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Introduction

Respiratory tract infections are the leading cause of death in the United States and worldwide. These infections, including viral upper respiratory infections (URIs) sinusitis, otitis pharyngitis, bronchitis, acute exacerbations of chronic bronchitis, and pneumonia, are also the leading cause of outpatient visits, accounting for 70% to 85% of all antibiotic prescriptions in adult and pediatric practice.[1] In addition, they account for the majority of adverse drug reactions (ADRs) encountered with common prescribing patterns.[2] Thus, any large-scale attempt to improve healthcare outcomes would unequivocally include respiratory tract infections.[3]

In this supplement to the *American Journal of Medicine,* leading academic authorities address the topic of diagnosing and treating respiratory tract infections. Throughout this series of scholarly reports are some important common themes. First, the conditions reviewed are those most commonly encountered in clinical practice, and represent the facet of infectious disease that is most often driven by empiric decisions and is a major cause of morbidity and mortality. Second, these conditions represent a highly frustrating facet of contemporary infectious disease practice: the difficulty of accurate sampling from the infected site, accompanied by a decline in the quality of microbiology in many laboratories and the difficulty in interpreting results. Practical issues such as cost and the need for rapid therapeutic decisions are also important considerations. Thus, although physicians believe that our approach is scholarly and defendable based on high-quality data, particularly for common and medically important conditions, this is a setting in which the majority of infections are treated empirically without the benefit of either microbiology or well-founded evidence-based practice guidelines.

Despite these limitations, there are some practical issues that justify common practices. The menu of pathogens that are responsible for the most respiratory tract infections includes influenza, parainfluenza, rhinovirus, metapneumovirus, respiratory syncytial virus, coronaviruses, and adenovirus. Recent progress in microbiology now permits rapid and accurate diagnostic testing.[4] Drawbacks are the cost of testing; the lack of antiviral drugs to treat these pathogens other than influenza; and the inability to exclude bacterial superinfections that are common, elusive to detect, and nearly always treatable. Thus, empiricism is a reality that reflects the current state of the art.

The bacterial pathogens in these infections are well known on the basis of extensive studies and include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, selected aerobic and microaerophilic streptococci such as *Streptococcus milleri*, and in a selected subset of infection, anaerobic bacteria. In community-acquired pneumonia (CAP) there also are the "atypical agents," including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. The notable exception is pharyngitis due to *S pyogenes*. Diagnostic testing for this pathogen is accurate and has become standardized, revolutionizing the management of this condition.

The reviews in this supplement provide a state-of-the-art approach to the management of the most common respiratory tract infections. Dr. Thomas M. File, Jr.'s case-study review of CAP is based largely on the consensus guidelines from the Infectious Diseases of America/American Thoracic Society (IDSA/ATS).[5] CAP is often viewed as the most important infectious disease in that it is common, usually treatable, yet frequently mismanaged. It is also the major infectious disease subjected to federal audit by the major US funding agency, Medicare, which evaluates management of CAP in every nonfederal hospital to determine compliance with stringent guidelines from the IDSA and ATS, regarding delays in starting antibiotic treatment. The priority of compliance is assured by public reporting and anticipated financial penalties.[6] The good news is that the guidelines and "door-to-needle times" priorities are evidence-based and the national performance has been notably improved by the audits and penalties. The bad news is 2 adverse outcomes: First, abuse of antibiotics reflects the fact that administering them is rewarded and overprescribing them is not punished; therefore, the "safe" position is to treat for pneumonia even if the more likely diagnosis is bronchitis, congestive heart failure, pulmonary embolism, or another condition.[7] Second, there has been a virtual loss of microbiology. The history of pneumonia in the United States is rich with classic studies to detect etiologic agents, but currently an etiologic diagnosis is established in <10% of cases.[8] The reason is complicated, but the case for em-

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Requests for reprints should be addressed to John G. Bartlett, MD, 1830 East Monument Street, Room 447, Baltimore, MD 21205.
E-mail address: jb@jhmi.edu.

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piricism is that it is difficult or often impossible to complete the diagnostic evaluation, including microbiology and radiologic studies, within the 6-hour time span allowed for the first dose of antibiotic. In addition, there also has been substantial distancing of microbiology from the site of care ("outsourcing"), a decline in the quality of clinical microbiology in many laboratories, and a sense that empiricism usually works, making these studies superfluous. All of these rapidly changing shifts in policy for the management of CAP make the review by Dr. File both timely and important.

