

Treatment with Appropriate Antibiotic Therapy in Community-acquired Respiratory Tract Infections

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In total, community-acquired respiratory tract infections (CARTIs) account for more than 116 million annual office visits, making them the most common condition for which antibiotics are prescribed in the United States^{1,2} and representing a large burden on clinicians' time. This burden is further complicated by the uncertainty surrounding these infections; when patients initially present with a suspected CARTI, the origin of the illness (viral or bacterial) must first be evaluated. Once a bacterial infection is suspected, the decision for antimicrobial therapy is typically empirical, with agent selection influenced by local bacterial susceptibility and previous experience.³

Epidemiology

Respiratory tract infections (RTIs) are responsible for 50 million deaths globally each year.³ The most frequently occurring CARTIs in the United States are acute rhinosinusitis (AS), acute exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP).⁴ These conditions, specifically CAP and AECB, are associated with significant morbidity and mortality rates.³

AS can be described as a bacterial infection of the paranasal sinuses lasting less than 30 days, in which symptoms resolve completely. There are 31 million cases of AS annually,⁵ making it the fifth most common diagnosis for which antibiotics are prescribed.⁶ In total, this condition accounts for 73 million restricted activity days per year.⁵

Chronic bronchitis is usually defined as a condition characterized by cough and sputum production on most days for a prolonged period of time recurring each year.

AECB, an acute exacerbation of this long-term process, is characterized by increased cough, sputum production, and dyspnea, in addition to development of sputum purulence. AECB should not be confused with acute bronchitis, which is a viral infection caused by environmental conditions. There are about 32 million cases of AECB annually among 11 million people,^{7,8} resulting in 1.5 million emergency hospital visits and 500 000 hospitalizations per year.⁹ Ninety percent of these cases are patients who are current or former smokers.¹⁰

Pneumonia is an infection of the lung parenchyma. CAP refers to pneumonia acquired outside of hospitals or extended-care facilities. More than 5 million cases of CAP occur annually, resulting in 10 million office visits, 1.1 million hospitalizations, and more than 45 000 deaths.^{3,11,12} CAP is associated with a significant overall mortality rate of >8%, making it the most common cause of death from infection.¹³ When focusing specifically on hospitalized patients, the mortality rate ranges from 8.5% to 15.8%,¹³⁻¹⁷ and when limited to the patients in the intensive care unit (ICU), the mortality rate is as high as 36.5%.¹⁷

Causative Pathogens. Typically, there are 3 pathogens that account for the majority of CARTIs: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.¹⁸⁻²⁰ Further, a group of atypical pathogens (*Legionella* spp, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*) account for significant morbidity and mortality rates in CAP. The specific percentages of these pathogens responsible for CARTIs are listed in the **Table**.

Antimicrobial Resistance. Empiric management of CARTIs has been challenged by the emergence of resistance to typical respiratory pathogens. In the 1980s, antimicrobial-resistant *S pneumoniae* became widespread in many parts of the world.²¹ In the United States, however, resistance did not become a significant problem until the 1990s. It is estimated that 34% of *S pneumoniae* isolates are resistant to penicillin,²¹ 20% to 30% are resistant to macrolide therapy,²² and 35% are resistant to trimethoprim-sulfamethoxazole.²¹ In fact, of the penicillin-resistant *S pneumoniae* isolates, 78% were multidrug resistant.²³

During the 1980s, penicillin resistance rates in the United States were at levels of 3% to 5%^{24,25}; however, these rates jumped to 17.8% by 1991 to 1992.²⁶ Ongoing surveillance studies clearly show that the problem of penicillin-resistant *S pneumoniae* has steadily risen from the early 1990s to reach the level of 34% resistant for the period of 1999-2000.²¹ Although penicillin-resistant *S pneumoniae* was identified as early as 1974,²⁷ macrolide-resistant *S pneumoniae* emerged at a later date. In 2000, a national, longitudinal, multicenter surveillance study was initiated to track the emergence and spread of resistance among CARTI pathogens.²³ In this study, data collected

from more than 200 medical centers confirmed the widespread prevalence of erythromycin resistance (minimum inhibitory concentration [MIC] ≥ 1 mg/L) to *S pneumoniae* across the United States. The resistance rates collected varied across geographic regions, ranging from 40.2% in the Southeast to 23.2% in the Northwest.²³ The continuing spread of resistance in typical respiratory pathogens reaffirms the importance of continued surveillance to guide optimum empiric therapy for patients with CARTIs.

