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Antibacterial treatment strategies in hospitalized patients: What role for pharmacoeconomics?

ABSTRACT

Antimicrobial agents continue to account for a significant portion of institutional pharmaceutical expenditures. Pharmacoeconomic analysis is a valuable tool in assessing antibacterial agents for their place in institutional formularies. This article reviews various types of pharmacoeconomic analyses, their respective limitations, and their roles in the antibacterial formulary decision-making process. We also discuss the current state of the antibacterial pharmacoeconomic literature, including the economic impact of antimicrobial resistance.

KEY POINTS

Pharmacoeconomic analysis adds an economic component to formulary decisions while taking several factors into account, including drug acquisition costs and outcomes.

The complexity of treating infectious diseases complicates the design of robust and generalizable pharmacoeconomic studies, particularly for new antimicrobial agents.

In designing pharmacoeconomic studies, consideration should be given to study perspective, choice of analysis type and control patients, severity of illness, comorbidities, adequacy of antibacterial treatment, and ensuring clear definitions of resistance.

Antimicrobial agents remain a significant cost category in institutional pharmaceutical budgets, so their use and evaluation for formulary inclusion have important economic implications. Historically, economic evaluation of a new medication prior to formulary addition compared the new agent with existing formulary agents only in terms of acquisition cost. This is an oversimplistic approach, however, since a number of factors beyond acquisition cost may contribute to the overall cost of using one drug versus another.

This article reviews various types of pharmacoeconomic analyses that can be used to evaluate antibacterial agents and how they can contribute to antibacterial formulary decision-making. We also examine the current state of the antibacterial pharmacoeconomic literature, including the economic impact of antimicrobial resistance, as well as limitations of pharmacoeconomic analyses.

STILL A MAJOR BUDGET ITEM

In the early 1990s, antimicrobial medications accounted for as much as one third of the drug budgets of US hospitals. Although this proportion has fallen to less than one quarter in the last few years, this decline is mostly due to increases in expenditures for other drugs (eg, cardiovascular and chemotherapy agents) as opposed to representing a decline in antimicrobial expenditures.

The National Institute of Health Care Management reported that "broad-spectrum" antibacterials (eg, ciprofloxacin [Cipro and others], levofloxacin [Levaquin]) and "enhanced" antibacterials (eg, amoxicillin-clavulanate [Augmentin and others], piperacillin-tazobactam [Zosyn]) were among the 25 therapeutic categories with the highest drug expenditures from 1999 to 2001. Together these antibacterial categories accounted for 7.8% and 6.7% of total retail drug expenditures in 1999 and 2001, respectively.[1,2] The years since 2000 have seen the advent of additional new antifungal agents and new antibacterials with activity against a broad spectrum of organisms—both anaerobic and aerobic species, as well as facultative gram-positive and

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Dr. Goldman reported that he has received fees for serving on speakers' bureaus for Enzon Pharmaceuticals, Wyeth Pharmaceuticals, Abbott Laboratories, Schering-Plough Corp., Forest Laboratories, and Pfizer Inc., and that he has received honoraria for writing from Wyeth. Dr. Nair reported that she receives a salary from Abbott Laboratories (her current employer) and that she has received honoraria for writing from Wyeth.

The authors reported that they prepared this article without assistance from any medical education company.

gram-negative organisms. Additionally, new agents are on the horizon to treat viral infections in hospitalized patients with compromised immune systems. Determining the appropriate use—and thus the hospital formulary status—of this multitude of antimicrobials can be complex.

FORMULARY MANAGEMENT AT A GLANCE

Formularies and formulary systems serve as an almost universal approach to rational drug utilization in US hospitals. Most institutions have a multistep approach to formulary decision-making; clear guidelines have been developed by the American Society of Health-System Pharmacists, and in-depth reviews of formulary decision-making are available.[3–7] In brief, evaluation of a new medication for the formulary typically includes a clinical, pharmacologic, safety, and toxicologic review, as well as a comparison with other medications in its class or therapeutic category and an economic evaluation.

