Empiric Therapy of Community-Acquired Pneumonia* Guidelines for the Perplexed?
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This article discusses the key clinical aspects of empiric therapy of community-acquired pneumonia (CAP). Antibiotic selection, severity of CAP, single vs multiple pathogens, pharmacokinetic considerations, antibiotic resistance, IV vs oral antibiotic therapy for CAP, oral therapy for non-ICU hospitalized patients with CAP, β-lactams, macrolides, ketolides, doxycycline, respiratory quinolones, and pharmacoeconomic implications are discussed.

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Key words: community-acquired pneumonia; community-acquired pneumonia antibiotic guidelines; doxycycline; IV to po switch therapy; macrolides/ketolides; natural/acquired antibiotic resistance; oral antibiotic therapy; respiratory quinolones

Abbreviations: CAP = community-acquired pneumonia; LOS = length of stay

“Simplify, simplify, simplify!”
Emerson

The rationale for antibiotic guidelines for community-acquired pneumonia (CAP) is to optimize outcomes and to minimize resistance at a reasonable cost to the patient and society. Numerous medical societies and groups have developed CAP guidelines. For related article see page 1888

Antibiotic guidelines are supposed to emphasize commonality in therapeutic approach. While guidelines have common features, they vary in antibiotic choice, route of antibiotic administration, resistance potential, inclusion/exclusion of the pulmonary severity index, and antibiotic cost. Not only do guidelines differ between infectious disease and pulmonary specialists, but they also differ on both sides of the Atlantic. There are differences between American and Canadian guidelines as well as among British, French, Italian, Spanish, and German guidelines. As if the presence of so many guidelines is not daunting enough, in addition, there are European Respiratory Society guidelines for the treatment of CAP. Dr. File in this issue has provided an overview of the current CAP guidelines with their many differences (see page 1888). It is not surprising that practitioners are often baffled by so many variations on what should be a common theme. With no other infectious disease is there such variability in therapeutic approach.

Clinical Overview of CAP

Non specialist physicians treating CAP are often perplexed by the number of CAP guidelines and by their differences. Practitioners believe that if specialists cannot agree on antibiotic treatment for CAP, then the traditional preguideline approach is perhaps just as good. Studies using antibiotic guidelines to treat CAP do not differ markedly in clinical outcomes, further adding to the prescribing physician’s bewilderment. Clinicians have been successfully treating CAP for decades without guidelines, so what’s the fuss?
Practitioners would more readily adhere to a simplified or streamlined CAP guideline. The greatest potential benefit of guidelines is not in improving outcomes but in decreasing antibiotic resistance and in controlling the cost of therapy. Practitioners would benefit from knowing the spectrum and activity of the antibiotics used against the common pulmonary pathogens causing CAP. Physicians need to be reminded of the pharmacokinetic and clinical equivalence of oral and IV therapy when using antibiotics with high bioavailability (eg, absorption ≥ 90%). Clinicians, including specialists and subspecialists, need to better understand the determinants of antibiotic resistance. Simplified and streamlined guidelines can do all of these things and present practicing physicians with a clinical approach that is not confusing and is optimal from the standpoint of outcome, but that also minimizes antibiotic resistance and is sensitive to economic issues.1–3

**Antibiotic Spectrum**

The first consideration in selecting an antibiotic for the treatment of CAP is the antibiotic spectrum. The antibiotic selected for CAP should have a high degree of activity against the usual typical pathogens responsible for CAP (ie, Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis and Legionella species, Mycoplasma pneumoniae, or Chlamydia pneumoniae among the nonzoonotic atypical pathogens). Pneumococci are the single most common bacterial pathogen causing CAP in hospitalized adults with CAP. H influenzae and M catarrhalis are more common in elderly patients with COPD. Aspirated oral pharyngeal anaerobes are the pathogens in aspiration CAP, which is most common in elderly patients who are in long-term care facilities or hospitals. Legionella is more common in elderly patients and compromised hosts with impaired cellular immunity. Legionella is relatively uncommon in young adults as a cause of ambulatory CAP. M pneumoniae and C pneumoniae along with respiratory viruses are the most common causes of CAP in ambulatory young adults. There are also important geographic differences. Legionella is apparently more common in the North American experience than in the European experience, and there are regional differences. Legionella is relatively common in some centers, and others have few or no cases, which should be taken into account in using or modifying CAP guidelines to reflect local patterns of pathogen distribution.4–7

