The Journal of the Society of Academic Medicine

Society of Academic Medicine is a Not-for-Profit Medical Society | Volume 1, Number 1, Fall 2009

IN THIS ISSUE:
Innovative Approaches to Common RTIs: The Role of Ultra–Short-Course Therapies

Appropriate use of antimicrobials in the outpatient setting

Donald Low, MD
Professor of Laboratory & Pathology
University of Toronto
Toronto, Ontario
Canada

Risk stratification and early empirical therapy of common RTIs

Thomas File, MD
Professor of Internal Medicine
Head ID Section
Northeastern Ohio Universities
Colleges of Medicine and Pharmacy
Rootstown, Ohio
Chief, Infectious Disease Service
Summa Health System
Akron, OH
United States of America

Innovations in the Treatment of Common RTIs

Francesco Blasi, MD
Dipartimento Toraco-Polmonare e
Cardiocircolatorio, University of Milan, IRCCS
Fondazione POMARE
Milan, Italy

Where Science and Medicine Meet

Innovative Approaches to Management of Common RTIs: The Role of Ultra–Short-Course Therapies

INTRODUCTION
—Javier Garau, MD

The focus of this program is on patients with community-acquired respiratory tract infections (RTIs) that are suitable for treatment on an outpatient basis, which are therefore, by definition, relatively mild or mild-to-moderate in severity. As the infections themselves are not immediately life threatening, the most important goal for physicians is treating the infection quickly and effectively, and avoiding treatment failures or recurrences that may be associated with infection by resistant organisms, which may be more difficult to treat, and may result in worse outcomes.

The first topic is *Appropriate Use of Antimicrobials in the Outpatient Setting* by Dr Donald Low, Professor of Laboratory and Pathology at the University of Toronto, Canada. Next, Dr Thomas File will discuss *Risk Stratification for Early Empiric Treatment of Common RTIs*. Dr File is Professor of Internal Medicine and Head of the Infectious Diseases Section at Northeastern Ohio Universities Colleges of Medicine and Pharmacy in Rootstown, Ohio. Finally, Dr Francesco Blasi, Professor of Respiratory Medicine at the University of Milan, Italy, will describe a new high-dose, single-dose, extended-release formulation of azithromycin in *Innovations in the Treatment of Common RTIs.*

While these community-acquired RTIs are not severe or life threatening, they are extremely common and susceptible to inappropriate use of antibiotics resulting from noncompliance or inappropriate use by patients, or possibly from physicians' initiation of empiric therapy based on minimal information. Our faculty and I believe that we can improve the clinical management of patients with these common infections by using risk-stratification instruments to identify patients who need to be admitted to the hospital versus those who may be treated safely in the outpatient setting, and by adhering to guidelines-based recommendations for treatment. We hope you find this program informative and helpful for your clinical management of patients with community-acquired RTIs.

APPROPRIATE USE OF ANTIMICROBIALS IN THE OUTPATIENT SETTING
—Donald Low, MD

Antibiotics continue to be the mainstay of treatment for bacterial infections, but it is now clear they are not the miracle drugs originally thought in the 1950s. Antibiotics have not eliminated these common diseases, but make it possible to keep them under control through proper prescribing and dosing. Proper use of antibiotics is particularly important in the clinical management of RTIs, which are among the most common infectious diseases. Up to one-third of the population in the United Kingdom consult their physicians for RTIs each year,[1] and worldwide, RTIs account for 6.7% of all mortality **(Figure 1)**.[2] While most RTIs are community-acquired infections and not serious or life threatening, RTIs represent a considerable burden in terms of healthcare resources because they are so common. Treatment failures are common, occurring in nearly 20% of all acute RTIs, and increase the cost of treatment as much as 2- to 5-fold **(Figure 2)**.[3] The frequency and impact of RTI treatment failures

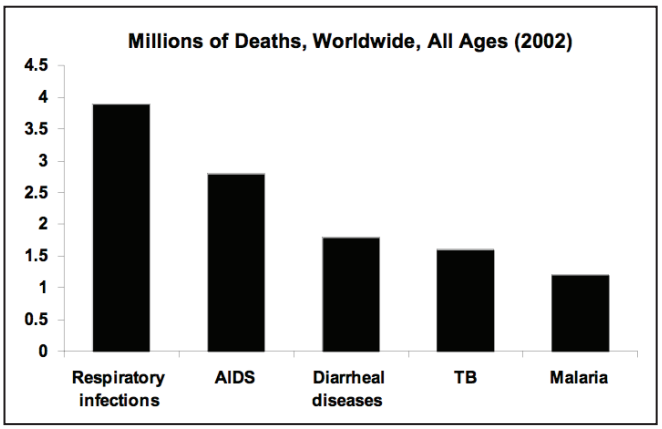


Figure 1. Deaths caused by infectious diseases, worldwide.[2]

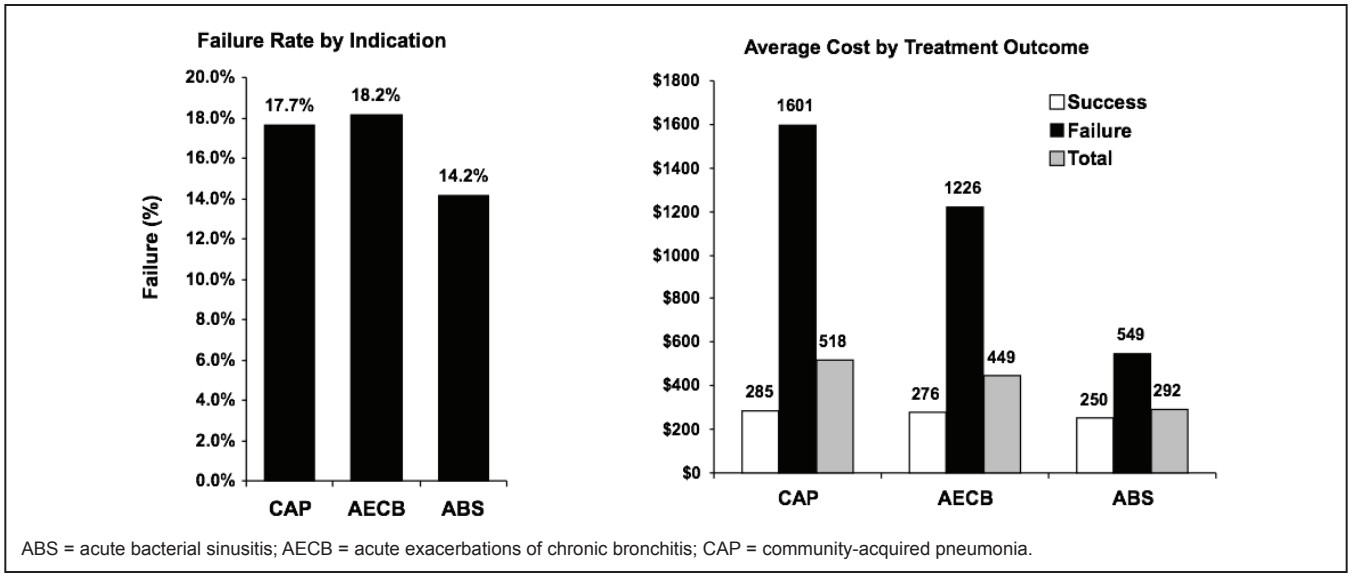


Figure 2. Economic impact of RTI treatment failures.[3]

underscore the importance of appropriate use of antibiotics, including selection of the best agent and best dosage for the initial treatment regimen.

