At the Threshold: Defining Clinically Meaningful Resistance Thresholds for Antibiotic Choice in Community-Acquired Pneumonia

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(See the editorial commentary by Lee on pages 1139–41)

Background. Community-acquired pneumonia caused by Streptococcus pneumoniae is a major source of morbidity and mortality. Macrolide antibiotics are recommended as empirical first-line therapy for patients with community-acquired pneumonia. Guidelines suggest a 25% rate of high-level macrolide resistance in the community as the threshold beyond which macrolides should not be used. We evaluated the implications of this threshold for clinical failure rates.

Methods. We developed a theoretical model linking the prevalence of macrolide resistance to patient outcomes, based on the epidemiological concept of risk difference. We estimated the risk of clinical failure as a function of the likelihood and impact of discordant therapy and of the probability of clinical failure even in the presence of optimal therapy. The model was parameterized on the basis of the best available data derived from the published medical literature, and clinical failures were valued monetarily using an expected net benefit approach.

Results. Under the proposed 25% resistance threshold, the risk difference for such therapy would be 1.2% (95% credible interval, 0.5%–3.1%) for death, 1.6% (95% credible interval, 0.5%–3.2%) for bacteremia, and 3.3% (95% credible interval, 1.1%–5.7%) for prolonged clinical course; excess risks of death were valued at $10,000 per empirical treatment of community-acquired pneumonia and were further elevated in high-risk populations. Excluding low-level resistance resulted in a 4-fold underestimation of projected risks.

Conclusion. A 25% resistance threshold that fails to consider low-level resistance will result in high excess rates of morbidity and mortality because of discordant therapy. Whether projected failure rates are classified as unacceptable is an important health policy question, because risk of clinical failure needs to be weighed against other considerations.
apparent increase in risk of clinical failure that accompanies lower-level resistance (defined as an MIC of 1–8 \(\mu g/mL\)) [6].

The concept of a resistance treatment threshold is not new, and resistance thresholds beyond which alternative antibiotic choices should be made for empirical antimicrobial therapy have been proposed for lower urinary tract infections, tuberculosis, and gonorrhea [7–9]. However, few efforts have been made to rationalize such threshold recommendations or to explicitly link rates of antimicrobial resistance to clinical outcomes.

In this study, our primary objective was to develop a simple, flexible model that would explicitly link population antibiotic resistance prevalence to elevation of risk for individual patients. A secondary objective was to assess the impact on clinical failure associated with the exclusion of strains with low-level antibiotic resistance from current IDSA/ATS guidelines. Although the model was developed with CAP as a focus, it can be readily applied to the empirical treatment of any infectious disease that may be resistant to antimicrobial therapy.

**METHODS**

We developed a theoretical model for evaluating the impact of antimicrobial resistance on patient outcome, based on the epidemiological concept of risk difference (RD) [10]. In this model, the importance of an increased prevalence of resistance relates to the increased likelihood that an adverse outcome will occur if an individual with CAP receives empirical treatment with the antibiotic to which resistance exists, relative to treatment with an antibiotic to which no resistance (or less resistance) exists.

The RD for failure with empirical macrolide use for CAP is:

\[
RD = \Delta F \times \rho,
\]

where \(\Delta F\) is the absolute difference in probability of clinical failure with the use of macrolide therapy to treat an infection that is macrolide resistant, \(\rho\) is the proportion of CAP caused by \(S.\ pneumoniae\), and \(\rho\) is the prevalence of macrolide resistance in pneumococcal isolates. The absolute risk of failure is:

\[
F = F_o + \Delta F \times \rho,
\]

where \(F_o\) is the risk of clinical failure even in the presence of optimal antimicrobial therapy. The derivation of this model is presented in detail in Appendix A (online only).

Of course, it is possible that different levels of resistance might confer different levels of risk of adverse outcomes to individuals who are given discordant therapy. Consistent with the IDSA/ATS guidelines [5], we assumed in the base case that there was no excess risk of failure for strains with an MIC $<16\mu g/mL$. However, the best available data suggest a homogeneous increase in the risk of clinical failure for any MIC $\geq 1\mu g/mL$ [6]. Extension of the model to incorporate heterogeneity of resistance phenotypes is described in Appendix B (online only).