Appropriate Management of CARTIs

The leading factor contributing to the increase in resistance is the inappropriate use of antibiotics. Although most of this inappropriate use stems from an inability to quickly and unequivocally determine the etiology of infection (viral vs bacterial), patient history and signs and symptoms of disease may provide insight into which patients have a high likelihood of bacterial infection. Once the decision has been made to initiate therapy, 2 factors should be taken into consideration when selecting an antibiotic for the treatment of CARTIs. The first factor is an agent's spectrum of activity. When treating CARTIs, the use of an antibiotic with a tailored spectrum of activity should ensure coverage of typical pathogens, resistant strains, and atypical pathogens, without coverage of nonrespiratory, gram-negative pathogens. The second factor is selecting an agent with a low potential to induce future antibiotic resistance. When treating CARTIs, the use of an antibiotic with chemical properties that may minimize the risk of developing resistance should be considered. Properties affecting resistance include potency, half-life, bactericidal activity, and binding affinity at multiple sites. Together, these 2 factors form the basis of a useful framework to select antibiotic agents for the treatment of CARTIs.

Spectrum of Activity. As previously discussed, the causative pathogens for CARTIs include *S pneumoniae*, *H influenzae*, and *M catarrhalis*, resistant pathogens, and atypical pathogens. When selecting antibiotic

Table. Pathogens Responsible for Community-acquired Respiratory Tract Infections

Pathogen	% Responsible for AS	% Responsible for AECB	% Responsible for CAP
Typical pathogens ¹⁸⁻²⁰			
<i>Streptococcus pneumoniae</i>	34	15-25	20-60
<i>Haemophilus influenzae</i>	35	30-59	3-10
<i>Moraxella catarrhalis</i>	0-8	3-22	—
Atypical pathogens ²⁰			
<i>Legionella</i> spp	NA	NA	2-8
<i>Mycoplasma pneumoniae</i>	NA	NA	1-6
<i>Chlamydia pneumoniae</i>	NA	NA	4-6

AS indicates acute sinusitis; AECB, acute exacerbations of chronic bronchitis; CAP, community-acquired pneumonia; NA, not available.

therapy for CARTIs, the clinician should select a product that not only covers these pathogens, but also has limited or no effect on nonrespiratory, gram-negative pathogens. This is the concept of a tailored spectrum.

The primary focus of empiric therapy for CARTIs relies on coverage of infections caused by typical respiratory pathogens: *S pneumoniae*, *H influenzae*, and *M catarrhalis*. A number of antibiotics available today meet this requirement, including beta-lactams, fluoroquinolones, ketolides, and macrolides. Yet coverage of these susceptible pathogens is not enough to guarantee adequate treatment of these infections.

Although not the leading cause of CARTIs, atypical pathogens may account for up to 20% of CAP cases.²⁸ These pathogens often go undetected because of the infrequent use of diagnostic tests. This factor underlies the recommendations in the Infectious Diseases Society of America, American Thoracic Society, and the American College of Clinical Pharmacy treatment guidelines to include empiric coverage of atypical pathogens when treating CAP.²⁹⁻³¹ These pathogens are covered by a number of antibiotics available today, including the fluoroquinolones, ketolides, and macrolides. The beta-lactam antibiotics do not provide coverage of atypical pathogens.

In addition to covering typical and atypical pathogens, the selected agent should be able to combat infections from resistant forms of typical respiratory pathogens. Resistant forms of *S pneumoniae* have increasingly become a public health problem. As stated, rates of penicillin-resistant *S pneumoniae* and macrolide-resistant *S pneumoniae* have rapidly increased over the past decade, and this increasing resistance has adversely influenced clinical outcomes. Two studies demonstrating this impact are described below.

