MEDICAL MICROBIOLOGY FOR THE NEW CURRICULUM
A Case-Based Approach

ROBERTA B. CAREY, Ph.D.
Former Associate Professor, Department of Pathology
Stritch School of Medicine
Director of Clinical Microbiology
Loyola University Medical Center
Maywood, IL
Centers for Disease Control and Prevention
Division of Healthcare Quality Promotion
Atlanta, GA

MINDY G. SCHUSTER, M.D.
Associate Professor, Infectious Diseases
University of Pennsylvania School of Medicine
Philadelphia, PA

KARIN L. McGOWAN, Ph.D.
Professor, Department of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Director, Microbiology Laboratory
Children’s Hospital of Philadelphia
Philadelphia, PA

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DEDICATION

**RBC:** To my family who gave me the time and encouragement to write a book and to the medical students who inspired me to translate my enthusiasm for microbiology into case presentations.

**MGS:** To my husband, Eric Bernstein, M.D. for his constant love, advice, support and inspiration, and to my children, Ali, David, and Kayla who remind me daily of how to find fun and excitement in learning something new.

**KLM:** To my parents, who taught me to reach for the stars . . . and to Pat, who loves and supports me every step of the way.
CONTENTS

Introduction, ix
The Art of Differential Diagnosis, xiii
Acknowledgments, xvii
List of Common Abbreviations, xix

Case One: Boy with Acute Pharyngitis, 1
Case Two: Student with Dysuria, 12
Case Three: Boy with Vomiting and Diarrhea after a School Picnic, 23
Case Four: Chronic Diarrhea in a Traveler, 35
Case Five: Boy with Skin Lesions, 47
Case Six: Student with a Skin Lesion Following a Trip to India, 57
Case Seven: Man with a Surgical Wound after a Prosthetic Hip Placement, 65
Case Eight: Boy with Fever and Right Leg Pain Following a Canoe Accident, 75
Case Nine: Woman with Acute Abdominal Pain and Cervical Discharge, 89
Case Ten: Woman with Acute Fever and Productive Cough, 99
Case Eleven: Nursing Home Resident with Fever, Cough, and Myalgias, 115
Case Twelve: Baby with Fever, Rhinitis and Bronchiolitis, 123
Case Thirteen: Woman with Fever, Cough, and Weight Loss, 132
Case Fourteen: Student with Chronic Fever, Dry Cough and Pneumonia, 144
Case Fifteen: Bone Marrow Transplant Recipient with Nodular Pneumonia, 155
Case Sixteen: Boy with Acute Fever, Headache, and Confusion, 167
Case Seventeen: Woman with Lymphocytic Meningitis, 182
Case Eighteen: Neonate with Fever and Vesicular Rash, 192
Case Nineteen: Renal Transplant Recipient with Chronic Meningitis, 201
Case Twenty: Man with Acute Fever and Periumbilical Pain, 213
Case Twenty One: Man with Two Weeks of Fever and a Systolic Murmur, 225
Case Twenty Two: Young Man with Fatigue and an Abnormal Liver Test, 236
Case Twenty Three: Fever of Unknown Origin in a Traveler, 246
Case Twenty Four: Student with Fever, Lymphadenopathy and Hepatosplenomegaly, 259

Index, 271
INTRODUCTION

Over 20 years ago, Harvard Medical School began a major reform of their curriculum called the “new pathways to general medical education.” Their original goal was to change how and what medical students were taught. The “new pathway” emphasized small group instruction, a self-directed approach to learning, and an integrated approach to the basic sciences and clinical experiences. Planning for the project began in 1982, and the new curriculum started in 1989. Since Harvard’s initiative, over a dozen medical schools in the United States have made major changes in their curricula and their approaches to teaching medicine. While each is unique, the new curricula share many features, described below.

All have worked to integrate the basic sciences with clinical experiences. Under the traditional model, medical students spent the first two years in lecture halls and laboratories focusing on the basic sciences such as anatomy, biochemistry, microbiology, pathology, and pharmacology. The second two years were spent in clinical settings. With the new core curriculum, clinical experiences start in the first month of medical school and continue for four years. In many of the programs, the basic science courses were shortened with the goal of revisiting the core concepts of the courses in the fourth year. In others, portions of the basic sciences are taught using clinical cases during the appropriate core clinical course. For example, concepts related to bacterial diarrhea are presented during a student’s rotation in gastroenterology, and faculty who were once confined to lecturing in basic science courses now join a team of physicians so that clinical and basic science concepts can be integrated and taught together.