Formulary decisions are communicated, implemented, and maintained using a number of ongoing formulary management strategies, which include drug use and clinical outcomes review, educational programs, and guidelines and restrictions for particular drugs or diseases. An institution's ability to successfully implement cost-containment strategies such as appropriate-use criteria, use restrictions, guidelines, intravenous (IV)-to-oral conversions, therapeutic substitution, and automatic stop orders is often critical in the formulary decision-making process.[8,9] Astute formulary management involves evaluating these various strategies to determine whether they provide cost savings or merely shift costs, and judiciously implementing specific strategies for specific drugs or situations to provide cost savings, better outcomes, and/or better patient care.

PHARMACOECONOMICS: RATIONALE AND APPLICATIONS

The growing demand to evaluate the actual results of health care interventions has spurred the growth of outcomes research, which evaluates the effect of interventions on patient-related (if not patient-specific) clinical outcomes, economic outcomes, and humanistic outcomes (eg, patient satisfaction and quality of life).[10]

Pharmacoeconomics is a subset of outcomes research focused on describing and analyzing the costs of drug therapy to health care systems and society.[11] It involves the comparison of costs and consequences (clinical, economic, humanistic) of interventions with pharmaceutical products and services.[12] The different costs that may be included in pharmacoeconomic analyses are outlined in the sidebar on this page. The costs and resources to be included depend on the perspective of the analysis.[10,13] For example, if the study is from a societal perspective, all types of costs should be included. However, if the study is from a hospital perspective, only direct medical costs may be included. If an intervention or program extends beyond 1 year, discounting should be applied to adjust future values to reflect the present value.[13] Although there is no set discounting rate, published standards are available (from government and previous studies).[14]

Types of costs that may be included in pharmacoeconomic analyses

Direct medical costs are the medical resources used to treat a disease or illness (eg, hospital care, drugs).

Direct nonmedical costs are the costs of nonmedical products and services that enable patients to receive treatment (eg, transportation to site of treatment).

Indirect costs are the costs of morbidity or mortality resulting from an illness (eg, loss in productivity).

Intangible costs refer to the pain and suffering caused by illness and/or treatment, and are difficult to quantify.

Beyond drug acquisition costs

Traditionally, formulary decisions took into account only drug acquisition costs, not the potential savings stemming from use of the better drug. Ideally, to merit inclusion in the formulary, a new antibacterial agent with improved efficacy should reduce the incidence and cost of treatment failure and/or result in better outcomes (or earlier achievement of comparable outcomes), which should offset the new agent's typically higher cost.[15]

Pharmacoeconomic analysis should be the preferred tool for guiding antibacterial formulary decisions and evaluating the economic impact of antibacterial use because it is usually based on clinical outcomes and does not merely evaluate drug acquisition costs. Pharmacoeconomics takes into account all types of outcomes associated with antibacterial use, such as treatment success or failure, indeterminate outcome, adverse events, and antimicrobial resistance. It also accounts for the cost of all resources used, such as professional services, hospitalization, emergency department care, laboratory tests, office visits, imaging and pathology studies, and drugs.[9]

A range of applications

Pharmacoeconomic analysis helps to identify therapies that reduce costs via efficient or optimal use of resources

Common types of pharmacoeconomic analyses

Cost-minimization analysis compares the costs of two or more interventions or treatments whose outcomes are assumed to be equivalent.[12] This type of analysis compares costs alone, whereas results in the other three types of analysis are calculated as ratios of costs to consequences. An example would be comparing the costs of using therapeutically equivalent drugs.

Cost-benefit analysis is used to compare costs and consequences of two or more alternatives with similar or different outcomes. The consequences or benefits are measured in monetary terms.[12,16] An example would be an analysis to decide whether to expand inpatient clinical services or implement an outpatient disease management program.