A study by Einarsson and colleagues demonstrated the difference in clinical outcomes of patients with pneumonia caused by penicillin-nonsusceptible pneumococci (PNSP) and penicillin-susceptible pneumococci (PSP). Patients with PNSP pneumonia had a significantly longer hospital stay (26.8 vs 11.5 days; $P = .001$) and a higher average cost of antibiotics (\$736 vs \$213; $P < .0001$) compared with those with PSP

pneumonia.³² A study examining the epidemiologic factors affecting mortality from pneumococcal pneumonia included patients residing in a surveillance area with CAP who required hospitalization. Increased mortality was associated with a number of factors including age, underlying disease, Asian race, and residence. When these factors were controlled for and deaths during the first 4 hospital days were excluded, mortality was significantly associated with a penicillin MIC of 4.0 or higher.³³

A number of studies have reported macrolide failures in the treatment of RTIs. This growing body of evidence suggests that macrolide failure is an increasing clinical problem.³⁴⁻⁴¹ One study, examining the development of breakthrough bacteremia during macrolide treatment of pneumococcal infection and its relationship to the macrolide susceptibility of the pneumococcal isolate, identified 86 patients with macrolide-resistant blood isolates of *S pneumoniae*.³⁹ This study further described the treatment failure of 19 patients with bacteremia caused by erythromycin-resistant *S pneumoniae*. The study authors concluded that the development of breakthrough bacteremia during macrolide therapy is more likely to occur in patients infected with an erythromycin-resistant pneumococcus.³⁹

Collateral Damage. The use of antibiotics with activity extending to nonrespiratory, gram-negative organisms can impact flora and pathogens, such as *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella pneumoniae*, and *Escherichia coli*, leading to the development of resistant strains of these organisms. This phenomenon has been referred to as collateral damage. Fluoroquinolone-resistant strains of *P aeruginosa*, *Serratia marcescens*, and *Acinetobacter baumannii* have been documented in 2 studies. The first study investigated the impact of fluoroquinolone administration on the emergence of fluoroquinolone-resistant, gram-negative bacilli from gastrointestinal (GI) flora.⁴² The investigators gathered stool samples from hospitalized patients in 2 internal medicine wards. Fluoroquinolone-resistant, gram-negative bacilli were isolated from the GI tracts

of 31% of these patients after a median hospitalization of 4 days. In these patients, fluoroquinolone-resistant strains of *P aeruginosa* (49.5%) were the most frequent, followed by *Pantoea agglomerans* and *S marcescens* (16%), *E coli* (8%), *A baumannii* (6%), *K pneumoniae* (3%), and *Proteus mirabilis* (1.5%).⁴² The only risk factor significantly associated with fluoroquinolone-resistant, gram-negative bacilli was the receipt of fluoroquinolone during the month before admission to the hospital.

A second study was designed to assess the national rates of antimicrobial resistance among gram-negative aerobic isolates recovered from ICU patients, comparing these rates with antimicrobial use.⁴³ From 1994 to 2000, a total of 35 790 gram-negative aerobic isolates were collected each year from patients in 77 to 117 ICUs in 43 states plus the District of Columbia. Most of the pathogens were cultured from the respiratory tract (51.5%), urine (16.0%), blood (13.8%), or wounds (11.8%). The most frequently isolated organisms were *P aeruginosa* (23%) followed by *Enterobacter* species (14.0%), *K pneumoniae* (13.6%), and *E coli* (11.3%). *Acinetobacter* species (5.8%), *S marcescens* (5.4%), *Stenotrophomonas maltophilia* (4.3%), *Proteus mirabilis* (3.6%), *Citrobacter* species (2.9%), and *Morganella morganii* (0.9%) were some of the remaining 38.1% of isolates. In total, the overall resistance to ciprofloxacin among aerobic gram-negative bacilli increased from 11% in 1990 to 1993, to 14% in 1994, and then to 24% in 2000. Most notably, the increase in ciprofloxacin resistance in *P aeruginosa* increased from 11% in 1990 to 1993 to 32% in 2000, correlating with a >2.5-fold increase in fluoroquinolone use over the previous 10 years.⁴³

