SUPPLEMENT ARTICLE

# Outpatient Parenteral Antimicrobial Therapy Today

**Joseph A. Paladino[1,2] and Donald Poretz[3]**

[1]Clinical Outcomes Research, CPL Associates, Amherst, and [2]Pharmacy, State University of New York at Buffalo, Buffalo, New York; and [3]Infectious Diseases Physicians, Annandale, Virginia

**Since its introduction in the 1970s, outpatient parenteral antimicrobial therapy (OPAT) has become a standard modality for patients with many infections requiring long-term intravenous antibiotic therapy. Delivery of OPAT may occur in physicians' offices, hospital clinics, specialized infusion centers, and currently most often, patient's homes, often self-administered. Patients are selected for OPAT by physicians familiar with both the course of their infections, their personal suitability for outpatient care, and the availability of reimbursement. OPAT is reportedly safe, effective, practical, and cost-effective. An OPAT Outcomes Registry contains information from >11,000 antibiotic courses administered from 1997 through 2000. Although a number of studies are purported to analyze the economic impact of OPAT on health care, a comprehensive, clinical outcomes-based pharmacoeconomic analysis, as described here, has, to our knowledge, yet to be done.**

A study from Minneapolis in 1977 [1] and studies from Oregon [2] and Canada in 1978 [3] demonstrated the feasibility of providing home intravenous (IV) antibiotic therapy to small numbers of persons well enough to leave the hospital but requiring continued IV therapy. Five years later, a home parenteral antibiotics service of a community hospital reported successful treatment of >150 patients with invasive infections, including osteomyelitis, bacteremia, septic arthritis, infected orthopedic appliance, pyelonephritis, and wound infection [4]. By 1998, an estimated 250,000 persons were being treated with outpatient IV antimicrobials annually, generating almost $2 billion in revenue [5]. The growth rate of the practice (then called community-based parenteral anti-infective therapy), estimated to be >10% annually, was fueled by a variety of factors, including increased emphasis on cost containment, the availability of antibiotics that can be administered once or twice daily, technological advances in vascular access and infusion devices, increased acceptance by both patients and physicians, and the increasing availability of structured services [6].

Reprints or correspondence: Dr Donald Poretz, Infectious Diseases Physicians, 3289 Woodburn Rd, Annandale, VA 22003 (donald2750@aol.com).

**Clinical Infectious Diseases 2010; 51(S2):S198–S208**

1058-4838/2010/5106S1-0004$15.00
DOI: 10.1086/653520

Renamed outpatient parenteral antimicrobial therapy (OPAT) in the early 2000s, the practice has become a standard modality for patients with stable infections requiring long-term IV antibiotics, such as osteomyelitis [7]. Many patients who, in the early days of OPAT, were hospitalized to initiate therapy and ensure a stable clinical status now begin and complete parenteral therapy in an outpatient program. In fact, OPAT has become a routine recommendation for many infections, including community-acquired pneumonia [8] and osteomyelitis [9].

## DELIVERY OF OPAT

OPAT is delivered according to 3 basic models: by a physician or other health care professional at an infusion center, by a visiting nurse or other health care professional at home, or by self- or caretaker-administration at home (Figure 1) [10]. A fourth model of OPAT, not described here, is encountered in long-term care facilities. For example, physicians familiar with OPAT may admit patients from either an acute care facility or home to a convalescent center, assisted living facility, skilled nursing facility, or long-term acute care hospital and act as their attending physician [11]. Alternatively, an infectious diseases clinician on the medical staff of a long-term care facility, having trained an OPAT team, can consult on any patient as requested by an attending physician. Each delivery model has its own distinct advantages and disadvantages.

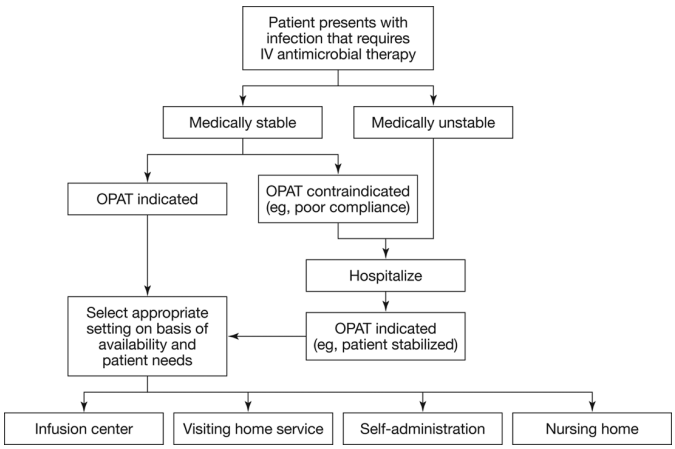


**Figure 1.** Models of outpatient parenteral antimicrobial therapy (OPAT) delivery. Adapted with permission from [10]. IV, intravenous.

***The infusion center.*** The infusion center model, which can be provided in a hospital clinic, an emergency department, a physician's office, or a freestanding OPAT facility, has the advantages of a readily available medical staff, equipment, and supervised administration but requires overhead costs and maintenance; its major disadvantage is that patients must travel to be treated [10]. Regardless of setting, such centers function essentially as day hospitals, a good way to extend hospital-level care to an outpatient setting. The change from hospital to outpatient facility is less drastic for patients than going directly to home care and may therefore be more acceptable to medical personnel and patients. A successful program can be expanded to also include home infusion, administered by a nurse specialist, the patient, or a trained caregiver. One limitation of the infusion center model is the difficulty of treating patients who need parenteral therapy more than once daily, putting a premium on medications that can be given once daily or on programmed infusion devices. In addition, physicians are restricted by Federal law from referring the patient to any outpatient care providers with whom they have a financial interest [10].

***The visiting nurse model.*** The visiting nurse model of OPAT offers the advantage of providing medical supervision during administration of parenteral therapy at home but can be costly [10]. A major advantage of home-based infusion is that it allows a nurse to evaluate the home situation for factors often overlooked in the hospital. The nurse can assess issues that could affect a patient's therapy in the home, such as the physical limitations and hazards in the home and disability or drug or alcohol abuse among family members. A limitation in this model may be the cost of a nurse specialist's time and travel. In some urban settings, 1 nurse can easily visit 5–10 patients in 1 working day, whereas in rural areas, travel time alone may make this cost prohibitive. Here again, antibiotics with very long half-lives and/or programmed infusion devices and patient and caretaker training are required to avoid the need for parenteral therapy >1 time per day and the associated increased costs in nursing services that may result .

