Handbook of

Outpatient Parenteral Antimicrobial Therapy For Infectious Diseases 3ed

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PEDIATRIC INFECTIOUS DISEASES SOCIETY

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Outpatient Parenteral Antimicrobial Therapy For Infectious Diseases 3ed

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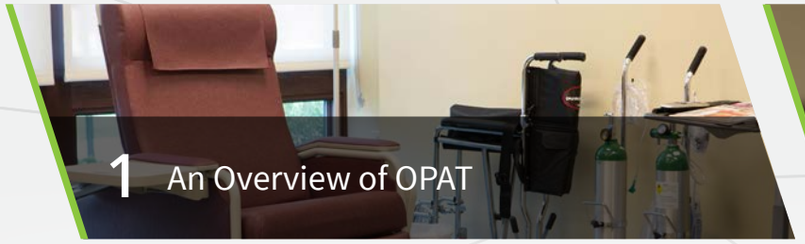

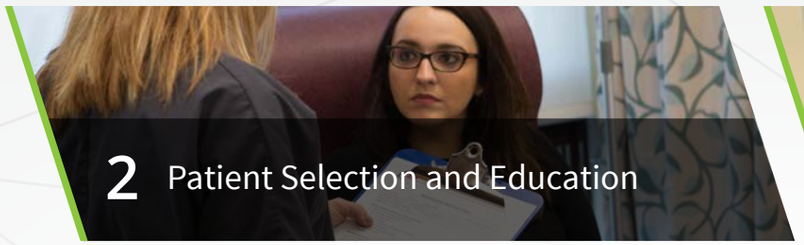

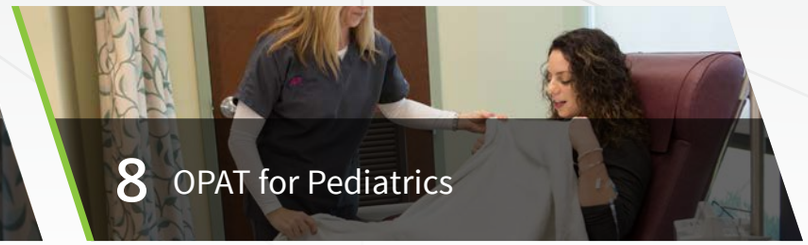

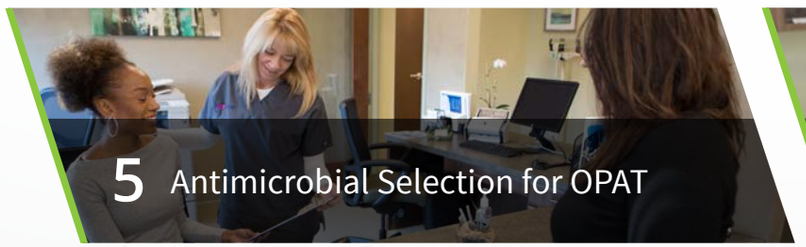

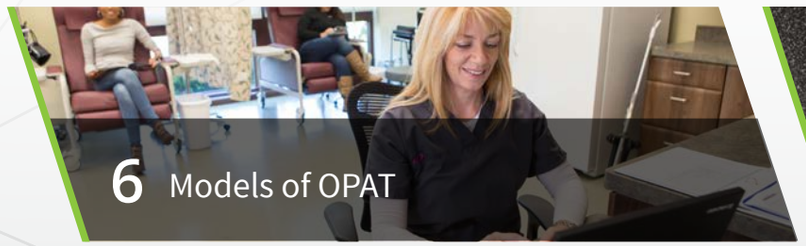

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INTRODUCTION AND ACKNOWLEDGEMENTS

The idea of sending patients home with an intravenous (IV) catheter to infuse their own parenteral antibiotics or to travel regularly to an infusion suite was unheard of in the early 1970s. Such outpatient parenteral antimicrobial therapy (OPAT) is now the standard of care. The growth of OPAT programs reflects dramatic progress in clinical, pharmaceutical, and technological research, resulting in the development of new drugs and IV infusion devices, which facilitate the delivery of outpatient care and enhance patient satisfaction. The current emphasis by payers on value-based care and bundled payments has further driven the impetus to move patients out of high-cost inpatient beds for therapeutic interventions traditionally delivered in hospitals.

The breadth of OPAT has expanded widely since its inception. Models of care vary, depending on patient preference, payer agreements, and access to regional resources. OPAT has been successfully delivered to a remarkable array of patient populations, including the very old and the very young, the very sick and the otherwise well, the homeless, and the uninsured. The list of antimicrobial agents deliverable by OPAT has also grown to include a wide range of antimicrobials, mirroring that of the inpatient formulary. There are a few currently available antimicrobials that have not been given successfully as OPAT in the right circumstances.

The *Handbook of Outpatient Parenteral Antimicrobial Therapy for Infectious Diseases* was originally published in 2006 under the leadership of Alan D. Tice, MD, FACP. We are pleased to offer an updated, electronic version of the original handbook, as a practical resource for infectious disease specialists starting an OPAT program, as well as for those physicians who have an interest in improving the outcomes and efficiency of their current OPAT practice. This eHandbook can support infectious disease specialists who are leading efforts to deploy OPAT within accountable care organizations and clinically integrated networks, demonstrating the remarkable cost savings, reduction in hospital-acquired conditions, and enhanced patient satisfaction that a successful OPAT program can deliver.

The content of the original handbook has been revised and updated with novel developments. Additionally, new chapters on healthcare reform and OPAT in pediatrics have been added.

To address newer reimbursement models and bundled-care programs, the future practice of infectious disease providers will likely require the routine measurement of quality and safety outcomes, as well as cost metrics. OPAT providers who are able to demonstrate improved patient outcomes, decreased cost, and appropriate shifting of care from inpatient to outpatient settings are more likely to be successful in this evolving medical climate.

Although there are many challenges associated with OPAT, the rewards in terms of benefits to patients and families are great. The future lies with the interest, creativity, and energy of infectious disease physicians, nurses, pharmacists, and other health care professionals who provide OPAT in each community.

It is often said that any scientific progress stands on the shoulders of giants. This eHandbook would not have been possible without the vision and effort of Dr Tice, who devoted much of his career to the development and understanding of OPAT and published the original handbook in 2006.

We sincerely acknowledge contributions by each of the chapter authors. Special thanks for the tireless efforts of Andres Rodriguez from Infectious Diseases Society of America (IDSA) and his colleagues who assisted in the update of this eHandbook. We thank Linnéa Elliott, Peter Ronick, Daniel Famer, and the entire team of The Curry Rockefeller Group, LLC, for their support in this collaboration. Lastly, we extend our thanks to the sponsoring organizations for their continued support.

We thank all of you for your interest in OPAT and hope the information contained within will be of value in improving the care you provide for your patients in the outpatient setting.

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1 An Overview of OPAT

Russell Petrak, MD, and Geneve M. Allison, MD, MSc, FACP

This handbook is intended to serve as a practical resource for infectious diseases specialists, spanning the continuum of those starting an outpatient parenteral antimicrobial therapy (OPAT) program, to those who have an interest in improving the outcomes and efficiency of their current OPAT practice. This handbook demonstrates how infectious diseases specialists have an opportunity to lead efforts to employ OPAT within accountable care organizations and clinically integrated networks, given the recent changes related to health care reform here in the United States.

OPAT, defined as the administration of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization, has been shown to be clinically efficient and cost effective.[1-5] First described in the United States in 1974,[1] OPAT has continued to grow over the past four decades with approximately 250,000 patients treated per year in the United States.[2, 3] The primary goal of an OPAT program is to allow patients to complete treatment safely and effectively in the comfort of their home or another outpatient site. Secondary goals include reducing inconvenience, avoiding potential exposure to nosocomial pathogens, and decreasing the expense of hospitalization to complete a prescribed intravenous (IV) antibiotic course.[4-6]

With the rapid rise in health care expenditures and the enactment of the Affordable Care Act, OPAT is well positioned as an alternative mechanism by which to treat serious infections. An organized and efficiently managed OPAT program is a valuable asset to physicians, hospitals, payers, and, most importantly, patients.[4, 5]

EFFICACY

The first study to show the efficacy of home IV antibiotic administration was published in the pediatric literature in 1974, demonstrating safe and effective treatment of chronic broncho-pulmonary infection associated with cystic fibrosis.[1] Since that time numerous studies have detailed the benefits of utilizing OPAT for various infections including cellulitis, osteomyelitis, septic arthritis, bacteremia, infected prosthetic joints, and pyelonephritis.[3, 7-13] OPAT has also been found to be effective in virtually all segments of the population, from children to the elderly.[1, 14, 15]

Efficacy has also been demonstrated in multiple practice settings including private practice, traditional academic programs, and the Veteran's Affairs medical centers.[6, 15, 16]

PATIENT BENEFITS

Patients treated outside the hospital, whether in a physician's office, a hospital outpatient facility, or at home, avoid problems inherent in the hospital system. These include unfamiliar, sometimes frightening surroundings, isolation from friends and family, lack of privacy, and increased risk of nosocomial infections. Children are at a particular disadvantage when it comes to hospitalization. Children are less adaptable to unfamiliar surroundings than most adults, have little understanding of their illness, and can easily feel threatened by the hospital environment and the painful procedures involved in treatment (see Chapter 8).[17]

When patients are allowed to recover in the comfort of their own homes, many can return to work or school. Avoiding the hospital setting also may facilitate the transition from the role of sick "patient" back to the familiar, functioning self, thus speeding both adaptation and recovery.[18-20]

With multiple options for OPAT delivery (see Chapter 6), treatment may be adjusted to each patient's lifestyle, functional status, family structure, and financial resources. Successful OPAT requires patients' participation as well as some level of responsibility for their own treatment program. To this end, patients and caregivers must be informed about their disease or infection; the therapeutic intervention, including handling and maintenance of the delivery system; and the problems to anticipate. The resulting knowledge and sense of control can facilitate recovery and, for some patients, can decrease pain and side effects. The fact that most people prefer being treated at home rather than in the hospital has been repeatedly demonstrated.[21-24]

OPPORTUNITY

The implementation, management, and supervision of an OPAT program provides infectious diseases physicians with an opportunity to define their value. Regardless of the eventual health care structure, the ability to treat patients successfully in

an outpatient setting is a tangible benefit to patients, hospitals, and payers. The cost containment benefits of OPAT have been amply demonstrated[11, 13, 16, 19], and the freeing up of hospital beds provides additional revenue generating opportunities. More recently, the potential to decrease hospital readmissions by way of adverse drug event avoidance, and the consequent financial penalties, has been clearly demonstrated.[25]

Infectious diseases specialists are ideally trained to direct a course of OPAT care by selecting the correct patient, the appropriate antimicrobial agent, define the duration of therapy, and quickly identify and address adverse reactions or secondary infections.[26, 27]

More recently, a significant percentage of patients have been primarily diagnosed and treated in an OPAT program without initial hospitalization,[13, 15, 16, 24] further reducing the likelihood of a secondary infection from a nosocomial source. This demonstration of value must include data that objectively defines a physician's or group's capabilities. Clinical outcomes, line infection rates, patient satisfaction, and hospital admissions (or readmissions if infusions begun as an inpatient) must be tracked and easily produced for review (see Chapter 9).

THE PHYSICIAN'S ROLE

Regardless of the model of OPAT (see Chapter 6), the infectious diseases physician needs to function as the pivotal clinician managing the patient's care. All medical decisions should be addressed by this physician including the indication for OPAT, the type of antimicrobial, duration of therapy, site of administration, the type of intravenous catheter, management of any possible complications. The rest of the OPAT team should consist of a clinical pharmacist knowledgeable in antimicrobial prescribing, nurses with specific training in infusion therapy, and an individual familiar with the financial issues concerning OPAT.

An algorithm for OPAT decision making allows the infectious diseases physician to systematically address the key issues (Figure 1.1 and Figure 2.1).[28] Once the decision has been made to enroll the patient into an OPAT program, the infectious diseases physician must also ensure that other providers, including the patient's attending physician, are informed and agree. The patient should be made aware of the collaboration and that his or her medical team is working synchronously and collegially. If the patient is being transferred from an inpatient setting to an OPAT program, it is necessary to document the plan in the medical record, write an order directing other support services, such as home health or PICC line team, and discuss the patient's wishes with a case manager. Local practice will dictate whether it is the primary team or the infectious disease consultant who is responsible for writing orders.

The infectious diseases physician, as an integral component of an OPAT program team, must be cognizant of the transition-of-care models available. This will allow for early detection of clinical issues, such as adverse drug reactions, and also nonclinical issues, such as transportation problems, that may translate into less than optimal outcomes, and possibly readmission to the hospital.

THE FUTURE

Future trends will likely include the regular and systematic collection of quality measures and outcomes as part of reimbursement models, including bundled-payment programs. OPAT providers who are able to demonstrate improved patient outcomes, decreased cost, and appropriate shifting of care from inpatient to outpatient settings are more likely to be successful in the current medical climate.

Although the challenges of OPAT are many, the rewards in terms of benefits to the health care armamentarium are great. The future lies with the leadership, creativity, and energy of infectious diseases physicians, nurses, pharmacists, and other health care professionals who provide OPAT in each community.

FIGURES & TABLES

Figure 1.1. A decision making algorithm for OPAT

View Full Diagram

IV, intravenous; PO, oral; OPAT, outpatient parenteral antimicrobial therapy.

Adapted from Williams DN, Rehm SJ, Tice AD, et al. Practice guidelines for community-based parenteral anti-infective therapy. IDSA Practice Guidelines Committee. *Clin Infect Dis*. 1997;25(4):787-801.

View Interactive Diagram

Patient with infection warranting antimicrobial therapy

Does the patient require intravenous antimicrobial therapy?

NO → Use oral antimicrobials

YES

Does the patient meet OPAT criteria? (see Figure 2.1)
- Medical care does not require hospitalization, patient stable for discharge
- Outpatient environment is safe & supportive
- Patient/caregiver capable of safe & effective drug administration, willing & able to participate
- Therapeutic monitoring feasible

YES

Is there more than one acceptable drug and or dosage regimen that can be employed safely and effectively?

NO → Initiate OPAT with the acceptable treatment regimen → NEXT

YES

Is there a significant cost difference between the acceptable treatment regimens?

NO → Is there a big convenience difference?

NO → Monitor fo
desired clin

YES

Consider using the least expensive regimen, but assess the practicality.

