Principles of Antibiotic Formulary Selection for P&T Committees
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Part 5: The Cost of Antimicrobial Therapy

OVERVIEW

As with antibiotic resistance, containing the cost of antibiotics is everyone’s responsibility. The main objective is to select antimicrobial agents that provide effective therapy at a reasonable cost. The expenditures for antimicrobial therapy are variable and depend on several factors:

- acquisition costs of the drug
- the route and frequency of administration
- combination therapy
- the need for monitoring and adjunctive therapy
- potential side effects and resistance
- therapy failure

The study of drug costs and their implications is termed pharmacoeconomics. The successful application of pharmacoeconomic principles to antimicrobial therapy requires maximizing therapeutic effectiveness while minimizing costs, with the primary emphasis on pharmacokinetic considerations. This article reviews the various pharmacoeconomic factors that affect antibiotic costs in relation to patients and institutions.1–5

ACQUISITION COST

The acquisition cost refers to the unit price of an antibiotic to the institution and applies to both orally and parenterally administered antimicrobials. These costs vary considerably from region to region. Considerable differences in expenses within a region are common and vary according to wholesalers’ costs, the quantity purchased, buying group arrangements, and rebate programs based on volume.

Because of the great variability of acquisition costs, I have often referred to the average wholesale prices (AWPs) as published in Red Book. Although many hospitals do not purchase antibiotics at the AWP, this publication is nonetheless a good source of antimicrobial cost comparisons.

In general, older drugs, particularly when their patents have elapsed, are less costly to acquire on a per-unit basis than drugs that are still protected by a patent. On the whole, most antibiotics are considerably less expensive as oral (PO) formulations than as intravenous (IV) preparations. For example, 400 mg of IV gatifloxacin (Tequin®, Bristol-Myers Squibb) costs approximately $16, but a 400-mg oral tablet costs about $6.6,7

ROUTE OF ADMINISTRATION

Antibiotics that are given intravenously incur an additional cost to the institution above the acquisition cost. This added cost is associated with the institution’s expense for storing, labeling, diluting, and administering the IV antibiotic. The average cost of administering a single dose of an antibiotic in the U.S., and at our institution as well, is $10 per IV dose. This cost may be higher or lower among institutions.

The cost also depends on the frequency of IV administration. Drugs having a relatively short half-life (e.g., penicillin G with a 30-minute half-life) should be given every four hours, when administered intravenously, to provide therapeutic concentrations throughout most of the dosing interval. The cost implications of a short dosing interval for IV drugs are profound. For example, the acquisition cost of IV ampicillin is only about $1 per day; on an every-four-hour dosing basis, however, the administration cost alone is $60 per day.

During the past two decades, the trend has been to develop antimicrobial agents with longer half-lives that permit dosing intervals of every 8, 12, or 24 hours. For an antimicrobial that is given once daily, an IV dose administration charge of only $10 is added to the drug’s acquisition cost. All other factors being equal, clinicians should opt for antibiotics with a long dosing interval, for pharmacoeconomic reasons.

In addition, when drugs with a long dosing interval are used, the chances of medication errors and the need for a large IV team are reduced.

Combination therapy that involves the use of multiple drugs magnifies the relative importance of IV administration for the total cost of the antibiotic to the institution. Using traditional “triple-antibiotic therapy,” with ampicillin (Principen®, Apothecan), gentamicin (Garamycin®, Schering), and clindamycin (Cleocin®, Pharmacia) as examples, it is readily apparent that the cost of administering these three drugs far exceeds their acquisition cost. If IV ampicillin is given every four hours, clindamycin every six hours, and gentamicin every eight hours, the administration cost of these three antibiotics alone is $130 per day. This is remarkable, because the acquisition cost (AWP) of these three antibiotics together would be less than $10 per day. Therefore, there are important pharmacoeconomic reasons for selecting monotherapy over multiple-drug therapy to reduce the cost-multiplying effect of IV administration costs to the total cost of antimicrobial therapy.

