# Outpatient Parenteral Antimicrobial Therapy

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**KEYWORDS**

• Outpatient parenteral antimicrobial therapy • Antibiotics • Adverse events
• Osteomyelitis • Endocarditis

**HOSPITAL MEDICINE CLINICS CHECKLIST**

1. Outpatient parenteral antimicrobial therapy (OPAT) began in the 1970s in the United States. It is estimated that 1 in 1000 Americans receives OPAT each year.
2. OPAT should only be considered in select patients once the active medical issues are stable and no longer require close, inpatient care.
3. Patients with endocarditis who are afebrile, have negative blood cultures, are clinically stable, and have received at least 1 to 2 weeks of inpatient antimicrobials (discussed later) can be considered for OPAT.
4. There are minimal data on using OPAT in patients with substance abuse. Abuse of alcohol, intravenous (IV) drugs, or other substances should be thoroughly evaluated during selection of appropriate candidates for OPAT.
5. A patient's home setting should be assessed before discharge to make sure it is a safe environment for the administration of OPAT.
6. Consider obtaining written consent from the patient or caregiver before discharging on OPAT to outline the responsibilities, describe possible adverse events, and improve patient or caregiver understanding.

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7. Communication is a key component for an OPAT team to successfully bridge the transition from inpatient to outpatient IV antimicrobial therapy.
8. When selecting the best antimicrobial, try to use guideline-supported antimicrobials with the narrowest spectrum and simplest dosing regimen.
9. Only certain antimicrobials are candidates for continuous infusion at home.
10. Tracking outcomes with OPAT is important to validate safety and efficacy of care provided.

## BACKGROUND AND DEFINITION

*What is OPAT?*

OPAT is the administration of any parenteral anti-infective agent in an outpatient setting. Potential sites of treatment include a patient's home, infusion center, outpatient clinic, emergency department, hemodialysis units, nursing home, or rehabilitation center.

## EPIDEMIOLOGY

*What has been the evolution of OPAT in the United States?*

The first reports of administering IV antibiotics at home in the United States were published in the 1970s.

There has been significant evolution of outpatient parenteral antibiotic therapy since these initial reports due to several factors[1,2]:

- Health care systems recognizing potential for cutting costs and shorter stays
- Advances in vascular access
- Increased availability of outpatient care
- Increased acceptance by health care providers, patients, and insurance companies
- Currently an estimated multibillion dollar/year industry
- Renamed OPAT in the early 2000s

By 1998, it was estimated that 250,000 people per year in the United States were being treated with OPAT.[1] It has also been reported that 1 in 1000 Americans receives OPAT on an annual basis.[2] Advances in ability and increase in use, however, have not been matched with evidence-based studies or large, prospective trials.

## PATIENT SELECTION

*What are the important criteria in selecting appropriate patients for OPAT?*

OPAT should only be considered once active medical issues are stable and no longer require close, inpatient care. A patient's clinical condition must be stable—this includes infection and other comorbidities. Does the patient require daily laboratory tests with subsequent adjustments in therapy? If patients' needs are better met in a hospital, then they are not OPAT candidates at the time.

Once a patient is stable for discharge but continues to require IV antimicrobials, then OPAT is an appropriate option if the patient is a good candidate. Key considerations in

determining the appropriateness of a patient for OPAT include: Are patients able to perform OPAT effectively? Can they make it to any appointments? Can they reliably give themselves the medications, take care of the IV access device, and report any problems? Do they have access to a telephone? Is the patient home environment adequate for home infusion? Is the home safe for a visiting health care provider? More autonomous individuals are good candidates to receive OPAT at home, whereas others might be better suited for infusion clinics or skilled nursing facilities. Although important in times of rising health care costs, financial concerns should not take priority over a patient's medical needs when making decisions regarding timing and location of OPAT.