Cost-effectiveness analysis compares costs and consequences of alternative therapies or interventions that have similar outcomes. Unlike cost-benefit analysis, the outcomes are measured in natural units (eg, serum triglyceride levels).[12,16] A primary or intermediate outcome can be measured as the consequence of the treatment or intervention. While primary outcomes are preferred (eg, lives saved or life-years saved), intermediate outcomes may be used if the relationship between intermediate and final outcomes can be estimated.[5] An example would be comparing reductions in cardiac risk by comparing various approaches to reduce serum triglyceride levels (intermediate outcome), assuming that such a reduction would reduce cardiac risk. The cost-effectiveness ratio is presented as an average or incremental ratio. The average cost-effectiveness ratio is the ratio of the mean value of cost and outcomes (consequences) for each alternative and helps to determine the overall affordability of an intervention. The incremental cost-effectiveness ratio represents the additional cost incurred to produce the additional effect as a result of a change in therapy; it is the ratio of the change in costs and effects and provides the relative efficiency of alternative options.[5]

Cost-utility analysis, like cost-effectiveness analysis, compares the costs and consequences of alternative therapies or interventions, but is adjusted for patient preferences or utility. The effect or consequence of the therapy or intervention is measured in terms of both quality and quantity of life.[12,16] An example would be comparing chemotherapy agents for breast cancer in terms of quality-of-life–adjusted survival.

while maintaining quality patient care.[5,9] In addition, pharmacoeconomics can serve a number of specific functions that facilitate formulary decision-making in a variety of other ways; some strategies are outlined below.

- Retrospective pharmacoeconomic evaluations can help confirm the appropriateness of past formulary decisions to add or change agents.[5]
- On adding a new therapy to the formulary, an incremental analysis (to determine the additional cost incurred to provide an additional effect, measured in dollars, clinical outcomes, or utility) can be done to help assess its value relative to previous therapies.[15]
- Pharmacoeconomic analysis can help to determine if a drug is clinically or economically beneficial in different scenarios involving different populations, bacterial sensitivities, or clinical treatment strategies. It also can compare treatments using different combinations of antibacterial agents for patients with different infections and comorbid conditions.
- Pharmacoeconomic analysis can help gauge how diagnostic accuracy, monitoring (eg, adverse events), and drug-related problems may change the economic implications of a treatment. Drug-related problems such as an untreated or inappropriate indication, an improper drug or dosage, poor adherence, adverse drug reactions, or use by populations not represented in clinical trials (eg, pregnant women and children) can affect the economic efficiency of antibacterial therapy.[15] Pharmacoeconomic evaluations that account for these factors can help determine the best choice of therapy and demonstrate the economic effects of different treatment strategies in these less than ideal situations.

TYPES OF PHARMACOECONOMIC ANALYSES

Pharmacoeconomic evaluations of specific therapies may be based on one of two approaches:

- Direct observation of relevant economic outcomes (eg, costs, hospital length of stay) associated with the treatment under evaluation versus a comparator
- Modeling of expected economic outcomes based on observed clinical outcomes associated with the specific treatments and known relationships between clinical and economic outcomes from other sources.

Four types of pharmacoeconomic evaluation are typically used to assess the costs and consequences of drug therapy—cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. These analyses differ in the outcome measures used, as detailed in the sidebar above. Cost-effectiveness and cost-minimization analyses are the most commonly used analysis types for assessing antibacterial drugs.

All four of these types of analysis may be based on

direct observational studies, clinical trials, a modeling approach, or a combination of these, depending on the availability of economic data in the direct comparison of treatments. When modeling is used, *decision tree analysis* is the most common approach.[15] Decision tree analysis helps to identify the best decision from all available options. It involves identifying available options and predicting the consequences or outcomes of each. A likelihood or probability is assigned for each outcome, as is a cost, and the combination of all this information is used to identify the best decision option.[17]

Related analyses

Related analyses include cost-of-illness analysis and health-related quality-of-life studies.