In most cases, the broad spectrum of antibiotics available today permits monotherapy; combination therapy is warranted in relatively few cases. The rationale for combination therapy includes (1) the prevention of resistance, (2) an increased antimicrobial spectrum, and (3) the potential synergy between the two agents.

With infectious disease, antibiotic combinations decrease resistance in only a few instances. This is best illustrated in the case of double or triple antituberculous therapy using carbencillin indanyl sodium (Geocillin®, Päitzer) plus gentamicin and with 5-flucytosine (Ancobon®, ICN) with amphotericin B (Fungizone®, Apothecan). Combinations of other antibiotics do not decrease resistance if one component has a high resistance potential. Newer antibiotics have such a wide spectrum that combination therapy is not usually needed to extend the spectrum, as with piperacillin/tazobactam (Zosyn®, Lederle),

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imipenem (Primaxin®, Merck), or meropenem (Merrem®, AstraZeneca).

Similarly, synergy is not needed for most bacterial infections; it occurs infrequently when two antibiotics are randomly combined. If synergy is desirable, it should be determined by testing in vitro; it should not be assumed that the combination of two antimicrobial agents will result in synergy.

The other obvious implication of the IV administration cost component is the absence of the IV expense when equivalent oral agents are used. Oral agents given in the same dose are much less expensive than their IV counterparts, and the IV administration charge is eliminated. Pharmacoeconomically, this means that the difference between the cost of IV and oral agents is magnified to an even greater extent.

OTHER COST FACTORS
Monitoring Costs
Various factors may need to be considered in relation to the acquisition and administration costs for hospitalized patients receiving IV antibiotic therapy, such as the cost of monitoring certain antibiotics. Traditionally, aminoglycosides have provided the best example of such hidden costs. For patients receiving IV gentamicin every eight hours, serial serum creatinine levels and periodic peak-and-trough gentamicin levels need to be monitored. The price of generic gentamicin might be less than $1 per day, but the cost of monitoring tests is often overlooked, even though this cost exceeds the acquisition cost of the drug itself. Antibiotics that warrant monitoring of platelets or periodic liver-function tests also illustrate cost factors that need to be calculated to determine the true cost of antimicrobial therapy with different agents.

Obligatory Costs of Additional Therapy
Obligatory combination therapy is another hidden cost factor to be considered in determining costs of antimicrobial usage. For example, the clinician who wishes to establish the cost of IV metronidazole (e.g., Flagyl®, Pharmacia) therapy for use in intra-abdominal or diabetic foot infections must consider the cost of the obligatory additional drug to be used with metronidazole. In diabetic foot infections, metronidazole is active against the Bacteroides fragilis portion of the infection, but another antimicrobial agent with antistaphylococcal and anaerobic gram-negative bacillary coverage must also be provided. The same is true for patients with intra-abdominal sepsis. Metronidazole should not be used alone and must always be combined with an agent with anaerobic gram-negative bacillary activity. For these reasons, the cost of the obligatory additional drug must be factored in to arrive at the actual cost of using metronidazole in this situation.

Side Effects
Side effects have been discussed in Part 4 of this series (P&T, September 2003). Antibiotics that are associated with laboratory abnormalities increase the institution’s actual cost of using the drug. Antibiotics that cause clinical side effects (e.g., Clostridium difficile diarrhea, seizures, phlebitis) should also be considered in any pharmacoeconomic analysis.

Resistance
The impact of resistant organisms in the hospital has been discussed in Part 3 of this series (P&T, August 2003). Using antibiotics with a known resistance potential may necessitate the use of other more expensive drugs if serious resistance problems are encountered. Opting for drugs with a low resistance potential minimizes the economic and medical implications of antibiotics that have been associated with problems of resistance.

Therapy Failure
The cost of failed therapy is not inconsequential and is often underestimated. It is important, from the start, to get things right. Patients’ needs are best served by initiating appropriate antimicrobial therapy as soon as possible after a working diagnosis is made, particularly in the case of patients who are critically ill. The sicker the patient, the more crucial it is to initiate the correct therapy at the outset.