There is now a new emphasis on problem-solving skills. Major changes in healthcare demand that physicians approach problems in innovative and inventive ways. In small group sessions, the new curricula stress problem solving as practiced by clinical preceptors.

Under the new curricula, students spend more time in ambulatory and outpatient settings. The traditional model stressed clinical rotations in inpatient settings only. As more and more healthcare is delivered in an outpatient setting, this lets the classroom more appropriately reflect the current clinical experience. In some schools, students are matched with
community physicians with whom they work for three years. This provides students a real-life perspective on chronic diseases as well as the role of primary-care physicians.

All of the programs allow students to explore new electives and self-directed study. Courses whose content includes medical ethics, clinical epidemiology, professionalism, physical diagnosis, medical economics, patient interviewing, population sciences, and health politics are appearing on medical school campuses for the first time. Lecture time at most schools has been shortened by 50%. This allows for an increase in the use of computer-aided courses and encourages students to acquire the skills and habits of self-instruction and to optimize their learning experience. In a number of schools, students have the option of a fifth or sixth year of study and have the opportunity to acquire an M.B.A., Ph.D., M.S., or law degree in addition to their M.D.

At many schools, there has been a shift from department-based courses to an approach based on individual organ systems. In an organ systems approach, when the heart and cardiovascular system are taught, all of the basic sciences involving the heart are taught at the same time. Such an approach requires the students to integrate the information in a very different way and avoids the redundancy that previously resulted from teaching each discipline as a separate course.

In summary, the new curricula have changed from being content-oriented to small group, case-based, interactive teaching. At the time this book was conceived, the authors were microbiology (RC, KLM) and infectious disease (MS) faculty participating in new curricula at their respective medical schools (University of Pennsylvania School of Medicine and Loyola University School of Medicine). Our goal was to create a case-based text that could be used by an integrated team teaching microbiology and/or infectious diseases. Our objective was not to attempt to cover every infectious disease or microorganism, but rather to use examples that would stress the key principles of microorganism pathogenesis, proper use of a clinical microbiology laboratory, and appropriate selection and use of antimicrobial agents. Because, sadly, many of the new curricula no longer include a laboratory component when teaching microbiology, we have tried to incorporate examples of material formerly stressed during microbiology labs. We have assumed that a faculty team including clinicians and basic scientists as well as students, residents, and fellows will be using this text and have tried to include case aspects such that every member of the team can participate. Each case has a patient history, differential diagnosis, clinical clues, laboratory data, pathogenesis, treatment and prevention, additional points, and references. The cases are presented as unknowns so that students will be challenged to create a differential diagnosis as they will in real life, making sure to include noninfectious causes that would present with similar clinical findings. Appropriate choice of lab tests needed to work through the differential diagnosis as well as instruction on specimen collection is included because these are areas that are rarely covered during core clinical rotations but that we believe to be incredibly important. Interpretation of laboratory results, pathogenesis, and treatment options are areas where we hope team members can participate in a discussion and dialog. Since different institutions have very different
approaches, especially in their use of laboratory tests, we anticipate (and hope) that students and team members will debate many of the points presented as they work through a case. Because it is impossible to cover all organisms in this text, the “Additional Points” section (Section 1.7 in Case 1, Section 2.7 in Case 2, etc.) was created to impart microbiology and medicine key points that are important adjuncts to the case and related pathogens causing similar infections. The reference section proved a challenge for all of us because, like our students, we all actively use the Internet when challenged to review or look up critical information. For that reason, we have included Websites as well as review articles that we have all found to be helpful.

