Outpatient Parenteral Antibiotic Therapy in an Academic Practice in Rhode Island

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ABSTRACT
Outpatient parenteral antimicrobial therapy (OPAT) is an increasingly utilized treatment modality that has been proven to be safe and cost effective for treating infections that require prolonged antimicrobial treatment. Adequate patient selection, a structured OPAT team with an effective communication system, and routine clinical monitoring are key elements to establish a successful OPAT program. The Miriam Hospital Infectious Diseases Clinic offers a multidisciplinary OPAT model coordinated by infectious diseases specialists and serves as a major referral center in Rhode Island.

KEYWORDS: OPAT, antibiotics, infection, Rhode Island

INTRODUCTION
Outpatient parenteral antimicrobial therapy (OPAT) refers to the administration of intravenous antimicrobials to patients who suffer from chronic infections that warrant parenteral therapy but these patients are otherwise stable enough to receive this therapy in an outpatient setting. Since its introduction in the 1970s, OPAT has been shown to be a safe, practical and cost-effective treatment modality.1 In the United States, it is estimated that more than 250,000 Americans receive OPAT services every year.2 OPAT helps to reduce healthcare costs by reducing the length of inpatient hospitalizations and the success of OPAT has been facilitated by the development of antimicrobials with convenient dosing schedules and the development and utilization of convenient and safe long-term IV catheters.3

STRUCTURE OF THE OPAT PROGRAM
The Miriam Hospital Infectious Diseases Clinic, located at 1125 North Main Street in Providence, is the largest provider of outpatient infectious diseases treatment in Rhode Island. The clinic provides longitudinal OPAT for persons who have been discharged from the hospital with IV antimicrobials and serves as a specialty referral resource to community healthcare providers in New England. Every month, the clinic sees approximately 100 new patients, of whom 75%

Figure 1. Structure of OPAT Program.
Once OPAT is considered appropriate, insertion of a long-term intravenous catheter for antimicrobial administration is arranged with interventional radiology or at an ambulatory infusion suite. A peripherally-inserted central catheter (PICC) is the most common type of catheter used for OPAT administration. PICC lines are inserted into the basilic or brachial veins and extend into the superior vena cava; position is confirmed with a chest x-ray. PICC lines can remain in place for over 90 days and seldom need to be exchanged. Midline peripheral intravenous catheters, tunneled venous catheters or ports inserted for other purposes (i.e. parenteral nutrition, hemodialysis or chemotherapy) can also be used for OPAT.

Antimicrobials are infused either at a skilled nursing facility or at home. For home administration, the OPAT program partners with a community-based infusion company which provides dedicated pharmacists, arranges for home delivery of the antimicrobial, and provides nursing and educational support. OPAT inside of the patient’s home often involves visiting nurses and the patient’s own family members who can assist with infusions. A patient can even be taught to self-administer the antimicrobial safely, thus increasing the patient’s independence and involvement with their own healthcare. Patients are typically seen by a visiting nurse at least once weekly to assess the IV catheter and to collect blood for routine laboratory testing as ordered by the prescribing physician. Constant communication and coordination between the patient and the OPAT team comprised of the pharmacist, visiting nurse, OPAT physician, and the referring physician has allowed us to successfully implement OPAT services to our patients. This process is greatly facilitated by a dedicated physician’s assistant based within the Miriam Hospital Infectious Diseases Clinic who acts as liaison between patients and OPAT physicians, evaluates patients for routine follow-up visits, and who is responsible for monitoring safety labs and adverse reactions to treatment. Patients discharged from the hospital are seen at the Clinic within 2-3 weeks, and then at regular intervals throughout the course of treatment.