Many factors can contribute to RTI treatment failures, with noncompliance high on the list. A meta-analysis of 46 treatment trials[4] showed that patients are not compliant with 40% of all antibiotic regimens, and another study showed that approximately 30% of all pediatric patients with RTIs are not compliant with their regimens.[5] Noncompliance rates as high as 60% were reported in Mexico.[6] There are many opportunities for patients to be noncompliant: they can fail to start the regimen (or even fail to fill the prescription); they can skip doses or change the dosing interval; they can double doses to make up for missed doses; and they can stop the regimen prematurely (eg, if they begin to feel well and decide the treatment has worked).[7] The potential consequences of noncompliance with RTI treatment include the emergence of antibiotic-resistant organisms,[8] which can increase the risk of treatment failure.

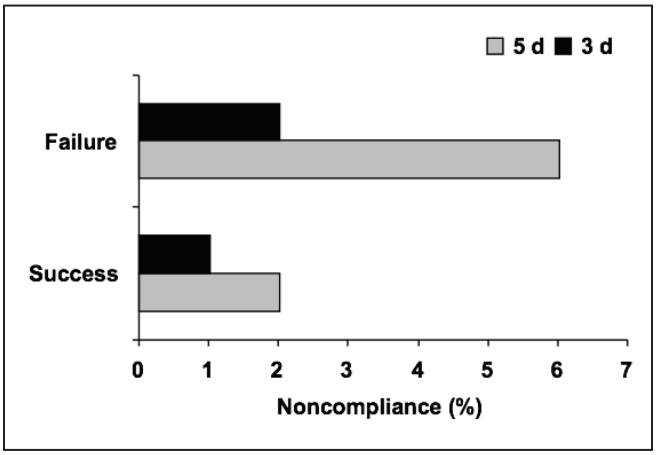


Figure 3. Shorter-course antibiotic therapy is associated with better compliance and lower rates of treatment failure in pediatric patients with CAP. [9]

Improving compliance can improve the likelihood of treatment success, and one way to do this is to shorten and simplify the course of treatment.[9] As **Figure 3** shows, pediatric patients with community-acquired pneumonia (CAP) were more likely to be noncompliant with a 5-day amoxicillin regimen than with a 3-day regimen, and the noncompliance in the 5-day group was associated with a higher rate of treatment failure.[9] Compliance issues aside, there are also data showing increased colonization with resistant organisms (penicillin-resistant *Streptococcus pneumonia*e) in children receiving long courses (>5 days) of oral beta-lactam antibiotics in low doses (lower than clinically recommended).[10] Clearly, low antibiotic exposure, either through noncompliance or low prescribed doses, can create an environment that supports emergence of resistant bacteria.

Just as a long-course, low-dose regimen can increase the risk of worse outcomes, short-course, high-dose antibiotic therapy has been shown to improve compliance and reduce the emergence of resistant organisms. Among 795 children with RTIs randomized to amoxicillin 90 mg/kg/day in 2 divided doses for 5 days or 40 mg/kg/day in 2 divided doses for 10 days, carriage of penicillin-nonsusceptible *S pneumonia*e (PNSP) was significantly lower in the short-course high-dose group (**Figure 4**), and compliance was significantly greater among those patients.[11]

THE IN-VITRO/IN-VIVO PARADOX

While rising rates of resistant pneumococci were documented in the 1980s and 1990s, this trend was not accompanied by an increase in RTI treatment failures. Even with reported rates of PNSP as high as 20%, very few cases of treatment failure in patients receiving adequate doses of aminopenicillins have been documented.[12] In fact, as of 2006, there was only a single report of documented microbiologic

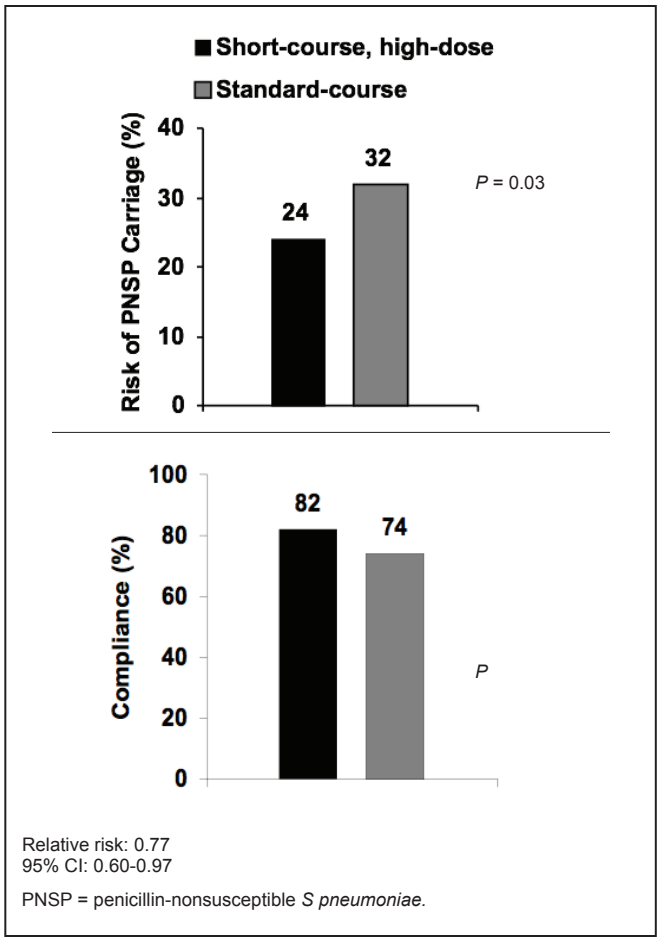


Figure 4. Better compliance and lower carriage of resistant bacteria with short-course, high-dose antibiotic therapy for RTIs.[11]

failure of a parenteral penicillin among patients with pneumococcal pneumonia with or without bacteremia, in contrast to more than 20 reported treatment failures with quinolones and more than 30 with macrolides.[12] For the penicillins, the explanation may lie in the fact that the original breakpoints defined for penicillin resistance were set too low, in an attempt to guard against the possibility of meningitis in all patients with pneumococcal infections. Recently, in the United States, new breakpoints have been determined, so that susceptibility to penicillin in *S pneumoniae* is now defined as a minimal inhibitory concentration (MIC) of ≤2 ug/mL (rather than ≤0.06 ug/mL previously); intermediate resistance, or nonsusceptibility, is now ≤4 or ≤8 ug/mL (rather than 0.12 to 1 ug/mL previously); and resistance is now at ≥8 ug/mL (rather than ≥2 ug/mL previously).[13] The revised definitions appear to be appropriate, as reports of emerging pneumococcal strains with MICs of 16 or 32 ug/mL appear to be linked to treatment failures, so it is likely that these organisms truly are resistant.