*What medical conditions can be treated using OPAT?*

Any infection that requires long-term antimicrobials is eligible for OPAT, once a patient is adequately stabilized and no longer requires close monitoring and hospitalization. Infections commonly treated with OPAT include

1. Skin and soft tissue infections
2. Osteomyelitis
3. Septic arthritis
4. Wound infection
5. Bacteremia
6. Endocarditis
7. Meningitis
8. Pneumonia
9. Urinary tract infection/pyelonephritis
10. Intra-abdominal infection

## GUIDELINES FOR PRACTICE

*Are there any guidelines or data for OPAT use with central nervous system infections?*

Tice and colleagues[3] reviewed 68 patients with central nervous system (CNS) infections who received OPAT from 1986 to 1997. Patients were treated for meningitis, brain abscess, encephalitis, shunt infections, or other CNS infections. Patients were carefully selected, as should always be the case with OPAT. Patients were evaluated at least twice weekly. All infections were cured. No deaths or life-threatening emergencies occurred. Two patients (one with abscess and one with meningitis) had seizures, a known late complication with CNS infections, especially brain abscesses. For this reason, prophylaxis may be considered and patients should avoid activities that put them or others at risk (driving or operating heavy machinery). Sixteen percent required hospitalization after starting OPAT for a variety of reasons that did not seem to be due to the outpatient setting. In conclusion, OPAT for CNS infections is an option, as long as patients are followed closely and seizure precautions are possible, including the availability of family members or caregivers if seizure were to occur.

*What is the role of OPAT treatment for infectious endocarditis?*

Infective endocarditis is a serious infection that requires vigilance due to the potential devastating complications that can develop. Complications include heart failure (15%–65%), embolization (22%–43%), and myocardial abscess (6%–41%). In

addition, patients may have persistent fever and bacteremia.[4] The median duration of bacteremia in a recent study was 8 to 9 days with methicillin-resistant *Staphylococus aureus* (MRSA) bacteremia and 3 to 4 days with methicillin-sensitive *S aureus* (MSSA) bacteremia while on therapy.[5] Endocarditis due to *S aureus* endocarditis is associated with a rate of embolization 2.4-fold greater than that of viridans streptococci. Embolization rates are highest before and up to 2 weeks after the initiation of antimicrobials.[6] Complications increase with persistent bacteremia, aortic valve disease, *S aureus* endocarditis, acute endocarditis, and prosthetic valve infection. In many patients with endocarditis, it is recommended that the first 2 weeks of IV antimicrobials be administered in an inpatient setting to monitor for complications. Patients who are afebrile, have negative blood cultures, and are clinically stable may be discharged to complete therapy with OPAT. Selected patients with endocarditis due to viridans streptococci, who are medically stable without complications, can be considered for OPAT after 1 week of inpatient antimicrobial therapy. Once discharged, close monitoring is essential. If a patient develops fever, cardiac arrhythmia, heart failure, or neurologic symptoms, same-day evaluation should be arranged. If this is not possible, then inpatient antimicrobial therapy may be preferred.

Guidelines for the treatment of endocarditis suggest inpatient care for the first 2 weeks of therapy if a patient has non-viridans endocarditis due to increased risk for life-threatening events, such as congestive heart failure, abscess, or embolic events leading to dramatic change in clinical status.[2,7] Endocarditis due to viridans group streptococci could be treated for 1 week in the hospital before discharge on OPAT.[4] Treatment of endocarditis due to enterococcus on an outpatient basis may be more difficult, because it requires weeks of aminoglycosides.

*What about substance abuse (specifically IV drug use) and outpatient IV antibiotics?*

The current Infectious Diseases Society of America (IDSA) OPAT guidelines recommend that problems with substance abuse, specifically alcohol and IV drug abuse, be evaluated before starting therapy.[2] Active substance abuse generally correlates with poor compliance, which is of particular concern with this modality of therapy given the level of patient education and involvement needed for successful outcomes. IV drug abuse raises specific concerns about the potential for using the required intravascular device for illicit drugs. For patients with active IV drug abuse, the guidelines recommend considering options, such as completing the course of therapy in a skilled nursing facility, providing intramuscular injections, or even daily placement and removal of a short-term IV catheter.[2]