The cases are grouped by disease presentation from the simpler cases to the more complex. Each case can stand on its own since technical terms, images, and concepts are embedded into the individual case, thus allowing each course director the ability to pick and choose when a case is to be presented to the students. This book is not meant to be a comprehensive microbiology text. It is designed to fill a unique niche created by the new curriculum. It is our hope that this book will be a skeleton for interactive learning and that clinical faculty will supplement the cases with their own clinical experience and the basic science faculty may enrich the cases with their expert knowledge of the pathogen’s structure and virulence factors. It is a dynamic text that will require updates for treatment and prevention as these evolve. We have tried to update each chapter as new information became available and to censor ourselves by restricting the contents to those essential for medical students who are overwhelmed by the amount of material they must assimilate.

SUGGESTED READING

THE ART OF DIFFERENTIAL DIAGNOSIS

A differential diagnosis is a list of possible causes of a patient’s symptoms. More than just an itemization of diagnoses, however, it is a process or method that involves formulation of hypotheses, intuition, and validation or confirmation. The ability to generate a comprehensive yet targeted differential diagnosis for an individual patient is an important skill that involves the art as well as the science of medicine. It is a skill that improves with clinical experience and cannot be fully learned by reading textbooks alone. Although there are several computer models available that can generate a differential diagnosis in many areas of medicine, these models have not replaced the efforts of the skilled clinician.

It has been said in medicine that when patients present with illnesses, they often “do not read the textbook,” meaning that there may be substantial variation in the presenting signs and symptoms in an individual patient compared to a textbook case. A corollary to this is that, in addition to common presentations of common diseases, there are both common presentations of uncommon diseases and uncommon presentations of common diseases. The expert clinician is alert to all of these possibilities.

The process of developing a differential diagnosis begins with the patient’s initial complaint and is expanded with the history of the present illness and past medical history. Data from the patient’s social history, including travel, exposures, sexual contacts, and living situation, may be particularly important in the field of infectious diseases. Often, the physical examination provides confirmation of the suspected diagnostic possibilities, and laboratory results can provide further evidence, or a final diagnosis. Part of the fun of medicine is the detective work employed in arriving at a differential diagnosis. The astute clinician must know which potential clues are important, which can be dismissed, and how best to prioritize all of the diagnostic possibilities. Empiric therapy may be directed at a variety of potential pathogens while awaiting a microbiologic diagnosis. The process of generating a differential diagnosis starts with a broad, inclusive list of possibilities, some of which are unlikely, to avoid the inadvertent
exclusion of the possible common presentation of an uncommon disease as well as the converse. Each added piece of clinical evidence allows you to narrow the differential diagnosis to a few possibilities that will direct the laboratory workup.

A common mistake is to not reconsider other possible diagnoses in the face of new data that do not support the initial provisional diagnosis. There must be flexibility in thinking even though there is a tendency to focus on confirmatory evidence and to dismiss contradictory evidence. It is, therefore, desirable for the differential diagnosis to evolve over time as more data about a patient become available and to even revisit possible diagnoses that may have been dismissed earlier in the process. Many students are first exposed to the art of differential diagnosis in clinical conferences where a student will present a difficult case to a seasoned clinician. The professor will often generate a differential diagnosis on the spot. Such a process is more akin to generating a “list” of possibilities rather than a demonstration of the necessary evolution of thought that occurs when one is faced with a real-life patient scenario.

There are several important principles in the art of differential diagnosis:

1. Be broad at first. Consider common and rare presentations of common and uncommon diseases. Although it is often said that “when you hear hoofbeats you should think of horses, not zebras,” it is important to consider the zebras as well. To get you started, we have included a section for each case called “Clinical Clues.” These “clues” are not meant to be exhaustive, but to highlight common associations that occur with common disease presentations. They are based on observations that you may make during the patient’s physical exam and answers to epidemiologic questions you should ask when taking the patient’s history. These clues may be helpful when you prepare your differential diagnosis.

2. Use each piece of data (presenting complaint, history of the present illness, past medical history, family and social history, laboratory results) to help you prioritize the differential diagnosis.

3. Don’t be afraid to go back and ask questions later that you may not have considered initially. The differential diagnosis is a work in progress.

4. Ask all the important questions, such as those about travel, exposures to other sick persons, sexual history, occupation, and pets. It is often helpful to ask open-ended questions, such as “Is there anything else you would like to tell me,” or “Is there anything I might have missed?”