**Model Parameters**

The identification of plausible values and ranges for parameterization of the above model requires estimation of the likelihood that CAP is caused by \(S. pneumoniae\), but it also depends, in part, on the definition of clinical failure. We identified 3 types of failure that are clinically relevant and that can be measured in clinical trials and observational studies: death, bacteremia, and delayed resolution of symptoms. Parameter values, ranges, and references are presented in table 1 and are described in detail below.

**Relative frequency and significance of high- and low-level resistance.** Both the absolute prevalence of macrolide resistance and the proportion of isolates with high-level resistance (MIC, $\geq 16\mu g/mL$) or low-level resistance (MIC, 1–8 \(\mu g/mL\)) varies from population to population. We obtained data on the prevalence and composition of resistance by MIC from 3 distinct sources: (1) from a population-based cohort of individuals with invasive bacterial disease in Toronto, Canada [6], (2) from the Global Respiratory Antimicrobial Surveillance Project (GRASP) from 2003–2005 [4, 18], and (3) from 145 US centers participating in the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States (PROTEKT US) study for 2005–2006 [19].

Toronto data are derived from a laboratory-based surveillance system that identifies hospitalized individuals with invasive pneumococcal disease on the basis of bacterial isolation from a normally sterile site specimen. GRASP and PROTEKT US data are based on clinical pneumococcal isolates obtained from consecutive unique outpatients or hospitalized individuals within 48 h after hospital admission in participating centers in the United States (45 geographically diverse centers for GRASP and 135 for PROTEKT US) and Europe (47 centers in 15 countries for GRASP) [4, 18, 19]. Resistance data from all 3 sources were based on susceptibility testing using broth microdilution methods, as recommended by the Clinical and Laboratory Standards Institute [26].

The prevalence of resistance at any MIC in these databases varied from 14% (Toronto) to 36% (PROTEKT US); the proportion of resistant isolates with an MIC $\geq 16\mu g/mL$ varied from 33% (GRASP) to 65% (PROTEKT US). We varied the impact of low-level resistance by incorporating a relative risk of failure with low-level resistance into models; the relative risk varied from 1, when strains with low- and high-level resistance have identical effect, to \(F_o/(F_o + \Delta F)\), when low-level resistance confers no excess risk.
Proportion of CAP cases that are pneumococcal in origin ($\pi$). The impact of macrolide resistance on clinical failure in CAP is likely to result predominantly from resistance in *S. pneumoniae*, because the other leading CAP etiologies are susceptible to macrolide agents [11]. In a meta-analysis of CAP, Fine et al. [11] reported that *S. pneumoniae* was the causative pathogen in 63% of cases for which a microbiological etiology was available. Similar estimates have been obtained from studies involving bacteremic patients with CAP and fatal CAP cases [5]. In the majority of CAP episodes, the pathogen is never identified. We used the results of serological studies to provide a base case estimate of the proportion of CAP cases that are attributable to pneumococci (29%) [12], although invasive diagnostic methods suggest that the proportion may be as high as 67% [13].

Probability of clinical failure with discordant therapy ($F_b$). The Clinical and Laboratory Standards Institute [26] defines macrolide resistance by an erythromycin MIC ≥1 μg/mL, and this definition is supported by reports of clinical failure at MIC levels exceeding this threshold [6, 26, 27], with a constant increase in the degree of risk irrespective of the underlying resistance mechanism or the degree of elevation of the erythromycin MIC beyond ≥1 μg/mL [6]. In the pre-antibiotic era, CAP-related mortality rates ranged from 25% to 35% [20–21], and one-third of cases were complicated by bacteremia [20]. These estimates likely exceed expectations in the modern era, because antibiotics are only 1 aspect of medical care that was lacking before 1940. The pneumococcal polysaccharide vaccine has been shown to reduce the rate of invasive pneumococcal disease by ~45% without decreasing the overall rate of pneumococcal pneumonia [29, 30]. Applying this hazard ratio (0.55) to estimated clinical failure rates, using rates of vaccine coverage in high-risk individuals (~70%) [31], we can expect that, if patients received no antibiotic therapy, the maximum rates of bacteremia and mortality would be closer to 23% and 18%, respectively.

Probability of clinical failure with optimal therapy ($F_o$). Antibiotic resistance is not a necessary prerequisite for treatment failure, and failure can occur even in the setting of optimal antimicrobial therapy ($F_o$). For example, in the study by Daneman et al. [6], one-third of macrolide treatment failures involved macrolide-susceptible isolates. Fortunately, the overall mortality for antibiotic-treated ambulatory CAP is negligible (1%), and the rate of bacteremia is also low (1.4%) [2, 23]. However, a significant fraction (~5%) of patients will exhibit delayed resolution of symptoms and signs [32, 24]. Recent studies have elucidated that most clinical failures stem from host factors, including comorbid illness, with a minority of failures attributable to microbiologic factors [25, 33].

