RTI RESISTANCE

BULLETIN 2

KNOW YOUR PATHOGENS: THE ANTIMICROBIAL RESISTANCE THREAT

FROM THE EDITORS' DESK

In the first issue of this series of e-Bulletins, we discussed the inappropriate use of antimicrobials to treat respiratory tract infections (RTIs) in the outpatient setting. Information gathered from signs, symptoms, and diagnostic techniques can be used to limit the overuse of antimicrobials by identifying infections that are more likely caused by viral pathogens.

A major consequence of inappropriate use of antimicrobials is the development of resistance. In today's environment, antimicrobial resistance has challenged physicians like no other time in the past. Surveillance studies are demonstrating that resistance rates by RTI pathogens, particularly *Streptococcus pneumoniae*, have stabilized but remain near peak levels and new multidrug-resistant strains are growing in prevalence. This comes at a time when few new antimicrobial agents are being approved or under development. Therefore, it is critical for physicians to use the available agents judiciously and effectively to prolong their utility for treating these infections.

Part of the clinicians' responsibility includes recognizing the potential for a resistant infection in their patients. When a bacterial infection is proven or strongly suspected, proper management will require the physician to recognize risk factors for a resistant pathogen. Physicians should also be aware of the local epidemiology of RTI pathogens as resistance rates can vary greatly between geographic regions. All of these factors should be taken into account when selecting empiric therapy to ensure an appropriate antimicrobial is administered and minimize the risk for clinical failure, hospitalization, and mortality.

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IN THIS BULLETIN

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TARGET AUDIENCE
This educational initiative has been designed to meet the needs of physicians and other healthcare professionals involved in the diagnosis, management, and treatment of outpatients with RTIs.

PURPOSE STATEMENT
The purpose of this multicomponent initiative is to educate primary care physicians and other healthcare professionals on when an antimicrobial agent is needed to treat an RTI, identifying the risk factors for a resistant RTI, and optimizing antimicrobial therapy. With this knowledge, healthcare professionals involved in the diagnosis, management and treatment of outpatients with RTIs will be able to tailor therapy to achieve successful outcomes.

LEARNING OBJECTIVES
At the conclusion of this activity, learners should be able to
- Identify the risk factors for a resistant RTI

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RTI ETIOLOGY

The most common pathogens that cause respiratory tract infections, such as community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute bacterial sinusitis, include the following:[1-6]

RTI Pathogens that Cause CAP	
Common Pathogens	**Atypical Pathogens**
Streptococcus pneumoniae	***Mycoplasma pneumoniae***
Haemophilus influenzae	***Chlamydophila pneumoniae***
Moraxella catarrhalis	***Legionella pneumophila***

BACTERIAL ETIOLOGY AND TESTING METHODS

The percentage of infections caused by each of these pathogens can vary considerably depending on type of infection, severity of illness, and even the method of isolation and testing. In a classic study that compared species identification of community-acquired pneumonia (CAP) infections by conventional testing methods (including sputum and blood culture) versus conventional testing plus needle aspiration, very different results were observed.[7] **Conventional testing methods** identified *M. pneumoniae* as the predominant pathogen (35% of infections) followed by *C. pneumoniae* (17%) and *S. pneumoniae* (17%). However, when **needle aspirates** were included in testing, *S. pneumoniae* was identified most often (30%) followed by *M. pneumoniae* (22%) and *C. pneumoniae* (13%). Furthermore, the pathogen was identified in only 50% of patients undergoing conventional testing techniques, compared with 83% of patients who underwent needle aspiration, demonstrating a key limitation of using conventional techniques in trying to identify the causative pathogen.

OTHER RTI PATHOGENS OF INTEREST

As discussed in the first bulletin of this initiative, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* are the most common pathogens to cause acute exacerbation of chronic bronchitis (AECB).[2] However, in patients with reduced lung function, there is an increased risk of infections caused by the gram-negative bacteria *Pseudomonas aeruginosa* and Enterobacteriaceae.[2] For CAP, *S. pneumoniae* remains the predominant pathogen for both mild and severe cases.[6] However, there has been increasing concern on the rising number of CAP cases caused by *Staphylococcus aureus*, particularly methicillin-resistant strains. These strains commonly exhibit resistance to several classes of commonly-used antimicrobials, including the macrolides and fluoroquinolones.[8, 9]

