Manual of Clinical Problems in Infectious Disease

With Annotated Key References

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Preface

A number of excellent textbooks describe the etiology, pathogenesis, clinical features, and therapy of infectious diseases. This manual is not intended to be a concise digest of those works. We felt that there was a need for a text that provides contemporary approaches and solutions to the infectious disease questions most frequently raised by students, house officers, and practicing clinicians. This manual represents our attempt to provide such a source of information.

We chose to limit the size of the manual and were arbitrary in the subjects selected. We make no pretense that we have covered all the areas of interest or controversy that might have deserved inclusion. We have made an effort to stress disorders amenable to antimicrobial therapy and to include the most contemporary literature.

We would like to express appreciation to those who have assisted us in the preparation of this book. We thank Mrs. Nellie Johnson, Librarian at the Boston Veterans Administration Medical Center, and the library staff at the University of Massachusetts School of Medicine for their assistance in the location of references, with special appreciation to librarians Beverly Marsden, Gael Evans, Jean Edmunds, and Dr. Donald Morton, the Director. We are grateful to Lois Kent, who did an excellent job in typing and proofreading the manuscript, and appreciation for secretarial assistance is extended as well to Kathy Scalley. We are grateful to our colleagues Drs. Neil Blacklow, Juan Canoso, Jack Faling, Waun Ki Hong, and Abe Zimelman for their support, help, and encouragement throughout the research and writing of this text. Thanks also are due to Dr. John Zawacki for his contribution to "Fever and Jaundice." Special recognition must be accorded to our wives, Roberta and Brenda, for their never-ending encouragement, support, suggestions, and editorial assistance, and deep gratitude to our parents for their love and inspiration.

N. M. G.
R. A. G.

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NOTICE

The indications and dosages of all drugs in this Manual have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the situations and the dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

Upper Respiratory Tract

Streptococcal Pharyngitis: Culture, Treat, or Both?

Sore throat is one of the most common problems seen in medical practice. Despite the frequency of pharyngitis and the many studies of it that have been made, its diagnosis and management are highly controversial subjects. Issues that are still unresolved include the following: Who should have a throat culture? How best can one differentiate a person with pharyngitis and a positive culture for group A streptococci from those who are streptococcal carriers with symptoms due to some other cause? What constitutes a positive throat culture? How sensitive is a single throat culture in detecting group A streptococci? What effect does specific therapy have on the natural course of the disease? Should treatment be started before culture results are available? Should treatment be given without taking a throat culture? How should contacts be managed?

The main problem in the diagnosis of pharyngitis is to determine whether or not group A streptococci are present on a throat culture. In their absence the differential diagnosis is pharyngitis of nonstreptococcal origin, usually presumed to be viral. Causes of non-group-A streptococcal pharyngitis include *Mycoplasma pneumoniae, Haemophilus influenzae, Neisseria gonorrhoeae, Corynebacterium diphtheriae*, groups C and G streptococci, viruses (adenovirus, coxsackievirus, herpes simplex, influenza, parainfluenza, cytomegalovirus, Epstein-Barr virus) and the organisms of Vincent's angina. Although frequently isolated, the pneumococcus and staphylococcus do not produce pharyngitis. In studies of the causes of pharyngitis, group A streptococci are identified in about 25 to 33 percent of patients and viral and various other causes such as *M. pneumoniae*, in 15 to 30 percent; in 45 percent of patients no agent is isolated. Group A streptococci are infrequent under 3 years of age, and when they are present, overt disease is usually absent. Clinical findings are unreliable in predicting the organism that will be found on culture. Although the presence of cervical adenopathy, leukocytosis, a temperature greater than 101° F (38.4°C), and exudates favors a streptococcal etiology, considerable overlap occurs. Exudates also occur commonly in patients with pharyngitis caused by *Mycoplasma* or virus. The presence of adenitis correlates best with a positive culture (50 percent yield). The rash of scarlet fever is the most reliable sign of a streptococcal cause; hoarseness suggests a nonstreptococcal cause.

Since the clinical findings, even when several criteria are met, fail to distinguish a viral from a streptococcal sore throat, the question whether to take a culture or just treat without a culture is controversial. In the setting of a streptococcal epidemic, treatment without a culture is appropriate and is not controversial. In the usual nonepidemic setting, arguments can be made for treating only patients with positive cultures (the currently recommended approach), treating all those with sore throats with antibiotics without a culture, or neither culturing nor treating any patient with a sore throat. The approach adopted depends on the clinician's weighing the rationale for treatment, the various costs to the patient, such as those for cultures and drugs, and the consequences of widespread antibiotic therapy (drug reactions, bacterial resistance).

The goals of therapy are fourfold: (1) to prevent nonsuppurative sequelae (rheumatic fever and acute glomerulonephritis), (2) to prevent suppurative complications such as sinusitis, peritonsillar abscess, otitis media, suppura-

tive cervical adenitis, and pneumonia; (3) to decrease the spread of infection; and possibly (4) to alter the natural history of the disease.