NEXT → Use the most convenient regimen to enhance adherence

YES

NEXT

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2

Patient Selection and Education

Geneve M. Allison, MD, MSc, FACP, and John Zurlo, MD

There are some fundamental medical and non-medical questions to answer in determining whether a patient is a candidate for OPAT:

- Is the patient clinically ready for discharge to an outpatient setting?
- Is the patient's infection amenable to outpatient treatment?
- Can the prescribed antibiotic(s) be administered in an outpatient setting? If not, are there alternatives?
- Is the patient (and/or caregiver) physically and mentally able to manage the treatment protocol?
- Can the patient afford the costs of treatment not covered by insurance?

These and other questions about patient eligibility and education will be addressed here.

PATIENT ELIGIBILITY: MEDICAL ISSUES

Fundamentally, the first assessment is whether the patient's infectious disease can be safely and effectively treated outside the hospital setting. Unfortunately there are no comparative trials that have assessed the outcomes of patients with similar infections randomized to receive inpatient care versus OPAT. Moreover, such trials are unlikely to be conducted in the future given the rise of OPAT as a standard care option over the last two decades.

Based on data from large case series, the majority of infections treated by OPAT are bone and joint infections, typically chronic osteomyelitis (including vertebral osteomyelitis/discitis), septic arthritis, and prosthetic joint infections.[1-5] Other common infectious diseases treated using OPAT include endocarditis, intra-abdominal infections, Lyme disease, meningitis, pneumonia, and septicemia (for infections amenable to OPAT, see Chapter 3).[6-8] In all cases, patients must first be clinically stabilized and otherwise ready for hospital discharge. Inpatient consultation by an infectious diseases specialist has been shown to facilitate the transition to OPAT and improve patient outcomes.[9]

OPAT SETTINGS

Once the patient is medically ready for hospital discharge, the next question is deciding on the out-of-hospital setting that is most appropriate given the individual's medical condition, capabilities, and support systems. However, in many cases, the choice of out-of-hospital venue will be determined by the patient's insurance coverage and his or her ability to pay for uncovered costs associated with treatment (see Chapter 10). The most common options for out-of-hospital antibiotic treatment are listed below.

- *Long-term Acute Care (LTAC) Hospital* – Patients sent to LTACs are those whose medical condition has stabilized in the hospital to some degree but who require ongoing acute medical care. LTACs typically have their own medical staffs who manage ongoing medical problems, including prescribing parenteral antibiotics. Under most circumstances, LTACs are not considered an OPAT setting.

- *Skilled Nursing Facility (SNF)* – Patients sent to a SNF typically, but not always, require ongoing nursing-level care. The facility takes the responsibility of delivering parenteral antibiotics. SNFs have their own medical providers who will often follow the guidance and treatment plans set up by the discharging OPAT physician. The supervision of SNF patients on OPAT is variably consistent, but very few discharging centers have the resources to provide additional oversight, once care has been handed off to the SNF. However, financial penalties related to readmissions may apply pressure on hospitals to perform more focused postdischarge oversight of OPAT patients in SNFs.

- *Infusion Center* – Due to insurance coverage, their own preferences, or because they lack the capability of infusing parenteral antibiotics at home, some patients will receive daily antibiotic infusions at an infusion center (or infusion suite). Infusion centers are often managed by a local hospital or physician group. This option is logistically feasible only for patients who live in reasonable proximity to the facility and who are receiving once daily infusion(s) (see Chapter 11). Weekend access must be available.

- *Treatment at Home* – For most OPAT programs, the majority of patients will receive OPAT at home, managed by a combination of a home infusion company and a visiting nurse service under the guidance of the discharging OPAT physician. Patients may administer infusions at home by themselves or with the help of caregivers. The remainder of this section focuses on factors involved in evaluating patients for home infusions.

PATIENT PHYSICAL AND MENTAL ABILITIES

There are no randomized trials that provide guidance regarding the minimum physical and/or mental abilities necessary to successfully manage OPAT at home. The decision to utilize OPAT typically is made by the team of caregivers including physicians, nurses, case managers, physical therapists, and members of the home care service team. In some cases, patients have the physical and mental capabilities to manage OPAT alone. Such patients who self-infuse will need an IV extension that allows for the use of both hands in catheter manipulation and infusion. Among patients who live alone, features which may signal inappropriateness of home OPAT include: visual impairment; significant problems with manual dexterity; dementia or developmental delays; serious uncontrolled mental illness or substance abuse; and a high degree of medical complexity. In many cases, patients can be managed successfully only with the help of a responsible caregiver.

OPAT for the Intravenous Drug User (IDU)

The decision about whether to employ OPAT in a home setting for an active IDU is both difficult and challenging. The common concern is that active IDU patients will utilize the central line at home for drug injection leading to line-related complications such as septicemia and thrombosis, and the possibility of overdose. While these concerns are real, there are surprisingly little data that have measured outcomes of patients with active IDU receiving OPAT. From the available evidence, along with anecdotal experience, it appears that some of these patients can receive OPAT safely. In one study, 29 active IDU patients received OPAT for a median duration of 18 days with endocarditis being the most frequent reason for antimicrobial treatment.[10] To be eligible, patients were required to have stable housing, simultaneously receive addictions treatment, agree to daily clinic visits, sign a contract for non-use of illicit drugs, and use tamper-proof seals over central catheters and infusion equipment. At follow-up 30 days after OPAT completion, only 6 patients (21%) suffered infection or treatment-related complications. There were no deaths and no tamper-proof seals were breached. While items such as tamper-proof seals are not widely available, this study does suggest that OPAT can be safely administered to a select group of IDU patients, in the right setting. Ultimately the decision about whether to proceed with OPAT in the IDU patient should be a joint decision made with all team members participating, including the infusion center team or home nursing agency who will be managing the patient in the outpatient setting.

THE HOME SITUATION

As a general rule, the safer and more stable the home situation is, the better it is for the patient, with fewer complications and better OPAT outcomes. The most important element may be the ability and commitment by the patients and/or their caregiver(s) to carefully follow all instructions given by the home management team.

Other key elements about the home situation that need to be considered:

- *Fixed address* – Having a fixed address seems to be an almost absolute requirement in qualifying for OPAT. A fixed address is more likely to be clean and stable, and to have all or most of the other necessary elements described below. There is anecdotal evidence where patients without a stable, fixed address have successfully completed OPAT, including homeless shelters or even automobiles, but these examples are very unusual. Such patients will most likely need additional tailored support to make these difficult settings safe and effective. To illustrate the importance, homeless patients in need of OPAT was provided respite residence, with 83% successfully completing the antibiotic therapy.[11]

- *Refrigerator, electricity, and running water* – Refrigeration and electricity are considered essential for OPAT because most antibiotics, typically supplied in 1-week increments, require refrigeration. Electricity is usually necessary for both refrigeration and in some cases to operate a water pump. Running water is important, but may not be essential if alcohol-based hand sanitizers are available.

- *Telephone service* – It is essential that the patient is able to quickly and easily reach members of the OPAT management team with questions or problems, and likewise, be reached in case of abnormal lab results, appointments, or any drug/supply issues. Mobile and/or landline telephone service is a necessity.

ACCESS TO MEDICAL STAFF

It is essential that patients have easy access to the OPAT team during treatment.[12] Access must be available 24 hours per day, 7 days per week. Providers (typically infectious diseases physicians) must themselves be available or have arranged coverage for off hours, including evenings and weekends. Patients should be given general instructions about the types of problems they may experience as a consequence of their infection, their antibiotic(s), and their intravenous access device. Patients should be encouraged to call with even minor concerns since most patients are not medically trained and may not be able to discern whether a problem is minor or significant. Similar lines of communication and 24-hour coverage are typically arranged by the home nursing agency and the pharmacy infusion company that delivers antibiotics and supplies. The visiting nurse is often the first person contacted by patients experiencing problems. Both the nursing agency and pharmacy must also have ready access to the infectious diseases physician.

PATIENT EDUCATION

Most patients, when told they will be infusing their own antibiotics at home, are naturally apprehensive about what to expect. The treating physician should assure the patient that there are standard procedures established specifically to manage home antibiotics, coordinated by experienced outpatient-based nursing agencies and pharmacies. Since most patients will initiate home OPAT from an inpatient setting, the process of educating the patient and, if necessary, the caregiver(s) needs to begin prior to discharge. Ideally the patient should be seen by a member of the home care team who should address the following elements of OPAT care:

I

IV catheter placement and management

The principal issues of catheter management include the importance of procedures to prevent infection and thrombosis (see Chapter 7)

Teaching sterile technique

The importance of proper hand washing prior to any IV catheter manipulation cannot be overemphasized. The steps necessary in the infusion process that require sterile technique should be demonstrated then observed

Teaching the steps in the home infusion process can and should be reinforced by educational videos and hard copy pamphlets (Table 2.1). To help the patients lay out all necessary supplies in a clean, uncluttered space, a sample may be used (see teaching schematics). Utilizing a "teach-back" educational method is recommended to ensure the patients know the required tasks and techniques before they are certified as ready to begin.[13]

In order to reap the benefits of OPAT, patient selection and education must be an explicit part of any OPAT program. While we are unlikely to see major trials comparing inpatient antimicrobial therapy with OPAT in the future, the principles in this chapter can assist with guidance in these important aspects of patient care. The decision points in selecting and educating patients for OPAT are summarized in a flow chart in Figure 2.1.

FIGURE AND TABLES

Table 2.1. Patient/caregiver skills establishing competency for OPAT

Demonstrate	How to attach the antibiotic delivery device to the IV catheter and deliver the antibiotic(s) on schedule.
Practice	How to conduct sterile technique to reduce the chances of catheter-related thrombosis and infection. For example: the SASH procedure.
Articulate	The risks and the signs of potential problems associated with home parenteral therapy, including catheter-related infections or thrombosis, and adverse reactions to antibiotics.

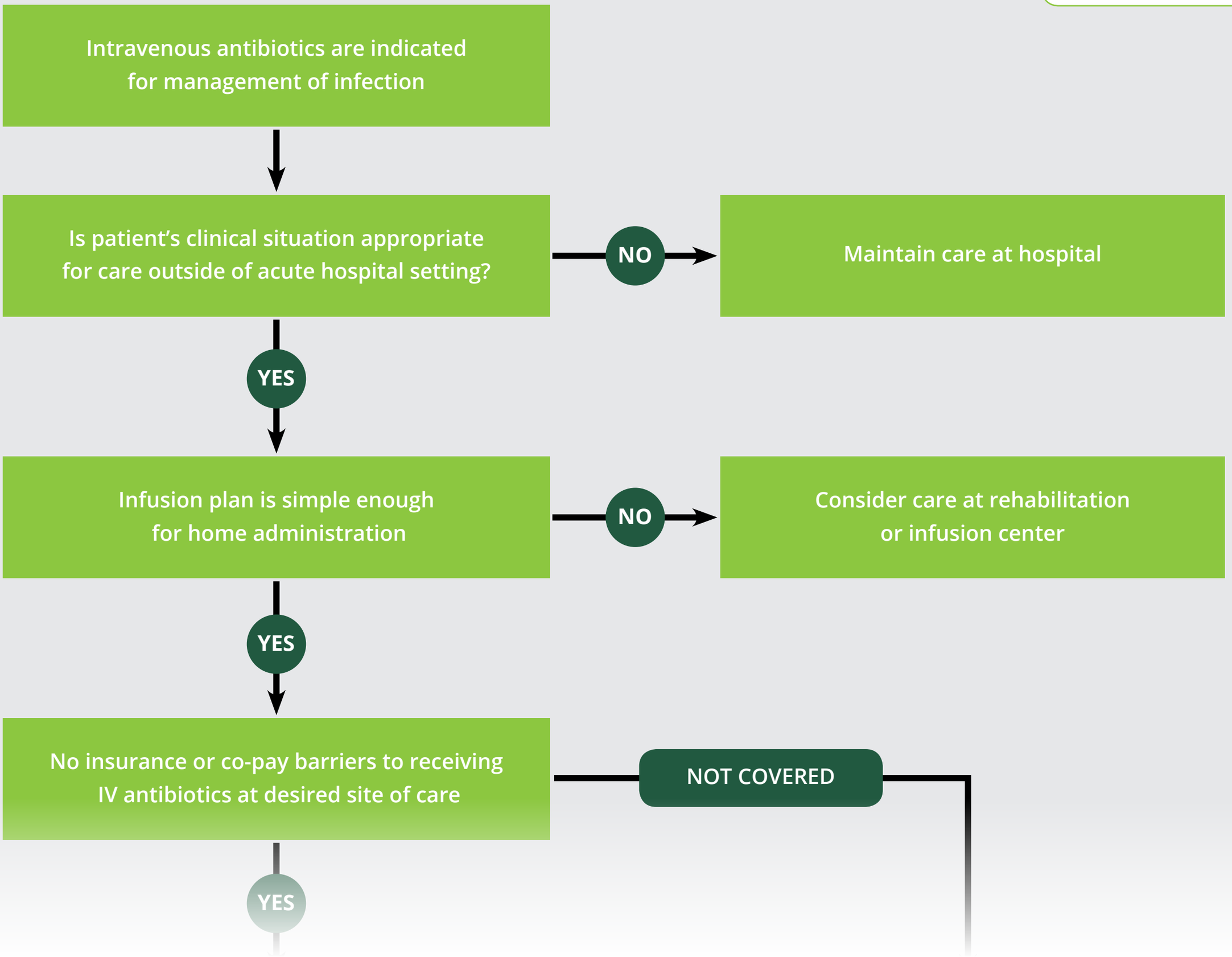
IV, intravenous; SASH [acronym], saline (flush), administration (medication), saline (flush), heparin (flush).

Figure 2.1. OPAT patient selection/education flow chart

View Full Diagram

Adapted from Tice AD, Rehm SJ, Dalovisio JR. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. *Clin Infect Dis*. 2004;38(12):1651-1672.