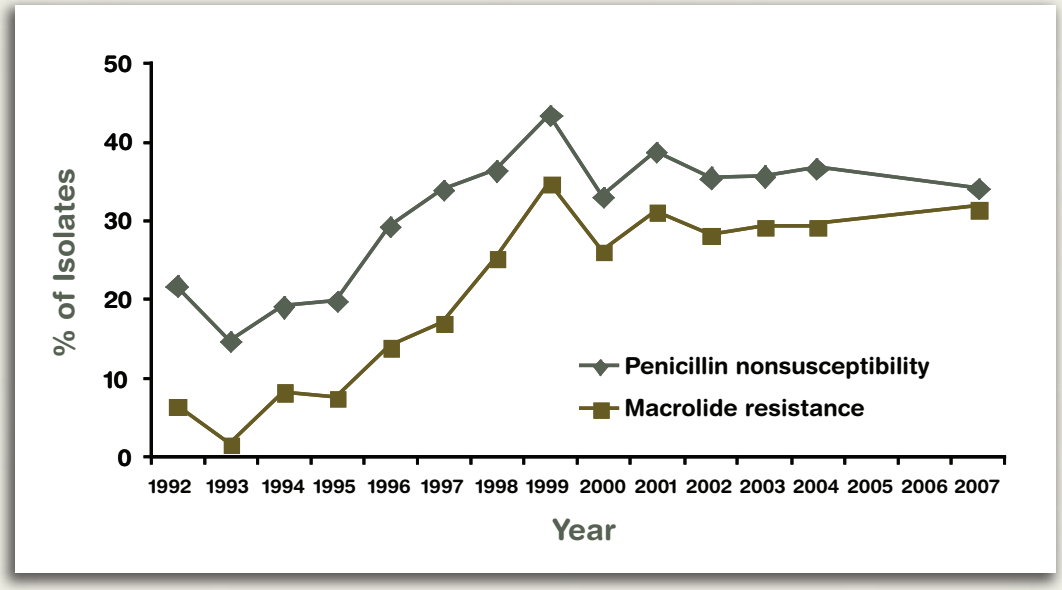
RTI RESISTANCE

Discussions of resistance by community-acquired respiratory tract pathogens have typically focused on *S. pneumoniae*. This pathogen causes the greatest proportion of these infections and has exhibited dramatic increases in resistance over the past two decades to commonly-used antimicrobial agents.

PENICILLIN RESISTANCE

A compilation of *S. pneumoniae* surveillance results in the United States has generally shown an increase in penicillin nonsusceptibility starting in the early 1990s and peaking around 1999 **(Figure 1)**.[10-14] Following this peak there has been a stabilization of nonsusceptibility rates at approximately 30%-35% (this includes isolates with intermediate and high-level resistance to penicillin). This trend has also been observed in other countries and may be a result of decreased use of antimicrobials for the outpatient treatment of RTIs as well as widespread use of the pneumococcal conjugate vaccine.[15-17]

Figure 1. Penicillin Nonsusceptibility and Macrolide Resistance Rates for *S. pneumoniae* in the United States, 1992 – 2007[12]



New CLSI Breakpoints and Penicillin Resistance

The clinical significance of penicillin resistance has been debated and has led to a recent revision of the CLSI breakpoints.[18, 19] Former penicillin breakpoints for *S. pneumoniae* were set at conservative levels to ensure effective treatment of meningitis, with breakpoints set for all isolates at ≤0.06 μg/mL, 0.12-1 μg/mL, and ≥2 μg/mL for susceptible, intermediate, and resistant, respectively. New penicillin breakpoints are separated by clinical syndrome and route of administration. Non-meningitis isolates are considered resistant at levels of 2 μg/mL or greater when using an oral agent, while a breakpoint of ≥8 μg/mL for resistance is used when parenteral therapy is considered. The impact of this change in the breakpoints has lowered the percent of isolates with intermediate or high-level resistance to less than 10% compared to over 30% with the former breakpoints.[19] Thus, an intravenous formulation of penicillin can be an effective choice for a high percentage of patients with these infections.

MACROLIDE RESISTANCE

With the introduction of clarythromycin and azithromycin, the macrolides have played a key role in the treatment of RTIs over the years. These agents are better tolerated than erythromycin but also remain in the body longer due to prolonged half-lives. The longer exposure to these agents potentially provides a more favorable environment for resistance development. The consequence has been a rapid increase in macrolide resistance beginning in the mid-1990s **(Figure 1)**.[10-14] Similar to penicillin non-susceptibility, macrolide resistance peaked at around 1999 and has remained stable near a level of 30%.

Clinical Consequences of Macrolide Resistance

Macrolide resistance has been associated with an increase in the risk of clinical failure.[20, 21] In one prospective, population-based study, pneumococcal bacteremia cases were identified among patients who received macrolide treatment.[22] Among patients infected with a macrolide-susceptible strain, macrolide treatment failure was observed in only 1.5% of patients (21 of 1397 patients). However, in patients with a strain exhibiting an MIC of 1 μg/mL or greater, clinical failure occurred in 16% of the patients (37 of 230). Because of the high prevalence of macrolide resistance and evidence suggesting that even low-level macrolide resistance can impact patient outcomes, future management guidelines may caution clinicians on using the macrolides as empiric first-line therapy.

