Cost-Effective Antibiotic Prescribing

Richard Gleckman, M.D., and Nelson M. Gantz, M.D.

Antibiotics are often misused, resulting in a high frequency of adverse effects, emergence of drug-resistant organisms, and excessive costs. The high cost of antibiotics is currently receiving the greatest attention. Considerable cost savings can be achieved by appropriate prescribing of antibiotics for patients receiving these drugs prophylactically as well as for those with established infections. This article cites specific examples of how cost-effective antibiotic prescribing practices can realize substantial cost savings without any diminished quality in patient care.
(Pharmacotherapy 1983; 3:239–248)

OUTLINE

Cost-Effective Prophylaxis

Therapy of Established Disease

 Appropriate Indications
 Use of "Therapeutic Equivalents"
 Single Agent Therapy
 Oral versus Parenteral Route
 Treatment Duration
 Hidden Costs
 Self or Family Administration

Control of Antibiotic Misuse

From the Division of Infectious Disease, Saint Vincent Hospital and University of Massachusetts Medical Center, Worcester.
Address reprint requests to Richard Gleckman, M.D., Saint Vincent Hospital, 25 Winthrop Street, Worcester, MA 01604.

No class of drugs in the hospital formulary is currently receiving closer scrutiny than the antibiotics. These agents are being subjected to intensive examination because of increased pharmaceutical lobbying efforts, concern over the emergence of drug-resistant organisms, and the continuous introduction of new compounds. Undoubtedly, however, the keen interest in antibiotics primarily stems from the fact that, as a class of drugs, they account for the single largest component of the pharmacy budget. In this age of cost-containment antibiotics will continue to remain in the limelight, particularly for those pharmacists and hospital administrators dedicated to holding the fiscal line.

We shall identify antibiotic prescribing practices, both prophylactic and therapeutic, that can be changed to permit cost reductions. We will also describe innovative approaches that are being implemented to counteract the spiraling costs of health delivery.

Cost-Effective Prophylaxis

It is often unappreciated that between one-fourth and one-half of all antibiotics prescribed within a hospital are dispensed for prophylaxis. Most of these agents are administered to surgical patients to prevent postoperative infections. It thus becomes apparent that if guidelines for perioperative antibiotic use are complied with, significant cost savings can be realized.

Postoperative wound infections are not only unsightly, but they contribute to morbidity and, most importantly, constitute a threat to the patient's life. These postoperative infections can cause extensive focal infection, bacteremia, hematogenous dissemination, septic shock and multiple organ failure. In addition, postoperative wound infections significantly increase the expense of hospitalization.[1]

Prophylactic antibiotics are indicated exclusively for selective clean and clean-contaminated surgical procedures. Clean procedures are those in which neither the respiratory, alimentary, genitourinary, or oropharyngeal cavities are entered and there is no break in technique. Clean-contaminated procedures are those in which these cavities are entered without unusual contamination. Antibiotic prophylaxis is indicated for a "clean" procedure when a prosthesis is being implanted, or the risk exists for a catastrophic infection. Antibiotic prophylaxis is indicated for a "clean-contaminated" procedure when the incidence and consequences of infection are great, and the responsible organisms are predictable and susceptible to antibiotics. Infections that are associated with frankly contaminated and dirty procedures merit antibiotics, but here the indication is not prophylaxis but definitive therapy of an established infection.

A number of factors have been identified that contribute to postoperative wound infections. Surgical factors have included the duration of the operation, the extent of local contamination, and the presence of hematomas, debris and foreign bodies.[2] Host factors that predispose to wound infections include age greater than 60 years, malnutrition, obesity, diabetes mellitus, malignant diseases and the presence of remote infection.[3]

Concerns about prophylactic antibiotics have focused on four issues: drug expense, adverse drug reactions, alterations in the patient's indigenous microflora with the risk for superinfection, and the emergence of drug-resistant organisms that pose a threat to other patients exposed to the hospital flora. These concerns can only be allayed by the intelligent use of perioperative antibiotics in well defined indications. Preferred prophylactic antibiotics should be nontoxic, inexpensive, and possess activity against the major pathogens likely to be encountered in the operative area. However, the antibiotics need *not* be active against every bacterial species present in the operative area. A very limited role exists for the second generation agent cefoxitin, and no indication exists for the third generation cephalosporins cefotaxime, moxalactam, and cefoperazone for perioperative prophylaxis.[4] These more expensive agents have not been found to be more effective than less expensive agents, and their unrestrained use could encourage the emergence of drug-resistant organisms.

Effective antibiotic prophylaxis requires attainment of significant tissue concentrations during the "critical period", the period of the early inflammatory response to bacterial contamination. As a general rule adequate tissue concentrations of an antibiotic during the critical period can be obtained by a single dose of the drug administered shortly before the operation, and additional doses dispensed either earlier or later are usually unnecessary. The most common error in surgical prophylaxis appears to be excessive duration of administration.[5] No study indicates value to extending prophylaxis beyond 48 hours. Limiting perioperative antibiotic prescribing to the first 48 hours would reduce drug-related adverse reactions, the rate of emergence of resistance microorganisms, and the cost of medications.

Table 1, 2, and 3 outline those clean and clean-contaminated surgical procedures that merit perioperative prophylactic antibiotics. The tables describe the indication for prophylaxis and also provide a recommended antibiotic program.

Among the first generation cephalosporins cefazolin is probably the preferred agent for prophylaxis. This drug produces the highest and most sustained serum concentrations, can be given as infrequently as every 8 hours, and when administered according to a three times daily schedule, is the least expensive cephalosporin. When cefaxolin is prescribed for prophylaxis 1 gram of the drug should be administered i.m. on call to the operating room or i.v. at anesthesia induction.