There is a paucity of data published regarding the use of OPAT in patients who abuse IV drugs. A hospital in Singapore performed a prospective, observational study to evaluate the safety of providing OPAT via peripherally inserted central catheter (PICC) lines to patients with known IV drug use.[8] This study required multiple criteria for enrollment, including adequate housing, reliable guardian, and a signed contract, which mandated daily OPAT clinic visits and an agreement to not access the PICC line or use nonprescribed drugs. Further measures during OPAT clinic visits were performed, which included daily inspection of PICC line sites and placement of security seals over PICC lines and infusers. A total of 906 patients were enrolled but only 29 (3.2%) met inclusion criteria. Overall, these 29 patients did well, with 28 (97%) completing their course of OPAT and the investigators concluded that carefully selected IV drug users could receive OPAT safely. The large number of patients excluded from this study, however, emphasizes the difficulty with providing care to this population and invokes concern about the

generalizability of the study findings. Further studies are needed to help elucidate the best approach in providing OPAT to patients with a history of or who actively abuse IV drugs.

*What aspects of the home environment should be evaluated before discharging someone with OPAT?*

The health care team evaluating a patient's candidacy for OPAT must be aware of a patient's home environment to insure the safety and quality of care. The opportunity to physically inspect and investigate the environment before discharge is rarely available and, therefore, this evaluation usually relies on a thorough interview of the patient and/or any caregivers.[1,2] Key issues to address are listed in **Box 1**.

*Are there any recommendations for improving patient understanding of OPAT before discharge?*

Assessing a patient's understanding of the complexities involved with OPAT can be challenging. The patient or patient's care provider is charged with several tasks.

List of patient or caregiver responsibilities

- Assume care of vascular access system
- Assume care of vascular access entry site
- Assume care of obtaining, storing, and administering antimicrobials
- Monitoring and reporting any problems (fever, rash, diarrhea, and arm swelling or pain)
- Keep appointments with OPAT clinic and other scheduled appointments
- Get appropriate laboratory tests drawn as instructed

Informed consent should be verbally obtained from all patients or caregivers before proceeding. Obtaining written consent on a form that outlines the required duties of the patient or caregiver is an even better method of documenting patient understanding.[2] Furthermore, it provides patients or caregivers with an outlined list they can review and emphasizes the importance of the patient role in the OPAT process.

**Box 1**
**Suitability of home environment for OPAT**

1. Does the patient have functioning utilities?

   Adequate light and heat, running water, and refrigeration for medications

2. Does the patient have a working telephone?

   Access to immediate communication is mandatory to allow for conveying critical laboratory results and allowing patient to contact health care facility with questions or problems

3. Is the home clean and safe?

   Important issue for patient health but also must be considered for health care practitioners making home visits

4. Does the patient have access to transportation?

   Mandatory for transport to clinic visits and access for emergency visits, if needed

## OPAT TEAM

*What components are needed to provide safe and effective long-term antibiotics?*

Infectious disease physician or physician with expertise in infectious diseases and antimicrobials
Primary care MD
Involved consultants if indicated (ie, podiatry or orthopedic surgery)
Nurse with expertise in OPAT, vascular access device care, and IV therapy
Pharmacist with expertise in OPAT and antimicrobials
Case manager
Rapid communication system—for patient and OPAT team—available 24 hours[2]

*Which patients might benefit from infusion center model versus home care?*

The disadvantage of the infusion center model is that it requires patients to travel regularly, often daily, to a health care facility to receive OPAT. The advantage, however, is that patients are seen regularly and there is ready access to expert medical care and personnel. This model is ideal for patients who do not require an inpatient setting but require closer observation and supervision for reasons, such as the medical condition treated, the regimen administered, or an unstable home environment (**Table 1**).

## ANTIBIOTIC CHOICE

*What factors should be considered in choosing an antibiotic?*

The first question should be, "Are IV antibiotics necessary?" Susceptible gram-negative bacteremias can frequently be treated with oral fluoroquinolones, because these agents achieve similar serum levels when given by either IV or oral route.[9] According to the IDSA MRSA practice guidelines for management of osteomyelitis, "Parenteral, oral, or initial parenteral therapy followed by oral therapy may be used depending on individual patient circumstances."[10] These circumstances may include cost of access placement and risk of complications. Certain infections, such as endocarditis and meningitis, should always be managed with IV antibiotics.

