FOURTH EDITION

CASES IN MEDICAL MICROBIOLOGY AND INFECTIOUS DISEASES
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by

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ASM Press
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For Lynn, whose idea this book was.
Peter

To those who have taught me in the areas of infectious diseases and clinical microbiology.
Dan

For my family, who endured many hours of my writing at home.
Melissa
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Finally, to the many patients and their families from whom we learned, thank you. Any shortcomings in this text are solely the responsibility of the authors.
INTRODUCTION

TO THE FOURTH EDITION

It has been almost a decade since the 3rd edition of this text was published. Much has happened in the world of infectious diseases during this time. First, there has been recognition that the problems of infectious diseases are truly global and that infectious diseases in one part of the world can be quickly transmitted to another. Prime examples of this were the severe acute respiratory syndrome (SARS), the 2009 H1N1 influenza A virus outbreak, and multidrug-resistant Gram-negative bacilli (MDR-GNB). Genes for multidrug resistance can be carried on extrachromosomal genetic elements, facilitating the spread of these drug resistance determinants to highly virulent organisms such as was seen in the Shiga toxin-producing *Escherichia coli* (STEC) outbreak due to the O104 serotype in Germany in 2011. These emerging pathogens are literally a plane ride away, no matter where they are found globally, and can be disseminated worldwide in a matter of days to weeks.

MDR-GNB, environmental mycobacteria, and molds are emerging as important pathogens in the ever-expanding population of immunocompromised hosts. These organisms, although of comparatively low virulence when compared to highly adapted human pathogens such as *Streptococcus pneumoniae* or group A streptococci, have distinct characteristics that make them very worrisome. First, they have evolved over millions of years, adapting to harsh environments which contain antimicrobial molecules. As a result, organisms such as *Acinetobacter baumannii*, *Mycobacterium abscessus* group, and *Fusarium* spp. have high levels of intrinsic drug resistance. Additionally, they have comparatively large amounts of DNA, giving them a broad genetic repertoire which allows them to survive in hostile environments such as hospital surfaces and equipment. Finally, many MDR-GNBs are genetically promiscuous, taking up DNA which may contain resistance genes from other species or genera of bacteria. This promiscuity has led to a new concept in antimicrobial resistance, the “antimicrobial resistome,” which describes all the antimicrobial-resistant genes in a particular environment.

Rapid expansion in our understanding of molecular biology has greatly enhanced our knowledge of the etiology and epidemiology of infectious diseases. The evolution of molecular diagnostics makes it possible to design a nucleic acid amplification test (NAAT) in a matter of days to detect newly emerging pathogens, such as was done with the 2009 H1N1 influenza A virus. Other applications of NAAT testing allow us to rapidly detect viruses which are not cultivable or were unknown when the 3rd edition of this book was published. DNA sequencing has led to a clearer understanding of how organisms such as members of the *Burkholderia cepacia* and *Mycobacterium chelonae/abscessus* complexes are involved in numerous disease processes. Using the tools of direct 16S rRNA gene sequencing, we have greatly improved the etiologic diagnosis of bacterial
endocarditis and septic arthritis, leading to an improvement in our understanding of these disease entities.

One of the most significant advances in the study of infectious disease in the past decade has been the Human Microbiome Project. Microbiome studies have shown that many of the microorganisms that are present in our bodies are not cultivable. This observation challenges our basic assumptions of defining a human pathogen based on its ability to grow in vitro or in animal models. The Human Microbiome Project is increasing our understanding of the role of microbial communities in chronic infection, such as those seen in chronic lung disease in cystic fibrosis patients and in chronic wounds of the extremities in diabetics. It is also likely that probing the microbiome will give us greater understanding of such disparate conditions as obesity, inflammatory bowel disease, and perhaps a variety of rheumatologic disorders.

The past decade offered examples of the impact that public health measures can have on the dissemination of infectious diseases following natural disasters. One of the most destructive hurricanes in U.S. history, Katrina, caused massive damage in New Orleans in August 2005 but was responsible for few deaths due to infection and no significant disease outbreaks, despite a complete collapse of that city’s infrastructure and significant damage to medical facilities. This is a testament to the public health interventions that were put in place soon after this catastrophe. This success is in stark contrast to the cholera outbreak that occurred following the magnitude 7 earthquake in Haiti in January 2010. Ironically, Haiti was essentially cholera free until the earthquake. The organism was shown to have been brought to Haiti by UN soldiers from Nepal who were there for humanitarian purposes. This outbreak began several months after the earthquake and the epidemic is still ongoing; as of this writing, more than 8,500 people have died. The reason for this difference is clearly one of resources. Haiti continues to struggle with repairing and upgrading its infrastructure to provide basic sanitation and clean water for its population, while New Orleans and its environs are essentially back to “normal.”