Prophylactic antibiotics are also indicated for patients with congenital valvular disease, acquired valvular heart disease or prosthetic valves who are to be subjected to dental, urinary tract, biliary tract or lower intestinal tract instrumentation or surgery. The prophylaxis is designed to prevent bacterial endocarditis. Detailed recommendations have been previously published to assist the physician in managing these patients.[6] The suggestion has also been made that patients with orthopedic implants be considered candidates for prophylactic antibiotics when they are exposed to procedures that could result in bacteremia. The implant could serve as a locus minoris resistentiae, and a deep wound infection would ensue. This suggestion has, however, neither been confirmed nor refuted by properly executed prospective controlled studies.

Table 4 lists those operative procedures where prophylactic antibiotic administration has been a common practice despite the lack of controlled studies and scientific justification. We feel that perioperative antibiotics should not be routinely prescribed for these procedures until properly performed clinical studies document their value.

Therapy of Established Disease

Appropriate Indications

Major cost savings and a reduction of adverse effects can be attained by appropriate antibiotic usage. A number of investigations have confirmed that at least 25 to 50% of prescribed antibiotics are not indicated. Approximately one quarter to one half billion dollars could be saved annually in the United

Table 1. "Clean" Surgical Procedures

Procedure	Infectious Event	Common Pathogen(s)	Antibiotic	Duration
Coronary artery bypass	Sternal wound infection	*Staphylococcus aureus*	First generation cephalosporin	Not to exceed 48 hours
Insertion of prosthetic heart valve	Endocarditis	*Staphylococcus aureus, Staphylococcus epidermidis*	First generation cephalosporin	Not to exceed 48 hours
Resection of abdominal aorta	Graft, deep wound infection	*Staphylococcus aureus,* Coliforms	First generation cephalosporin	Not to exceed 48 hours
Femoral artery bypass	Graft, deep wound infection	*Staphylococcus aureus,* Coliforms	First generation cephalosporin	Not to exceed 48 hours
Insertion of prosthetic hip	Prosthetic infection	*Staphylococcus aureus, Staphylococcus epidermidis*	First generation cephalosporin or oxacillin	Not to exceed 48 hours
Internal fixation of hip fracture	Deep wound infection	*Staphylococcus aureus*	First generation cephalosporin or oxacillin	Not to exceed 48 hours

Table 2. "Clean-Contaminated" Surgical Procedures

Procedure	Infectious Event	Common Pathogen(s)	Antibiotics	Duration
Radical neck dissection in which upper aerodigestive tract is opened from the neck	Deep wound infection	*Staphylococcus aureus,* Streptococci Klebsiella sp, Peptococci, Peptostreptococci Bacteroides sp (Usually not *B. fragilis*)	Cefazolin	One day
Elective vaginal hysterectomy	Pelvic cellulitis vaginal cuff abscess, pelvic abscess	Enterococci, Bacteroides sp *E. coli*	Cefazolin	One day
Elective abdominal hysterectomy	Wound infection, pelvic infection	Streptococci, Peptococci Peptostreptococci, Staphylococci, Bacteroides sp	Cefazolin	One day
Cesarian section (initial for "high risk" patients)[a]	Wound infection, endometritis	Streptococci, Peptococci, Peptostreptococci Bacteroides sp	Cefazolin administered after the umbilical cord is clamped	One day

[a]High risk patients for Cesarean section prophylaxis include women from the lower socioeconomic status, obese women and patients who have internal fetal monitoring. Some experts also recommend prophylaxis for those women with prolonged labor, membranes ruptured more than 6 hours or women subjected to multiple vaginal examinations.

States, without compromising patient care by more appropriate antibiotic prescribing.[1-9] One example of the problem of antibiotic misuse is the practice of prescribing antibiotics for those disorders in which studies have failed to demonstrate any benefit from drug therapy. No justification exists to treat non-pregnant women or elderly chronically catheterized patients with asymptomatic bacteriuria.[10] Similarly, antibiotics appear to be of no proven value when administered to patients with acute symptomatic bronchitis or acute symptomatic exacerbations of chronic bronchitis.

Acute bronchitis, an inflammatory disorder of the trachea and bronchi, occurs predominantly in the winter and is often preceded by an upper respiratory infection. Invariably a self-limited disease, acute bronchitis is caused most frequently by viruses. Antibiotic treatment is not indicated for this inflammatory process. Acute exacerbations of chronic bronchitis, consisting of a change in the color, consistency and amount of sputum as well as increasing cough and dyspnea, have been ascribed to viruses (rhinovirus, coronavirus, influenza), *Mycoplasma pneumoniae* and bacteria, including *Haemophilis influenzae,*

Table 3. "Clean-Contaminated" Surgical Procedures

Procedure	Infectious Event	Common Pathogen(s)	Antibiotic	Duration
Gastroduodenal surgery ("high risk" patient)[a]	Prevent wound infection	Streptococci Coliforms	Cefazolin	One day
Biliary surgery ("high risk" patient)[b]	Prevent wound infection	E. coli, Klebsiella sp Streptococci, Clostridia, Enterococci	Cefazolin	One day
Elective colorectal surgery	Prevent wound infection	E. coli, other coliforms Bacteroides (including B. fragilis), other Anaerobes	Erythromycin base with neomycin	Afternoon and night prior to surgery
Elective colon surgery (patient unable to take oral medication)	Prevent wound infection	E. coli, other coliforms, Bacteroides (including B. fragilis), other Anaerobes	Cefoxitin	Single injection prior to surgery

[a]High risk patients for gastroduodenal surgery include those patients operated on for gastric ulcer, gastric carcinoma, bleeding duodenal ulcer and obstructing duodenal ulcer.

[b]High risk patients for biliary surgery include those patients older than 70 years and patients with an obstructed biliary tract, or who have had prior biliary tract surgery.