5. Be cognizant of the fact that it is human nature to look for supporting evidence of a pet theory and to dismiss contradictory evidence. Keep rechecking your top few diagnoses with each new piece of clinical and laboratory data. Don’t be “married” to your initial diagnosis.

6. Use your differential diagnosis to generate an efficiently prioritized laboratory workup. The speed at which this must be accomplished depends on the severity of the illness. You will not be faulted for ordering a multitude of tests on a patient who is critically ill and has a vague
constellation of signs and symptoms. For many patients, however, an initial negative evaluation may be followed by an observation period of “wait and see” to find out if something will “declare itself,” rather than ordering numerous tests up front.

7. As Albert Einstein said, “Everything should be made as simple as possible, but not too simple.” Enjoy the process!
ACKNOWLEDGMENTS

We want to acknowledge Marilyn A. Leet for her assistance with photography and Dr. Robert Jerris for sharing his virology images.
<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>C</td>
<td>Celsius or centigrade</td>
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<td>microgram</td>
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1.1. PATIENT HISTORY

The patient was a 6 year-old male who had been in good health with no significant medical problems. In late September he presented to his pediatrician’s office with a complaint of sore throat, fever, headache, and swollen glands in his neck for the past 36 h. On physical examination (PE), he had a fever of 38°C (100.4°F), a red posterior pharynx, yellowish exudate on his tonsils, and multiple, enlarged, tender cervical lymph nodes (Fig. 1.1). There were no other pertinent symptoms.

1.2. DIFFERENTIAL DIAGNOSIS

This patient had acute pharyngitis, the painful inflammation of the pharynx and surrounding lymphoid tissues.

Infectious Causes

The major causes of pharyngitis in an immunocompetent host are bacterial and viral. Mycobacteria, fungi, and parasites do not cause acute pharyngitis in a normal host.
CASE ONE

Boy with Acute Pharyngitis

**FIGURE 1.1** Acute pharyngitis.

**Bacteria**

*Arcanobacterium haemolyticum*—a much less common cause of pharyngitis seen predominantly in teenagers and young adults

*Corynebacterium diphtheriae*—rarely seen in the United States but should be considered with an appropriate travel history to Africa, Asia/South Pacific, South America, Haiti, Albania, and the former Soviet Republic countries

*Mycoplasma pneumoniae*—a cause of pharyngitis in teenagers and young adults

*Neisseria gonorrhoeae*—considered if suspecting child abuse

Streptococci, groups C and G—a cause of self-limited pharyngitis in young adults

*Streptococcus pyogenes* [group A strep (GAS)]—this is the most common bacterial cause of pharyngitis

**Viruses**

Adenovirus—causes pharyngitis, conjunctivitis, and acute respiratory disease

Epstein-Barr virus—causes infectious mononucleosis, which is seen predominantly in the 15–25 year-old age group and frequently starts with pharyngitis

Other respiratory viruses—rhinovirus, coronavirus, parainfluenza virus, influenza A and B viruses, coxsackievirus, cytomegalovirus

**Fungi and Parasites**

There are no agents in these categories that routinely cause acute pharyngitis.
1.3. LABORATORY TESTS

A patient with GAS pharyngitis typically has a sore throat, fever, and pain on swallowing, as well as erythema with or without exudate on the tonsils and tender cervical lymph nodes. There are no clinical indicators that would make it possible to accurately predict the cause of this child’s pharyngitis. Laboratory tests are required to make a diagnosis.

When deciding whether to perform a laboratory test, clinical and epidemiological features as well as the availability and usefulness of treatment must be considered. While viruses are the most common cause of acute pharyngitis in both adults and children, lab testing for viruses is not warranted because antiviral agents are not used to treat acute pharyngitis. Given the age of this patient, the absence of travel, and the lack of suspicion of child abuse, GAS is the most likely etiologic agent. Since GAS pharyngitis is the most commonly occurring form of pharyngitis for which antibiotic therapy is indicated, lab testing should be directed at ruling out GAS. Appropriate laboratory tests for this would include:

- **Rapid strep test.** This is not a culture; the test detects a unique carbohydrate on the cell wall of GAS.

- **Throat culture.** This test will grow the GAS organism from a throat specimen taken from the patient and will require overnight incubation at the minimum. Most labs offer a specific “rule out GAS” throat culture.