As discouraging as the emergence of MDR-GNBs and the failure to control disease epidemics due to scarce resources might be, much has been accomplished in the past decade in improving the lives of those afflicted with or at risk for infectious disease. Two advances clearly stand out. First, the demonstration that the spread of HIV could be greatly reduced by pre-exposure prophylaxis gives hope that this epidemic that has caused so much suffering can be blunted. Second, new biologics including vaccines and monoclonal antibody preparations are playing an important role in not only infectious diseases but other diseases where there is a malfunctioning of the immune system.

Two vaccines of particular note have been the conjugate 7-valent, now 13-valent, *Streptococcus pneumoniae* vaccine and a malaria vaccine. The conjugate pneumococcal vaccine has been shown to reduce disseminated disease not only in its target group, young children, but also in the entire population—a clear example of herd immunity. A prototype malaria vaccine has shown success in phase 3 clinical trials and has great promise for...
reducing malaria disease burden especially among young children, the vaccine’s targeted population.

New monoclonal antibodies show tremendous promise for the treatment of a variety of diseases due to immune dysregulation while at the same time placing individuals at peril for unintended consequences of this therapy. As a result, care providers are faced with “black box” warnings which advise of potentially fatal infectious disease complications of these promising therapies.

The 4th edition of this text provides cases that will illustrate many of these issues. The goal of this edition continues to be to challenge students to develop a working knowledge of the variety of microorganisms that cause infections in humans. This working knowledge is rapidly expanding due to the rapid and increased deployment of NAAT and sequence analysis for detection and identification of microorganisms. As a result, many of the cases have a significant molecular diagnostic component. The “Primer on the Laboratory Diagnosis of Infectious Diseases” has been updated and expanded to reflect the increasing importance of molecular-based assays.

The basic format of this edition is consistent with that of the previous three editions. The cases are presented as “unknowns” and represent actual case presentations of patients we have encountered during our professional duties at two university teaching hospitals. Each case is accompanied by several questions to test knowledge in four broad areas:

- The organism’s characteristics and laboratory diagnosis
- Pathogenesis and clinical characteristics of the infection
- Epidemiology
- Prevention, and in some cases, drug resistance and treatment

This edition features a new section titled “Advanced Cases,” which replaces the section titled “Emerging and Re-Emerging Infectious Diseases.” The types of cases that are seen by our infectious disease consult services and discussed in our weekly infectious disease case management conferences will be found here. These include newly recognized disease agents as well as highly complex cases where the interaction of the immune system and human pathogens can be more closely examined. The Advanced Cases section has all new cases.

This edition contains 74 cases, of which 42 are new. The new cases explore many of the issues described above in this introduction. The 32 cases that have been retained have been updated to reflect the current state of the art as it relates to the organism causing the infection.

The most significant change in the 4th edition is that we bid adieu to one of the authors of the first three editions, Dr. Lynn Smiley, and welcome a new author, Dr. Melissa Miller. This work was Dr. Smiley’s idea, an idea that she helped bring to fruition through...
Introduction to the Fourth Edition

three editions. She now passes the mantle to Dr. Miller. Dr. Miller, Director of the Molecular Microbiology Laboratory at UNC Health Care, brings a wealth of knowledge on the molecular aspects of infectious diseases, especially in the fields of virology and antimicrobial resistance. This expertise is essential to produce a contemporary text in medical microbiology and infectious disease. We welcome her!
TO THE STUDENT

This text was written for you. It is an attempt to help you better understand the clinical importance of the basic science concepts you learn either in your medical microbiology or infectious disease course or through your independent study. You may also find that this text is useful in reviewing for Part I of the National Board of Medical Examiners exam. It should be a good reference during your Infectious Disease rotations.

Below is a sample case, followed by a discussion of how you should approach a case to determine its likely etiology.

SAMPLE CASE

A 6-year-old child presented with a 24-hour history of fever, vomiting, and complaining of a sore throat. On physical examination, she had a temperature of 38.5°C, her tonsillar region appeared inflamed and was covered by an exudate, and she had several enlarged cervical lymph nodes. A throat culture plated on sheep blood agar grew many beta-hemolytic colonies. These colonies were small with a comparatively wide zone of hemolysis.

What is the likely etiologic agent of her infection?

The first thing that should be done is to determine what type of infection this child has. She tells you that she has a sore throat, “my throat hurts.” On physical examination, she has sign of an inflamed pharynx with exudate, which is consistent with her symptoms. (Do you know what an exudate is? If not, it’s time to consult the glossary in the back of this text.) She also has enlarged regional lymph nodes, which support your diagnosis of pharyngitis (sore throat).

What is the etiology of her infection? The obvious response is that she has a “strep throat,” but in reality there are many agents which can cause a clinical syndrome indistinguishable from that produced by group A streptococci, the etiologic agent of “strep throat.” For example, sore throats are much more frequently caused by viruses than streptococci. Other bacteria can cause pharyngitis as well, including *Mycoplasma* spp., various *Corynebacterium* spp., *Arcanobacterium* sp., and *Neisseria* gonorrhoeae. All of these organisms would be in the differential diagnosis, along with other perhaps more obscure causes of pharyngitis.