Streptococcus pneumoniae, gram-negative bacilli and "normal respiratory flora." Antibiotics have been prescribed to shorten the duration of the exacerbation, prevent respiratory failure or forestall progressive pulmonary deterioration that often occurs in patients with chronic bronchitis. No evidence has emerged that antibiotics can accomplish any of these desired goals. In fact, Nicotra and associates could not document any beneficial effect by the addition of antibiotics to the conventional modes of therapy in patients with acute exacerbations of chronic bronchitis requiring hospitalization.[12]

It has become ritual to prescribe antibiotics to noncompromised patients with localized cutaneous abscesses. For patients with normal host defenses drainage is adequate therapy, and antibiotics are not indicated.[13]

In addition to the problem of prescribing antibiotics for disorders in which no benefit has been established, physicians often equate "best" treatment with the newest, invariably more expensive, antibiotic.

Table 4. Prophylaxis Common Despite Scientific Proof

1. Pacemaker implantation
2. Insertion of ventricular shunts for hydrocephalus
3. Cystoscopy when the urine is sterile
4. Transurethral resection of the prostate when the urine is sterile
5. Transhepatic cholangiogram
6. Simple hand laceration
7. Third molar surgery

Penicillin G remains the drug of choice for pneumococcal pneumonia, community-acquired aspiration pneumonia, dental infections, streptococcal pharyngitis and syphilis. Although the more expensive cephalosporins possess an expanded spectrum of activity, cure rates are not improved by prescribing these antibiotics instead of penicillin. Only when controlled studies show enhanced efficacy or reduced toxicity should the newer, more expensive agent be prescribed. Similarly, the inexpensive sulfonamides remain highly effective agents to treat community-acquired symptomatic bacterial cystitis in women.[14] In the absence of a history of an allergic reaction to sulfonamide, there is no reason to prescribe the more expensive compounds, such as cefaclor, cephalexin, cefadroxil, nitrofuratoin or trimethoprim-sulfame-thoxazole, when treating a woman with symptomatic, community-associated bacterial cystitis.

Use of "Therapeutic Equivalents"

Generic gentamicin is available at a cost that is approximately one-third that of the other aminoglycosides tobramycin, netilmicin, or amikacin. For hospitals, particularly community hospitals, where gentamicin-resistant Gram negative bacilli are uncommon pathogens, generic gentamicin can be selected as the preferred aminoglycoside. In other hospitals, generic gentamicin can be substituted for the other aminoglycosides as soon as results of antibiotic susceptibility tests permit. For patients with suspected or established infections caused by Pseudomonas aeruginosa, tobramycin should be selected while awaiting the results of antibiotic susceptibility tests. Tobramycin is also preferred by some experts for treating patients with renal insufficiency who have infections requiring an aminoglycoside; the rationale

is based on a lower frequency of nephrotoxicity, as measured by serum creatinine values. Amikacin should be selected to treat infections caused by *Proteus vulgaris* or *Providencia stuartii* while awaiting susceptibility reports. For patients with nosocomial gram negative infections requiring an aminoglycoside, tobramycin or amikacin should be selected initially if gentamicin resistant strains are prevalent in the hospital. As soon as the results of antibiotic susceptibility tests are available, gentamicin can be substituted for tobramycin or amikacin. With the above exceptions, gentamicin can be selected initially or after the results of susceptibility tests are known; this strategy will result in considerable cost savings to patients.

Cephalosporins account for up to one third of total pharmacy drug expenditures. The first generation cephalosporins cephalothin, cephapirin and cefazolin have essentially the same spectrum of activity. Pharmacokinetically, cephalothin and cephapirin are interchangeable, but use of cephapirin can result in substantial savings. Because of its more favorable pharmacokinetic profile, cefazolin can be given in doses that are one third those of cephalothin or cephapirin, with comparable effectiveness. Cefazolin also requires less frequent dosing per day than cephalothin (four versus six times). Since cefazolin can be given intramuscularly, intravenous administration costs are saved. Cefazolin also is subject to competitive pricing since it is sold by two drug companies. With desirable pharmacokinetic properties as well as the ability to purchase the drug on bid, cefazolin is probably the first generation cephalosporin of choice.

Single Agent Therapy

A common error in antibiotic prescribing is the failure to modify therapy when the results of antimicrobial susceptibility tests are available. An example of this error is the severely ill patient presenting with high fever, sweats, chills, hypotension and no obvious source of infection. Broad spectrum therapy with two antibiotics is usually prescribed pending the results of cultures and antimicrobial susceptibility tests. Initial therapy should not dictate later therapy, however. When the infecting organism is known and the susceptibility report is available, it is often possible to discontinue the initial broad spectrum combination drugs and prescribe a single, less expensive and potentially less toxic agent. While multiple drugs may be preferred therapy to treat selected infections such as *Pneumocystis carinii* pneumonia, malaria, toxoplasmosis, tuberculosis, enterococcal endocarditis, infection caused by *Psuedomonas aeruginosa* or gram negative bacteremia in an immunosuppressed host, a single pathogen usually requires therapy with only one antibiotic.[15] Prescribing more than one drug to the patient is not only more expensive, but this practice often entails greater risk for untoward events.