View Interactive Diagram



Teaching Schematic - Dial-A-Flow

WASH HANDS:

HAVE A CLEAN WORKSPACE : FLAT, SMOOTH, WELL LIGHTED
GATHER SUPPLIES : TRASH CAN
RED BIOHAZARD CONTAINER
ALCOHOL SWABS
IV TUBING
SALINE (2)
HEPARIN (1 OR 2)
WHITE CAP
MEDICATION

NURSE VISIT ON _____ FOR PICC DRESSING
CHANGE & LABS IF ORDERED

1

WIPE _____ PRIOR
TO EACH FLUSH AND IV

2

SALINE

WHITE CAP

PERFORATED

PLUNGER

PUSH UP ON PLUNGER
WHILE HOLDING ON TO
WHITE CAP TO BREAK SEAL.
REMOVE CAP. PUSH UP
THE PLUNGER GENTLY
TO REMOVE AIR.
FLUSH PICC

3

4

PLACE TO HANG BAG

WHITE TAB
(PULL OFF)

TWIST &
TURN TO
INSERT

CHECK EXPIRATION DATE
PATIENT NAME
MEDICATION & DOSE
CLARITY OF SOLUTION
NO LEAKS
ATTACH IV TUBING TO
ACCESS - OPEN CLAMP ON
TUBING & ACCESS

5

6

SALINE

WHEN INFUSION COMPLETE
CLOSE CLAMP ON IV TUBING.
FLUSH PICC LINE
WITH SALINE AFTER
ANTIBIOTIC

7

8

HEPARIN

FLUSH WITH HEPARIN
TO KEEP PICC FROM CLOTTING.
CLOSE CLAMP PRIOR TO
REMOVING SYRINGE TO
MAINTAIN POSITIVE PRESSURE.

9

WHITE CAP

IV TUBING END

PLACE WHITE CAP ON END
OF IV TUBING AFTER INFUSION
IS COMPLETED.
USE A NEW ONE EACH TIME

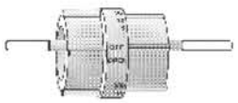
10

11

HEPARIN

FLUSH SECOND LUMEN
ONCE DAIILY WITH HEPARIN
IF APPLICABLE

DIAL A FLOW



SET AT _____ TO OBTAIN _____ DROPS PER MINUTE

IV TUBING

1) TAKE OUT OF PACKAGING
2) REMOVE PAPER
3) STRAIGHTEN TUBING, DON'T TOUCH THE FLOOR
4) CLOSE CLAMP
5) TAKE WHITE CAP OFF IV BAG
6) REMOVE COVER OF SPIKE ON TUBING
7) INSERT SPIKE INTO IV BAG
8) HANG ON IV POLE
9) SQUEEZE AND RELEASE DRIP CHAMBER TILL1/2 FULL
10) OPEN CLAMP AND ALLOW FLUID TO RUN THROUGH TUBING
11) CLOSE CLAMP AND SET DIAL

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Teaching Schematic - Intermate

INTERMATE

NURSE VISIT ON _____FOR IV LINE DRESSING CHANGE AND LABS (IF ORDERED)

WASH HANDS FIRST

USE A CLEAN, FLAT, SMOOTH WORKSPACE WITH GOOD LIGHTING

GATHER SUPPLIES: TRASH CAN AND/OR BIOHAZARD BAG

BIOHAZARD CONTAINER (SHARPS)
ALCOHOL SWABS
SALINE (2)
HEPARIN (1 OR 2)
MEDICATION –TAKE MEDICATION OUT OF THE REFRIGERATOR _____.
CHECK LABEL ON MEDICATION BOTTLE FOR: EXPIRATION DATE, YOUR NAME & DATE OF BIRTH, MEDICATION NAME & DOSE.

1

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO MEDICATION TUBING WITH 10 TWISTS OF A NEW ALCOHOL PAD.

2

SALINE

TO PREPARE ALL SYRINGES: HOLD CAP OF SYRINGE WITH FINGER, WHILE PUSHING UP ON PLUNGER (THIS BREAKS THE SEAL). REMOVE CAP. PUSH UP ON THE PLUNGER GENTLY TO REMOVE AIR. RECAP SYRINGE IF YOU HAVE TO PUT IT DOWN. FLUSH IV LINE.

3

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO MEDICATION TUBING WITH 10 TWISTS OF A NEW ALCOHOL PAD.

4 INTERMATE (MEDICATION BOTTLE)

CHECK LABEL ON MEDICATION BOTTLE AS LISTED ABOVE. UNWRAP THE MEDICATION TUBING FROM THE TOP OF THE MEDICATION BOTTLE. REMOVE THE BLUE CAP FROM THE END OF THE MEDICATION TUBING. CONNECT MEDICATION TUBING TO IV LINE. OPEN THE WHITE CLAMP ON THE MEDICATION TUBING. MAKE SURE THE CLAMPS ON IV LINE ARE OPEN. INFUSION IS NOW RUNNING. YOUR MEDICATION WILL INFUSE OVER

_____.

THE MEDICATION IS COMPLETE WHEN THE BALLOON IN THE BOTTLE HAS COMPLETELY DEFLATED.

5

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO MEDICATION TUBING WITH 10 TWISTS OF A NEW ALCOHOL PAD.

6

SALINE

FLUSH IV LINE WITH SALINE.

7

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO MEDICATION TUBING WITH 10 TWISTS OF A NEW ALCOHOL PAD.

8 HEPARIN

FLUSH WITH HEPARIN TO KEEP IV LINE FROM CLOTTING. CLOSE CLAMP PRIOR TO REMOVING SYRINGE TO PREVENT BLOOD BACK UP.

STEPS 9 & 10 ARE ONLY APPLICABLE IF YOU HAVE 2 LUMENS ON YOUR IV LINE

9

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO MEDICATION TUBING WITH 10 TWISTS OF A NEW ALCOHOL PAD.

10 HEPARIN

FLUSH 2ND LUMEN ONCE DAILY WITH HEPARIN.

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Teaching Schematic - IV Push Medication

IV PUSH MEDICATION

WASH HANDS FIRST

USE A CLEAN, FLAT, SMOOTH WORKSPACE WITH GOOD LIGHTING

GATHER SUPPLIES: TRASH CAN OR BIOHAZARD BAG
BIOHAZARD CONTAINER (SHARPS)
ALCOHOL SWABS
SALINE (2)
HEPARIN (1 OR 2)
MEDICATION - CHECK LABEL ON MEDICATION SYRINGE FOR: EXPIRATION DATE, YOUR NAME & DATE OF BIRTH, MEDICATION NAME & DOSE.

NURSE VISIT ON _____FOR IV LINE DRESSING CHANGE AND LABS (IF ORDERED)

1

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO THE MEDICATION SYRINGE WITH 10 TWISTS OF A NEW ALCOHOL PAD.

2

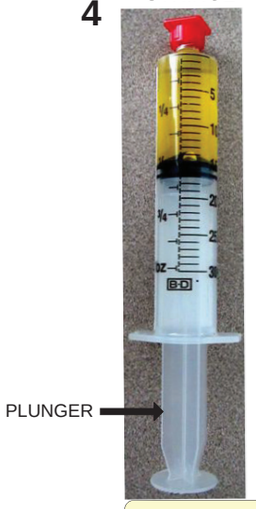
TO PREPARE ALL SYRINGES:
HOLD CAP OF SYRINGE WITH FINGER WHILE PUSHING UP ON PLUNGER (THIS BREAKS THE SEAL). REMOVE CAP. PUSH UP ON THE PLUNGER GENTLY TO REMOVE AIR. RECAP SYRINGE IF YOU HAVE TO PUT IT DOWN. FLUSH IV LINE.

3

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO THE MEDICATION SYRINGE WITH 10 TWISTS OF A NEW ALCOHOL PAD.

4

MEDICATION SYRINGE



CHECK LABEL ON MEDICATION SYRINGE AS LISTED ABOVE. REMOVE RED CAP FROM SYRINGE. CONNECT MEDICATION SYRINGE TO IV LINE. MAKE SURE CLAMPS ARE OPEN ON IV LINE. PUSH UP ON THE PLUNGER SLOWLY, TO GIVE THE MEDICATION OVER _____ MINUTES.

YOUR MEDICINE IS TO BE GIVEN OVER _____ MINUTES

5

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO THE MEDICATION SYRINGE WITH 10 TWISTS OF A NEW ALCOHOL PAD.

6

SALINE

FLUSH IV LINE WITH SALINE.

7

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO THE MEDICATION SYRINGE WITH 10 TWISTS OF A NEW ALCOHOL PAD.

8 HEPARIN

FLUSH WITH HEPARIN TO KEEP IV LINE FROM CLOTTING. CLOSE CLAMP PRIOR TO REMOVING SYRINGE TO PREVENT BLOOD BACK UP.

STEPS 9 & 10 ARE ONLY APPLICABLE IF YOU HAVE 2 LUMENS ON YOUR IV LINE

9

WIPE IV LINE PRIOR TO EACH FLUSH AND/OR CONNECTION TO THE MEDICATION SYRINGE WITH 10 TWISTS OF A NEW ALCOHOL PAD.

10 HEPARIN

FLUSH 2ND LUMEN ONCE DAILY WITH HEPARIN.

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3

Infections Amenable to OPAT

Nabin Shrestha, MD, and Ajay Mathur, MD

Decisions regarding outpatient treatment of infections vary with the institution, the prescribing physician, the individual patient's condition and wishes, and the patient's insurance coverage. The range of infections amenable to treatment with OPAT also depends on the type of OPAT infrastructure available. For OPAT in an infusion center, treatments are generally limited to antibiotics that require once-daily administration. For OPAT at home, the daily number of infusions required is generally not a restriction. The limiting factor may be the ability of the patient or a caregiver to learn to administer the medications.

Infections that are most commonly treated via OPAT are infective endocarditis and other cardiovascular infections, osteoarticular infections, abdominal infections, and skin and soft tissue infections.[1,2] Other commonly treated infections include respiratory, genitourinary, and central nervous system (CNS) infections (Table 5.1).[1]

INFECTIVE ENDOCARDITIS AND CARDIAC DEVICE INFECTIONS

Infective endocarditis has an annual incidence of about 3 to 9 cases per 100,000 persons in developed countries.[3] Staphylococci, streptococci, and enterococci are responsible for the majority of these infections.[4] In recent years, *Staphylococcus aureus* has become the most common cause of infective endocarditis, driven largely by advances in treatments that require vascular invasion, such as prolonged vascular access, hemodialysis and cardiac pacing.[5]

Patients at increased risk for infective endocarditis include those with preexisting valvular heart disease, those with cardiac hardware, those with injection drug use, and those with indwelling vascular access devices. All patients with infective endocarditis should be hospitalized for an adequate evaluation. In the past, patients with infective endocarditis received all their treatment in an inpatient setting. With the evolution of OPAT, this has changed. Several studies have shown that selected patients with infective endocarditis can be safely treated via OPAT.[6-8] It is now accepted practice for patients to be initially treated in the hospital and then discharged on OPAT once clinically stable, to complete the remainder of the treatment course as OPAT.[9-11]

Advances in cardiac care have led to a proliferation of cardiac devices such as cardiovascular implantable electronic devices (CIEDs; eg, pacemakers and defibrillators) and left ventricular assist devices. Many of the infections associated with these devices involve infective endocarditis.[5]

Evaluation

Successful outpatient treatment depends largely on an appropriate inpatient evaluation. Evaluation of infective endocarditis includes identifying the causative pathogen and determining the extent of valvular damage caused by the infection. In the preoperative period and in medically treated patients, identification of the causative pathogen is done via blood cultures. Determining the extent of valvular damage requires echocardiographic examination. Transesophageal echocardiography is more sensitive than transthoracic echocardiography in finding lesions caused by infective endocarditis and should always be performed in the evaluation unless contraindicated by comorbid conditions.[12]

Many patients with infective endocarditis require surgery for their care, and medical therapy alone is futile. The presence of prosthetic heart valves or perivalvular abscesses makes it unlikely that a cure can be achieved without surgery.[3-5] The presence of large vegetations (Figure 3.1), ongoing embolic complications, or persistent bacteremia despite antibiotic therapy also portends trouble with continued medical therapy alone. Infections with pathogens such as *Staphylococcus aureus*, *Staphylococcus lugdunensis,* and *Candida* species are more likely to require surgery.[3-5]

Treatment

The traditional course of treatment for infective endocarditis is 4 to 6 weeks of IV antibiotic(s) to which the causative microorganism is susceptible (see Table 5.1). Treatment guidelines for infective endocarditis have been published by various societies, such as the American Heart Association, the European Society for Cardiology, and the British Society for Antimicrobial Chemotherapy.[13-17] Most viridans group streptococci are susceptible to penicillin. They may also be treated with ceftriaxone, which allows for the convenience of once-daily dosing.[13-17]

Staphylococcal infections are best treated with oxacillin or nafcillin, if susceptible. Both of these require multiple infusions per day. Their administration is greatly facilitated by the availability of programmable multidose infusion pumps; these can be loaded with the daily dose of medication, which is then administered by the pump in divided doses according to the instructions provided. It is possible but very inconvenient, and frankly impractical, to expect a patient or his/her caregiver to faithfully administer a medication every four hours for several weeks, which is what would be required to administer oxacillin or nafcillin in the absence of a programmable multidose infusion pump (see Chapter 7: *Infusion Administration Methods*).

The most commonly used antibiotic for the treatment of methicillin-resistant staphylococcal infections is vancomycin (see Table 5.1). The advantage of vancomycin over other options is its low cost. The drug cost of alternative antibiotics could be 10 to 50 times higher. Alternative antibiotics are daptomycin and ceftaroline. Disadvantages of vancomycin over the other treatment options include more adverse reactions, need for therapeutic drug monitoring, and more effort in monitoring treatment.[13-17]

Enterococcal infections are best treated with ampicillin, if susceptible. If ampicillin is not an option owing to resistance or allergy, the next treatment option is vancomycin. If vancomycin is not an option, the treatment of choice is daptomycin. The endocarditis treatment guidelines recommend addition of aminoglycosides in the treatment of enterococcal endocarditis. Such treatment places patients at substantial risk of aminoglycoside toxicity, and patients so treated should be closely monitored.[13-17]

It has been suggested that patients with uncomplicated infective endocarditis caused by viridans group streptococci could be discharged on OPAT after 1 week of hospitalization.[11] This is a reasonable suggestion for uncomplicated infective endocarditis caused by any pathogen, provided the patient has been adequately evaluated for complications.[3-5, 13-17]

Treatment of cardiac device infections includes removal of the cardiac device when possible, and antibiotic therapy, usually parenteral. Guidelines for treatment of CIED infections have been published.[18]

OSTEOARTICULAR INFECTIONS

Infections of bones and joints lend themselves well to OPAT because patients may otherwise be healthy, and a prolonged 4- to 6-week course of treatment is necessary.[19,20]

Studies have shown that the likelihood of failure and amputation are higher with concomitant diabetes mellitus and peripheral arterial disease, but not clearly with increasing age.[19] Patients may also experience severe pain and spasms that require hospitalization for pain control and subsequent physical therapy. They may also be in a cumbersome body jacket or cast that limits the motion of the spine.[21]

Evaluation

The purpose of evaluation is to confirm a diagnosis of an osteoarticular infection, identify the causative microorganism, and define the anatomical extent of infection. Radiographic imaging provides an anatomical picture of the site and extent of involvement. X-rays reveal presence of bony destruction and sometimes evidence of soft-tissue swelling. Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive than plain radiographs in detecting the presence of osteomyelitis and associated abscesses, and defining extent of involvement (Figure 3.2).[21]

Blood cultures are not sensitive in identifying the causative pathogen in patients with osteoarticular infections, but they should always be done in patients who appear ill. When possible, a sample of bone from an affected area should be obtained for microbiological examination before initiation of antibiotics.[21] Identification of the causative pathogen will allow for more directed therapy.