***Self-administration.*** The concept of patient self-administration arose from successful experience in training patients and their families to provide long-term total parenteral nutrition at home [12]. The days-to-weeks–long courses of IV antibiotics required for severe infections are now being self-administered by many patients, particularly those who feel otherwise well enough to return to work or school. (However, because of recent changes in pharmacy practice, for sterility concerns, it is no longer acceptable for patients to mix their own infusion medications, except for those that cannot be mixed in an infusion pharmacy clean room because of cost or short shelf life.) The self-administration model offers considerable financial savings, although an infusion facility may still be needed to provide initial doses of antimicrobials, vascular access, patient training, pharmacy services, and medical supervision.

A recent report of home IV antimicrobial therapy involved 205 patients discharged from a Veterans Affairs tertiary care medical center that had an infectious diseases clinic, including a trained outpatient IV infusion team [13]. During the 3.5 years (July 2000 through December 2003) of the study, patients received 231 courses of home IV antimicrobials: 107 among those aged ⩾60 (mean age, 69) and 124 among those aged <60 years (mean age, 51).

The most common indications for therapy were osteoarticular infection (52%), bacteremia (14%), and skin and soft-tissue infections (13%) [13]. *Staphylococcus aureus* was the predominant pathogen (39% of all episodes). Of the *S. aureus* isolates identified among older and younger patients, 26% and 11%, respectively, were methicillin resistant; these percentages would likely be much higher at present, because of the increasing prevalence of methicillin-resistant *S. aureus* (MRSA) infection and the increasing presence of community-associated MRSA [14]. Underlying illnesses included diabetes mellitus,

**Table 1. Key Elements Required for an Outpatient Parenteral Antimicrobial Therapy (OPAT) Program**

| Element |
|---|
| Health care team |
| An infectious diseases specialist or physician knowledgeable about infectious diseases and the use of antimicrobials in OPAT |
| Primary care or referring physicians available to participate in care |
| Nurse expert in intravenous therapy, access devices, and OPAT |
| Pharmacist knowledgeable about OPAT |
| Case manager and billing staff knowledgeable about therapeutic issues and third-party reimbursements |
| Access to other health care professionals, including a physical therapist, a dietitian, an occupational therapist, and a social worker |
| Communications |
| Physician, nurse, and pharmacist available 24 h per day |
| System in place for rapid communication between patient and team members |
| Patient education information for common problems, adverse effects, precautions, and contact lists |
| Outline of guidelines for follow-up of patients with laboratory testing and intervention as needed |
| Written policies and procedures |
| Outline of responsibilities of team members |
| Patient intake information |
| Patient selection criteria |
| D. Patient education materials |
| Outcomes monitoring |
| Patient response |
| Complications of disease, treatment, or program |
| Patient satisfaction |

**NOTE.** Reprinted from [29].

coronary artery disease, neuropathy, and peripheral vascular disease. Most patients had percutaneous IV central catheter (PICC) lines placed before hospital discharge; tunneled central venous catheters and infusion ports were rarely used unless chemotherapy or parenteral nutrition was also required.

A member of the IV therapy team, who verified that patients could safely perform infusions at home, instructed patients, their families, or other caregivers in infusion techniques [13]. Patients and their families assumed responsibility for storage and mixing of the antimicrobial agents, infusion of the drug, flushing of the catheter, and daily observation of the catheter site. For only 10 courses in older patients and 3 in younger patients, a visiting nurse helped with the infusion. Dressings over the catheter site were changed weekly, either by visiting nurses or, for patients who could travel, during a weekly visit to the hospital's infectious diseases clinic.

Vancomycin was the antimicrobial agent most frequently used (46% of all episodes), with cefazolin, ceftriaxone, and ertapenem covering most others. Nephrotoxicity was observed in 10 courses (4.3%). Venous access device complications were frequent but rarely serious, with the most common being occlusion of a PICC line. A total of 27 courses in older patients (25%) and 27 courses in younger patients (22%) resulted in cure by the end of home IV antimicrobial therapy. Home IV antimicrobial therapy was considered as failure in only 9 cases in older adults (8%) and 7 courses in younger adults (6%).

Overall, 70 courses in older patients (65%) and 89 in younger patients (72%) were deemed to have resulted in stable or improved infections at the conclusion of IV therapy [13]. Oral antimicrobial therapy, mostly for osteoarticular and complicated skin and soft-tissue infections, was given when home IV antimicrobials were finished in patients with stable and improved infection. Home IV antimicrobial therapy was considered as failure in only 9 courses (8.4%) in older and 7 (5.6%) in younger adults was and, in all cases, was attributed to a difficult-to-treat infection and not to the choice of home IV therapy [13].

***The home infusion company.*** The most common method of OPAT delivery in the United States is a combination of the visiting nurse and self-administration model, sometimes offered as an extension of an infusion center, whether based in the hospital, a doctor's office, or a visiting nurse service [10]. More often, however, home infusion services are coordinated by a commercial company, usually organized around pharmacy ser-

