, or polymyxin B may be effective (6,7,11–16).

## MDR *K. pneumoniae*

### *Epidemiological Considerations*

*K. pneumoniae* is an aerobic GNB that colonizes respiratory secretions and urine. It is a common cause of severe community-acquired pneumonia (CAP) in alcoholics, but not nonalcoholics. *K. pneumoniae* is also among the aerobic GNB pathogens causing NP/VAP. It is an infrequent, but important cause of central venous catheter (CVC) infections as with *P. aeruginosa*. Excluding IV line infections, *K. pneumoniae* is a common colonizer and an infrequent pathogen in immunocompetent hosts (7,17,18).

*K. pneumoniae* causes a more slowly cavitating necrotic pneumonia than MSSA/MRSA or *P. aeruginosa*. On CXR/chest CT, cavitation with *K. pneumoniae* CAP or NP occurs after three to five days. *K. pneumoniae* may cause NP in normal hosts but only causes CAP in alcoholics. When *Klebsiella pneumoniae* is the pathogen, *K. pneumoniae* is difficult to eradicate because it produces abundant material that resists phagocytosis and antibiotic penetration (7,10).

### *K. pneumoniae* Infections

*K. pneumoniae* CAP or NP/VAP may be treated optimally using monotherapy with third-generation cephalosporin (excluding ceftazidime) or a carbapenem. The addition of another antibiotic for possible synergy, i.e., an aminoglycoside, azthreonam, fluoroquinolone is unnecessary and may be antagonistic or may increase resistance potential.

For *K. pneumoniae* urosepsis amikacin, third-generation cephalosporins (excluding ceftazidime) or meropenem are useful. For *K. pneumoniae* CAB, oral cephalosporins are usually effective after urinary catheter removal/replacement. For *K. pneumoniae* CVC line infections, the primary therapeutic intervention is CVC removal. When the CVC is removed, antimicrobial therapy should be continued for seven days post-CVC removal (7,17,18).

### *Antibiotic Therapy of MDR K. pneumoniae Infections*

Classically, *K. pneumoniae* is susceptible to cephalosporins and aminoglycosides. Aminoglycosides have modest anti-*Klebsiella* activity but cephalosporins are highly active against *K. pneumoniae*. Traditionally, double-drug antibiotic therapy was used to treat serious systemic *K. pneumoniae* infections because the available antibiotics, i.e., aminoglycosides, had limited anti-*K. pneumoniae* activity and first-generation cephalosporins were combined with aminoglycosides for potential synergy. Currently, the anti-*K. pneumoniae* activity of third-generation cephalosporins, or carbapenems, and tigecycline provide the optimal therapy.

Most strains of community-acquired *K. pneumoniae* are susceptible and not MDR variety. Nosocomial *K. pneumoniae* infections, i.e., NP/VAP, urosepsis, and particularly, CAB infections are often of the MDR variety. MDR *K. pneumoniae* are often extended-spectrum beta-lactamases (ESBL) or carbapenemase (KPC) producers. In some cases metallo-beta-lactamases are an emerging problem among MDR *K. pneumoniae* isolates. Such highly resistant MDR *K. pneumoniae* strains are often almost pan-antibiotic resistant. Frequently such MDR *K. pneumoniae* strains are susceptible only to gentamicin or tigecycline (6,7,10,17,18).

For MDR *K. pneumoniae* nosocomial urosepsis or NP/VAP due to empiric therapy with tigecycline ± gentamicin is effective and often is the only choice available. Because ~33% of tigecycline is excreted into the urine, therapeutic urinary concentrations may not be achievable with the usual tigecycline dosing, i.e., 100 mg (IV) × 1 dose followed by 50 mg (IV) q12h. Since

tigecycline is a drug, with few, if any side effects, the dose may be increased without adverse effects if administered in sufficient volume and if given *slowly* intravenously. For MDR *Klebsiella* urosepsis/UTI, "high dose" tigecycline has been successfully used. Tigecycline may be given in "high dose" as 400 mg (IV) × one dose followed by 200 mg q24h. Since urinary levels of tigecycline are ~25% of simultaneous serum levels, higher serum concentrations result in higher urine concentrations that *may* be effective against MDR *K. pneumoniae* urinary isolates with relatively high MICs. For the oral antibiotic therapy of *K. pneumoniae* CAB, fosfomycin is usually effective after urinary catheter removal/replacement (6,19,20).

### **MDR *A. baumannii***

#### *Epidemiologic Considerations*

*A. baumannii* are skin organisms that also thrive in aqueous environments. *A. baumannii* are organisms of low virulence with minimal invasive potential. For these reasons, *A. baumannii* commonly colonize but may infect patients in the CCU. Common sites of colonization are respiratory secretions and urine (21–24).

#### *A. baumannii* Infections

As with *P. aeruginosa*, *A. baumannii* colonization of respiratory secretions in ventilated patients is often a diagnostic consideration. *A. baumannii* infections are a rare cause of NP. *Acinetobacter baumannii* NP occurs most commonly in clusters or outbreaks in the CCU (4,5). *Acinetobacter* colonization of aqueous solutions in respiratory support equipment is usually responsible for *A. baumannii* outbreaks of NP. Isolated *A. baumannii* NP is distinctly unusual. Clinicians must be careful to distinguish as with *P. aeruginosa* the clinical significance of *A. baumannii* in respiratory secretions of ventilated patients with fever, leukocytosis, and pulmonary infiltrates. In excluding outbreaks, nearly always *Acinetobacter* isolates recover from respiratory secretions, represent colonization rather than infection indicative of *A. baumannii* NP, and should not be "covered" with antimicrobial therapy (7,10). *A. baumannii* commonly colonize the skin and expectedly *A. baumannii* is occasionally are implicated in central IV line infections.

#### *Antibiotic Therapy of A. baumannii* Infections

*A. baumannii*, unlike *P. aeruginosa* and *K. pneumoniae*, has, by definition always been a MDR GNB. There have always been fewer antibiotics effective against *Acinetobacter* than *P. aeruginosa* or *K. pneumoniae*. Few strains of *A. baumannii* are susceptible to third-generation cephalosporins or cefepime. Some strains of *A. baumannii* are susceptible to meropenem or ertapenem. The most common *Acinetobacter* infection encountered in the CCU are CVC infections and CAB. The primary therapeutic intervention in treating CVC infections, regardless of the infecting organism, is removal or replacement. It cannot be emphasized too strongly that antibiotics will not be effective even if reported as susceptible without CVC removal. Similarly for CAB, removal/replacement of the urinary catheter is the key therapeutic intervention without which antibiotics will rarely be effective in eradicating the bacteriuria (6,10).

For MDR *A. baumannii* central venous catheter (CVC) infections, meropenem, ampicillin, sulbactam, and tigecycline have been effective. The optimal antibiotics for MDR *A. baumannii* in this setting are ampicillin/sulbactam in penicillin-allergic patients, or meropenem or doripenem may be useful. Nearly all isolates remain susceptible to colistin or polymyxin B. For CAB due to pan-resistant *A. baumannii*, fosfomycin is often the only oral antibiotic that may be effective after urinary catheter removal/replacement.

The antibiotic resistance concerns are intimately connected with the development of MDR GNBs that are common colonizers and infrequent pathogens in the CCU. The first consideration is not to cause or worsen resistance in the CCU by the use of high-resistance potential antibiotics for overzealous empiric therapy particularly of NP. The second important consideration is to eliminate an existing resistance problem due to MDR GNBs. This is best achieved by formulary substitutions involving the replacement of high-resistance potential antibiotics with those of low resistance potential that are effective against the MDR strain problematic to the CCU/institution, i.e., *P. aeruginosa*, *K. pneumoniae*, or *A. baumannii* (1,2). This

can be achieved most simply by avoiding the unnecessary treatment of colonized respiratory secretions or urine (6,7,10). Other important measures to minimize the evolution of MDR GNBs is not to use antibiotics in place of abscess drainage or to “cover” surgical drains. Lastly, all of the efforts to prevent, limit, or eliminate MDR GNB strains will be futile if not combined with an effective infection control containment program that will limit the spread of these organisms within the CCU and the institution (1,2,14,25–30).

Clinicians should differentiate colonization from infection before considering empiric antimicrobial therapy in non-critically ill patients in the CCU. In general, colonization should

**Table 1** Antimicrobial Therapy of Susceptible and MDR *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*

	Susceptible strains	MDR strains
• <i>P. aeruginosa</i>		
Serious systemic infection	Meropenem Cefepime Cefoperazone Piperacillin ± amikacin	<i>If meropenem susceptible:</i> Meropenem <i>If meropenem resistant:</i> Doripenem Colistin Polymyxin B Fosfomicin
CAB only → PO	Levofloxacin	
• <i>K. pneumoniae</i>		
Serious systemic infection	Tigacycline Levofloxacin Moxifloxacin 3 <sup>rd</sup> generation (except ceftazidime) Cefepime Carbapenems Levofloxacin	Tigecycline Colistin Polymyxin B
CAB only → PO		Fosfomicin
• <i>A. baumannii</i>		
Serious systemic infection	Meropenem Ertapenem	Sulbactam/ampicillin Colistin Polymyxin B Doripenem Fosfomicin
CAB only → PO	Fosfomicin	

*Abbreviations:* CAB, catheter-associated bacteriuria; MDR, multidrug resistant; PO, by mouth.

**Table 2** Clinical Significance of *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*

Organism	Colonization Common	Infections in Normal Hosts	Infections in Compromised Hosts
• <i>P. aeruginosa</i>	<ul style="list-style-type: none"> <li>Respiratory secretions (ventilated patients)</li> <li>Urine (CAB)</li> <li>Wounds</li> <li>Aqueous medications/irrigant solutions</li> </ul>	<ul style="list-style-type: none"> <li>Nosocomial urosepsis (following urologic instrumentation)</li> <li>NP/VAP</li> </ul>	<ul style="list-style-type: none"> <li>Burns</li> <li>Bronchiectasis/cystic fibrosis (CAP)</li> <li>Febrile neutropenia</li> </ul>
• <i>K. pneumoniae</i>	<ul style="list-style-type: none"> <li>Respiratory secretions (ventilated patients)</li> <li>Urine (CAB)</li> <li>Aqueous medications/irrigant solutions</li> </ul>	<ul style="list-style-type: none"> <li>NP/VAP</li> <li>CVC infection</li> </ul>	<ul style="list-style-type: none"> <li>Alcoholics (CAP only)</li> </ul>
• <i>A. baumannii</i>	<ul style="list-style-type: none"> <li>Respiratory secretions (ventilated patients)</li> <li>Urine (CAB)</li> <li>Wounds</li> <li>Aqueous medications/irrigant solutions</li> </ul>	<ul style="list-style-type: none"> <li>NP/VAP (sporadic outbreaks only)</li> <li>CVC infections</li> </ul>	<ul style="list-style-type: none"> <li>NP/VAP (sporadic outbreaks only)</li> <li>CVC infections</li> </ul>

*Abbreviations:* CAB, catheter-associated bacteriuria; CAP, community-acquired pneumonia; CVC, central venous catheter; NP, nosocomial pneumonia; VAP, ventilator associated pneumonia.

not be treated/covered and is difficult to eradicate. Because colonization is difficult to eradicate, antibiotic therapy of colonization predisposes to the development of MDR *P. aeruginosa*, *K. pneumoniae*, or *A. baumannii*

Infections due to MDR GNBs are treated with antibiotics to which the MDR strain is susceptible. Therapy of MDR GNBs may be via the oral route for noncritical infections, i.e., CAB or via the IV route for serious systemic infections in critically ill patients (Tables 1 and 2) (6,10).

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# 29 | Antibiotic Kinetics in the Febrile Multiple-System Trauma Patient in Critical Care

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## INTRODUCTION

In no place throughout clinical medicine is the role of antibiotics more important than in the severely injured patient. Judicious and appropriate antibiotics are important for preventive indications when the traumatized patient requires a surgical procedure. Specific antibiotic therapy is necessary when infectious complications occur at the site of injury. Nosocomial infections occur at numerous locations during the critical care management and during the prolonged convalescence of these patients, antimicrobial chemotherapy for treatment. In the patient with an injury severity score  $> 30$ , antibiotics are employed frequently during the hospitalization and the emergence of resistant and unusual pathogens make the appropriate management of the infectious complications of these patients a formidable challenge.

The principals in the utilization of antibiotics for different indications in the trauma patient have become established over the last several decades. For preventive indications, the antibiotic should be given immediately prior ( $< 60$  minutes) to the skin incision for invasive interventions. The antibiotic should have activity against the likely pathogens to be encountered in the procedure. Prolonged preventive antibiotics after the procedure do not benefit the patient and should be stopped within 24 hours of the procedure. Infections that occur at the site of traumatic injury require antibiotic therapy against the clinically suspected and the culture-documented pathogens, in conjunction with aggressive surgical drainage and debridement of the primary focus. Because of the impact of the critical care unit, hospital microflora, and antecedent antibiotic treatment, nosocomial infections will notoriously be secondary to resistant organisms and must have susceptibility evidence to guide choices of treatment.

Although the above principals in the use of antibiotics are generally accepted, infection continues to be the major cause of death for injured patients without severe head injury who survive the initial 48 hours following the insult. The reasons for infectious deaths in the face of optimum antibiotic utilization are (i) the magnitude of contamination exceeds the capacity of the host and therapy to control, (ii) profound immunosuppression attends the injury, and (iii) antimicrobial resistance produces an array of pathogens that become very elusive to treat.

An important consideration that should be contemplated is whether the pathophysiologic changes of the severely injured patient create a clinical scenario where otherwise conventional antibiotic strategies may fail. This chapter will detail the systemic changes that are the result of the systemic activation of the human inflammatory cascade, and why these changes require a reassessment of antibiotic dosing strategies in febrile multiple-trauma patients. Finally, new strategies for the utilization of antibiotics in these patients will be proposed.

## NORMAL PHARMACOKINETICS OF ANTIBIOTICS

The study of the biological processes that ultimately determine antibiotic concentration at the effector site is referred to as pharmacokinetics. The biological processes that comprise pharmacokinetics include absorption, volume of distribution, biotransformation, and drug excretion. For antibiotics, the quantitative evaluation of each of these components is used to design the dose and the treatment interval that will be employed for clinical trials and

subsequent use of the drug. The clear objective of pharmacokinetic assessment is to provide antibiotic concentrations, which will ensure activity against the likely pathogens that are consistent with quantitative susceptibility information. A second objective is to maintain antibiotic concentrations within the nontoxic concentrations. In the process of drug development, antibiotics are studied in healthy, normal volunteers. Even in phase 3 prospective, randomized trials, the severity of illness that is evaluated with a new antibiotic product is not extreme. Witness the fact that phase 3 trials of peritonitis customarily are studying largely perforative appendicitis patients. The studies are geared to have few, if any, deaths, and obviously the studies are aimed at having no differences in the clinical outcomes. Only when new antibiotics are approved for use is there a meaningful trial of the drug in a critically ill population.

