Treatment of pneumococcal pneumonia: What’s in an MIC?*

The idea that inappropriate or inadequate antimicrobial therapy of infection leads to excess morbidity and patient mortality is intuitive; however, the actual study of outcomes in patients who receive inappropriate antimicrobial therapy has been reported a surprisingly small number of times. The article by Dr. Lujan and colleagues (1) in this issue of Critical Care Medicine adds to this growing literature. In their study, 100 adult patients with bacteremic pneumococcal pneumonia were evaluated to examine the effect of discordant antimicrobial therapy—defined as a failure to provide the patient with at least one antimicrobial with in vitro activity against their clinical isolate within 24 hrs of their admission—on patient outcomes, specifically, 28-day mortality.

Similar to other studies of patients with bacteremic pneumococcal pneumonia (2–6), the mortality rate in the authors’ study population was considerable (16%). However, this study extends our current knowledge of the disease by demonstrating the effect of antimicrobial resistance and subsequent discordant antimicrobial therapy on patient outcomes. Specifically, receipt of discordant therapy as a result of infection with a resistant Streptococcus pneumoniae isolate resulted in a significantly higher chance of 28-day mortality (odds ratio = 27.3).

Whether penicillin resistance increases mortality in nonmeningeal pneumococcal disease has been an area of controversy. Studies demonstrating excess mortality in patients infected with resistant S. pneumoniae (7, 8) have been countered by balanced studies failing to find any evidence of excess mortality (3, 9–12). Many of these studies have limitations, including small sample sizes, a failure to differentiate between intermediate-level (minimal inhibitory concentration [MIC] = 0.12–1.0 µg/mL) and high-level (MIC ≥ 2 µg/mL) penicillin resistance, a failure to adjust for severity of illness and patient co-morbidities, and a failure to account for the type of empirical antimicrobial therapy patients received. By clearly delineating MIC cut points for susceptible, intermediate, and resistant S. pneumoniae isolates, using adjustment for patient co-morbidities, and clearly identifying specific antimicrobial regimens given to individual patients, Dr. Lujan and colleagues (1) go a long way in redressing limitations present in previous studies, although the small sample size of their study generates some uncertainty about the magnitude of their findings.

That said, a recently published study, which also took account of limitations present in older studies, reached opposite conclusions. Yu et al. (6) found that discordant antimicrobial therapy among 360 patients with bacteremic pneumococcal disease who received monotherapy was only associated with excess mortality when the isolate displayed high-level resistance (MIC ≥ 3 µg/mL) to cefuroxime. No excess mortality was seen when patients received discordant therapy with penicillins or ceftriaxone. Their findings were unchanged even when deaths within 3 days of initiating treatment were excluded from the analysis, which may not be preventable by even highly active therapy (13). As with the study by Dr. Lujan and colleagues (1), the numbers of patients receiving discordant therapy was small (n = 25), and one cannot rule out the possibility of a type II error.

Is there an explanation for this incongruence? Perhaps. It is well known that the dose and dosing interval of an antimicrobial have just as important an effect on the likelihood of clinical success of therapy as the MIC of the infecting organism. Specifically, for beta-lactam drugs, the likelihood of clinical success is maximized when the serum antimicrobial drug concentration is maintained above the infecting organism’s MIC for at least 40% to 50% of the dosing interval (14). Therefore, S. pneumoniae isolates with relative (MIC = 0.12–1.0 µg/mL) or even full penicillin resistance (MIC ≥ 2 µg/mL) may be successfully treated if large enough doses of penicillin are given in frequent enough dosing intervals (15). It is this phenomenon that likely explains the failure of previous studies to find outcome differences between patients infected with penicillin-resistant and penicillin-sensitive S. pneumoniae isolates and why the National Committee for Clinical Laboratory Standards have recently redefined nonmeningeal breakpoints for S. pneumoniae with various beta-lactam agents (16, 17). Under these new guidelines, amoxicillin and amoxicillin/clavulanate MIC breakpoints increased from ≤0.5, 1, and ≥2 µg/mL to ≤1, 2, and 4 µg/mL, respectively, and MIC breakpoints for ceftaxime/ceftriaxone increased from ≤0.5, 1, and ≥2 µg/mL to ≤1, 2, and ≥4 µg/mL, respectively. Raising the breakpoints effectively decreases the number of organisms resistant to the antibiotic. For example, using these new breakpoints, rates of amoxicillin and amoxicillin/clavulanate resistance among 329 S. pneumoniae isolates with high levels of resistance to penicillin (MIC ≥ 2 µg/mL) was only 29% in a recent study (18).

