

The Impact of Antimicrobial Resistance on Health and Economic Outcomes

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Despite an increasing prevalence of antimicrobial-resistant pathogens, the health and economic impact of colonization and infection with these organisms has not been fully elucidated. We explore how antimicrobial resistance can affect patient outcomes by enhancing virulence, causing a delay in the administration of appropriate therapy, and limiting available therapy. Next, we examine the different perspectives held by hospitals, third-party payers, patients, and society on the impact of resistance. Finally, we review methodological issues in designing and assessing studies that address the clinical outcomes for patients infected or colonized with resistant pathogens, including adjustment for important confounding variables, control group selection, and the quantification of economic outcomes.

Although the problem of antimicrobial resistance has attracted the attention of both the medical community and the general public, the magnitude of the impact of resistance on health and economic outcomes remains largely unknown. Rates of antimicrobial resistance among hospital and community pathogens have increased considerably during the past decade [1]. Relatively few resources have been allocated to understand, prevent, and control the spread of resistance on global, national, and local levels. Moreover, because each clinician's perspective is focused primarily on individual patients and, to a lesser degree, public health, attention to the issues that affect the spread of resistance often is not a part of clinical decision-making. The goal of the present article is to provide a framework for reading and interpreting studies that examine the clinical outcomes for patients infected with antimicrobial-resistant pathogens (table 1). First, we discuss the reasons that antimicrobial resistance affects outcomes and the different perspectives of the impact of resistance on patients, hospitals, and society. Second, we address methodological issues in designing studies that quantify the impact of antimicrobial resistance.

Assessing the implications of increasing prevalences of antimicrobial resistant pathogens is important for several reasons. First, information about resistance may be important in defining the prognosis for the individual patient with infection. Second, knowledge about the outcome of infections with resistant organisms gives physicians and hospitals an impetus to use good infection and antibiotic controls to prevent such infections. Finally, understanding the effect of antibiotic resistance on patient outcomes is relevant for policymakers, who must make decisions about funding of programs to track and prevent the spread of antimicrobial-resistant organisms.

ANTIMICROBIAL RESISTANCE AND CLINICAL OUTCOMES

Antimicrobial-resistant pathogens affect patient outcomes in different ways. Resistance genes can alter the fitness of a bacterial pathogen, making it more or less virulent; the presence of resistance in a bacterial pathogen can lead to a delay in the administration of appropriate antimicrobial therapy; and the antimicrobial therapies required to treat resistant pathogens can be toxic or inadequate.

The effect of resistance on microbiological fitness. The relationship between antimicrobial resistance and microbiological fitness differs depending on the organism, type of antibiotic therapy, and mechanism of resistance [2]. In most cases, when

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Table 1. Points to consider when reading antimicrobial resistance outcome studies.

Type of outcome examined	
Mortality	In-hospital only In-hospital and after discharge All-cause Attributable to infection
Morbidity	Length of stay Intensive care unit admission Need for surgery or other procedures Activity level at discharge Loss of functional time (missed work and activities)
Economic	Hospital cost Hospital charges Resource utilization Health care costs
Perspective of study	
Hospital	Hospital morbidity, mortality, and cost
Third-party payer	In- and out-of-hospital health care costs
Patient	Decreased functional status, loss of work, and decreased availability of antibiotic therapy
Society	Total health care costs and loss of classes of antibiotics
Comparison group	
Not infected	Interpret as impact of added infection
Infected with susceptible strain	Interpret as impact of resistance
Colonized with resistant strain	Interpret as the impact of progressing from colonization to infection
Factors that improve quality	Adjustment for variables, including length of stay, severity of illness, and comorbidities before infection

mutations leading to resistance are associated with reduced fitness, compensatory mutations that result in regained fitness arise [3]. Resistant strains seen in the clinical setting are largely those that are able to both survive and effectively spread in high-density antibiotic environments, such as health care facilities and day care centers; thus, they are well-adapted organisms and are usually fitter than a random selection of strains belonging to the same species. However, to date, no studies have demonstrated a correlation between increased fitness in organisms with resistance mutations and adverse clinical outcomes.

