The Economic Burden of Drug Resistance

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In recent years, researchers have made substantial progress in the development of methods to measure the burden of resistance and the application of those methods to the limited data available. Our understanding of the costs incurred by patients infected with resistant strains in hospital settings is much better than it was 10, or even 5, years ago. Research on the impact of resistance in the community is more limited. When multiple treatment options are available and prescribed treatment is empirical, resistance will lead to higher expenditures on drugs but not necessarily to increased patient morbidity and mortality. Understanding to what degree prescribing patterns are driven by real versus perceived limitations of first-line drugs is important for assessing the ability of public health campaigns to change the behavior of patients and providers.

The burden of resistance refers to the costs, deaths, and patient morbidity that would not have occurred in the absence of resistance. Measuring the burden of resistance is important for ranking resistance alongside other public health priorities and for assessing the value of infection control measures, newer antibiotics, and related interventions.

THE BURDEN OF RESISTANCE: THE ECONOMIC APPROACH

Economists sometimes refer to the burden of resistance as the negative externality associated with use of anti-infectives. At the risk of simplification, the burden of resistance is important for ranking resistance alongside other public health priorities and for assessing the value of infection control measures, newer antibiotics, and related interventions.

COMPONENTS OF THE BURDEN OF RESISTANCE

When resistance increases, physicians switch from older to newer antibiotics as empirical therapy, persons in the community and health care workers take additional steps to prevent the transmission of infectious agents, and infected patients become nonresponsive to older therapies. Together, these components constitute the burden of resistance.

In areas where resistant organisms are prevalent, physicians use alternative drugs rather than the medication that would be preferred on the basis of cost, dosing schedule, or side-effect profile in the absence of resistance. This substitution occurs for most patients with new diagnoses, not just those with infections due to resistant organisms. An example of a physician switch-
ing from an older to a newer antibiotic as empirical therapy is a physician in the community prescribing amoxicillin-clavulanate to treat an ear infection instead of amoxicillin, in response to concerns about rising rates of resistance in the community. It does not matter whether this is the recommended practice or whether patients with diagnoses of ear infections benefit from antibiotics at all. Because the cost would not have been incurred in the absence of resistance, the incremental cost of amoxicillin-clavulanate over amoxicillin is a cost of resistance. In the case of ear infection, costs attributable to “resistance-induced antibiotic substitution” are $20 million annually (1996 US dollars) [2].

Little is known about the costs of infection control policies that have been adopted in response to concerns about the transmission of resistant strains. Surely, these constitute a large portion of the burden of resistance in the developed world, where hospitals have increased handwashing, isolation of patients, and other practices after outbreaks of methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. One study found that requiring all health care workers and visitors to wear gowns and gloves in a medical intensive care unit increased costs by >$70,000 annually. By preventing transmission, however, the intervention saved >$490,000 on care for patients with vancomycin-resistant enterococci [3]. Costs associated with infection control are also probably substantial in countries in which malaria is prevalent; to the extent that mosquito nets, application of insecticides, and improved drainage are viewed as alternatives to treating resistant strains with expensive new therapies, they should be considered a component of disease burden as well.

To date, most burden-related studies have attempted to measure the excess health care costs and patient morbidity and mortality associated with resistant strains in hospitals. The focus on inpatient costs is probably related to the simultaneous availability of data regarding susceptibility, cost, and outcomes as well as the perceived burden of nosocomial infections in relation to community-acquired respiratory infections, especially in terms of mortality.

Recent studies of the attributable cost of resistant nosocomial infections suggest that hospitals can realize cost savings by taking steps to reduce transmission [4]. The attributable cost studies published in the medical literature are mostly comparative (i.e., cohort) observational studies in which cost (as opposed to disease) is the outcome variable. Some studies compare costs between patients infected with resistant organisms and uninfected persons, although the more relevant comparison for purposes of measuring the burden of resistance is between infected persons with and without resistant strains [5].

The limited evidence indicates that infections due to methicillin-resistant S. aureus tend to increase both costs—estimates range from 44% to 244%—and mortality risk [6]. The wide disparity in cost estimates is probably due to differing research strategies, including the use of severity-of-illness measures as controls, the type of information used to represent patient hospital costs, and the site of infection (e.g., surgical or bloodstream). Although reporting the absolute dollar costs associated with resistance is important for conducting cost-effectiveness or cost-benefit analysis of a particular intervention, reporting the cost differences as relative proportions between different infections facilitates comparison across institutions.