Cost-of-illness analyses assess the resources used as a result of the illness (including treatment of the condition) and thereby determine the economic impact of the illness on society.[12] These analyses also serve to highlight the unmet therapeutic need—and corresponding economic need—for new treatments.

Health-related quality of life. In addition to the above types of pharmacoeconomic analyses, there is a growing literature on health-related quality of life. This research area provides insights into such patient outcomes as physical, social, and mental well-being and aims to provide a complete picture of the illness and its treatment.[18]

Adjust for assumptions with sensitivity analysis

Pharmacoeconomic studies conducted using any of these types of analysis will necessarily be based on a number of assumptions. For this reason it is important to conduct sensitivity analyses to determine the validity and robustness of the results obtained[5] and the limits of applying results to different patient populations and settings.[15]

PHARMACOECONOMIC ANALYSES OF ANTIBACTERIAL THERAPY: SAMPLE STUDIES

Direct comparisons of antibacterial therapies

Numerous pharmacoeconomic evaluations of antibacterial agents have been published, and a comprehensive review is beyond the scope of this article. Below we focus on a few examples of well-done pharmacoeconomic analyses with clear outcomes in order to illustrate how various types of evaluations are used. These studies were selected from the literature to represent the most common pharmacoeconomic analyses for evaluation of antibacterial drugs. Study details and major results are summarized in **Table 1**.

Cost-effectiveness analyses. Drummond et al[19] evaluated the costs, consequences, and cost-effectiveness of sequential IV and oral moxifloxacin (Avelox) monotherapy compared with amoxicillin-clavulanate with or without clarithromycin (Biaxin and others) in hospitalized patients with community-acquired pneumonia who needed parenteral treatment. Treatment with moxifloxacin resulted in more patients achieving clinical cure within 5 to 7 days after therapy, increased the speed of response, and reduced length of stay by 0.81 days **(Table 1)**. Treatment with moxifloxacin was found to be cost-effective, mainly as a result of the reduced length of stay.

Walters et al[20] attempted to determine the cost-effectiveness of three regimens—(1) sequential IV-to-oral ciprofloxacin plus IV metronidazole, (2) IV ciprofloxacin plus metronidazole, and (3) IV imipenem-cilastatin (Primaxin)—in hospitalized patients with intra-abdominal infections. Decision tree analysis was used to compare the regimens. Among patients able to receive oral therapy, sequential IV-to-oral treatment with ciprofloxacin and metronidazole was more cost-effective than the comparator regimens **(Table 1)**. Among patients unable to receive oral therapy, no differences were found among the three regimens.

Cost-minimization analyses. Samsa et al[21] compared azithromycin (Zithromax and others)–based and levofloxacin-based protocols for treating patients hospitalized with community-acquired pneumonia (see **Table 1** for specific regimens). The regimens were determined to be equally efficacious based on demonstration of clinical equivalency during the study. Data on medical resource utilization were collected through the 30 days following hospital discharge; costs of the study medications, hospital stay, home care, postdischarge medical utilization, and lost work days were included. As detailed in **Table 1**, the azithromycin-based protocol was associated with lower costs than the levofloxacin-based protocol.[21]

In a recent analysis of US patients hospitalized with complicated skin and skin structure infections, Mallick et al[22] compared hospital length of stay between those treated with IV tigecycline (Tygacil) and those treated with IV vancomycin plus IV aztreonam (Azactam). Treatment with tigecycline was associated with a shorter hospital stay after adjusting for identified risk factors **(Table 1)**. Given similar efficacy between the two treatment groups,[23] these researchers performed cost-minimization modeling to determine the economic implications of this reduction in length of stay. Based on daily costs of hospitalization for patients with complicated skin and skin structure infections identified from a US

