Asking the Right Questions: Morbidity, Mortality, and Measuring What’s Important in Unbiased Evaluations of Antimicrobials

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(See the Major Article by Prasad et al, on pages 1699–709.)

In this issue of Clinical Infectious Diseases, Prasad et al present a meta-analysis of 13 randomized trials comparing outcomes of tigecycline with control antimicrobials [1]. Their results show an absolute mortality increase of 0.7% (95% confidence interval [CI], 1–1.2) with tigecycline, translating into 1 excess death for every 143 patients treated (95% CI, 83–1000). The estimates of increased mortality were consistent across diseases, with greater mortality in the more serious and life-threatening diseases. An evaluation of noncure showed evidence of greater lack of effectiveness with tigecycline, with an absolute difference of 2.9% (95% CI, 0.6–5.2). This translates into 1 person experiencing noncure for every 34 patients treated (95% CI, 19–166). Although these data hint at lack of effectiveness as the cause for increased mortality, it is not possible to rule out unknown toxicity of tigecycline contributing to both lack of effectiveness and increased mortality.

The authors’ conclusions are similar to a US Food and Drug Administration (FDA) evaluation in a public health warning [2]. The authors’ methods are thorough and include more information than previously published meta-analyses [3–5]. Because these trials are randomized with similar designs and outcome measures one can causally ascribe the increased mortality to tigecycline and not to other confounding factors.

These results have implications for both clinical practice and for the methodology of antimicrobial studies, evaluations by regulatory agencies, and marketing by pharmaceutical companies.

The results have clinical significance, because any increase in mortality is clinically important. The numbers needed to harm show that a substantial number of patients could be harmed, especially in common, serious diseases in which lack of effectiveness can result in death. Clinical trials in infectious diseases are primarily designed as noninferiority trials in which the goal is to rule out the new drug may be as much as 10%–15% less effective than older agents [6]. The outcome measure is usually clinical response, which is a composite of mortality, signs, and symptoms, usually measured weeks after randomization. Therefore, individual trials have insufficient sample size to detect differences in mortality or clinical response in the range of those in this meta-analysis. This increases the importance of evaluating integrated summaries of safety and effectiveness at the time of initial drug review, as well as continuing to evaluate drug over the entire life cycle after approval.

The implications for clinical practice are for clinicians to carefully consider when to administer tigecycline. Should the drug be reserved for seriously ill patients with disease due to resistant pathogens that are susceptible to tigecycline? Unfortunately, patients and clinicians are left with little direct evidence from controlled trials in the settings where the drug is needed most. Tigecycline was developed in part because of in vitro activity against drug-resistant pathogens [7]. However, were these trials designed to answer the most important questions? Tigecycline was not studied to show superiority to other drugs on outcomes important to patients in disease due to drug-resistant pathogens. The drug was evaluated in noninferiority studies in patients with disease due to susceptible pathogens. These studies are useful in proof of principle that tigecycline has effectiveness or safety signals in general in the diseases under study.

Clinicians often must extrapolate from clinical trials in disease due to susceptible pathogens, combined with evidence of “adequate” in vitro minimum inhibitory
concentrations and animal studies of drug-resistant pathogens. However, recent evidence shows that patient factors are at least as important, if not more important, in affecting outcomes in patients with infection due to drug-resistant pathogens [8, 9]. In addition, minimum inhibitory concentrations and animal models are not as predictive of drug effectiveness as is widely believed. Nonrandomized assessments of pharmacodynamic analyses also may be biased by differences in baseline patient variables. Patients with lower concentrations of drug may also be more severely ill at baseline and more likely to have adverse outcomes independent of drug concentrations [10]. Although preclinical evaluations and pharmacodynamic data are necessary components in the early evaluation of drugs, they are not substitutes for evidence from clinical trials in patients. An evaluation of antimicrobial approvals since 1960 showed that about one-quarter of anti-infective drugs obtain regulatory approval despite 100% of these drugs having promising in vitro activity and animal models [11]. Thus, the Bayesian prior probability that in vitro activity and animal models predict effectiveness and safety in human disease is low. This principle is reinforced from recent clinical trials. Daptomycin failed to demonstrate noninferiority in pneumonia [12]. A clinical trial of doripenem in ventilator-associated pneumonia was terminated early because of increased mortality, confirming earlier data showing increased mortality in hospital-acquired pneumonia [13].

The issue is that patients who are infected with drug-resistant pathogens are inherently different from those with susceptible pathogens. Therefore, both the natural history of disease and treatment effects between drugs may be different in these patients [14]. These differences in patient factors must be accounted for in observational studies [15]. Randomization gives equal probability of distributing baseline patient factors between groups, thereby minimizing selection bias. Although it is tempting to assume that tigecycline would be better than nothing in the treatment of disease due to drug-resistant pathogens, this hypothesis has not been directly evaluated. Of concern is that the treatment effects between drugs shows worse outcomes for tigecycline and doripenem in the sickest patients with infection due to susceptible pathogens. This would also raise concern regarding the effectiveness of the drugs in more serious illness due to drug-resistant pathogens. It is not known whether the mechanism of increased morbidity and mortality is lack of effectiveness or increased toxicity (or both); therefore, combining these drugs with another drug with in vitro activity may not mitigate the risk.