The effect of resistance on antimicrobial therapy. Several studies have demonstrated that resistance frequently leads to a delay in the administration of microbiologically effective therapy, which may be associated with adverse outcomes [4–6]. A mismatch between the empirical therapeutic agent and subsequent susceptibility results for a particular organism is one of the most significant factors that delays effective therapy. For example, Lautenbach et al. [6] demonstrated that patients with extended-spectrum β -lactamase (ESBL)–producing *Klebsiella pneumoniae* and *Escherichia coli* infections were treated with

effective antibiotics a median of 72 h after infection was suspected; matched control subjects infected with non-ESBL-producing strains of *K. pneumoniae* and *E. coli* received appropriate antibiotics a median of 11.5 h after infection was suspected. Patients infected with ESBL-producing strains also had significantly longer hospitalizations and greater hospital charges than control subjects. In addition, the emergence of resistance during therapy (which arises almost invariably to the agent listed) has also been shown to affect outcomes negatively and significantly [7, 8].

Infections caused by antimicrobial-resistant organisms also may require more toxic therapy that can lead to adverse outcomes. The use of colistin for highly resistant *Pseudomonas* or *Acinetobacter* infections is associated with a high risk of renal dysfunction [9]. In addition, some agents used to treat the resistant strain of an organism are less effective than the agents used to treat the susceptible strain of the organism—for example, vancomycin for the treatment of deep-seated methicillin-resistant *Staphylococcus aureus* (MRSA) infections [10]. Finally, patients infected with organisms that are resistant to all available antimicrobials often require surgical procedures to remove the nidus

of infection; patients with infections that are not amenable to surgical debridement have high mortality rates [11].

DIFFERENT PERSPECTIVES OF THE IMPACT OF ANTIMICROBIAL RESISTANCE

The impact of antimicrobial resistance can be assessed from the perspective of the hospital, a third-party payer, the patient, and society [12]. Studies that examine one perspective can underestimate the full effect of antimicrobial resistance; therefore, it is important to recognize the perspective of a study to appropriately interpret its results.

Hospital perspective. The hospital perspective of the impact of resistance has been studied the most often. Data about in-hospital morbidity, mortality, and the costs associated with antimicrobial resistance are relatively easy to retrieve, and hospitals are most likely to implement changes in response to information assessed at the hospital level. A number of studies published recently have evaluated the impact of antibiotic resistance through the assessment of in-hospital mortality rates and the length of hospitalization. Fewer studies have examined economic outcomes. The majority of published studies have shown an association between antibiotic resistance and adverse outcomes on the order of a 1.3–2-fold increase in mortality, morbidity, and cost for patients with resistant versus susceptible infections [7, 8, 13–15].

It is important to recognize that the hospital perspective of the impact of antimicrobial resistance provides a limited view of the health care impact of resistance because significant portions of clinical care are now provided in rehabilitation facilities, in nursing homes, and at home. Limited data exist regarding costs at these sites because the sources of such information—third-party payers—are protective of data that they collect, and linking claims data with microbiology results without breaching patient confidentiality is difficult.

Patient perspective. Measurements of mortality and length of hospitalization measure the short-term direct effect of resistance on the affected patient. However, indirect and long-term consequences of resistant infections may have important implications. For example, a patient with a history of MRSA infection who presents with a new fever is usually placed in isolation and empirically treated with vancomycin, even though he or she may not have MRSA infection. Other patient-level outcomes that need further elucidation include the long-term effects of having a resistant infection on future health, the loss of work and family time associated with increased hospitalization time and subsequent recovery, and even the emotional impact of having a resistant infection.

Antimicrobial resistance also has an effect on patients who have not had an infection with a resistant organism. Because of increasing rates of resistance among common pathogens,

broader-spectrum agents are now required for the empirical therapy of many common bacterial infections. These agents are usually more expensive, have more deleterious effects on protective microflora, and, occasionally, are more toxic or less effective. For example, third-generation cephalosporins or fluoroquinolones are recommended for the treatment of hospitalized patients with community-acquired pneumonia, exemplifying the loss of use of narrow-spectrum agents, such as penicillin, for the treatment of common diseases when rates of resistance at the population level reach a certain threshold.