Close examination of the ten S. pneumoniae isolates from patients receiving discordant therapy in the study by Dr. Lujan and colleagues (1) finds that seven were highly resistant to aminopenicillins (ampicillin and amoxacillin; MIC ≥ 8 g/mL) and eight were resistant to macrolides (erythromycin, azithromycin, clarithromycin). It is interesting that eight of ten patients who received discordant therapy were treated with an aminopenicillin or ureidopenicillin (pipercillin, mezlocillin) in doses and intervals that had little chance of achieving serum levels above their infecting organism’s MIC for 40% or more of the dosing interval, which, as noted, has been suggested as the minimal amount of time for successful treatment of pneumococci (14, 19). Only two of 100 isolates examined in this study were resistant to third-generation cephalosporins based on 2002 National

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876

Crit Care Med 2004 Vol. 32, No. 3
Committee for Clinical Laboratory Standards guidelines; however, the ceftriaxone dose given to the individual patient deemed to have received discordant therapy (2 g/24 hrs rather than 1 g/24 hrs) likely resulted in a favorable pharmacokinetic/pharmacodynamic profile. A similar level of detail on individual antibiotic/MIC combinations was not provided in the study published by Yu et al. (6), making it impossible to predict the likelihood of therapeutic failure/success based on pharmacokinetic/pharmacodynamic variables.

What do the results of the study by Dr. Lujan and colleagues (1) mean for clinical practice? It is clear from this study and others that the risk of receiving discordant therapy is directly related to the likelihood of being infected with a resistant S. pneumoniae isolate. Multiple studies (6, 10, 12), including this one, have repeatedly demonstrated that patients who have significant co-morbidities, especially those with an underlying immunocompromised state, and those who have received previous antimicrobials are at the highest risk for infection with resistant S. pneumoniae. It comes as no surprise then that these are the same patients who are most likely to require hospitalization for treatment of their lower respiratory tract infection, which is one of the reasons that published guidelines recommend different empirical antimicrobial regimens depending on underlying patient risk factors and treatment location (20–23). Most of the subjects who received discordant therapy in the study by Dr. Lujan and colleagues (1) were treated with amoxicillin/clavulanate monotherapy at relatively low doses, perhaps explaining why this study, in contrast to others, found excess mortality associated with discordant therapy. The results of the study by Dr. Lujan and colleagues (1) suggest that using ceftazime or ceftriaxone (in combination with a macrolide or a fluoroquinolone) for empirical treatment of hospitalized patients with community-acquired pneumonia can reduce the likelihood of discordant therapy and ensure that appropriate pharmacokinetic/pharmacodynamic variables for clinical success are met, although there is no reason to believe that use of higher doses of aminopenicillins in empirical regimens or monotherapy with a respiratory fluoroquinolone would not have a similar effect.

The questions surrounding the apparent disconnect between in vitro antimicrobial resistance and clinical outcomes in patients with pneumococcal pneumonia is not simply answerable by looking at the MIC of the infecting organism. It is also important to take into account the dosage and the dosing interval of the drugs used in empiric regimens for treatment of community-acquired pneumonia. The study by Dr. Lujan and colleagues (1) is an advancement over previous studies in that it provides the reader with this information and gives us a model on which larger studies should be based. Namely, future studies should: 1) define concordance/disCORDance of antimicrobial therapy based on revised National Committee for Clinical Laboratory Standards criteria, 2) specific information on dosage of antimicrobials used to treat patients and the dosing intervals at which these drugs are given should be provided, and 3) adjustment for the presence of co-morbidities and severity of illness should be performed when assessing therapeutic effect on clinical outcomes. The results of this study and pharmacokinetic/pharmacodynamic work performed by others suggest that the use of aminopenicillins in currently accepted dosing regimens for the empiric treatment of community-acquired pneumonia should be approached with some caution in individuals at high risk for infection with highly resistant strains of S. pneumoniae. In these patients, increasing the dose of the aminopenicillin used or using a third-generation cephalosporin in its place should increase the likelihood of clinical success.

