It is clear that TDM is not a substitute for directly observed therapy (DOT). Also, TDM is not a particularly good tool for identifying noncompliant patients. If noncompliance is suspected, such patients require an effective DOT program, that is, one in which a responsible individual verifies that the patient has swallowed the drug doses. TDM does not guarantee successful treatment, but it does eliminate drug malabsorption as a cause of treatment failure. TDM can be particularly effective in guiding therapy with the second-line drugs, when one is trying to balance effective dosing against dose-related toxicities. Serum concentrations inform the clinician on the need to push the doses, especially in the face of a slow response to treatment. When low serum concentrations are documented with standard drug doses, higher doses are required, even if they exceed the so-called "maximum" doses. The true maximum dose is the highest dose that a patient can tolerate, hopefully while achieving the desired therapeutic response. Serious dose-related toxicities are relatively uncommon with the antituberculosis drugs, with the exceptions of cycloserine, and, under conditions such as renal failure, with ethambutol, streptomycin, and the other aminoglycosides. Our experience clearly shows that higher daily doses (>600 mg) of rifampin do not produce the flu-like symptoms, provided that serum concentrations stay within the target range of 8-24 μg/mL; this also appears to be true with twice weekly regimens. Finally, TDM is an excellent tool for adjusting doses in response to drug interactions, which are common in patients with AIDS.

TDM services should use sensitive assays that remain specific for the drug of interest even in the presence of multiple other medications. These assays should be extensively validated, and should conform to the guidelines set forth by the College of American Pathologists. The exact times of doses and blood draws must be recorded. Interpretation of the results is best provided by those familiar with pharmacokinetic principles and the clinical management of patients with mycobacterial infections. If carefully performed and selectively applied, TDM is a powerful tool for optimizing drug therapy in patients with difficult-to-treat mycobacterial infections.

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Prescription of Macrolides in Community-Acquired Pneumonia

Science or Art?

All physicians attending to patients in the acute care context are familiar with community-acquired pneumonia (CAP). Streptococcus pneumoniae is the leading etiology in all series, but the perspectives presented by specialists vary according to the setting in which they work, ie, outpatient care,1 medical wards,2 or critical care.3 A range of
reviews published in this decade have discussed in detail the approach to diagnosis, evaluation of severity, and initial antimicrobial therapies. Despite these contributions, controversy still surrounds the question of the most rational approach for initiating an antibiotic regimen. Should the initial choice be based on the form of presentation or on other variables? What is the precise role of the microbiology laboratory? These are among the most debated points.

Empiric treatment is difficult because of the diversity of potential pathogens and their divergent patterns of susceptibility. As a consequence, several authors have used statistical tools to distinguish scientifically between Legionnaires’ disease and such other common causes of pneumonia as pneumococcal infection on the basis of clinical findings, nonspecific laboratory findings, or chest roentgenographic results. The observation that Legionella micdadei, also known as Pittsburgh pneumonia agent, has peculiar roentgenographic abnormalities and a greater tendency to subclinical manifestation lends support to these efforts. However, this pathogen is extremely rare; Legionella pneumophila (LP) may have a wide spectrum of manifestations. In fact, the various strains of LP differ widely in terms of virulence. Moreover, this approach ignores the key role of the state of the immunologic response by different hosts to the pathogen. This factor is easily recognizable by the appearance of bilateral nodular opacities, which may expand and cavitate, in patients receiving corticosteroids—unlike other patients with LP pneumonia. Finally, the length of illness is also important, as demonstrated by the increased severity in those patients with delay in appropriate therapy.

In this issue of CHEST (see page 1195), Sopena and colleagues show that clinical features (diarrhea and increased creatine kinase) can predict microbial etiology in CAP in the emergency department (ED), and they propose that based on this information, physicians should prescribe a macrolide antibiotic and apply rapid diagnostic techniques. However, the authors themselves observe that these manifestations are absent in the majority (75% and 68%, respectively) of patients with CAP caused by LP, calling into question the practical implications of these findings. My interpretation is that a macrolide cannot be prescribed on the basis of clinical or biological markers present in the ED. Chest roentgenographic findings also inevitably result in missed diagnosis.