Antibiotics are clearly effective in preventing rheumatic fever. The reported attack rates with untreated streptococcal pharyngitis vary between 0.4 and 2.8 percent. With treatment, 98 percent of the expected cases of rheumatic fever can be prevented. One of the major challenges in preventing rheumatic fever is identifying high-risk people with streptococcal pharyngitis; overcrowded living conditions, for example, increase the risk of rheumatic fever. In a study of patients with rheumatic fever, one-third were found to have had an antecedent asymptomatic streptococcal infection. Another one-third of patients had had a sore throat but did not seek medical care. Consequently, in this study, 67 percent of patients with rheumatic fever had disease that could not have been prevented. There is no convincing evidence that acute nephritis can be prevented by treating a streptococcal sore throat. Suppurative complications such as retropharyngeal abscess are infrequent in the antibiotic era. Antibiotics decrease the spread of infection that occurs by droplets and may affect as many as 25 to 50 percent of the family of an affected person. In a patient on therapy, no group A streptococci will be detected by the third day. The argument that therapy alters the disease course significantly is not convincing in the controlled studies, although anecdotal evidence may dispute this.

About one-half of patients with cultures that are positive for group A streptococci will show a rise in antistreptococcal antibodies, and such patients are at risk of the development of nonsuppurative complications. The other half of the group will have elevated streptococcal antibody titers when first seen that do not subsequently increase, and they are streptococcal carriers. Since serologic studies are usually not done when patients present with a sore throat, and since other simple tests to detect carriers are not available, all patients with a positive culture are treated as a group. Except for some nasal carriers, chronic carriers are not a major source of spreading the streptococcal organism.

The question of the number of colonies constituting a positive culture is also unresolved. While some studies correlated heavy growth on culture with severity of clinical findings and a greater rise in antibody titer compared with that seen with scant growth of Group A streptococci on a throat culture, other workers did not confirm these associations. A single throat culture will detect about a 90 percent incidence of positives. However, Weinstein reported that in a study of patients with scarlet fever, a single throat culture failed to detect 30 percent of patients with this disease. A repeat culture may be required to establish a diagnosis.

The answer to the question whether or not to start antibiotics before culture results are available depends on the clinical situation. Penicillin treatment delayed for 9 days after the onset of the sore throat still may prevent rheumatic fever, but patients with a history of rheumatic fever or those who may be difficult to contact should begin treatment at the time of obtaining the culture. Although the value of early therapy in decreasing symptoms has not been determined, the practice of treating patients without a culture does not provide data on the etiologic agents most prevalent in the community. Further, a diagnosis established by a culture may save unnecessary antibiotic therapy.

The value of culturing contacts is also a subject of controversy. More extensive culturing should be done in the family members of patients with rheumatic fever, in members of households where there are recurrent sore throats, and in children in schools where there are cases of rheumatic fever or nephri-

tis. Further research will improve guidelines and settle many of these unresolved issues. (N.M.G.)

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Infectious Mononucleosis: Differential Diagnosis

Infectious mononucleosis is an acute illness characterized by a triad of clinical, hematologic, and serologic abnormalities. Frequent symptoms include a prodrome of nonspecific complaints (malaise, fatigue, sweats, headache, anorexia), followed by fever and a sore throat that usually cause the affected person to seek medical attention. Lymphadenopathy, especially in the posterior cervical nodes, pharyngeal inflammation, and splenomegaly are generally present. Typical laboratory findings include at least 50 percent lymphocytes (10 to 20 percent are atypical) and abnormal liver function test results. The detection of heterophile antibodies either by the classic Paul-Bunnell test or a more rapid "mono slide test" completes the triad.

Heterophile antibodies agglutinate sheep or horse red blood cells and show incomplete absorption with guinea pig kidney and complete absorption by beef erythrocytes. Some consider the test positive if the titer of sheep agglutinins does not decrease more than three dilution tubes after guinea pig absorption and is reduced by at least four dilutions by beef erythrocytes. The height of the titer does not correlate with either the severity or duration of the illness. Today, most laboratories perform a mono slide test which has a 95 percent sensitivity and shows false-positives infrequently. Technical problems, either with the performance or interpretation of the test result, constitute the major cause of error.

In 90 percent of patients with a mononucleosis illness, heterophile antibodies are detected, and the diagnosis is straightforward. However, the characteristic clinical and laboratory features may not be present when the patient is first evaluated, but may develop as the disease evolves. Similarly, a positive heterophile test may not appear until the second or third week of a puzzling illness. All cases of heterophile-positive mononucleosis are caused by the Epstein-Barr virus (EBV) and should be called EBV mononucleosis.