The specimen required for each of these tests is a throat swab. Use of a double-swab format allows one to obtain sufficient specimen to perform both tests if necessary. As with any microbiology test, the quality of the results is contingent on whether the laboratory receives a well-taken specimen. The double swab should be firmly rubbed over much of the surface of both tonsils and the posterior pharyngeal area and rolled to ensure that there is ample specimen is on each swab tip. If exudate is present, it should also be sampled on the same swabs. Care should be taken to avoid touching other areas of the oropharynx, mouth, and tongue.

Direct Gram stains from throat swabs are not at all useful because many bacteria normally reside in the throat, including nonpathogenic streptococci that have Gram stain appearance identical to that of GAS.
1.4. RESULTS

Rapid tests for detection of GAS directly from throat swabs are based on the detection of the group A–specific carbohydrate N-acetylglucosamine. While the sensitivity of these tests varies considerably, the specificity when compared to culture is excellent, ranging within 95–100% in most studies. For this reason, a positive antigen test is considered diagnostic of GAS and does not require throat culture confirmation. A negative antigen test result, however, must be confirmed with a throat culture. In comparison to most rapid tests, which take 5–10 min to perform, a throat culture requires 48 h to complete. The disadvantage of time delay when performing a throat culture has led to widespread use of the rapid antigen tests.

The rapid antigen test performed on one of the swabs obtained from this patient was negative (Fig. 1.2); the second swab was used to perform the throat culture. Culture of a throat swab on a single sheep blood agar plate is still the gold standard for confirming GAS pharyngitis. Assuming that an adequately collected specimen was submitted, a throat swab culture has a sensitivity of 90–95% for the detection of GAS. Once the swab is cultured, the plate should be incubated at 35–37°C for 18–24 h before reading. While many cultures will be positive after the initial overnight incubation, it is recommended that the plates be reincubated and examined again after another 24 h incubation. A considerable number of GAS do not appear until the second day and would be missed without the additional incubation time.

Streptococci demonstrate three types of hemolysis when grown on sheep blood agar: alpha (α), beta (β), and gamma (γ) (Fig. 1.3). α-Hemolysis is a result of incomplete destruction of red blood cells resulting in a green coloration of the media immediately surrounding the colony. β-Hemolysis
is complete lysis and destruction of the red blood cells resulting in a distinct clear zone around the colony. γ-Hemolysis is actually no hemolysis, and the result is the absence of a visible effect around the colony.

Group A streptococci are β-hemolytic and should show a distinct clear zone around each individual colony; however, not all β-hemolytic colonies are GAS, and further testing of β-hemolytic colonies is required. Even if a patient has GAS pharyngitis, many other bacteria representing normal colonizing flora will be present on the culture plate along with the GAS (Fig. 1.4).
The plate is visually inspected for colonies that display β-hemolysis, and, if present, such colonies are further tested using the catalase test and a Gram stain for microscopic examination. The catalase test checks for the production of the enzyme catalase, using hydrogen peroxide as a substrate. A single β-hemolytic colony is mixed with a drop of 3% hydrogen peroxide on a glass slide, and immediate bubbling is seen if the test is positive (Fig. 1.5). Streptococci are gram-positive cocci in chains and are catalase-negative (no bubbles). In contrast, staphylococci (which can also display β-hemolysis) are gram-positive cocci in clumps or clusters and are catalase-positive. Gram-positive, catalase-negative cocci would then be further tested.

The bacitracin disk test provides a presumptive identification of GAS because >95% of GAS demonstrate a zone of growth inhibition around a disk containing the antibiotic bacitracin (Fig. 1.6). While this is a commonly used test in physician’s offices, it requires another 18–24 h of incubation to perform. An alternative used by many clinical laboratories because it gives an immediate result is the PYR test, which detects the enzyme L-pyroglutamylaminopeptidase and can be performed within minutes using a single β-hemolytic colony. GAS are positive for PYR (Fig. 1.7).

The definitive method of identifying the β-hemolytic streptococci is by detecting the group-specific cell wall carbohydrate antigen directly from an isolated bacterial colony. These unique antigens classify the β-hemolytic streptococci into serogroups, designated by Dr. Rebecca Lancefield, as groups A, B, C, D, F, G, and so on. Kits containing group-specific antisera attached to latex beads are commercially available for this purpose and are used by many clinical microbiology laboratories. A single isolated colony is mixed with a drop of group-specific antibody, and if clumping of the coated latex particles occurs, it specifically identifies the serogroup.