When focusing on agents with a tailored spectrum of action for the treatment of CARTIs, one must consider agents with the ability to combat infections caused by the typical respiratory pathogens *S pneumoniae*, *H influenzae*, and *M catarrhalis*, which are responsible for the majority of cases. Selected agents must be able to cover resistant strains and also have activity against atypical respiratory pathogens. Although sufficient coverage of potential causative agents should be the first consid-

eration when empirically treating CARTIs, the use of agents lacking coverage of nonrespiratory, gram-negative pathogens should also be considered in an effort to reduce resistance in these pathogens.

Low Potential to Induce Future Antibiotic Resistance

The second factor guiding the selection of an agent for empiric treatment of CARTIs is to select an agent with a low potential to induce future antibiotic resistance. Chemical properties of antibiotics that may minimize the risk of pathogens developing resistance include bactericidal activity, half-life, structural attributes, and potency.

Bactericidal Activity. Typically, antibiotics have been classified by the magnitude of bacterial kill they exhibit during a 24-hour period. Those that kill 99.9% (or >3 log) of the initial bacterial inoculum are considered bactericidal, whereas agents killing anything less are considered bacteriostatic.⁴⁴ Examples of bacteriostatic agents include macrolides, tetracyclines, and sulfonamides; examples of bactericidal agents included penicillins, cephalosporins, fluoroquinolones, ketolides, and aminoglycosides.⁴⁵⁻⁴⁷ Bactericidal antibiotics have a lower propensity to induce resistance compared with bacteriostatic agents, because bactericidal antibiotics quickly eradicate pathogens. Implications for resistance are related to exposure to suboptimal drug levels. This occurs when concentrations of the antibacterial agents fall below MIC for an extended period, a situation that can arise when an antibiotic has a prolonged half-life. While half-lives of antibiotics vary, azithromycin stands out because of its very long half-life of 60 to 70 hours.⁴⁸ The extensive exposure to subtherapeutic levels of azithromycin can lead to mutations among bacteria that are not quickly eradicated.⁴⁹ Three studies illustrate the development of resistance to azithromycin because of this phenomenon.⁵⁰⁻⁵²

In an in vitro study, 12 strains of *S pneumoniae* (6 azithromycin susceptible, 6 azithromycin nonsusceptible) were repeatedly exposed to subinhibitory concentrations of azithromycin. On subculturing, 5 of the 6 ini-

tially azithromycin-susceptible parent strains yielded azithromycin-resistant mutants, whereas the MICs of the 6 initially resistant strains rose quickly, demonstrating that development of resistance to azithromycin can occur after repeated exposure to subinhibitory concentrations of the drug.⁵⁰

A prospective study examined the impact of community-based azithromycin treatment on the carriage and resistance of *S pneumoniae*.⁵¹ A single dose (20 mg/kg) of azithromycin was given to 79 aboriginal children with trachoma. Before treatment, 1.9% of the children carried resistant strains, whereas 55%, 35%, and 6% carried resistant strains at the 2- to 3-week, 2-month, and 6-month follow-up visits, respectively, suggesting that the selective effect of azithromycin allowed for the growth of preexisting azithromycin-resistant strains of *S pneumoniae*.⁵¹

In a third study by Kastner and Guggenbichler, clarithromycin was compared with azithromycin regarding the promotion of resistance in the oral flora of children receiving treatment for an upper or lower RTI.⁵² Clarithromycin has an elimination half-life of 3 to 7 hours compared with 60 to 70 hours for azithromycin. One week after the initiation of treatment, the percentage of patients with macrolide-resistant isolates was 60% for the clarithromycin group and 68% for the azithromycin group. The influence of extensive half-life was more pronounced at 6 weeks, with only 33% of the clarithromycin group having macrolide-resistant isolates compared with 87% of the azithromycin group, illustrating azithromycin's influence on the development of resistant isolates. In addition, 11.7% of the patients receiving azithromycin therapy became reinfected versus only 1.6% of the clarithromycin patients.

