**Doxycycline for Community-Acquired Pneumonia**

Sr—I read with interest the article by Johnson [1] suggesting a more prominent role for doxycycline in empiric therapy for community-acquired pneumonia (CAP). A response by Lederman et al. [2] described an in vitro susceptibility survey that compared tetracycline with doxycycline against bacterial pathogens causing CAP. The survey emphasized the relative lack of susceptibility of *Streptococcus pneumoniae* to doxycycline, potentially limiting its usefulness for empiric treatment of CAP.

Some key points about doxycycline were not included in either article. Lederman et al. [2] argue the doxycycline is not much better than tetracycline in terms of pneumococcal resistance. Although the susceptibility breakpoint against *S. pneumoniae* is the same for tetracycline and doxycycline (i.e., ≥2 μg/mL), the pharmacokinetics/pharmacodynamics of doxycycline are very different from those of tetracycline. Interpretation of susceptibility breakpoints should be based on achievable serum concentrations. Serum concentrations of ≥2 μg/mL are difficult to achieve with tetracycline (the peak serum concentration after a 500-mg dose is ~1.5 μg/mL) but are easily achieved with doxycycline (the peak serum concentration after a 100-mg intravenous or oral dose is ~4 μg/mL, and it is ~8 μg/mL after a 200-mg intravenous or oral dose).

It is not appreciated by many clinicians that doxycycline is 5 times more lipid-soluble than tetracycline and has a much longer half-life (8 h vs. 18–22 h). Accordingly, when doxycycline is used for treatment of CAP, dosing should be initiated using a loading regimen, either intravenously or orally, depending upon the severity of the pneumonia. Doxycycline, 200 mg iv or po q12h, rapidly achieves therapeutic concentrations in serum/lung, with a peak serum concentration of ~8 μg/mL. Without a loading regimen, optimal concentrations of doxycycline are achieved after 4–5 half-lives (i.e., ~5 days into therapy). This has led some physicians to conclude that doxycycline has failed early in the course of treatment, not appreciating that administration of the usual 100-mg intravenous or oral dose, without a loading regimen, results in suboptimal concentrations during the first 5 days of treatment. If a patient with CAP is ill enough to be hospitalized and doxycycline is selected, a loading regimen should be used [3, 4].

It is also not widely appreciated that the high dose of doxycycline (i.e., 200 mg iv or po q12h) demonstrates concentration-dependent killing kinetics. Doxycycline demonstrates concentration-dependent killing kinetics with the loading regimen, whereas, with 100 mg given intravenously or orally twice daily and without a loading regimen, doxycycline obyes time-dependent killing kinetics. Clinically, this means that clinicians treating moderate to severe infectious diseases for which doxycycline is indicated (e.g., empiric treatment of CAP), a loading regimen should be used to initiate therapy, to be assured of a rapid and optimal therapeutic response. A loading doxycycline regimen (200 mg iv or po q12h) results in a serum concentration of ~8 μg/mL, which is greater than the susceptibility breakpoint. This pharmacokinetic difference best explains why doxycycline is effective when tetracycline is not, even though the in vitro breakpoints against *S. pneumoniae* are the same. If achievable serum concentrations were used to define tetracycline-resistant pneumococci, there would be few strains found to be resistant to doxycycline [4–6].

Although the current concern is on penicillin-resistant pneumococci, doxycycline remains highly effective against ampicillin-susceptible/resistant strains of *Haemophilus influenzae*, as well as against β-lactamase-producing strains of *Moraxella catarrhalis*. In addition, although doxycycline is not as active as the respiratory quinolones against atypical pathogens (e.g., *Legionella* species, *Mycoplasma* species, and *Chlamydia pneumoniae*), it is nevertheless much more active than erythromycin.

In my experience, doxycycline monotherapy is inexpensive and reliable, because it provides excellent coverage against all of the atypical pathogens, as well as the common bacterial pathogens, including all but highly penicillin-resistant strains of *S. pneumoniae*. For most of the world and for areas of the United States where economic factors are the prime determinants of antibiotic selection, doxycycline provides an excellent alternative to more-expensive β-lactam/macrolide or respiratory quinolone empiric therapy for CAP [3, 4, 7].

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**References**