**Table 1**
**Models of OPAT**

| | Advantages | Disadvantages |
|---|---|---|
| Self-administration | Increased patient autonomy<br>Reduced costs | Less support<br>Compliance<br>Need for training |
| Visiting nurse | Ability to inspect home<br>Supervision/support<br>Skilled clinical assessment | Cost/length of travel<br>Safety of providers |
| Infusion center | Expert resources available<br>Supervision of OPAT<br>Often MD available | Cost<br>Patient needs to travel |
| Skilled nursing facility | Complete 24-h supervision<br>Other services (rehabilitation) | Cost<br>Loss of patient autonomy<br>Nosocomial infections |

If the IV route is most appropriate, several principles should influence antibiotic infection:

- First, antibiotics concordant with disease-specific guidelines should be administered if possible. If multiple antibiotics are acceptable, then the agent with the simplest dosing regimen and narrowest antibacterial spectrum is preferred.
- Second, medications that are considered stable in solution are optimal for OPAT. An antimicrobial is "considered stable in solution if it retains $\geq$90% of it original concentration for $\geq$24 hours at room temperature, or for 4–7 days under refrigeration."[11] Most antimicrobials are delivered to patients premixed. If they are unstable in solution, then patients may receive less than full doses due to degradation.
- Third, rapid IV infusion and continuous infusion strategies may be available for certain diseases, making patient lifestyle and preference important considerations.

Ampicillin, ampicillin/aulbactam, meropenem, imipenem, doxycycline, and trimethoprim/sulfamethoxazole are not ideal OPAT antibiotics because they are unstable in solution and must be given multiple times a day. Oral doxycycline and trimethoprim/sulfamethoxazole may be alternatives due to their high oral bioavailability.

### *Rapid IV Infusions*

Most cephalosporins can be given via a rapid IV infusion over a few minutes, allowing minimal disruption to a patient's daily schedule. Ceftriaxone is particularly useful due the ease of once-daily rapid IV administration. Other cephalosporins available for home administration include cefepime (usually twice a day or continuous infusion) and cefazolin (3 times a day or continuous infusion).

If a carbapenem is necessary, ertapenem is a good choice because it is given via a convenient once-daily infusion. Ertapenem cannot be used interchangeably with meropenem/imipenem/doripenem because it does not cover *Pseudomonas aeruginosa*, *Acinetobacter* species, or enterococci. It is useful, however, for treatment of diabetic foot infections and multidrug-resistant gram-negative infections (extended-spectrum β-lactamase *Escherichia coli*). For MRSA infections, vancomycin and daptomycin are both good candidates for OPAT.

Once-daily aminoglycoside therapy can be considered in selected, motivated patients. Aminoglycoside levels and frequent laboratory monitoring, however, are needed (discussed later).

Liposomal amphotericin is a once-a-day infusion that also may require premedication and close monitoring and can only be considered after a long course of inpatient therapy in highly selected patients who require prolonged treatment.

### *Continuous Infusions*

Oxacillin and nafcillin are given 4 to 6 times a day, which is not feasible on an outpatient basis, so are frequently administered as a continuous infusion during OPAT (**Fig. 1**). Penicillin G and piperacillin/tazobactam are candidates for continuous infusion therapy as well. Penicillin G can be considered an option in susceptible enteroccocal infections because ampicillin is not ideal for OPAT. If vancomycin needs to be given more frequently than twice daily, then a continuous infusion could be considered (**Table 2**).

#### *Which antibiotics can be given via continuous infusion?*

Antimicrobials that are stable in solution at room temperature for a prolonged period (discussed previously) and exhibit time-dependent pharmacodynamics are