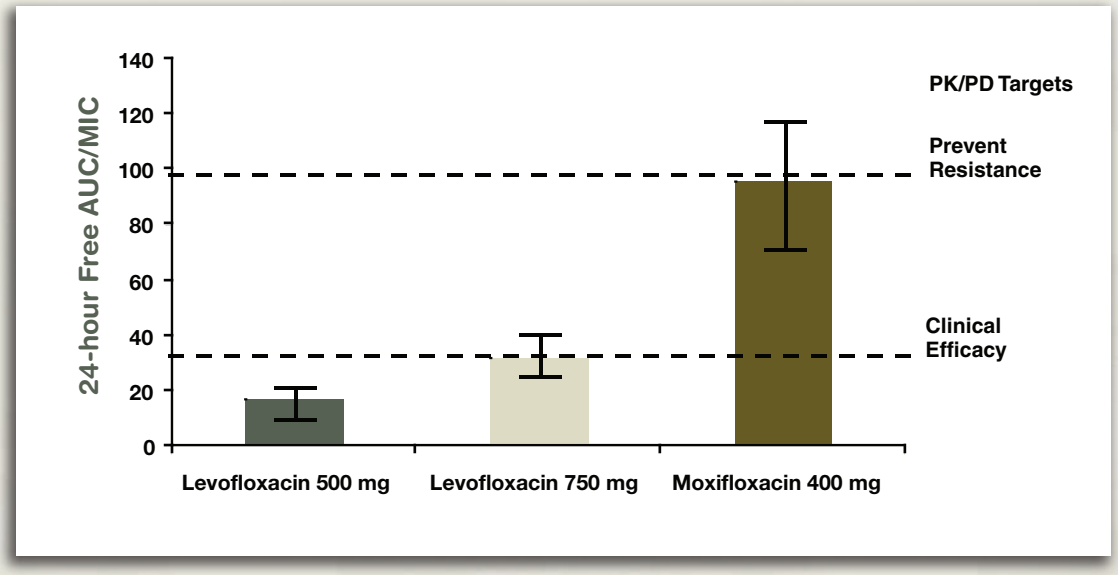
FLUOROQUINOLONE RESISTANCE

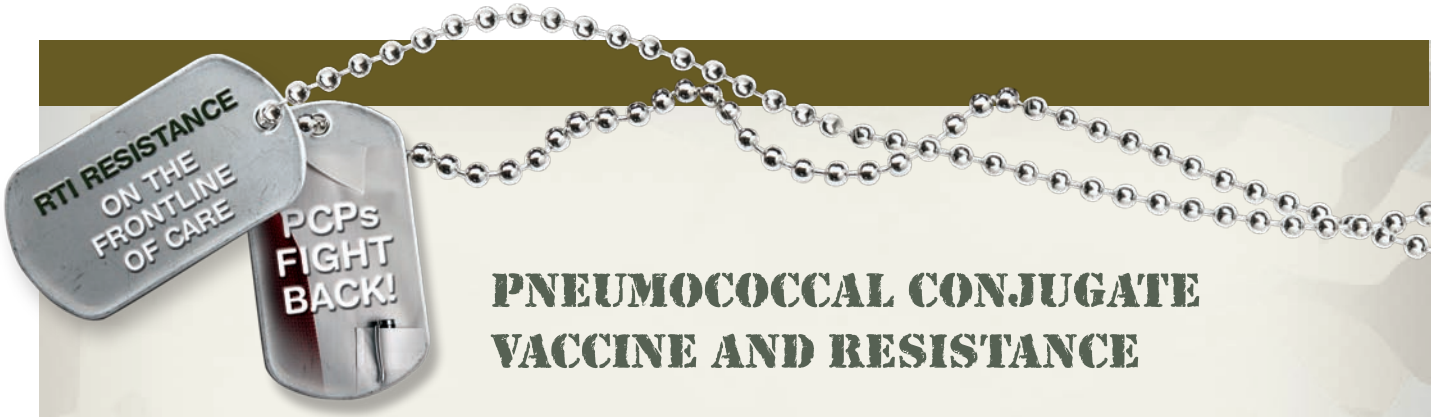
During the late 1990s, fluoroquinolone use increased rapidly for the treatment of RTIs. This increased concern that this class would follow a similar resistance pattern as penicillin and macrolide resistance, potentially reaching resistance rates of 25% or more.[23, 24] However, resistance levels stabilized in the early 2000s and have remained less than 2% for levofloxacin and less than 1% for moxifloxacin.[24, 25] The reason for this stabilization is not fully understood and is a bit surprising given the continued widespread use of this class. One explanation is that the use of these agents has been optimized to meet pharmacokinetic and pharmacodynamic targets that increase the probability of bacterial eradication and reduce the risk of resistance development.

The fluoroquinolones exhibit concentration-dependent bactericidal activity and clinical efficacy has been associated with the ratio of the area under the concentration-time curve (AUC) to the minimal inhibitory concentration (MIC) of the pathogen.[26, 27] For *S. pneumoniae*, an AUC/MIC ratio of 30-35 is generally needed to achieve clinical efficacy. However, studies have indicated that an AUC/MIC of 100 or greater is needed to prevent resistance development.[26, 27] The traditional dosing of levofloxacin (500 mg once-daily) would not typically attain the target AUC/MIC of 35 and would increase the risk of resistance development **(Figure 2)**.[28] The revised dosing regimen of 750 mg once-daily for levofloxacin nearly doubles the AUC compared to the 500-mg dose and increases the probability of meeting PK/PD targets for clinical efficacy.[28, 29]

Newer fluoroquinolone agents with greater in vitro activity against *S. pneumoniae*, such as moxifloxacin, also increase the probability that treatment will meet not only the target for clinical efficacy but also the target to inhibit the development of resistance.[28]

Figure 2. Comparison of fluoroquinolones for reaching PK/PD targets for *S. pneumoniae* infections[28]





PNEUMOCOCCAL CONJUGATE VACCINE AND RESISTANCE

Benefits of Pneumococcal Vaccine

The availability of the pneumococcal conjugate vaccine for children has provided significant benefits in reducing the incidence of invasive disease, such as bacteremia and meningitis.[30-32] Some research has also suggested that these vaccines can provide limited protection against CAP, though more research is needed to fully evaluate this.[31] The widespread use of the 7-valent conjugate vaccine in children has also impacted the level of penicillin resistance by *S. pneumoniae*.[33] This has been attributed to the fact that the serotypes included in the vaccine were those that were the most common causes of infection and most likely to carry resistance genes. The use of the vaccine de-selected for these resistant strains and the serotypes that replaced them were susceptible to penicillin. Therefore, the vaccine not only reduced the number of cases of invasive disease but also increased the susceptibility of *S. pneumoniae* that caused infections.

