MAYO CLINIC

Practical Considerations in the Use of Outpatient Antimicrobial Therapy for Musculoskeletal Infections

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CME Activity

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Learning Objectives: Educational objectives. On completion of this article, readers should be able to: (1) select the appropriate antimicrobial therapy for musculoskeletal infections; (2) determine the route and duration of administration of antimicrobials and identify complications of long-term intravenous catheters; and (3) perform clinical and laboratory monitoring of the efficacy and toxicity of outpatient parenteral antimicrobial therapy and recognize its adverse effects and their management.

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Abstract

Successful treatment of many musculoskeletal infections often requires an extended course of outpatient antimicrobial therapy, much of which is administered parenterally outside the hospital under the guidance of an infectious disease specialist. Delivery of outpatient parenteral antimicrobial therapy (OPAT) may occur in physicians' offices, ambulatory infusion centers, or hospital clinics but most frequently is done in patients' homes, often by the patients themselves. In this article, we outline the essential elements of outpatient antimicrobial therapy for musculoskeletal infections with particular emphasis on OPAT, including patient selection and evaluation; antimicrobial administration, including the route, duration, and complications of central venous access; and clinical and laboratory monitoring of antimicrobial therapy. We believe that primary care physicians, orthopedists, and infectious disease specialists caring for patients with musculoskeletal infections should become familiar with the use of, indications for, and complications of OPAT.

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Achieving a successful outcome in patients with musculoskeletal infections requires a close collaboration among various subspecialists, including orthopedists, plastic and vascular surgeons, infectious disease specialists, and primary care physicians. The medical management of many musculoskeletal infections often involves prolonged antimicrobial therapy, much of which is administered parenterally outside the hospital under the guidance of an infectious disease specialist. Intravenous antimicrobial therapy is typically administered at the patient's home, at an ambulatory infusion center, or at a rehabilitation or skilled nursing facility via a peripherally inserted central catheter (PICC).

OUTPATIENT PARENTERAL ANTIMICROBIAL THERAPY

Patient Evaluation and Selection

Patients who are candidates for outpatient parenteral antimicrobial therapy (OPAT) can have a variety of musculoskeletal infectious syndromes such as osteomyelitis, prosthetic joint infections, diabetes-related foot infections, and soft tissue or surgical site infections. Available data from the medical literature and expert opinion support the effectiveness of prolonged, directed, systemic antimicrobial therapy (4-6 weeks or longer) for adults with many musculoskeletal infections.[1-6] Although numerous studies have been designed to analyze the economic impact of OPAT on health care, a properly conducted comprehensive, clinical outcome-based pharmacoeconomic analysis has not been undertaken. One study reported that the cost per day of OPAT ranged from $122 in 1984 to $183 in 2000 to $107 (excluding the cost of intravenous lines and vancomycin therapeutic drug monitoring) in 2002 (2010 adjusted values, $263, $234, and $135, respectively).[7] At each time point, these values represent a cost that is less than that of 1 day in an acute care hospital.

The primary goals of OPAT are to ensure that patients will be able to complete their parenteral antimicrobial therapy safely and effectively in the comfort of their homes or in another supervised setting to avoid the costs and inconveniences of a prolonged hospital stay. Our experience as dedicated infectious disease specialists whose focus is on the treatment of musculoskeletal infections has shown that most of these patients can receive OPAT once the appropriate surgical procedure has been performed and the infection is stabilized.[8] Outpatient parenteral antimicrobial therapy does not constitute a replacement for surgical intervention. Key elements required for an OPAT program as recommended by the Infectious Diseases Society of America (IDSA) guidelines[9] are outlined in Table 1.

We follow the IDSA guidelines' quality standards for an OPAT program. It is important that a qualified health care provider, preferably an infectious disease specialist, determine the need for OPAT and ensure that alternative routes of administration are not indicated or feasible. In addition, it is imperative to ascertain that the patient's infection is stabilized and does not require any further hospi-

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

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 hours per day
System in place for rapid communication between patient and team members
Patient education information about 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
Patient education materials
Outcomes monitoring
Patient response
Complications of disease, treatment, or program
Patient satisfaction

From Tice et al; IDSA. Practice guidelines for outpatient parenteral antimicrobial therapy: IDSA guidelines. *Clin Infect Dis.* 2004;38(12):1651-1672,[9] with permission from Oxford University Press.

talization. The patient should have a reliable mode of transportation to an ambulatory infusion center, or, if arrangements for home health care have been made, one must ensure that the home health care personnel can reach the patient safely and reliably. Access to running water, adequate light and heat, and refrigeration needed to store compounded medications are prerequisites for OPAT.[7] Furthermore, the patient should have access to a phone in case of an emergency. Although these criteria are seemingly simple and straightforward, in our practice, we have encountered numerous difficulties related to an inability of the home health care personnel to reach the patients.

