Antibiotic Resistance: Who Will Pay the Bills?

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(See the article by Roberts et al, on pages 1175–84.)

The rapid emergence of antimicrobial resistance among bacteria is a public health crisis. Infections with antimicrobial-resistant bacteria increase patient morbidity and mortality and greatly increase the cost of medical care [1–4]. The number of resistant bacteria and the diversity of molecular mechanisms of resistance have increased sharply in recent years [5, 6], but the development of newer, effective antimicrobials has not kept pace [7].

Professional and government organizations have trumpeted this growing problem. In 2004, the Infectious Diseases Society of America (IDSA) released its report, “Bad Bugs, No Drugs: as Antibiotic Discovery Stagnates, A Public Health Crisis Brews” [7]. The National Institute of Allergy and Infectious Diseases recently called for research to expand our understanding of how to treat acute infectious diseases while minimizing the emergence of resistance among bacteria that colonize the skin or mucous membranes or that are resident in our environment [8]. A recent editorial published in the pages of this journal, “The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community” [9], urged the medical community to lead a concerted grassroots effort to address the antimicrobial resistance crisis. Finally, the US Congress introduced legislation, the Strategies to Address Antimicrobial Resistance (STAAR) Act, that seeks to stem the emergence of infections due to resistant organisms through expanded federal funding of surveillance programs, prevention and control initiatives, and research efforts. A goal shared by all parties is the expansion of effective, evidence-based strategies that can reduce the burden of antimicrobial resistance.

The IDSA has proposed guidelines for developing institutional antimicrobial stewardship programs [10]. Given both the frequency of inappropriate antimicrobial use and the association between antimicrobial use and the emergence of resistance, antimicrobial stewardship programs may help reduce the selective pressure responsible for the emergence and propagation of antimicrobial-resistant pathogens. However, implementation of antimicrobial stewardship programs requires support from hospital leadership, including significant initial financial investments. Although studies support the safety, effectiveness, and financial benefits of such programs, important questions remain unanswered. First, it is often difficult to precisely quantify patient outcomes that are attributable to antimicrobial-resistant infection (ARI). In addition, robust measurement of the impact of introduction of an institutional antimicrobial stewardship program on both patient outcomes and direct medical costs will likely require either a large, multicenter, cluster-randomized trial or, if performed at a single institution, a quasi-experimental design and analysis, which is fraught with methodological limitations.

In this issue of the Clinical Infectious Diseases, Roberts et al [11] answer the first of these challenges. This well-conducted epidemiologic study estimated the impact of ARI at a large, urban public teaching hospital. The investigators found that ARIs are associated with an attributable mortality rate of 6.5% and that patients with ARI are twice as likely to die than are noninfected patients. Length of stay increased by a mean of 11 days, and the cost attributable to an ARI ranged from $18,588 and $21,208 per episode. Conservatively estimated, the combined hospital and societal cost, including medical care and loss of productivity, for 188 patients with ARI was a staggering $13.35 million.

In addition to addressing an issue of paramount importance, the investigators should be applauded for their rigorous methodological approach to combat the issues that often complicate the measurement of outcomes associated with antimicrobial resistance in observational studies. Observational studies attempt to es-
timate the effects of an exposure (in this case, antimicrobial resistance) by comparing outcomes (eg, mortality, length of stay, and hospital cost) between exposed and unexposed subjects, while accounting for the nonrandom distribution of the exposure of interest. Without random assignment, exposed and unexposed groups may differ in a myriad of ways, rendering observed differences in outcomes attributable not to the effects of the exposure of interest but, rather, to the confounding influence of differences between the exposed and unexposed populations. One of the most important confounders in studies that examine the outcomes of antimicrobial resistance is severity of illness. For example, sicker patients are more likely to develop ARIs and, to have bad outcomes (eg, death or a prolonged hospital stay) independent of any potential relationship between antimicrobial resistance and these adverse outcomes. Roberts et al [11] used several different techniques to address the important issue of confounding due to severity of underlying illness. By constructing a propensity score to compute the predicted probability of an infection due to a resistant organism for all patients in the cohort, Roberts and colleagues matched patients with the same risk of developing ARI (those with similar characteristics, including multiple measures of severity of illness) and compared outcomes between patients who did and those who did not develop an ARI. Although this analytic method is often an effective tool for dealing with confounding, such adjustment retains the fundamental limitations of more traditional multivariable regression; propensity analyses can only account for measured factors, and therefore, residual confounding may remain. Reassuringly, however, the authors found similar results when they used other analytic methods to adjust for confounding.

Despite the analytic rigor of this study, its limitations must be considered. First, the control group used in this study consisted of patients without infection. The majority of previous studies that addressed the impact of ARI have used patients infected with the susceptible strain of the same organism as the ARI as the comparator group. The comparison made by Roberts et al [11] assesses whether having an ARI is worse than no infection. Although this is an important comparator group, the comparison may result in a much higher estimates for the outcomes attributed to resistance than derived when compared with infections due to nonresistant organisms. Also, previously validated measures of severity of illness are potentially less appropriate in the study of nosocomial infections. For example, Acute Physiology and Chronic Health Evaluation (APACHE) scores measured at admission may not accurately predict severity of illness immediately before the onset of a nosocomial ARI. Similarly, it is essential to consider the potential relationship between length of stay prior to the onset of infection to length of stay after the ARI when assessing whether ARI is associated with prolonged attributable length of stay. Obviously, there is a direct correlation between length of stay prior to infection and overall length of stay, mortality, and cost. On a minor note, reporting the point estimate (odds ratio) of the total cost of ARI would have produced a more generalizable estimate of the financial impact of ARI, because absolute values of costs may not be applicable outside the institution in which they were collected or in countries outside the United States.

Despite the potential limitations, the findings of Roberts et al [11] are significant, making a strong case for both the medical and financial benefits of reducing antimicrobial resistance. This is an important and timely question, considering the national focus on the prevention of health care–acquired infections, a significant proportion of which are caused by antimicrobial-resistant organisms, and the call for institutions to develop antimicrobial stewardship programs. These data should help inform decisions regarding the structure and implementation of health care initiatives designed to improve patient care while controlling unnecessary costs, paving the way for studies designed to identify the most effective interventions to achieve this lofty goal.

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References