TABLE 1
Overview of direct economic evaluations of antibacterial agents

Study (year)	Regimens compared*	Patient population	Type of analysis/ outcomes measured	Primary findings
Drummond et al[19] (2003)	• Sequential IV and oral moxifloxacin (Avelox) • Amoxicillin-clavulanate ± clarithromycin	622 hospitalized patients with CAP requiring parenteral therapy	Cost-effectiveness analysis; cost and outcomes data collected for 21 days and evaluated based on clinical cure rates 5–7 days post-treatment	• Moxifloxacin associated with higher clinical cure rate (80.7% vs 75.4%), faster response (1 day sooner for median time to first return to apyrexia), and reduced LOS (7.64 vs 8.45 days) • Moxifloxacin deemed cost-effective, yielding savings of 2,000 euros (~$2,462 in 2006 dollars) per additional patient cured, mainly due to reduced LOS
Walters et al[20] (1999)	• Sequential IV-to-oral ciprofloxacin + IV metronidazole • IV ciprofloxacin + IV metronidazole • IV imipenem-cilastatin (Primaxin)	446 hospitalized patients with intra-abdominal infections	Cost-effectiveness analysis fitted into a decision tree model to compare economic outcomes; primary clinical outcome measure was treatment success or failure as assessed by investigators	• Among patients able to receive oral therapy, sequential IV-to-oral ciprofloxacin + metronidazole was cost-effective ($7,835 per successful outcome) compared with the two IV-only treatment arms ($9,334 per successful outcome) • Among patients unable to receive oral therapy, no difference in treatment cost or success rates between IV therapies
Samsa et al[21] (2005)	• IV azithromycin + IV ceftriaxone, followed by oral azithromycin • IV levofloxacin (Levaquin) followed by oral levofloxacin	163 hospitalized patients with CAP	Cost-minimization analysis (regimens equally efficacious clinically); direct medical cost data collected through 30 days postdischarge, including study medications, hospital LOS, home care, postdischarge medical utilization, and lost work days	• Direct medical costs per patient were $2,481 lower with azithromycin-based regimen ($9,274) than with levofloxacin regimen ($11,755)
Mallick et al[22,23] (2005, 2006)	• IV tigecycline (Tygacil) • IV vancomycin + IV aztreonam (Azactam)	186 hospitalized patients with complicated skin and skin structure infections	Cost-minimization analysis (regimens equally efficacious clinically) based on pooled data on hospital LOS from two clinical trials	• Tigecycline associated with 1.85-day reduction in LOS ($P = .0015$) after adjusting for identified risk factors • Reduction in LOS translated to expected per-patient cost savings of $1,469 with tigecycline

IV = intravenous; CAP = community-acquired pneumonia; LOS = length of stay

*Except for agents with trade names listed in parentheses, the listed antibacterials are multisource drugs that are available from various manufacturers.

multihospital audit ($794),[24] modeling showed that the above reduction in length of stay with tigecyline versus vancomycin/aztreonam translated to an expected cost savings of $1,469 ($794 × 1.85 days).[23]

Discussion. All of the above four analyses were based on prospective randomized trials. Drummond et al[19] did not collect resource utilization data for the adverse events in their study, but the low incidence of adverse events suggested that such events would not have a large impact on the economic results. Walters et al[20] collected adverse event data only in terms of length of stay (ie, adverse events that extended the hospital stay). Both Drummond et al[19] and Walters et al[20] used primary outcomes (clinical cure and treatment success, respectively) as their end points.

Cost-of-illness studies

Cost-of-illness studies serve important purposes in many disease states, including complicated infections.

Such studies provide at the outset, when combined with estimates of disease prevalence, important information on the magnitude of the burden an illness poses to health care payers or to society in general. They also may serve as critical parameters for modeling the expected economic benefit of specific treatments when cost data are not directly available from head-to-head observational studies. Most cost-of-illness studies in complicated infections have focused on the public health and economic impact of antimicrobial resistance. Although this topic has been reviewed extensively,[25–27] it is helpful to consider in the present discussion.