Upper respiratory tract infections are the most common infections seen in primary care. Treatment of these conditions is among the most controversial management decisions owing to the inability to distinguish viral from bacterial infections and thus know which patient should receive antibacterial medications. The exception is pharyngitis where there is that 1 treatable pathogen—group A streptococcus, and a point-of-care test for a rapid diagnosis.[9] This test has revolutionized the management of pharyngitis in many healthcare systems.

Dr. Jack B. Anon discusses the diagnostic challenge of sinusitis, where there is nothing equivalent to the rapid streptococcus test. Some studies have used invasive diagnostic methods that verify the apparent importance of selected pathogens. But in the individual case there is nothing to assist in determining the case that merits antibacterials: imaging is usually useless, it is difficult to get uncontaminated specimens from the site of infection, and few physicians are prepared to get the endoscopic samples sometimes suggested. Some guidelines recommend clinical clues such as duration of symptoms, tooth pain and sinus tenderness, but critical analysis shows that none of these are clearly validated.[10] The Cochrane Library review concluded that placebo-controlled trials of antibiotics are inconclusive about whether there is a convincing therapeutic response.[11] The FDA now requires placebo-controlled trials based on their concurring opinion that the evidence that antibacterial agents offer a benefit is inclusive. Some have suggested that the best method to evaluate outcome in such studies is the patient outcome record (POR).[12] Unfortunately, there is no lack of a validated POR method.

Thus, the clinician has little help from the history, physical examination, or laboratory results to determine which patient with sinusitis needs an antibiotic. The case-study presentation by Dr. Anon offers clarification and insight on the diagnostic challenge with sinusitis.

Next, Dr. Hartmut Lode provides a comprehensive and scholarly review on ADRs associated with the most commonly prescribed antibiotics for respiratory tract infections. This component of the supplement is particularly important given that URIs are treated with antibiotics. Said on page 1.[3] Of particular interest are the within-class differences. Also of interest are the plethora of rare but unusual ADRs associated with fluoroquinolones, including cardiac arrhythmias due to QTc prolongation, hyperglycemia and hypoglycemia, tendon rupture, and possible central nervous system toxicity. The major concern is the underemphasized role of these agents as the causes of *Clostridium difficile* colitis. Fluoroquinolones were rarely implicated in these infections until about 2000, when reports surfaced of an epidemic from Quebec, with subsequent reports of epidemics in the United States and Europe.[13,14] The implicated strain was NAP-1, a strain type that was rarely noted in previous years.[14] The presumed reason for the epidemic was the extensive use of fluoroquinolones combined with in vitro resistance of the NAP-1 strain to these agents.[14,15] The reason for the high rate of morbidity and mortality was that NAP-1 produces large amounts of both toxin A and toxin B. The rate of attributable mortality ranges from 4% to 17%.[16] One hospital controlled a major epidemic only by stepping use of the fluoroquinolone class. It should be noted that most of the infections discussed in this supplement are in outpatients, in whom *C difficile* infection is a far less frequent complication. Nevertheless, *C difficile* infection is a serious complication, especially when using the newly defined hospital-associated category.[17] Also important are the broad-spectrum β-lactams, including amoxicillin, amoxicillin-clavulanate, and some oral cephalosporins. This is important because diarrhea is among the most common ADRs of antibiotics. Most cases are minor, but those associated with signs of colitis require a *C difficile* toxin assay.

Like Dr. File, Drs. Marcos I. Restrepo and Christopher R. Frei also address CAP but emphasize the economics of hospitalization, which increases the cost of CAP 25-fold. Their analysis provides perspective on costs associated with variations in antibiotic selection. Both their contribution and the CAP review by Dr. File emphasize the 2007 IDSA/ATS guidelines, which advocate a fluoroquinolone or a cephalosporin (ceftriaxone or cefotaxime) plus azithromycin for patients with moderate illness requiring hospitalization. Conversely, the recent guidelines of the British Thoracic Society,[18] advocate the use of oral or intraveneous amoxicillin plus oral or intravenous clarithromycin in this setting.

John G. Bartlett, MD
Johns Hopkins University
School of Medicine
Baltimore, Maryland, USA

AUTHOR DISCLOSURES

The author of this article has disclosed the following industry relationships:

John G. Bartlett, MD, has served on the Advisory Board for J&J Pharmaceuticals, Optimer Pharmaceuticals, and Salient Pharmaceuticals.

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