Because of this lack of evidence, it is not surprising that approximately half of recommendations in treatment guidelines are based on opinion or case series [16, 17]. Therefore, it is important to gain information on drugs in the treatment of disease due to drug-resistant pathogens from appropriately designed trials that include sufficient numbers of patients with disease due to drug-resistant pathogens to draw confirmatory conclusions, either before or after initial approval [18].

The results of this meta-analysis raise issues in clinical research and regulatory review of antimicrobials. There has been much discussion regarding treatment of disease due to drug-resistant pathogens, including preservation of currently available drugs and attempts to stimulate new antimicrobial development. Some have suggested stimulating development by changing the regulatory approval criteria for antimicrobials to make it easier for drug sponsors to obtain approvals for disease due to drug-resistant pathogens.

However, if public dollars are used to incentivize development, the public should gain useful information in return. Several suggestions provide incentives for information that is already available. For instance, some claim that animal models, in vitro activity, and pharmacodynamics modeling are closely linked to outcomes in patients and, therefore, should be the basis for approval of drugs for disease due to drug-resistant pathogens. However, the data from this meta-analysis and the lack of predictive ability of these kinds of data would argue against this proposal. Clinicians already must make decisions based on this information, not because it is optimal, but because it is all they have. In addition, some favor organism-based approvals rather than disease-specific approvals. This would mean that drugs would be approved for Staphylococcus aureus infection instead of “disease X” due to S. aureus. Such claims are misleading, because drugs will not have been studied in all diseases due to S. aureus and would imply safety and effectiveness of the drug without evidence. The failure of daptomycin and doripenem in respiratory tract indications, while showing effectiveness in other diseases, argues against such broad approvals.

The current designs of noninferiority trials contain biases that make it more difficult to detect differences between drugs when such differences exist. The data on tigecycline, daptomycin, and doripenem are examples of clinically important differences between drugs. Therefore, the idea that all antimicrobials are equally effective and that is impossible to show superiority of one agent to another are not supported by these data. Second, the inability to evaluate mortality in current trials is not because there is no mortality to measure. Instead, patients enrolled in trials are chosen to represent a less severely ill population. However, if the drug is to be used in more severely ill patients, then it should be studied in this population, rather than determining important differences between drugs after approval. Administration of antimicrobials before randomization and enrollment of patients who may not have
the disease under study can bias trials toward showing no difference. Better diagnostics will aid in addressing these issues. Finally, there are issues related to the outcome measures used in antimicrobial trials. These definitions have been based on nonstandardized assessments of a composite of signs that are surrogate end points and symptoms that are not clearly defined and left for individual investigators to decide [19, 20]. These end points are neither well-defined nor reliable, and inclusion of surrogate end points in the composite may not reflect effects on outcomes of primary importance to patients, such as symptoms and ability to function in their daily lives. Misclassification bias may result in inaccurate measurements of differences between drugs. Ability to show differences on an end point does not validate that end point if what is measured is not well defined and reliable [21, 22]. Mortality is always an important outcome in serious and life-threatening diseases and is the only outcome in some diseases, such as hospital-acquired pneumonia, for which noninferiority hypotheses can be based [23, 24].

Finally, the historical evidence on antimicrobials shows that, in some diseases, the treatment effect occurs early during the course of the intervention. More patients recover the longer one waits to evaluate outcomes; however, these outcomes are not to the result of drug effect but the natural history of the disease. Therefore, waiting weeks to evaluate a treatment effect that occurs in the first few days also dilutes differences between drugs. Carrying observations forward in time does not obviate these issues, especially when there is no predefined hypothesis for investigators to evaluate outcomes earlier in the course of treatment in a standardized way. Evaluation of differences between drugs at a later time point tested in a superiority hypothesis can still be performed; however there is little evidence in diseases, such as pneumonia and skin infections, on which to base a noninferiority hypothesis of treatment effect. The utility of later evaluations is based on the natural history of the disease under study in terms of the likelihood of relapse and evidence of later treatment effects from prior studies. The natural history of adequately treated pneumonia shows that few patients fail to experience sustained cure after initial response. In contrast, in diseases such as *Clostridium difficile*-associated diarrhea, drugs may be similar in effects early and differ on sustained cure at later times. The FDA, in collaboration with the Foundation for the National Institutes of Health, has begun the task of developing evidence-based, well-defined, and reliable outcome measures for antimicrobial trials based on patient and clinician input [25].

Some have argued that designing trials appropriately is not feasible. However, it is neither feasible nor ethical to design studies that cannot provide generalizable knowledge to address their primary research questions because of serious flaws in their design [26]. The issue is not to make trials perfect. In fact, federal law and legal precedent outline that these issues of appropriate trial design are a minimal standard for drug approval, which when not met, cannot provide adequate evidence regarding drug effects [27].

The data from Prasad et al show the importance of overall evaluations of antimicrobials and that, even after approval, we must continue to evaluate the evidence on drugs in their particular context of use. Clinicians and patients need not just new options but options on which there is sufficient evidence to make informed decisions to maximize the best outcomes for patients.

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