The relationship between resistance to macrolide antibiotics and treatment failure is also confusing, but for different reasons. Only anecdotal reports are available regarding treatment failures associated with macrolide-resistant bacteria,[14-19] and in response to the observation that treatment failures are relatively rare with macrolides, the most recent guidelines of the Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) recommend that macrolides may be used empirically in patients with RTI except in areas with a 25% rate of high-level macrolide resistance, defined as an MIC ≥16 ug/mL.[20]

The explanation for this apparent inconsistency between in vitro susceptibility and in vivo efficacy involves the mechanism of action of macrolides and the mechanisms of resistance, along with their pharmacokinetic characteristics. Macrolides inhibit bacterial protein synthesis by binding to the peptidyl transferase center in the 23S RNA component of the 50S ribosomal subunit. This confers activity against common pathogens such as *S pneumonia*e and against atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[20-22] The 2 main mechanisms of resistance involve the macrolide efflux pump (M phenotype), which is by far the most common in North America and is generally associated with low-level resistance (MIC ≥1 and ≤8 ug/mL), and target modification, which results in decreased affinity of the macrolide molecule for its target in the ribosome and is associated with high-level resistance (MIC >64 ug/mL).[21] The apparent contradiction or paradox between high rates of macrolide-resistant *S pneumonia*e in the United States[23] and very rare instances of macrolide treatment failure in patients with CAP caused by drug-resistant *S pneumoniae*[24] may be explained by the fact that ≈80% of macrolide resistance in North America involves the efflux pump mechanism, which does not appear to be linked to treatment failure, and the fact that macrolide penetration and concentration in respiratory tissues is much greater than levels achieved in the blood.[24] **Figure 5** shows the significantly greater concentration of azithromycin in alveolar macrophages than in plasma; note that the Y-axis is a logarithmic scale, and the differences in concentrations are >100-fold.[25]

These observations of continuing clinical effectiveness are reflected in the most recent IDSA/ATS Consensus Guidelines for treatment of outpatient CAP[20]: in previously well patients, the recommendation for first-line empiric therapy is to use an advanced macrolide or doxycycline. In patients with a medical comorbidity or recent antibiotic use, for whom a different antibiotic should be used in the subsequent course, empiric therapy may include a respiratory fluoroquinolone (gemifloxacin, levofloxacin, or moxifloxacin), a high-dose beta-lactam (amoxicillin or amoxicillin/clavulanate) plus a macrolide or doxycycline, or ceftriaxone, cefpodoxime, or cefuroxime plus a macrolide or doxycycline.

Another important consideration involves the availability of an alternative to the fluoroquinolones, particularly in patients who have taken a course of fluoroquinolone therapy during the previous 3 months and may be more likely to be infected with fluoroquinolone-resistant organisms. This is particularly important as the broad use of fluoroquinolones for RTIs apparently results in many instances of inappropriate use. In a study of 100 consecutive patients seen in the emergency department and discharged on a fluoroquinolone, 81 were treated inappropriately: 43 should have been given

another agent, according to guidelines recommendations, and 27 had no infection documented.[26] Among the 19 who were appropriately given a fluoroquinolone, only 1 was given a prescription for the correct dose and duration of therapy. Clearly, such patterns of use increase the risk of emergence of resistant organisms.

In conclusion, macrolides continue to have a role in CAP as monotherapy in appropriately selected outpatients and as part of combination therapy in inpatients, and as an alternative to overuse of fluoroquinolones. It appears clear that in vitro macrolide resistance does not necessarily correspond to treatment failures, and that macrolides are appropriate for empiric therapy in adults with outpatient CAP as monotherapy in previously healthy adults with no risk factors for drug-resistant *Streptococcus pneumoniae* ("DRSP") infection, and in combination with a beta-lactam for adults at risk for infection with DRSP.

RISK STRATIFICATION FOR EARLY EMPIRIC TREATMENT OF COMMON RTIs

—Thomas File, MD

Despite the availability of clear guidelines for the treatment of community-acquired RTIs (CARTIs), there is a lot of overuse and misuse of antibiotics for these very common infections. A survey of patients in Los Angeles County in 2003[27] showed that only one-third of adults knew how to use antibiotics correctly, fewer than one-half reported completing their prescribed courses of antibiotic treatment, about one-third reported obtaining antibiotics from friends or family members, and nearly one-half requested antibiotics from their physicians for viral conditions. This pattern of widespread inappropriate use is certainly attributable to a lack of education in the general population, but some of the inappropriate use may also be attributable to physicians' practices and the fact that many factors have potential impact on the most appropriate

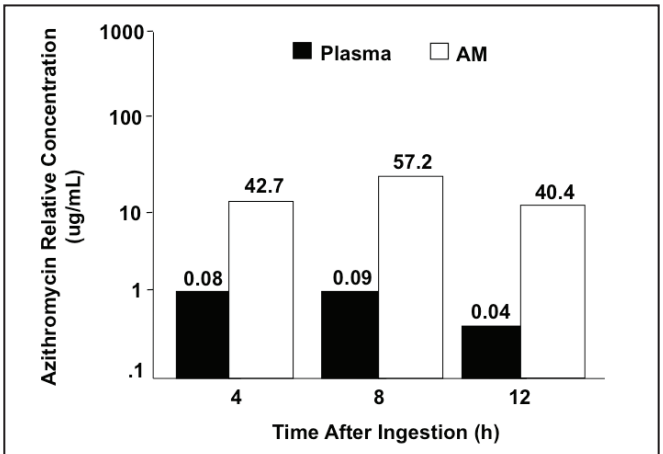


Figure 5. Significantly greater concentration of azithromycin in alveolar macrophages than in plasma. Note that the Y-axis is a logarithmic scale and the differences in concentration are in the range of 100-fold to 1,000-fold.[25]

Patient-specific factors	Antimicrobial-specific factors
• Possible pathogens/ copathogens	• Spectrum of activity
• Likelihood of resistant organisms	• Proven clinical efficacy
• Severity of infection	• PK/PD
• Patient characteristics	• Potential for resistance
• Age	• Potential to induce resistance
• Allergy to antimicrobials	• Adverse effects
• Concomitant disease states	• Toxicity profile
• Pregnancy	• Convenient dosing
	• Drug and food interactions
	• Drug costs vs overall costs of care

CARTI = Community-acquired RTI.
PK/PD = Pharmacokinetics/pharmacodynamics.

Table 1. Considerations in empiric antibiotic selection for CARTIs.[28]

treatment choice for each individual patient (**Table 1**).[28]

In fact, while the IDSA/ATS guidelines provide broad recommendations that are applicable to previously healthy adults with no risk factors for infection with resistant organisms, most guidelines also recommend patient stratification for more precise targeting of therapy to provide each patient with the most appropriate antibiotic regimen.[20,24,29,30] Patient stratification includes assessing the need for antimicrobial therapy (eg, viral vs bacterial etiology), determining the severity of illness and prognosis, predicting the likely pathogen and likelihood of resistance, and identifying the appropriate antibiotic and duration of therapy for empiric use.

The goals of stratification include avoiding antimicrobial treatment when it is not indicated (eg, for viral infections), and, in general, to support use of the "3 D's"—the right Drug, at the right Dose, for the right Duration. Selecting the right Drug includes considering likely pathogens and local resistance patterns, and other aspects of patient stratification; selecting the right Dose involves consideration of the drug's pharmacokinetics and pharmacodynamics; and selecting the right Duration involves considerations such as improved compliance and lower rates of treatment failure with shorter courses of antibiotic therapy.