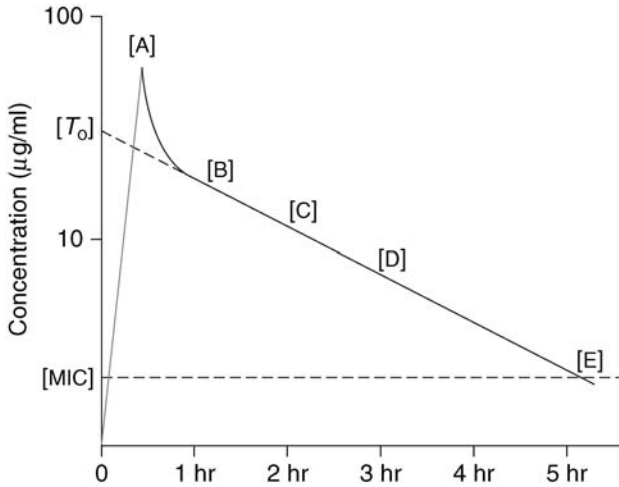
Absorption of antibiotics that will be used in the multiple-system trauma patient will be nearly 100% since all are given intravenously. This results in rapid distribution of the drug throughout the body water compartments to which it will have access. Intramuscular antibiotic administration would generally not be prudent in the trauma patient because severe soft tissue injury, shock, and expanded interstitial water volume would make systemic uptake less dependable. Oral antibiotics have generally not had a place in trauma patients during hospitalization since many will have nasogastric tubes in place or may have post-injury gastrointestinal ileus. The favorable bioavailability of quinolones, linezolid, and perhaps others in development may result in some reevaluation of the use of oral antibiotics in hospitalized trauma patients. Utilization of the gastrointestinal tract for nutritional support has been very effective in many trauma patients, and the intestinal tract may evolve as a route for the administration of antibiotics.

The distribution of the antibiotic after administration becomes a critically important issue. Each antibiotic has a unique volume of body water that it accesses following intravenous administration. The physiochemical properties of the drug that govern the distribution in the patient include the electrical charge of the molecule in solution, its solubility, its movement through cell membranes of different tissues, its lipophobic or lipophilic character, and whether metabolism is a requirement for elimination from the body. The distribution of the drug in body water is further modified by its degree of protein binding, since highly bound drugs will functionally be restricted in the extracellular water volume.

Unique features of the patient will also affect the distribution of the antibiotic and accordingly its concentration in serum at any point in time. Cardiac output, regional blood flow, and the volumes of intravenous fluids that are administered will change elimination and distribution. The route of drug elimination may be adversely affected by either preexisting or acquired abnormalities of renal or hepatic function. Disease processes affecting protein concentrations in plasma will particularly impact the drug that is highly protein bound.

In Figure 1, the concentrations of a hypothetical antibiotic in the serum of a patient are illustrated after intravenous administration. A rapid peak concentration is achieved that is largely dictated by the rate of infusion. The distribution of the drug throughout the various compartments and tissues that are accessed result in an equilibrium concentration, and from that point, the elimination of the drug proceeds in a consistent fashion. A semilogarithm plot is used for the concentration at each time point and this yields a linear configuration to the elimination plot. Extrapolation of the semilogarithm elimination plot to time-zero permits calculation of the volume of distribution ( $V_d$ ) of the drug in this specific set of clinical circumstances. The volume of distribution equals the total dose of drug given ( $D$ ) divided by the time-zero theoretical concentration ( $T_0$ ), or  $D/(T_0) = V_d$ . Thus, 1 g of an antibiotic ( $1 \times 10^6 \mu\text{g}$ ) with an extrapolated ( $T_0$ ) = 50  $\mu\text{mL}$  results in a  $V_d = 20,000 \text{ mL}$ , or 20 L. In an 80-kg patient, this would customarily be expressed at 0.25 L/kg.

The linear configuration of drug elimination over time permits calculation of the biological elimination half-life ( $T_{1/2}$ ). The  $T_{1/2}$  is the period of time required for the equilibrated plasma concentration of the drug to decline by 50%. The expectation is that the plasma concentration reflects the dynamic processes of equilibration of the central pool (i.e., plasma) with the multiple different pools and compartments in which the drug is present. Antibiotics are generally considered to have a single  $T_{1/2}$  that describes elimination of the drug, but some may have a second  $T_{1/2}$  that describes clearance at low concentrations.



**Figure 1** Illustrates the clearance curve of a theoretical antibiotic. The ordinate is the antibiotic concentration expressed in  $\log_{10}$ . The abscissa is time in hours. [A] represents the peak concentration after intravenous administration. [B] represents the maximum concentration after full equilibration of the antibiotic with all body water compartments to which that drug has access. [C] is the concentration of the antibiotic after one  $T_{1/2}$ . [D] is the concentration after the second  $T_{1/2}$ . [E] is the time intercept when the concentration of the drug reaches the [MIC] for the target organism that would be treated with the antibiotic being studied.  $[T_0]$  is the extrapolated concentration of the drug assuming full equilibration of the entire administered dose and without any elimination. From  $[T_0]$  and the dose of administration, the  $V_d$  can be calculated.  $V_d$  is a theoretical calculation that can be influenced by factors other than the actual body water of drug distribution. Thus, this calculated variable may actually be greater than total body water ( $>0.6$  L/kg).

Knowledge of the  $V_d$  and  $T_{1/2}$  allows the design of dose and dosage intervals for the antibiotic. If our theoretical drug in Figure 1 was deemed to have toxicity at concentrations above  $80 \mu\text{g/mL}$  then it would be desirable to have the concentration below that threshold for the treatment interval. Furthermore, the treatment interval between individual doses requires an understanding of the rate of declining concentrations of the drug and the minimum inhibitory concentration (MIC) of the drug against the likely pathogens to be encountered. If the MIC for likely pathogens was  $5 \mu\text{g/mL}$ , and the  $T_{1/2}$  of our drug was two hours, then four  $T_{1/2}$  would give a drug plasma concentration of  $6.25 \mu\text{g/mL}$ , which remains above the target MIC. Thus, a rational configuration of the use of this drug would be a 1 g dose that was re-dosed every eight hours. This theoretical design obviously assumes that maintenance of the drug concentration must be above the MIC at all time intervals. The post-antibiotic effect is seen where certain antibiotics (e.g., aminoglycosides) bind irreversibly to bacterial cell targets (e.g., ribosomes), and the action of the antibiotic persists after the therapeutic concentration is no longer present. Antibiotics with a significant post-antibiotic effect can have treatment intervals that are greater than would be predicted by the above model. Nevertheless, the above strategy is generally used for the design of the therapeutic application of drugs in clinical trials. The design is derived from studies in healthy volunteers and clinical trials are generally performed in patients without critical illness.

Biotransformation is the process by which the parent drug molecule is metabolized following infusion. Some antibiotics require biotransformation to have antimicrobial activity (e.g., clindamycin), others will have metabolism result in inactivity of the drug, while still others may have both the parent drug and the metabolite with retained biological activity (e.g., cefotaxime).

Biotransformation may occur via a number of pathways, although hepatic metabolism is most common. It may occur within the gastrointestinal tract, the kidney epithelium, the lungs, and even within the plasma itself. Hepatic biotransformation may result in the metabolite being released within the blood, resulting commonly in attenuation of action and facilitation of



elimination via the kidney. Hepatic metabolism may result in the inactivated metabolite being eliminated within the bile.

Clearly, abnormalities within the organ responsible for biotransformation will affect the process. Intrinsic hepatic disease from cirrhosis will alter hepatic biotransformation. The cytochrome P-450 system requires molecular oxygen, so poor perfusion or oxygenation of the liver from any cause will impact hepatic metabolism of specific drugs. Cytochrome P-450 may be induced by other drugs or be competitively inhibited. Drug interaction becomes yet another variable to influence concentration.

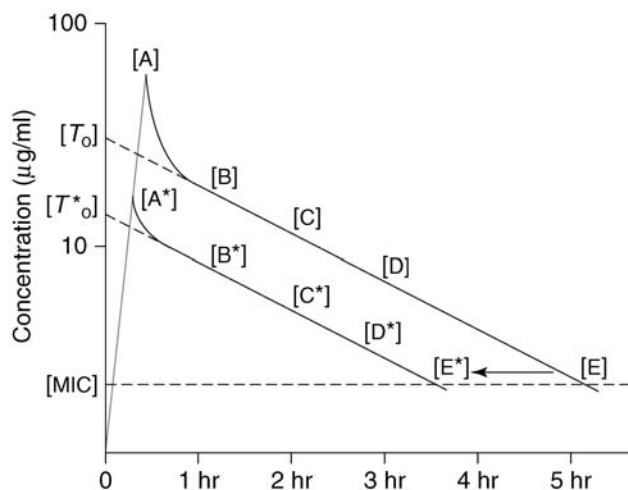
Excretion of the antibiotic occurs with or without biotransformation. Some drugs are eliminated unchanged by the kidney into the urine, or excreted by the liver into the bile. The rate of elimination of the unchanged drug directly affects the  $T_{1/2}$ . Excretion of unchanged drug via the biliary tract, which in turn can be reabsorbed, may create an enterohepatic circulation that results in prolonged drug presence in the patient. When either the intact drug or metabolic product is dependent on a specific organ system for elimination, intrinsic disease becomes an important variable in the overall pharmacokinetic profile.

### **PATHOPHYSIOLOGY OF INJURY AND FEVER**

The extreme model to characterize abnormal pharmacokinetics for any drug used in patient care would be in the febrile, multiple-system injury patient. Extensive torso and extremity injuries result in soft tissue injuries that activate the human systemic inflammatory response. This systemic inflammatory response requires extensive volume resuscitation for maintenance of intravascular volume and tissue perfusion. Extensive tissue injury also results in tissue contamination. Blunt chest trauma requires intubation and prolonged ventilator support, and exposure of the lung to environmental contamination. The injuries lead to prolonged incapacitation and recumbence. The patients are immunosuppressed from the extensive injuries, transfusions, and protein-calorie malnutrition. Following the injury itself, infection becomes the second wave of activation of systemic inflammation. Infection becomes a complication at the sites of injury, at the surgical sites of therapeutic interventions, and as nosocomial complications at sites remote from the injuries. Fever and hypermetabolism are common and add an additional compounding variable at a time when antimicrobial treatment is most important in the patient's outcome. Antibiotics are invariably used in the febrile, multiple-injury patient, but they are dosed and re-dosed using the model of the healthy volunteer initially employed in the development of the drug. Are antibiotics dosed in accordance with the pathophysiologic changes of the injury and febrile state?

Extensive tissue injury and invasive soft-tissue infection share the common consequence of activating local and systemic inflammatory pathways. The initiator events of human inflammation include (i) activation of the coagulation cascade, (ii) activation of platelets, (iii) activation of mast cells, (iv) activation of the bradykinin pathway, and (v) activation of the complement cascade. The immediate consequence of the activation of these five initiator events is the vasoactive phase of acute inflammation. The release of both nitric oxide-dependent (bradykinin) and independent (histamine) pathways result in relaxation of vascular smooth muscle, vasodilation of the microcirculation, increased vascular capacitance, increased vascular permeability, and extensive movement of plasma proteins and fluid into the interstitial space (i.e., edema). The expansion of intravascular capacitance and the loss of oncotic pressure mean that the  $V_d$  for many drugs will be expanded. Shock, injury, and altered tissue perfusion have been associated with the loss of membrane polarization, and the shift of sodium and water into the intracellular space. At a theoretical level, there is abundant reason to anticipate that the conventional dosing of antibiotics may be inadequate in these circumstances (Fig. 2).

The vascular changes in activation of the inflammatory cascade also result in the relaxation of arteriolar smooth muscle and a reduction in systemic vascular resistance. The reduction in systemic vascular resistance becomes a functional reduction in left ventricular afterload, which combined with an appropriate preload resuscitation of the severely injured patient leads to an increase in cardiac index. The hyperdynamic circulation of the multiple-trauma patients leads to the "flow" phase of the postsuscitative patient. Increased perfusion of the kidney and liver results in acceleration of excretory functions and potential enhancement



**Figure 2** Illustrates the influence upon the clearance curve of the theoretical antibiotic in Figure 1 of an increase in extracellular and/or intracellular water in a trauma patient that has fever secondary to invasive infection. The peak concentration  $[A^*]$  and the equilibrated peak concentration  $[B^*]$  are less than those concentrations observed under normal circumstances. The  $[T^*_0]$  is reduced because of the increase in  $V_d$ . In this model, the  $T_{1/2}$  has not changed, but the time point where the drug concentration  $[E^*]$  intercepts the  $[MIC]$  is 1.5 hours sooner (illustrated by the arrow) than would ordinarily be the case  $[E]$ .

**Table 1** Pathophysiologic Changes of the Systemic Inflammatory Response that is Triggered by Injury, Fever, and Sepsis

Pathophysiologic change	Theoretical pharmacokinetic effect
Increase in extracellular water	Increased volume of distribution; reduced peak concentration; reduction in AUC
Increased intracellular water	Increased volume of distribution; reduced peak concentration; reduction in AUC
Change in vascular permeability	Reduction in serum proteins; adverse effects upon highly protein-bound drugs
Elevated cardiac output	Increased hepatic and renal perfusion; reduction in biological elimination half-life
Reduction in vascular resistance	Reduced hepatic and renal perfusion, reduced drug clearance
Systemic inflammatory response syndrome	Endothelial damage, reduced microcirculatory flow, hepatic and renal dysfunction, and increased half-life and drug clearance

Each of the pathophysiologic parameters has a theoretical impact upon antibiotic pharmacokinetics. *Abbreviation:* AUC, area under the curve.

of drug elimination. It can be anticipated that  $T_{1/2}$  will be reduced. Subsequent organ failure from the ravages of sustained sepsis results in impairment of drug elimination and prolongation of  $T_{1/2}$ .

Severe injury results in the infiltration of the soft tissues with neutrophils and monocytes as part of the phagocytic phase of the inflammatory response. Proinflammatory cytokine signals are released from the phagocytic cells, from activated mast cells, and from other cell populations. The circulation of these proinflammatory signals leads to a febrile response with or without infection. The febrile response is associated with systemic hypermetabolism and autonomic and neuroendocrine changes that further amplify the systemic dyshomeostasis. Pro-inflammatory signaling up-regulates the synthesis of acute-phase reactants and down-regulates the synthesis of albumen, which further impacts the restoration of oncotic pressure and predictable drug pharmacokinetics. The summed effects of injury, fever, and the sequela of systemic inflammation result in pathophysiologic alterations (Table 1) that compromise the effectiveness of antibiotic therapy because of suboptimal dosing.

**CLINICAL DATA**

The discussion to this point has focused upon the theoretical argument that pathophysiologic changes of multiple injury, fever, and systemic inflammation will have on antibiotic pharmacokinetics. A review of the literature identifies a paucity of clinical studies in the

multiple-injury patient, despite the fact that antibiotics are used for a wide array of indications in these patients. The effects of pathophysiologic changes upon antibiotic therapy will be cited among studies of critically ill and severely septic patients in the intensive care unit, and not exclusively in multiple-trauma patients.

### Preventive Antibiotics in the Injured Patient

Preventive antibiotics have been used for over 30 years in trauma patients (1). The recognized principals of preoperative administration of an antibiotic with activity against the likely pathogens to be encountered have been the hallmark of utilization in this setting. However, trauma patients have blood loss and large volumes of resuscitation in the period of time leading up to, and during, the operative intervention. The sequestration of the resuscitation volume into injured tissue results and the obligatory expansion of the extracellular water volume all contribute to a vastly expanded  $V_d$ . Should antibiotic doses be modified in this clinical setting?

Ericsson et al. (2) studied penetrating abdominal trauma patients with a regimen of preventive antibiotics that employed clindamycin and amikacin. In a limited number of preliminary-study patients, they noted that conventional doses of 7.5 mg/kg amikacin given preoperative resulted in suboptimal peak serum concentrations (13.5 to 18.0  $\mu$ /mL) compared with effective therapeutic peak concentrations (25 to 28  $\mu$ /mL) at 30 minutes after infusion when 11 mg/kg of the drug was administered.

The explanation for the lower antibiotic concentrations in the conventional dosing regimen was found in the larger  $V_d$  and short  $T_{1/2}$  that were seen in the trauma patients compared to normal controls. In a study of eight patients that averaged 37 years of age and had normal creatinine, each received between 6.7 to 11 mg/kg of amikacin. The measured  $V_d$  was 20.9 L compared with the estimated normal of 14.3 L. The  $T_{1/2}$  was measured at 1.9 hours and the estimated normal  $T_{1/2}$  for amikacin was 3.3 hours. Subsequent studies of an additional 28 trauma patients confirmed the impact of the increased  $V_d$  and the increased elimination rates of the drug in adversely affecting preventive antibiotic concentrations (3).