The use of a combination of antibiotics has been the conventional initial therapy for patients with intraabdominal and pelvic sepsis. Until the results of cultures and susceptibility tests are available, usually an aminoglycoside with clindamycin, metronidazole, chloramphenicol or one of the extended spectrum pencillins (carbenicillin or ticarcillin) is prescribed to assure activity for the anaerobic components, particularly *Bacteroides fragilis,* as well as the facultative gram-negative rods contributing to these infections.[16] Recently, cefoxitin therapy has been compared with the combination of clindamycin plus amikacin for the treatment of mixed aerobic/anaerobic infections.[17] A prospective randomized trial of 70 patients given these therapies revealed no difference in therapeutic efficacy or incidence of toxicity. However, the cost of cefoxitin therapy was significantly less than the cost of the drug combination.[17] These results were confirmed in a subsequent study of 90 patients given either cefoxitin or a combination of clindamycin and an aminoglycoside for the treatment of polymicrobial pelvic and abdominal infections.[18] Therefore, it appears that cefoxitin alone may well be as safe and therapeutically effective as the standard combination treatments when it is administered to selected patients with community-acquired mixed anaerobic/aerobic infections that result from appendicitis, diverticulitis, bowel trauma, pelvic inflammatory disease or endometritis. However, it would be preferable to add an aminoglycoside to cefoxitin for those patients with intraabdominal or pelvic infections who have received antibiotics within the preceding weeks or who have experienced a nosocomial abdominal or pelvic infection.

Oral versus Parenteral Route

Considerable cost savings can be achieved by changing from parenteral to oral antibiotic administration and by replacing hospitalization with carefully supervised home treatments. Oral therapy eliminates the cost of intravenous solutions and sets and the personnel time involved in preparation and infusion. Recent studies have confirmed the efficacy and reduced expense of oral antibiotics prescribed for selected children with osteomyelitis and septic arthritis.[19-22] In 1973, it was reported that favorable results ensued when oral antibiotic therapy was prescribed for hospitalized patients with serious infections.[23] Fourteen patients with osteomyelitis were treated successfully with oral cephalexin after they had received a short course of parenteral cephaloridine. However, it was not until 1978 when Tetzlaff and associates reported on 35 children with osteomyelitis and septic arthritis, who had been treated with a brief initial course of intravenous therapy followed by oral antibiotics, that major attention was directed to this novel cost saving approach.[20] The children with acute osteomyelitis and septic arthritis were hospitalized for the entire course of therapy. Parenteral therapy was given initially for about one week, and

then oral antibiotics were administered for a mean of approximately 3 weeks. Drug absorption was monitored by measuring serum antibiotic concentrations and by determining serum bacterial activity. The oral antibiotics were well tolerated and all infections except one responded well.[20] In 1979, Prober and associates reported on their experience treating 63 children with serious staphylococcal infections (predominantly osteomyelitis). The children were treated with a short course of parenteral therapy followed by oral administration of antibiotics.[24] Once the children became asymptomatic they were discharged from the hospital for supervised oral therapy at home. The children were seen once or twice weekly in an outpatient setting; serum bactericidal levels of the antibiotics were monitored.

This report and subsequent studies appear to indicate that with careful monitoring oral antibiotic therapy can be as effective as the standard prolonged intravenous therapy for specific skeletal infections in children.[25, 26] Oral therapy is cost effective, particularly when given at home, and this form of treatment is not associated with the inherent risks of intravenous infusion, namely, chemical phlebitis and bacteremia. Home oral therapy permits increased patient comfort for the child. However, oral therapy necessitates careful sequential clinical monitoring; demonstration of therapeutic serum bactericidal antibiotic concentrations is essential.[24] Since follow-up evaluations beyond 2 years on children who have received oral therapy have not been reported, prolonged vigilance will be required to detect recrudescent disease; relapses have been detected more than 10 years after the first attack of osteomyelitis.[26]

Hospitalization and parenteral antibiotic therapy has been considered the conventional treatment program for women with acute symptomatic community-acquired bacterial pyelonephritis. However, this infection can be treated in an outpatient setting when diagnosis is secure, the patient does not appear "toxic", the patient can tolerate oral medication, clinical and laboratory "follow-up" can be obtained, and the patient has not recently received antibiotics or been subjected to instrumentation. Trimethoprim-sulfamethoxazole possesses a spectrum of activity that encompasses most organisms that cause community-oriented bacterial pyelonephritis in women, and this drug has been successfully used for the outpatient treatment of symptomatic pyelonephritis.[27]

Metronidazole administered orally is well absorbed even in the presence of food. Consequently, the serum concentrations of metronidazole that are achieved are similar after either oral or intravenous administration of the drug.[28] Patients who are responding to parenteral metronidazole therapy can be successfully switched to oral metronidazole when the clinical situation dictates, and this results in substantial savings. If a patient is unable to swallow tablets, the drug can be given as a liquid preparation that can be formulated by the hospital pharmacist.

Treatment Duration

Duration of drug therapy contributes to antibiotic costs. Virtually all recommendations as to how long drug therapy should continue are empiric, even for common disorders such as pneumococcal pneumonia and streptococcal cellulitis.[29, 30] Since limited information is available on the precise duration of drug therapy, patients are probably treated for unnecessarily long periods. As new data emerge, however, we learn that antibiotic therapy can often be shortened, thereby resulting in cost savings and diminished toxicity.