Simulations

We used the model and parameters described above to estimate the clinical failure rate that would be expected to result for a given prevalence of macrolide resistance in *S. pneumoniae*. For base case analyses, excess and absolute failure rates were calculated arithmetically by substituting base case values from table 1 into equations (1) and (2). The equations make the impact of increasing values for model parameters on failure rates predictable (i.e., predicted failure rates for a given prevalence of antibiotic resistance >0% will increase with an increase in any parameter value). However, we attempted to evaluate the clinical impact of uncertainty in parameter estimates on projected failure rates through probabilistic sensitivity analyses using Monte Carlo (random number–based) [34] simulations, with parameter values drawn from triangular distributions

Table 1. Input data for macrolide resistance threshold estimation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case estimate (range)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of CAP that is pneumococcal in origin ($\pi$)</td>
<td>29 (15–67)</td>
<td>[11–17]</td>
</tr>
<tr>
<td>Prevalence of macrolide resistance among <em>Streptococcus pneumoniae</em> isolates ($\rho$)</td>
<td>25 (14–36)</td>
<td>[4–6, 18, 19]</td>
</tr>
<tr>
<td>Proportion of macrolide-resistant isolates with MIC ≥16 μg/mL</td>
<td>50 (33–65)</td>
<td>[4–6, 18, 19]</td>
</tr>
<tr>
<td>Relative risk of clinical failure associated with low-level vs. high-level macrolide resistance*</td>
<td>0.06 (0.06–1)</td>
<td>[6]</td>
</tr>
<tr>
<td>Probability of clinical failure associated with discordant therapy ($F_b$), by type of clinical failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>18 (5–35)</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>33 (5–50)</td>
<td>[20]</td>
</tr>
<tr>
<td>Delayed resolution</td>
<td>50 (10–90)</td>
<td>[20]</td>
</tr>
<tr>
<td>Probability of clinical failure associated with optimal therapy ($F_o$), by type of clinical failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (0–2)</td>
<td>[2, 22]</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.4 (0–2)</td>
<td>[23, 22]</td>
</tr>
<tr>
<td>Delayed resolution</td>
<td>5 (2–10)</td>
<td>[24, 25]</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of isolates, unless otherwise indicated. CAP, community-acquired pneumonia.

* Relative risk of failure when no excess risk is associated with low-level macrolide resistance is equivalent to $F_o/F_b$. 

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Figure 1. Projected risk difference and absolute risks of clinical failure (death, bacteremia, and prolonged hospitalization) following empirical macrolide therapy for individuals with community-acquired pneumonia, assuming a prevalence of high-level macrolide resistance of 25% among Streptococcus pneumoniae isolates. Boxes represent model-based point estimates, and vertical lines denote 95% credible intervals derived from probabilistic simulations. In the probabilistic sensitivity analysis, we conducted simulations while simultaneously varying all of the parameters, including: the baseline failure rate (Fb), the optimal failure rate (FO), the proportion of community-acquired pneumonia cases that are pneumococcal in origin (\( \rho \)), the proportion of macrolide-resistant isolates with an MIC \( \leq 16 \mu g/mL \), and the relative risk of failure associated with low-level versus high-level macrolide resistance.

Figure 2. Projected relationship between pneumococcal macrolide resistance rates and excess risk of death, showing mortality risks associated with empirical macrolide therapy over a range of resistance-prevalence values. Thick solid line represents deterministic model-based estimates. Diagonal dashed lines represent 95% credible intervals for death. Vertical dashed lines indicate the prevalence of high-level resistance (HLR) and the prevalence of HLR and low-level resistance (LLR) combined in Toronto, Canada; in an international surveillance system (Global Respiratory Antimicrobial Surveillance Project [GRASP]); in a US-based surveillance system (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States [PROTEKT US]); and at the high-level resistance threshold proposed by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines [5]. If only HLR is relevant to clinical failure, projected risks of death with empirical macrolide therapy are those seen at the lower prevalence estimates; if LLR enhances the risk of failure, the 25% resistance threshold has already been exceeded in the GRASP and PROTEKT US networks. Subgroup analyses in populations with increased risk of clinical failure (because of age or comorbidity) demonstrated bounded by the plausible values presented in table 1. We also modeled the impact of increasing age and comorbidity based on the observation that the relative increase in probability of death with increasing age has changed little over the past 120 years (although the absolute risk of death due to CAP has decreased \( \sim 10 \)-fold) [20, 35].