That being said, it is as important to know what to include in empiric CAP therapy as what does not need to be covered. Klebsiella pneumoniae causes CAP essentially only in individuals with alcoholic liver disease. Similarly, Staphylococcus aureus CAP is primarily a complication of viral influenza pneumonia. Escherichia coli, usually from a urinary tract source, may rarely present as CAP in elderly male patients. Pseudomonas aeruginosa CAP occurs only in patients with cystic fibrosis or extensive bronchiectasis. No other Gram-negative aerobic pathogens are important causes of CAP. Such epidemiologic information is important in devising treatment guidelines to avoid excessive coverage of rare pathogens in CAP.4,5,7–9

**Severity of CAP**

Comorbidities are another cause of confusion. Comorbidities in some guidelines are a therapeutic modifier. Additional therapy is sometimes added to some guidelines. Severe systemic disorders have prognostic significance and can predict complications/ICU admission, but should have no effect on antibiotic selection. The following analogy emphasizes the point. Patients with asplenia with overwhelming, often fatal, S pneumoniae bacteremia are treated with penicillin or a β-lactam. Patients with intact B-cell immunity and non–life-threatening S pneumoniae bacteremia are treated the same way (ie, with the same drug, dose, route of administration, and duration of therapy). Adding another drug because the patient has advanced lung, heart, liver, or renal disease makes little sense since the target of therapy is the pathogen, which is unaffected by morbidities. As with comorbidities, the severity of infection is not a reason to increase the spectrum morbidities or to add another antibiotic. Severity is primarily dependent on the underlying functional capacity of the lung, heart, and immune system. If the patient with severe CAP is treated initially with appropriate empiric monotherapy (eg, a respiratory quinolone), what is the rationale for expanded coverage? In a patient with severe chronic bronchiitis, pulmonary function may be so compromised by CAP that even a relatively avirulent pathogen (eg, M catarrhalis) may present clinically as severe CAP requiring ICU admission. Coverage already includes penicillin-resistant S pneumoniae, all common bacterial pathogens, and Legionella. There is no reason for adding P aeruginosa coverage in non–cystic fibrosis/chronic bronchiectasis patients. Therapeutic choice is determined by the probable pathogen and should not be based on the severity of illness. Severity determines ICU admission and the initial mode of antibiotic administration, not the choice of antibiotics.10–12
**Single vs Multiple Pathogens in CAP**

The concept of copathogenicity is another source of confusion for those in practice. Virtually all studies claim that multiple pathogens have the same problem, that is, the purported copathogens are reported using two different diagnostic techniques. A positive blood culture finding together with serologic evidence of recent/past infection does not prove copathogenicity any more than fatigue in a cancer patient should be ascribed to a positive Epstein-Barr virus serologic finding. Most of the adult population has serologic evidence of previous exposure to *M pneumoniae* and *C pneumoniae*, not to mention *H influenzae*. Patients with CAP secondary to a bacterial pathogen with serologic evidence of another organism does not prove copathogenicity. Even compromised hosts (eg, patients who have received organ transplants) may have multiple pathogens, but they clinically present one at a time—sequentially, not simultaneously as copathogens.4–6–9

**IV-to Oral Switch Therapy for CAP**

The single most important advance in the treatment of CAP has been in the area of pharmacokinetics. Traditionally, the duration of treatment for CAP has been 2 weeks. Treatment has been shortened in healthy individuals and has been extended in those with serious systemic disorders. Patients with severe CAP who are admitted to ICUs traditionally have been treated IV for the duration of their hospitalization. Also, hospitalized patients not requiring intensive care were treated entirely with 2 weeks of IV therapy. Siegel et al13 were the first to show that the outcomes were similar in patients who were treated exclusively via the IV route for 2 weeks as in those who initially received IV therapy for 48 h and completed their course of treatment with 12 days of oral antibiotic therapy. This study and others led to the widespread acceptance of IV-to-oral switch programs, which have had a profound effect on the treatment of CAP. IV-to-oral switch programs have several important advantages, including decreasing hospital length of stay (LOS), all but eliminating phlebitis and IV line infections, and greatly decreasing antibiotic costs. The oral equivalent of an IV administered antibiotic is considerably less expensive than its IV counterpart. The daily cost of an oral respiratory quinolone is approximately one third of its parenteral counterpart, independent of the added cost of IV antibiotic administration. With IV-to-oral switch therapy, patients are happier, leave the hospital more quickly with fewer complications, and have outcomes that are comparable to those for patients receiving IV therapy alone.14–16