A prospective study examined the wound and intra-abdominal infection rates of penetrating abdominal trauma patients who received different doses of amikacin (2). The data are illustrated in Table 2. Significantly, higher doses of amikacin resulted in statistically reduced infection rates in all patients studied. Subgroup analysis indicated that lower infection rates were identified in patients with high-volume blood loss and in patients with injury severity scores  $>20$ . No improvement in rates infections was seen in patients when colon injury was present, indicating that high inocula of surgical site contamination cannot likely be overcome by preventive antibiotics. This observed uncertainty about antibiotic pharmacokinetics in the setting of blood loss and injury has led to some experimental investigation in the use of continuous infusion of antibiotics as a means to overcome the problem. Another strategy has been to simply not use potentially toxic agents like the aminoglycosides, but rather choose

**Table 2** Differences in Clinical Outcomes of Infection when 7.5 mg/kg of Amikacin is Compared with 10 mg/kg of Amikacin in Trauma Patients with Penetrating Abdominal Trauma

Patient characteristic	7.5 mg/kg	$\geq 10$ mg/kg	<i>P</i> =	Comment
All patients	21/87 (24%)	5/63 (8%)	$<0.01$	The dose does matter!
No colon injury	12/57 (21%)	1/48 (2%)	$<0.005$	Small inoculum responds well to preventive drug
Colon injury	9/30 (30%)	4/15 (27%)	N.S. <sup>a</sup>	Large inoculum eliminates effectiveness
Blood loss $>6$ L	16/43 (37%)	3/27 (11%)	$<0.02$	Loss of antibiotic?
ISS <sup>b</sup> $>20$	11/32 (34%)	1/18 (6%)	$<0.025$	Large dose is necessary for large injuries.
ISS <sup>b</sup> $<20$	10/55 (18%)	4/45 (9%)	N.S. <sup>a</sup>	May have been a type-2 statistical error

<sup>a</sup>Not significant.

<sup>b</sup>Injury severity score.

$\beta$ -lactam alternatives where toxicity concerns are minimized and larger doses can be safely utilized.

The data that evaluate other antibiotics in preventive indications in trauma patients is very limited. Rosemury et al. (4) studied ceftizoxime in 53 celiotomies of trauma patients who received a conventional dose of preoperative antibiotic. They identified lower antibiotic concentrations in selected patients in the recovery room, and found that lower postoperative antibiotic concentrations were predictive of postoperative infections. They identified blood loss, extensive intraoperative resuscitation, and expanded  $V_d$  as likely causes for reduced postoperative antibiotic concentrations and recommended consideration for increased preoperative dose of preventive antibiotics. Similarly, Dalley et al. (5) studied  $\beta$ -lactam antibiotics used for prophylaxis in burn surgery and found inadequate plasma concentrations for targeted organisms. They recommended re-dosing or continuous infusion as a requirement for effective use of preventive antibiotics in this population.

### Aminoglycosides

The aminoglycosides more than any antibiotic group have been studied most extensively in the setting of critical illness. Nephro- and ototoxicity have been the driving issues that have stimulated pharmacokinetic studies of the aminoglycosides. However, the data indicate that perhaps more patients have been underdosed than have received toxic levels of these antibiotics. Given that gentamicin and the other aminoglycosides have been demonstrated to have highly variable pharmacokinetics even with patients that appear to have normal kidney function (6), it is not surprising that physiologic changes of trauma and clinical fever will further compound an already difficult situation.

Niemiec et al. (7) studied 100 trauma and other surgical patients in the surgical intensive care unit. All study patients received at least one aminoglycoside with the majority receiving gentamicin or tobramycin. The  $V_d$  increased approximately 50% greater than normal for this population with one patient demonstrating a threefold increase. The  $T_{1/2}$  was highly variable with a range from 1.6 to 63 hours;  $T_{1/2}$  increased with age. Using individual patient pharmacokinetic parameters, adjustments in gentamicin doses ranged from 1.4 to 15.5 mg/kg/day for these patients. In similar studies by Reid et al. (8), gentamicin and tobramycin were both found to require dramatic increases in the dosing of the drug in intensive care unit patients largely due to the increased  $V_d$  that was observed. In this latter study, drug elimination rates were strongly influenced by the patient's serum creatinine as a marker of clinical renal function. Despite larger doses that were required, doses of the aminoglycosides were given less frequently with patients having a creatinine above 1 mg/dL.

Summer et al. (9) studied 22 sepsis/septic shock patients following the administration of intravenous tobramycin at 2 mg/kg. They identified 59% of patients that had blood concentration of the antibiotic that was significantly below expected concentrations. The expanded  $V_d$  was considered to be responsible for the low blood concentrations.

Dasta and Armstrong (10) studied aminoglycoside pharmacokinetics in 181 critically ill patients in a surgical intensive care unit. The  $V_d$  was identified at 0.36 L/kg which was 60% to 70% above expected normal. The  $T_{1/2}$  was highly variable with a range of 1.1 to 69.3 hours. Additional studies have validated that the observations of increased  $V_d$  and highly variable  $T_{1/2}$  are applicable to all of the aminoglycosides in trauma (11) and intensive care unit patients (12).

Understanding these changes of aminoglycosides under circumstances of trauma, fever, and critical illness should lead to pharmacokinetic dosing and changes in the management of these patients. Zaske et al. (13) reported improved survival in burn patients undergoing dosing changes to address the pharmacokinetic changes. Once-daily dosing of aminoglycosides has become very common at present, but again the pharmacokinetic observations have demonstrated that conventional doses will be inadequate, especially for the younger trauma patient with normal renal function.

### Vancomycin

Like the aminoglycosides, the pharmacokinetics of vancomycin is highly variable among patients with normal renal function (14). Reid et al. (7) studied the pharmacokinetics of

vancomycin in infected surgical intensive care unit patients. They assumed and documented that the  $V_d$  of vancomycin was essentially that of total body water, or 0.6 L/kg. While the linear regression for  $V_d$  for vancomycin did cluster about 0.6 L/kg, the variability was quite high with an  $R^2$  for the relationship only being 0.15. In selected cases, the  $V_d$  was so high that it actually exceed the theoretical maximum of 1.0 L/kg, reflecting probably tissue binding of the antibiotic. Pharmacokinetic dosing required a 20% increase in the predicted dose of vancomycin, but a 50% increase in the interval between doses reflected a longer  $T_{1/2}$  than expected. In a more recent study, Vázquez et al. (15) note that 3 g of vancomycin was required every 24 hours to effectively treat patients in septic shock, but also noted that the adverse pharmacokinetic profile of the patients quickly reverted to normal when the infection was receding and that risks of toxicity can quickly evolve.

Vancomycin pharmacodynamics in burn patients has been noted to be quite variable. Rybak et al. (16) noted that  $V_d$  was quite variable, but only averaged about 10% more than control patients or intravenous drug abusers. Vancomycin clearance was 143 mL/min in the burn patient which was more than twice as great as that seen in control patients (68 mL/min). Vancomycin patients required larger and more frequent doses of the drug to achieve satisfactory peaks and troughs during therapy. The hyperdynamic circulation of the burn patient with normal kidney function was thought to be the basis for accelerated drug clearance. Garrelts and Peterie (17) made similar observations with respect to a reduced  $T_{1/2}$  in burn patients receiving vancomycin.

### **$\beta$ -Lactam Antibiotics**

Studies of the cephalosporin antibiotics have been limited with many of the commonly used drugs (e.g., cefazolin) not having been studied in trauma or febrile states. Virtually all have been in the third-generation group of cephalosporins. Van Dalen and Vree (18) studied  $V_d$  and  $T_{1/2}$  in critically ill patients after the administration of ceftriaxone, the most commonly employed third-generation cephalosporin. They identified that the pharmacokinetics patterns were very similar to the aminoglycosides with an expanded  $V_d$  and wide inter-patient variability with  $T_{1/2}$ . They concluded that unique nomograms needed to be developed to permit dosing of ceftriaxone that was consistent with each patient's unique severity of disease profile. Yet another study demonstrated similar findings with a 90% increase in  $V_d$  and that drug clearance was increased in patients with normal renal function (19). Patients with diminished renal function demonstrated a very prolonged  $T_{1/2}$  and posed a serious problem of potential drug accumulation.

Hanes et al. (20) studied ceftazidime in critically ill trauma patients. They identified that the  $V_d$  went from  $0.21 \pm 0.03$  L/kg in healthy volunteers to  $0.32 \pm 0.14$  L/kg in the trauma patients. It was felt that the large dose of the antibiotic (2 g every eight hours) overcame the pharmacokinetic changes in that only 8% of patients had subtherapeutic serum concentrations beneath the MIC. Dailly et al. (21) studied ceftazidime in burn patients that were not in the acute post-injury phase and noted an increased  $V_d$  but also identified lower clearance of the drug. They suggested that the expanded  $V_d$  could serve as a reservoir for the drug and result in slow return to the circulation, which would explain the reduced clearance. Gomez et al. (22) noted a significantly increased  $V_d$  and an increased  $T_{1/2}$ , but antibiotic clearance and bioavailability (i.e., "area under the curve") were not changed. Angus et al. (23) studied intermittent versus continuous infusion of ceftazidime in septic patients and concluded that every eight hour dosing of the drug left the patient at-risk for subtherapeutic concentrations because of the increased  $V_d$ . They concluded that continuous infusion would prove to use less total drug and would ensure reliable therapeutic drug concentrations.

Cefepime is a commonly used antibiotic especially later in the trauma patient's course when fever and nosocomial infection are significant issues. Bonapace et al. (24) studied 12 patients with burns (average of 36% total body surface) with suspected or documented infection and found a reduction in concentrations due to increased  $V_d$  but that doses of 1 g every 8 hours, and 2 g every 12 hours resulted in blood concentrations above the MICs of organisms likely to be targeted by this drug. Lipman et al. (25) studied 10 patients that were critically ill with sepsis and found that 80% of trough levels were beneath the MIC<sub>50</sub> for *Pseudomonas aeruginosa*. Kieft et al. (26) studied cefepime in patients with the septic syndrome

and identified nearly a doubling of the  $V_d$  and a prolonged  $T_{1/2}$ . They indicated that 2 g every 12 hours still resulted in adequate trough concentrations for expected MICs of pathogens, but also noted a widely variable pharmacokinetic profile in their patients, especially in the elderly.

The pharmacokinetics of aztreonam were studied in 28 critically ill, mostly trauma patients, with gram-negative infections (27). The  $V_d$  was nearly doubled over anticipated values for this study population. The patients were a relatively young group (age = 35 years) and received 2 g of aztreonam every six hours. Trough levels were above the MICs of likely pathogens, despite the increase in  $V_d$ . The larger dose of aztreonam was the likely reason that adverse effects were not seen from the increase in  $V_d$ . McKindley et al. (28) similarly identified increased  $V_d$  in trauma patients with pneumonia, but also identified prolongation of the  $T_{1/2}$ .

### Carbapenems

The carbapenem antibiotics are a subgroup of the  $\beta$ -lactams that are commonly used to treat the most difficult of infected trauma patients, especially with hospital-acquired bacteria. The data with imipenem have been quite variable. Boucher et al. (29) found that average  $V_d$  was comparable to controls in patients with burns, but did note the highly variable observations in the burn group. Dailly et al. (30) noted increased  $V_d$  and increased imipenem clearance rates in burn patients. McKindley et al. (26) also noted increased  $V_d$  and noted significantly lower plasma concentrations in trauma patients with pneumonia, while Belzberg et al. (31) noted very unpredictable  $V_d$  and  $T_{1/2}$  in critically ill patients and noted that very high  $V_d$  and low serum concentrations may contribute to treatment failures in this population of patients. Fish et al. (32) made the unique observation of the efficient clearance of imipenem by continuous venovenous hemofiltration and have indicated that this variable in addition to pharmacokinetic changes may be an additional reason to increase antibiotic administration. Similar pharmacokinetic observations were made with meropenem (33).  $V_d$  and  $T_{1/2}$  tended to be similar to normal adult measurements in surgical patients with intraabdominal infection and other surgical infections.

In a comparative trial of imipenem and meropenem, Novelli et al. (34) found differences in the two drugs. Following a standardized infusion of 1 g., they found a higher peak concentration and area-under-the-serum concentration-time curve with imipenem, while the  $V_d$  was higher for meropenem.

Profound changes in ertapenem pharmacokinetics have been reported in critically ill patients. Burkhardt et al. (35) treated 17 patients with ventilator-associated pneumonia. They found that the  $V_d$  of ertapenem nearly doubled, and that peak concentration- and the area-under-the-serum concentration-time curve were dramatically reduced. Of interest, the  $T_{1/2}$  was minimally changed. Ertapenem is a highly protein-bound drug (85% to 95%) and they associated these changes with the decline in the serum albumin of the patients. However, acute declines in serum proteins are certainly markers of the severity of infection, and the changes in ertapenem pharmacokinetics are still likely to be consequences of the systemic manifestations of severe infection.

### Quinolones

While specific data in the trauma patient are not available, the quinolone group of antibiotics appear to follow a different pattern of pharmacokinetic change in the critically ill patient and can be anticipated to have a different pattern in the injured patient as well. Lipman et al. (36) studied 18 critically ill patients at several days into the patients' treatment with ciprofloxacin. While normal volunteers will have a  $V_d = 1.8$  L/kg and a  $T_{1/2}$  will be four to five hours, adverse changes were not seen in severely infected patients treated with ciprofloxacin. The  $V_d$  was 1.2 to 1.4 L/kg and  $T_{1/2}$  was 3.2 to 3.9 hours. Peak and trough concentrations did not appear to be influenced by the septic state. These observations with ciprofloxacin were confirmed in patients with intraabdominal infection (37). A single study has identified selected patients where high MIC requirements may not be uniformly achieved in critically ill patients, and recommended 1200 mg daily to ensure optimal concentrations (38).

Studies with levofloxacin in patients with critical illness (39) and with ventilator-associated pneumonia (40) have similarly demonstrated no adverse changes in pharmacokinetic profiles. A single levofloxacin study identified pharmacokinetic changes that may have

significance for pathogens with high MIC breakpoints (41). The observation that the quinolone group of antibiotics have very large  $V_d$  that exceeds total body water means that increases in extracellular water volume have little impact. This potentially constitutes an advantage for this group of antibiotics in the febrile, critically ill patient, and perhaps in the trauma patient as well.

### Linezolid

A significant number of reports have identified treatment failures for both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) infections from treatment with vancomycin (42–45). This has led to considerable interest in the identification of alternative antibiotic treatment for both community-associated and hospital-acquired staphylococcal infections. Linezolid is the first of a new class of oxazolidinone antibiotics that appears to have a particular role in the treatment of MRSA infections. The  $V_d$  of this drug in patients and normal volunteers has been at 0.6 to 1.0 L/kg, which like the quinolones is a  $V_d$  that exceeds total body water.  $T_{1/2}$  has been reported from four to seven hours. Whitehouse et al. (46) reported linezolid pharmacokinetics on 28 patients with gram-positive infections in the intensive care unit. They found a  $V_d = 0.63$  L/kg and  $T_{1/2} = 2.6$  hours. Trough concentrations were adequate for the treatment of susceptible organisms. Of note, no modification was necessary for either renal or hepatic dysfunction. The combined observations of the quinolones and linezolid suggest that antibiotics with  $V_d$  that exceed total body water are less likely to be adversely affected by physiologic changes of injury, critical illness, and sepsis.