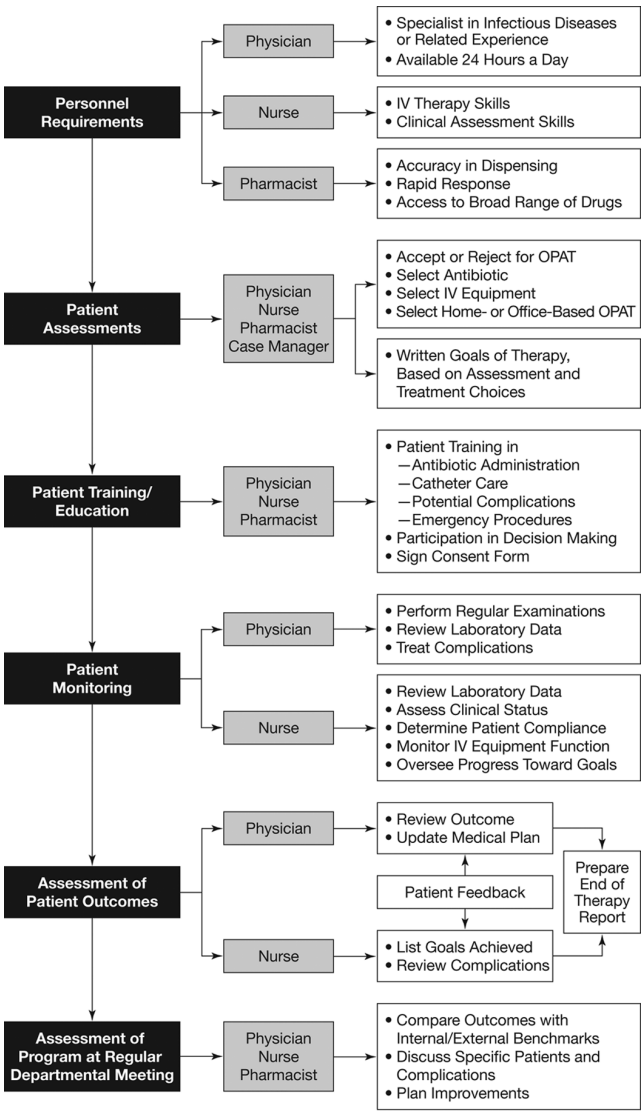


**Figure 2.** The outpatient parenteral antimicrobial therapy (OPAT) team. Adapted with permission from [18]. ©1998 WB Saunders Company; published by Elsevier. IV, intravenous.

vices. Such companies provide nurses and pharmacists who are trained in OPAT medication and IV equipment. A hospital may contract with a home infusion company to assume all or part of the duties involved in delivering OPAT. The hospital may provide initial patient assessment and training with the company providing the actual treatment, or the hospital may provide nursing care, with the company responsible only for provision of drugs and possibly expert infusion nurse backup and support. State licensure is required in most states for provision of hands-on nursing care in a patient's home and for preparation and dispensing of medications for patient self-administration at home [10]. Finally, home infusion therapy may be offered by large home care agencies that deliver a variety of nursing services to home care patients.

In any case, attending or referring physicians prescribe the drug and indicate the duration of therapy and the clinical and laboratory parameters to be monitored throughout the course of treatment. The prescribing physician bears ultimate responsibility for the care of the patient and the outcome of his or her therapy regardless of who administers the medication: nurse specialist, patient, or caregiver [15].

The health maintenance organization (HMO) structure is well suited to the provision of OPAT. Patients can be referred from many sources, including primary care physicians, emergency departments, infectious diseases consultants, nurses, pharmacists, and hospital discharge planners. Reimbursement issues do not occur because all HMO services are automatically covered, and physician supervision and control are usually ensured.

Table 1 outlines the key elements required for an OPAT program [10]. Regardless of organizational structure, OPAT

**Table 2. Criteria for Evaluation and Selection of an Outpatient Parenteral Antimicrobial Therapy (OPAT) Provider**

| Criterium |
|---|
| Medical director or advisor knowledgeable in infectious diseases and OPAT |
| Outlined roles of prescribing physician, medical director, nurse, and pharmacist |
| Standards for nurse, pharmacist, physician, and other patient care personnel regarding training, experience, and licensure |
| Accreditation or certification (eg, JCAHO) |
| Experience providing OPAT |
| Policies |
| Frequency of physician and nurse clinical assessments |
| Staffing and on-call policies |
| Frequency of reports to physicians |
| Reporting of laboratory results to physicians within 24 h |
| Willingness to share local quality assurance and outcomes information |
| Willingness to share charge information regarding individual patients |

**NOTE.** JCAHO, Joint Commission on the Accreditation of Healthcare Organizations. Adapted from [29].

requires communication and coordination of effort among the prescribing physician, nurse specialist, pharmacist, and patient. The benefits of a team approach to OPAT have been well documented [6, 16, 17]. Figure 2 describes the general responsibilities of each member of the team [10, 18].

Factors to be considered by physicians in selecting an OPAT provider agency are outlined in Table 2 [10]. Although not complete, the outline may provide referring physicians with a useful checklist of the basic elements required of any program that provides IV infusion therapy. The referring physician must always keep in mind, however, that he or she remains responsible for the referred patient's care regardless of who actually administers treatment. The checklist may also be helpful in making comparisons among available programs.

## PATIENT SELECTION FOR OPAT

Although no inviolate rules govern the selection of patients for OPAT, responsible physicians must choose candidates on the basis of their assessment of each patient's clinical status, including the medical stability of infection, and their relationship with and/or confidence in available OPAT programs [19]. In general, patients should be afebrile with stable vital signs, and the infection should be reasonably stabilized and nonprogressive. At least 1 report describes early discharge of patients with cellulitis, community-acquired pneumonia, or pyelonephritis before defervescence, however, which did not adversely affect outcomes [20]. This finding corroborates the results of an earlier study of carefully selected hospitalized patients who received an abbreviated course of IV antibiotic therapy, followed by a switch to potent oral agents to complete the therapeutic course. In that study, it was required that patients demonstrate an improvement of clinical signs and symptoms of infection and be able to take and absorb oral medications [21]. Of course, any concomitant disease should also be stabilized. Some diagnoses, such as endocarditis, community-acquired pneumonia in frail older persons, sepsis, and central nervous system infections, may be best managed with an initial hospitalization period. However, even some of these conditions have been treated using OPAT alone in accordance with a responsible physician's judgment [10, 22–24].

Patients who require other treatments, such as wound care, ventilatory support, physical therapy, or frequent diagnostic studies, can often be treated outside the hospital with careful planning and adequate support systems [19]. Patients, family members, or other caregivers can be trained to change dressings, maintain equipment, and report observations. If treatments require skilled personnel, agencies can often provide the needed ancillary services.

Because the opportunity to inspect a patient's home environment before discharge from the hospital and beginning outpatient therapy is rare, the prescribing physician must rely on thorough interviews with patients and their caregivers to determine that a minimum level of safety and support will be available [19]. Any question regarding such issues should be answered by a home visit. Patients receiving OPAT should have running water, adequate light and heat, and refrigeration available to store compounded medications. Access to a working telephone is essential to ensure connection to professional or emergency assistance. Adequate transportation to the clinic for evaluation is also required.