The critical factor in IV-to-oral switch programs is to select an antibiotic that has a high degree of bioavailability (ie, ≥90%). With rapid and efficient oral absorption, blood and tissue levels are virtually the same orally and IV with equivalent doses of the antibiotic. All agree that antibiotic therapy for CAP should be initiated as soon as possible to optimize outcome and to minimize LOS.14,15

Because orally administered antibiotics with high bioavailability used for CAP are rapidly and efficiently absorbed in nearly all individuals, the rationale for initial IV therapy in hospitalized patients with CAP should be questioned. How important can 2 initial days of IV therapy be in a 14-day course, particularly if the first 2 days of the antibiotic therapy are given IV followed by 12 days of equivalent oral antibiotic administration? Presently, there are sufficient data to suggest that non-ICU hospitalized patients with moderate to moderately severe CAP may be treated entirely via the oral route as effectively as IV.

**Oral Antibiotic Therapy for CAP**

If IV-to-oral switch therapy was good, then oral therapy for hospitalized patients with moderate to moderately severe CAP is very good indeed. The pharmacoeconomic implications for oral therapy for non-critically ill hospitalized patients with CAP are important. This means that IV antibiotic therapy for CAP should be largely relegated to patients with severe CAP in the ICU setting. Oral therapy, which has traditionally been used for the treatment of mild-to-moderate CAP in the outpatient setting, can now be extended to include non-ICU patients hospitalized with moderate to moderately severe CAP. This principle will simplify the therapeutic approach (ie, guidelines for CAP in ambulatory and hospitalized patients). At least, it will emphasize that the route of administration is less important than the spectrum and resistance potential of the antibiotic selected.3,14,17

A frequent question for IV-to-oral switch therapy or for exclusively oral therapy relates to the ability of the patient to take medications orally. The only patients excluded from the advantage of orally administered antibiotic therapy for CAP include those with nausea, vomiting, or a disorder that would severely impair GI absorption. In the general population, such patients are relatively few. Therefore, unless patients are critically ill with severe CAP in an ICU setting, non-ICU hospitalized patients with CAP and intact GI absorption may be managed optimally with an orally administered antibiotic with the appropriate spectrum, high bioavailability, and minimum pneumococcal resistance potential.2,15,18
Pneumococcal Resistance

Pneumococcal resistance potential is a concern reflected in several CAP guidelines. This is an important therapeutic consideration, particularly if highly penicillin-resistant *S pneumoniae* strains are prevalent in the community. Conversely, even if strains of penicillin-resistant *S pneumoniae* are not prevalent in the community, the drugs used to treat CAP should be those with a low resistance potential to minimize future resistance problems. Occasional resistant strains secondary to point mutations may occur with virtually any antibiotic used for CAP. Such resistant clones may be spread by ineffective infection control containment measures through hospitals, cities, countries, or continents, and may be responsible for much of reported pneumococcal resistance. However, clonally resistant strains of *S pneumoniae* that are widely dispersed geographically should not be considered in the same category as *S pneumoniae* acquired resistance related to antibiotic use. The antibiotics used to treat CAP should have a low potential for inducing resistance and minimize acquired antibiotic resistance associated with antibiotic use.18–20

The antibiotics that have been associated with acquired resistance to pneumococci (*eg*, penicillin-resistant *S pneumoniae*) are primarily trimethoprim-sulfamethoxazole, tetracycline, and macrolides. Because of prescribing habits and their inclusion in several guidelines, macrolides have been used for years to treat mild cases of CAP or have been added for atypical coverage to β-lactam regimens. The use of macrolides to treat CAP, even if a successful outcome is achieved, should be limited, because their use has been associated with increasing penicillin resistance among *S pneumoniae*. It is naïve to think that if a macrolide is used in a combination regimen with a β-lactam to cover atypical organisms, it will not induce resistance among pneumococci in the community. To use macrolides as monotherapy is also problematic on two levels. Approximately 20% of *S pneumoniae* strains are naturally resistant to macrolides not related to antibiotic use. In addition, macrolides have been associated with acquired penicillin resistance. If a strain of *S pneumoniae* that is being treated with a macrolide is initially sensitive, it may develop acquired resistance.