Single dose therapy has emerged as the preferred treatment tactic for acute, symptomatic bacterial cystitis in young women.[14] When compared to the conventional 7–10 day course of treatment single dose therapy is less expensive, safer, equally effective, and associated with better compliance. Single dose treatment of women with bacterial cystitis has not resulted in bacteremias, hospitalization or death.[31] Single dose treatment should be limited to women who are not pregnant, have neither renal insufficiency nor structural abnormalities of the urinary tract, and are able to provide post-treatment cultures. The following antimicrobial agents are safe and effective single dose therapy: sulfisoxazole 1 g; trimethoprim 80 mg; trimethoprim-sulfamethoxazole 2 regular-strength tablets and amoxicillin 3 g.[4–5] No explanation exists for why cephalosporins have consistently failed as single dose therapy.[14]

A single oral dose of 2 grams of metronidazole (eight 250 mg or four 500 mg tablets) is less expensive, as effective, and as well tolerated as the conventional 7–10 day course of therapy to treat vaginitis caused by *Trichomonas vaginalis*.[32] Studies have also documented the efficacy of shorter treatment courses employing regimens of ampicillin, tetracycline or erythromycin to treat disseminated gonococcal infection.[33] Formerly, disseminated gonococcal infections were treated for a minimum of 2 weeks by the intravenous route exclusively. Adults with disseminated gonococcal infection can be effectively treated with a one week program consisting initially of 2 million units of penicillin G administered every 4 hours followed by oral ampicillin or amoxicillin prescribed as 500 mg four times daily.[34, 35] Hospitalization is usually recommended to establish the diagnosis of disseminated gonococcal disease since misdiagnosis occurs not infrequently with this disorder.[33] Selected patients can complete the oral regimens in an outpatient setting or, alternatively, they can be treated entirely without hospitalization.[35] Acceptable oral regimens consist of giving amoxicillin (500 mg four times daily), tetracycline (500 mg four times daily), or erythromycin (500 mg four times daily) for at least 7 days.[35] The following requirements should be met before home treatment is recommended: the diagnosis should be well established; the patient should be considered compliant; complications, such as purulent joint effusions, must be

absent; and the patient must be able to return for follow-up observations.

The standard treatment for pulmonary tuberculosis consists of the combination of isoniazid (INH)-ethambutol, INH-rifampin, or rifampin-ethambutol prescribed for 18–24 months. Prolonged chemotherapy is expensive and is associated with compliance and toxicity problems. Studies have confirmed that specific regimens given for 6 to 12 months to adults with uncomplicated pulmonary tuberculosis are as effective as more prolonged therapy and have the advantage of being less expensive and well tolerated.[36, 37] Short course treatment regimens for adults consist of administering INH (300 mg) and rifampin (600 mg) daily for 6 to 12 months. If the patient has had previous antituberculosis therapy or has emigrated from an area such as Asia or Africa, where high levels of initial drug resistance exist, then the INH-rifampin should be supplemented with streptomycin (12–25 mg/kg), pyrazinamide (30 mg/kg), or ethambutol (15–25 mg/kg) daily for the first 2 months, pending the results of susceptibility tests. If resistance to INH or rifampin is found by susceptibility tests, then short course chemotherapy is not indicated. A regimen should be selected using two or three drugs to which the organisms are susceptible, and it should be given for a period of 18 to 24 months.[38] For the abbreviated treatment to be successful, patient compliance is critical. Patients should be seen monthly, pill counts should be performed, urines should be tested for the presence of INH and rifampin, and bacteriologic examinations of sputum must be done. Treatment should be continued until at least 6 months have elapsed from the time of conversion of the sputum culture from positive to negative. For most patients, the total duration of therapy will be 9 months. Patients should be followed closely for 1 year after completing the short course regimen in order to detect relapse. For non-compliant patients, after an initial phase of daily INH-rifampin treatment administered for 1 to 2 months, therapy can be continued twice-weekly with INH (15 mg/kg) and rifampin (600 mg) for 7 to 10 months.[38] The medications must be administered under supervision, and patients who receive intermittent rifampin should be monitored for the development of thrombocytopenia and a "flu syndrome." These abbreviated treatments cannot be recommended for children, for patients harboring drug-resistant organisms, for patients with extra-pulmonary tuberculosis, for patients with unique predisposing concomitant disease, such as silicosis or diabetes, or patients who have experienced previous drug failure or microbiological relapse.

Conventional therapy for endocarditis caused by penicillin-susceptible streptococci, defined as those strains with a minimum inhibitory concentration of $\leq$ 0.1 μg/ml, consist of either 12 million units of penicillin per day administered intravenously alone for four weeks or 12 million units of parenteral penicillin for four weeks and concomitant streptomycin (1 g/day)

during the initial two weeks. A regimen consisting of penicillin and streptomycin prescribed for only two weeks appears to be as safe and as effective as these four week regimens.[39, 40] No data are available showing that the relapse rate after the two week treatment course exceeds that of the conventional 4–6 week treatment program. The patients are treated in the hospital and receive procaine penicillin (1.2 million units every six hours) and streptomycin (500 mg every 12 hours) intramuscularly for 2 weeks. Short term therapy is not, however, recommended for patients who have had symptoms that exceed three months or have infection involving a prosthetic valve.[39] Preexisting vestibular disease, the presence of complications, (mycotic aneurysm, shock, cerebritis), abnormal renal function, or the identification of streptococcal endocarditis caused by resistant (MIC > 0.1 μg/ml) or nutritionally dependent strains precludes short course therapy. The principal disadvantages of the two week regimen are the frequent intramuscular injections required and the risk of streptomycin-induced otoxicity.

Hidden Costs

The total cost of antibiotic therapy consists of a number of components, only one of which is the drug price. "Hidden" costs — administration sets and supplies, tests for laboratory monitoring, pharmacy preparation time and nursing time — are usually omitted in cost analyses. These ancillary costs can account for approximately one-half of the total expense of antibiotic therapy.[41] Potentially less toxic antibiotics that require minimal laboratory monitoring for evidence of adverse reactions can decrease drug costs. For example, laboratory monitoring of renal function and aminoglycoside serum concentrations can contribute as much as one-third of the total antibiotic costs when aminoglycoside antibiotics are prescribed.[41] An antibiotic such as cefazolin that possesses desirable pharmacokinetic properties (i.e., infrequent dosing, reduced dosage and diminished nephrotoxicity when compared with other first generation cephalosporins) and can be prescribed by the intramuscular route can decrease these "hidden" costs considerably. For example, by substituting intramuscular cefazolin for an intravenous beta-lactam resistant penicillin, a savings of $78 per day could occur.[42] When studies demonstrate that different antibiotics provide equivalent therapeutic efficacy and safety, these "hidden" costs should be considered when antibiotic recommendations are being offered.