One of the most important considerations in patient stratification is determining the site of care—ie, evaluating the severity of the patient's illness and deciding whether the patient can be treated safely as an outpatient or if hospital admission is appropriate. Clearly, it is important to avoid admitting patients who do not need to be admitted, because of cost considerations and to avoid exposing the patient to the risk of nosocomial infection; most patients are more comfortable at home and many may recover more quickly if treated at home. It is equally important to avoid outpatient treatment when the patient needs to be admitted, in order to benefit from more intensive monitoring, the ready availability of multiple diagnostic modalities, etc. Because there are so many factors to consider for each patient, the decision to admit or not to admit the patient for treatment of CAP may be more art than science. This has led to the development of several prediction tools, which enable the physician to standardize the

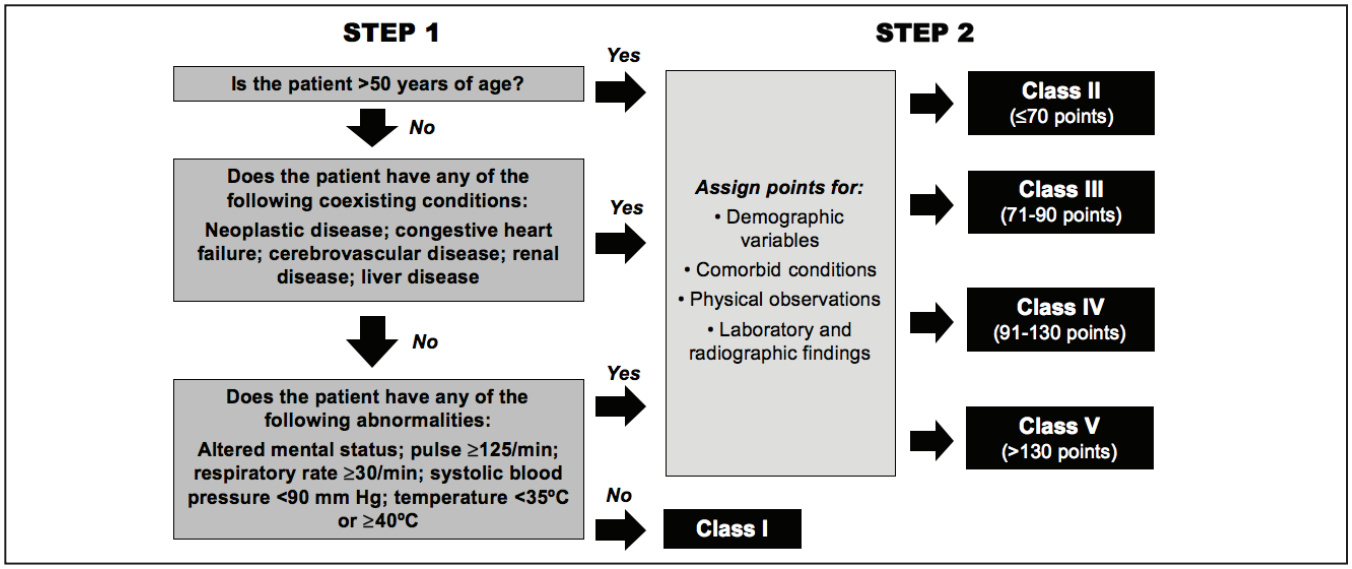


Figure 6. The Pneumonia Severity Index (PSI), or PORT score.[31]

evaluation of the patient's status and prognosis and to base the decision on validated scientific data.

The Pneumonia Severity Index (PSI), also known as the Pneumonia Patient Outcomes Research Team (PORT) score,[31] is probably the best-known and most extensively validated stratification protocol. It has been in use for more than 10 years and has been shown to reduce the proportion of low-risk patients admitted to the hospital by identifying those who can be treated safely as outpatients. In the first step (**Figure 6**),[31] the patient is asked 3 questions: (i) his or her age (>50 years?), (ii) pre-existing (comorbid) medical conditions, and (iii) current status (stable vital signs?). These questions can be asked via telephone, and if the answer to all 3 is "no," the patient is low risk (Class I) and may be treated as an outpatient. If any of the answers is "yes," the scoring algorithm (**Table 2**)[31] is applied, and the patient is assigned points. The total point score determines the assignment to a risk category or Class (**Table 3**), which indicates whether the patient should be admitted, observed briefly at the hospital, or discharged home.[31] In 2003,[32] the PSI was modified to include assessment of pre-existing conditions that might compromise home care, such as hypoxemia, severe social or psychiatric problems, or inability to take oral medications. Then, after calculating the PORT score, clinical judgment should be used and may override the recommendation based on the risk category, if, for example, the physician considers it safe to recommend home care, based on the patient's overall health status, availability of adequate caregiver support at home, etc.

The PSI is effective, but requires consideration of many variables. In 2003, Lim and colleagues developed the CURB-65 patient stratification protocol, which is an acronym for Confusion, Urea (blood urea nitrogen, or BUN), Respiratory rate, Blood pressure, and age ≥65 years (**Figure 7**).[33] With <2 points, the patient is most likely suitable for treatment at home; with 2 points, some degree of hospital-based observation and treatment should be considered; with ≥3 points, the patient should be admitted to and managed in the

Patient Characteristic	Points
Age	**No. of years (-10 for female)**
Cancer	30
Liver disease	20
CHF, CVD, Renal disease	10
RR >30/min, SBP <90 mm Hg, Confusion	20
Temp <35°C, >50°C	15
Pulse, beats/min	10
BUN; Sodium <130 mmol/L	20
Glucose >250 mg/dL; Hct <30%	10
pO_2 <60 mm Hg	10

CHF = congestive heart failure; CVD = cerebrovascular disease; R = respiratory rate; SBP = systolic blood pressure; BUN = blood urea nitrogen; Hct = hematocrit.

Table 2. PORT Prediction Rule, step 2: Algorithm for assignment of points.[31]

Total Points	Class	Mortality (%)	How to Treat
	I	0.1	Outpatient
≤70	II	0.6	Outpatient
71-90	III	0.9-2.8	Brief hospital observation
91-130	IV	8.2-9.3	Inpatient
>130	V	27.0-29.2	Inpatient ICU

Risk categories according to 2 validation cohorts (38,039 inpatients and 2287 in- and outpatients)

Table 3. PORT Prediction Rule: risk categories.[31]

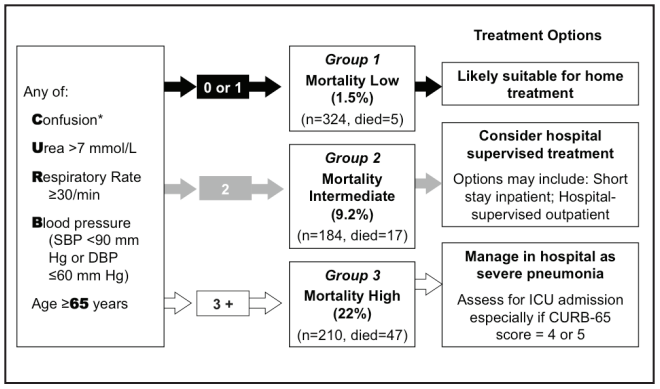


Figure 7. The CURB-65 patient stratification protocol.[33]

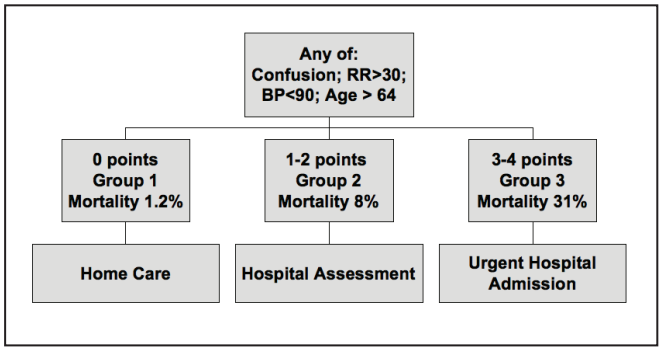


Figure 8. The simpler CRB-65 patient stratification protocol does not require a blood test.[33]

hospital. The CRB-65, a simpler variant that does not require a blood test, may be useful for rapid assessments when the results of a blood test are not immediately available (**Figure 8**).[33]