Treatment

Common pathogens causing osteoarticular infections include both gram-positive and gram-negative microorganisms. The most common bacteria that cause osteomyelitis are *S. aureus*, coagulase-negative staphylococci, and gram-negative bacilli.[19-21]

Treatment of infections associated with prosthetic implants includes removing the prosthetic material whenever possible. Patients with prosthetic joint infections treated while retaining the prosthesis should be treated with lifelong suppressive antibiotic therapy (see IDSA Guidelines).[22]

Osteoarticular infections with *S. aureus* and coagulase-negative staphylococci are best treated with parenteral antibiotics. Oxacillin or nafcillin are the best antibiotics for methicillin-susceptible strains. The treatment options for osteoarticular infections caused by methicillin-resistant staphylococci are the same as those for infective endocarditis.[17, 19-22]

Many gram-negative osteoarticular infections can be treated with an oral quinolone.[21,23] Associated debilitation may be a factor in selecting the site of OPAT because treatment in an infusion center may not be possible owing to the patient's inability to get there on account of pain. Self-administration at home or treatment in skilled nursing facilities may be more appropriate for such patients.[19-21]

The duration of antimicrobial treatment depends on the extent and depth of infection, the bones and microorganisms involved, the extent of surgical debridement, and host comorbid conditions.

Uncomplicated osteomyelitis in children, for example, responds well to 1 or 2 weeks of IV antimicrobial therapy followed by oral agents (if adequate serum levels can be reached) for another 2 to 4 weeks.[24] Diskitis/vertebral osteomyelitis in the adult, on the other hand, is a deep, serious, and difficult-to-treat infection that does not lend itself well to surgical intervention. Standard recommendations are IV infusion of antimicrobial agents for a minimum of 6 weeks.[21]

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections include impetigo, ecthyma, cellulitis, erysipelas, furuncles, carbuncles, skin and subcutaneous abscesses, pyomyositis, necrotizing fasciitis, myonecrosis, wound infections, and surgical site infections.

Traditionally, patients with severe skin and soft tissue infections were hospitalized, treated with IV antibiotics in the hospital, and discharged on oral antibiotics once improved. The development of OPAT has allowed for discharge from the hospital sooner, on IV antibiotic therapy.[17] Where practice arrangements allow, selected patients may be treated with IV antibiotics entirely as outpatients, thus avoiding hospitalization. In some settings, patients have been started on IV antibiotics in the emergency department and then referred directly to OPAT infusion programs.

Evaluation

Most skin and soft tissue infections are caused by streptococci or staphylococci. An important part of evaluating such infections is to determine if there is deep invasive infection and to evaluate whether it is likely that more-resistant pathogens may be involved. Noninfectious conditions may mimic skin infections, and their recognition can prevent unnecessary antibiotic treatment.[25]

Necrotizing soft tissue infections will usually need surgical debridement in addition to antibiotic therapy.[26] Systemic toxicity out of proportion with what would be expected from the extent of cellulitis or limb tenderness proximal to the area of redness should raise concern for a necrotizing soft tissue infection.

For patients who appear ill, blood cultures should be done before initiating antibiotics whenever possible.

Treatment

The Infectious Diseases Society of America (IDSA) has issued guidelines for the treatment of skin and skin structure infections.[25] When parenteral antimicrobial therapy is required, ceftriaxone is appropriate for streptococcal infections. Oxacillin and nafcillin are appropriate for methicillin-susceptible *S. aureus* infections. If a mixed infection is to be treated, ampicillin-sulbactam, piperacillin-tazobactam, or ertapenem may be used, or a combination of parenteral and oral antibiotics covering the desired antimicrobial spectrum may be used. Vancomycin, daptomycin, and ceftaroline are effective options for treatment of methicillin-resistant *S. aureus* (MRSA) infections.[25] Another option is dalbavancin, a long-lasting agent that has recently been approved as a single-dose (30 min IV infusion) for the treatment of acute bacterial skin and skin structure infections, including MRSA.[27] The role of other long-acting agents, such as talavancin and oritavancin, is still evolving.

Trimethoprim-sulfamethoxazole, clindamycin, doxycycline, and linezolid are oral options for the treatment of MRSA infections when oral therapy is appropriate.[28] Dicloxacillin and cephalexin may be appropriate for treatment of *S. aureus* infections when methicillin resistance is not a concern. Amoxicillin and cephalexin are oral options for oral treatment of streptococcal infections when oral treatment is appropriate.[25,28]

Amoxicillin-clavulanate, quinolones, and metronidazole are useful oral antibiotics that may be used instead of IV antibiotics or in combination with easily administered IV antibiotics for treatment of skin and soft tissue infections, particularly when mixed infections are being treated. [25,28]

WOUND INFECTIONS

Infections may complicate a variety of wounds, from soft tissue traumatic wounds to surgical wounds. Depending on the depth of injury and the tissues involved, IV antimicrobial therapy may be necessary. Wounds caused by penetrating injury often involve significant tissue damage and provide fertile ground for a wide variety of infecting microorganisms. Such infections may require debridement as well as aggressive parenteral therapy with antimicrobials. Bite wounds, particularly of the hand, or wounds caused by fist-to-mouth injuries are also prone to severe infections requiring IV antimicrobials and early surgery[25]. Foot infections are a common problem in patients with diabetes mellitus and could potentially be limb- or life-threatening.[29]

The microorganisms in wound infections vary considerably. Community-acquired infections are often caused by *S. aureus*, streptococci, and at times, anaerobes, depending on the site and type of injury. Surgical wound infections may be caused by resistant nosocomial pathogens. Such bacteria may vary from gram-negative bacteria such as *Pseudomonas, Enterobacter,* and *Acinetobacter* species and *Escherichia coli*, to the resistant gram-positive bacteria such as MRSA, coagulase-negative staphylococci, and enterococci, some of which may be resistant to vancomycin.[25]

Evaluation

For deeper wounds, imaging using plain radiographs, CT, or MRI will be necessary to obtain a reasonable understanding of the extent of infection. The appropriate radiographic modality to be used will depend on the anatomical site.[25]

Cultures can be very helpful in selecting appropriate antimicrobial treatment. In interpreting wound culture results, it is important to understand that surface culture may not necessarily reflect the true pathogens. Deeper cultures are more likely to identify the true pathogens but may not always be available. Many wounds may be polymicrobial, and antibiotic selection must be made taking into consideration the possibility that there may be more to the microbial etiology than microorganisms isolated in culture.[25]

Treatment

Surgical debridement of necrotic tissue is an important part of the management of wound infections. Pathogen-directed therapy is always best for wound infections if appropriate culture results are available. In many instances, empiric antimicrobial therapy

is necessary. Ampicillin-sulbactam and piperacillin-tazobactam provide broad coverage for a wide variety of infected wounds, but a major disadvantage is the need for frequent administration. Ertapenem is a broad-spectrum agent with broad-spectrum gram-negative bacterial and anaerobic coverage, with an added advantage of requiring administration only once a day. For infections acquired in the hospital, empiric antibiotic therapy should include coverage for methicillin-resistant staphylococci, and often *Pseudomonas aeruginosa*.[25] Combinations of once-daily parenteral antibiotics with oral antibiotics may be used to facilitate OPAT if treatment is planned in an infusion center. Serious diabetic foot infections will require surgical debridement in addition to antibiotic therapy (see IDSA Guidelines).[29]

ABDOMINAL INFECTIONS

Abdominal and pelvic infections may be treated with OPAT once any necessary surgical procedures have been done.

Evaluation

The imaging modality of choice for determining the presence and extent of intra-abdominal infections is the CT scan.[30,31]

Treatment

The most important decision in abdominal/pelvic infections is a determination of whether surgical intervention is necessary, and if so, whether the required intervention is an emergency.

Urgent surgical intervention may be required if there are peritoneal signs on examination. Antibiotic therapy will be necessary whenever the disease process includes spillage of enteric contents into the peritoneal cavity. Treatment outcomes could be poor in the setting of undrained intra-abdominal abscesses of any significant size.[30]

Empiric antibiotic treatment should include broad-spectrum coverage for enteric gram-negative bacteria, anaerobic bacteria, and enteric streptococci (see IDSA Guidelines).[31] Piperacillin-tazobactam, imipenem-cilastatin, meropenem, doripenem, and ceftazidime/cefepime in combination with metronidazole are reasonable antibiotic choices. In treating intra-abdominal infections, antibiotic selection must be undertaken with the understanding that these infections are usually polymicrobial infections even if only one pathogen has been isolated in culture.[31]

RESPIRATORY TRACT INFECTIONS

The first report of outpatient IV antimicrobial therapy, by Rucker and Harrison in 1974, involved the treatment of respiratory tract infections in children with cystic fibrosis.[32] Respiratory tract infections now account for a much smaller proportion of infections treated with OPAT.

Most respiratory tract infections can be treated with oral antibiotics when antimicrobial therapy is warranted. Parenteral antibiotic therapy may be considered for patients with severe or resistant infections or for patients unable to take oral medications. Infections treated may include pneumonia, lung abscess, and empyema.

Evaluation

The diagnostic evaluation includes confirming the diagnosis, identifying the causative pathogen(s), and determining the severity of infection. An important part of the evaluation is to decide if a patient needs to be hospitalized, which antibiotic should be used for treatment, and whether parenteral antibiotic therapy is necessary when the patient is discharged from the hospital. This will require assessment for hemodynamic stability, hypoxemia, preexisting conditions, and ability to take oral medications. Various severity score measures for pneumonia have been developed in order to help decide whether a patient should be hospitalized for treatment; the best known of these are the Pneumonia Severity Index (PSI) and the CURB-65 criteria.[33,34]

The anatomic extent of respiratory tract infection is evaluated using plain chest radiographs, and in some instances CT imaging.

Culture of respiratory specimens may help in identifying the causative pathogen. Sputum culture is the least invasive method of obtaining a respiratory sample. When there is strong clinical reason to pursue a microbiological diagnosis, bronchoscopy with bronchoalveolar lavage or transbronchial biopsies may be necessary. Patients with suspected complicated parapneumonic effusions or empyema should have the pleural fluid sampled.[35]

Treatment

Patients with community-acquired pneumonia who are sick enough to be hospitalized are usually treated with IV antibiotics. The treatment guideline from the IDSA and the American Thoracic Society advocates the use of a respiratory quinolone or an injectable β-lactam antibiotic for inpatient empiric therapy for community-acquired pneumonia, and an injectable β-lactam antibiotic for patients sick enough to require admission to the intensive care unit.[35] When patients improve, a decision about whether to continue IV antibiotic therapy at discharge or switch to an oral antibiotic has to be made. This decision involves weighing the response to treatment, comorbid conditions, ability to take oral medications, and outpatient treatment resources available.

Patients with empyema will not improve with antibiotic therapy alone. They will need adequate chest tube drainage or decortication. When possible, co-management with a thoracic surgeon would enhance the likelihood of a desirable clinical outcome. After adequate surgical control of pleural space infection, a course of parenteral antibiotic therapy may be appropriate.[35]

CENTRAL NERVOUS SYSTEM INFECTIONS

Central Nervous System Infections (CNS) include meningitis, encephalitis, ventriculitis, brain abscess, subdural empyema, and cranial or spinal epidural abscess. Iatrogenic infections include ventriculitis associated with ventriculostomy drains and deep brain stimulator infections.

Community-acquired bacterial meningitis in adults is most commonly caused by *Streptococcus pneumoniae* or *Neisseria meningitidis*.[36] Immunocompromised patients may have *Listeria* meningitis. Neonates may also have meningitis caused by enteric gram-negative bacteria. Meningitis caused by *Haemophilus influenza* type b is uncommonly seen now owing to successful vaccination efforts. Intracranial abscesses may be caused by anginosus group streptococci.[37] Brain abscesses caused by spread from paranasal sinuses and dental infections are often polymicrobial.[38]

Common causes of postneurosurgical infections include staphylococci, *Propionibacterium acnes*, and gram-negative microorganisms including *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella* species, *Enterobacter* species, and *Acinetobacter*.[39]

Evaluation

All patients with CNS infections should be hospitalized initially for a proper evaluation. Cerebrospinal fluid examination is essential for an appropriate diagnostic evaluation in patients with suspected bacterial meningitis. CNS abscesses will require CT or MRI for diagnosis (Figure 3.3).[36-39]

Treatment

Treatment for CNS infections will require the administration of IV antibiotic therapy. Initial treatment is usually empiric and directed against the expected pathogens.[36,39] By the time patients are discharged from the hospital after stabilization of a community-acquired bacterial CNS infection, they are usually on an antibiotic such as ceftriaxone or ampicillin. Patients with postneurosurgical infections should be on pathogen-directed therapy that might include vancomycin, piperacillin-tazobactam, or ceftazidime. Once a diagnosis is established and the patient stabilized clinically, treatment may be completed in an outpatient setting.[40]

URINARY TRACT INFECTIONS

Urinary tract infections are very common. They can usually be treated with oral antibiotics.[40] Patients hospitalized with sepsis secondary to urinary tract infections may be treated with intravenous antibiotics in the hospital. Once they are better and ready to be discharged from the hospital, they can often be safely transitioned to oral antibiotic therapy to which the infecting microorganism is susceptible. In these instances, OPAT is not necessary. However, not all uropathogens are susceptible to oral agents; extended-spectrum β-lactamase (ESBL)-producing organisms, for instance, may require parenteral therapy, potentially delivered by OPAT.[41,42]

Evaluation

The most important evaluation is whether a patient actually has a urinary tract infection. Too often a diagnosis of urinary tract infection is based on a positive urine culture. In many of these cases the positive urine culture does not represent a urinary tract infection, and antibiotic therapy is not necessary. Patients with urinary tract infections should almost always have a positive urine culture in the absence of antibiotic therapy. Negative urine culture in the absence of antibiotic therapy is a strong argument against urinary tract infection. Patients with severe urinary tract infection could have secondary bacteremia.[42] Blood cultures should be obtained in patients who appear to be severely ill.