Antimicrobial resistance. As early as 20 years ago, Holmberg et al[28] reviewed the contemporary literature and concluded that antimicrobial resistance was not only an important health problem but also an economic burden to society. Antimicrobial resistance has since been estimated to cost the United States up to $5 billion annually.[25]

However, many of the reported cost-of-illness studies have not been particularly well designed to evaluate increases in expenditures attributable to resistance. Early case-control studies did not take into account whether patient populations were infected by resistant as opposed to susceptible organisms. Some of these reports were also based on large database analyses that lacked sufficient clinical information.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a key focus of the literature on the economic impact of resistance.[29–31] These studies have highlighted extended length of stay as the predominant driver of MRSA-related costs in patients with complicated infections.

Other studies have examined the economic impact of antimicrobial resistance in the context of other microorganisms. Three well-designed analyses are pertinent to the discussion here.[32–34]

One study was a retrospective cohort investigation that matched 233 hospitalized patients with vancomycin-resistant enterococci (VRE) (case group) on a 1:3 basis with 647 hospitalized control patients according to hospital location, date, and length of stay prior to infection.[32] The objective was to determine the economic impact of VRE. Multivariate analysis showed that VRE was associated with increases in mortality, surgical procedures, and admissions to the intensive care unit, as well as with an excess cost of more than $12,000 per case.

In a retrospective cohort study of more than 200 patients with respiratory or blood isolates of either penicillin-susceptible or -nonsusceptible *Streptococcus pneumoniae*, Klepser et al[33] found that length of stay and cost of care were significantly greater for patients in the nonsusceptible group than for those in the susceptible group. There was no difference in clinical outcomes, and patients in the nonsusceptible group had more antibiotic use prior to their present infection.

Gram-negative organisms are more complicated, since the various species likely necessitate differentiated studies. As *Pseudomonas aeruginosa* is a relatively common nosocomial isolate that poses treatment challenges, Carmeli et al[34] designed a study to evaluate the clinical and economic impact of bloodstream infections caused by resistant and susceptible *P aeruginosa,* including those organisms that became resistant during therapy. Resistance was clearly defined and outcomes included mortality, secondary bacteremia, length of stay, and hospital charges. A total of 421 patients were identified, of whom 70% had *P aeruginosa* isolates that were considered susceptible. Thirty patients had isolates that were susceptible at baseline but then became resistant during therapy. This group of patients had significant increases in mortality and length of stay relative to patients with isolates that remained susceptible throughout therapy.

Many factors affect the outcomes of patients infected with resistant organisms, including infection acuity, underlying diseases, and the actual hospital epidemiology. The definition of resistance also must be taken into consideration—ie, how many antibacterials the organism is resistant to and how effective the remaining active agents are. In addition, some organisms are more virulent than others and play a larger role in poor outcomes. It is clear, however, that resistant organisms have a significant effect on outcomes and costs. It is therefore possible that appropriate stewardship can improve antimicrobial utilization and reduce rates of resistance.[35]

Cost of inadequate initial therapy. Berger et al recently used a large US multihospital database to retrospectively examine the impact of failure of initial empiric therapy on the overall cost of hospital treatment for patients who received IV antibiotics for complicated skin and skin structure infections[24] or complicated intra-abdominal infections.[36]

Their analysis of skin and skin structure infections involved a cohort of 23,846 patients, 24% of whom experienced failure of initial IV antibiotic therapy, defined as the need for drainage/debridement or a change in antibiotic regimen (except for de-escalation or IV-to-oral switches).[24] Patients in whom initial IV antibiotic therapy failed had a threefold increase in inpatient mortality compared with those in whom ini-

TABLE 2
Clinical and economic consequences of failure of initial empiric intravenous (IV) antibiotic therapy[24,36]

Hospitalized patients with complicated skin and skin structure infections (N = 23,846)