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REFERENCES
16. National Committee for Clinical Laboratory
Poor outcomes associated with low lipid and lipoprotein levels*

It has been >75 yrs since the association was made between low cholesterol levels and disease (1). Subsequently, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein (HDL) cholesterol have been shown to be substantially reduced in patients with many disorders, including infection (2), cancer (3), and critical illness (4). The severity of illness relates to the extent of reduction because lower lipoprotein concentrations have been found in patients with systemic inflammatory response syndrome (SIRS) compared with patients without SIRS (5).

There is also an awareness of the possible adverse effects of hypolipidemia (6). In observational studies, low cholesterol levels have been associated with enhanced mortality (7) and with the development of infectious disorders (8). Poor clinical outcomes have also been associated with low total or HDL cholesterol concentrations in patients with critical illness (9) or burn injury (10).

In the current issue of Critical Care Medicine, Dr. Chenaud and colleagues (11) present data in patients admitted to a surgical intensive care unit supporting a link between low apolipoprotein A-I concentrations and progression in SIRS criteria. From analysis of 63 subjects, they defined two groups (SIRS exacerbation and SIRS no exacerbation) based on whether progression in SIRS criteria occurred. They found apolipoprotein A-I and HDL cholesterol concentrations to be significantly lower in the SIRS exacerbation group. There were substantial quantitative differences between the SIRS exacerbation and nonexacerbation groups for C-reactive protein (66.9 vs. 9.5 ng/mL, respectively) and interleukin-6 (174 vs. 129 pg/mL, respectively). These differences were not statistically significant, probably due to the small number and heterogeneity of subjects. Blood levels of inflammatory mediators are important and bear on the mechanism for the low cholesterol, apolipoprotein, and lipoprotein concentrations. We have previously shown an inverse correlation between interleukin-6 and apolipoprotein A-I levels in patients in a surgical intensive care unit (9). Cytokines may be the connection between activity of disease and lipoprotein concentrations because cytokines help regulate apolipoprotein synthesis. Decreased synthesis of apolipoproteins has been demonstrated in hepatic cell lines exposed to tumor necrosis factor-a, interleukin-1B, and interleukin-6 (12), and lower lipid levels have been found in humans given cytokines parenterally (13, 14).

What is the importance of reduced apolipoprotein A-I concentrations in the intensive care unit setting? The authors demonstrate an inhibitory effect of patient serum on monocyte activation by T-cell membranes that correlated with the concentration of apolipoprotein A-I. Therefore, low apolipoprotein A-I levels might not suppress inflammatory responses to stimuli at a time when excessive cell activation is deleterious. This idea is supported by studies using this same in vitro system with apolipoprotein A-I isolated from normal human serum (15).

The known interaction of lipoproteins, especially HDL, with endotoxin (16) may also be contributing to the outcomes in this study. Of interest was the occurrence of a septic event in 5 of 29 subjects in the SIRS exacerbation group vs. no events in the 34 subjects in the no exacerbation group. HDL, the primary lipoprotein containing apolipoprotein A-I, has been effective in animal and human models for neutralizing endotoxin (17, 18). Kitchens et al. (19) demonstrated that HDL and other lipoproteins undergo changes during the acute phase that enhance endotoxin binding and neutralization, despite reduction in absolute lipoprotein levels. Nevertheless, more is likely better. Finally, how can all this information be applied to the treatment of acutely ill patients? It is reasonable to consider apolipoprotein A-I concentrations in assessing risk for progression in patients with critical illness. Ultimately, proof of the importance of apolipoprotein A-I, lipoproteins, or lipids in critically ill patients will depend on the ability to alter outcomes by increasing the concentration of the factor of interest. Recombinant apolipoprotein A-I Milano combined with phospholipid in a 1/1 ratio has been

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*See also p. 632.

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