Depending on the clinical circumstances, radiographic imaging may be necessary. Plain radiographs can identify the presence of nephrolithiasis. Ultrasonography can identify the presence of hydronephrosis or significant post-void residuals, which may be of clinical significance. CT imaging can find evidence of pyelonephritis, nephrolithiasis, hydro- or pyonephrosis, renal abscesses, or perinephric abscesses.

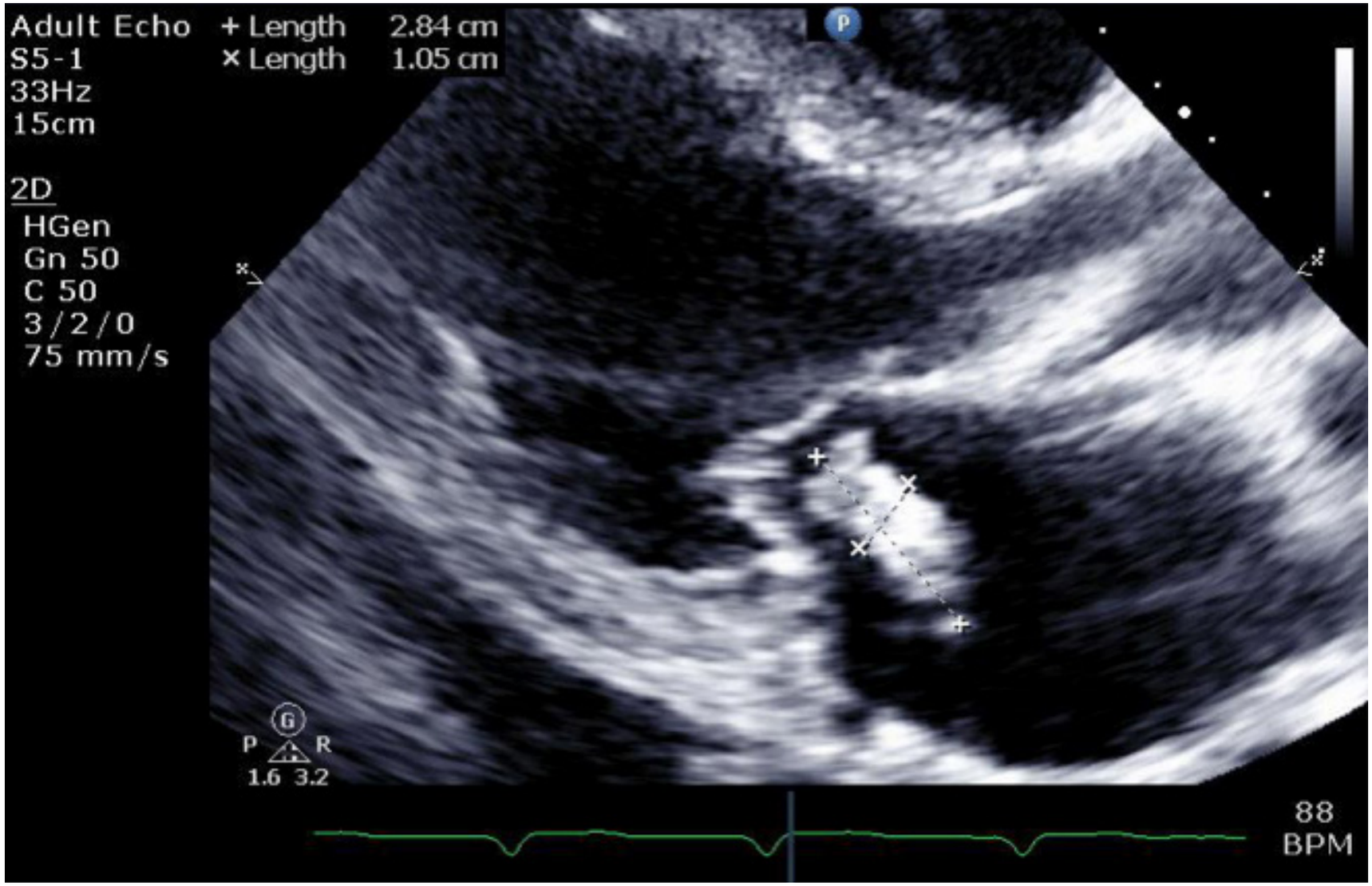
Treatment

When a patient has a urinary tract infection, the first treatment decision is whether the patient can be treated with an oral antibiotic. If such treatment is not an option, OPAT becomes necessary.[41,42]

Urinary tract infections caused by microorganisms resistant to oral medications may be successfully treated with parenteral medications. Many of these infections can be treated with penicillins, cephalosporins, or carbapenems. Many treatment options, such as ceftriaxone, ertapenem, and aminoglycosides are amenable to once-daily dosing.

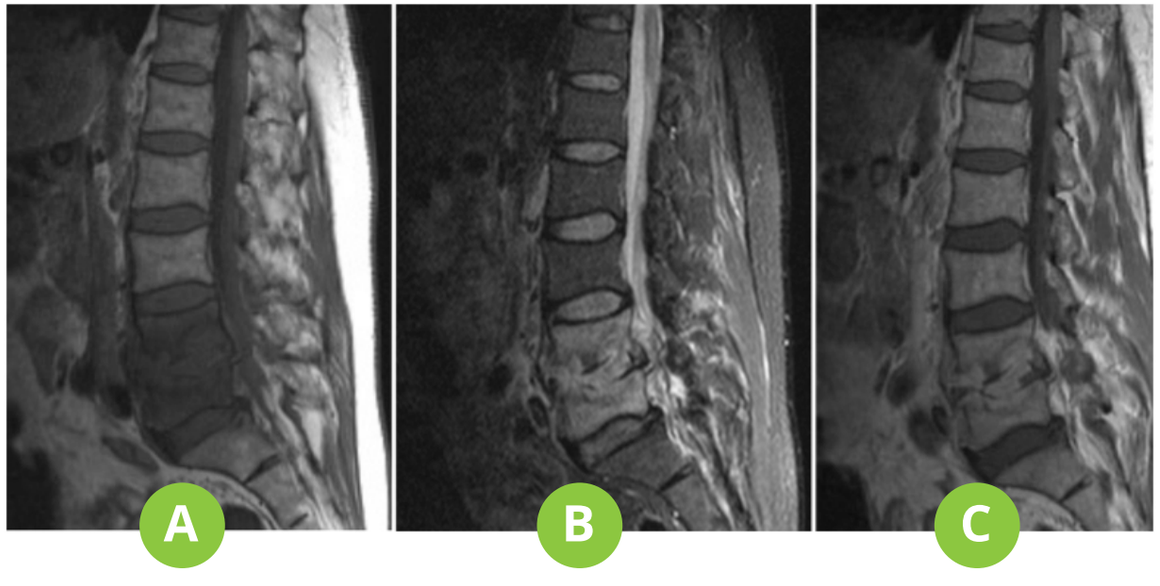
FIGURES AND TABLES

Figure 3.1. Infective endocarditis



Transthoracic echocardiographic image showing a large vegetation attached to the mitral valve.

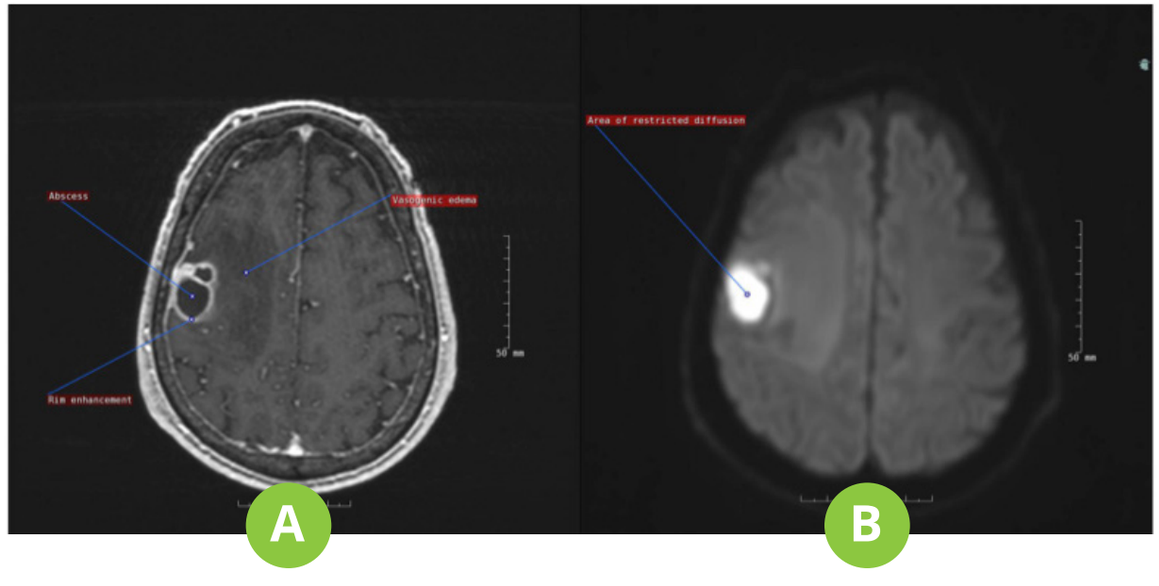
Figure 3.2. Spondylodiskitis (vertebral osteomyelitis)



Sagittal MRI images of a patient with L4-5 disk infection showing decreased signal intensity from edema in the infected disk and adjacent vertebral bodies on a T1-weighted image (**panel A**), increased signal intensity from edema of the L4-5 disk and adjacent vertebral bodies on a STIR image (**panel B**), and contrast-enhancement of the infected disk and adjacent vertebral bodies on a T1-weighted post-contrast study (**panel C).**

Courtesy Maja Babic, MD, Section of Bone and Joint Infections, Department of Infectious Diseases, Cleveland Clinic.

Figure 3.3. Brain abscess



T1-weighted post-contrast study (**panel A**) showing an abscess with rim-enhancement and surrounding vasogenic edema, and a diffusion-weighted image (**panel B**) showing restricted diffusion (bright signal) in the area of the abscess, in a patient with a *Nocardia* brain abscess.

Courtesy Adarsh Bhimraj, MD, Section of Neurological Infections, Department of Infectious Diseases, Cleveland Clinic.

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4

Monitoring of OPAT

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Optimal monitoring of patients receiving OPAT is essential in order to ensure the best clinical outcomes and reduce the chances of an unintended and, most importantly, unobserved complication.

Monitoring of patients receiving OPAT includes:

- Evaluating the response of the infection to treatment
- Ensuring the safety of the drugs being administered (to recognize toxicities and minimize harm)
- Therapeutic drug monitoring for those drugs that require levels to be maintained within target ranges
- Monitoring of the vascular access device for complications
- Ongoing evaluation of the potential for drug interactions
- Management of side effects
- Evaluation for secondary infection, such as *Clostridium difficile* colitis

Unfortunately, there are few studies that truly inform the ideal monitoring protocol for OPAT. In particular, the optimal frequency of both laboratory measurements and follow-up evaluations for patients on OPAT has not been well established.

In the real world, monitoring protocols must conform logistically to the available resources of each OPAT program, which vary considerably. This chapter discusses the logistical aspects of OPAT monitoring programs, the recommendations for safety laboratory, therapeutic drug monitoring, and various approaches to the common clinical and laboratory monitoring problems seen in OPAT.

OPAT MONITORING STRUCTURES

Just as there are different models for the delivery of OPAT (see Chapter 6), differences also exist in the ways in which OPAT providers and programs monitor patients on IV antimicrobial therapy. Patients on OPAT require both clinical follow-up and laboratory monitoring; dedicated OPAT programs require structures to ensure both monitoring elements are achieved. In the infusion suite OPAT model, clinical and laboratory monitoring may be achieved simultaneously, with frequent visits, laboratory blood samples may be drawn at the time of clinical evaluation. In other programs, patients may be seen by health care personnel less frequently, necessitating that laboratory blood samples be obtained by visiting nurses, or at outside laboratory facilities. Without appropriate clinical and laboratory monitoring, patients are at risk of inappropriate antibiotic dosing and toxicity, unnecessary prolongation of therapy, vascular access complications, and hospital readmission.

There are little data regarding the optimal monitoring structure for patients receiving OPAT, or how often patients should be seen by the supervising physician. Wide variability exists in the frequency of clinical follow-up. Routine clinical monitoring is necessary to assess toxicities not identified through laboratory review (eg, neuropathy or otovestibular toxicity), and to ensure efficacy of treatment. Patients receiving IV antimicrobials at an outpatient infusion center or skilled nursing facility, may be evaluated daily by nursing, pharmacy, and/or physician staff, while patients receiving OPAT in the home setting, are typically seen less frequently.

Previous OPAT guidelines from the Infectious Diseases Society of America (IDSA) recommended weekly or more frequent follow-up visits by physicians, although this practice is not routinely followed, particularly among home infusion patients.[1] In a 2004 survey of the IDSA's Emerging Infections Network (EIN), only 29% of infectious diseases physicians saw their OPAT patients weekly.[2] Barriers to frequent visits include lack of available time in physicians' schedules, geographic distance from managing physicians, the need for patients to be seen by multiple care providers for follow-up, and patient mobility challenges, especially for those patients with orthopedic infections.

For OPAT models in which weekly clinical follow-up is not feasible, decisions about timing of visits should be individualized, with more frequent assessments necessary for patients with higher acuity illness, greater comorbidity, and higher risk for adverse outcomes. Patients for whom clinical follow-up may inform decisions on either the continued need for antimicrobial therapy, or a switch to oral therapy, should also be seen earlier and more often than stable patients for whom duration and route of therapy are not likely to change (eg, patients with Lyme disease).

Optimally, outpatient OPAT visits would be coordinated with other necessary visits to improve adherence to care. In practice, the frequency and timing of patient visits are determined by both clinical and logistic factors. Patients at home who are not seen by the OPAT clinician weekly still require weekly evaluation and dressing change of the vascular access device by a visiting nurse.