In a study that evaluated the predictive value of each of these scores (PORT, CURB-65, and CRB-65), all 3 were found to be similarly effective in terms of sensitivity and specificity.[34] Overall, it may be best for physicians to take the best of each approach.[35] The PSI was developed to identify low-risk patients and prevent their unnecessary admission to the hospital, but can underestimate the need for hospital or ICU admission for some patients; it may also overestimate the need for expensive resources because of its focus on age and comorbidity, and lack of focus on disease severity. The CURB-65 effectively helps physicians avoid overlooking severe illness, but its usefulness may be limited in the elderly and in those with medical comorbidities. The best approach may be to use either approach to identify low-risk patients, but to add vital signs and illness severity information to the PSI, and to add assessment of comorbid illness and vital sign stability to the CURB-65—and to add consideration of social factors to both.[35]

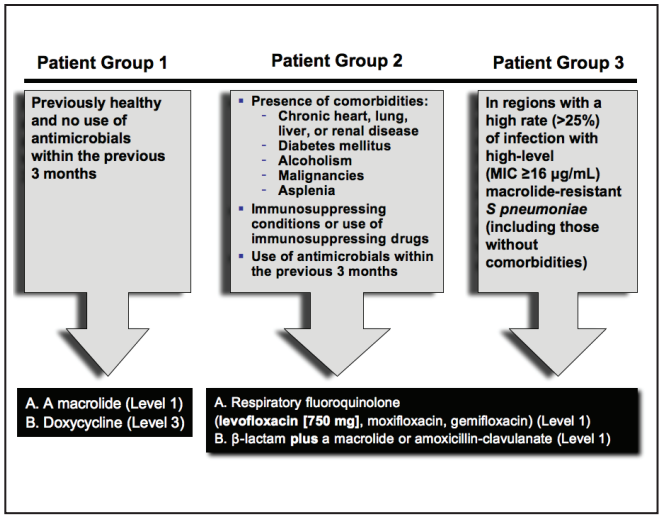


Figure 9. IDSA/ATS guidelines for outpatient treatment of CAP.[20]

TREATMENT SELECTION BASED ON THE RISK OF ANTIMICROBIAL RESISTANCE

Once the patient has been evaluated and the location of treatment has been determined, the physician has to choose which antibiotic to prescribe, and one of the key considerations in that decision is the likelihood of infection with a resistant strain. Patients who may have an increased risk of infection with a drug-resistant strain of *S pneumonia*e include those with antibiotic use in the last 90 days, nosocomial or nursing home acquisition, extreme old (or young) age, underlying illness, community or household exposure to patients infected with resistant organisms, epidemiologic or geographic association, or institutionalization.[22,36] These considerations are reflected in the guidelines for empiric treatment of acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), and CAP.

For ABS, low-risk patients (those with mild disease and no recent antibiotic use) should be treated with amoxicillin, amoxicillin/clavulanate, cefpodoxime proxetil, cefurozime, or cedinir. Patients allergic to beta-lactam antibiotics may be treated with trimethoprim/sulfamethoxazole (TMP/SMX), doxycycline, or a macrolide. Patients with moderately severe disease or those with mild disease who have been treated recently with an antibiotic should receive levofloxacin or moxifloxacin, amoxicillin/clavulanate, ceftriaxone, or combination therapy.[29]

For AECB, low-risk patients (≤4 exacerbations/year, no comorbid illness, and FEV_1 >50%) may be treated with a 2nd-generation macrolide, a 2nd- or 3rd-generation cephalosporin, amoxicillin, doxycycline, or TMP/SMX. Patients with complicated AECB (>4 exacerbations/year, cardiac disease, FEV_1 <50%, need for home oxygen therapy, use of chronic oral corticosteroids, or antibiotic use in the past 3 months) should be treated with a fluoroquinolone or a beta-lactam/beta-lactamase inhibitor combination. Those with chronic suppurative bronchitis (multiple risk factors of those listed for complicated AECB and FEV_1 typically <35%) should receive antibiotic therapy tailored to the pathogen.[30]

The IDSA/ATS guidelines for outpatient treatment of CAP are summarized in **Figure 9**.[20] First-line therapy for previously healthy patients who have not been treated with an antibiotic during the past 3 months should be a macrolide or doxycycline;

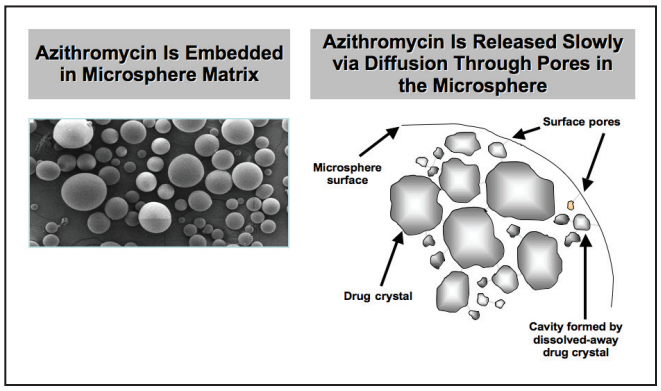


Figure 10. The extended-release formulation of azithromycin, Zmax® (azithromycin extended release) for oral suspension, uses microspheres to delay release of the drug.[45,46]

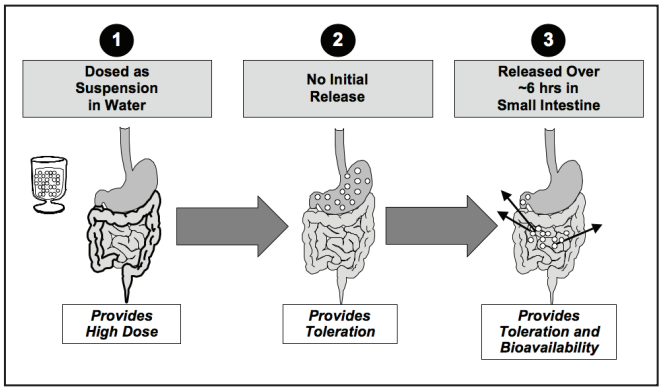


Figure 11. Azithromycin microspheres, in an oral suspension formulation, make it possible to administer a high dose at once. Delaying release until the drug reaches the small intestine improves tolerability and bioavailability.[45,46]

patients with risk factors for DRSP, or in areas with high rates (>25%) of high-level macrolide resistance (MIC ≥16 ug/mL), should receive a respiratory fluoroquinolone, a beta-lactam plus a macrolide, or amoxicillin/clavulanate.

Regarding the timing of administration of empiric antibiotic therapy, it would seem obvious that sooner is better, but there are relatively few data available to support this. In 2 large retrospective analyses of patient databases, early antibiotic administration for CAP was shown to have a favorable effect on 30-day mortality antibiotic therapy: in one study,[37] administration within 8 hours was shown to reduce 30-day mortality by 15%, and in the other,[38] antibiotic therapy administered within 4 hours was shown to reduce 30-day mortality by approximately 12%. However, data from prospective trials with smaller patient populations[39,40] have not shown a survival benefit associated with antibiotic administration between 4 and 8 hours. Therefore, considering the survival benefit associated with treatment within 4 hours but also weighing concerns related to diagnostic uncertainty and inappropriate antimicrobial therapy,[41,42] current performance measures in the United States provide physicians with a goal to initiate treatment within 6 hours after the patient presents to the office or hospital.