Consequences of Pneumococcal Vaccine: The Rise of Serotype 19A

An unintended consequence of the pneumococcal vaccinations has been serotype replacement (that is, an increase in the percentage of cases of invasive pneumococcal disease caused by serotypes not covered by the vaccine). One major concern has been an increase in the number of infections caused the multidrug-resistant serotype 19A.[34, 35] This serotype is not currently included in the 7-valent conjugate vaccine and one study that included 103 sites in the US showed that the percent of infections caused by 19A has increased from 0.8% in 2002 to 5.6% in 2006.[36] This serotype was responsible for 14.9% of all isolates collected from children 2 years or younger. Isolates of serotype 19A exhibit nearly complete resistance to penicillin, amoxicillin/clavulanate, and erythromycin, along with other commonly used antimicrobials **(Table 1)**.[35, 36] The strain remains susceptible to the fluoroquinolones. Vaccines in development, including the 13-valent conjugate vaccine, will include this serotype to offer protection against invasive disease caused by these strains.

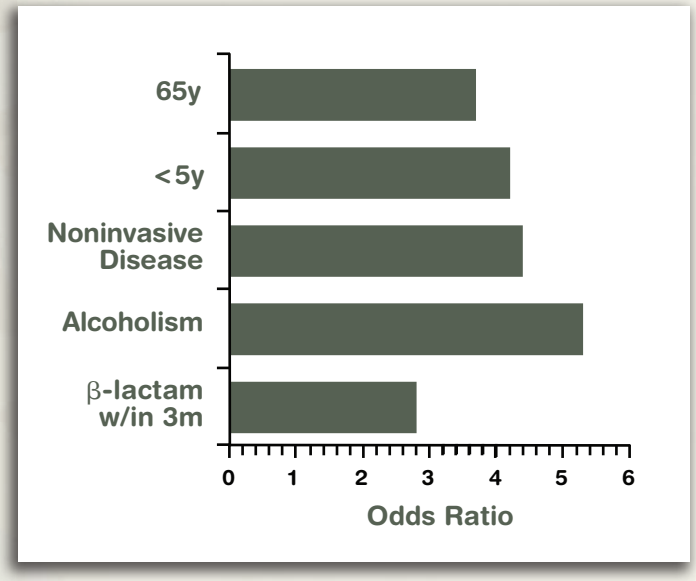
Table 1. Susceptibility of 562 Isolates of *S. pneumoniae* serotype 19A collected from 103 US sites, 2002-2006[35, 36]

Antimicrobial	% Susceptible
Penicillin	0
Amoxicillin-clavulanate	2.5
Cefuroxime	0.2
Erythromycin	0
Clindamycin	2.1
Levofloxacin	99.6
TMP-SMX	0.2
Tetracycline	0.2

IDENTIFYING PATIENTS WITH A RESISTANT INFECTION

For primary care physicians, it is important to recognize the prevalence of resistant pathogens that commonly cause RTIs. Additionally, in order to ensure that your patient receives an effective treatment for an RTI, it will be critical to identify patient factors that can increase the risk of a resistant infection. Several studies have identified these risks, and they include age of 65 or greater as well as less than 5 years old, noninvasive or colonized disease (such as sinusitis), alcoholism, and the recent use of a beta-lactam antibiotic **(Figure 3)**.[37-39] Each of these factors can increase the risk of a resistant infection, though they provide little evidence in telling which antimicrobial the pathogen may be resistant against.

Figure 3. Risk factors for penicillin resistance in *S. pneumoniae*[37-39]



Other Considerations
Immunosuppression
Including steroids
Multiple medical comorbidities
Exposure to day care child
Exposure to any antibiotic

PRIOR ANTIMICROBIAL USE

Prior antimicrobial use is the strongest predictor of antimicrobial resistance. A study by Vanderkooi and colleagues compared resistance in patients with RTIs who were treated with an antimicrobial in the previous 3 months versus those who were not exposed to an antimicrobial.[38]

Macrolide resistance in patients not previously exposed to a macrolide was less than 10% and those exposed to prior erythromycin had a slight increase in resistance (approximately 15%) **(Figure 4A)**. However, this rate increased dramatically for those patients who had previous exposure to clarythromycin (>25%) and azithromycin (>50%). Similar results were observed with patients who had prior use of the fluoroquinolones **(Figure 4B)**. Those patients with no prior antimicrobial exposure or exposure to a non-fluoroquinolone antimicrobial had resistance rates below 2%. However, isolates from patients with recent fluoroquinolone exposure had resistance rates over 8%.

This study strongly suggests that an RTI patient with recent antimicrobial use should be treated with an alternative class of agents. If the same class must be used, the patient should be monitored closely to ensure a sufficient clinical response is achieved or if a different regimen should be considered.