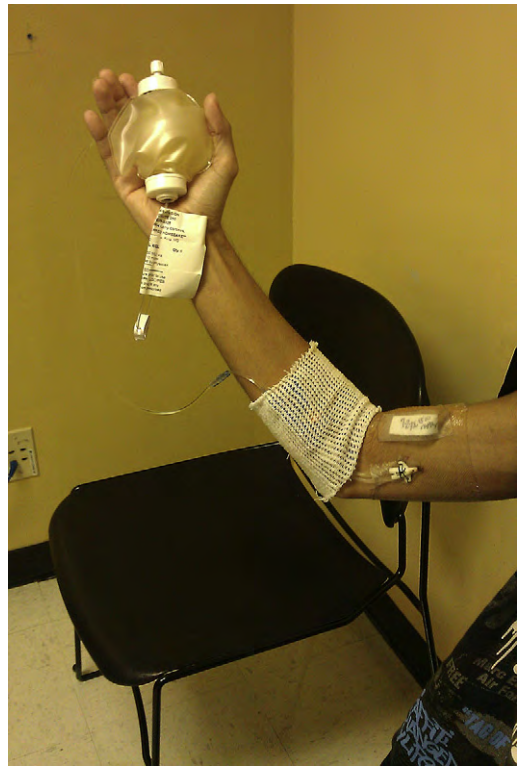

**Fig. 1.** A patient receiving cefazolin as a continuous infusion of 6 g over 24 hours via a PICC line administered by an elastomeric pump.

candidates for continuous infusion. If a drug exhibits time-dependent killing, then optimal efficacy is attained by maintaining the drug concentration above the minimum inhibitory concentration (MIC) of the offending organism for as long as possible. For these agents, achieving drug concentrations at many multiples of the MIC does not produce improved bacterial killing—making the maximum serum concentration less important.

Antimicrobials that best fit this description include penicillins, cephalosporins, carbapenems, and aztreonam. Drugs frequently given as a daily, 24-hour continuous infusion include oxacillin, nafcillin, penicillin G, piperacillin/tazobactam, and many cephalosporins, including cefazolin, cefoxitin, cefotaxime, ceftazidime, and cefepime. As discussed previously, ampicillin, ceftaroline, meropenem, and imipenem are not stable in solution and should not be administered as 24-hour continuous infusions. In addition, continuous infusions of ceftriaxone are not necessary due to the prolonged half-life of this compound.

Vancomycin is not a true time-dependent antimicrobial. Pharmacokinetic studies suggest the ratio of the area under the serum drug concentration versus time curve and the MIC (AUC/MIC) best describes vancomycin's activity.[12] According to the IDSA vancomycin guidelines, "Continuous infusion regimens are unlikely to substantially improve patient outcome when compared with intermittent dosing. Therefore, based on the available evidence, there does not appear to be any difference in patient outcomes between vancomycin administered by continuous infusion or by intermittent administration."[12] Because vancomycin is dosed based on actual body weight,

**Table 2**
**Continuous infusions**

| Antimicrobial | Utility for OPAT | Frequency of Dosing/Dosing Strategies |
|---|---|---|
| Vancomycin | Good | • Can be given twice daily.<br>• When higher doses are needed, a continuous infusion can be considered.<br>• Need to monitor levels periodically. |
| Penicillin G, oxacillin, nafcillin, piperacillin/tazobactam, cefazolin, cefepime, cefoxitin, cefotaxime, ceftazidime | Good | • All can be given via 24-h continuous infusion.<br>• Cefepime can also be administered twice daily, if preferred. |
| Ampicillin, ampicillin/sulbactam, meropenem, imipenem, doripenem | Poor | • These β-lactams are not stable in solution and cannot be administered via 24-h infusion.<br>• Need to be administered 3 to 4 times a day, making OPAT difficult. |
| Ceftriaxone, ertapenem | Good | • Once-daily infusions are ideal for OPAT.<br>• Neither is active against *Pseudomonas*. |
| Fluoroquinolones, doxycycline, linezolid | Oral is preferred | • Due to similar serum levels with oral versus IV administration, the oral route is preferred.<br>• Avoid divalent cations (Fe, Ca, Mg) when oral route is used for fluoroquinolones and doxycycline because these decrease oral bioavailability. |
| Aminoglycosides | Moderate | • Doses range from once daily to 3 times a day, which can be difficult at times.<br>• Need to monitor drug levels and monitor for nephrotoxicity and ototoxicity. Please see the third answer in Adverse Events. |
| Daptomycin | Good | Convenient once-daily infusion |

sometimes high doses are required to achieve adequate drug levels. Because 3-times-daily and 4-times-daily vancomycin is difficult to administer as OPAT, some clinicians elect to administer vancomycin via a continuous infusion in these cases.