Self or Family Administration

Prolonged administration of intravenous antibiotics, i.e., therapy that exceeds 4 weeks in duration, has emerged as the preferred treatment course for patients with osteomyelitis, infective endocarditis and systemic fungal infections. Traditionally, these patients have remained in the hospital for the dura-

tion of treatment even though one to two weeks after the onset of therapy many patients feel well and are anxious to return home to complete their treatment. One innovative approach to the treatment of these serious infections has focused on the use of self-administration of intravenous antibiotics in the home.[43, 44] The cost of home parenteral antibiotic therapy is about one-fourth to one-third of the in-hospital cost.[45]

The concept of home intravenous therapy is not new. Successful home intravenous programs have included patients with hemophilia who receive clotting factors, patients with parenteral alimentation, and patients sustained by chronic hemodialysis. In 1974, Rucker and Harrison were the first investigators to report on the use of intravenously administered antibiotics given in the home.[43] Sixty-two children with cystic fibrosis were treated at home with either intravenous gentamicin or colistimethate for the management of Pseudomonas-related pulmonary infections. In that study, 127 infectious episodes were treated at home, resulting in a 68% reduction in the need for hospitalization. The patients were seen once weekly, and no major complications were noted.[43] Subsequent reports on parenteral administration of antibiotics at home appeared in 1978,[45, 46] (Table 5) and to date 363 patients have been treated at five centers in the United States and Canada.[44–50] Almost half of the patients (150) were treated at home in a program developed at the Fairfax Hospital, a large community-teaching hospital in the Washington, D.C. area.[44]

Patients selected for home treatment are considered to have responded satisfactorily to the intravenous program initiated in the hospital and require only a more extended course of intravenous antibiotics. Home intravenous programs are coordinated by a team consisting of infectious disease specialists, pharmacists and nurses skilled in performing intravenous infusion. One to two days prior to discharge the patients and a family member are taught the techniques necessary to care for an i.v. cannula. The cannula is changed twice a week at home by a visiting nurse or in the hospital's outpatient department. The duration of home i.v. therapy averaged two to three weeks. In each of the published series, patients with osteomyelitis and septic arthritis have predominated, but patients with other infections have also been successfully managed (Table 5). A vast array of antibiotics have been used, and the solutions, which have been prepared in the hospital pharmacy, are kept refrigerated at home. Antibiotics with long half-lives, such as cefazolin, are preferred since they permit dosing every six or eight hours. Patients may be given a four or five day supply of antibiotic, depending on the stability of the drug, and they are instructed to return to the outpatient department once or twice weekly to have their progress evaluated. All studies have monitored patients for complications of the initial infection, compliance, adverse effects, including antibiotic toxicities and i.v. compli-

cations, and superinfection. To date, all programs have confirmed the safety and efficacy of this form of therapy. Long-term follow-up is not available in all of the studies, but short term efficacy data parallel the experience of in-hospital care.[44] Patients have been able to return to work and to school.

Home antibiotic programs require compliant patients, appropriate close monitoring, and the 24 hour-a-day availability of a hospital team consisting of a pharmacist, i.v. nurse and physician. Successful programs also require that insurance carriers reimburse patients for these out-of-hospital extended charges. To date, Medicare has not paid for outpatient antibiotic therapy, and some insurance carriers will reimburse policy holders for only 80% of the charges.

It appears that for selected patients substantial cost savings can be realized with this novel approach to prolonged antibiotic therapy.[51] Success of home intravenous antibiotic programs mandates careful selection of patients. Those selected must be well enough to go home (except for the need for intravenous therapy), be compliant, and be proficient or have a family member trained in the administration and aseptic care of an i.v. cannula.

Control of Antibiotic Misuse

Various strategies have been advocated to reduce antibiotic misuse. Approaches have included physician education, omission from formulary, restriction of selected antibiotics by pharmacists or infectious disease specialists, peer audits of prescribing practices, and surveillance of drug use by clinical pharmacists.[52] An additional strategy for improving antibiotic prescribing practices consists of providing more readily accessible information on antibiotics to clinicians.[53] Unfortunately, these efforts have often had limited success.[54] In a study by Jones et al, hospital staff did not improve their usage of antibiotics after an intensive educational program.[54] A greater impact on unjustified antibiotic usage has been reported in studies employing direct control measures. Substantial savings resulted when usage of selected antibiotics required either an infectious disease consultation or written justification by the physician.[55, 56] McGowan and Finland demonstrated that by removing an antibiotic from the restricted list, there was a marked increase in usage of that agent.[57] In a study by Durbin and associates, physicians were required to indicate the rationale for antibiotic usage.[58] Depending on the category selected, drugs were discontinued after 2 days for prophylaxis, after 3 days for empirical therapy, and after 7 days for a therapeutic indication. A new prescription form had to be completed for the drug to be reordered. This program resulted in a 50% reduction in the mean duration of antibiotic prophylaxis. There was, however, little impact on antimicrobial use on the medical service with the prescription system.