Societal perspective. The current understanding of the impact of antimicrobial resistance on society as a whole is limited. The Office of Technology Assessment estimated that the national cost of antibiotic resistance in the United States was \$4 billion per year in 1995 dollars [16]; however, this assessment took into account only directly affected patients and not other ramifications of resistance, which would likely increase the estimate by several-fold. Further study of the impact of resistance beyond the patient and hospital levels will be essential to guide decision-makers.

METHODOLOGICAL ISSUES IN MEASURING THE IMPACT OF RESISTANCE

Controlling for length of stay (LOS). An important issue in the design of studies that examine the outcomes of antimicrobial resistance is the appropriate adjustment for differences in hospital LOS before the onset of infection in patients with resistant infections and in the comparison group. There is a direct correlation of hospital LOS before the event and the cost, future LOS, and mortality. This can be accomplished by matching case and control patients on the basis of LOS before infection or by including this variable in a multivariate analysis. In addition, and care must be taken to control for preinfection illness severity and comorbidities.

Selection of the control group. Studies that address the outcomes of antibiotic resistance can be designed in different ways. The majority of studies to date have compared outcomes in patients infected with the resistant strain of an organism with patients infected with the susceptible strain of the same organism. This design assesses the independent impact of the acquisition of a resistance determinant—for example, the comparison of outcomes among patients with central line infections caused by MRSA compared with the outcomes among those who have methicillin-susceptible *S. aureus* infection. Other studies have compared outcomes among patients infected with a resistant organism with outcomes among uninfected control subjects selected on the basis of specific criteria. This comparison assesses the burden of having a resistant infection rather than no infection (e.g., the measurement of the consequences of developing a surgical site infection caused by MRSA that

prophylaxis with cefazolin did not prevent). The latter type of comparison results in a much higher estimate of adverse events attributable to resistance. For example, Engemann et al. [17] demonstrated that the median hospital charge for patients with MRSA surgical site infections (\$92,363) is significantly higher than the median hospital charge for those with methicillin-susceptible *S. aureus* surgical site infections (\$52,791) and that patients with either type of infection have a significantly higher median charge than do patients without infection (\$29,455).

Adjustment for severity of illness. In studies assessing the impact of antimicrobial resistance, adjustment for underlying illness severity and comorbidities is essential, because patients with resistant infection often have more-severe underlying diseases that can independently result in adverse outcomes. Various methods have been proposed and used to grade illness severity, including subjective scores, intensive care unit (ICU) data-driven measures, administrative severity scores, and measurements of active comorbidities. However, there is currently no well-validated illness severity score for infectious disease outcomes.

McCabe and Jackson [18] used a simple 3-category score to predict mortality in patients with bacteremia due to gram-negative organisms. This scoring system is widely used but is subjective and is based completely on the judgement of the individual reviewing the patient record. No objective physiological data are included, which limits its generalizability from study to study. From our experience, this system works well as predictor of mortality but not as a predictor of morbidity and cost.

Other scores that have been proposed also have significant limitations. The APACHE score relies heavily on physiological parameters, the majority of which are collected only in ICU settings, and it has only been validated to predict mortality for patients in ICUs [19]. Scoring systems such as the Medical Illness Severity Grouping System admission severity group score and the All-Patient Refined Diagnosis Related Groups [20], which were developed for administrative purposes, for risk adjustment, have questionable utility in predicting infectious-disease outcomes and need further evaluation. Other surrogate markers for the severity of illness include measuring the number of comorbidities that patients have before infection, the number and type of invasive devices at time of inclusion, the number of cultures done, and whether the patient was admitted to the ICU before infection.

Timing of the onset of infection. Most studies consider the time of the first positive culture result to be representative of the onset of the infection. This may underestimate the true impact of resistance, because positive culture results are often obtained either several hours after the infection starts or after therapy has failed, such as in the management of refractory urinary tract infections. Outcomes are also more likely to be

affected by the delay when the infection is severe or when the patient is critically ill or immunocompromised.