The diagnosis of EBV mononucleosis is more difficult when the disease is mild, during the early phase of the illness, or when unusual features occur. The disease should be considered in the differential diagnosis of a patient with predominant involvement in the following systems: (1) neurologic (aseptic meningitis, encephalitis, polyneuritis, mononeuritis, Guillain-Barré syndrome); (2) hematologic (hemolytic anemia, thrombocytopenia, neutropenia); (3) gastrointestinal (hepatitis, pancreatitis, splenic rupture); (4) cardiac (pericarditis, myocarditis); (5) pulmonary (airway obstruction, pneumonia, pleural effusion); or (6) renal (acute nephritis). In most instances the classic features are present, and these complications are rare, mainly limited to case reports. The diagnosis of infectious mononucleosis should also be suspected in the very young (under 5 years of age) and in the elderly, although the peak occurrence is between 15 to 25 years. The presence of EBV antibody correlates 100 percent with lack of susceptibility to infection.

In the remaining 10 percent of patients with a mononucleosis-like illness the heterophile serologic test findings will be repeatedly negative. In children less than 5 years old, heterophile test results are rarely positive. Diseases that should be considered in the differential diagnosis of the illness include the following: (1) pharyngitis usually caused by group A streptococci or other viral agents; (2) cytomegalovirus (CMV); (3) toxoplasmosis; (4) rubella; (5) hepatitis viruses; (6) hematologic malignancies; (7) drug reactions (para aminosalicylic acid, phenytoin sodium [Dilantin], mephenytoin [Mesantoin]);

(8) secondary syphilis; and (9) EBV (positive EBV antibody test and negative heterophile test). Depending on the population, CMV will be detected in 43 to 70 percent of patients with a heterophile-negative mononucleosis either by serologic studies or urine culture. Illness caused by CMV may occur following blood transfusions, but, more often, no source is identified. Mononucleosis caused by CMV resembles the infection caused by EBV, except for minimal pharyngeal involvement. It is usually seen in persons over 20 years of age. An ampicillin-induced skin rash occurs with both agents. The other major cause of heterophile-negative mononucleosis is EBV, accounting for 10 percent of cases in one report. Since this virus does not grow in routine tissue cultures, the best confirmatory test is to demonstrate EBV-specific antibodies. Detecting specific IgM antibody to EBV will usually confirm the diagnosis. The other causes, such as toxoplasmosis or rubella, may be identified by appropriate serologic or cultural studies. Finally, there is a small group of patients in whom the infecting organism cannot be identified. (N.M.G.)

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Chronic Bronchitis

Chronic bronchitis is defined as a disorder characterized by sputum production for at least 3 months a year for more than 2 years in the absence of other causes of chronic sputum production. Extensive investigations of the epidemiology, anatomy, pathophysiology, radiology, microbiology, and drug ther-

apy of chronic bronchitis have failed to provide definitive guidelines for the management of this common disorder. The role of bacterial infection, the etiologic agents, the requirements for antibiotic therapy, the optimal antibiotic selection, the duration of antibiotic treatment, and the criteria for exacerbation and resolution of episodes of chronic bronchitis remain controversial subjects. The information gained from special techniques (immunologic studies of sera, enzymatic analysis of sputum, quantitative analysis of sputum, transtracheal aspiration) has not provided additional useful clinical information. Investigators have studied patients intensively, but unfortunately have been unable to define clearly either the causal relationship between viral and *Mycoplasma* infections and exacerbations or the relationship between the qualitative or quantitative isolation of *H. influenzae* or *S. pneumoniae* and exacerbations. In view of the lack of a precise definition of an exacerbation and the inability to identify the role of bacteria in these exacerbations, all published drug evaluation studies must be considered suspect.

Accepting this limitation of our knowledge (the "unsteady state of the art"), why are antibiotics prescribed for exacerbations of chronic bronchitis, and what medications are recommended? The two most powerful arguments for administering antibiotics can be summarized as follows: (1) Acute respiratory infection is the most commonly identified cause of death in chronic obstructive lung disease; and (2) a double-blind controlled study has established the short-term superiority of antibiotics (in terms of clinical improvement, prevention of deterioration, subsidence of purulent sputum, eradication of organisms) as compared with a placebo. However, these data apply to a restricted segment of the total chronic bronchitis population.

No study has established the drug of first selection for the treatment of acute exacerbations of chronic bronchitis. Some clinicians prefer to administer ampicillin or amoxicillin, reserving tetracycline for the penicillin-allergic patient. Authorities have recommended that 4 gm of ampicillin be administered daily to ensure therapeutic levels of the drug in the sputum (to enhance eradication of the offending bacteria and to prevent relapse). This dose is not well tolerated, however, and most physicians prefer to prescribe 2 gm a day. Custom, not scientific evidence, has established the 2-week course of therapy.

Cephalexin and cephradine should not be prescribed for an infectious exacerbation; the cephalosporins are not more effective and are more expensive than ampicillin or tetracycline. Trimethoprim-sulfamethoxazole has recently been approved by the F.D.A. for this indication. There is no need for smears or cultures of sputum or for a complete blood count, since the results of these procedures have not proved helpful in the management of the vast majority of patients with community-acquired exacerbations of chronic bronchitis. (R.A.G.)

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