**PATIENT SELECTION AND CLINICAL INDICATIONS**

Candidates for OPAT therapy include clinically stable patients who can understand the risks and benefits of therapy, have a safe environment to support care, and can assume the costs of therapy through their health insurance provider. OPAT should be avoided in patients for whom oral antibiotic therapy is equally effective, continued hospitalization is warranted, or if a safe environment for OPAT cannot be established. Patients with active injection drug use often require continued antimicrobial administration in a monitored setting and are not appropriate for OPAT. OPAT is typically used to treat bacterial infections; however certain severe fungal, viral or even protozoal infections might require prolonged intravenous antimicrobials. The most common conditions treated with OPAT include skin and soft tissue infections, bone and joint infections, endocarditis, bloodstream infections, complicated urinary tract infections, meningitis, and respiratory infections. In 2013, the Miriam Hospital Infectious Diseases Clinic treated a total of 712 patients with OPAT. As displayed in [Figure 2](#), bone and joint infections including osteomyelitis, discitis, septic arthritis, and prosthetic joint infections were the most common indications followed by bacteremia/endovascular infections and skin/soft tissue infections. The majority of these infections require a prolonged course of intravenous treatment [at least 4-6 weeks]. Some infections including those that involved retained foreign bodies such as orthopedic hardware may require a longer course of therapy (months) sometimes followed by suppressive oral antibiotic therapy.
Table 1. Commonly Prescribed Antimicrobials, Dosing Schedules, Pathogens, and Types of Infections in the Adult OPAT Program
(Individual treatment decisions should be based on the antimicrobial susceptibility of pathogens and appropriate use of guidelines from the Infectious Diseases Society of America, www.idsociety.org)

<table>
<thead>
<tr>
<th>Antimicrobial Class</th>
<th>Antimicrobial drug</th>
<th>Adult Dosing Schedule</th>
<th>Pathogens</th>
<th>Common diagnoses treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Penicillin G</td>
<td>3-4 MU every 4 hours or 18-24 MU via continuous infusion over 24 hours</td>
<td>Streptococci</td>
<td>Endocarditis</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>2 gm every 4-6 hours</td>
<td>Enterococcus Listeria monocytogenes</td>
<td>Endocarditis/bacteremia Meningitis</td>
</tr>
<tr>
<td></td>
<td>Nafcillin</td>
<td>2 gm every 4 hours or 12 gm via continuous infusion over 24 hours</td>
<td>MSSA</td>
<td>Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections</td>
</tr>
<tr>
<td></td>
<td>Ampicillin-Sulbactam</td>
<td>1.5-3 gm every 6 hours</td>
<td>Streptococci MSSA Gram-negatives* Anaerobes</td>
<td>Diabetic foot infections Aspiration pneumonia Intra-abdominal infections</td>
</tr>
<tr>
<td></td>
<td>Piperacillin-Tazobactam</td>
<td>3.375-4.5 gm every 6 hours</td>
<td>Streptococci MSSA Gram-negatives Anaerobes</td>
<td>Intra-abdominal infections Pleuro-pulmonary infections</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cefazolin</td>
<td>1-2 gm every 8 hours</td>
<td>MSSA</td>
<td>Septic arthritis Osteomyelitis Skin/soft tissue infections</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>1-2 gm every 24 hours (2gm every 12 hours for CNS dosing)</td>
<td>Streptococci MSSA Gram-negatives*</td>
<td>Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>1-2 gm every 8 hours</td>
<td>Streptococci MSSA Gram-negatives</td>
<td>Intra-abdominal infections Pleuro-pulmonary infections Osteomyelitis CNS infections</td>
</tr>
<tr>
<td>Monobactam</td>
<td>Aztreonam</td>
<td>1-2 gm every 8 hours</td>
<td>Gram-negatives</td>
<td>Intra-abdominal infections Pleuro-pulmonary infections Genitourinary tract infections</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vacnomycin</td>
<td>15mg/kg every 12 hours</td>
<td>Streptococci Enterococcus MSSA MRSA</td>
<td>Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections CNS infections</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Gentamicin</td>
<td>1mg/kg every 8 hours for synergy in combination with a beta-lactam antibiotic</td>
<td>Enterococcus MSSA MRSA</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Lipopeptide</td>
<td>Daptomycin</td>
<td>6mg/kg every 24 hours</td>
<td>MSSA MRSA Enterococcus</td>
<td>Endocarditis/bacteremia Septic arthritis Osteomyelitis Skin/soft tissue infections</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Meropenem</td>
<td>1-2gm every 8 hours</td>
<td>Streptococci MSSA Gram-negatives Anaerobes</td>
<td>Intra-abdominal infections Skin/soft tissue infections CNS infections</td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td>1 gm every 24 hours</td>
<td>Streptococci MSSA Gram-negatives* Anaerobes</td>
<td>Intra-abdominal infections Skin/soft tissue infections Osteomyelitis</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Acyclovir</td>
<td>10 mg/kg every 8 hours</td>
<td>Herpes simplex virus Varicella zoster virus</td>
<td>CNS infections Disseminated infections</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Amphotericin B (liposomal preparations)</td>
<td>5mg/kg every 24 hours</td>
<td>Aspergillus Zygomycetes Candidiasis Cryptococcus</td>
<td>Invasive fungal infections CNS infections</td>
</tr>
</tbody>
</table>
ANTIMICROBIAL SELECTION AND ADMINISTRATION