The availability of reimbursement must be a factor in patient selection. Most private health insurance plans cover OPAT; in fact, some have come to expect it as the standard of care, to the point where they may refuse to cover further hospitalization [19]. Medicare covers the drugs but not the infusion supplies or service required for OPAT. Secondary insurance will sometimes cover extra charges related to OPAT, but this is quite variable.

When the US Congress passed the Medicare Modernization Act in 2003, lawmakers added coverage for home infusion drugs, including antibiotics, antivirals, and antifungal agents [25]. Unfortunately, the Centers for Medicare and Medicaid Services interpreted the law to cover only the drugs and not the services and supplies associated with home infusion therapy, including pharmacy and care coordination services, medical supplies and equipment, and nursing services. As a result, Medicare patients who are candidates for home infusion therapy must stay in the hospital, live in a nursing home, or travel to a physician's office, clinic, or emergency department that offers OPAT. Needless to say, this is not only inconvenient or difficult

**Table 3. Properties of Frequently Prescribed Antimicrobials at Various Temperatures**

| Drug | Half-life, h | Phlebitis risk rating[b] | Optimal dilution,[c] mg/mL | Duration of stability, by storage temperature[a] | | |
|---|---|---|---|---|---|---|
| | | | | −20°C | 5°C | 25°C |
| Acyclovir[d] | 2–3.5 | 1 | 5 | ND | 37 days | >37 days |
| Amphotericin B | 24–360 | 3 | 0.1 | ND | 35 days | 5 days |
| Liposomal amphotericin B | 24–360 | 2 | 4 | ND | 24 h | 5 days |
| Amphotericin B lipid complex | 24–360 | 2 | 1 | ND | 48 h | 6 h |
| Ampicillin | 1 | 2 | 30 | ND | 48 h | 8 h |
| Ampicillin-sulbactam | 1 | 2 | 20 | ND | 48 h | 8 h |
| Caspofungin | >48 | 1 | 0.2–0.3 | ND | 24 h | 1 day |
| Cefazolin | 1–2 | 1 | 10–20 | 30 days | 10 days | 1 day |
| Cefepime | 2 | 1 | 5–10 | ND | 7 days | 1 day |
| Cefoperazone | 1.5–25 | 1 | 40 | 96 days | 80 days | 80 days |
| Ceftazidime | 1.4–2 | 1 | 1–40 | 90 days | 21 days | 2 days |
| Ceftriaxone | 5.4–10.9 | 1 | 10–40 | 180 days | 10 days | 3 days |
| Cefuroxime | 1–2 | 1 | 5–10 | 30 days | 180 days | 1 day |
| Chloramphenicol | 1.5–4 | 1 | 10–20 | 180 days | 30 days | 30 days |
| Clindamycin | 2–3 | 1 | 6–12 | 56 days | 32 days | 16 days |
| Daptomycin | 8.1 | 1 | ND | ND | 48 h | 12 days |
| Doxycycline[e] | 22–24 | 2 | 0.1–1 | 56 days | 48 h | 3 days |
| Erythromycin lactobionate | 1.5–2 | 3 | 0.1–0.2 | 30 days | 14 days | 1 day |
| Ertapenem | 4 | 2 | 20 | ND | 24 h | 6 h |
| Ganciclovir | 2.5–3.6 | 1 | 5 | 364 days | 35 days | 5 days |
| Gentamicin | 2–3 | 1 | 0.6–1 | 30 days | 30 days | 30 days |
| Imipenem-cilastatin | 0.8–1.3 | 2 | 2.5–5 | ND | 2 days | 10 h |
| Linezolid | 4.5 | 1 | 2 | ND | ND | ND |
| Meropenem | 1.5 | 1 | 5–20 | ND | 24 h | 4 h |
| Nafcillin | 0.5–1.5 | 3 | 2–40 | 90 days | 3 days | 1 day |
| Oxacillin | 0.3–0.8 | 2 | 10–100 | 30 days | 7 days | 1 day |
| Penicillin G[f] | 0.4–0.9 | 2 | 0.2 | 84 days | 14 days | 2 days |
| Quinupristin-dalfopristin | 3; 1 | 3 | 2 | ND | 54 h | 5 h |
| TMP-SMZ[d] | 8–11; 10–13 | 2 | 8 | ND | ND | 6 h |
| Tobramycin | 2–3 | 1 | 0.2–3.2 | 30 days | 4 days | 2 days |
| Vancomycin | 4–6 | 2 | 5 | 63 days | 63 days | 7 days |

**NOTE.** Adapted from [29]. ND, no data; TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Data are from [30].

[b] Degree of tendency to cause phlebitis: 1, mild; 2, moderate; 3, high.

[c] Optimal solutions may vary from saline to 5% dextrose, depending on the antibiotics.

[d] Should not be refrigerated.

[e] Protect from sunlight.

[f] Degradation products can form after a few hours.

for Medicare patients, it also results in higher costs for the Medicare program.

In January 2009, bills that would extend coverage for home infusion services to Medicare beneficiaries, a benefit available to most patients in the private sector, were introduced in the House of Representatives (H.R. 574) and the Senate (S. 254), and both were referred to committee, the first step of the legislative process [25, 26]. These bills are both reintroductions of previous House and Senate bills that died in committee in 2007 and 2008 [25, 26].

## OUTPATIENT ANTIMICROBIALS

When selecting antimicrobials for OPAT, prescribing physicians must consider a number of factors in addition to those addressed in the hospital setting, including dosage schedules, long-term toxicity, and drug stability [10]. Almost any antimicrobial can be used, although drugs with long half-lives are the most frequently prescribed, with specific choices depending on patient population, likely diagnosis, anticipated duration of therapy, and physician preference. The cost effectiveness of the

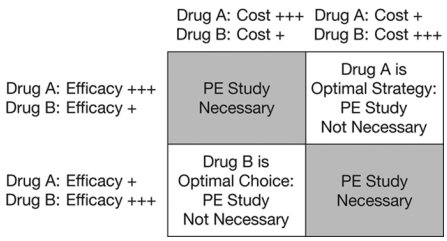


**Figure 3.** Evaluation of the necessity of economic analysis (comparison of drugs A and B). No study is needed if drug A costs more and is less effective *(bottom left)* or if drug B costs less and is more effective *(top right).* Analysis is necessary, however, when drug A costs more and is more effective *(lower left)* or when drug B costs less and is less effective *(top left).*

medications should also be considered, as long as patient care is not compromised.