Figure 4A. Prevalence of macrolide resistance based on prior macrolide use[38]

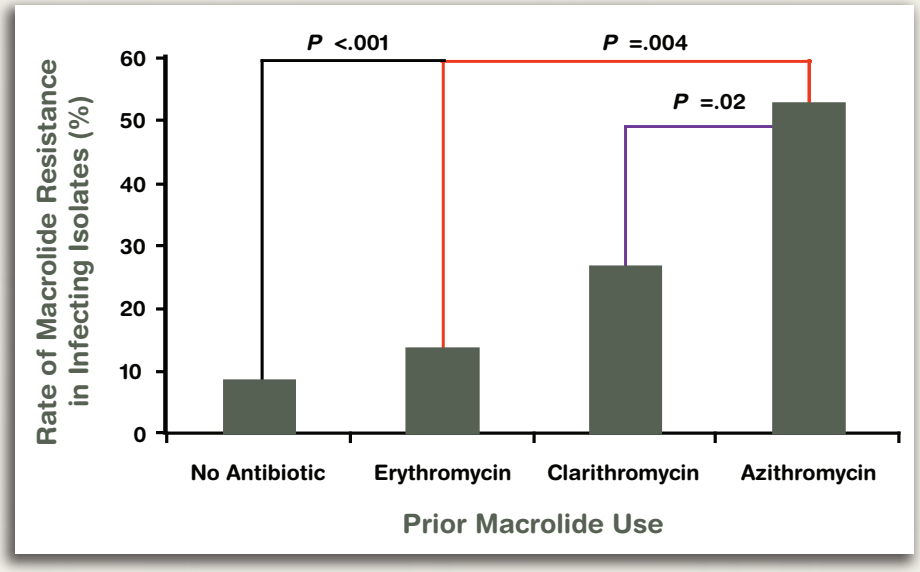
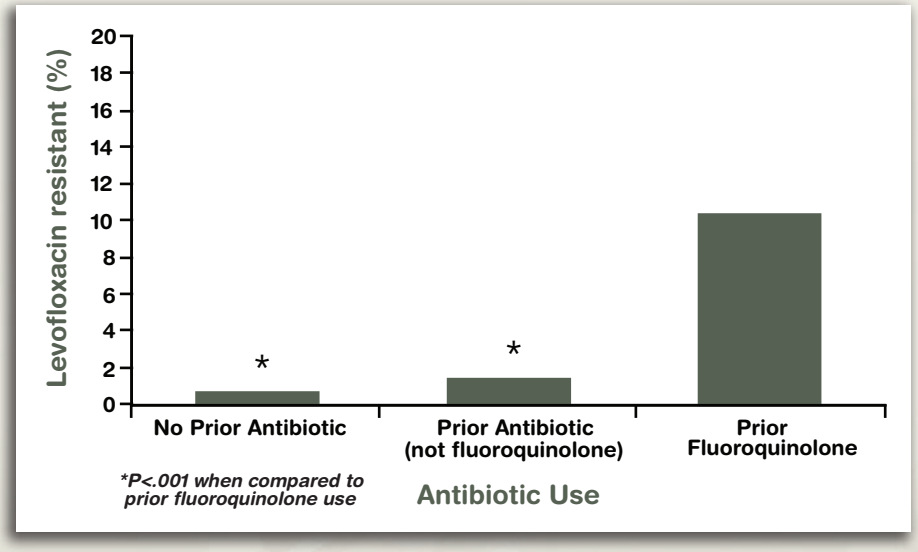


Figure 4B. Prevalence of fluoroquinolone resistance based on prior antimicrobial use[38]



EMPIRIC THERAPY PRINCIPLES

The latest CAP management guidelines released by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) offer some principles for selecting empiric antimicrobial therapy.[40] Antimicrobial therapy should be initiated as soon as possible after the diagnosis is made. However, the guidelines do not provide a specific optimal window of time for the first dose.

TREAT THE MOST LIKELY PATHOGEN

It is also important to treat the most likely pathogens, which include *S. pneumoniae* and *H. influenzae*. The atypical pathogens must also be considered as these can cause a substantial percentage of CAP cases in North America. Other pathogen considerations should be based on the local epidemiology as well as patient factors (such as any recent travel). Clinical signs and symptoms cannot be used to differentiate etiology. As discussed earlier, patients should also be evaluated for the risk of a resistant infection based on age, prior antimicrobial use, recent hospitalization, comorbidities, and exposure to a child in day care.

ANTIMICROBIAL SELECTION FOR OUTPATIENTS

- In previously healthy individuals with no prior antimicrobial use within the past 3 months, a macrolide or doxycycline is recommended for empiric treatment.
- If the patient presents with comorbidities or had recent prior antimicrobial use, a respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended.
- If there is a high rate of high-level macrolide resistance in the geographic area, a cephalosporin should be considered in place of these agents, such as ceftriaxone, cefpodoxime, or cefuroxime.

TO CULTURE OR NOT TO CULTURE?

Outpatients

The use of cultures can help to guide antimicrobial selection and ensure an effective agent is used. However, given the time and cost associated with culturing as well as the low yield of positive results with sputum samples, routine culturing may not be practical in the primary care setting.