### MANAGEMENT OF PHARMACOKINETIC CHANGES

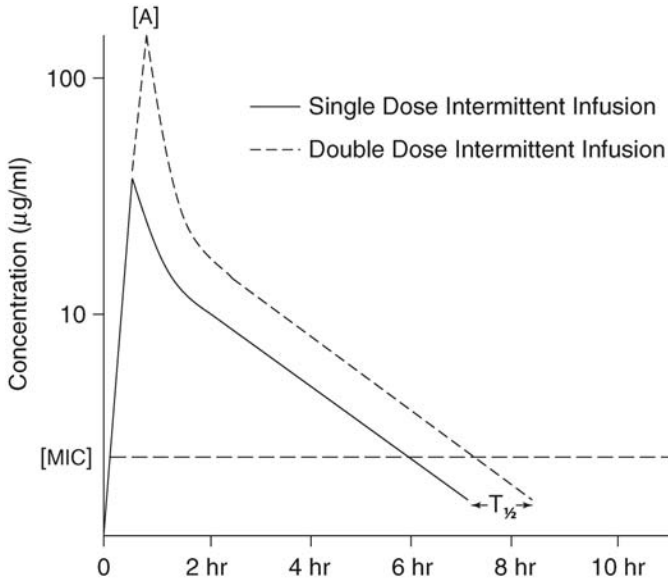
As clinical evidence has demonstrated that the pathophysiological changes of severe injury, fever, and the human septic response adversely affect the functional concentrations of antibiotics, modifications in how antibiotics are dosed and the frequency of administration has become the focus of new strategies. Traditional pharmacokinetic dosing could be employed, where peak and trough measurements permit the clinician to adjust the total dose, the dosing interval, or both. This becomes a biological titration where doses are empirically modified and remeasurement is undertaken to assess favorable changes in subsequent peak/trough concentrations. This has been a traditional way of managing aminoglycosides and in some cases vancomycin use. Most clinical pharmacokinetic dosing has been geared to avoid toxicity and only secondarily to the maintenance of therapeutic concentrations.  $\beta$ -Lactams, fluoroquinolones, and other antibiotics that have a favorable therapeutic ratio are not commonly pharmacokinetically dosed, and most clinical laboratories do not have the analytical methods for measurement. Measurement of these nontoxic agents will be an expense that most will not be willing to accept.

### Increase the Dose/Frequency of the Drug

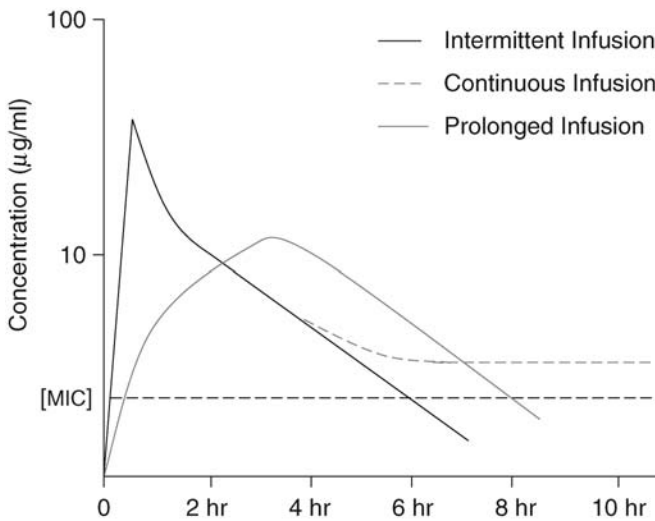
One strategy to overcome the reduction in antibiotic concentrations in the febrile, trauma patient is to either increase the dose or shorten the dosing interval. Figure 3 illustrates the potential benefit of increasing the dose. Doubling of the intravenous dose actually adds only one half-life to the duration of the drug concentration above the target concentration for the MIC. It does give a high peak concentration, which may be of value for antibiotics like the aminoglycosides that are concentration-dependent and have a sustained post-antibiotic effect (47). Another strategy is to shorten the dosing interval. For example, a q6h drug might be shortened to give the same dose to q4h to reduce the interval of subtherapeutic concentration. Increasing the dose or shortening the dosing interval can only be entertained when the antibiotic being used has a favorable therapeutic ratio. The rate of clearance of the drug and the  $V_d$  are dynamic processes, and very high concentrations of the antibiotic can be the result when dosing is increased in a patient with rapidly resolving pathophysiological hemodynamics of the systemic inflammatory response.

### Continuous Antibiotic Infusion

Antibiotic infusions are commonly given as 30 to 60 minute infusions. This results in the rapid spike in antibiotic concentration in serum that is identified in Figure 1. A very large amount of



**Figure 3** Illustrates the enhanced serum concentration of antibiotics that are achieved when the dose is doubled of a hypothetical drug with a normal dosing interval of six hours and a  $T_{1/2}$  of 1.5 hours. Doubling the dose only extends the duration of antibiotic concentration above the [MIC] target by one half-life. Point [A] identifies the peak concentration after doubling the dose.



**Figure 4** Illustrates the effects of continuous infusion and prolonged infusion upon the serum concentrations of the theoretical antibiotic model. Continuous infusion is begun after the initial intermittent full dose has been administered. The drug concentration flattens out at a level designed to continuous concentrations above the [MIC] target. The prolonged infusion results in an area under the curve that is similar to the same dose given normally, but the slower increase in the peak concentration results in slower total drug elimination.

drug is cleared in the first half-life, while the amount of drug that is cleared in the third or fourth half-life is relatively small. If the antibiotic is given by a continuous infusion, it is possible to sustain the antibiotic concentration above the desired concentration target, but without the peaks and troughs that characterize the normal rapid administration.

The strategy has been to give a standard dose of the antibiotic and then begin the infusion of the drug at an hourly rate that approximates the ordinary total 24-hour administration under conventional delivery methods (Fig. 4). Some trials have indicated that distributing the infusion rate over 24 hours permits maintenance of antibiotic concentrations at target levels, but with a reduction in overall total drug that is given.

Clinical trials that have compared continuous infusion to conventional drug administration are summarized in Table 3. The greatest interest in continuous infusion has been in the  $\beta$ -lactam agents. These are time-dependent agents without an appreciable post-antibiotic effect, which makes a sustained antibiotic concentration that is above the target threshold a treatment goal (60). Reviews and meta-analysis of continuous infusion have extolled the



**Table 3** Selection of Studies where Continuous Infusion of Antibiotics Was Compared with Intermittent Infusion

Authors	Antibiotic(s)	Type of infection	Patients continuous/ intermittent
Adebri et al. (48)	Linezolid	Septic patients	8/8
Angus et al. (23)	Ceftazidime	Septic melioidosis	10/11
Bodey et al. (49)	Cefamandole + carbenicillin	Fever of unknown origin/neutropenia	74/92
Buijk et al. (50)	Ceftazidime	ICU patients	12/6
Feld et al. (51)	Tobramycin + cefamandole	Septic granulocytopenia	30/46
Feld et al. (52)	Sisomicin	Infections in neutropenia	60/61
Georges et al. (53)	Cefepime	Critically ill	26/24
Hanes et al. (20)	Ceftazidime	Nosocomial pneumonia (trauma patients)	17/14
Lau et al. (54)	Piperacillin + tazobactam	Intra-abdominal infection	130/132
McNabb et al. (55)	Ceftazidime	Nosocomial pneumonia	17/18
Roberts et al. (56)	Ceftriaxone	Critically ill	29/28
Sakka et al. (57)	Imipenem	Nosocomial pneumonia	10/10
Van Zanten et al. (58)	Cefotaxime	Exacerbation chronic lung disease	47/46
Wysocki et al. (59)	Vancomycin	Severe staphylococcal infections	61/58

Many of the studies are not powered with sufficient patients to give an assessment of outcomes. Numerous different drugs have been studied. A prospective, randomized trial with a large population of well-stratified patients is needed to answer the question of continuous infusion of antibiotics as a superior treatment strategy.

*Abbreviation:* ICU, intensive care unit.

virtues of this delivery method (61,62), but evidence to show consistently superior outcomes have been lacking. Studies have suffered from small number of patients and an absence of consistent severity in the study populations. Because the continuous infusion technique adds an additional therapeutic imposition at the bedside in the intensive care unit, additional evidence is necessary to validate the utility of this method.

### Prolonged Antibiotic Infusion

A compromise position between conventional intermittent and continuous infusion is the concept of prolonged or extended infusion of antibiotics. As was noted in Figure 1, intermittent infusion results in a peak concentration and the peak is in part dictated by the rapidity with which the drug is infused. After equilibration, elimination begins consistent with the  $T_{1/2}$  of the drug. If the infusion is extended over three hours instead of 30 minutes, then the peak concentration will be somewhat diminished, but the rate of total drug elimination will also be delayed. Prolonged administration affords an extended period of time for the drug to have therapeutic concentrations (Fig. 4). This extension of therapeutic concentrations has the potential for use under circumstances of adverse  $V_d$  changes in febrile, multiple-trauma patients. Studies with carbapenems (63,64) and piperacillin-tazobactam (65,66) have shown favorable pharmacokinetic profiles with prolonged infusion, but clinical evidence that compares this method with conventional antibiotic administration strategies are needed.

### SUMMARY

The actual number of studies that have examined the febrile multiple-trauma patients is few, and conclusions about pharmacokinetic changes in this population must be extrapolated at this time from studies of intensive care unit patients, septic patients, burn patients, and others with critical illness. It is clear that more clinical studies are needed and that alternative administration strategies should be explored to improve clinical outcomes. However, it is clear that antibiotic concentrations are adversely affected for most drugs as the injured and septic patient progressively accumulates "third space" volume. The quinolones and perhaps linezolid are exceptions. Clearance of antibiotics appear to be highly variable and clearly are influenced by drug concentration changes, cardiac output changes and their influence upon

kidney and liver perfusion and the intrinsic coexistent dysfunction of the kidney or liver. For most antibiotics used in the multiple-trauma patient, it is likely that they are underdosed and that inadequate antibiotic administration contributes to both treatment failures and to emerging patterns of antimicrobial resistance. More studies of antibiotic pharmacokinetics in the multiple-system injured patient are necessary.

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# 30 | Antibiotic Therapy in the Penicillin Allergic Patient in Critical Care

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## INTRODUCTION

Empiric antimicrobial therapy is a necessity in the critically ill patient with a life-threatening infectious disease. Several factors go into antibiotic selection including (i) spectrum of activity against the presumed pathogens, which is related to the source of infection or organ system involved; (ii) pharmacokinetic and pharmacodynamic considerations which affect dosing and concentration in the source organ for the sepsis; and (iii) the resistance potential of the antibiotic needs to be considered. Although cure of the patient is the immediate priority, drug selection has a subsequent effect on the flora of the critical care unit (CCU) and eventually may impact on the flora of the hospital. The fourth consideration is the safety profile of the drug, which has to do with adverse side effects and interactions, as well as the patient's allergic drug history. One of the most common problems encountered in treating critically ill patients is the question of penicillin allergy.

## DETERMINING THE TYPE OF PENICILLIN ALLERGY

There are no good data on the incidence of penicillin allergy. Some studies are done using skin testing to derive the data. Other studies are based on clinical information, i.e., questioning the patient or relatives regarding the nature of the penicillin allergy. Often penicillin allergy is mentioned, but further or detailed question reveals that it is not truly an allergic reaction at all. Patients, if they are able to respond, are either vague or very clear about the nature of their penicillin allergy. In the critical care setting, there is often no way to get a drug allergy history. Relatives are usually uncertain as to the nature of the allergic reaction of the patient. There is poor correlation between the patient reporting penicillin allergy and subsequent penicillin skin testing. In critical care medicine, the patient's history is the only piece of information that the clinician has to work with to make a decision regarding the nature of possible penicillin allergy (1–6). Because  $\beta$ -lactam antibiotics are one of the most common classes of antibiotics used, the question of using these agents in patients with penicillin allergy is a daily consideration. The clinical approach to the patient with a potential skin allergy involves determining the nature of the penicillin allergy as well as selecting an agent with a spectrum appropriate to the organ source of the sepsis. Penicillin allergies may be considered as those that result in anaphylactic reactions, i.e., anaphylaxis, laryngospasm, bronchospasm, hypotension, or total body hives, and those that result in non-anaphylactic reactions, i.e., drug fever or skin rash. Patients with non-anaphylactoid skin reactions may safely be given  $\beta$ -lactam antibiotics with a spectrum appropriate to the site of infection. Patients with a history of an anaphylactic reaction to penicillin should be treated with an antibiotic of another class that has a spectrum appropriate to the focus of infection (7–11).

## PENICILLIN ALLERGIC REACTIONS

In the critical care setting, when urgent antimicrobial therapy is necessary, there is no time for skin testing to rule out or confirm penicillin allergy. Patients who are communicative can indicate, on direct questioning, the nature of their penicillin reaction. Often times what is considered a penicillin reaction by the patient is in fact an unrelated drug side effect. Patients often report a vague history of penicillin allergy during childhood that has not recurred subsequently, while others report penicillin allergy occurred in close relatives but not themselves. Some patients were told they had a drug fever due to penicillin, but did not

develop a rash, yet others report the reaction to a penicillin antibiotic was limited to a maculopapular rash. Responses to any of these indicate that if the patient had a reaction to penicillin, it was of the non-anaphylactoid variety. Patients with drug fever or rash due to penicillins may be safely given penicillins again (12,13). Reactions to  $\beta$ -lactams are stereotyped such that if the patient had a fever as the manifestation of penicillin allergy, on re-challenge, the patient will develop fever again as opposed to another clinical manifestation of penicillin allergy. Patients with drug fevers or drug rashes due to penicillins, at worst, will only have a similar non-anaphylactic reaction upon re-challenge with penicillin. Alternately, they may have no reaction at all if the  $\beta$ -lactam chosen is sufficiently different antigenetically than the one initially causing the reaction. It is not uncommon in clinical practice with third-generation cephalosporin allergies to have patients not react to cefoperazone, which is the most antigenemic member of third-generation cephalosporins. Among the second-generation cephalosporins, cefoxitin is the least likely to cross-react with other second-generation cephalosporins (12–14).

### **CROSS REACTIONS BETWEEN PENICILLINS AND $\beta$ -LACTAMS**

When cephalosporins were first introduced, the reported cross-reactivity rate with penicillins was high as 30%. Subsequently, actual cross allergic reactions were <3%. Many of the cross-reactions initially reported between penicillins and cephalosporins were nonspecific allergic reactions not based on penicillin/cephalosporin cross-reactivity. Patients with a penicillin allergy who have had a non-anaphylactic reaction may safely be given a  $\beta$ -lactam antibiotic. In the unlikely event the patient has a reaction, the patient would develop a drug fever or rash, but not anaphylaxis. The  $\beta$ -lactam class of drugs includes the penicillins, the semi-synthetic penicillins, the modified penicillins, the amino-penicillins, and the ureido-penicillins (15–22).

### **CARBAPENEMS AND MONOBACTAMS**

From an allergic perspective  $\beta$ -lactams may be divided into carbapenems and non-carbapenems. Among the non-carbapenems are first-, second-, third-, and fourth-generation cephalosporins. Allergy to one is likely to result in cross-reactivity with another with the exceptions of cefoxitin among the second-generation cephalosporins, and cefoperazone among the third-generation cephalosporins. Although carbapenems are structurally related to  $\beta$ -lactam antibiotics from an allergic perspective, they should not be regarded as  $\beta$ -lactam antibiotics. Carbapenems, e.g., meropenem, do not react with other  $\beta$ -lactams or penicillin-derivatives. Therefore, carbapenems are frequently used as an alternative class of antibiotics to  $\beta$ -lactams and do not cross-react with any penicillin or  $\beta$ -lactam to such an extent that the reaction would be reportable in the literature. Carbapenems in general, and meropenem in particular is completely safe to give patients with known/suspected history of penicillin anaphylaxis. The more likely the history of anaphylaxis to penicillin, the more confidently can the clinician safely use meropenem (23–25).