Evidence of patient tolerance and a low incidence of toxic reactions are prerequisites for agents to be used outside the hospital, where patients cannot be closely monitored [10]. The prescribing physician and OPAT providers must be aware of the specific adverse effects associated with prolonged IV antimicrobial therapy, such as cytopenia or renal toxicity, both of which may occur after several weeks of apparently uneventful treatment.

The development of antimicrobials with long enough half-lives to permit infrequent administration has been a major factor contributing to the growth of OPAT. The less often a drug has to be administered, the more convenient therapy is for patients, thus facilitating compliance. Less frequent schedules also require less staff time in terms of training and troubleshooting. Currently, a number of antimicrobials can be given once daily, and at least one that promises a once-weekly administration schedule is awaiting Food and Drug Administration approval [27, 28]. Antimicrobial stability is another consideration unique to home administration, which often requires storage of a drug for at least a few days after being mixed. Table 3 lists the parameters of the antimicrobials used for OPAT [10, 29].

## VASCULAR ACCESS

Issues to be considered in initiating OPAT, in addition to type of infusion system, include the patient's clinical status, age, and vein condition; the diagnosis, current vascular access, antimicrobials prescribed, and frequency of administration; the need for a programmable infusion pump; and the anticipated duration of therapy [10, 31]. For example, conventional 1-in peripheral short catheters are appropriate for patients with good veins who are receiving a short course (rarely >10 days) of therapy. Because peripheral lines are associated with clotting, infiltration, and phlebitis, recommended standards, which are based on hospital rather than outpatient risks, require that lines be assessed daily and changed every 2 or 3 days [31]. Not all infusion programs comply with these standards, however; if patients are doing well, many OPAT providers find that they can leave lines in for a week [10]. Lines should be irrigated or flushed regularly, however, to ensure patency, generally once daily or after each infusion if administered more frequently.

Midline catheters that extend from an insertion site just distal to the antecubital fossa almost to the axillary vein are designed for therapy courses of 1–6 weeks [10]. Because blood flow is greater in the upper arm than in the lower arm, the midline catheter is associated with dilution of the pH and osmolarity of the infused agents, thus reducing the risk of infiltration and phlebitis.

Central venous catheters are recommended for infusion of some antimicrobials, such as vancomycin, potassium penicillin, amphotericin B, and quinupristin-dalfopristin, to prevent peripheral phlebitis [10]. The development of central lines that can be passed into the superior vena cava from a peripheral insertion site has proven to be a significant advantage for OPAT. Although some of these PICCs cause a sterile phlebitis for 5–10 cm from the insertion site within 1–2 days, this local reaction responds to hot packs and antiinflammatory agents. The length of the PICC should be recorded when it is placed and removed. A chest radiograph should be performed after placement to confirm the position of the catheter tip. Some PICCs have been left in place for >1 year. The PICC line is usually placed by an interventional radiologist or nurse specialist, either in the hospital before discharge or in an OPAT facility [32].

## ECONOMIC CONSIDERATIONS OF OPAT

The economic issues regarding the delivery of OPAT are multiple, varied, and depend on the perspective being examined [33]. Obviously, provision of IV therapy outside rather than

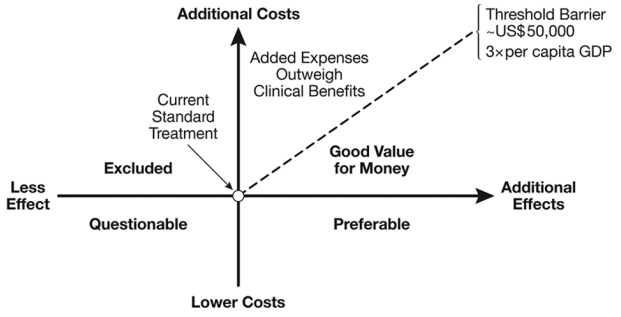


**Figure 4.** Identification of the quadrant in which a medication or clinical service is located. A new drug can be excluded if it costs more and has less effect than the agent currently being used *(upper left)* or it costs less and has greater effect *(lower right).* If, however, the drug costs less for less effect *(lower left)* or costs more for more effect *(upper right),* the former may or may not raise cost-benefit questions, but the latter raises the question of whether cost or benefit is higher—the basic question in pharmacoeconomic analysis. GDP, gross domestic product.

**Table 4. Outcomes Measures from the US Outpatient Parenteral Antimicrobial Therapy Outcomes Registry, Based on 7892 Cases and 10,844 Courses of Antimicrobial Therapy, 1997–2001**

| Variable | No. (%) of patients |
|---|---|
| Clinical outcome | |
| Improved | 7189 (96.6) |
| Failed | 92 (1.2) |
| No change | 153 (2.0) |
| Bacteriological outcome | |
| No culture | 6614 (88.8) |
| Culture negative | 666 (8.9) |
| Persistent pathogen | 109 (1.5) |
| New pathogen | 60 (0.8) |
| Program outcome | |
| Completed | 7096 (92.2) |
| Ended early | 323 (4.1) |
| Hospitalized | 275 (3.5) |
| Died | 39 (0.5) |
| Antibiotic outcome | |
| Completed | 8715 (82.1) |
| Adverse event | 492 (4.6) |
| Clinical failure | 78 (0.7) |
| Resistant organism | 44 (0.4) |
| Adverse events ($n$ = 593) | |
| Rash | 34 |
| Nausea/vomiting | 12.8 |
| Fever | 11.4 |
| Nephrotoxicity | 7 |

**NOTE.** Reprinted with permission from [45]. ©2002 by the British Society for Antimicrobial Chemotherapy.

inside the hospital is less costly. However, the interest of everyone involved—hospital administrator, payer, physician, provider, and patient—may not be served; each may or may not be aligned or oriented to outpatient care. The hospital, which is paid according to the number of occupied bed-days, may be threatened by OPAT. The living conditions of some patients may be inadequate or unsafe for OPAT. From the insurance company's perspective, the usual charge for a day of IV antibiotic treatment in a hospital is currently >$1000, compared with $200–$300 for OPAT [33]. The patient may realize no savings, but the ability to return to work or to maintain an income may be critical in supporting the family.