Outcome measure	Pts with initial Tx failure	Pts with initial Tx nonfailure	*P* for difference
In-hospital mortality	1.2%	0.4%	< .001
Duration of IV antibiotic therapy (days)	8.5	4.2	< .001
Hospital length of stay (days)	9.4	5.1	< .001
Inpatient charges	$8,920	$4,142	< .001

Hospitalized patients with complicated intra-abdominal infections (N = 2,061)

Outcome measure	Pts with initial Tx failure	Pts with initial Tx nonfailure	*P* for difference
In-hospital mortality	9.3%	1.4%	< .001
Duration of IV antibiotic therapy (days)	9.9	5.1	< .001
Hospital length of stay (days)	11.3	6.7	< .001
Inpatient charges	$17,539	$9,152	< .001

tial therapy did not fail, and they received an additional 4.3 days of IV antibiotic therapy, were hospitalized an additional 4.3 days, and incurred an additional $4,778 in inpatient charges **(Table 2)**.

In the analysis of complicated intra-abdominal infections, 25% of the cohort of 2,061 patients did not respond to initial IV antibiotic therapy.[36] Compared with their counterparts who responded to initial therapy, these patients had a sixfold increase in mortality, received an additional 4.8 days of IV antibiotic therapy, stayed in the hospital 4.6 days longer, and incurred an additional $8,387 in inpatient charges **(Table 2)**.

It should be noted that these data from Berger et al are currently available only in abstract form and that both studies are retrospective reviews of a large database. It would be helpful if the definition of antibiotic failure were specified clearly, since factors such as lack of surgical intervention could influence antibiotic failure rates. On the basis of clinical experience and the information in these abstracts, it seems clear that patients who do not respond to initial interventions fare worse than those who do respond. These studies complement others[37] demonstrating that early initiation of appropriate antimicrobial therapy plays a role in clinical success.

GAPS IN THE LITERATURE

Adverse events and their treatment have an important effect on the clinical and economic benefits of antibacterial agents and should be evaluated prior to inclusion of agents in the formulary.[38] A study by Classen et al[39] showed that antibacterial-related adverse events accounted for 23.3% of all adverse drug reactions among hospitalized patients. However, very few pharmacoeconomic studies have evaluated the cost of adverse events due to antibacterial agents.[38]

An electronic literature search using MEDLINE to identify pharmacoeconomic studies of antibacterial agents retrieved a wide array of articles, with a greater number of studies on certain infections (eg, community-acquired pneumonia) than on others. Because broad-spectrum antibacterials may be used against a wide variety of infections and microorganisms, and because each organism can cause several types of infection, the number of possible organism-drug combinations is considerable. Accounting for this abundance of possible scenarios makes pharmacoeconomic evaluations and extrapolation of results complex and challenging. In addition, various infections differ in severity and may have different guidelines for treatment. Although guidelines might make it simpler to evaluate certain infections, results may not be generalizable to other infections caused by the same organism in different practice settings (eg, other hospitals or nursing homes). In addition, it may be difficult to identify clear end points or summary outcomes for treatment of certain infections.

The relevance of these types of studies plays into the design of the pharmacoeconomic evaluations described in the previous sections. The epidemiology

in an individual institution may skew the applicability of an economic analysis if resistance patterns are different from those studied, as differing prevalences of resistant organisms clearly can affect economic outcomes.

LIMITATIONS OF PHARMACOECONOMIC ANALYSES

Despite its potential utility, pharmacoeconomic analysis is associated with several general limitations as well as drawbacks specific to its use in antibacterial formulary decision-making.