### **NON $\beta$ -LACTAM ANTIBIOTICS IN PATIENTS WITH PENICILLIN ANAPHYLACTIC REACTIONS**

In patients giving a history of an anaphylactic reaction, i.e., anaphylaxis, laryngospasm, bronchospasm, hypotension, or total body hives, it is important to select a non  $\beta$ -lactam antibiotic to avoid complicating the already serious situation in the critical care setting. As with non-anaphylactoid penicillin reactions, anaphylactic reactions tend to be stereotyped with repeated exposures. Patients who develop laryngospasm as the manifestation of their penicillin allergy do not develop total body hives on subsequent re-exposure but will repeatedly develop laryngospasm as the main manifestation of their anaphylactic reaction. As with other manifestations of anaphylaxis, the reactions are stereotyped and will be repetitive and not change to another anaphylactoid manifestation. Fortunately there are so many highly effective non  $\beta$ -lactam antibiotics available at the present time, that invariably there are many appropriate non  $\beta$ -lactam antibiotics to choose from to treat the life-threatening infections encountered in the CCU (Table 1) (22–25).

Antibiotic classes that have no allergic cross-reactivity with  $\beta$ -lactams include the macrolides, tetracyclines, clindamycin, chloramphenicol, TMP/SMX, aminoglycosides,

**Table 1** Antimicrobials Safe to Use in Penicillin-Allergic Patients in the CCU

<i>Antibacterials</i>	<i>Antivirals</i>
Carbapenems	Amantadine
Meropenem	Rimantadine
Imipenem <sup>a</sup>	Acyclovir
Ertapenem <sup>b</sup>	Gancyclovir
Monobactams	Valganciclovir
Aztreonam	<i>Aminoglycosides</i>
Quinolones	Gentamicin
Ciprofloxacin	Tobramycin
Levofloxacin	Amikacin
Moxifloxacin	<i>Tetracyclines</i>
<i>Antifungals</i>	Doxycycline
Amphotericin B/Lipid preparations	Minocycline
Minocycline	
Flucytosine	<i>Other</i>
Fluconazole	Clindamycin
Itraconazole	Chloramphenicol
Caspofungin	TMP-SMX
Voriconazole	Rifampin
Voriconazole	Colistin
Micafungin	Polymyxin B
	Vancomycin
	Quinupristin/dalfopristin
	Linezolid
	Daptomycin
	Tigecycline

<sup>a</sup>Allergic reactions very uncommon.

<sup>b</sup>No data.

metronidazole, polymyxin B, vancomycin, quinupristin/dalfopristin, linezolid, daptomycin, quinolones, monobactams, and as previously mentioned, carbapenems. In thirty years of clinical experience in infectious disease, the author has never had to resort to penicillin desensitization to treat a patient. There is always an alternative, non  $\beta$ -lactam antibiotic, which is suitable for virtually every conceivable clinical situation. Although penicillin sensitivity testing/desensitization is a potential consideration in the non-critical ambulatory patient, in the critical care setting there is no time or need for penicillin testing/desensitization. If there is any question about a penicillin allergy in a non-communicative patient in the CCU, then monotherapy or combination therapy with one of the non  $\beta$ -lactam antibiotics mentioned above is appropriate and safe. The non  $\beta$ -lactam antibiotics most useful in the critical care setting for the most common infectious disease syndromes encountered are presented here in tabular form (Tables 2 and 3) (22,26).

**Table 2** Clinical Approach to  $\beta$ -Lactam Use in Those with Known or Unknown Reactions to Penicillin

	Nature of reported penicillin allergy	$\beta$ -Lactams safe to use
Non-anaphylactic reactions	Drug fever	1st, 2nd, 3rd, and 4th generation cephalosporins
	Drug rash	
	<i>E. multiforme</i>	Avoid penicillins or cephalosporins
Anaphylactic reactions	Steven–Johnson Syndrome	
	Hypotension	Meropenem <sup>a</sup>
	Laryngospasm	
	Bronchospasm	Imipenem <sup>b</sup>
	Generalized hives	Ertapenem <sup>c</sup>

<sup>a</sup>No/minimal potential for allergic cross reactions.

<sup>b</sup>Very low, but definite potential for allergic cross reactions.

<sup>c</sup>No data.

**Table 3** Antibiotics Safe in Penicillin-Allergic Adult Patients in the CCU

Clinical Syndrome	PCN allergy	Non-PCN allergic
<ul style="list-style-type: none"> <li>Acute bacterial meningitis               <ul style="list-style-type: none"> <li><i>H. meningitidis</i></li> <li><i>H. influenzae</i></li> <li><i>S. pneumoniae</i></li> <li>MSSA</li> <li><i>Listeria</i></li> </ul> </li> </ul>	Meropenem (meningeal dose) <sup>a</sup>	Ceftriaxone <sup>b</sup>
<ul style="list-style-type: none"> <li>Brain abscess</li> </ul>	<ul style="list-style-type: none"> <li>Chloramphenicol</li> <li>Meropenem (meningeal dose)<sup>a</sup></li> <li>Chloramphenicol</li> </ul>	Ceftriaxone <i>plus</i> metronidazole
<ul style="list-style-type: none"> <li>Severe CAP (typical/atypical pathogens)</li> </ul>	<ul style="list-style-type: none"> <li>Levofloxacin<sup>d</sup></li> <li>Moxifloxacin</li> <li>Doxycycline</li> </ul>	Ceftriaxone <i>plus either</i> doxycycline <i>or</i> azithromycin
<ul style="list-style-type: none"> <li>NP/VAP</li> </ul>	<ul style="list-style-type: none"> <li>Levofloxacin<sup>d</sup></li> <li>Meropenem</li> </ul>	Cefepime Piperacillin/tazobactam
<ul style="list-style-type: none"> <li>ABE               <ul style="list-style-type: none"> <li>MSSA/MRSA</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Daptomycin</li> <li>Linezolid</li> <li>Minocycline</li> <li>Vancomycin</li> </ul>	<ul style="list-style-type: none"> <li><i>plus</i> amikacin</li> <li>Nafcillin</li> <li>Cefazolin</li> <li>None</li> </ul>
<ul style="list-style-type: none"> <li>Cholangitis</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Tigecycline</li> </ul>	Cefoperazone Piperacillin/tazobactam
<ul style="list-style-type: none"> <li>Liver abscess</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Tigecycline</li> </ul>	Cefoperazone Piperacillin/tazobactam
<ul style="list-style-type: none"> <li>Intra-abdominal source (colitis, peritonitis, or abscess)</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Tigecycline</li> <li>Ertapenem</li> <li>Moxifloxacin<sup>c</sup></li> <li>Levofloxacin <i>plus either</i> metronidazole <i>or</i> clindamycin</li> </ul>	<ul style="list-style-type: none"> <li>Piperacillin/tazobactam</li> <li>Cefoxitin</li> <li>Cefoperazone</li> <li>Ceftizoxime</li> </ul>
<ul style="list-style-type: none"> <li>Pelvic source (peritonitis, abscess, septic pelvic thrombophlebitis)</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Ertapenem</li> <li>Tigecycline</li> <li>Moxifloxacin</li> <li>Levofloxacin <i>plus either</i> metronidazole <i>or</i> clindamycin</li> </ul>	<ul style="list-style-type: none"> <li>Piperacillin/tazobactam</li> <li>Cefoxitin</li> <li>Cefoperazone</li> <li>Ceftizoxime</li> </ul>
<ul style="list-style-type: none"> <li>Urosepsis               <ul style="list-style-type: none"> <li>GNB</li> <li>Group D enterococci</li> <li><i>E. faecalis</i> (VSE)</li> <li><i>E. faecium</i> (VRE)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Vancomycin</li> <li>Linezolid</li> <li>Meropenem</li> <li>Linezolid</li> <li>Quinupristin/dalfopristin</li> </ul>	<ul style="list-style-type: none"> <li>Piperacillin/tazobactam</li> <li>Ampicillin</li> <li>None</li> </ul>
<ul style="list-style-type: none"> <li>Complicated wound infections (cSSSIs)</li> </ul>	<ul style="list-style-type: none"> <li>Tigecycline</li> <li>Meropenem</li> <li>Ertapenem</li> <li>Moxifloxacin</li> <li>Levofloxacin <i>plus either</i> metronidazole <i>or</i> clindamycin</li> </ul>	Piperacillin/tazobactam
<ul style="list-style-type: none"> <li>Necrotizing fasciitis</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Tigecycline</li> <li>Ertapenem</li> </ul>	<ul style="list-style-type: none"> <li>Piperacillin/tazobactam</li> <li>Cefoxitin</li> </ul>
<ul style="list-style-type: none"> <li>Sepsis (unknown source)</li> </ul>	<ul style="list-style-type: none"> <li>Meropenem</li> <li>Tigecycline</li> </ul>	Piperacillin/tazobactam

<sup>a</sup>2 g (IV) q8h. <sup>b</sup>2 g (IV) q12h. <sup>c</sup>For mild/moderately severe infection. <sup>d</sup>750 mg (IV) q24h.

**Abbreviations:** PCN, penicillin; CAP, community-acquired pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole; I.T., intrathecal; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; VAP, ventilator associated pneumonia; ABE, acute bacterial endocarditis; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci; GNB, gram-negative bacilli.



## CONCLUSION

The incidence of penicillin allergy in the general population has been estimated to be between 1% and 10%, but no good reliable data exist on the actual incidence of penicillin allergy. Penicillin data derived from penicillin skin testing does not correlate with penicillin reactions in the clinical setting. Many patients reporting penicillin allergy have in fact had reactions to penicillin, which are not on an allergic basis. Penicillin reactions are of the non-anaphylactic or anaphylactic variety if they are indeed penicillin reactions. Penicillin reactions may occur on a single exposure to a penicillin or  $\beta$ -lactam antibiotic. From questioning or previous history, patients' bona fide penicillin reactions may be classified as anaphylactic or non-anaphylactic. Because the cross-reactivity between  $\beta$ -lactams and penicillin is so low,  $\beta$ -lactam antibiotics may be used in patients who have had drug fever or a drug rash as the primary manifestation of their penicillin allergy. Should the patient develop an allergic cross-reaction between the  $\beta$ -lactam and the penicillin, the allergic manifestation will be of the same type as encountered previously.

In patients with a history of anaphylactic reactions to penicillin, it is essential to use a non  $\beta$ -lactam antibiotic, i.e., a carbapenem, monobactam, quinolone, clindamycin, TMP/SMX, quinupristin/dalfopristin, linezolid, vancomycin, daptomycin, clindamycin, metronidazole, polymyxin B, or an aminoglycoside. As with non-anaphylactic penicillin cross-reactions, anaphylactic reactions to penicillin also tend to be stereotyped, and upon repeated exposure have the same clinical expression as initially manifested in their allergic response. It is important to remember that although meropenem is structurally a  $\beta$ -lactam, meropenem also does not cross react with those with penicillin allergies, including those with anaphylactic reactions (27–31). This has been shown in a large prospective clinical study (32,33).

Because the therapeutic armamentarium at the present time is so extensive, it is rarely necessary to de-sensitize a patient in the critical care setting to receive a  $\beta$ -lactam when so many antibiotics are available and effective.

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# 31 | Adverse Reactions to Antibiotics in Critical Care

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## INTRODUCTION

Each year drug-related adverse events cause an estimated 140,000 visits to U.S. emergency departments. Antibiotics are considered responsible for 19% of these visits (1). Life-threatening reactions include arrhythmias, hepatotoxicity, acute renal failure, and antiretroviral therapy-induced lactic acidosis. During the latter half of the 20th century 6% to 7% of hospitalized patients experienced a serious adverse drug reaction (2). Approximately 5% of serious inpatient reactions were fatal, making hospital-related adverse drug reactions responsible for approximately 100,000 deaths in the United States annually. Patients who are elderly (3), have renal insufficiency (4), or are HIV-infected (5) have an especially high risk of reactions. Many of these reactions result in intensive care unit (ICU) admission.

More than 70% of ICU patients receive antibiotics for therapy or prophylaxis, with much of this use being empiric and most of the recipients receiving multiple agents (6,7). The clinical presentation of an adverse drug reaction may be very different in an ICU patient than in a more healthy individual because of both the severity of the ICU patient's illness (which often requires that the patient be heavily sedated and paralyzed) and the multiple therapies that he or she often requires. Therefore, attributing a particular adverse reaction to a specific antibiotic can be extremely difficult, may involve several factors operating in unison, and can tax the minds of the brightest clinicians.

Adverse reactions associated with drug use include allergies, toxicities, and side effects. An *allergy* is a hypersensitivity reaction to a drug. Many are IgE-mediated and occur soon after drug administration. Examples of IgE-mediated type 1 hypersensitivity reactions include early-onset urticaria, anaphylaxis, bronchospasm, and angioedema. Non-IgE-mediated reactions include hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. *Toxicity* is a consequence of administering a drug in quantities exceeding those capable of being physiologically "managed" by the host, and is generally due to either excessive dosing and/or impaired drug metabolism. Examples of toxicity caused by excessive dosing include penicillin-related neurotoxicity (e.g., twitching, seizures) and the toxicities caused by aminoglycosides. Decreased drug metabolism or clearance may be due to impaired hepatic or renal function. For example, penicillin G neurotoxicity may be precipitated by aminoglycoside-induced renal failure. *Side effects* reflect the large number of adverse reactions that are neither immunologically mediated nor related to toxic levels of the drug. An example is the dyspepsia caused by erythromycin. A patient's genotype can predispose her or him to an allergic reaction (e.g., abacavir-related hypersensitivity) or to toxicity by affecting drug metabolism (e.g., isoniazid-related peripheral neuropathy is more likely in a patient who acetylates the drug slowly).

This review describes adverse reactions and important drug interactions involving antibiotics. It concentrates on those agents likely to be used in critical care and is not encyclopedic. The Table 1 summarizes and prioritizes the most common antibiotic-related adverse reactions seen in the ICU. This article only briefly discusses antiretroviral drugs and antibiotic dosing; it does not address issues specific to pregnant or pediatric patients.



## ANAPHYLAXIS

Anaphylaxis is an acute hypersensitivity reaction that can result in immediate urticaria, laryngospasm, bronchospasm, hypotension, and death. In the critical care setting, these reactions may be masked by underlying conditions or other therapies. While anaphylaxis can be precipitated by antigen-antibody complexes, it is usually IgE mediated. The binding of antibiotic epitopes to specific preformed IgE antibodies on the surface of mast cells results in the release of histamine and other mediators that lead to the aforementioned clinical presentations.  $\beta$ -Lactams are more often associated with these reactions than other antimicrobials. Best data exist for penicillin, where the risk of anaphylaxis is about 0.01% (8). Death occurs in one of every 100,000 courses of this agent (9). Conversely, only 10% to 20% of patients who claim to have an allergy to penicillin are truly allergic as determined by skin testing (10). Fifty percent of patients with a positive skin test will have an immediate reaction when challenged with penicillins (11). Approximately 4% of patients with a history of penicillin allergy who test positive to penicillin will experience a reaction (only rarely anaphylaxis) when given a cephalosporin (12). First-generation cephalosporins and cefamandole share a side chain similar to the chain present in penicillin and amoxicillin, and there is an increased risk of allergic reactions to these cephalosporins in penicillin-allergic patients. Other second-generation and third-generation cephalosporins have different side chains than penicillin and amoxicillin; a recent meta-analysis found no increased risk of allergic reactions to these cephalosporins in penicillin-allergic patients when compared with patients without a penicillin allergy (13). While early studies concluded that there is an increased risk of reactions in penicillin-allergic patients given carbapenems, recent studies have demonstrated that administering meropenem and imipenem to these patients is safe (14–17). Aztreonam can be given safely to patients with a history of anaphylaxis to all  $\beta$ -lactams except ceftazidime (9).