The IDSA/ATS guidelines suggest minimal evaluation for bacterial etiology in outpatients as most patients do well with empiric antimicrobial therapy.[40] It may be useful to conduct further diagnostic tests in certain cases, such as those suspected of *Legionella*, community-acquired methicillin-resistant *S. aureus* (MRSA), and tuberculosis, as well as cases associated with outbreaks, specific risk factors, and atypical presentation.

Hospitalized Patients

For hospitalized CAP patients, the guidelines also suggest culturing as optional, though patients with severe CAP should be considered to undergo

- blood cultures
- urinary antigen tests to identify *Legionella* and *S. pneumoniae* infections
- expectorated sputum cultures.

For patients requiring intubation, an endotracheal aspirate sample should be obtained for culture.

Use of the Urinary Antigen Test

The urinary antigen test for *S. pneumoniae* can offer a rapid and simple test to check for the presence of *S. pneumoniae*, especially for patients where a sample for culture cannot be obtained in a timely fashion or when antimicrobial therapy has not already started. The assay has a reasonable specificity (90%), though the sensitivity can range as low as 50%-80% in pneumonia patients, and 80%-90% in bacteremic patients.[40, 41] In a prospective study that included 269 CAP patients with no identified pathogen, the *S. pneumoniae* urinary antigen test was able to detect the pathogen in only about a quarter of the patients, thus questioning the routine use of this assay in diagnosis.[41] There has also been noted a high degree of false-positives in children who are frequently colonized with *Streptococcus* species. Therefore, this test should be used as an ancillary test and not as a substitute for culture.

Use of Blood Cultures

The routine use of blood cultures for inpatients may provide some, but limited, benefits and is associated with higher costs and inappropriate antimicrobial use. Pre-treatment blood cultures of hospitalized CAP patients typically yield only 5%-14% of positive results.[40] Cases of false-positives can outnumber true pathogen identification in less seriously ill patients, and so blood cultures should be reserved for patients at higher risk of bacteremia and death. A recent addition to the quality improvement initiatives of the Hospital Quality Alliance of the Centers for Medicare & Medicaid Services recommends blood cultures of all pneumonia patients in the emergency department prior to administration of the first dose of antimicrobials.[42]

CASE DISCUSSION

A 56-year-old male patient presents with fever, cough, and shortness of breath, with a respiratory rate of 32/minute. A chest X-ray is performed and suggests a lower respiratory tract infection. He is alert and normotensive (116/82 mmHg) and is given a 3-day course of azithromycin. The patient returns 4 days later with little improvement: fever, respiratory rate of 33/minute, blood pressure of 94/56 mmHg.

QUESTION:

How would you manage this patient?

DISCUSSION:

It is likely that this patient is infected with a pathogen that exhibits resistance to macrolides since he has not shown any improvement after completion of the azithromycin regimen. It may be useful to submit a sputum sample for culture to identify the pathogen and get its susceptibility profile. Antimicrobial therapy with another class of agents, such as the fluoroquinolones or β-lactams, is strongly recommended. If the patient has an adequate support system and is available for follow-up, he should be treated on an outpatient basis and closely monitored.

CLINICAL CONSIDERATIONS

Recent surveillance results are indicating that *S. pneumoniae* resistance has stabilized for commonly-used antimicrobials, including penicillin, macrolides, and the fluoroquinolones. However, resistance to penicillin and macrolides remain at elevated levels that could impact clinical outcomes. The use of the pneumococcal conjugate vaccine has provided important benefits in reducing invasive disease. However, it will be important to continue surveillance for monitoring the presence of multidrug-resistant serotypes that are not covered in the current vaccines. When selecting appropriate empiric therapy, it will be critical for the clinician to evaluate the patient for the risk of a resistant infection. Recent prior antimicrobial use is a significant risk factor for a resistant infection, and an alternative antimicrobial class should be used in these cases, when possible. Cultures can be useful under certain circumstances in the outpatient setting, but routine use of cultures should be reserved for the more severely ill patients requiring hospitalization.

Below is a list of steps to consider when managing patients suspected of a bacterial RTI. These steps can help guide the selection of an appropriate antimicrobial agent to ensure a successful outcomes and minimize the development of resistance.

1. Patient factors to consider:
- a. Presence of risk factors for a resistant infection
- b. Recent prior antimicrobial use (if so, prescribe a different class of agent)

2. Environmental factors to consider:
- a. Local resistance trends of common respiratory tract pathogens
- b. Occurrence of a local outbreak

3. Consider antimicrobials that are highly active against the suspected pathogen

4. Prescribe an appropriate dose and duration of therapy to:
- a. Eradicate the infection
- b. Minimize the risk of resistance development

5. Emphasize to the patient the importance of:
- a. Initiating therapy as soon as possible (if a first dose is not given at the office visit)
- b. Following the prescription order instructions
- c. Using precautions to minimize exposure to others (i.e., stay home from work, school, etc.)