In addition, the study population represents less than 50% of patients admitted to the ED, because 219 patients with uncertain pathogens were excluded from study. This should be considered before generalizing the authors’ findings to all patients admitted to the ED. In the study by Sopena and colleagues, three LPs were diagnosed by culture, 23 by antigeneuria, and 34 (retrospectively) by serology. Agreement between two of these methods was found in only seven cases, which indicates that an early diagnosis with these techniques was obtained in only half of the 48 patients with LP. A collaborative multicenter study of severe CAP in Spain has demonstrated that the incidence of LP is easy to underestimate, particularly in the most severe episodes, because serology is available only in the convalescent phase of those patients who survive. Antigenuria has high specificity but may only register positive after a number of days. All these data emphasize the difficulty of early diagnosis of this etiology. Although the reader is not told how many of the enrollees had severe pneumonia, and little information on outcome parameters for both groups is reported, it is suggested that 20.4% of cases of CAP due to LP in this hospital required admission to the ICU. This figure, in addition to the high incidence of LP among patients with severe CAP, highlights the need for routine screening for LP in all patients with severe episodes. Similarly, I believe that prompt coverage for LP is mandatory in all those patients who require ICU admission or who develop progressive respiratory failure.

The study by Sopena and colleagues is nonetheless extremely important as it offers a broad overview of the presentation of CAP at the ED. Moreover, it reopens discussion of whether macrolides should be prescribed in patients with CAP. Key questions include: in which patients are macrolides indicated? which pathogens may not be appropriately treated? and which macrolide should be chosen?

In the early 1990s, a consensus statement from the American Thoracic Society recommended that macrolides alone represented the correct option for treating CAP in outpatients aged ≤60 years with no comorbidity. A recent validation has suggested that this approach could be cost-saving, compared with noncompliant therapies. Unfortunately, the increasing emergence of resistance among S pneumoniae has become a motive of concern. Recent reports from Europe indicate that S pneumoniae are resistant to macrolides in only 8.3% of the population infected by penicillin-sensitive strains. However, multidrug resistance is very frequent among penicillin-resistant pneumococcus (PRP), and macrolide resistance can be found in up to one third of these strains. At the end of the 1990s, the increasing incidence of penicillin-resistant pneumococcus worldwide is raising doubts about this choice for empiric treatment in populations at high risk for penicillin-resistant pneumococcus and suggests the need for an update of current recommendations for the next decade.

Erythromycin has historically been the drug of
choice for LP, but the newer macrolide agents, particularly azithromycin and clarithromycin, which are currently available in most countries with an intravenous formulation, have superior in vitro activity and greater intracellular and lung tissue penetration. Gastrointestinal intolerance, ototoxicity related to the 4-g dose of erythromycin, and the requirement for administration of large volumes of fluids, which represents a therapeutic problem in patients with acute renal failure or who develop ARDS, favor the replacement of erythromycin as the drug of choice.

Unlike the heterogeneous groups of patients with ambulatory CAP, patients with CAP and severe sepsis, shock, or respiratory failure represent a relatively select subgroup in whom most experts agree that combination therapy with a macrolide plus a β-lactam is the standard therapy. However, introduction of third-generation quinolones may change this scenario in the next decade. As a class, fluoroquinolones have the greatest activity against LP in experimental models. Indeed, ciprofloxacin, ofloxacin, or pefloxacin have all been successfully used for the treatment of Legionnaires’ disease. Unfortunately, these agents are almost ineffective against anaerobes and have poor activity against most aerobic Gram-positive cocci (including pneumococci). These drawbacks represent an important limitation for their use in CAP. However, third-generation fluoroquinolones have excellent activity against these pathogens, and preliminary communications suggest that monotherapy with these agents can be even more effective than standard therapy.

Whereas further clinical trials with these newer fluoroquinolones are warranted, I prefer to decide my prescription strategies for CAP on the basis of the severity of the patient’s condition, the presence of comorbidities, and the epidemiologic pattern in each geographical area, rather than according to clinical presentation. Studies that evaluate the impact of specific diagnostic tests on outcome (mortality, resolution of symptoms, return to work, or return to usual activities) are lacking and should be a research priority. Meanwhile, although some laboratory tools or certain clinical data, as suggested by Sopena and colleagues, may help in a few cases, I believe that initial antibiotic choice for pneumonia remains an art.