## CARDIOTOXICITY

A survey of intensivists at our institution found that the antibiotic adverse reaction that concerns them the most is QT prolongation with ventricular arrhythmia. In patients with susceptible substrate (e.g., coronary artery disease), precipitators (e.g., drugs and/or electrolyte disturbances) can cause torsades des pointes and sudden death (18). Often, QT prolongation precedes the drug-induced arrhythmia. However, drug-induced QT prolongation does not always result in torsades des pointes nor do medications that can cause torsades always prolong the QT interval. Antibiotics that can prolong the QT interval include macrolides, fluoroquinolones, azoles, pentamidine, and quinine. A cohort study of patients receiving oral erythromycin found a two-fold increased risk of sudden death in patients receiving this macrolide (19). Combining antibiotics and other drugs (e.g., amiodarone, haloperidol, diltiazem) that prolong the QT interval can increase the risk of torsades des pointes and sudden death (18). To avoid prescribing multiple medications that prolong the QT interval and predispose patients to torsades des pointes, intensivists and pharmacists can look up [www.azcert.org](http://www.azcert.org). Clinicians should consider using alternative antibiotics in patients with a baseline QTc interval  $>500$  milliseconds. If the QTc interval increases by 30 to 60 milliseconds or to more than 500 milliseconds, replacing known offending agent(s) with a different drug should be considered (18).

Myocardial depression, hypotension, and sudden death have been reported with vancomycin use, generally in the setting of rapid administration in the perioperative period (20,21). Similarly, rapid administration of amphotericin B has been associated with ventricular fibrillation and asystole, especially in patients with renal dysfunction (22). Amphotericins and pentamidine infusions can precipitate hypotension.

## NEPHROTOXICITY

Acute renal failure is common in ICU patients and associated with a risk of mortality of  $>60\%$  (23). Numerous agents used in the ICU are capable of affecting renal function. Mechanisms include decreased glomerular filtration, acute tubular necrosis, interstitial nephritis, and crystallization of the drug within the tubules. With regard to antibiotics, the aminoglycosides

and amphotericins are the prototypical classes associated with acute renal failure; the availability of drugs with similar spectrums of activity that are significantly less likely to cause acute renal failure is the major reason that use of these drugs has markedly declined in the last two decades. As with other antibiotic-associated adverse reactions, the likelihood of antimicrobial-induced nephrotoxicity is greater in patients with conditions or on medications that independently cause this complication.

Depending upon the criteria used to define acute renal failure, aminoglycoside-induced nephrotoxicity occurs in 7% to >25% of patients who receive these drugs (24). It usually results from tubular epithelial cell damage and presents as acute tubular necrosis. When using a small change in serum creatinine as the criterion for renal dysfunction (22) one study found that gentamicin (26%) is more nephrotoxic than tobramycin (12%) and that nephrotoxicity usually becomes evident between 6 and 10 days after starting the aminoglycoside. However, other investigations have challenged this conclusion (25). Aminoglycoside-induced acute tubular necrosis is usually non-oliguric and completely reversible. However, occasional patients require temporary dialysis and a rare patient requires chronic dialysis. Factors that contribute to aminoglycoside-induced nephrotoxicity include dose, duration of treatment, use of other tubular toxins (26), and elevated trough aminoglycoside levels (25). Even patients with peak and trough levels within recommended ranges can develop nephrotoxicity. Meta-analyses (27,28) and prospective evaluation (29) have demonstrated that once a day dosing of an aminoglycoside in immunocompetent adults with normal renal function is effective treatment for infections caused by gram-negative bacilli (employing bacteriologic cure as an end point) and is less toxic than traditional multiple daily dosing. Vancomycin can also cause renal tubular injury; the larger vancomycin doses currently recommended for treatment of pneumonia and bacteremia are associated with an increased incidence of nephrotoxicity (30).

Until recently, amphotericin B was the drug of choice for severe fungal infections due to *Candida* or *Aspergillus*. This agent is still used for cryptococcal meningitis, an AIDS-associated illness that occasionally requires treatment in an ICU. Amphotericin B can affect the renal tubules, renal blood flow, or glomerular function; renal dysfunction is seen in at least 60% to 80% of patients who receive this drug (31). However, renal dysfunction is usually transient, and few patients suffer serious long-term renal sequelae. Rarely, irreversible renal failure develops when the agent is used in high doses for prolonged periods (32). Risk factors for amphotericin B toxicity include abnormal baseline renal function, daily and total drug dose, and concurrent use of other nephrotoxic agents (e.g., aminoglycosides, diuretics) (31,33). However, some studies have not found that other drugs enhance amphotericin B-induced nephrotoxicity (22). Reversing sodium depletion and optimizing volume status prior to infusing the drug can decrease the risk of amphotericin B-induced nephrotoxicity (31,34). Liposomal preparations of amphotericin B are associated with a lower risk of nephrotoxicity compared with the parent compound. Nephrotoxicity with azoles and echinocandins is very rare.

$\beta$ -Lactams, fluoroquinolones, sulfonamides, vancomycin, and rifampin can occasionally cause interstitial nephritis. Methicillin was the first antibiotic shown to be associated with interstitial nephritis (35); nephritis can also be caused by numerous other  $\beta$ -lactams (36), usually following prolonged and/or high-dose therapy. Historically, renal failure was believed to be acute in onset and associated with fever, chills, rash, and arthralgias. However, the presentation of antibiotic-induced interstitial nephritis can be variable, and it should be suspected in any patient on a potentially offending agent who develops acute renal dysfunction. Urinary eosinophilia supports the diagnosis, but is present in less than half of the patients. Conclusive documentation of this disease requires renal biopsy. Discontinuation of the offending agent generally reverses the process and permanent sequelae are unusual.

Sulfonamides, acyclovir, and ciprofloxacin can crystallize in the renal tubules causing acute renal failure (37). Sulfonamides can also block tubular secretion of creatinine; this causes the serum creatinine to rise but glomerular filtration rate is unchanged. Polymyxins cause reversible, dose-related nephrotoxicity. Patients on rifampin often develop orange-colored urine of no clinical consequence.

## HEMATOLOGICAL ADVERSE REACTIONS

### Anemia

Linezolid (38–40), amphotericin B, chloramphenicol, and ganciclovir cause anemia by suppressing erythropoiesis. Chloramphenicol (infrequently used in the United States) frequently causes a reversible anemia that is more common if circulating drug concentrations exceed the recommended range. In approximately 1 of every 25,000 recipients, chloramphenicol causes an idiosyncratic irreversible aplastic anemia (41).  $\beta$ -Lactams (especially second- and third-generation cephalosporins), nitrofurantoin, and rarely aminoglycosides can cause hemolytic anemia. Patients who are glucose 6-phosphate dehydrogenase deficient are predisposed to sulfonamide- and dapsone-induced hemolytic anemia.

### Leukopenia

Antibiotic-induced leukopenia and/or agranulocytosis are generally reversible. Anti-infectives that can cause neutropenia or agranulocytosis include trimethoprim-sulfamethoxazole (42,43), most  $\beta$ -lactams (44,45), vancomycin, macrolides, clindamycin, chloramphenicol, flucytosine, and amphotericin B. Severe neutropenia develops in 5% to 15% of recipients of  $\beta$ -lactams (45) and is associated-with duration of therapy >10 days, high doses of medication, and severe hepatic dysfunction (46,47). Likelihood of neutropenia is <1% when shorter courses of  $\beta$ -lactams are used in patients with normal liver function (47). Only rare patients develop infection as a result of this decrease in functioning leukocytes. Vancomycin-induced neutropenia is uncommon and generally only occurs after over two weeks of intravenous treatment (49). The etiology appears to be peripheral destruction or sequestration of circulating myelocytes. Prompt reversal of the neutropenia generally occurs after vancomycin is discontinued.

### Thrombocytopenia

Antibiotic-related thrombocytopenia may result from either immune-mediated peripheral destruction of platelets or a decrease in the number of megakaryocytes (49). The oxazolidinone linezolid is the antimicrobial most likely to cause platelet destruction (38–40). In one study, linezolid-induced thrombocytopenia occurred in 2% of patients receiving less than or equal to two weeks of therapy, 5% of those receiving two to four weeks of therapy, and 7% of those receiving more than four weeks of drug (39). Severe linezolid-induced thrombocytopenia (and anemia) is significantly more common in patients with end-stage renal disease (51). Vancomycin can stimulate the production of platelet-reactive antibodies that can cause thrombocytopenia and severe bleeding (51). Sulfonamides, rifampin, and rarely  $\beta$ -lactams (including penicillin, ampicillin, methicillin, cefazolin, and cefoxitin) have also been reported to induce platelet destruction (45,52). Prompt recognition and removal of the offending agent is appropriate therapy. Chloramphenicol-induced thrombocytopenia is usually dose-related and, if not associated with aplastic anemia, is reversible following discontinuation of the drug.

### Coagulation

Malnutrition, renal failure, hepatic failure, malignancy, and medications can all predispose critically ill patients to bleeding. Although many studies have found an association between antibiotics and clinical bleeding (53), in-depth, statistically validated investigations may be necessary to establish causation in complex patients with multiple underlying diseases (54). Such an approach established a relationship between cefoxitin and bleeding.

Dysfunctional platelet aggregation, an important mechanism by which selected antibiotics may cause bleeding, is mostly noted with penicillins. Among penicillins, it is most likely with penicillin G and advanced-generation penicillins (55). The problem is dose-related, may be exacerbated by renal failure, and is additive to other factors seen in critically ill patients that could, in their own right, be associated with dysfunctional platelet aggregation (55,56). Most commonly, the reason for dysfunctional platelet aggregation is that carboxyl groups on the acyl side chain block binding sites located on the platelet surface resulting in the inability of platelet agonists such as adenosine diphosphate to affect aggregation (55). This process is best identified by performing a template bleeding time, and will be missed if only the international normalized ratio (INR) and partial thromboplastin times are measured.

It should be suspected in patients with bleeding not accounted for by abnormalities in INR or partial thromboplastin time, and often presents as diffuse oozing from sites of cutaneous trauma (e.g., recent tracheostomy and intravascular catheters).

Probably the most common reason for antibiotic-associated bleeding in the ICU is prolongation of the INR (57). Historically, antibiotics associated with INR prolongation include cefamandole, moxalactam, cefoperazone, cefmetazole, and cefotetan (58). All of these products contain an N-methylthiotetrazole side chain that can interfere with hepatic prothrombin synthesis (59). Antibiotics can also prolong the INR by affecting the normal gastrointestinal flora and thereby impairing vitamin K absorption; this effect can be profound and life-threatening in patients on warfarin. Sulfonamides can displace warfarin from its binding site on albumin and thereby enhance its bioavailability. Metronidazole can inhibit warfarin metabolism.

## DERMATOLOGICAL ADVERSE REACTIONS

Rashes are common in ICU patients and present as highly variable conditions with implications ranging from innocuous to life threatening. The problem is complicated because skin abnormalities in ICU patients can be caused by disease, pressure, and medications. Identifying an offending agent may be difficult because of the large number of medications administered to ICU patients and difficulties in temporally associating the rash with initiation of any single agent. Virtually any antimicrobial agent may cause a rash, but this problem occurs most commonly with  $\beta$ -lactams, sulfonamides, fluoroquinolones, and vancomycin (60). Factors that should lead the clinician to suspect a serious drug reaction include facial edema, urticaria, mucosal involvement, palpable or extensive purpura, blisters, fever, or lymphadenopathy. The presence of significant eosinophilia is associated with more severe disease. Maculopapular eruptions associated with antibiotics are especially common, usually occurring within one to two weeks after starting the offending agent and often becoming generalized and pruritic. The sensitivity of skin testing is low for  $\beta$ -lactam-induced maculopapular rashes. In patients with thrombocytopenia or other coagulopathies, hemorrhage into the skin may modify the appearance of the rash. The pathogenesis of most maculopapular rashes is unknown (9). Discontinuation of the offending agent is usually the most important strategy. In some instances, the likely offending agent can be continued and the rash will stabilize or disappear. In patients with penicillin-induced mild or moderately severe maculopapular rashes, it is generally safe to use cephalosporins (61). If the rash is severe or associated with mucosal lesions or exfoliation, the offending agent should almost always be discontinued.

Stevens-Johnson syndrome is erythema multiforme with mucosal involvement. The most commonly implicated antibiotics are the aminopenicillins and sulfonamides. Onset is typically one to three weeks after starting the offending agent. Clinically, the rash can present as symmetrical target lesions, maculopapular and urticarial plaques, and/or vesicular lesions. The presence of the latter portends severe disease (62). Stevens-Johnson syndrome can involve mucosae of the eyes, mouth, entire gastrointestinal tract, and the genitourinary tract. Up to 25% of cases may be restricted to the oral mucosa. Constitutional symptoms are usually present. Mortality is up to 5%. Diagnosis can be proven by skin biopsy with immunofluorescent staining. Infections (for which the offending antibiotic may have been prescribed), including pneumococcal, mycoplasmal, and staphylococcal infections can cause a similar rash. Stevens-Johnson syndrome can evolve into toxic epidermal necrolysis; mortality of this condition is 30% (62). Sulfonamides are the antibiotics most often associated with toxic epidermal necrolysis. Although the benefits of corticosteroid therapy are unproven, these products are often used for treatment.

"Red man" ("redneck") syndrome is a transient reaction to vancomycin characterized by flushing of the head and neck typically beginning within an hour of the start of an infusion (63). Severe cases have been associated with angioedema, hypotension, chest pain, and rarely, severe cardiac toxicity and death (20). Incidence may be as high as 47% in patients and is substantially higher in human volunteers (64). One study documented a dose-related increase in circulating histamine concentrations that correlated with the severity of the reaction (65). The problem is more frequently associated with rapid administration (i.e., <30 minutes) and with larger doses. Histamine antagonists may abort the syndrome in patients who require



vancomycin and who continue to have red man syndrome despite slow administration of the drug (63,66).

A particularly difficult problem in the ICU is differentiating between septic and drug-induced (chemical) phlebitis. Both may be associated with redness, heat, tenderness and a "cord" at the peripheral catheter site. Therapy for the former is removal of the catheter and appropriate antibacterial agents, while the latter is treated with catheter removal and moist heat. Presence of lymphangitic streaking or purulent drainage from the catheter site generally indicates infection. Antibiotics most likely to cause phlebitis include potassium penicillin, cephalosporins, vancomycin, streptogramins, and amphotericin B.

## NEUROTOXICITY

### Ototoxicity

Drug-induced ototoxicity in the ICU can result in hearing loss or vestibular dysfunction. The severity of underlying illness of ICU patients and the use of sedatives or paralyzing agents may make it impossible to diagnose these complications. Although routine audiography has been promulgated for some hospitalized patients given potentially ototoxic drugs (67), in practice such testing is not routinely employed. Therefore, the clinician must recognize the circumstances that could result in ototoxicity and take steps to decrease its likelihood.

Erythromycin and azithromycin can cause bilateral hearing loss and/or labyrinthine dysfunction that is usually reversible within two weeks of discontinuing the agent (68,69). However, permanent hearing loss or vertigo can occur (70). These complications are dose-related and usually occur in the presence of renal and/or hepatic dysfunction (71). A prospective study in patients with pneumonia documented sensorineural hearing loss in approximately 25% of patients treated with 4 g of erythromycin daily, while no patients who received lesser doses or control agents developed this condition (68).