A recent study showed that appropriately selected, counseled, and monitored patients with a history of intravenous drug use can be treated via OPAT centers.[10] Another prospective observational study showed that by instituting policies, contracts, line seals, and counseling of such patients, OPAT can be instituted without risking PICC abuse.[11] However, we cannot overemphasize the caution and judgment required when determining the need for OPAT in active or former intravenous drug users. The decision to initiate OPAT for such patients needs to be made on an individual basis, often in consultation with a psychiatric liaison, and only when an alternative route of administration is not appropriate or indicated. In our practice, we often recommend that these patients undergo OPAT in a supervised setting such as a step-down unit, specialized rehabilitation center, or nursing home. It is important to take into account the time required to coordinate the OPAT before discharge to avoid unnecessary prolongation of hospitalization.[8]

Selection of Antimicrobial Therapy

The selection of the appropriate intravenous antimicrobial for use in OPAT should follow the same principles that guide the selection of antimicrobial therapy in other clinical circumstances. Assessment before initiation of any antimicrobial therapy allows the infectious disease specialist to consult with the orthopedic surgeon regarding culture ascertainment, arrange for specialized cultures with the microbiology laboratory, obtain details regarding prior microbiology data as well as prior medical and surgical therapy, and select the optimal type and dose of antimicrobial therapy.[12] The most efficacious antimicrobial should be chosen according to the microorganism(s) causing infection and results of in vitro susceptibility testing; clinical circumstances of the patient, including comorbidities, antimicrobial allergies and intolerances, and renal and hepatic function; and available clinical data or experience supporting the use of the particular antimicrobial for a given musculoskeletal infection.[8,12] Antimicrobial bone concentration may be an important factor in eradicating the organism from the bone. In the rabbit model for *Staphylococcus aureus* osteomyelitis, Mader et al[6] found clindamycin (a bacteriostatic agent against staphylococci) to have the greatest bone-to-serum ratio, followed by vancomycin, nafcillin, moxalactam, tobramycin, cefazolin, and cephalothin. However, the significance of bone antibiotic concentration is unclear. Peak and trough serum bacteriostatic and bactericidal levels are employed to assess the bacteriostatic and bactericidal capabilities of the treatment antibiotic, and most investigators strive for a minimum serum bactericidal dilution of 1:8 or higher. In clinical practice, when optimal antibiotics are selected by minimum inhibitory concentration testing, the likelihood of success in the treatment of osteomyelitis is governed by the adequacy of debridement surgery rather than by the adequacy of serum bactericidal levels.[13]

The development of antimicrobials with long half-lives has allowed for less frequent administration of these antimicrobials and has significantly contributed to the growth of OPAT and facilitated compliance.[7] Whenever possible, we prefer to administer parenteral antimicrobials once or twice daily. For example, we commonly use ceftriaxone for the treatment of musculoskeletal infections caused by β-hemolytic streptococci and methicillin-susceptible staphylococci. Although vancomycin may be more conveniently administered in patients receiving hemodialysis, we recommend that patients with musculoskeletal infections due to methicillin-susceptible *S aureus* who are undergoing dialysis receive a β-lactam agent such as nafcillin or cefazolin whenever possible because vancomycin has been shown to be inferior for methicillin-susceptible *S aureus* infections.[8] Parenteral antimicrobials commonly used for OPAT at our institutions are listed in Table 2. It is recommended that the first dose of a newly prescribed intravenous antimicrobial be administered in a supervised setting equipped for emergencies to deal with any allergic reactions and anaphylaxis.[14]

Antimicrobials that require more frequent administration are typically delivered via electronic ambulatory infusion pumps.[15,16] There are some disadvantages associated with using such pumps, including their high cost and frequent malfunctions. The drugs selected must be stable in solution for up to several days at room temperature.[15] The most common agents that are stable for use in these pumps are nafcillin, intravenous penicillin G, or piperacillin-tazobactam. Other agents such as ampicillin, ampicillin-sulbactam, and imipenem are not suited for administration via ambulatory infusion pumps because they are unstable at room temperature for prolonged periods.[15] Aminoglycosides, which have concentration-dependent killing and prolonged postantibiotic effects,

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TABLE 2. Intravenous Antimicrobials Commonly Used for the Outpatient Treatment of Patients With Musculoskeletal Infections