The macrolides that are used to treat patients with mild CAP in the ambulatory setting have been successful because, in the main, the patients are young, without coexisting systemic diseases, have predominately atypical pulmonary pathogens, and improve with or without therapy. In hospitalized patients with moderate or moderately severe CAP, empiric monotherapy with a macrolide is not optimal. Parenteral erythromycin should not be used because of natural pneumococcal resistance, suboptimal pharmacokinetics, and limited *H influenzae* activity. Erythromycin, like other macrolides, accumulates in alveolar macrophages, accounting for its early use in the treatment of Legionnaires disease. However, compared to other anti-Legionella agents, it is the least potent anti-Legionella antibiotic and, in the past, often has required the addition of rifampin to treat severe Legionella CAP. There is no rationale for adding rifampin to doxycycline, azithromycin, or quinolones, which have much more activity against Legionella than erythromycin. In opting for macrolide monotherapy for the initial treatment of patients hospitalized with CAP, the usual agent is azithromycin. As with other macrolides, about 20% of *S pneumoniae* strains are naturally resistant to azithromycin. Pharmacokinetically, the advantage of azithromycin is prolonged but very low serum concentrations. In hospitalized patients with moderate to moderately severe CAP, initial high serum concentrations are important in therapeutic success. There have been a number of therapeutic failures reported21–25 using IV azithromycin monotherapy in patients with *S pneumoniae* CAP. Therapeutic failure in these cases was not the result of natural resistance but rather low initial serum concentrations. Azithromycin added to a β-lactam in combination regimens for atypical coverage also introduces the potential for increasing acquired penicillin resistance among pneumococci, even though it is not the intent of therapy. Some antibiotics that have been used for the treatment of CAP have not been associated with widespread *S pneumoniae* penicillin resistance, including β-lactams, doxycycline, telithromycin, and respiratory quinolones (*eg*, levofloxacin, gatifloxacin, or moxifloxacin).26–30

Antibiotic Resistance vs Antibiotic Use

The mechanisms of antibiotic resistance are well-known to medical practitioners. Unfortunately, a mechanistic explanation does not explain the association between resistance and the use of certain antibiotics. Certainly, antibiotic use (ie, “antibiotic tonnage”) is not related *per se* to antibiotic resistance. Certain antibiotics (*eg*, ceftriaxone and doxycycline) may be used in high volume, even inappropriately, without incurring resistance. Antibiotic resistance is associated with certain antibiotics from a variety of antibiotic classes and is not related to antibiotic use *per se*. Many guidelines are concerned about limiting the inappropriate use of antibiotics to curtail the increase in penicillin-resistant *S pneumoniae*, which has been noted worldwide. Most penicillin resistance worldwide is of the intermediate
Antibiotic Resistance Potential

Among the fluoroquinolones, levofloxacin has a low resistance potential. Despite a high volume of levofloxacin use over several years, there have been few reports of levofloxacin-resistant strains of S pneumoniae. Gatifloxacin and moxifloxacin have an even lower resistance potential than levofloxacin, and strains of S pneumoniae that are resistant to gatifloxacin or moxifloxacin are rare. Respiratory quinolones are not only effective against highly penicillin-resistant S pneumoniae strains, but their use does not increase resistance. CAP guidelines are concerned that the overuse of antibiotics, particularly respiratory quinolones, may lead to increased S pneumoniae resistance. Widespread use-related penicillin resistance has been associated only with trimethoprim-sulfamethoxazole, tetracycline, or macrolide use. The same is not true with amoxicillin/clavulanic acid, doxycycline, or the respiratory quinolones. Their widespread use has not been associated with increased pneumococcal resistance. From a resistance perspective, β-lactam use per se has not increased high-level penicillin resistance. Macrolides are the primary culprit. Their use alone or in combination in treating patients with CAP should be questioned because of their S pneumoniae resistance potential. In patients who are unable to tolerate β-lactams or respiratory quinolones, doxycycline or telithromycin are efficacious against S pneumoniae, and their use does not foster the development of resistance.28,29,37–40