Another approach that could reduce indiscriminate antibiotic usage is for hospitals to develop their own antibiotic guidelines similar to those developed

Table 5. Self Administration of Parenteral Antibiotics at Home

Author	Location	Year	Number of Patients	Diagnosis (Number of Patients)	Duration of Follow Up	Outcome: % Failure
Antoniskis et al[46]	Oregon	1971–76	13	Osteomyelitis (11) Endocarditis (2)	4–6 mo	8
Stiver et al[45]	Winnipeg	1974–76	23	Osteomyelitis and septic arthritis (14) Endocarditis (2) Other (7)	Not stated	Frequency of adverse effect and outcome similar to hospital treated patient
Stiver et al[50]	Winnipeg	After 1976	95	Osteomyelitis and septic arthritis (45) Endocarditis (14) Cystic fibrosis (10) Other (26)	Not stated	10
Kind et al[48]	Minnesota	1976–77	15	Osteomyelitis (8) Endocarditis (2) Septic arthritis (2) Other (3)	12–36 mo	0
Williams et al[47]	Minnesota	1977–79	59	Osteomyelitis (?) Other (?)	Not stated	—
Swenson[49]	Washington	1979	8	Osteomyelitis (4) Other (?)	Not stated	—
Poretz et al[44]	Virginia	1980	150	Osteomyelitis (82) Septic arthritis (12) Pyelonephritis (10) Wound infection (10) Other (36)	Not stated	0.5 (Short term efficacy)

by the Veterans Administration Ad Hoc Interdisciplinary Advisory Committee on Antimicrobial Usage.[59] The guidelines should be developed by a multidisciplinary committee composed of physicians who prescribe antibiotics as well as representatives from infectious diseases, pharmacy, and hospital administration.[60] There should be agreements as to what constitutes appropriate and unacceptable antibiotic usage. Once antimicrobial surveillance data to monitor compliance are accumulated, corrective action will require peer pressure from chiefs of services and strong administrative support.

References

1. **Green JW, Wenzel RP.** Postoperative wound infection: a controlled study of the increased duration of hospital stay and direct costs of hospitalization. Ann Surg 1977;185:264–8.
2. **Howard JM, Barker WF, Culbertson WR et al.** Postoperative wound infections: the influence of ultraviolet irradiation on the operating room and of various other factors. Ann Surg 1964;160(suppl):32–81.
3. **Ehrenkranz NJ.** Surgical wound infection occurrence in clean operations. Am J Med 1981;70:909–14.
4. **Gleckman R, Gantz NM.** The third-generation cephalosporins: a plea for restraint. Arch Intern Med 1982;142:1267–8.
5. **Shapiro M, Townsend TR, Rosner B et al.** Use of antimicrobial drugs in general hospitals: patterns of prophylaxis. N Engl J Med 1979;301:351–5.
6. **Kaplan EL, Anthony BR, Bisno A et al.** Prevention of bacterial endocarditis. Circulation 1977;56:139A–143A.

7. **Kunin CM, Tupasi T, Craig WA.** Use of antibiotics: a brief exposition of the problem and some tentative solutions. Ann Intern Med 1973;79:555–60.
8. **Simmons HE, Stolley PD.** This is medical progress? Trends and consequences of antibiotic use in the United States. JAMA 1974;227:1023–8.
9. **Maki DG, Schuna AA.** A study of antimicrobial misuse in a university hospital. Am J Med Sci 1978;275:271–82.
10. **Gleckman R.** The controversy of treatment of asymptomatic bacteriuria in nonpregnant women-resolved. J Urol 1976;116:776–7.
11. **Tager IB, Speizer FE.** Role of infection in chronic bronchitis. N Engl J Med 1975;292:563–71.
12. **Nicotra MB, Rivera M, Awe RJ.** Antibiotic therapy of acute exacerbations of chronic bronchitis. A controlled study using tetracycline. Ann Intern Med 1982;97:563–71.
13. **Meislin HW, Lerner SA, Graves MH et al.** Cutaneous abscesses. Ann Intern Med 1977;87:145–9.
14. **Fang LST, Rubin NET, Rubin RH.** Clinical management of urinary tract infection. Pharmacotherapy 1982;2:91–9.
15. **Rahal JJ Jr.** Antibiotic combinations: the clinical relevance of synergy and antagonism. Medicine 1978;57:179–95.
16. **Harding GKM, Buckwold FJ, Ronald AR et al.** Prospective, randomized, comparative study of clindamycin, chloramphenicol, and ticarcillin, each in combination with gentamicin, in therapy for intraabdominal and female genital tract sepsis. J Infect Dis 1980;142:384–93.
17. **Scheife RT, Tally FP, McGowan K et al.** Cost comparison of two antimicrobial regimens for treating mixed aerobic-anaerobic infections. Am J Hosp Pharm 1981;38:1466–9.
18. **Drusano GL, Warren JW, Saah AJ.** A prospective randomized controlled trial of cefoxitin versus clindamycin-aminoglycoside in mixed anaerobic-aerobic infections. Surgery 1982;154:715–20.
19. **Feigin RD, Pickering LK, Anderson D et al.** Clindamycin treatment of osteomyelitis and septic arthritis in children. Pediatrics 1975;55:213–23.
20. **Tetzlaff TR, McCracken GH, Nelson JD.** Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr 1978;92:485–90.
21. **Bryson YJ, Connor JD, LeClerc M et al.** High-dose dicloxacillin treatment of acute staphylococcal osteomyelitis in children. J Pediatr 1979;94:673–5.
22. **Dunkle LM, Brock N.** Long-term follow-up of ambulatory management of osteomyelitis. Clin Pediatr 1982;21:650–5.