Timing of the measurement of the severity of the underlying illness. An often overlooked issue in the accurate assessment of underlying disease severity is the importance of the timing of the assessment of illness severity. Illness severity is strongly influenced by the presence of infection and, therefore, may represent an intermediate variable in the chain of events between exposure (i.e., the infection) and the outcome of interest, if it is assessed when the patient is actively infected. Because adjustment for an intermediate variable usually causes an underestimation of the effect of the exposure of interest on the outcome [21], care must be taken to assess the severity of illness >48 h before the first signs of infection. Results of studies that assign the illness severity score at the time of the infection should be interpreted with caution, because they may underestimate the magnitude of the effect that resistance has on outcomes [22].

Defining mortality and morbidity. Mortality is relatively easy to define, although it is important to distinguish between all-cause mortality and disease-specific mortality, as well as in-hospital and postdischarge mortality. Morbidity is harder to define; therefore, markers for morbidity are used, such as hospital LOS, need for surgery or admission to the ICU, cost, and functional status at discharge. The latter can be expressed as discharge to a nursing home or intermediate- or long-term care facilities.

Assessing the economic burden of antimicrobial resistance. Three approaches to evaluating the economic burden of resistance in the hospital can be used: measurement of hospital costs, hospital charges, and resources used. Hospital costs include operating costs, as well as the cost of drugs, tests, and other patient care activities [23]. A hospital must ensure that its costs are reimbursed; therefore, it assigns fees to hospital resources that are seen on a patient's bill as charges. Larger insurance companies, Medicare, and Medicaid will not pay the amount on the bill because they receive discounts; therefore, the charge on the bill for all patients is greater than the actual hospital costs, to cover these "losses" [24]. Hospital costs can be a useful outcome measure for an individual hospital because they best reflect the actual economic burden of the hospital; however, they can be difficult to retrieve. In contrast, hospital charges are less reflective of actual cost but are usually easy to retrieve from administrative databases and are consistent from patient to patient in most settings. They tend to be an overestimation of the actual cost, although adjustment using ratios of cost to charge can be done [25]. Resource utilization more specifically assesses what services or procedures are used by a patient. However, for comparative purposes, the use of resources must be translated into monetary values. All of these economic measures of health care are not necessarily set by a

market-based pricing system. The costs of care for a specific patient are artificial and arbitrary computations that may vary between sites and at different time periods.

Hospitals may use different ways to limit costs based on their method of reimbursement. For example, if reimbursement occurs per diem, the hospital will focus on reducing costly days of stay, such as ICU or surgery days, rather than the total LOS, whereas, if reimbursement occurs on the basis of the diagnosis-related group or capitation, total expenses are the focus of cost reduction. The majority of studies that have evaluated the economic burden of resistance have been performed in the United States and, therefore, have measured total costs or charges.

The OR, risk ratio, or hazard ratio of the total costs or charges of patients infected with resistant organisms compared with those infected by susceptible organisms within a single institution over a relatively short period of time, with appropriate adjustment for potential confounders, provides the most generalizable estimate of the magnitude of the impact of resistance. In contrast, absolute values of cost or charge cited in studies should be interpreted with more caution, because they may not be applicable beyond the institution in which they were collected. Multicenter studies must report measures that are standardized across institutions.

CONCLUSIONS

Although the pace at which resistance is spreading continues to increase, the health care community has limited data on the magnitude of the effect of this problem on health and economic outcomes. Further study in this area is essential, including work to assess the impact of resistance at the societal level and the development of methods to assess illness severity in patients with infectious diseases. The implementation of measures that can improve the outcomes for patients with resistant infections is essential. These measures include a continued emphasis on the prevention of the emergence and spread of resistance through rational antibiotic use and appropriate infection-control measures. Strategies to minimize the delay of the administration of appropriate antibiotic therapy are essential, as are techniques to facilitate the earlier identification of resistant organisms.

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