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New Macrolides or New Quinolones as Monotherapy for Patients With Community-Acquired Pneumonia

Our Cup Runneth Over?

For the past decade, the atypical pathogens as a group (Legionella pneumophila, Chlamydia pneumoniae, and Mycoplasma pneumoniae) have become accepted as relatively common causes of pneumonias in both the outpatient and inpatient setting. As a result, recommendations for more widespread use of antimicrobial agents active against these pathogens have become well-accepted.1,2

In the community-acquired pneumonia study by Mundy and colleagues in this issue of CHEST (see page I201), only 7.5% of the patients were classified as being infected by an atypical pathogen. Almost 40% of these patients failed to receive antimicrobial therapy considered to be active against Legionella (tetracyclines, macrolides, quinolones) and yet none died. The authors concluded that routine administration of macrolides may not be necessary.

However, some caution must be exercised regarding the authors’ conclusion of the necessity for coverage against the atypical pathogens. The atypical pathogen that is most virulent is Legionella, which was present in only 3.4% of their study population. It has been well-established that mortality rates for both M pneumoniae and C pneumoniae are low, even when antibiotic therapy is not given. In fact, the primary effect of administration of antibiotics against M pneumoniae is not to lower mortality but to decrease the duration of cough and other symptoms.

We believe that the incidence of Legionella infection is cyclic as has been shown for M pneumoniae. The frequency of Legionella pneumonias seen in our community has ranged from 1 to 9% in different years. Had the incidence of legionellosis in the study by Mundy and colleagues been higher, we wonder if the mortality rate might also have been higher. Circumstantial data from uncontrolled studies suggest that delay of appropriate antibiotic therapy can be linked to increasing mortality.3-5

Major developments in antimicrobial therapy have occurred in the 5 years since the study by Mundy and coworkers was conducted. Thus, the issue that Mundy and colleagues raised as to whether addition of a macrolide (erythromycin) is cost-effective and that perhaps β-lactam therapy as monotherapy is sufficient given the low mortality observed in their study, has become less relevant to the physician or hospital pharmacist. Both newer macrolides and newer quinolones that are parenteral are now commercially available to physicians (Table 1), and in many ways, superior to erythromycin, the only antibiotic active against the atypical pathogens that was used by the authors in their study conducted from 1990 to 1991.

First, the newer macrolides and newer quinolones not only have superior in vitro activity against the three atypical pathogens,6-7 but most also have superior in vitro activity when compared to erythromycin for Haemophilus influenzae and Moraxella catarrhalis. Second, the newer macrolides and quinolones can be given once or twice daily. Azithromycin need only be given for 5 to 10 days rather than the 7 to 21 day range of erythromycin. Thus, compliance, a factor of underestimated importance, is easier with these new agents. Third, controlled randomized clinical trials have validated the efficacy of the newer macrolides and quinolones; they are comparable to the standard β-lactam agents for empiric therapy for community-acquired pneumonia, in both outpatient and hospitalized patients.8-12 Fourth, both the newer macrolides and quinolones have fewer gastrointestinal side effects than erythromycin.13 Fifth, surprisingly, the cost of the 4-g daily dose for a course of parenteral erythromycin often recommended for Legionnaires’ disease is moderately expensive and comparable or even more expensive than the cost required for the newer macrolides.13

Thus, the issue is no longer whether the addition of erythromycin to a β-lactam regimen is required as suggested by Mundy and colleagues, but whether monotherapy with a macrolide or a quinolone can replace the combination of β-lactam agent plus erythromycin! The potential Achilles’ heel of both new macrolide and quinolone regimens deals with antibiotic resistance, a theoretical concern that has become a clinical reality. The penicillin-resistant pneumococci are often resistant in vitro to both erythromycin and the newer macrolides. The major advantage of the new quinolones is that they are active in vitro against the penicillin-resistant pneumococci in contrast to the cephalosporins, β-lactam/β-lactamase inhibitor agents, and the macrolides. Clinical experience will be needed to demonstrate if the in vitro superiority of the newer quinolones against penicillin-resistant pneumococci translates

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