6. For patients who have failed initial therapy:
- a. Consider the reason for failure (i.e., drug, dose, duration, route of administration, etc.)
- b. Re-assess site of care
- c. Consider additional microbiologic tests (culture and susceptibility test)

REFERENCES

1. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest.* May 2000;117(5 Suppl 2):380S-385S.
2. Sethi S, Murphy TF. Acute exacerbations of chronic bronchitis: new developments concerning microbiology and pathophysiology--impact on approaches to risk stratification and therapy. *Infect Dis Clin North Am.* Dec 2004;18(4):861-882.
3. File TM, Jr., Garau J, Blasi F, et al. Guidelines for empiric antimicrobial prescribing in community-acquired pneumonia. *Chest.* May 2004;125(5):1888-1901.
4. Sethi S, Evans N, Grant BJ, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* Aug 15 2002;347(7):465-471.
5. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* Jan 2004;130(1 Suppl):1-45.
6. File TM. Community-acquired pneumonia. *Lancet.* Dec 13 2003;362(9400):1991-2001.
7. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. *Am J Med.* Apr 1999;106(4):385-390.
8. Bassetti M, Nicco E, Mikulska M. Why is community-associated MRSA spreading across the world and how will it change clinical practice? *Int J Antimicrob Agents.* Jul 2009;34 Suppl 1:S15-19.
9. Tenover FC, Goering RV. Methicillin-resistant *Staphylococcus aureus* strain USA300: origin and epidemiology. *J Antimicrob Chemother.* Sep 2009;64(3):441-446.
10. The Alexander Network. Available at: http://www.alexandernetwork.com. Accessed September 3, 2008.
11. Doern GV, Brown SD. Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000-01. *J Infect.* Jan 2004;48(1):56-65.
12. File TM. The science of selecting antimicrobials for community-acquired pneumonia (CAP). *J Manag Care Pharm.* Mar 2009;15(2 Suppl):S5-11.
13. Karchmer AW. Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US--an update. *Clin Infect Dis.* Sep 1 2004;39 Suppl 3:S142-150.
14. Karlowsky JA, Thornsberry C, Jones ME, Evangelista AT, Critchley IA, Sahm DF. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST Surveillance Program (1998-2002). *Clin Infect Dis.* Apr 15 2003;36(8):963-970.
15. Sahm DF, Brown NP, Thornsberry C, Jones ME. Antimicrobial susceptibility profiles among common respiratory tract pathogens: a GLOBAL perspective. *Postgrad Med.* Sep 2008;120(3 Suppl 1):16-24.
16. Fenoll A, Granizo JJ, Aguilar L, et al. Temporal trends of invasive *Streptococcus pneumoniae* serotypes and antimicrobial resistance patterns in Spain from 1979 to 2007. *J Clin Microbiol.* Apr 2009;47(4):1012-1020.
17. Molstad S, Erntell M, Hanberger H, et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. *Lancet Infect Dis.* Feb 2008;8(2):125-132.
18. Lynch JP, 3rd, Zhanel GG. Streptococcus pneumoniae: does antimicrobial resistance matter? *Semin Respir Crit Care Med.* Apr 2009;30(2):210-238.
19. Centers for Disease Control (CDC). Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*--United States, 2006-2007. *MMWR Morb Mortal Wkly Rep.* Dec 19 2008;57(50):1353-1355.
20. Rzeszutek M, Wierzbowski A, Hoban DJ, Conly J, Bishai W, Zhanel GG. A review of clinical failures associated with macrolide-resistant *Streptococcus pneumoniae*. *Int J Antimicrob Agents.* Aug 2004;24(2):95-104.
21. Van Kerkhoven D, Peetermans WE, Verbist L, Verhaegen J. Breakthrough pneumococcal bacteraemia in patients treated with clarithromycin or oral beta-lactams. *J Antimicrob Chemother.* Mar 2003;51(3):691-696.
22. Daneman N, McGeer A, Green K, Low DE. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. *Clin Infect Dis.* Aug 15 2006;43(4):432-438.
23. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med.* Jul 22 1999;341(4):233-239.
24. Canadian Bacterial Surveilance System. Fluoroquinolone-Resistant Pneumococci: Canadian Bacterial Surveillance System, 1997-2008. 2009; Available at: http://microbiology.mtsinai.on.ca/data/sp/sp_2008.shtml#figure6. Accessed September 3, 2009.
25. Sahm DF, Brown NP, Draghi DC, Evangelista AT, Yee YC, Thornsberry C. Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001-2005. *Postgrad Med.* Sep 2008;120(3 Suppl 1):8-15.
26. Gunderson BW, Ross GH, Ibrahim KH, Rotschafer JC. What do we really know about antibiotic pharmacodynamics? *Pharmacotherapy.* Nov 2001;21(11 Pt 2):302S-318S.
27. McKinnon PS, Davis SL. Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. *Eur J Clin Microbiol Infect Dis.* Apr 2004;23(4):271-288.
28. Moran G. Approaches to treatment of community-acquired pneumonia in the emergency department and the appropriate role of fluoroquinolones. *J Emerg Med.* May 2006;30(4):377-387.
29. Rodvold KA, Danziger LH, Gotfried MH. Steady-state plasma and bronchopulmonary concentrations of intravenous levofloxacin and azithromycin in healthy adults. *Antimicrob Agents Chemother.* Aug 2003;47(8):2450-2457.
30. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J.* Mar 2000;19(3):187-195.
31. Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. *Pediatr Infect Dis J.* Sep 2006;25(9):779-781.
32. Black S, Shinefield H, Baxter R, et al. Impact of the use of heptavalent pneumococcal conjugate vaccine on disease epidemiology in children and adults. *Vaccine.* Apr 12 2006;24 Suppl 2:S2-79-80.
33. Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. *Pediatr Infect Dis J.* Jun 2004;23(6):485-489.
34. Farrell DJ, Klugman KP, Pichichero M. Increased antimicrobial resistance among nonvaccine serotypes of *Streptococcus pneumoniae* in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. *Pediatr Infect Dis J.* Feb 2007;26(2):123-128.
35. Critchley IA, Jacobs MR, Brown SD, Traczewski MM, Tillotson GS, Janjic N. Prevalence of serotype 19A *Streptococcus pneumoniae* among isolates from U.S. children in 2005-2006 and activity of faropenem. *Antimicrob Agents Chemother.* Jul 2008;52(7):2639-2643.
36. Farrell DJ, Sieradzan R, Brown SD. The multidrug-resistant *Streptococcus pneumoniae* serotype 19A clone (MDR19A) continues to spread rapidly in the USA. Paper presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20, 2007, 2007; Chicago, IL. Abstract #C2-197.
37. Clavo-Sanchez AJ, Giron-Gonzalez JA, Lopez-Prieto D, et al. Multivariate analysis of risk factors for infection due to penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae*: a multicenter study. *Clin Infect Dis.* Jun 1997;24(6):1052-1059.
38. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis.* May 1 2005;40(9):1288-1297.
39. Harwell JI, Brown RB. The drug-resistant pneumococcus: clinical relevance, therapy, and prevention. *Chest.* Feb 2000;117(2):530-541.
40. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* Mar 1 2007;44 Suppl 2:S27-72.
41. Gutierrez F, Masia M, Rodriguez JC, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. *Clin Infect Dis.* Feb 1 2003;36(3):286-292.
42. Center for Medicare & Medicaid Services (CMS). Hospital Quality Alliance (HQA) 2004-2007. Available at: http://www.cms.hhs.gov/HospitalQualityInits/downloads/HospitalHQA2004_2007200512.pdf. Accessed September 3, 2009.