Penicillins
Penicillin G
Cephalosporins
Cefazolin
Ceftriaxone
Cefepime
β-Lactam–β-lactamase inhibitor combination
Piperacillin-tazobactam
Carbapenems
Meropenem
Ertapenem
Glycopeptides
Vancomycin
Daptomycin
Tetracyclines
Tigecycline

Adapted from Osmon DR, Berbari EF. Outpatient intravenous antimicrobial therapy for the practicing orthopaedic surgeon. *Clin Orthop Relat Res.* 2002;(403):80-86,[8] with permission from Wolters Kluwer Health.

may be administered once daily. Implementation of such a regimen may reduce the incidence of nephrotoxicity and ototoxicity.[9]

Identification and Management of Complications of Long-term Intravenous Catheter Use

Prolonged intravenous antimicrobial therapy is commonly administered via PICCs. They are typically 50 to 60 cm long and uncuffed; cuffed and/or tunneled PICCs are occasionally inserted by a trained infectious disease physician for patients at high risk for infections or for those who have had multiple line-associated infections. Axillary vein access with a tunnel to exit the axilla is sometimes necessary in morbidly obese patients. PICC lines are typically inserted by a trained nurse or physician into the basilic or brachial vein.[15] Noninfectious complications of PICCs are rare and include sterile phlebitis, thrombosis of one of the veins in which the catheter is inserted as well as one of the central veins, pulmonary emboli, migration of the catheter tip, erosion of the catheter through the vein, or clotting of the catheter.[15] Superior vena cava syndrome has been observed after PICC placement in patients with cystic fibrosis.[17] In cases of superior vena cava syndrome, clinical examination may identify swelling of the arm, local signs or symptoms of pain and erythema, facial swelling and plethora, chemosis, dyspnea, or Pemberton sign. These signs and symptoms should prompt evaluation with computed tomography of the chest. Patients who have had multiple PICCs placed can experience vein thrombosis and obstructions at the level of the subclavian or axillary vein, often with the development of collateral circulation (J.R.C., MD. Unpublished data. 2010) (Figure). Sterile phlebitis responds to hot packs and anti-inflammatory agents. Venous thrombosis is a known complication of PICC line placement. In a recent study, the overall rate of thrombosis was 3.9%, with a thrombosis rate of 1% for 4F catheters, 6.6% for 5F catheters, and 9.8% for 6F catheters. At our institutions, all PICCs are placed under ultrasound guidance, and alteplase is used for declotting the catheter. Urokinase has also been used successfully for declotting.[18] Lines should be flushed regularly to ensure patency, typically daily or after each infusion if drugs are administered more frequently.[7]

The use of sutureless devices may reduce the complications associated with peripherally inserted central venous catheters, including PICC-related bloodstream infections, when compared with the traditional method of suturing.[19] However, in our experience, there has been very little difference between the rate of in-hospital central venous line infections associated with PICCs secured with 1 suture plus a sutureless device (2/452 [0.44%], Infectious Diseases PICC Insertion Team, Medical University of South Carolina. Unpublished data. 2010) and those secured with a sutureless device alone (3/414 [0.72%], Nurse PICC Insertion Team, Medical University of South Carolina. Unpublished data. 2010). Interventional radiologists at our institution use 2 sutures and no sutureless device, and

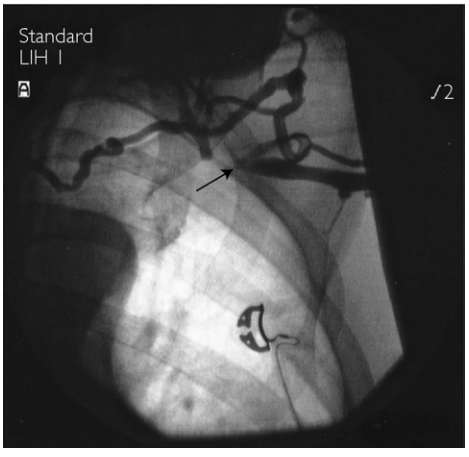

FIGURE. Subclavian vein occlusion and collateral circulation in patient with peripherally inserted central catheter.