A stepwise approach to antimicrobial therapy should be avoided because it is costly and forfeits precious time. If an antimicrobial that is less potent than another one is prescribed for a particular indication, the potential for a delayed or ineffective therapeutic response is present. Precious time is wasted when one awaits a therapeutic response that could have been achieved more quickly with a more effective agent.

The chances of curing an infection are best in the early stages. If there is a delay in therapeutic response or if therapy is unsuccessful, the patient must still be given a more potent antibiotic to eradicate the infection. A more potent and effective antibiotic might, in fact, appear to be more costly on a per-unit basis than a less effective antibiotic, but it is more cost-effective in terms of outcome because it does not result in drug-related failure. Sometimes the most effective agent is not the least expensive one to acquire but is, in the clinical setting, the one that is cost-effective, such as piperacillin/tazobactam, the carbapenems (e.g., meropenem), linezolid (Zyvox®, Pharmacia), and others.

PRINCIPLES OF COST-EFFECTIVE ANTIMICROBIAL THERAPY
Cost-effective antimicrobial therapy begins at the formulation level. P&T committee members who select antibiotics for each major clinical area of usage should choose one or two agents in each antibiotic category to meet the needs of the institution. The antibiotics in each category should satisfy all of the factors that are important in selection—the spectrum of coverage, appropriate pharmacokinetic properties, a low potential for resistance, and a good safety profile—before cost analysis is undertaken.

P&T committees should view the acquisition cost in the proper clinical perspective by taking into account the true cost of the antibiotic when IV administration charges are factored in. All other things being equal, the committee should opt for drugs with less frequent dosing intervals to minimize the impact of the cost of the IV route.
Intravenous-to-Oral Switch Therapy

Antibiotics that have an oral equivalent should have a decided advantage at the formulary level. With intravenously administered antibiotics, the single most important cost factor, after acquisition costs, is the frequency of administration. The single most important cost-saving strategy for institutions is an extensive IV-to-PO switch program. Because the cost of oral agents is generally much lower than that of their IV counterparts, every effort must be made to switch to equivalent oral therapy as soon as is clinically possible.

No other single change has the pharmacoeconomic implications of IV-to-PO switch therapy. Switching to oral antibiotic therapy means not only lower antibiotic costs but also fewer side effects and an earlier hospital discharge, thereby decreasing the patient’s length of stay—an important consideration in institutional reimbursement systems. The main attributes of oral antibiotic therapy, after cost considerations are taken into account, are the drug’s dosing frequency and safety profile, both of which affect patient compliance. The more expensive the oral agent, the more acceptable the inconvenience of frequent dosing and the additional side effects might be.12–17

Choosing the Preferred Antibiotic

At the hospital formulary level, rarely is the choice between a “good” agent and a “poor” one; rather, the choice is between good agents with minor differences in cost and side-effect profiles or resistance potentials. These represent the most difficult decisions that hospital formulary committees must make; in another sense, though, they are the least important problems faced by P&T committees, because either choice would be cost-effective and acceptable to most members of the hospital medical staff. Because expenses are an overriding consideration in today’s managed health care systems, cost considerations may persuade a formulary committee to accept a tolerable level of infrequent side effects to conserve financial resources. Only in rare circumstances should cost be the sole consideration in decision-making, however.

CONCLUSION

The hospital P&T committee’s task is best summarized as follows: to select IV antibiotics (preferably with longer dosing intervals, a low resistance potential, and a good safety profile) that have oral equivalents for an IV-to-PO switch program. Working in concert with the pharmacy department and infectious disease clinicians, P&T committees should implement a comprehensive IV-to-PO switch program in the institution.

The most cost-effective approach would be not to use not the least expensive agent but to use the one that is the most potent and free of side effects and resistance, with conversion to an oral equivalent as soon as possible in the clinical setting. It is essential to choose the best, but not necessarily the least expensive, agents for the initial critical phase of infection. Switching to an oral agent as early as possible is the most efficient use of hospital resources and therefore benefits both the patient and the institution.18–21

REFERENCES