Aminoglycosides cause ototoxicity or vestibular dysfunction in 10% to 22% of patients and it can be permanent (24,72). Hearing loss is the result of cochlear hair cell apoptosis (73). Factors associated with aminoglycoside-induced cranial nerve VIII dysfunction include dose, dosing frequency, duration of treatment, advanced age, fever, anemia, baseline creatinine clearance, and concomitant use of other ototoxic agents (72,74,75). Cumulative dose is important and clinicians should be wary of administering repeated courses of aminoglycosides. Use of an early vancomycin preparation was associated with sensorineural hearing loss (76). It is unknown whether newer vancomycin preparations cause ototoxicity (77).

### Other Neurotoxicities

Antibiotics can also occasionally cause peripheral nerve or acute central nervous system dysfunction (e.g., seizures, abnormal mentation). Most peripheral neuropathies occur with prolonged administration of selected antibiotics (e.g., metronidazole or linezolid), a situation not likely to occur in ICU patients.

Hallucinations, twitching, and seizures can be caused by penicillin, imipenem/cilastatin, ciprofloxacin, and rarely by other  $\beta$ -lactam antibiotics (78,79). Seizures may be the result of  $\beta$ -lactams interfering with the function of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (80). Intravenous aqueous penicillin G may cause central nervous system toxicity when normal-sized adults are given more than 20 to 50 million units per day (78). Patients with abnormal renal function, hyponatremia, or preexisting brain lesions can experience neurotoxicity at lower doses.

The maximum recommended dose of imipenem-cilastatin in adults with normal renal function is 4 g/day. Seizures may occur more often with this agent than with other  $\beta$ -lactams. Initial human data found the incidence of seizures to be 0.9% to 2.0% (81,82). Postmarketing assessments place this percentage at 0.1% to 0.15% (82). Animal studies confirm that neurotoxicity with imipenem/cilastatin may be noted at substantially lower blood levels than with other  $\beta$ -lactams (80). Our practice has been to virtually never employ imipenem/cilastatin in doses of  $>2$  g/day unless treating *Pseudomonas aeruginosa* infections. Seizures have not been noted in more than two decades of regular use at the authors' institution.

Fluoroquinolone use has been associated with central nervous system adverse effects including headache and seizures in 1% to 2% of recipients (83). Hallucinations, slurred speech,

and confusion have been noted; these generally resolve rapidly once the offending agent is discontinued. The presence of an underlying nervous system disorder may predispose to neurotoxicity.

Serotonin syndrome is due to impaired serotonin metabolism and is characterized by agitation, neuromuscular hyperactivity, fever, hypotension and even death. Linezolid is a weak inhibitor of monoamine oxidase. Although linezolid itself does not cause serotonin syndrome, combining this drug with other monoamine oxidase inhibitors can result in toxicity. A small percentage (<5%) of patients on selective serotonin reuptake inhibitors who are given linezolid develop serotonin syndrome (84–88). If it is necessary to start linezolid in a patient requiring a selective serotonin reuptake inhibitor, the patient should be watched for signs of serotonin syndrome and the responsible medications promptly discontinued if signs develop.

Neuromuscular blockade has been reported with aminoglycosides (78) and polymyxins. Clinical presentation is acute paralysis and apnea that develop soon after drug administration. Because of this potential toxicity, aminoglycosides should be avoided in patients with myasthenia gravis.

Polymyxins can cause paresthesias and peripheral neuropathy. Trimethoprim/sulfamethoxazole use can precipitate aseptic meningitis (89). Linezolid can cause optic neuropathy. With the first dose, approximately one-third of patients receiving voriconazole usually experience transient visual changes. The mechanism of this reaction is unknown; neurotoxicity or a direct effect on the retina is possible. No irreversible visual sequelae have been described.

## HEPATOTOXICITY

Liver function test abnormalities are common in ICU patients. Sepsis, severe hypoxemia, congestive heart failure, and primary hepatobiliary disease are the usual causes. Abnormalities are generally classified as either hepatitis, cholestasis, or mixed (90,91). Rifampin commonly causes hepatitis that is occasionally severe. Semisynthetic penicillins are frequent causes of cholestatic hepatotoxicity, especially when combined with clavulanic acid. Cephalosporins, imipenem-cilastatin, tetracyclines, macrolides, sulfonamides, quinolones, clindamycin, chloramphenicol, streptogramins, nitrofurantoin, azoles, and ganciclovir can also cause hepatotoxicity (90). Prolonged courses of high dose ceftriaxone can cause both hepatitis and cholestasis by promoting biliary sludge formation.

## MUSCULOSKELETAL ADVERSE REACTIONS

In patients with *Staphylococcus aureus* bacteremia, those treated with daptomycin were more likely to experience an elevation in creatine kinase than those treated with comparators (92). Although the clinical significance of this increase is uncertain, it is recommended that daptomycin be discontinued if the creatine kinase is >1000 U/L in patients with symptoms of myopathy or >2000 U/L in asymptomatic patients. Streptogramins can cause severe arthralgias and myalgias.

## ELECTROLYTE AND GLUCOSE ADVERSE REACTIONS

Amphotericin B can cause clinically significant hypokalemia, hypomagnesemia, and renal tubular acidosis. Electrolyte abnormalities must be anticipated with replenishment of the appropriate electrolyte to prevent future problems. Fluconazole can also cause hypokalemia.

Aqueous penicillin G is generally administered as the potassium salt (1.7 MEq K<sup>+</sup>/million units of penicillin). With doses of >20 million units per day, patients (especially those with renal failure) may develop clinically important hyperkalemia. A sodium preparation of aqueous penicillin G is manufactured and should be employed when the risk of hyperkalemia is significant. Intravenous pentamidine use is associated with potentially life-threatening hyperkalemia. Ticarcillin disodium should be used carefully in patients requiring salt restriction.

Because pentamidine can induce profound hypoglycemia, patients on this medication require frequent monitoring of their blood sugar. Linezolid can cause lactic acidosis (88).

## FEVER

Best available data suggest that up to one-third of hospitalized patients will experience fevers (93) that are commonly noninfectious (94,95). Although nosocomial fever prolongs length of stay, it is not a predictor of mortality (94). Management of nosocomial fever remains controversial. Most authorities recommend antibiotic restraint in stable patients pending the results of a thorough evaluation for the cause of the fever (96). However, empiric antibiotics should be started promptly in most patients in whom fever is associated with significant immunosuppression (e.g., asplenia, neutropenia) or hemodynamic instability. Numerous medications have been associated with fever; intramuscular administration may also result in temperature rise (97). Among antibiotics,  $\beta$ -lactams, sulfonamides, and the amphotericins most commonly cause fever. Sulfonamide-induced fever is especially common in HIV-infected patients. In contrast, fluoroquinolones and aminoglycosides are unusual causes of drug-related fever. In the opinion of the authors, neither the degree nor characteristics of the fever help define its cause. Fever of both infectious and noninfectious etiologies may be high-grade, intermittent, or recurrent (98). Rigors may occasionally be noted with noninfectious causes of fever.

Diagnosis of drug fever is made on the basis of a strong clinical suspicion, excluding other causes, and resolution of the fever following discontinuation of the offending agent. A clinical "pearl" is that the patient frequently appears better than the physician would suspect after seeing the fever curve. The presence of rash and/or eosinophilia also favors this diagnosis. Resolution of fever after the offending agent is discontinued can take days, because it depends upon the rate of the agent's metabolism.

## ANTIBIOTIC-ASSOCIATED DIARRHEA AND COLITIS

Since antibiotics first became available, it has been recognized that these products can cause diarrhea. In the ICU, additional causes of diarrhea include nutritional supplementation, other medications, underlying diseases, and ischemic bowel. In addition to being a nuisance, antibiotic-associated diarrhea can result in fluid and electrolyte disturbances, blood loss, pressure wounds, and (when associated with colitis) occasionally bowel perforation and death. Early recognition of antibiotic-associated diarrhea is important because prompt treatment can often minimize morbidity and prevent the rare fatality.

*Clostridium difficile* is currently the most common identifiable cause of nosocomial diarrhea. However, most cases of antibiotic-associated diarrhea are not caused by this organism. Rates vary dramatically among hospitals and within different areas of the same institution occurring in up to >30 patients per 1000 discharges (99). Although almost all antibiotics have been implicated, the most common causes of *C. difficile* diarrhea are cephalosporins, fluoroquinolones, clindamycin, and ampicillin (100). Antibiotic use changes the colonic flora allowing the overgrowth of *C. difficile*. This organism then causes diarrhea by releasing toxins A and B that promote epithelial cell apoptosis, inflammation, and secretion of fluid into the colon. Nosocomial acquisition of this organism is the most likely reason for patients to harbor it (101). Hospital sources of *C. difficile* include hands of personnel, inanimate environmental surfaces, and asymptomatic patient carriers. In addition to antibiotic use, risk factors for acquisition include cancer chemotherapy, severity of illness, and duration of hospitalization. The clinical presentation of antibiotic-associated diarrhea and colitis is highly variable, ranging from asymptomatic carriage to septic shock. Secondary bacteremia has been reported (102). Time of onset of diarrhea is variable, and diarrhea may develop weeks after using an antibiotic. Most commonly, diarrhea begins within the first week of antibiotic administration. More severe cases are associated with the presence of pseudomembranous colitis. Unusual presentations of this disease include acute abdominal pain (with or without toxic megacolon), fever, or leukocytosis with minimal or no diarrhea (103). On occasion, the presenting feature may be intestinal perforation or septic shock (104). In the ICU, patients may have numerous other reasons for diarrhea, abdominal pain, fever or leukocytosis. Clinical predictors that can help identify patients with *C. difficile* colitis include: onset of diarrhea more than six days after the initiation of antibiotics, hospital stay >15 days, fecal leukocytes on microscopy, and the presence of semiformal (as opposed to watery) stools (105).

In ICU patients with abdominal pain, work-up for *C. difficile* colitis should ideally be performed prior to abdominal surgery. Diagnosis can be made by the less sensitive (~67%) rapid enzyme immunoassay or a more sensitive (~90%) but slower tissue culture assay (106). The finding of pseudomembranes on sigmoidoscopy is also diagnostic and can negate the need for exploratory laparotomy. Optimal therapy of *C. difficile* diarrhea/colitis depends on severity of disease and the need for ongoing antimicrobial therapy. Antiperistaltic agents should be avoided. If feasible, the offending antibiotic should be discontinued. In mild cases this may suffice, and specific antibiotic therapy for *C. difficile* may be unnecessary.

For many years, oral metronidazole was the agent of choice for most patients requiring treatment. A recent study demonstrated that using oral vancomycin is more effective in seriously ill patients (107). Consequently, it is now recommended that any patient requiring intensive care should be treated with enteral vancomycin if she has leukocytosis  $\geq 15,000$  cells/mm<sup>3</sup> or a creatinine level  $\geq 1.5$ -fold more than the level prior to the onset of the *C. difficile* infection (personal communication). Metronidazole is the only agent that may be efficacious parenterally (108); vancomycin given intravenously is not secreted into the gut. In especially severe cases, patients can be treated with the combination of high-dose intravenous metronidazole and nasogastric or rectal infusions of vancomycin. Although therapy with other agents such as intravenous immunoglobulin and stool enemas has been promulgated, this approach has not been compared directly to other standard regimens.

### ANTIBIOTIC-RESISTANT SUPERINFECTIONS

In the ICU, the use of antibiotics can predispose recipients to colonization and infection with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species (mostly *E. faecium*), multidrug resistant gram-negative bacilli, and fungi. Detailed discussion of these superinfections is beyond the scope of this chapter.

### SUMMARY

Antibiotics are commonly used in the ICU. Adverse effects are regularly encountered and must be anticipated. The multiplicity of medications and underlying conditions in ICU patients affect the presentation and management of adverse reactions. When possible, the intensivist should employ the fewest number of antibiotics necessary, choosing those least likely to interact with other drugs and cause adverse reactions.

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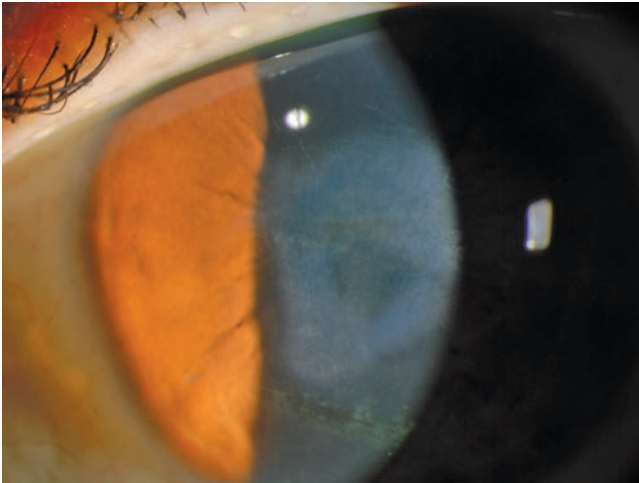
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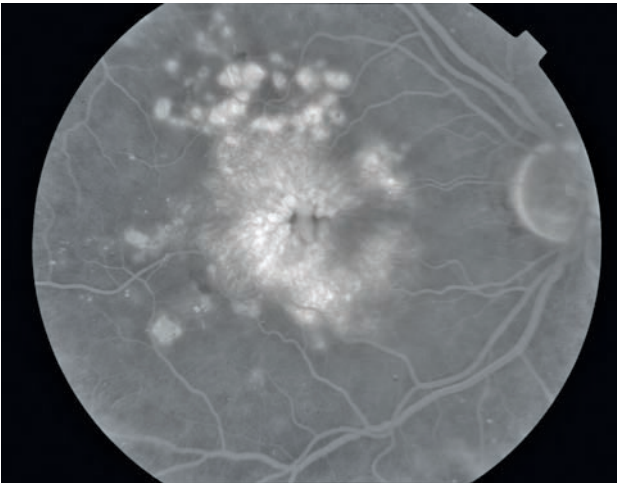
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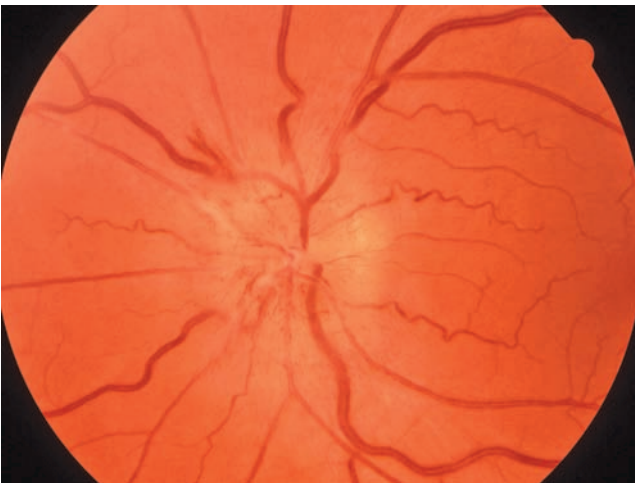




**Figure 4.1** Interstitial keratitis (*see page 67*).



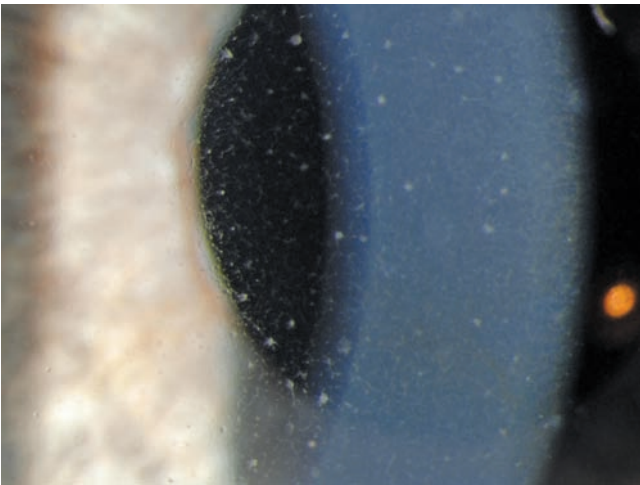
**Figure 4.2** Cystoid macular edema (*see page 67*).