Additional counseling of patients and their caregivers to ensure that other toxicities (eg, otovestibular dysfunction or neuropathy) are promptly reported is important.

A dedicated OPAT program should ensure that appropriate clinical follow-up is arranged and communicated to the patient and his or her caregivers prior to hospital discharge or at initiation of OPAT care. Such models should also anticipate the need for unscheduled care, ensuring that a system exists for rapid evaluation of potentially important side effects such as fever, rash, and diarrhea, and for complications from the infection being treated. Tracking of visits to ensure patients are not lost to follow-up is essential, especially with venous access devices in place.

LABORATORY MONITORING SCHEDULE

Weekly laboratory monitoring is recommended for most patients on OPAT.[1] Complete blood counts (CBCs) should be measured even for patients receiving parenteral antibiotics with little or no potential to cause cytopenias, since an elevated white blood cell (WBC) or eosinophilia, may be early important clues to the development of secondary infections (eg, catheter-related infections [CDI]), or allergic drug reactions. For patients not seen weekly, additional monitoring structures need to be in place, to ensure that laboratory tests are obtained and reviewed by the responsible physician, pharmacist, or other OPAT team member. Open channels of communication among the patient, their in-home caregivers, infusion nurse, pharmacists, and other OPAT team members, are necessary to ensure this occurs. Active tracking of laboratory test results represents a significant burden of work for many OPAT programs, but is essential for patient safety. In one study, patients on OPAT, whose laboratory results were nonavailable, had a 2.5-fold increased risk of readmission in multivariate analysis.[3] The positive role of the infectious diseases physician in facilitating safe OPAT monitoring cannot be overstated. Adherence to monitoring recommendations is significantly enhanced when the physicians are involved in the care.[3-5]

Laboratory tests that are drawn outside of the context of a clinical visit, or by an external care provider, may not be reported to the OPAT care team in a timely fashion, which can result in important delays in recognition of antimicrobial toxicity and the need for dose adjustment. Systems to ensure that results are

reported in a timely way are necessary, and actively tracked, when not available. Prescheduled weekly laboratory tests should be collected early in the week (eg, Monday or Tuesday), so that the results may be acted upon, or repeated as necessary, during the week when OPAT practices are fully staffed.

The burden of OPAT laboratory tracking is substantially alleviated when laboratory results are available in an electronic health record (EHR) system, available to the physician and/or OPAT team. In practice, however, laboratory results often arrive from outside facilities by FAX, which challenges detection of important trends in specific results (eg, creatinine levels or white blood cell counts). When laboratory results are not available in a single electronic medical record, additional procedures for managing the volume of OPAT laboratory results, and tracking them over time, should be developed. Weekly "virtual" visits by care team members to review laboratory results, and treatment progress, is one such strategy endorsed in the United Kingdom.[6] In high volume OPAT programs, a dedicated support team is often required; however, the availability of an OPAT team is far from universal. In a 2012 survey of Emerging Infections Network (EIN) members, lack of a dedicated OPAT team was reported as the single greatest barrier to providing safe OPAT services.[7]

Given the medical complexity of many patients who receive OPAT, interpretation and management of laboratory abnormalities may not always be straightforward. When multiple clinicians are involved in the care of a patient, the OPAT clinician may receive laboratory results that require intervention, but were not ordered in the context of OPAT care (eg, potassium or international normalized ratio [INR]). When important organ toxicity is identified, nonantimicrobials should also be considered as possible offending agents. While alterations in renal function may require dose adjustment of antimicrobials, medications not prescribed by the OPAT physician may also require adjustment. Communication with other care team providers is essential to ensure that all laboratory results are acted upon appropriately, but not redundantly, to avoid harm. Communication with other care providers is necessary to ensure that the full complement of non-OPAT medications is reviewed and that optimal care is provided.

SAFETY MONITORING

Most patients receiving OPAT require laboratory monitoring to ensure the safety of the antimicrobials being administered. Scheduled laboratory studies allow for important toxicities (eg, nephrotoxicity or hepatotoxicity) to be identified before they lead to clinically apparent illness, thereby allowing changes in medications to be made. Recognition of changing renal function also allows for optimal dosing of antimicrobial medications that are cleared renally, thereby ensuring that dosing remains efficacious as renal function improves, and that toxic doses can be avoided when renal function declines.

Minimum recommendations for laboratory monitoring have been developed, which include weekly CBCs with differential and serum creatinine for most antimicrobial agents (Table 4.1).[1] Recommendations for monitoring are based on known adverse events associated with specific therapies, though patients at increased risk of toxicity, and those in whom concerning trends are identified should be monitored more frequently.

Nephrotoxicity

Reports of nephrotoxicity among patients receiving OPAT vary significantly according to the drugs being used, the patient population, and the OPAT duration, ranging from <1% to 17% in published studies.[1,8-12] Nephrotoxicity risks are highest with vancomycin, the aminoglycosides, and amphotericin. Renal function should be monitored in patients receiving medications that are renally cleared, even if the agents themselves are not known to be nephrotoxic, to ensure that dose adjustments do not need to be made during treatment. Patients on medications with higher nephrotoxicity potential, and those receiving more than 1 nephrotoxic agent, may require more frequent serum creatinine monitoring. Further discussion of nephrotoxicity, and management of elevated serum creatinine, is reviewed below.

Electrolyte imbalances

Measurement of serum electrolytes is not required for patients receiving most antimicrobials, but is recommended for patients receiving certain β-lactams, particularly those with salt formulations (eg, nafcillin sodium, which can result in hypokalemia), trimethoprim/sulfamethoxazole, or amphotericin. Magnesium, calcium, and phosphorus should also be monitored for OPAT patients receiving pentamidine, cidofovir, or foscarnet.

Hepatitis

Drug-induced hepatitis is less common than nephrotoxicity, but may be important.[1,9,11] Monitoring of liver function studies is recommended for patients receiving certain β-lactams (eg, nafcillin, oxacillin, ceftriaxone, and carbapenems), rifampin, or azole antifungal therapies. Most drug-induced hepatitis leads to a hepatocellular injury pattern, with elevations of aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT), though cholestatic injury patterns may occur, particularly with ceftriaxone, rifampin, and azole antifungals.

Cytopenias

Drug-induced cytopenias, including leukopenia and thrombocytopenia, are rare, occurring in <1% of OPAT courses.[1,9] Of drugs commonly administered in OPAT, cytopenias occur most commonly with β-lactam and vancomycin therapy.[1]

Cytopenias may reflect direct cytotoxic effects of a drug on marrow precursors, or may be mediated by increased immune-mediated destruction. Cytopenias may occur many weeks, or even months, into an OPAT course and are often detected only by screening. As some patients with significant neutropenia may not have leukopenia, all patients on OPAT who require CBC screening, should have WBC differentials obtained with each CBC.

Metabolic disorders

Creatine phosphokinase (CPK) should be measured weekly for patients receiving daptomycin. Myopathy may be more likely to occur in patients receiving other drugs that are associated with myopathy (eg, 3-hydroxy-3-methyl-glutaryl-CoA reductase [HMG-CoA reductase] inhibitors), and with higher weight-based dosing strategies.

THERAPEUTIC DRUG MONITORING

Treatment with vancomycin and aminoglycosides requires therapeutic drug monitoring (TDM) to ensure that efficacious levels are being achieved and to reduce the chance of nephrotoxicity and otovestibular toxicity. TDM has been demonstrated to both improve clinical efficacy and diminish nephrotoxicity.[13] Patients being discharged from the hospital on these agents usually have their levels obtained prior to discharge, but because changes in drug distribution and clearance may continue to occur after discharge, vigilance throughout the antimicrobial course is warranted. Among antimicrobials commonly used in OPAT, vancomycin and the aminoglycosides have the highest likelihood of nephrotoxicity and therefore require close attention. As a result of the continual need to monitor and adjust levels, care of patients receiving these agents is more labor-intensive for OPAT staff.[14] Although at a minimum weekly TDM is recommended (see Chapter 5), more frequent monitoring should be performed in medically labile patients when renal function fluctuates, and when dosing changes are made.

Vancomycin

In 2009, vancomycin dosing guidelines were developed with input from the American Society of Health-System Pharmacists, the IDSA, and the Society of Infectious Diseases Pharmacists.[15] Due to rising minimal inhibitory concentrations (MIC) among methicillin-resistant *Staphylococcus aureus* (MRSA) isolates and based on pharmacokinetics and drug distribution, these

guidelines recommend more aggressive dosing for serious infections, with target troughs in the 15–20 mg/L range. These higher trough levels are recommended for infections due to MRSA and for certain deep-seated infections, such as osteomyelitis, intracranial infections, and endocarditis. Because vancomycin levels take time to reach steady-state concentrations, trough values (drawn immediately before a dose) should be obtained prior to the fourth steady-state dose. Vancomycin peak values are no longer recommended as part of monitoring.

The recommendations in the 2009 vancomycin dosing guidelines have been widely adopted and in many settings have led to routine recommendations for vancomycin troughs in the higher 15-20 mg/L target range, even when higher trough levels are not clinically indicated. Associated with this trend toward more aggressive dosing has been the unwelcome trend of increasing vancomycin-associated nephrotoxicity. Numerous reports have identified higher trough values, including those recommended in the new dosing guidelines, as an important risk factor for vancomycin-associated nephrotoxicity.[8,10,16,17] Infections due to gram-positive organisms other than MRSA (eg, coagulase-negative staphylococci) and in sites where antimicrobial distribution is less restricted (eg, skin and soft tissue) may be effectively treated with lower target vancomycin trough levels, thereby reducing the risk of nephrotoxicity. Trough levels should be maintained above 10 mg/L to avoid the development of resistance. Regardless of the target trough level, patients discharged on IV vancomycin for OPAT should have clearly defined target levels for the OPAT clinician, based on the organism being treated, the vancomycin MIC, if known, and the infection being treated.

Aminoglycosides

Aminoglycosides are used less commonly in the OPAT setting, but when employed need similar attention to TDM to ensure efficacy while minimizing the nephrotoxicity, vestibular toxicity, and ototoxicity risks. Monitoring strategies for aminoglycosides vary depending on both the indication and the dosing regimen. For example, lower doses are employed when aminoglycosides are administered for gram-positive synergy than when administered for treatment of gram-negative infections, with lower target peak and trough levels. Once daily extended-interval dosing strategies are useful in OPAT and may be associated with less toxicity than conventional multiple-dosing strategies. Monitoring of midpoint serum levels and use of aminoglycoside nomograms for monitoring are recommended.[1]

APPROACHES TO COMMON CLINICAL PROBLEMS

With the patient discharged to receive OPAT at home, at an infusion center, or at a skilled nursing facility, and with follow-up clinical and laboratory monitoring in place, the ordering clinician is often called upon to address certain clinical situations, sometimes on a daily basis. The first line of communication typically involves a nurse or advanced practice clinician that is part of the OPAT team, who triages problems and refers those that require a management decision to the responsible clinician. Problems related to the catheter, including occlusion and thrombosis, are discussed in detail in Chapter 7.

Fever

Fever, sometimes associated with sweats and/or rigors, is among the most common and serious problems patients may experience while receiving OPAT. The clinician should start by assessing the fever history, including its duration, the temperature measurement (objectively documented versus "feels feverish"), and any association with the antibiotic infusion. Common causes of fever in the OPAT setting include progression of the underlying infection, infections associated with the IV catheter, drug fever, and secondary infections, including *C. difficile* infection (CDI, discussed under diarrhea, below).

The clinician should first consider whether fever may be due to the underlying infection being treated. For most OPAT patients, their underlying infection will have stabilized prior to their hospital discharge. Yet, for some infections, late complications may occur. For example the patient being treated for endocarditis may later develop a myocardial or metastatic abscess. For any infection, fever may develop if the microbiology of the infection has not been fully determined, either due to cultures not being collected, or due to negative or incomplete cultures at the time of inpatient workup. In these cases, the prescribed antimicrobials may not lead to the eradication of infection, and clinical reevaluation may be necessary.

IV catheters can become infected due to improper technique during insertion. Special care should be taken when there is altered skin integrity around the catheter site due to underlying skin disease, when there is a reaction to the occlusive dressing, or due to failure of sterile technique during catheter manipulation, particularly during antibiotic infusion. At times the catheter site will show obvious signs of infection, including erythema, induration, tenderness, or drainage. In most cases of catheter-related infection, however, there are no obvious signs of inflammation. Fever in association with antibiotic infusion is often a helpful clue towards identifying a catheter-related infection.

Antibiotics themselves may cause drug fever. β-lactams and vancomycin, both among the most common agents used for OPAT, are also among the most common drugs associated with drug fever. Most drug fevers occur within one to two weeks of antibiotic initiation, but the range is variable and drug fever may begin many weeks into a course of treatment. The pattern of fever is not always helpful in identifying the source as a drug fever. Accompanying clinical features are not always present,

but may be helpful if noted; some drug fevers are associated with the development of a typical diffuse, morbilliform drug rash, eosinophilia, transaminitis, and/or acute kidney injury. To complicate matters further, many OPAT patients are receiving more than one drug (antibiotics or other medications) that can cause drug-related fever. After the physician has considered other possible causes, the diagnosis of drug-related fever is most often a diagnosis of exclusion.

Management of the febrile OPAT patient must be individually based on the patient's underlying infection, the duration and intensity of fevers, comorbidity, and the OPAT setting. During the initial evaluation, it is critical to glean as much information as possible from the patient, his or her caregivers, and particularly from the visiting nurse on the scene, to narrow down the possible causes of fever. Equally important is the determination of the patient's clinical status. The visiting nurse is often helpful when it comes to recognizing patients in need of urgent evaluation; most patients with persistent or high fever will require clinical evaluation. Additional evaluation thereafter depends on the history and suspected source of fever. Evaluation of suspected catheter-related infection requires blood cultures to be drawn, typically from all catheter ports and peripherally, which can usually be done by a visiting nurse (see Chapter 7). For suspected drug-related fever, a change to a different agent can be considered, if such an option exists. Finally, diagnosis of *C. difficile* colitis requires a stool specimen for toxin assay, which may be collected at home. Patients who are clinically unstable with fever may require readmission.