In conclusion, currently available data support early initiation of empiric antibiotic treatment for community-acquired RTIs. A recently published analysis of a large patient database[43] showed that increased survival and decreased progression from mild to serious CAP were associated with early initiation of an effective antibiotic at an adequate dose, sufficient to provide a 24-hour area under the inhibitory curve (AUIC) to MIC ratio >100. The message for physicians may be summarized as: To reduce the risk of progression from a mild RTI to serious illness, select the most effective treatment initially and begin treatment as soon as possible. Patient stratification is an important part of this process, enabling us to provide each patient with the most effective therapy. And by identifying the most effective therapy for each patient, we may be able to use shorter courses of therapy, which would be likely to improve compliance and the patient's overall clinical outcome.

INNOVATIONS IN THE TREATMENT OF COMMON RTIs

—Francesco Blasi, MD

Therapy for AECB and CAP has evolved considerably in the decades since antibiotics were first introduced, from sulfonamides and penicillins through fluoroquinolones, advanced cephalosporins, and advanced macrolides and ketolides. Currently, upper and lower RTIs are the most common indications for antibiotic therapy.[44] Ongoing innovations enable us not only to select the most appropriate antibiotic for each patient, but the most appropriate formulation and dosage regimen as well, to optimize treatment success and compliance with the prescribed regimen, and to reduce the risks of emergence of resistant organisms.

A new formulation of azithromycin, Zmax® (azithromycin extended release) is an oral suspension that uses microspheres (**Figure 10**)[45,46] to delay release of the drug until after it passes through the stomach, so that it can be absorbed over ≈6 hours in the small intestine (**Figure 11**).[45,46] Administration of the single 2-gram dose makes it possible to achieve 3 times

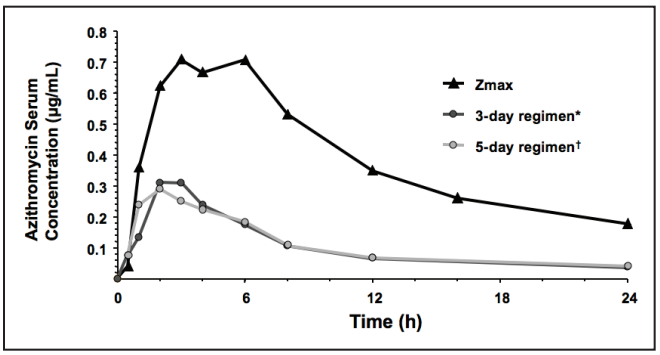


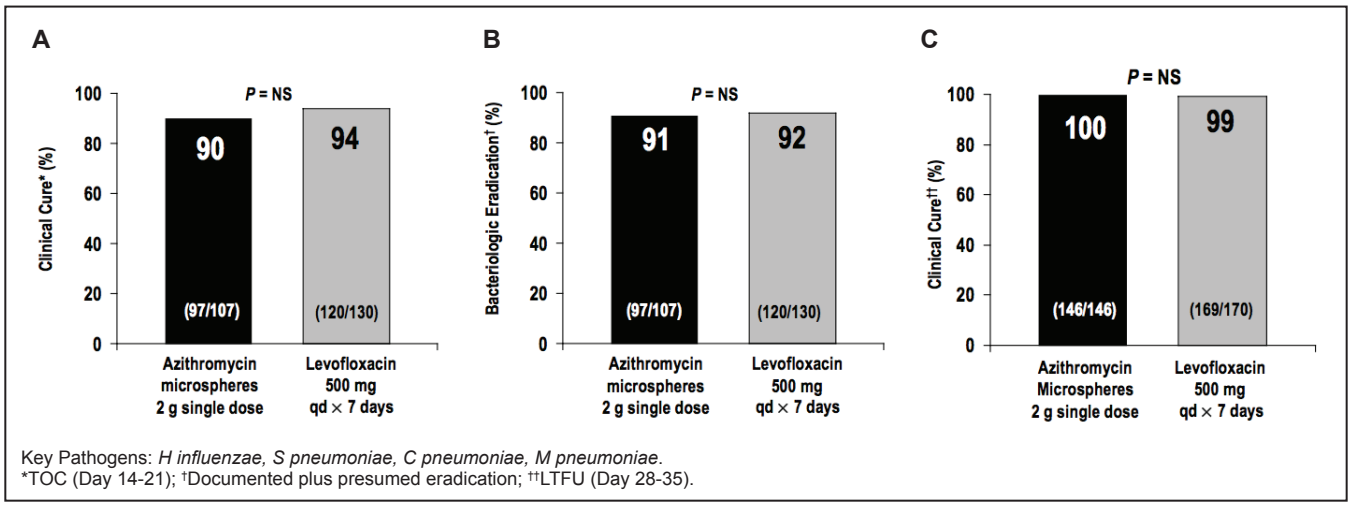
Figure 12. The single 2-gram dose administered with azithromycin microspheres provides 3 times greater systemic azithromycin exposure on Day 1 compared with 3-day and 5-day oral azithromycin regimens.[45]

greater systemic azithromycin exposure on Day 1, compared with 3-day (500 mg qD) and 5-day (500 mg on Day 1, then 250 mg qD on Days 2-5) azithromycin regimens (**Figure 12**).[45]

In animal models of acute otitis media, both higher doses and front-loading of the dose[47,48] have been shown to reduce bacterial load more effectively than standard doses, providing support for this approach. With regard to clinical use, it is clear that administration of the full antibiotic course in a single dose optimizes compliance.[49-51] Once the dose has been taken in the presence of a supervising health care provider, the patient has no opportunity to delay or miss doses.