The expected economic costs of clinical failure were estimated as the absolute excess risk of failure with empirical macrolide therapy, multiplied by failure-related costs, as described in detail in Appendix C (online only). For each failure end point, we performed 100,000 simulations with TreeAge Pro 2007 software (TreeAge). We estimated 95% credible intervals as intervals containing 95% of all simulation results for a given prevalence of resistance.

RESULTS

Base case estimates of the absolute and excess risks of clinical failure with use of a macrolide agent at the proposed IDSA/ATS threshold (\( \rho = 0.25 \)), under the assumption that only high-level macrolide resistance is clinically meaningful, are presented in figure 1. Upper and lower bounds represent 95% credible intervals generated through probabilistic sensitivity analyses, which include variation in the proportion and impact of low-level resistance. It is estimated that the RD for clinical failure is 1.2% (95% credible interval, 0.5%–3.1%) for death, 1.6% (95% credible interval, 0.5%–3.2%) for bacteremia, and 3.2% (95% credible interval, 1.1%–5.7%) for prolonged duration of illness. Absolute probabilities of failure are generated by adding baseline failure rates to RD estimates.

Using the model, it is also possible to predict ranges of absolute or excess failure probabilities for individual patients treated with macrolide antibiotics on the basis of local, regional, or national epidemiology and depending on whether excess risk is associated with only high-level resistance or with both high- and low-level resistance. The estimated excess risks of death associated with empirical macrolide treatment of CAP in a population with a high-level resistance prevalence of \( \geq 25\% \) and based on Toronto, GRASP, and PROTEKT US surveillance data are presented in figure 2. The higher the prevalence of resistant strains, the greater the risk associated with empirical macrolide therapy; none of these locales exceed the IDSA/ATS threshold based on high-level resistance alone, but if low-level resistance confers excess risk, then the 25% threshold has already been exceeded in the GRASP and PROTEKT US networks. Subgroup analyses in populations with increased risk of clinical failure (because of age or comorbidity) demonstrated
that the excess risk of clinical failure with empirical antimicrobial therapy was magnified in a linear fashion by increasing risk of clinical failure, and this risk was amplified further by increasing resistance prevalence (figure 3).

We explored the impact on projected clinical failure associated with uncertainty in other model parameters. The impact of uncertainty in the likelihood of \textit{S. pneumoniae} as the causative agent of CAP and the uncertainty in the impact of macrolide resistance on the likelihood of clinical failure are presented graphically in figure 4. It can be seen that, when either the probability of failure with discordant therapy or the likelihood of infection with \textit{S. pneumoniae} was low, variation in the other parameter had relatively little impact on probability of death. However, when either of these parameters was large, variation in the other parameter resulted in large changes in the likelihood of clinical failure. Qualitatively similar results were seen for bacteremia and prolonged clinical course as outcomes of interest (data not shown).

We explored the clinical impact of excluding low-level resistance from the IDSA/ATS guidelines in a series of 2-way sensitivity analyses (figure 5). It can be seen that, when either the effect or the prevalence of strains with low-level resistance is low, the exclusion of low-level resistance from the threshold results in little change in the projected impact of resistance on excess risk of death. However, when the effect of low-level resistance is significant and the prevalence of low-level resistance is high, the projected excess risk of death associated with empirical macrolide therapy increases by 4-fold.

Using cost estimates described in Appendix C (online only), we estimated that the hidden costs associated with a 1.2% absolute increase in risk of death at a 25% resistance prevalence threshold would have a value of $8000–$20,000, depending on the life expectancy of individuals conditional on not dying of pneumonia. By contrast, the hidden costs of a prolonged duration of illness were only $80 per treatment at a 25% resistance prevalence threshold.