A major economic benefit of OPAT is the reduction in the cost of nosocomial infections, because outpatient care may reduce expenses, morbidity, and mortality. Approximately 5% of hospitalized patients develop an infection during hospitalization [34]. Each infection is estimated to cost $2100, with a total cumulative cost of >$2 billion annually. Moreover, hospitals are now recognized as dangerous and costly breeding grounds for multidrug-resistant organisms, including the currently epidemic MRSA. The economic liability of extended hospitalization because of MRSA infection, at a mean US hospital cost >$1000 per day, is enormous [35]. A multicenter study that evaluated the hospital-wide effects of drug resistance on duration of hospitalization and overall costs concluded that patients with MRSA bacteremia remained in critical care units a mean of 5 days longer than matched patients with methicillin-susceptible *S. aureus* bacteremia. Moreover, the hospital bills for patients infected with MRSA bateremia were a mean of $3000 more per patient [36]. Furthermore, as reviewed in a more recent study, the costs of treating hospitalized patients with MRSA infection, compared with those for treating patients with methicillin-susceptible *S. aureus* infection, increased by $9000–$17,422 per patient [37].

Comparison with hospitalization aside, little current information exists on which to base a pharmacoeconomic analysis of OPAT (Figure 3), although there have been a number of articles [38–45] describing the costs of OPAT over the past 25 years. The bottom line is that cost per day ranged from $122 in 1984 [38] to $183 in 2000 [42] to $107 (excluding cost of IV lines and vancomycin therapeutic drug monitoring) in 2002 [45] (2010 values: $263, $234, and $135, respectively). All represent a cost considerably less than that of 1 day in an acute care hospital. The definition of pharmacoeconomics, however, is a description and analysis of the cost and consequences (ie, outcomes) of pharmaceutical goods (ie, drugs) and services, such as OPAT, to patients, health care systems (ie, providers), and society.

As with any scientific study, the basic steps of an economic analysis begin with the question, how specific is the analysis to be? Then, from what or whose perspective is the analysis to be performed: patients, providers, payers, or society? Third, what are the outcomes to be assessed: mortality, morbidity, return to normal, or cure? Fourth, what is the alternative to the treatment program being analyzed (OPAT)? In this case, it is hospitalization.

Pharmacoeconomic analyses are performed according to one of several pharmacoeconomic methods: cost of illness, cost consequence, cost minimization, cost effectiveness, cost benefit, or cost utility. For example, a cost-benefit analysis (with a benefit-to-cost ratio) is appropriate for evaluating a program or service such as OPAT. Input is dollars, and outcome is dollars—a matter of return on investment. A cost-effectiveness analysis is generally used to compare the efficacy of competing medications in the treatment of specific disorders. Cost-utility analysis, which concerns quality of life or humanistic, patient-recorded outcomes, is not often performed for acute infectious diseases. Although validated instruments are available for measuring both the general and disease-specific aspects of patients' lives, there are no validated quality-of-life instruments specific to an infectious disease, except for HIV.

The next step is to measure resource consumption. How

**Table 5. Microorganisms Associated with Bacterial Osteomyelitis**

| Microorganism | Most common clinical association |
|---|---|
| *Staphylococcus aureus* (including methicillin-resistant strains) | Most frequent microorganism in any type of osteomyelitis |
| Coagulase-negative staphylococci | Associated with foreign body and after surgery, especially with prophylactic antibiotics |
| Enterobacteriaceae | Nosocomial infections or injection drug abuse |
| Streptococci | Associated with human or animal bites, diabetic foot ulcers, decubitus ulcers |
| Anaerobic bacteria | Associated with human or animal bites, diabetic foot ulcers, decubitus ulcers |
| Salmonella | Sickle cell disease |
| *Streptococcus pneumoniae* | Sickle cell disease |
| *Pasteurella multocida* | Animal or human bites |
| *Eikenella corrodens* | Animal or human bites |
| *Mycobacterium tuberculosis* | In tuberculosis-prevalent populations |

**NOTE.** Adapted with permission from [46]. ©1997 Massachusetts Medical Society. All rights reserved.



many antibiotic doses were given? How much fluid was used? How many days were spent in the hospital? A dollar amount is then placed on each resource according to the chosen perspective: is it a cost, a payout, or a charge? Then, whatever the perspective, the analysis is performed according to the chosen method.

When is an economic analysis necessary? Not, of course, for a drug or service that costs less and is more effective than the alternative drug or service, nor, conversely, for a new agent with higher cost and lower efficacy (Figure 3). However, the lower-cost or less-effective and higher-cost or more-effective agents raise questions of cost effectiveness (Figure 4). In short, despite the number of studies purported to analyze the economic impact of OPAT on health care, a comprehensive, clinical outcomes-based, properly conducted pharmacoeconomic analysis has not yet been done, to our knowledge.

## THE OPAT OUTCOMES REGISTRY

The US OPAT Outcomes Registry provides information about treated infections being treated [9], pathogens found, and primary antibiotics used, as well as information for sites to compare their own program over time and to benchmark themselves and their experience with the aggregate of the other sites [46]. Although no longer operational because of economic and staffing issues, it contains information from 24 contributing sites in the United States on >8000 patients who have received >11,000 antibiotic courses from 1997 through 2000.

Outcomes indicators have been developed for patients receiving OPAT, including measures of clinical and microbiological outcome and program success or failure. Adverse effects sufficient to stop therapy are also recorded (Table 4) [46]. In addition, data compiled from >500 patients with osteomyelitis in the United States found that lower-limb infections were most common (in 187 patients), followed by hand (36), lower torso (17), head (14), upper torso (12), arm (11), and neck (1) infections [9]. Among these patients, the most frequently used antibiotic was vancomycin, in part because of the increasing problems with MRSA. Although osteomyelitis is frequently treated for 4–6 weeks, duration varied greatly from patient to patient and also from the different reporting sites, because of the prevalence patterns of infecting organisms. The pathogens most frequently isolated in osteomyelitis are shown in Table 5 [47].