## ADVERSE EVENTS

*Why should the first dose of an IV antibiotic be administered in a monitored setting?*

According to the ISDA practice guidelines for OPAT, the first dose of IV antimicrobial should be given "in a supervised setting, such as a physician's office, ambulatory care department, or the hospital" before the patient is discharged home.[2] If a patient

exhibits signs of an adverse reaction, especially anaphylaxis, then this can be more readily treated in the monitored setting.

*What adverse events are seen with long-term antibiotics?*

*Clostridium difficile* infection (CDI) is associated with all antibiotics. Not all diarrhea is related to CDI, however, because antibiotics can alter the normal colonic flora, which leads to diarrhea as well. If a patient develops abdominal discomfort, fever, or unexplained leukocytosis, then CDI should be considered. Nausea, rash, and drug fever can occur due to most antimicrobials. Other agents, such as high-dose β-lactams and linezolid, have been associated with bone marrow suppression after long-term use.

Complications of the vascular device, including infection, thrombosis, and malfunction, can also occur.

*What kind of monitoring is recommended for a patient receiving long-term antibiotics?*

According to the OPAT guidelines,[2] all antimicrobials (except fluoroquinolones and caspofungin) require a weekly complete blood cell count (CBC) and basic chemistry testing. More toxic antimicrobials require twice-weekly testing. Twice-weekly CBC testing is suggested for pentamidine and ganciclovir. Twice-weekly basic chemistry testing is suggested for aminoglycosides, pentamidine, amphotericin, and foscarnet. Once-weekly liver function testing is suggested for various antimicrobials, including oxacillin, nafcillin, carbapenems, fluoroquinolones, clindamycin, daptomycin, quinupristin-dalfopristin, all antifungals, and foscarnet. Weekly creatine kinase levels are recommended for daptomycin due to the risk of rhabdomyolysis.

For aminoglycosides, 8-hour to 10-hour postinfusion levels with nomogram guidance are needed. The frequency of these levels depends on the stability of the drug levels and creatinine. Patients should be advised to monitor for tinnitus, hearing loss, vertigo, or ear fullness. If this develops on therapy, then audiometry testing may be needed and the aminoglycoside may need to be discontinued.

All patients who require prolonged vancomycin therapy should have at least one steady-state vancomycin minimum serum concentration (ie, trough) assay performed. If vancomycin is planned for a short course (fewer than 5 days), then frequent vancomycin troughs are not necessary. For treating serious infections with vancomycin, a goal trough of 15 to 20 is sometimes desired. In these cases, weekly vancomycin troughs are recommended.[12]

## MONITORING OUTCOMES

*What is the benefit of monitoring the outcomes of patients receiving long-term antibiotics?*

Monitoring outcomes is essential for continuous performance improvement. Tracking data prospectively is essential to validate the safety, efficacy, and cost savings of an OPAT program. These data are also helpful to identify other resources needed and any barriers to providing optimal care. The goal of OPAT is to allow patients to safely complete courses of antimicrobial therapy outside the confines of the inpatient setting. Because the home environment is not designed for providing health care, patient safety must be continually assessed. Given the absence of performance standards, prospective outcome monitoring allows an OPAT program to trend its performance and address any issues in a timely manner to optimize the quality of care provided.

*What outcomes should be monitored?*

The IDSA OPAT guidelines have specific recommendations for outcome measures[2]:

- Clinical status (improved, failure, or no change)
- Bacterial infection status (culture negative, persistent pathogen, or new pathogen)
- Program outcome (completed planned therapy or reason for not completing)
- Antibiotic use (completed course or reason for not completing course)
- Vascular access complications (described)
- Additional measures (return to work or school or survival status)

The Good Practice Recommendations Working Group in the United Kingdom suggests a more condensed set of measures is more practical on a daily basis in their good practice recommendations for OPAT in adults in the United Kingdom[13]:

- OPAT success or OPAT failure (reason given)
- Specific data on adverse events, such as adverse drug reactions, vascular access complications, *Clostridium difficile* colitis, and *S aureus* bacteremia

## CLINICAL GUIDELINES

Practice guidelines for OPAT therapy are listed by Tice and colleagues.[2]

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