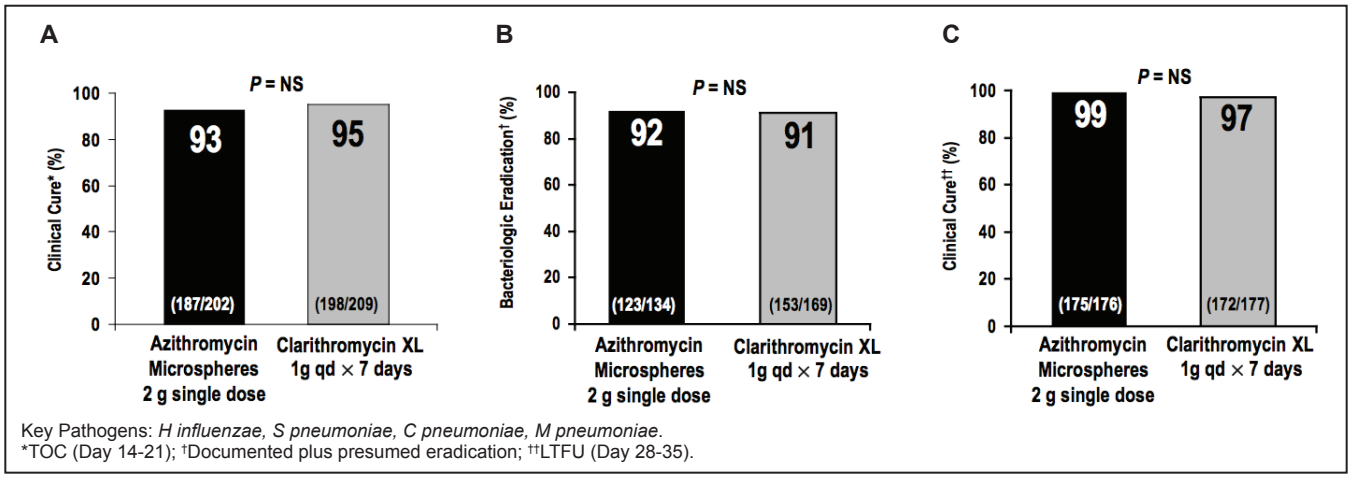
The azithromycin microspheres oral suspension single-dose high-dose formulation was evaluated in 2 clinical trials involving patients with mild-to-moderate CAP appropriate for outpatient treatment. In the trial reported by D'Ignazio and colleagues,[49] 211 patients with CAP were randomly assigned to receive a single 2-gram dose of azithromycin microspheres on Day 1 and placebo (two capsules) on Days 2 to 7, and 212 patients received two 250-mg levofloxacin capsules on Days 1 to 7 plus a liquid placebo on Day 1. The results, summarized in **Figure 13**,[45,49] show that the single 2-gram azithromycin microspheres dose was as effective as levofloxacin 500 mg/day for 7 days in terms of clinical cure, as measured at the Test of Cure visit between Days 14 to 21 (**Figure 13a**), bacterial eradication (**Figure 13b**), and clinical cure as measured at the long-term follow-up visit between Days 28 to 35 (**Figure 13c**). During this trial, all patients receiving azithromycin microspheres were fully compliant with active therapy, while 4.7% of patients receiving levofloxacin did not complete the entire 7-day course of treatment.[45,49]

In the trial reported by Drehobl and colleagues,[50] 247



Key Pathogens: *H influenzae, S pneumoniae, C pneumoniae, M pneumoniae*.
*TOC (Day 14-21); †Documented plus presumed eradication; ††LTFU (Day 28-35).

Figure 13. Comparable efficacy of azithromycin microspheres (single 2-gram dose) and levofloxacin 500 mg/day for 7 days in patients with CAP suitable for outpatient treatment, in terms of clinical cure as measured between Days 14-21 **(Figure 13a)**, bacterial eradication **(Figure 13b)**,[49] and clinical cure at long-term follow-up, Days 28-35 **(Figure 13c)**.[45]



Key Pathogens: *H influenzae, S pneumoniae, C pneumoniae, M pneumoniae*.
*TOC (Day 14-21); †Documented plus presumed eradication; ††LTFU (Day 28-35).

Figure 14. Comparable efficacy of azithromycin microspheres (single 2-gram dose) and clarithromycin XL 1 g/day for 7 days in patients with CAP suitable for outpatient treatment, in terms of clinical cure as measured between Days 14-21 **(Figure 14a)**, bacterial eradication **(Figure 14b)**, and clinical cure at long-term follow-up, Days 28-35 **(Figure 14c)**.[50]

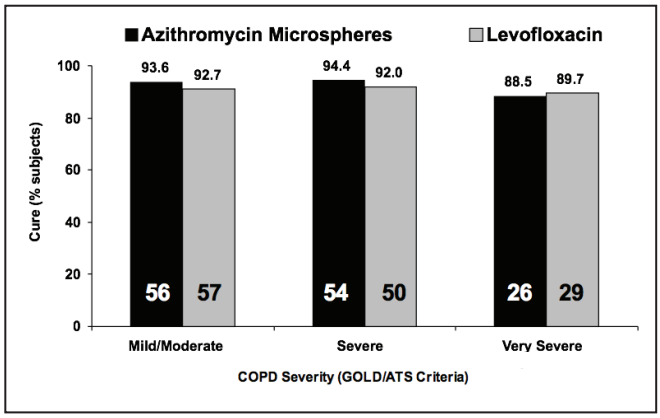


Figure 15. Comparable efficacy of azithromycin microspheres (single 2-gram dose) and levofloxacin 500 mg/day for 7 days in patients with community-acquired AECB across the range of COPD severity from mild/moderate to very severe.[52]

	Azithromycin Microspheres (N = 1292)	Comparators (N = 1304)
	No. (%) of Subjects	
Any treatment-related AE	295 (22.8)	229 (17.6)
Diarrhea/loose stools	151 (11.6)	71 (5.4)
Nausea	51 (3.9)	28 (2.1)
Abdominal pain	35 (2.7)	27 (2.1)
Headache	17 (1.3)	8 (0.6)
Vomiting	14 (1.1)	9 (0.7)

Table 4. Pooled adult safety data from clinical trials of azithromycin microspheres single 2-gram dose formulation vs comparator drugs.[45]

patients with CAP were randomly assigned to receive the azithromycin microspheres dose on Day 1 and capsule placebos on Days 2 to 7, as in the D'Ignazio trial, and 252 patients received two 500-mg clarithromycin XL (extended-release) capsules on Days 1 to 7 and a liquid placebo on Day 1. As Figure 14[50] shows, the single 2-gram azithromycin microspheres dose was as effective as clarithromycin XL 1g/day for 7 days in terms of clinical cure, as measured at the Test of Cure visit between Days 14 to 21 (**Figure 14a**), bacterial eradication (**Figure 14b**), and clinical cure as measured at the long-term follow-up visit between Days 28 to 35 (**Figure 14c**). During the trial, 100% of patients randomized to receive azithromycin microspheres were compliant with the regimen, while 5.9% of those in the clarithromycin XL arm did not complete the 7-day course of treatment. Similarly, 8.1% of patients in the azithromycin microspheres group were noncompliant with placebo during the 6-day placebo period.[50]

Azithromycin microspheres were also as effective as levofloxacin 500 mg/day for 7 days in a randomized, placebo-controlled trial in patients with AECB,[51] with similar cure rates (94% and 93%) at the Test of Cure visit (Days 14-21) and at the long-term follow-up visit between Days 25 and 38 (98% and 98%). In a retrospective analysis of data from this trial,[52] azithromycin microspheres were shown to be as effective as levofloxacin across the spectrum of chronic obstructive pulmonary disease (COPD) severity (**Figure 15**)—including patients with very severe disease, who tend to have exacerbations associated with infection by more difficult-to-treat bacteria.

Table 4[45] shows pooled safety data for azithromycin microspheres, comparing rates of adverse events in clinical trials of the new formulation with rates in the various comparator drug treatment groups. The diarrhea or loose stools that may occur in approximately 1 in 10 patients treated with the azithromycin microspheres oral suspension formulation usually develops approximately 4 to 6 hours after the patient ingests the dose, so the drug has already been absorbed and the patient does not need to be re-dosed. In most cases, diarrhea or loose stool resolves within 24 to 48 hours.

In summary, the azithromycin microspheres single-dose high-dose formulation is effective in CAP and community-acquired AECB and is well tolerated, with optimal compliance and, therefore, minimal risk of emergence of resistant organisms due to poor compliance.