The structural attributes of antibiotics are important to drug activity and the development of antimicrobial resistance. The ability to bind at more than one site could influence the induction of resistance by allowing for antimicrobial action even after mutation of one of the sites. For example, both macrolides and ketolides bind to domain V of 23S ribosomal ribonucleic acid (rRNA) within the 50S subunit.⁵³ They also interact

with the binding domain II on 23S rRNA, but do so quite differently.⁵³⁻⁵⁵ Ketolides possessing a carbamate extension at positions 11/12 allow for strong binding to domain II, whereas the macrolides form a weak bond to domain II.^{53,54} When methylation occurs at domain V of the target site (one of the principal resistance mechanisms), macrolide resistance is noted. However, the ketolides can overcome resistance due to their strong binding affinity for domain II.⁵³ The significance of structural differences between macrolides and ketolides is discussed in depth by John A. Sbarbaro, MD, MPH, FCCP, in the next article of this supplement.

Potency is a product of MIC-antibacterial effect and pharmacokinetics (drug delivery). Potency may be examined by measuring drug levels in the lung epithelial lining fluid. When macrolides are examined in this fashion for their potency in treating infections with *S pneumoniae*, azithromycin is the least potent, whereas clarithromycin is the most potent.⁵⁶⁻⁵⁹ Although azithromycin is the least potent macrolide, it continues to be among the most widely used. This correlates with the evidence that azithromycin is more likely than clarithromycin to select for macrolide resistance with *S pneumoniae*.^{51,60} The low potency of azithromycin, along with its extensive half-life, has been implicated in the development of macrolide resistance to *S pneumoniae*.⁵¹

A study of Canadian national surveillance data examined trends in macrolide resistance to *S pneumoniae* in 9 Canadian provinces.⁶¹ Of these provinces, the coastal provinces (British Columbia, Newfoundland) demonstrated the lowest rates of resistance (~5%) in 2002. The prairie provinces (Alberta, Manitoba, Saskatchewan) and Ontario showed resistance rates between 9% and 14%, and Quebec and the maritime provinces (New Brunswick, Nova Scotia) showed rates nearing or exceeding 20%. When macrolide use was scrutinized for the same year, azithromycin consumption in Canada was lowest in the coastal provinces, accounting for <20% of the total prescribed macrolides. In contrast, azithromycin accounted for >44% of all macrolides in Quebec, New Brunswick, and Nova Scotia, the 3 provinces with the highest rates of

resistance. The study authors concluded that provinces that had a high use of a less potent macrolide (azithromycin) had higher resistance rates, whereas provinces that consumed more of the more potent macrolides (clarithromycin and erythromycin) showed lower development of resistance.

Conclusion

Empiric management of CARTIs has been challenged by the emergence of resistance to typical respiratory pathogens. When selecting antibiotics for CARTI management or for inclusion on a managed care formulary, 2 factors should be taken into consideration: spectrum of activity and the potential to induce future antibiotic resistance. Antibiotics designed with a tailored spectrum of activity (ie, coverage of typical pathogens, resistant strains, and atypical pathogens, while avoiding coverage of non-respiratory, gram-negative pathogens) can improve CARTI treatment outcomes while avoiding collateral damage. Also, when treating CARTIs, the use of an antibiotic with chemical properties that may minimize the risk of developing resistance should be considered. Properties affecting resistance include potency, half-life, bactericidal activity, and binding affinity at multiple sites. These principles provide a useful framework for the empiric choice of antibiotics to treat CARTIs. This approach should provide improved clinical and microbiologic outcomes while decreasing the risk for collateral damage in the development of resistance in nonrespiratory, gram-negative pathogens.

In CARTI management, antibiotic costs account for a small proportion of the total cost of therapy.⁶² When applying the antibiotic selection principles discussed in this article, total costs of care must be considered, because the most cost-effective option for CARTI management may be found among more expensive antibiotics. The next 2 articles in this supplement provide a review of the characteristics of the ketolide class of antibiotics, review the supporting safety and efficacy research for the ketolides, and present pharmacoeconomic data examining cost issues associated with CARTI management.

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