Included costs are often incomplete or imprecise

A large proportion of pharmacoeconomic studies of antibacterial agents consider only the acquisition costs of the agents and do not take into account hospitalization costs, which make up a major portion of overall expenditures in the treatment of infectious diseases. Some studies take into account the acquisition and dispensing costs of the antibacterial agents and other drugs used to treat the infection and any adverse events. These studies are based on an assumption that the remainder of the costs associated with the hospitalization are fixed and constant between groups. Using hourly wages to calculate dispensing and administration costs may not have much of an impact on hospital costs. Additionally, the viability of time and motion studies to calculate labor and material costs associated with treatment may be limited. Even the inclusion of the entire cost of hospitalization may still not capture all costs related to an infectious episode because costs related to the episode may have been incurred before treatment was begun and may not be included. In addition, the infection may not be the sole reason for the hospitalization. Separating out all the costs related to other diagnoses might be difficult and thus may require the use of estimates.[40]

No single ideal method for calculating costs

The costs calculated in a prospective study may not be generalizable because most prospective studies are randomized controlled trials that do not represent normal conditions in general practice. Retrospective collection of cost data may pose difficulties in separating the costs of treating the infection from the costs of treating other diagnoses. In addition, cost data may be collected from a single institution, which limits their generalizability. Another method used to determine costs, expert opinion, is limited in that it does not report actual patient-incurred costs and does not allow for much variation, which may pose statistical challenges. As a result, no single method for calculating costs is appropriate in all situations.[40]

Each type of analysis has drawbacks

Each type of analysis has its limitations. In cost-minimization analysis, it might be difficult to establish that clinical outcomes are equivalent.[16] Cost-effectiveness analysis compares only one outcome or a single summary measure of related outcomes at a time, and some diseases may not have a distinct measure or a summary measure that can serve as an overall indicator of the effect of an intervention. In addition, cost-effectiveness analysis measures only the affordability and efficiency of a treatment and not whether the clinical outcomes gained are worth the cost of treatment.[5] The drawback of cost-benefit analysis is the difficulty of assigning monetary values to certain outcomes. For example, if the outcome or consequence evaluated is years of life saved, assigning a monetary value to life might be problematic.[12,16] Use of average ratios calculated to interpret comparisons of interventions may not reveal the magnitude of the cost and consequences or the differences between treatments. As a result, ratios do not provide useful information in terms of budget impact.[5]

Timeliness, generalizability, other limits

The timeliness of pharmacoeconomic analyses is often problematic due to the time lag associated with publication. Pharmacoeconomic studies are rarely available when formulary decisions on new drugs are being made, and even if studies are available, their reliability and robustness might be questionable. Modeling a study from different perspectives and using different assumptions may present different and sometimes contradictory results. In addition, these assumptions may be incorrect or inappropriate.[5] Moreover, pharmacoeconomic evaluations in a specific institution, under specific conditions and for specific populations, may not be applicable to other institutions or situations. Likewise, infections or illnesses may differ in degree of severity and risk, which again limits generalizability.[3] Similarly, patterns of antimicrobial resistance may develop differently over time in different settings, which further limits applicability between settings.[15] Other potential limitations include biased industry sponsorship and lack of in-house expertise in economic evaluation.[5]

CONCLUSIONS

The complexity of both infectious diseases and their treatments makes it difficult to design robust and generalizable pharmacoeconomic studies, especially for new antibacterial agents. As a result, pharmacy and therapeutics committees often must rely on studies conducted on a small scale after a drug has been intro-

duced to the market. Economic evaluation of antibacterials is important but should not be the primary driver of utilization. Careful consideration of a drug's effectiveness and safety relative to other agents on the formulary must precede economic considerations.

Translating the pharmacoeconomic literature to the individual institutional level is challenging, especially when it comes to length of stay and institution-specific resource use. Also, the issues of antimicrobial resistance and initial therapy failure should be taken into consideration so as to maximize use of the most effective agents up front and assure adequate dosing.

Despite its limitations, pharmacoeconomic analysis is a valuable tool in assessing antibacterial agents for their place in the formulary. It adds an economic component to formulary decisions while accounting for factors in addition to drug acquisition cost. When possible, institution-specific pharmacoeconomic studies should be considered to validate published data. The design of such studies should give careful consideration to the study perspective, the choice of analysis type and control patients, the severity of illness, patient comorbidities, the adequacy of antibacterial treatment, and ensuring clear definitions of resistance.

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