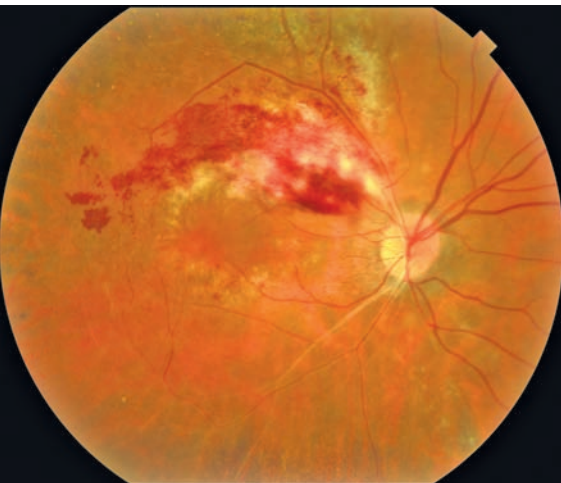
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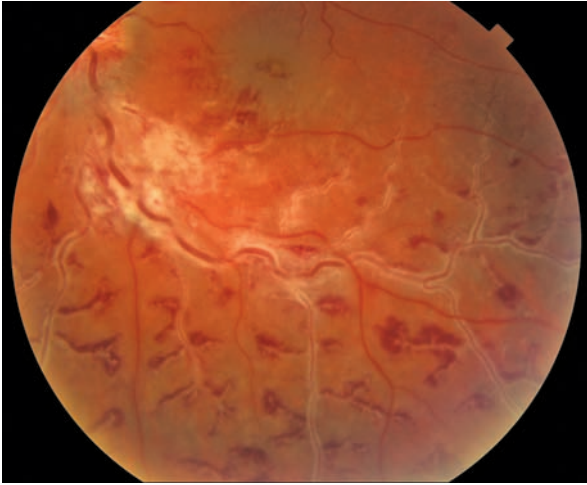
**Figure 4.4** Branch retinal artery occlusion (*see page 69*).



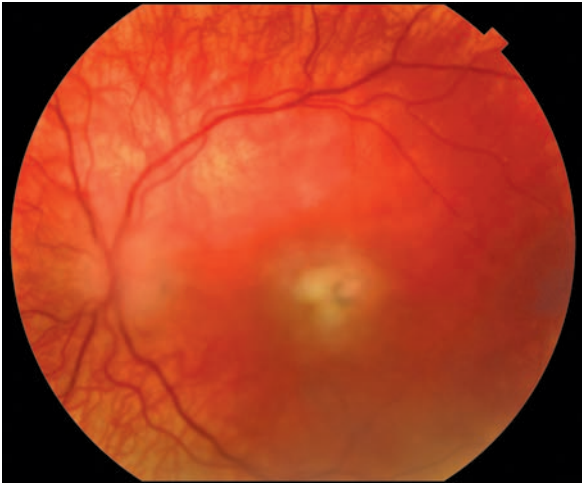
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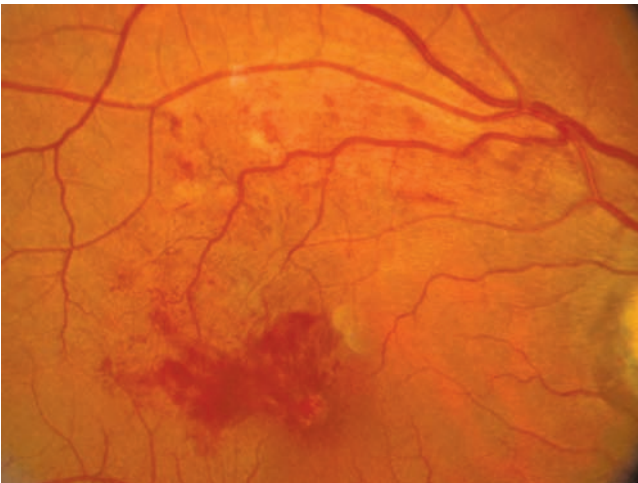
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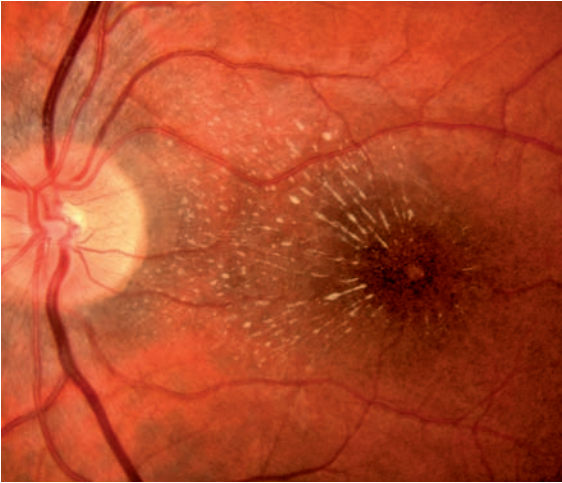
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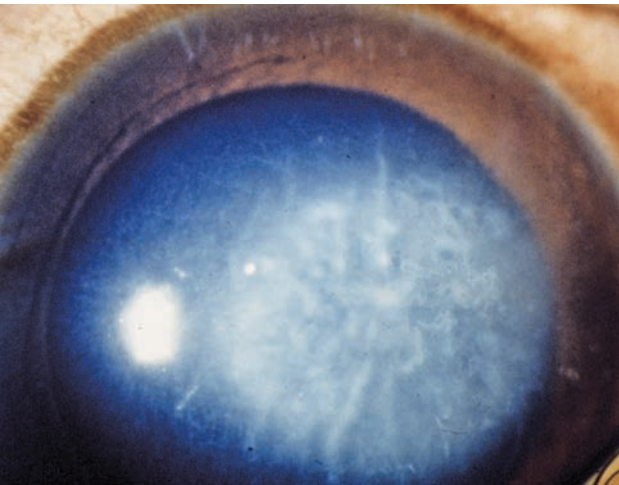
**Figure 4.8** “Headlight in the fog” (see page 70).



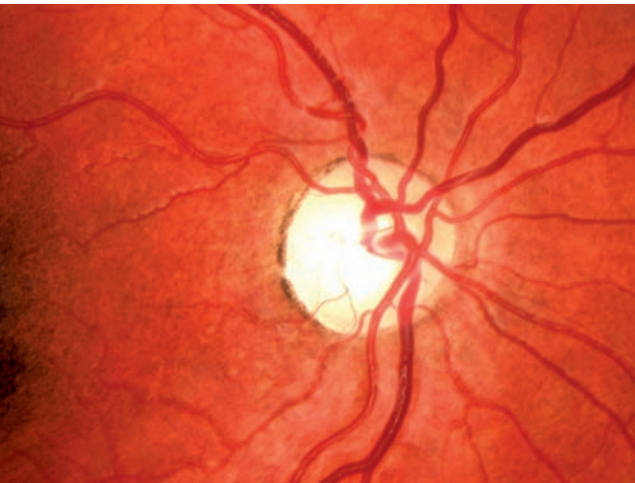
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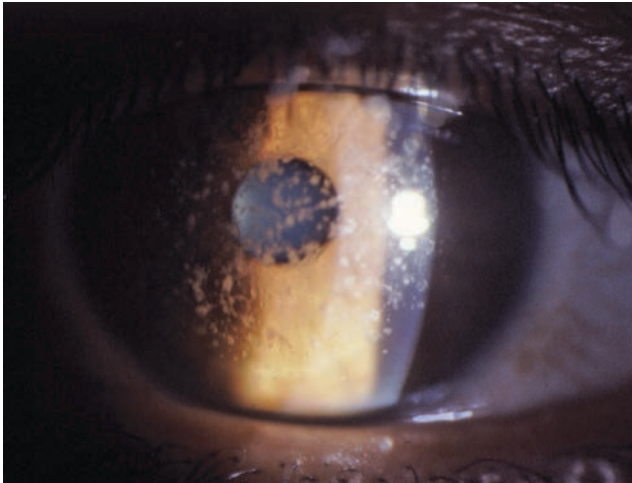
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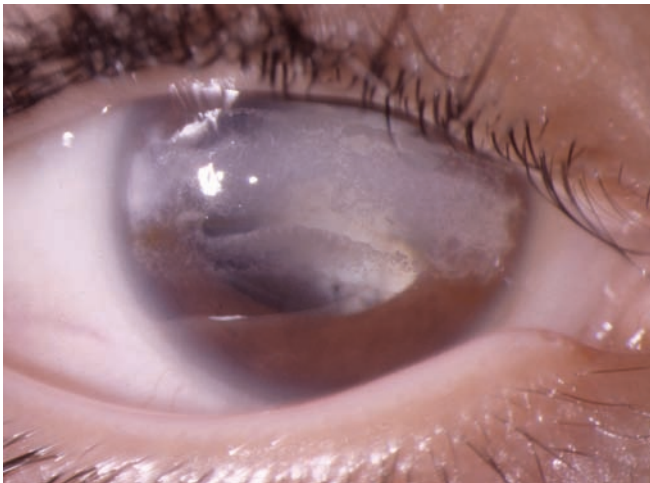
**Figure 4.11** Pseudodendritic keratitis (see page 71).



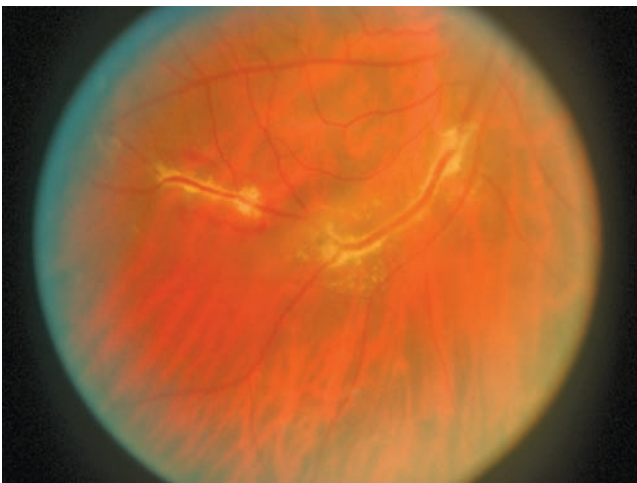
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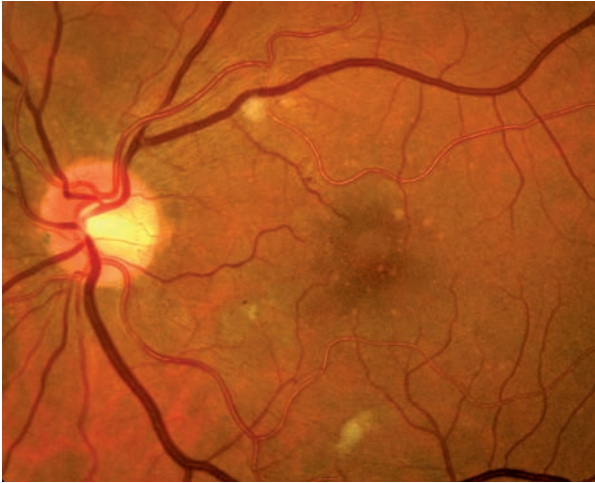


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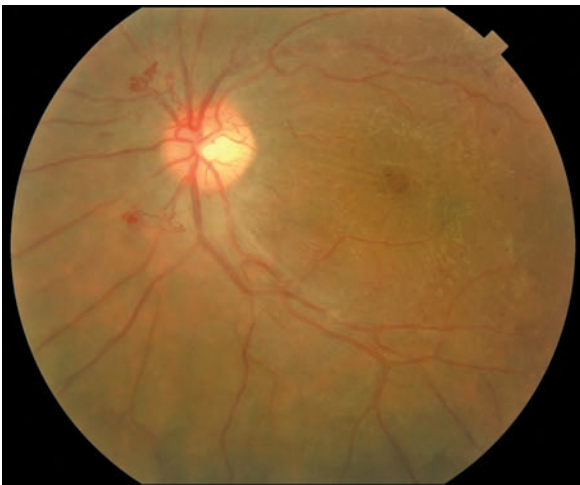


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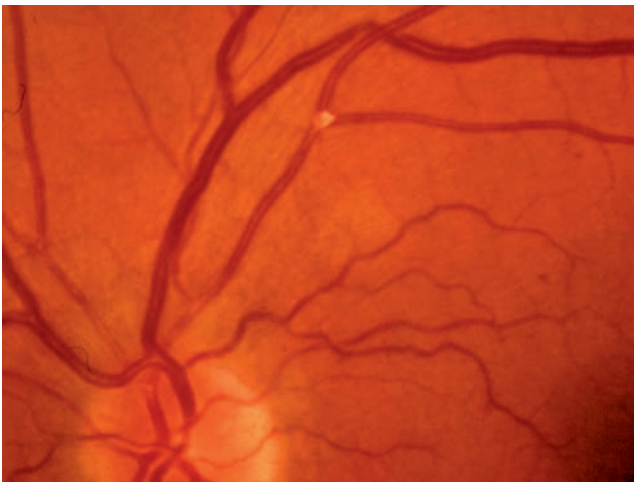




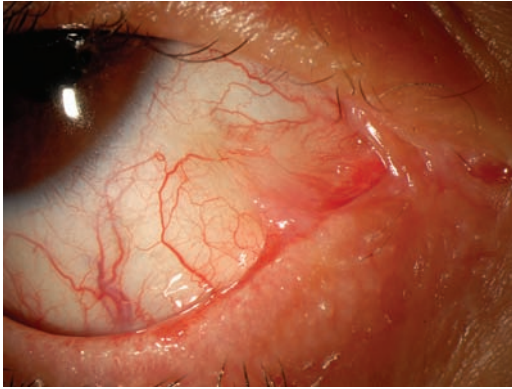
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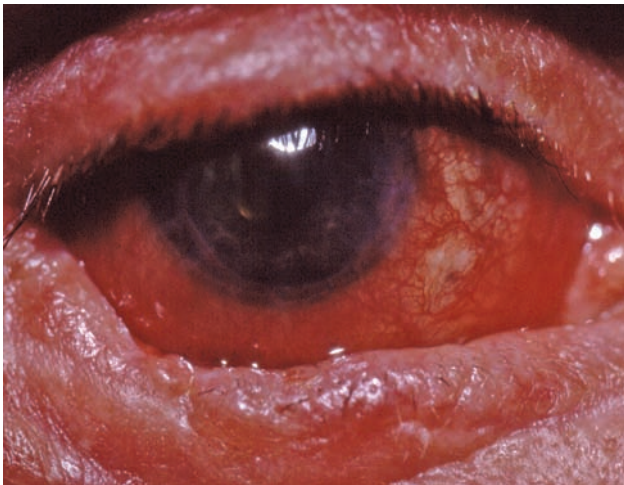
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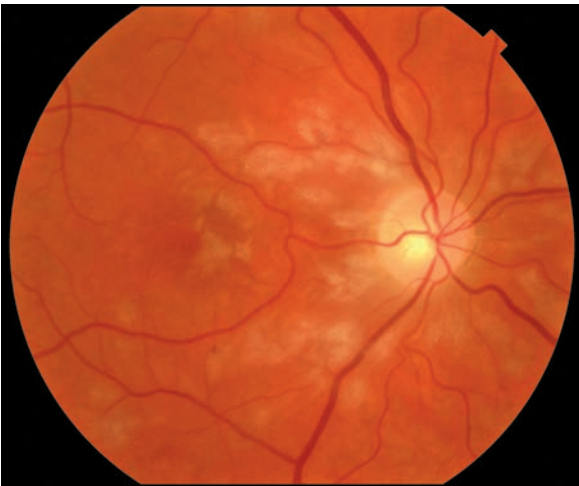
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## Infectious Disease

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—David J. Dries, MD, University of Minnesota Medical School

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