Antibiotic Guidelines for CAP

Guidelines for the treatment of CAP have changed over the years, suggesting that the ultimate guideline has not yet been devised. CAP guidelines will continue to evolve with or without a general consensus on the optimal treatment for CAP. Several concepts have emerged that should be incorporated in existing guidelines or should be the basis of a new simplified guideline for both sides of the Atlantic Ocean, allowing for geographic variation and differences in subspecialty orientation. The old notion that IV therapy is somehow better than equivalent oral therapy (absorbed in 30 to 60 min) should finally be put to rest. It is difficult to make an argument in favor of IV therapy over oral therapy for CAP when blood and tissue levels are essentially the same. Outcome studies show the equivalency of oral and IV therapy for CAP. Unless the patient is in the ICU or requires therapeutic blood and lung levels of an antibiotic in <30 min, then obviously IV therapy is the preferred initial mode of antibiotic administration.

Oral Antibiotic Therapy for Non-ICU Hospitalized Patients With CAP

However, the time has come for a paradigm shift; patients who are hospitalized with moderate to moderately severe CAP, and who are not in the ICU, should be treated entirely via the oral route. Clinicians gained confidence using IV-to-oral switch regimens, which have been shown to be equivalent to full courses of parenteral antibiotic therapy for CAP. The advantages of treating non-ICU hospitalized patients with CAP entirely via the oral route are compelling in terms of decreasing LOS, duration of antibiotic therapy, complications, and total cost to the institution for antimicrobial therapy. Oral treatment with doxycycline, telithromycin, high-dose amoxicillin/clavulanic acid, or respiratory quinolones has the proper spectrum, little or no resistance potential, good safety profiles, and is relatively inexpensive compared to parenteral therapy. When the pharmacoeconomic advantages of oral therapy for hospitalized patients with moderate to moderately severe CAP are fully appreciated by third-party payers, then third-party reimbursement will soon follow.31–46

Some will question the rationale for treating hospitalized patients solely with oral therapy. The answer is that hospitalized patients may be treated solely with oral therapy because they need to be hospitalized for monitoring of cardiac and pulmonary function, or may have other systemic diseases (eg, liver disease or renal disease) that require in-hospital observation, in-hospital diagnostic proce-
resistance potential, have a good safety profile, and have the great advantage of favorable pharmacokinetic profiles, such that blood/lung levels are the same whether the drug is administered orally or IV in areas in which combination therapy offers no advantage and has several disadvantages, as explained.

Sometimes, much is made of the ability to differentiate typical from atypical pathogens, which has potential implications for therapeutic recommendations. While, from a public health and prognostic standpoint, efforts should be made to identify atypical pathogens, the issue is less important therapeutically if clinicians are using antibiotics that cover both typical and atypical pathogens (eg, doxycycline, telithromycin, or a respiratory quinolone). It does not matter much whether Legionella is common or uncommon if one is treating S pneumaniae and other respiratory pathogens optimally without the risk of causing resistance. The respiratory quinolones are, in many ways, ideal agents for this purpose. Arguments against more extensive respiratory quinolone usage for treating CAP is based on a concern about developing resistance, on the variable incidence of Legionella, and on cost. If empiric oral monotherapy can be used for all hospitalized patients with moderate to moderately severe CAP, excluding those in the ICU setting, then respiratory quinolones are more cost effective than their IV counterparts. Simplified streamlined guidelines incorporating these concepts, such as the one proposed, will emerge.

**Conclusions**

The wave of the future is empiric, oral monotherapy with a carefully chosen agent that has the right spectrum, has good pharmacokinetic properties, is available orally and IV, has a low resistance potential, and is moderately priced. It matters little which agents are chosen so long as they fulfill the criteria mentioned above. In the end, guidelines are just that... guidelines that may need to be modified locally, depending on circumstance. Opinion leaders should help practicing clinicians understand the principles underlying the rationale of guidelines. Credibility is lost if organisms are covered that are seen only in select subpopulations, if there is redundant coverage, if there are unwarranted concerns regarding antibiotic resistance, or if the costs of oral vs IV administration are not viewed. Conceptual clarity expressed by opinion leaders will do much to demystify the bewildering number of alternatives in the multitude of guidelines that have perplexed most practitioners rather than given them the guidance that they need.
REFERENCES


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