Comparative studies face challenges in controlling for the confounding influence of the severity of the underlying disease and in finding appropriate measures to represent the opportunity cost of resources [7]. Recent studies have addressed the confounding issue by matching patients on the basis of severity-of-illness measures, such as APACHE [8], or by use of propensity score methods [9]. Although neither approach can overcome confounding due to unobserved patient characteristics, both do a good job of making the best use of the information at hand.

**FUTURE NEEDS**

Although single-center studies are informative, the extreme skewness of medical costs makes it difficult to draw inferences from sample sizes that for most other end points would be sufficient. Therefore, collection of multiyear single-institution data or single-year data across multiple settings is necessary to obtain statistically valid conclusions. The Chicago Antimicrobial Resistance Project has made notable progress on this front. The project is a 5-year hospital-based demonstration program to evaluate control interventions for antimicrobial drug-resistant infections in patients within the 3 hospitals that constitute the Cook County Bureau of Healthcare Services. The goals of the project include improving infection control to reduce nosocomial infection, improving antibiotic use to reduce antimicrobial resistance, and improving microbiology laboratory reporting techniques. Specific tasks include development of an electronic clinical data warehouse incorporating laboratory, pharmacy, and administrative data from the 3 hospitals and review of infection control surveillance and antibiotic prescribing practices [10]. Cost data will be collected for 1500 patients. Investigators anticipate that ~225 will have a nosocomial infection, of which 75 will have a nosocomial infection due to a resistant strain. Detailed severity-of-illness measures are also being collected to facilitate comparisons between groups. Preliminary results should be available in 2005.

The developing world is another area where improved data collection efforts would be useful for estimating the burden of resistance. Currently, little is known about the costs associated with treating malaria due to resistant strains and treating diseases due to other tropical pathogens. At the very least, we can perform rough calculations to assess the costs of resistance-
induced drug substitution, in the case of malaria. The World Health Organization recommends a change in first-line treatment when 25% of patients treated experience recrudescence of infection. This is an arbitrary figure; an optimal switching policy would balance the cost of the second-line drugs against the benefit of prompt treatment, as in Goodman et al. [11]. Nevertheless, at some point, whether it is above or below the 25% threshold, physicians change from first-line therapies. Phillips and Phillips-Howard [12] calculated that the use of quinine versus chloroquine as first-line treatment of 150 million patients with malaria would increase spending by as much as $100 million (1990 US dollars), a relatively large amount for the countries in which malaria is endemic. A recent Institute of Medicine report recommended that chloroquine be replaced with artemisinin combination therapy as first-line treatment for malaria, at an added cost of $300–$500 million [13, 14]. The Institute of Medicine further recommended that development agencies and industrialized countries pay the costs of this replacement so as not to increase the burden on developing countries.

Finally, studies are needed to assess the clinical implications of resistance in the community. Whereas many studies have focused on inpatient settings, the majority of antibiotic prescriptions are for common respiratory infections. We must understand the implications of resistance in the community to fully grasp the burden of resistance. Before cost studies can be done, however, more information is needed on the clinical consequences of infection with resistant pathogens. Patients may be infected with strains that, according to standard definitions, are “resistant” yet still can be effectively treated with first-line antibiotics. To the extent that resistance does lead to treatment failure [15], costs will increase. For example, the medical costs associated with treating an episode of otitis media for which the patient receives a second antibiotic, potentially indicating treatment failure, are $389 (2001 US dollars) but are only $169 in cases in which patients do not receive a second drug [16]. Part of the difficulty in measuring costs in the community is that costs are incurred in multiple settings. When such data are difficult to obtain, simulation models may help to integrate estimates from different sources [17].

CONCLUSION

In recent years, researchers have made substantial progress in development of methods to measure the burden of resistance and application of those methods to the limited data available. We are still a long way from producing a reliable estimate that captures the total burden of resistance to society. However, except for its use in making the case for more research funding, a national or global burden figure is not, in itself, particularly interesting. Disease- or pathogen-specific estimates are much more valuable to clinical decision makers.

Our understanding of the costs associated with methicillin-resistant S. aureus and vancomycin-resistant enterococci is much better than it was 10, or even 5, years ago. Although biased to some degree by unobserved case mix, these estimates have real value in enabling hospital administrators to assess the cost-effectiveness of infection control measures. As the use of electronic charts makes it easier to observe inpatient resource use, administrators and physicians should routinely collect cost and usage data to quantify potential cost savings associated with interventions and protocol changes.

Outside the inpatient setting, the burden of resistance is heavily weighted toward higher expenditures on antibiotics, as opposed to patient morbidity and mortality. Understanding to what degree prescribing patterns are driven by real versus perceived limitations of older, first-line drugs is important for assessing the value of these expenditures and for improving the ability of public health campaigns to change behavior of patients and providers.

Acknowledgments


References

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