REFERENCES

1. British Thoracic Society. The burden of lung disease. 2001. www.brit-thoracic.org.uk. Accessed January 16, 2009.
2. World Health Organization (WHO). World Health Report 2003: Shaping the Future. http://www.who.int/whr/en/. Accessed January 16, 2009.
3. Barron JJ, Grochulski WD, Merchant S, Spooner JJ, Waugh WJ, Keating KN. Treatment costs associated with commonly used branded antibiotics for the management of acute sinusitis, chronic bronchitis and pneumonia. *J Applied Research.* 2004;4(1):24-36.
4. Kardas P, Devine S, Golembesky A, Roberts C. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. *Int J Antimicrob Agents.* 2005;26(2):106-113.
5. Hoppe JE, Blumenstock G, Grotz W, Selbmann HK. Compliance of German paediatric patients with oral antibiotic therapy: results of a nationwide survey. *Pediatr Infect Dis J.* 1999;18(12):1085-1091.
6. Reyes H, Guiscafre H, Munoz O, Pérez-Cuevas R, Martinez H, Gutiérrea G. Antibiotic noncompliance and waste in upper respiratory infections and acute diarrhea. *J Clin Epidemiol.* 1997;50(11):1297-1304.
7. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother.* 2002;49(6):897-903.
8. Thomas JK, Forrest A, Bhavnani SM, et al. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother.* 1998;42(3):521-527.
9. MASCOT: Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. *Lancet.* 2002;360(9336):835-841.
10. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of ß-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA*.1998;279(5):365-370.
11. Schrag SJ, Peña C, Fernandez J, et al. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage. *JAMA*. 2001;286(1):49-56.
12. Peterson LR. Penicillins for the treatment of pneumococcal pneumonia: does in vitro resistance really matter? *Clin Infect Dis*. 2006;42(2):224-233.
13. Morbidity and Mortality Weekly Report (MMWR). Effects of New Penicillin Susceptibility Breakpoints for *Streptococcus pneumoniae* — United States, 2006–2007. December 19, 2008;57(50):1353-1355.
14. Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multidrug-resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. *Clin Infect Dis*. 2000;31(2):613-615.
15. Kelley MA, Weber DJ, Gilligan P, Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. *Clin Infect Dis*. 2000;31(4):1008-1011.
16. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumonia*e. *Clin Infect Dis*. 2002;35(5):556-564.
17. van Kerkhoven D, Peetermans WE, Verbist L, Verhaegen J. Breakthrough pneumococcal bacteraemia in patients treated with clarithromycin or oral beta-lactams. *J Antimicrob Chemother*. 2003;51(3):691-696.
18. Daneman NA, McGeer A, Green DE, et al. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. *Clin Infect Dis.* 2006;43(4):432-438.
19. Daneman N, Low DE, McGeer A, Green KA, Fisman D. At the threshold: defining clinically meaningful resistance thresholds for antibiotic choice in community-acquired pneumonia. *Clin Infect Dis.* 2008;46(8):1131-1138.
20. 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*. 2007;44(suppl 2):S27-S72.
21. Bozdogan B, Appelbaum PC. Macrolide resistance in streptococci and Haemophilus influenzae. *Clin Lab Med*. 2004;46(2):455-475.
22. File TM, Neiderman MS. Antimicrobial therapy of community-acquired pneumonia. *Infect Dis Clin N Am.* 2004;18(4):993-1016, xi.
23. Brown SD, Rybak MJ. Antimicrobial susceptibility of *Streptococcus pneumonia*e, *Streptococcus pyogenes* and *Haemophilus influenzae* collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study. *J Antimicrob Chemother*. 2004;54(suppl 1):i7-i15.
24. Niederman MS, Mandell LA, Anzneto A, et al; American Thoracic Society. Guidelines for the management of adults with community acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy and prevention. *Am J Respir Crit Care Med*. 2001;163(7):1730-1754.
25. Rodvold KA, Gotfried MH, Danziger LH, Servi RJ. Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. *Antimicrob Agents Chemother*. 1997;41(6):1399-1402.
26. Lautenbach E, Larosa LA, Kasbekar N, et al. Fluoroquinolone utilization in the emergency departments of academic medical centers. *Arch Intern Med*. 2003;163(5):601-605.
27. Los Angeles Public Health. L.A. Health. County of Los Angeles Department of Health Services; September 2003. www.lapublichealth.org. Accessed April 16, 2009.
28. Jones O. In: Speight TM, Holford NH, eds. *Avery's Drug Treatment: A Guide to the Properties, Choice,*

Therapeutic Use and Economic Value of Drugs in Disease Management, 4th Edition. 1997;1456-1514.
29. Anon JB, Jacobs MR, Poole MD, et al; Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(suppl 1):1-45.
30. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF, and the Chronic Bronchitis Working Group; on behalf of the Canadian Thoracic Society and the Canadian Infectious Diseases Society. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can Respir J*. 2003;10(suppl B):3B-32B.
31. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
32. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. *Ann Inter Med*. 2003;138(2):109-118.
33. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.
34. Capelastegui A, España PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Resp J*. 2006;27(1):151-157.
35. Niederman MS, Feldman C, Richards GA. Combining information from prognostic scoring tools for CAP: an American view on how to get the best of all worlds. *Eur Resp J*. 2006;27(1):9-11.
36. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A; Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis*. 2005;40(9):1288-1297.
37. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278(23):2080-2084.
38. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med*. 2004;164(6):637-644.
39. Benenson R, Magalski A, Cavanaugh S, Williams E. Effect of a pneumonia clinical pathway on time to antibiotic treatment, length of stay, and mortality. *Acad Emerg Med*. 1999;6(12):1243-1248.
40. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest*. 2005:127(4):1260-1270.
41. Metersky ML, Sweeney TA, Getzow MB, Siddiqui F, Nsa W, Bratzler DW. Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia. *Chest*. 2006;130(1):16-21.
42. File TM, Gross PA. Performance measurement in community-acquired pneumonia: consequences intended and unintended. *Clin Infect Dis*. 2007;44(7):942-944.
43. File TM Jr, Schentag JJ. What can we learn from the time course of untreated and partially treated community-onset *Streptococcus pneumonia*e pneumonia? A clinical perspective on superiority and noninferiority trial designs for mild community-acquired pneumonia. *Clin Infect Dis*. 2008;47(suppl 3):S157-S165.
44. Petersen I, Hayward AC. Antibacterial prescribing in primary care. *J Antimicrob Chemother.* 2007;60(suppl 1): i43-i47.
45. Pfizer Inc, data on file.
46. Chandra R, Liu P, Breen JD, et al. Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. *Clin Pharmacokinet.* 2007;46(3):247-259.
47. Babl FE, Pelton SI, Li Z. Experimental acute otitis media due to nontypeable *Haemophilus influenzae*: comparison of high and low azithromycin doses with placebo. *Antimicrob Agents Chemother*. 2002;46(7):2194-2199.
48. Girard D, Finegan SM, Dunne MW, Lame ME. Enhanced efficacy of single-dose versus multi-dose azithromycin regimens in preclinical infection models. *J. Antimicrob Chemother.* 2005;56(2):365-371.
49. D'Ignazio J, Camere MA, Lewis DE, Jorgensen D, Breen JD. Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. *Antimicrob Agents Chemother.* 2005;49(10):4035-4041.
50. Drehobl MA, De Salvo MC, Lewis DE, Breen JD. Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest*. 2005;128(4):2230-2237.
51. Zervos M, Breen JD, Jorgensen DM, Goodrich JM. Novel, single-dose microsphere formulation of azithromycin versus levofloxacin for the treatment of acute exacerbation of chronic bronchitis. *Infect Dis Clin Pract.* 2005;13(3):115-121.
52. Martinez FJ. Acute exacerbation of chronic bronchitis: expanding short-course therapy. *Int J Antimicrob Agents*. 2005;26(suppl 3):S156-S163.

Add Local PI/SMPC here
(This page will not print)