Bacteriologic outcome was assessed after a pathogen's identity was confirmed on repeat culture [9]. In 237 of the 255 patients analyzed for bacteriologic outcome, no culture was performed at the end of therapy. Of the 18 cultures that were performed, results were negative for 14; of the remaining 4 patients, 2 had developed a secondary infection with a different organism, and in 2, the original infecting organism had persisted. Clinical outcome determinations were made by the treating physician on the last day of therapy; subsequent follow-up was not possible because of time and economic issues. Of the 266 patients analyzed, only 3 experienced therapy failure and 4 others showed no change, for an overall adjusted failure rate of ~2.5%.

Future applications of the OPAT Outcomes Registry include assessment of new anti-infective agents, thus providing outcome indictors when new antibiotics are released, preventing selection bias in phase 2 and 3 trials by presenting data on all patients treated with the selected agent, and allowing continual follow-up for adverse effects of new antibiotics, an ongoing mechanism to compare them with the older agents [46]. The indicators of clinical, microbiological, and program outcomes will help in the evaluation of different treatment regimens, including the most effective antibiotic dosages and duration of

therapy. Such data can be presented in an interactive format, on the Internet or pocket PC devices, allowing an added perspective in antibiotic decision making with continual updating of a critical mass of data providing statistically significant values for analysis in many disease states. Finally, the registry data can be used to monitor antibiotic resistance by collecting microbiologic findings at the start and end of therapy.

## THE FUTURE

The administration of IV antimicrobials on an outpatient basis has been shown to be safe, efficacious, practical, and cost-effective. It also offers a more comfortable and productive alternative to patients, many of whom are able to return to their jobs, school, or other daily activities during treatment. Its limits remain uncertain, however, and its incipient problems remain unexplored. For example, much less supervision and environmental control is available in patients' homes than in the hospital. Patients are at greater risk of severe reactions to medication or rapid deterioration of their conditions, resulting in the refusal of some OPAT programs to accept patients without a telephone or ready access to transportation or ambulance services. The incidence of adverse events and their prevention has yet to be comprehensively studied.

Other challenging questions involve OPAT. Why, for example, must osteomyelitis be treated with IV antibiotics for 6 weeks, rather than 41 days or 42.7 days? Why not substitute well-absorbed oral drugs? Clinical studies are needed to answer these questions and are already being considered by the Infectious Diseases Society of America and the Food and Drug Administration.

Outpatient health care is involved in a diversity of commercial organizations. As large national health care corporations merge, promising increasingly great consolidation of the industry, small local companies continue to proliferate, contracting with third-party insurance companies, sometimes to the disadvantage of patients receiving OPAT [43]. According to the experience of at least 1 patient who was discharged to home after the initiation of infusion therapy, a home care company charged 500% more than the hospital for an infusion session [48]. In some cases, the hospital may elect to pay for the costs of uninsured patients receiving OPAT rather than absorb the costs of a hospitalization. The need for stricter controls and oversight of reimbursement is great and must be addressed. Thus, despite the many benefits of OPAT to the health care system, patients, and their families with regard to both cost benefit and quality of life, a number of challenges to its further growth and expansion remain to be confronted.

## Acknowledgments

***Potential conflicts of interest.*** J.A.P. is a consultant for, receives grant support from, and/or is a member of the speakers' bureau for Astellas, Cubist, Forest, Schering-Plough, Targanta (Medicines Company), and Wyeth. D.P. has received a research grant from Cubist Pharmaceuticals.

***Financial support.*** Cubist Pharmaceuticals.

***Manuscript preparation.*** Jean Fitzpatrick of the Curry Rockefeller Group provided assistance in preparing and editing the manuscript.

***Supplement sponsorship.*** This article is part of a supplement entitled "Meeting the Challenges of Methicillin-Resistant *Staphylococcus aureus* with Outpatient Parenteral Antimicrobial Therapy," which is based on the proceedings of an advisory board meeting of infectious diseases specialists in November 2007 that was sponsored by Cubist Pharmaceuticals.

## References

1. Kind AC, Williams DN, Gibson J. Outpatient intravenous antibiotic therapy: ten years' experience. Postgrad Med **1985**; 77:105–108, 111.
2. Antoniskis A, Anderson BC, Van Volkinburg EJ, Jackson JM, Gilbert DN. Feasibility of outpatient self-administration of parenteral antibiotics. West J Med **1978**; 128:203–206.
3. Stiver HG, Telford GO, Mossey JM, et al. Intravenous antibiotic therapy at home. Ann Intern Med **1978**; 89:690–693.
4. Poretz DM, Eron LJ, Goldenberg RI, et al. Intravenous antibiotic therapy in an outpatient setting. JAMA **1982**; 248:336–339.
5. Poretz DM. Evolution of outpatient parenteral antibiotic therapy. Infect Dis Clin North Am **1998**; 12:827–834.
6. Williams DN, Rehm SJ, Tice AD, Bradley JS, Kind AC, Craig WA. Practice guidelines for community-based parenteral anti-infective therapy. IDSA Practice Guidelines Committee. Clin Infect Dis **1997**; 25: 787–801.
7. Wynn M, Dalovisio JR, Tice AD, Jiang X. Evaluation of the efficacy and safety of outpatient parenteral antimicrobial therapy for infections with methicillin-sensitive *Staphylococcus aureus.* South Med J **2005**; 98: 590–595.
8. Gleason PP, Kapoor WN, Stone RA, et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. JAMA **1997**; 278:32–39.
9. Tice A. The use of outpatient parenteral antimicrobial therapy in the management of osteomyelitis: data from the Outpatient Parenteral Antimicrobial Therapy Outcomes Registries. Chemotherapy **2001**; 47(Suppl 1):5–16.
10. Tice AD. An overview of outpatient parenteral antimicrobial therapy. In: Tice AD, ed. Handbook of outpatient parenteral antimicrobial therapy. 2nd ed. Tarrytown, NY: CRG Publishing, **2005**:9–21.
11. Petrak RM. Outpatient antibiotic therapy in long-term care facilities. Infect Dis Clin North Am **1998**; 12:995–1008.
12. Howard L, Michalek AV. Home parenteral nutrition (HPN). Annu Rev Nutr **1984**; 4:69–99.
13. Cox AM, Malani PN, Wiseman SW, Kauffman CA. Home intravenous antimicrobial infusion therapy: a viable option in older adults. J Am Geriatr Soc **2007**; 55:645–650.
14. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; EMERGency ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med **2006**; 355:666–674.
15. Liang BA. Case in health law. Cost containment and physician obligations: mandates for patient advocacy. Virtual Mentor **2006**; 8: 157–161.
16. Rehm SJ. Outpatient intravenous antibiotic therapy for endocarditis. Infect Dis Clin North Am **1998**; 12:879–901.
17. Tice AD. Outpatient parenteral antimicrobial therapy for osteomyelitis. Infect Dis Clin North Am **1998**; 12:903–919.
18. Kunkel MJ. Quality assurance and outcomes in outpatient parenteral antibiotic therapy. Infect Dis Clin North Am **1998**; 12:1023–1034.
19. Nolet BR. Patient selection in outpatient parenteral antimicrobial therapy. Infect Dis Clin North Am **1998**; 12:835–847.
20. Eron LJ, Passos S. Early discharge of infected patients through appropriate antibiotic use. Arch Intern Med **2001**; 161:61–65.
21. Paladino JA, Sperry HE, Backes JM, et al. Clinical and economic eval-