Diarrhea

Diarrhea is a common side-effect of many different antibiotics. Most antibiotic-associated diarrhea is not due to CDI, but rather a consequence of the agent itself, likely due to alterations in the normal microbiome. Most antibiotic-related diarrhea will resolve naturally, once the patient discontinues the offending agent, but may be, at times, severe enough to result in volume depletion that may be problematic in severely debilitated patients. CDI should be considered in an OPAT patient with the complaint of frequent, watery diarrhea, particularly in the presence of fever, abdominal pain, blood, or pus in the stool, or severe prostration. Laboratory abnormalities that suggest CDI and prompt urgent evaluation, include leukocytosis, acidosis (as measured by low serum bicarbonate), and acute kidney injury.

Rash and Pruritus

Rashes occur frequently in patients on OPAT and are in some cases caused by the antibiotic agent (directly or indirectly). Cutaneous reactions to antibiotics can manifest in multiple ways, including a diffuse morbilliform rash (most commonly), urticaria (rarely with anaphylaxis), palpable purpura (indicative of vasculitis), exfoliation, erythema multiforme, drug reaction with eosinophilia, systemic symptoms (DRESS), and photosensitive eruption. Further discussion of these various reactions and their treatments is beyond the scope of this chapter.

Antibiotics are also a risk factor in the development of candidal skin infections, most commonly seen in intertriginous areas of the body. Diabetes and obesity are frequent underlying comorbidities. Topical antifungal agents are first line therapy, but oral azoles can be used in severe cases. Rashes may also be

seen underneath, and surrounding, dressings placed to maintain sterility of the vascular access device, representing an allergic reaction to the dressing. Hypoallergenic dressings are available, which may relieve “tape” dermatitis.

Pruritus also occurs without rash, which can be vexing to the patient and clinician. Dry skin is a common offender and use of emollients may offer ample relief. Pruritus may also result from nonallergic mast cell activation, as seen with opiates and vancomycin; antihistamines may help to alleviate this. Cholestatic liver injury can rarely cause pruritus in patients receiving antibiotics.

When a patient develops severe pruritus, or a rash that could be antibiotic-related, the clinician may simply choose to change the offending antibiotic, if alternative therapies are available. If the rash is not clearly drug-related, if the alternatives are limited, or if the cutaneous reaction is severe, the OPAT patient may require further evaluation in association with a dermatologist and/or allergist.

APPROACHES TO COMMON LABORATORY ABNORMALITIES

Laboratory abnormalities may be a result of the underlying infection, a consequence of the antibiotics being given, or unrelated to the infection or antibiotic. While, in some cases, the cause may be obvious, in other it may be quite elusive. When blood specimens for lab testing are collected from a peripherally inserted central catheter (PICC), or other vascular devices, rather than via peripheral vein, erroneous results may occur. Inappropriate catheter blood sampling may be associated with hemodilution, resulting in low blood count values. Likewise an inadequate flush prior to the blood draw may lead to errors in TDM.

When suspected, erroneous laboratory test results should be promptly repeated through cutaneous phlebotomy. Specific antimicrobials may also lead to false laboratory results due to drug-laboratory interactions. Daptomycin, for example, may lead to false prolongations in prothrombin time and/or elevations in the INR, which are distinct from INR changes, due to vitamin K depletion.[18] An understanding of these important interactions may prevent unnecessary and potentially harmful interventions. What is the best approach to laboratory abnormalities that may occur among patients managed by an OPAT program?

Elevated Serum Creatinine

When faced with a rising creatinine in an OPAT patient, there are two principal decision points. The first is whether the elevation is a consequence of one or more of the antibiotics being used. In that case, a decision must be made about discontinuing the offending agent. The second decision, whether or not an antibiotic is thought to be the cause, is whether to adjust the dose of the remaining agent(s) based on the creatinine clearance. Antibiotics most commonly associated with acute kidney injury include vancomycin, aminoglycosides, and amphotericin.

In many OPAT programs, vancomycin is one of the most commonly used agents. Until recently vancomycin-induced nephrotoxicity was associated with older drug formulations and thought to be uncommon. More recently, increasing target vancomycin levels have been associated with an increase in the incidence of nephrotoxicity (Figure 4.1).[17,19-22] While concomitant aminoglycoside treatment has been long known to increase the frequency of nephrotoxicity, more recent studies suggest that concomitant piperacillin-tazobactam may also increase the frequency of vancomycin nephrotoxicity, which represents a challenge given the frequency with which these medications are used in combination in OPAT patients.[23]

Aminoglycosides are used infrequently in OPAT, but when used, they are an important cause of antibiotic-induced nephrotoxicity. Risk factors for aminoglycoside-induced nephrotoxicity include older age, diabetes, and preexisting kidney impairment. Once-daily aminoglycoside dosing, often used in the OPAT setting, is associated with a reduced incidence of nephrotoxicity.[24] Young patients with cystic fibrosis, who typically receive parenteral tobramycin for pulmonary exacerbations due to *Pseudomonas* sp., have a lower risk of nephrotoxicity. However, with the rise of drug-resistant gram-negative organisms in medically-complex

hospitalized patients, the use of aminoglycosides may increase in the future, with a subsequent increase in nephrotoxicity.

Beta-lactam antibiotics are generally an uncommon cause of nephrotoxicity, though drug-induced interstitial nephritis and serum sickness may lead to rises in creatinine. Among the β-lactams, the antistaphylococcal penicillins (ie, oxacillin, nafcillin) are the most common causes of nephritis. Although it may occur in the absence of other clinical features, interstitial nephritis should be suspected when a rise in serum creatinine is accompanied by fever, rash, and/or eosinophilia.

Amphotericin B is well known as a nephrotoxic agent, but fortunately, with the availability of broad-spectrum azole antifungals, is used infrequently. When it is used, it is most often administered in one of the less nephrotoxic lipid formulations. The dose of amphotericin B (in any of its formulations) should be adjusted for declines in creatinine clearance, to reduce the toxic effect of the drug on the kidneys, rather than as a means of reducing blood levels. Other agents less commonly used in OPAT, which have known nephrotoxicity potential, include trimethoprim/sulfamethoxazole (TMP/SMX), cidofovir, and foscarnet.

Cytopenias

Weekly CBCs with differentials are recommended for most antimicrobials administered in the OPAT setting, and leukopenia, anemia, and thrombocytopenia are commonly encountered in OPAT patients. Often, the cytopenia may reflect a patient's underlying medical condition rather than the antimicrobial therapy. For example, cytopenias are common in patients with underlying malignancies, especially leukemia and lymphoma. Neutropenia is a well-known complication of certain agents, including ganciclovir (common), penicillin G, and TMP/SMX. It is seen less commonly in patients receiving other β-lactam agents or vancomycin. When it occurs, vancomycin-induced neutropenia may be abrupt and severe. Anemia is an uncommon antibiotic-associated complication; notable exceptions include penicillin G (hemolytic anemia), amphotericin B (anemia of chronic disease with long-term use), and foscarnet (anemia seen in acquired immune-deficiency syndrome [AIDS] patients). Thrombocytopenia may be a result of decreased platelet production from bone marrow suppression or increased destruction. Linezolid is a frequent cause of thrombocytopenia, attributed to bone marrow suppression. Thrombocytopenia attributed to linezolid generally occurs after two weeks of therapy. Other antimicrobial agents associated with thrombocytopenia (typically antibody-mediated) include β-lactams, TMP/SMX, and vancomycin. In addition to drug effect, a decline in platelet count that occurs during therapy may also result from resolution of inflammatory thrombocytosis; if available, comparison with premorbid platelet levels may help to clarify.

Eosinophilia

Eosinophilia is common among patients receiving OPAT, occurring in approximately 25% of patients.[25] Among antimicrobials, eosinophilia is most commonly associated with β-lactams, vancomycin, and TMP/SMX. In all cases, other potential causes of eosinophilia should be considered, including exposure to environmental allergens, herbal supplements, other newly-introduced medications, and rarely parasitic infection. Most patients with mild eosinophilia (defined as

absolute eosinophil count <1500/mL) will not suffer a significant hypersensitivity reaction, though eosinophilia has been shown to increase the likelihood of later rash or kidney injury among OPAT patients.[25] In the presence of other clinical features suggestive of a hypersensitivity reaction (rash or fever), or DRESS syndrome (associated with vancomycin), the offending agent should be promptly discontinued. When mild and/or seen as an isolated laboratory finding, it may be reasonable to continue the antimicrobial, while closely monitored, and counsel the patient to report the development of rash. Ultimately, the decision to continue or terminate a particular agent rests with the clinician and is based on the patient's status, the need for a particular antibiotic, the availability of alternatives, and the expected duration of treatment.

Liver Profile Abnormalities

The antibiotics used in OPAT are usually not associated with severe hepatotoxicity, though there are a few notable exceptions. Rifampin, commonly used in oral form along with IV β-lactam antibiotics to treat staphylococcal orthopedic implant infections, is known to cause hepatotoxicity. Other occasionally hepatotoxic agents include azole antifungal drugs.

Ceftriaxone occasionally causes elevations in alkaline phosphatase and bilirubin, due to bile sludging (pseudocholelithiasis), but only rarely have ceftriaxone, antistaphylococcal penicillins (ie, nafcillin or oxacillin), or carbapenems, been associated with drug-induced hepatitis. As with other laboratory abnormalities, elevated liver enzymes can be caused by many different factors, including medications, underlying diseases, and viral hepatitis. Isolated elevations of alkaline phosphatase may reflect bone remodeling, rather than cholestatic liver injury in patients with osteomyelitis, or recent orthopedic surgery. Measurement of γ-glutamyl transpeptidase (GGT) may help to clarify whether the alkaline phosphatase is of hepatic origin.

Elevated Creatine Phosphokinase (CPK)

Daptomycin is the only OPAT agent for which routine monitoring of CPK is recommended. Dose-dependent CPK elevations are frequently seen in patients receiving daptomycin, though symptoms of myopathy are not always present. Daptomycin should be discontinued for symptomatic patients, especially if the CPK is above 1000, or levels at ~5x the upper limits of normal (ULN), provided an alternative therapy is available. For asymptomatic patients, it is generally recommended that the drug be discontinued if the CPK level rises above 2000 U/L, or levels at ~10× the ULN.[26]

COMPLETION OF OPAT

When a patient receiving OPAT approaches completion of IV antibiotic therapy, the OPAT physician should assure that the infection has been adequately treated, follow-up on any clinical or laboratory toxicities that developed during the course of treatment, and make a determination about the disposition of the IV catheter. After completion of OPAT, a decision has to be made whether follow-up visits by the OPAT physician are necessary. These decisions should be individualized based on the infection being treated, the clinical status of the patient at the end of treatment, and the availability of other clinicians who are following the patient for the same problem. For example, a patient with uncomplicated osteomyelitis, not requiring additional antibiotic treatment, may be followed by his or her orthopedic surgeon without additional input from the OPAT physician. On the other hand, a patient with endocarditis may require follow-up visits with a cardiologist and/or cardiothoracic surgeon, as well as posttreatment evaluation by the infectious diseases physician to assure microbiologic cure. For patients who experienced toxicity while on treatment, it is important to ensure that follow-up is arranged, either with the OPAT clinician or another provider.

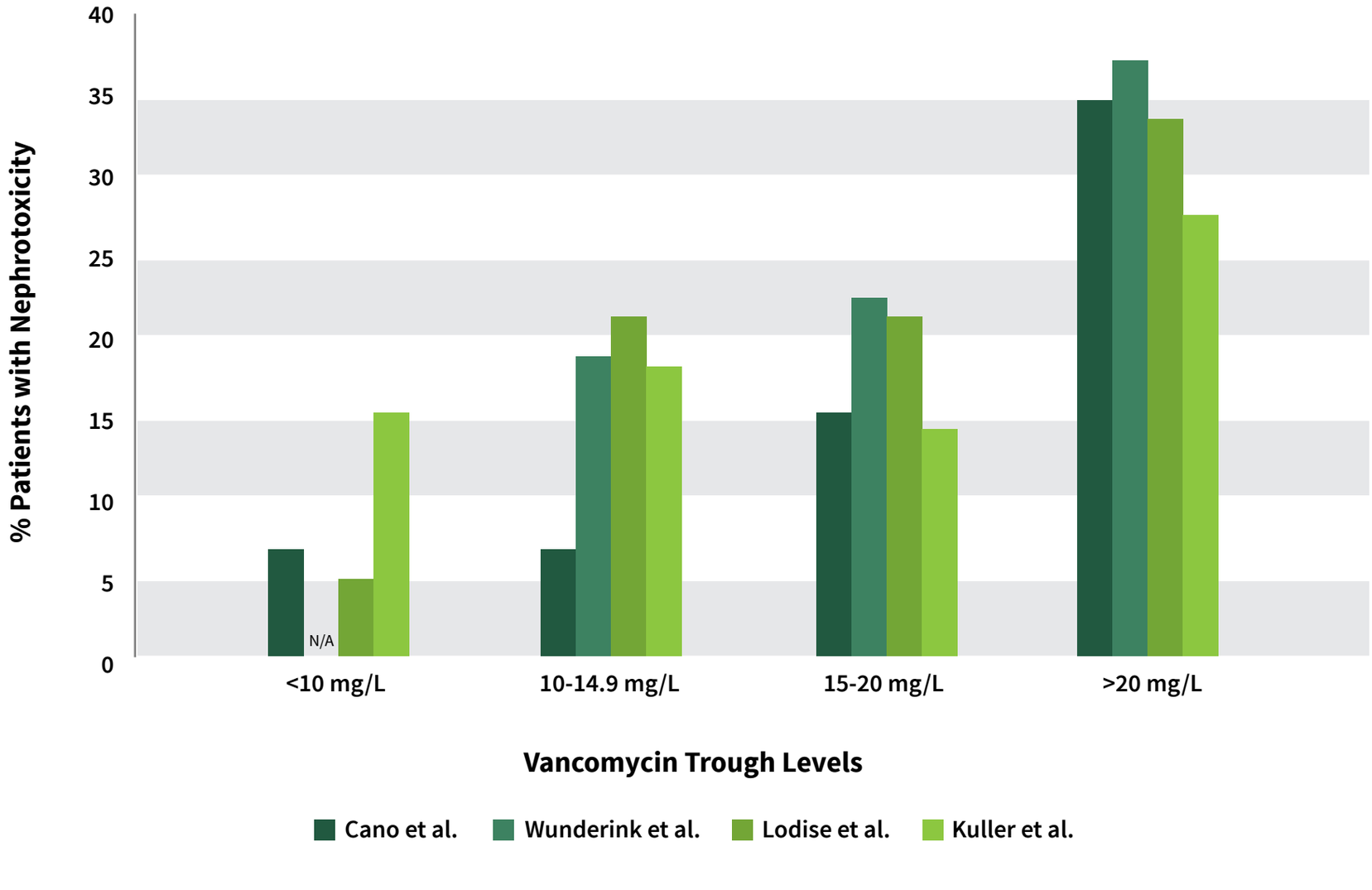
Finally, a decision should be made about the disposition of the IV catheter. In most cases, the catheter should be removed promptly upon discontinuation of treatment. For patients with underlying diagnoses, such as malignancy, continued central venous access may be required. The disposition of the catheter should be determined in consultation with the patient's primary treatment team.