SELF-ASSESSMENT, EVALUATION, AND CREDIT APPLICATION

Release Date: October 29, 2009 Expiration Date: October 29, 2010 Center Serial #: CV3113-2

Select your professional title: ☐ Physician ☐ Physician Assistant ☐ Other _____

Select your practice setting: ☐ Teaching hospital ☐ Community hospital ☐ LTAC ☐ Other _____

Your evaluation and suggestions will help improve the quality of future continuing education activities. Please answer the following general questions and provide written comments. Thank you for your cooperation.

SELF-ASSESSMENT
(Please check the most appropriate answers)

Which of the following is not considered an atypical respiratory pathogen?

☐ *Mycoplasma pneumoniae*
☐ *Chlamydophila pneumoniae*
☐ *Legionella pneumophila*
☐ *Moraxella catarrhalis*

In 2007, what percent of *S. pneumoniae* isolates were resistant to macrolides?

☐ 10%
☐ 30%
☐ 50%
☐ 70%

The widespread use of the pneumococcal conjugate vaccine has led to an increased proportion of infections caused by which *S. pneumoniae* serotype?

☐ 6A
☐ 9
☐ 19A
☐ 23

Which of the following is not considered a risk factor for a resistant pneumococcal infection?

☐ Age greater than 65 years
☐ No prior antimicrobial use
☐ Exposure to a day care child
☐ Multiple medical comorbidities

Prior use of which macrolide confers the highest risk for a macrolide-resistant infection?

☐ Erythromycin
☐ Clarithromycin
☐ Azithromycin
☐ All macrolides confer a similar amount of risk for a macrolide-resistant infection

LEARNING OBJECTIVES: Was the learning objective met?

	Yes	Somewhat	No
1. Identify the risk factors for a resistant RTI	☐	☐	☐

If you answered 'No', please explain why

SCIENTIFIC CONTENT: Please rate

	Excellent	Good	Fair	Poor
1. The scientific content of this activity was	☐	☐	☐	☐
2. The level of expertise of the authors was	☐	☐	☐	☐

OVERALL EVALUATION

	Yes	Somewhat	No
1. This activity met my expectations.	☐	☐	☐
2. The content was relevant to my practice.	☐	☐	☐
3. This activity was fair and balanced?	☐	☐	☐
4. This activity was without commercial bias.	☐	☐	☐

If you answered 'No' to 3 or 4 please explain.

LEARNING FORMAT

	Yes	Somewhat	No
1. The format enhanced achievement of learning objectives.	☐	☐	☐
2. The format was easy to follow and understand.	☐	☐	☐

PRACTICE APPLICATION

1. What aspects of this activity were most relevant to your practice?

2. Will you make changes to your practice setting based on participation in this activity? Why or why not?

3. What aspects of RTI do you need to learn more about in order to improve your practice performance?

DO YOU HAVE (1) ANY SUGGESTIONS FOR IMPROVING THIS ACTIVITY or (2) ANY ADDITIONAL COMMENTS?

CREDIT APPLICATION (Please Print Clearly) Name and Degree _____

Address _____ City _____ State _____ ZIP _____

Email _____ May we contact you by e-mail? ☐ Yes ☐ No

Type of Credit requested ☐ MD/DO *AMA PRA Category 1 Credit™* ☐ Other _____

I certify that I have reviewed in its entirety *RTI Resistance On the Frontline of Care: PCPs Fight Back!* Bulletin 2: *Know Your Pathogens: The Antimicrobial Resistance Threat* Signature _____ Date _____