However, further laboratory information narrows the differential diagnosis considerably; small colonies that are surrounded by large zones of hemolysis are consistent with beta-hemolytic streptococci, specifically group A streptococci. On the basis of presenting signs and symptoms and the laboratory data, this child most likely has group A streptococcal pharyngitis.
Specific aids have been added to the book to assist you in solving the cases.

1. The book begins with “A Primer on the Laboratory Diagnosis of Infectious Diseases.” The purpose of this section is to explain the application and effectiveness of different diagnostic approaches used in the clinical microbiology laboratory. We recommend that you read this primer before beginning your study of the cases.

2. At the beginning of each book section is a brief introduction and a list of organisms. Only organisms on this list should be considered when solving the cases in that section. These lists have been organized on the basis of important characteristics of the organisms.

3. A table of normal values is available inside the front cover of this book. If you are unsure whether a specific laboratory or vital sign finding is abnormal, consult this table.

4. A glossary of medical terms which are frequently used in the cases is available at the end of the text. If you do not understand a specific medical term, consult the glossary. If the term is not there, you will have to consult a medical dictionary or other medical texts.

5. Figures demonstrating microscopic organism morphology are presented in many of the cases, as are key radiographic, laboratory, clinical, or pathologic findings. They provide important clues in helping you determine the etiology of the patient’s infection. Because many medical schools have abandoned “wet” labs where medical students get to do “hands-on” microbiology, we felt it was important to have a richly illustrated text.

A FINAL THOUGHT

The temptation for many will be to read the case and its accompanying questions and then go directly to reading the answers. You will derive more benefit from this text by working through the questions and subsequently reading the case discussion.

Have fun and good luck!
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>Newborn</th>
<th>Age 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 4,000–12,000/μl</td>
<td>[4–12 × 10⁹/liter]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils 2,000–7,500/μl</td>
<td>[2–7.5 × 10⁹/liter]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils 40–400/μl</td>
<td>[0.04–0.40 × 10⁹/liter]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets 150,000–400,000/μl</td>
<td>[150–400 × 10⁹/liter]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>pO₂ 85–100 mmHg</td>
<td>[11.3–13.3 kPa]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CD4 count 430–1,185/μl (adults)</td>
<td>[Same]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin 13.4–17.4 g/dl</td>
<td>12.3–15.7 g/dl</td>
<td>[Same]</td>
<td>[Same]</td>
<td></td>
</tr>
<tr>
<td>Hematocrit 40–54%</td>
<td>38–47%</td>
<td>[0.4–0.54 liter/liter]</td>
<td>[0.38–0.47 liter/liter]</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate 0–20 mm/h</td>
<td>0-30 mm/h</td>
<td>[ESR is usually calculated by age: male (ESR = 0.5 × age); female (ESR = 0.5 × (age + 10)); alternatively, the American values given here usually apply.]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT 10–53 U/liter</td>
<td>7–30 U/liter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST 11–40 U/liter</td>
<td>9–26 U/liter</td>
<td>35–140 U/liter</td>
<td>20–60 U/liter</td>
<td></td>
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<tr>
<td>Creatinine 0.8–1.5 mg/dl</td>
<td>0.6–1.2 mg/dl</td>
<td>Lower for children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (male and female) = 70–150 μmol/liter</td>
<td></td>
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<tr>
<td>Creatinine kinase 61–200 U/liter</td>
<td>30–125 U/liter</td>
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<tr>
<td>Albumin 3.5–5.0 g/dl</td>
<td>[35–50 g/liter]</td>
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<tr>
<td>Serum glucose (fasting) 65–110 mg/dl</td>
<td>[&lt;3.6–6.1 mmol/liter]</td>
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<tr>
<td>Alkaline phosphatase 39–117 U/liter</td>
<td>[Same]</td>
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<tr>
<td>Total bilirubin 0–1.2 mg/dl</td>
<td>[0–20 μmol/liter]</td>
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<tr>
<td>Lactate dehydrogenase 108–215 U/liter</td>
<td>[Same]</td>
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<tr>
<td>CSF glucose 50–75 mg/dl</td>
<td>[2.8–4.2 mmol/liter, or 2/3 blood glucose]</td>
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<tr>
<td>CSF protein 15–45 mg/dl</td>
<td>[0.15–0.45 g/liter]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CSF total nucleated cells 0–3/μl</td>
<td>[Same]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Body temperature 37°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate 60–100/min; higher for infants and children</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory rate 9–18/min; higher for infants and children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure 90–150/50–90; lower for infants and children</td>
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</tbody>
</table>

*Values in brackets indicate European equivalents. If no value is given, the American value is used.