TABLE 3. Types of Catheter-Related Infections

Type of Infection	Signs
Asymptomatic colonization	Presence of 15 bacterial colonies on semiquantitative culture of catheter tip that has been removed from an asymptomatic patient
Exit-site infection	Cutaneous and subcutaneous erythema, pain, induration, or purulence within 2 cm of the cutaneous exit site of the catheter
Pocket infection	Signs of inflammation overlying subcutaneous reservoir of a port device or purulent exudate in the subcutaneous pocket occupied by the reservoir
Tunnel infection	Erythema, tenderness, and induration of the skin and subcutaneous tissue overlying a tunneled central catheter and 2 cm from the skin exit site
Catheter-related bloodstream infection	Presence of the same microorganism isolated from a semiquantitative culture of the catheter tip and from a blood culture of a patient with fever and no other apparent source of infection

From Gilbert DN, Dworkin RJ, Raber SR, Leggett JE. Outpatient parenteral antimicrobial-drug therapy. *N Engl J Med.* 1997;337(12):829-838,[15] with permission from the Massachusetts Medical Society.

their infection rate is 1.8% (9/601). Hickman catheters generally have a lower rate of complications related to vein stenosis, and they should be preferred over PICCs in patients with renal disease and an impending need for hemodialysis because PICCs may cause vein stenosis that can impede future arteriovenous fistulas.[20,21]

Types of catheter-related infections are listed in Table 3. The IDSA has published guidelines for the management of catheter-related infections.[22] On the basis of the Centers for Disease Control and Prevention definition of line-associated infection, we consider that bacteremia with no other identifiable source in patients with a PICC is sufficient evidence to incriminate the PICC as the source of the infection. Most of these complications (excluding PICC colonization) require removal of the PICC in addition to appropriate antimicrobial therapy for cure. In selected clinical circumstances and depending on the pathogen, the use of antibiotic lock therapy may be implemented in an attempt to salvage the line. A detailed discussion of antibiotic lock therapy is beyond the scope of this article.

ORAL ANTIMICROBIAL THERAPY

In general, there is little difference between the oral and parenteral route as long as both routes provide adequate serum and bone concentrations. Traditionally, the parenteral route has been the preferred modality of administration for many musculoskeletal infections, particularly for treatment of osteomyelitis in adults and for prosthetic joint infections. However, if fully bioavailable (ie, quinolones, metronidazole, linezolid), antimicrobials can be administered orally.[23-26] β-Lactams should not be used orally because of their low bioavailability. We use oral antimicrobials with excellent bioavailability (drugs that achieve similar serum or tissue concentrations whether given orally or intravenously) whenever possible. Prerequisites for oral administration are susceptibility of the microorganism to these agents, a functional gastrointestinal tract, no known drug-drug interactions that will decrease their efficacy, and their use for a specific indication that is supported by the available clinical data.[8,12] Antimicrobial agents that encourage adherence and have minimal adverse effects should be used when-

TABLE 4. Selected Oral Antimicrobial Agents With Excellent Oral Bioavailability Commonly Used to Treat Patients With Musculoskeletal Infections

Quinolones
Ciprofloxacin
Levofloxacin
Moxifloxacin
Metronidazole
Linezolid
Rifampin
Trimethoprim-sulfamethoxazole
Azoles
Fluconazole
Itraconazole
Voriconazole

Adapted from Osmon DR, Berbari EF. Outpatient intravenous antimicrobial therapy for the practicing orthopaedic surgeon. *Clin Orthop Relat Res.* 2002;(403):80-86,[8] with permission from Wolters Kluwer Health.

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ever possible. Oral agents that are commonly used to treat patients with musculoskeletal infections are listed in Table 4.

We do not routinely use fluoroquinolones without rifampin for the treatment of staphylococcal infections because of the potential development of resistance.[27] A quinolone-rifampin combination plays a role in the treatment of staphylococcal implant-associated infections. Rifampin has bactericidal activity against surface-adhering, slow-growing, and biofilm-producing microorganisms. Its activity against staphylococci has been tested in vitro, in animal models, and in clinical studies.[28-30] Currently, there is evidence to support its efficacy for staphylococcal implant-associated infections.[28-30] In the postoperative period, we recommend starting rifampin once the results of susceptibility testing are known and surgical drains are removed to minimize the development of resistance. To avoid rapid development of resistance, rifampin should never be used as monotherapy.

Linezolid is occasionally used as an alternative to parenteral therapy for staphylococcal infections. Its prolonged use is limited by bone marrow suppression, which often occurs after 14 days of therapy; neuropathy, including optic neuritis (occurring after 28 days of therapy); and its interactions with monoamine oxidase inhibitors and selective serotonin reuptake inhibitors, which may lead to a serotonin syndrome. It can also cause lactic acidosis and DRESS (drug rash and eosinophilic systemic symptoms) syndrome with acute interstitial nephritis.[31,32]