**DISCUSSION**

Rising rates of macrolide resistance have been neglected by previous pneumonia treatment guidelines in Canada and the United States, which have listed macrolide antibiotics as a first-line option for outpatient therapy [2]. In contrast, European guidelines have relegated macrolide antibiotics to second-line treatments, to be reserved for cases of penicillin hypersensitivity in "countries with low pneumococcal macrolide resistance" [36, p. 1140]. We estimate that the quantitative resistance prevalence threshold of 25% in current IDSA/ATS guidelines, as a threshold for high-level resistance beyond which macrolides should not be used as empirical first-line therapy for CAP, endorses therapy-attributable mortality in \(~1\) of every 100 persons treated with empirical macrolide therapy. The excess risks associated with empirical outpatient treatment of older individuals and those associated with underlying medical comorbidities are likely to be even higher.

It has not been our intention to determine whether such failure rates are acceptable or unacceptable [37]. However, it is reasonable to note that equivalent or smaller absolute in-

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**Figure 3.** One-way sensitivity analysis of the changing risk of clinical failure (death) in the presence (F\textsubscript{a}) or absence (F\textsubscript{b}) of effective antimicrobial therapy. Curves assume that the relative risk (RR) in each of these parameters, because of increasing age or comorbidity, would be equivalent. Each curve represents a unique resistance prevalence (\(p\)). The proportion of cases of community-acquired pneumonia attributable to \textit{Streptococcus pneumoniae} is a constant (30%). Risk differences increase for both increasing RR and increasing \(p\).

**Figure 4.** Probabilistic sensitivity analysis of the probability of community-acquired pneumonia (CAP) due to \textit{Streptococcus pneumoniae} and risk of clinical failure (death) with discordant therapy. When either parameter is large, small changes in the other parameter result in a marked increase in excess risk (risk difference [RD]) of death. When \textit{S. pneumoniae} is assumed to be a relatively uncommon cause of CAP, changes in resistance prevalence are less influential.
versus high-level macrolide resistance.

The simple model presented here also highlights other factors that mediate the impact of antibiotic resistance prevalence on the likelihood of clinical failure. First, the overall contribution of *S. pneumoniae* to the community burden of CAP is a critical determinant of the impact of antibiotic resistance on clinical outcome. In nonpneumococcal CAP cases, there is, at present, little concern for discordant therapy with macrolide agents, and therefore, macrolide resistance is unlikely to influence clinical outcome.

Our descriptive model is subject to some limitations and would benefit from future research into the natural history of CAP and the impact of antimicrobial therapy. As Levins [40] has pointed out, models provide a simplified representation of complicated biological systems. This simplicity is both a strength and a weakness: simple models may exclude some of the complexity of the real world, but they provide a framework that allows insights and intuitions that might be obscured in real-world systems (or in excessively complicated models) [40]. Any model is necessarily constrained by the quality of data used, and the point estimates used in our formulas are derived from evidence of varying strength, although the framework presented here is sufficiently flexible that the model can be easily updated as better evidence becomes available. The credible intervals generated in probabilistic simulations serve as an index of the degree of uncertainty surrounding our model projections.

In general, our estimated baseline failure rates may be overestimates of true failure rates, in that the majority of prior research regarding CAP outcomes has focused on patients who require hospitalization or who present to the emergency department [11], and mortality rates from before the advent of antibiotics may be inflated by the lack of other aspects of modern medical care, including newer resuscitation and ventilation strategies. Similarly, rates of macrolide resistance may be overestimated by surveillance datasets that include only cases for which isolates are obtained (and in which, therefore, cases of invasive disease and drug-resistant strains are frequently over represented). Second, our model does not take into account the availability of alternative agents, the costs and toxicities of different antibiotic choices, and concerns regarding the potential downstream development of resistance to other agents (e.g., fluoroquinolones). These issues are critical features of guideline development, but they have been excluded from the current model to focus on the impact of antibiotic choices on the treatment outcome for the individual patient. Ethically, this should be the preeminent concern of the patient’s treating physician; logistically, we need to first consider the impact of drug resistance on individual failure rates before we can begin to discuss other external issues.

Figure 5. Probabilistic sensitivity analysis of the prevalence and risk associated with low-level macrolide resistance (MIC, 1–8 μg/mL). When low-level resistance is uncommon or the risk of clinical failure associated with low-level resistance is small, exclusion of low-level resistance from failure thresholds has little influence on projected clinical failure (death) risk. However, when isolates with low-level macrolide resistance are common and are associated with enhanced risk of clinical failure, exclusion of isolates with low-level macrolide resistance from the calculation of resistance thresholds leads to an underestimation of the risk of clinical failure. RR, relative risk of failure associated with low-level versus high-level macrolide resistance.
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