23. **Walker SH.** Staphylococcal osteomyelitis in children. Success with cephalordine-cephalexin therapy. Clin Pediatr 1973;12:98–100.
24. **Prober CG, Yeager AS.** Use of the serum bactericidal titer to assess the adequacy of oral antibiotic therapy in the treatment of acute hematogenous osteomyelitis. J Pediatr 1979;95:131–5.
25. **Kolyvas E, Ahronheim G, Marks MI et al.** Oral antibiotic therapy of skeletal infections in children. Pediatrics 1980;65:867–71.
26. **Prober CG.** Oral antibiotic therapy for bone and joint infections. Pediatr Infect Dis 1982;1:8–10.
27. **Abraham E, Baraff LJ.** Oral versus parenteral therapy of pyelonephritis. Curr Ther Res 1982;31:536–42.
28. **Shank WA, Amerson AB.** Metronidazole: an update on its expanding role in clinical medicine. Hosp Form 1981;16:283–97.
29. **Anon.** For how long should antimicrobial therapy continue (editorial). J Infect 1980;2:299–301.
30. **Neu HC.** Current practices in antimicrobial dosing. Rev Infect Dis 1981;3:12–8.
31. **Fang LST, Rubin NET, Rubin RH.** Efficacy of single-dose and conventional amoxicillin in urinary-tract infections localized by the antibody coated bacteria technique. N Engl J Med 1978;298:413–6.
32. **Lossick JG.** Treatment of Trichomonas vaginalis infections. Rev Infect Dis 1982;4(suppl):801–18.
33. **Thompson SE III.** Treatment of disseminated gonococcal infections. Sex Trans Dis 1979;6(suppl):181–4.
34. **Thompson SE III.** Gonococcal tenosynovitis-dermatitis and septic arthritis. JAMA 1980;244:1101–2.
35. **Anon.** Sexually transmitted diseases treatment guidelines. Morbidity Mortality Weekly Reports 1982;31(suppl):335–605.
36. **Dutt AK, Jones L, Stead WW.** Short-course chemotherapy for tuberculosis with largely twice-weekly isoniazid-rifampin. Chest 1979; 75:441–7.
37. **British Thoracic Association.** A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report: Results during the 24 months after the end of chemotherapy. Am Rev Resp Dis 1982;126:460–2.
38. **Anon.** Guidelines for short-course tuberculosis chemotherapy. Morbidity Mortality Weekly Reports 1980;29:97–105.
39. **Wilson WR, Geraci JE.** Antimicrobial therapy for penicillin-sensitive streptococcal infective endocarditis: Two-week regimens. In: Bisno AL, ed. Treatment of infective endocarditis. New York: Grune and Stratton, 1981: 61–73.
40. **Tan JS, Terhune CA Jr, Kaplan S et al:** Successful two-week treatment schedule for penicillin-susceptible streptococcus viridans endocarditis. Lancet 1971;2:1340–3.
41. **Rapp RP, Bannon CL, Bivins BA.** The influence of dose frequency and agent toxicity on the cost of parenteral antibiotic therapy. Drug Intell Clin Pharm 1982;16:935–8.
42. **Dudley M, Barriere S.** Cost comparisons among antimicrobial agents (letter). N Engl J Med 1982;307:689.
43. **Rucker RW, Harrison GM.** Outpatient intravenous medications in the management of cystic fibrosis. Pediatrics 1974;54:358–60.
44. **Poretz DM, Eron LJ, Goldenberg RI et al.** Intravenous antibiotic therapy in an outpatient setting. JAMA 1982;248:336–9.
45. **Stiver HG, Telford GO, Mossey JM et al.** Intravenous antibiotic therapy at home. Ann Intern Med 1978;89:690–3.
46. **Antoniskis A, Anderson BC, Volkinburg JV et al.** Feasibility of outpatient self-administration of parenteral antibiotics. West J Med 1978;128:203–6.
47. **Williams DN, Kind AC, Gibson JA et al.** Outpatient intravenous antibiotics experience with 65 patients. Am J Intrav Ther Clin Nutr 1982;9:33–40.
48. **Kind AC, Williams DN, Persons G et al.** Intravenous antibiotic therapy at home. Arch Intern Med 1979;139:413–5.
49. **Swenson JD.** Training patients to administer intravenous antibiotics at home. Am J Hosp Pharm 1981;38:1480–3.
50. **Stiver HG, Trosky SK, Cote DD et al.** Self-administration of intravenous antibiotics: an efficient, cost-effective home care program. CMA J 1982;127:207–11.
51. **Frame PT.** Outpatient intravenous antibiotic therapy (editorial). JAMA 1982;248:356.
52. **Kunin CM.** Evaluation of antibiotic usage: A comprehensive look at alternative approaches. Rev Infect Dis 1981;3:745–53.
53. **Cooke D, Salter AJ, Phillips I.** Antimicrobial misuse, antibiotic policies and information resources. J Antimicrob Chemother 1980;6:435–43.
54. **Jones SR, Barks J, Bratton T.** The effect of an educational program upon hospital antibiotic use. Am J Med Sci 1977;273:79–85.
55. **Zeman BT, Pike M, Samet C.** The antibiotic utilization committee: An effective tool in the implementation of drug utilization review that monitors the medical justification and cost of antibiotic use. JAMA 1974;48:73–6.
56. **McGowan JE Jr, Finland M.** Infection and antibiotic usage at Boston City Hospital: Changes in prevalence during the decade 1964–1973. J Infect Dis 1974;129:421–8.
57. **McGowan JE Jr, Finland M.** Usage of antibiotics in a general hospital: effect of requiring justification. J Infect Dis 1974;130:165–8.
58. **Durbin WA Jr, Lapidas B, Goldmann DA.** Improved antibiotic usage following introduction of a novel prescription system. JAMA 1981;246: 1796–1800.
59. **Kunin CM, Efron HY.** Guidelines for peer review, Veterans Administration Ad Hoc Interdisciplinary Advisory Committee on Antimicrobial Use, Audits of Antimicrobial Usage. JAMA 1977;237:1001–7, 1134–7, 1241–5, 1366–9, 1481–4, 1605–8, 1723–5, 1859, 1860, 1967, 1968, 1968–70.
60. **Counts GW.** Review and control of antimicrobial usage in hospitalized patients. JAMA 1977;238:2170–2.