uation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. Am J Med **1991**; 91:462–470.
22. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med **1997**; 336:243–250.
23. Fine MJ, Medsger AR, Stone RA, et al. The hospital discharge decision for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med **1997**; 157:47–56.
24. Fine MJ, Hough LJ, Medsger AR, et al. The hospital admission decision for patients with community-acquired pneumonia: results from the pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med **1997**; 157:36–44.
25. H.R. 574: Medicare Home Infusion Therapy Coverage Act of 2009. The Library of Congress. Thomas. http://www.govtrack.us/congress/bill.xpd?bill=h111-574. Accessed 30 November 2009.
26. S. 254: Medicare Home Infusion Therapy Coverage Act of 2009. The Library of Congress. Thomas. http://www.govtrack.us/congress/bill.xpd?bill=s111-254. Accessed 30 November 2009.
27. Chen AY, Zervos MJ, Vazquez JA. Dalbavancin: a novel antimicrobial. Int J Clin Pract **2007**; 61:853–863.
28. Das B, Sarkar C, Biswas R, Pandey S. Review: Dalbavancin—a novel lipoglycopeptide antimicrobial for gram-positive pathogens. Pak J Pharm Sci **2008**; 21:78–87.
29. Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy: IDSA guidelines. Clin Infect Dis **2004**; 38:1651–1672.
30. Williams DN, Raymond JL. Community-based parenteral anti-infective therapy (CoPAT): pharmacokinetic and monitoring issues. Clin Pharmacokinet **1998**; 35:65–77.
31. Gorski LA. Integrating standards into practice—revised standards for home care infusion: what has changed? Home Healthc Nurse **2006**; 24:627–631.
32. Mortlock N. Intravenous therapy in the acute care setting. In: Hankins J, Lonsway RA, Hendrick C, Perdue M, eds. Infusion therapy in clinical practice. 2nd ed. Philadelphia, PA: WB Saunders, **2001**:469–500.
33. Tice AD. Pharmacoeconomic considerations in the ambulatory use of parenteral cephalosporins. Drugs **2000**; 59(Suppl 3):29–35.
34. Jarvis WR. Selected aspects of the socioeconomic impact of nosocomial infections: Morbidity, mortality, cost, and prevention. Infect Control Hosp Epidemiol **1996**; 17:552–557.
35. The American Hospital Association Hospital Statistics. Emerging trends in hospitals. Chicago, IL: American Hospital Association, 1998–1999.
36. Welch KE, Goff DA, Fish DN, et al. A multi-center economic analysis of bacteremia caused by methicillin-resistant *Staphylococcus aureus*. In: Proceedings of the 39th Interscience Conference of Antimicrobial Agents and Chemotherapy (San Francisco). September 1999. Washington, D.C.: ASM Press; **2000**.
37. Paladino JA, Sunderlin JL, Price CS, Schentag JJ. Economic consequences of antimicrobial resistance. Surg Infect (Larchmt) **2002**; 3: 259–267.
38. Poretz DM, Woolard D, Eron LJ, Goldenberg RI, Rising J, Sparks S. Outpatient use of ceftriaxone: a cost-benefit analysis. Am J Med **1984**; 77:77–83.
39. Eisenberg JM, Kitz DS. Savings from outpatient antibiotic therapy for osteomyelitis. Economic analysis of a therapeutic strategy. JAMA **1986**; 255:1584–1588.
40. Chamberlain TM, Lehman ME, Groh MJ, Munroe WP, Reinders TP. Cost analysis of a home intravenous antibiotic program. Am J Hosp Pharm **1988**; 45:2341–2345.
41. Kane RE, Jennison K, Wood C, Black PG, Herbst JJ. Cost savings and economic considerations using home intravenous antibiotic therapy for cystic fibrosis patients. Pediatr Pulmonol **1988**; 4:84–89.
42. Wai AO, Frighetto L, Marra CA, Chan E, Jewesson PJ. Cost analysis of an adult outpatient parenteral antibiotic therapy (OPAT) programme. A Canadian teaching hospital and Ministry of Health perspective. Pharmacoeconomics **2000**; 18:451–457.
43. Dalovisio JP, Juneau J, Baumgarten, Kateiva J. Financial impact of a home intravenous antibiotic program on a Medicare managed care program. Clin Infect Dis **2000**; 30:639–42.
44. Bernard L, El-hajj B, Pron B, et al. Outpatient parenteral antimicrobial therapy (OPAT) for the treatment of osteomyelitis: Evaluation of efficacy, tolerance and cost. J Clin Pharm Ther **2001**; 26:445–451.
45. Carmeli Y, Mozaffari E. Use of insurance claims data to assess outpatient antimicrobial therapy for gram-positive infections. Pharmacotherapy **2002**; 22:55S-62S.
46. Nathwani D, Tice A. Ambulatory antimicrobial use: the value of an outcomes registry. J Antimicrob Chemother **2002**; 49:149–154.
47. Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med **1997**; 336: 999–1007.
48. Berlin LH. Home care can cost more than hospitals. New York Times 26 June **1988**; 4:26.