CLINICAL AND LABORATORY MONITORING OF TREATMENT EFFICACY AND TOXICITY

Complications related to antimicrobials in an outpatient setting are similar to those in the inpatient setting. Common complications of antimicrobial therapy include rash, nausea, vomiting, diarrhea, *Clostridium difficile*–associated colitis, and oropharyngeal or vaginal candidiasis; more unusual complications include ototoxicity from vancomycin or aminoglycosides.[8] Patients should be educated and counseled about possible antimicrobial adverse effects and toxicities and should be instructed to report any adverse effects or complications to their physician immediately. Common adverse effects of antimicrobial therapy, including hematologic, renal, or dermatologic (rash) complications, tend to occur about 1 month after treatment initiation.[33] Several studies have shown that antibiotic-associated diarrhea occurs in 3% to 10% of adults receiving antibiotics.[33-37] *C difficile* infection (CDI) causes 15% to 25% of all cases of antibiotic-associated diarrhea.[38] Some antibiotics are associated with a relatively high risk of *C difficile* acquisition, particularly clindamycin (relative risk [RR], 9.0), cephalosporins (RRs range from 7.8 for cefaclor to 36.2 for cefotaxime), and β-lactams (RRs range from 2.0 for penicillin to 22.1 for ampicillin and amoxicillin-clavulanic acid).[38] Recently, fluoroquinolones have been implicated as common causes of CDI. In a patient receiving antimicrobial therapy who has diarrhea, the clinician should suspect CDI in the presence of fever (28% of cases), abdominal cramps (22% of cases), leukocytosis (50% of cases), or hypoalbuminemia. These symptoms should prompt laboratory testing of stool samples and initiation of treatment according to IDSA published guidelines.[39]

In a study of 269 patients, nephrotoxicity occurred in 8% of patients receiving vancomycin (with or without other nephrotoxic antimicrobials) but was far more common in patients receiving amphotericin B.[33] In this study, vancomycin and β-lactam antimicrobials were the most frequent causes of leukopenia. Higher vancomycin troughs of 15 to 20 μg/mL required for treatment of methicillin-resistant *S aureus* are associated with an increased risk of nephrotoxicity. In a recent prospective cohort study of 95 patients with methicillin-resistant *S aureus* infections, nephrotoxicity occurred in 12% of the high-trough vancomycin group.[40] The authors suggested that a complete blood cell count and differential, serum electrolytes, and serum creatinine levels be monitored at least weekly in patients undergoing intravenous antimicrobial therapy, according to the IDSA guidelines.[9] The use of daptomycin has been associated with an elevation in the creatine kinase level, with a reported incidence of 2.8% in phase 3 clinical trials.[41] Rhabdomyolysis is an infrequent but serious adverse event reported with daptomycin use. Serum creatine kinase levels should be monitored weekly in patients receiving daptomycin. In most cases, the onset of symptoms and creatine kinase elevations occur 7 to 10 days after initiation of treatment.[42,43] In addition, liver function tests should be considered in patients receiving ceftriaxone or nafcillin.[8]

High-risk patients or those receiving aminoglycosides or amphotericin B products may need more frequent (twice weekly) monitoring. Patients receiving prolonged aminoglycoside therapy should have their serum peak and trough concentrations determined initially after the third or fourth dose and after each change in dosage. When trough concentrations increase, more frequent determination of serum creatinine levels are needed. Determination of aminoglycoside and serum creatinine levels should help guide the treatment, although ototoxicity and vestibular toxicity do not always correlate with the drug level.[9] When aminoglycosides are used, patients should be instructed to report otologic or vestibular symptoms (tinnitus, vertigo, sensation of fullness in the ears). The development of otologic or vestibular symptoms during aminoglycoside treatment should prompt discontinuation of therapy and evaluation by an audiologist.[9] Frequent

determination of drug levels can pose some difficulties for home health care agencies because it requires knowledge and precision in regard to timing. If the timing of drug administration is not judiciously correlated with the timing of acquisition of the peak and trough levels, the drug levels obtained may lead to unnecessary adjustments of the dose of the antimicrobial drug.

CONCLUSION

The administration of outpatient parenteral antimicrobial therapy has been proved to be an efficacious, safe, practical, and cost-effective method. It allows patients to return to their daily activities with minimal discomfort or disruptions of their schedules. Outpatient intravenous antimicrobial therapy is a vital component of the medical treatment of many musculoskeletal infections. Oral therapy can be administered in selected circumstances. We have provided an overview of the process of patient selection and administration criteria for primary care physicians, orthopedists, and infectious disease specialists in an attempt to better understand its indications, safety, and effectiveness.

Correspondence: Address to Camelia E. Marculescu, MD, MSCR, Division of Infectious Diseases, Medical University of South Carolina, 135 Rutledge Ave, 12th Floor MSC 752, Charleston, SC 29425 (marcule@musc.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.org.

The Symposium on Antimicrobial Therapy will continue in an upcoming issue.

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