The antimicrobial agent for OPAT should be selected based on the susceptibility testing of the infecting organism, pharmacokinetic and pharmacodynamics properties, safety profiles of the possible antimicrobials to be used, and the patient’s drug allergy history. Ideally, the selected antimicrobial should be bactericidal, should reliably penetrate into the site of infection (including biofilms in the case of infections that involve retained foreign bodies), and can be administered at a convenient dosing schedule. The half-life of the drug determines the dosing, where as its temperature and pH stability defines mixture frequency and optimal storage. Antibiotics with time dependent-killing activity such as B-lactams require frequent dosing and may be best given through a continuous infusion, if preparation remains stable. Long half-life drugs that allow once daily dosing are preferred, such as ceftriaxone and ertapenem. Parenteral antibiotics commonly used in our practice include vancomycin, cephalosporins and daptomycin for gram-positive infections; ertapenem, third/fourth generation cephalosporins and aztreonam for gram-negative infections. Aminoglycosides are used in combination therapy for enterococcal endocarditis.

LABORATORY MONITORING AND COMPLICATIONS OF THERAPY

Adverse events and response to therapy are monitored at scheduled intervals through routine lab work and clinic visits according to the Infectious Diseases Society of America (IDSA) OPAT guidelines. Most antimicrobials require weekly complete blood count and renal function tests; some antimicrobials also require weekly liver function tests. Serum drug concentrations help monitor the potential for toxicity as well as predicted efficacy for certain antimicrobials including the aminoglycosides and vancomycin. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be useful surrogate markers of inflammation that can be helpful in monitoring response to therapy, particularly in hematogenous osteomyelitis.6,7

Adverse events encountered during OPAT therapy can be classified as either catheter-related or antimicrobial-related. Complications associated with indwelling intravascular devices include bloodstream infections, thrombosis, mechanical obstruction and chemical phlebitis.8 Regular flushing of the catheter to ensure patency, use of local anticoagulants, and sutureless vascular devices can reduce the rate of these complications.8 Most of our patients have routine catheter dressing changes by skilled nurses that help identify early catheter-related complications and arrange for a new vascular access if warranted. Possible complications associated with the antimicrobials themselves include: drug-related hypersensitivity reactions including rash or more severe cutaneous or systemic reactions (anaphylaxis); antibiotic-associated diarrhea, bone marrow suppression that may include leukopenia or thrombocytopenia; and secondary infections such as mucosal candidiasis.10 Clostridium difficile infection (CDI) occurs in 15–25% of antibiotic-associated diarrhea cases and although fluorquinolones, clindamycin, and broad-spectrum B-lactams are most frequently implicated, it can potentially occur with any antibiotic exposure.11,12 Co-administration of probiotics might reduce the risk of CDI, although evidence is inconclusive.13 Certain antimicrobials are associated with higher risk of nephrotoxicity [i.e. aminoglycosides, vancomycin and amphotericin B]. Patients who receive aminoglycosides are at risk of developing vestibular and oto-toxicity and routine clinical assessment is recommended to avoid permanent hearing loss and disequilibrium. The rate of hospital admissions due to OPAT related complications is approximately 9% in other academic institutions.14 Clinicians prescribing OPAT are responsible for educating their patients on possible side effects related to their therapy and to provide education regarding monitoring for adverse events.

CONCLUSIONS

OPAT has become increasingly utilized for the treatment of infections that require a prolonged course of treatment. OPAT enables patients to return home and regain their independence and also helps to decrease healthcare costs. The Miriam Hospital Infectious Diseases Clinic has successfully implemented a multidisciplinary OPAT program. Our goal is to continue to safely deliver OPAT services, optimize the delivery of these services, and improve patient outcomes in RI for those who require prolonged antimicrobial treatment.

References

9. Marculescu CE, Berbari EF, Cantey JR, Osmon DR. Practical considerations in the use of outpatient antimicrobial therapy for


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