The culture performed using the second swab taken from this patient was positive for β-hemolytic group A streptococcus (S. pyogenes). This is sufficient to confirm the diagnosis of GAS pharyngitis.
1.5. PATHOGENESIS

Streptococcal pharyngitis is spread via aerosols from person to person, or less commonly by eating contaminated food. *S. pyogenes* is a successful pathogen since it possesses several virulence factors that allow it to invade tissue and escape host defenses. Some strains produce pyrogenic exotoxins, which cause serious systemic illness, such as toxic shock-like syndrome, which is associated with a high morbidity and mortality. The principal virulence factors produced by *S. pyogenes* are listed in Table 1.1.
TABLE 1.1. *Streptococcus pyogenes* Virulence Factors

<table>
<thead>
<tr>
<th>Virulence Factor</th>
<th>Activity and Importance</th>
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<tbody>
<tr>
<td>M protein</td>
<td>Major virulence factor allowing bacteria to resist phagocytosis by host cells</td>
</tr>
<tr>
<td></td>
<td>Appears as hair-like projections on cell surface</td>
</tr>
<tr>
<td></td>
<td>&gt;80 different serotypes</td>
</tr>
<tr>
<td></td>
<td>Immunogenic (type-specific antibody is protective)</td>
</tr>
<tr>
<td>Streptolysin O</td>
<td>Hemolyzes red blood cells</td>
</tr>
<tr>
<td></td>
<td>Activity destroyed by oxygen</td>
</tr>
<tr>
<td></td>
<td>Immunogenic [antistreptolysin O (ASO) antibody formed during infection; can be used to diagnose recent infection]</td>
</tr>
<tr>
<td>Streptolysin S</td>
<td>Hemolyzes red blood cells</td>
</tr>
<tr>
<td></td>
<td>Oxygen-stable</td>
</tr>
<tr>
<td></td>
<td>Nonimmunogenic (no antibody formed)</td>
</tr>
<tr>
<td>Streptokinase DNases Hyaluronidase</td>
<td>Hydrolytic enzymes allowing bacteria to spread in host tissues</td>
</tr>
<tr>
<td></td>
<td>Immunogenic (antibodies can be used to diagnose recent infection)</td>
</tr>
<tr>
<td>Hyaluronic acid capsule</td>
<td>Protects bacteria from killing by phagocytosis</td>
</tr>
<tr>
<td>Strep pyrogenic exotoxins (Spe A, B, C)</td>
<td>Cause release of host cytokines (interleukin, tumor necrosis factor), resulting in multisystem organ failure known as toxic shock-like syndrome</td>
</tr>
</tbody>
</table>

Infection with *S. pyogenes* may present in children as scarlet fever, which is fever and sore throat with a diffuse rash. The rash is caused by an erythrogenic exotoxin that has now been designated as one of the streptococcal pyrogenic exotoxins or Spe. The incidence of scarlet fever fell significantly in the 1950s largely because of the widespread use of penicillin.

The two major sequellae of untreated *S. pyogenes* infection, rheumatic fever (RF) and acute glomerulonephritis (GN), occur weeks after the streptococcal infection. The organism can no longer be cultured from the throat or skin when the patient presents with symptoms of RF or GN. RF occurs in <3% of people with strep pharyngitis. The patient presents with swelling and pain in more than one joint (migrating arthritis) and with a new heart murmur due to damage to the heart muscle and heart valves. The patient may also have a group of neurologic symptoms, including jerky or twitching movements (chorea). GN may occur 10 days or later after a skin infection with *S. pyogenes*. The patient has signs and symptoms of kidney dysfunction, such as swollen ankles and eyelids (edema), elevated blood pressure (hypertension), blood and protein in the urine, and decreased urine output. Deposition of antigen–antibody–complement complexes can be seen in a kidney biopsy using immunofluorescent stains.

The damage to the heart and kidney is not caused by systemic infection with the bacteria, but is theorized to be a result of direct damage