FIGURES AND TABLES

Table 4.1. OPAT monitoring recommendations

Antimicrobial Class/Agent(s)	Frequency of Testing (per week)				Comments
	CBC/diff platelets	Renal Profile[a]	Chemistry[b]	Liver Profile	
ANTIBACTERIALS					
Aminoglycosides	1	1-2	1-2	---	Monitor trough levels[c] weekly and with dose changes; otovestibular toxicity
β-lactams[d]	1	1	1	1[e]	Watch electrolytes (salt formulations)
Clindamycin	1[f]	---	---	---	Consider change to PO
Daptomycin	1	1	---	---	Baseline and weekly CK, discontinue if symptomatic and CK>1,000 U/L (~5x ULN) or asymptomatic and CK>2,000 U/L (~10x ULN)
Fluoroquinolones	1[f]	1[g]	---	---	Consider change to PO; monitor for DDI
Metronidazole	1[f]	---	---	---	Consider change to PO; monitor for neuropathy with prolonged use

Figure 4.1. Meta-analysis of the relationship between initial trough vancomycin levels and the incidence of nephrotoxicity[17, 19-22]



N/A, not applicable.

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5

Antimicrobial Selection for OPAT

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A successful OPAT episode of care requires that the antimicrobial regimen is clinically effective, safe, relatively easy to administer, and affordable. When selecting antimicrobials for OPAT, there are a number of issues to consider, including suitability for a given OPAT environment (see Chapter 11), ease of administration, and the long-term toxicity and stability of the agent. Such considerations often lead to the selection of an entirely different antimicrobial regimen than the one used in the hospital. Modifications can include changes in the frequency, route, and mode of administration, or perhaps selection of a different antimicrobial. The pharmacokinetic (PK; time course of drug concentrations in a biologic matrix such as blood after administration) and pharmacodynamic (PD; the relationship between drug concentrations and pharmacologic effect) properties of each particular drug guide antimicrobial selection. This chapter explores each of these considerations.

Common antimicrobial agents utilized in OPAT, along with common infections and microbiologic pathogens treated are listed in Table 5.1.[1,2] When considering the recently published experience with OPAT in the United Kingdom,[3] one should keep in mind that models of care there often include more extensive nursing support in the home than is typically available in the US, and we should avoid generalizing the findings.

Because patients cannot be monitored at home as closely as in the hospital setting, when selecting antimicrobials for OPAT, it is preferable to establish evidence of tolerance prior to discharge and to choose agents with a low incidence of toxicity (Table 5.2). Although likely to be familiar and comfortable with short-course antimicrobial exposure, prescribers must be aware of the consequences of longer infusion courses. For example, after several weeks of therapy with semisynthetic penicillins (eg, piperacillin, nafcillin), it is relatively common for patients to develop myelosuppression or acute kidney injury (interstitial nephritis).[3-5]

PRACTICAL CONSIDERATIONS

A central principle in designing an antimicrobial course in the outpatient environment is ease of administration or practicality. Whether self-administered, or administered by a family member or health care provider, the doses should be easy to initiate and administer. They should require minimal manipulation of the IV line and have as little impact on normal activities of daily living as possible. These considerations include the type of venous access device, the type of infusion device (if used), properties of the selected antimicrobial (including its solubility, stability, pharmacokinetics, and pharmacodynamics), and the need for and recommended frequency of laboratory monitoring. Use of easy-to-operate infusion devices, antimicrobials with infrequent dosing, prolonged stability, few or no serious side effects, and no need for laboratory monitoring, are ideal features of an OPAT plan.

Antimicrobials may be administered by intramuscular (IM) injection or by IV through gravity infusion, by pump, by elastomeric device, or by rapid IV bolus ("IV push"). Often, financial considerations will dictate which method to choose. For example, Parkland Hospital, a publicly supported safety-net institution, in Dallas County, Texas, runs a robust home OPAT program financed entirely on county funds. As finances do not extend to the provision of infusion pumps, the gravity drip chamber is the only available antimicrobial delivery method for self-administration at home. Frequency of administration may also influence drug selection; thus, drugs that require very frequent dosing or resupply (eg, nafcillin or ampicillin-sulbactam) are simply not used in the Parkland home OPAT model.[6] When feasible, less frequent administration schedules enhance convenience and promote compliance. The resulting less frequent line manipulations are also thought to reduce catheter-associated complications, including mechanical (eg, hematoma, catheter migration and fracture), infectious (eg, central line associated bloodstream infection [CLABSI]), and thrombotic events (eg, catheter-associated thrombosis).[7,8]

Drug stability is of significant importance in home administration. Ideally, a reconstituted antimicrobial should be stable in the recommended storage conditions for up to 1 week after mixing. Therefore, the short-lived stability of some β-lactam antibiotics renders them impractical for home OPAT (see Chapter 5: *Stability*).

Conversely, some methods of administration enhance practicality. IV push delivery over 1-2 minutes can be utilized for many antimicrobials, in particular, the cephalosporins.[9] In general, such drugs can be supplied in ready-to-use syringes for IV push or IM administration. This form of delivery generally has the lowest supply cost and can be considered in special populations (eg, children) where intermittent and/or continuous infusion delivery may not be practical (see Chapter 5: *Special Considerations for Patients with Chronic Kidney Disease Receiving Intermittent Hemodialysis*). More recently, the PK and safety of ertapenem and daptomycin administered via IV push were found to have no significant differences when given via the standard 30 to 60 minute infusion.[10,11] Two recently

approved lipoglycopedtides, dalbavancin and oritavancin, have extremely long half-lives, enabling once weekly or single-dose administration.[12,13] While these agents are costly, such long-lasting products may allow select patients to be treated in the outpatient setting, with the appealing opportunity to avoid placement of a central venous catheter and the potential to save on the non-drug related costs of OPAT.

Utilizing appropriate shorter courses of therapy is another strategy to simplify OPAT and reduce antibiotic consumption and complications.[2,14,15] Antimicrobial stewardship programs can play an important role in avoiding excess treatment by indentifying optimal antibiotic duration using clinical evidence from treatment guidelines and randomized controlled trials.[14] A strategy to simplify outpatient antimicrobial therapy for selected infections is transitioning parenteral antimicrobial agents to an oral form of the same, or similar, agent with good bioavailability (see Chapter 5: *Pharmacokinetics and Pharmacodynamics*).[16] Mandatory infectious diseases consultations to approve OPAT and the subsequent decision to change to oral, or no further antibiotics, has been shown to be accompanied by significant cost savings, while not associated with increased adverse outcomes.[17,18] Additional benefits may include earlier discharge and fewer central-line related complications. A summary of recommended treatment duration guidelines derived from the Infectious Disease Society of America (IDSA) Treatment Guidelines and a recent review for select infections commonly encountered in OPAT can be found in Table 5.3. [14,19-29]

Often, multiple antimicrobial agents can be consolidated to fewer or even one agent, depending on culture results. Fewer antimicrobial agents, utilization of oral therapy, and less frequent dosing schedules, offer many advantages in terms of cost savings, safety, and convenience. See Table 5.4 for a summary of strategies to simplify the OPAT regimen.

PHARMACOKINETICS AND PHARMACODYNAMICS

The PK and PD should be considered in selecting an antimicrobial and designing the dosage regimen. Reviews of PK/PD considerations in the design of OPAT regimens have been previously published and are summarized below.[30-33] Once a selection of potentially useful antiinfective agents have been identified, based on proven efficacy, knowledge of the PK/PD profiles of the drug should be used to make a final selection and assist in the design of the dosing regimen. The goal is to select an agent and dosing regimen that is efficacious and practical with low risk for toxicity and resistance. Dose optimization with application of PK/PD parameters can minimize antimicrobial toxicity and resistance.[34-36] Drugs that can be administered once daily are well suited for OPAT, because a once-daily regimen is convenient for the patient or caregiver and it minimizes IV catheter manipulations. Drugs suitable for once-daily dosing usually have prolonged half-lives (eg, ceftriaxone, telavancin), or PD properties allowing infrequent dosing (eg, daptomycin; Table 5.4). Time-dependent antimicrobials with short half-lives necessitating numerous daily doses (eg, nafcillin), may be suitable for continuous or intermittent automated infusion if stable (ie, maintain ≥90% of initial concentration) at room and external body temperatures for the entire infusion period.

When an antimicrobial is infused, the resulting maximum plasma drug concentration (C_{max}) is a result of the amount administered, the apparent volume of distribution, and the rate of renal and/or hepatic elimination from the body. Drug clearance (expressed as the volume of blood from which the drug is totally removed per unit of time) is related to half-life, which is defined as the time it takes for the concentration of drug in the blood to fall by half.

Drugs with short half -lives, such as the β-lactam antibiotics, require frequent dosing in order to maintain adequate serum concentrations. If a medication must be given more often than every 8 hours, OPAT becomes a challenge without the use of a programmable ambulatory infusion pump, which can be expensive, require some training, and are not always available.

Development and utilization of antimicrobials that can be administered infrequently has been a major factor contributing to the growth of OPAT. Numerous agents, based upon PK variables, such as prolonged half-life, and various PD features, now allow for once-daily dosing (eg, ceftriaxone, daptomycin, or ertapenem; Table 5.4). For patients with significant renal impairment, once-daily, or even less frequent dosing, are often appropriate for antimicrobial agents with primarily renal elimination (eg, vancomycin). In addition, the hydrophilicity, or lipophilicity, of a drug can be used to predict a number of PK features (Figure 5.1). For example, lipophilic agents generally have enhanced penetration in some tissues (ie, bone, lung, or brain) and are more often hepatically cleared.[37] In addition to PK properties, antimicrobial dosing regimens must take into account the PD properties of a drug, particularly the relationship between the drug concentration in the sampled biologic matrix (usually serum or blood), and its in vitro microbiologic activity. Important

antimicrobial PD parameters include (Figure 5.2):

- The antimicrobial profile (eg, concentration-dependent versus time-dependent killing)

- The presence, or absence, of a post-antibiotic effect (PAE), the transient suppression of bacterial growth after the concentration falls below the pathogen's minimum inhibitory concentration (MIC)

Concentration-dependent killing occurs when higher drug concentrations are associated with greater rates and extent of bacterial killing. Some concentration-dependent antimicrobials also demonstrate a prolonged PAE.[38] Aminoglycosides, fluoroquinolones, metronidazole, ketolides, and daptomycin, all exhibit concentration-dependent killing properties, and a prolonged PAE. Despite gentamicin's relatively short half-life of 2-3 hours in young patients with normal renal function, the characteristics of concentration-dependent killing and a prolonged PAE lend themselves to high dose/extended interval dosing (eg, 7 mg/kg IV every 24 hours). Theoretically, using these PD characteristics, we may optimize bacterial killing and improve patient outcomes, while also reducing the risk of nephrotoxicity and antimicrobial resistance.[34,36,39] Currently, extended interval dosing (eg, once-daily) is commonly employed for aminoglycosides. Specifically, the commonly accepted PD target goal for aminoglycosides (eg, gentamicin and tobramycin) for the treatment of systemic Gram-negative infections is a peak C_{max}-to-MIC ratio of 10:1 or higher.[40-42] This is best achieved by utilizing a high-dose/extended interval dosing strategy.

In contrast, time-dependent killing is characterized by a strong relationship between the percentage of time (T) that the concentration of an antibiotic (eg, β-lactams) exceeds the organism's MIC (T>MIC) during a dosing interval. Maximized T>MIC can be achieved with shorter dosing intervals, extended dose infusions, and continuous infusions.[43] Linezolid, macrolides, clindamycin, tetracyclines, and vancomycin, also are considered time-dependent killing antimicrobials. For a summary of antimicrobial pharmacodynamics and dose-optimization, including goals of therapy and suggested monitoring, see Table 5.6.

SPECTRUM OF ACTIVITY

For a known infectious organism, a narrow-spectrum agent offers the advantage of specific activity with less disruption of the host's normal protective microbial flora. The risk of inducing antimicrobial resistance is also reduced. However, utilization of targeted therapy must be balanced with the practicality of the regimen. For example, penicillin or nafcillin, dosed every 4 or 6 hours, provide optimal targeted therapy for viridans streptococci or methicillin-sensitive *Staphylococcus aureus* (MSSA) infections, respectively; whereas ceftriaxone or daptomycin administered once-daily may be more practical for OPAT when programmable ambulatory pumps are not available, which are necessary for delivery of short-acting penicillin. In addition, when the microbial cause of an infection is not known (eg, febrile neutropenia in a chemotherapy patient), or in the case of polymicrobial infections, such as diabetic foot infection or intra-abdominal infections, the luxury of using a narrow spectrum of activity therapy may not be feasible.

Even after a specific pathogen has been identified, a broad-spectrum agent may still be the appropriate choice. For example, a patient with a significant penicillin allergy and a complicated intra-abdominal infection may need moxifloxacin instead of piperacillin/tazobactam. On the other hand, a patient with a central nervous system infection may require ceftriaxone instead of cefazolin, because of its volume of distribution and enhanced penetration into the cerebral spinal fluid.

STABILITY

In the hospital and infusion suite settings, IV medications are usually mixed on an as-needed basis, with only a few hours between preparation and infusion. Therefore, the stability of an antimicrobial in solution is of only modest concern. At home, where patients may use premixed medications over intervals of 3 to 7 days, the stability factor is a critical consideration in the choice of antimicrobial, the storage conditions, and the method of delivery. Stability information and other clinically relevant properties for some of the most commonly used antimicrobials in the setting of OPAT are listed in Table 5.7. [44-46]

The less often a medication has to be mixed and dispensed, the lower the cost in terms of staff time and facility usage. Many home infusion companies dispense medications for a week at a time, a reasonable option for long-term OPAT if close clinical follow-up is available. Many agents can be stored in a refrigerator after reconstitution for long periods of time (eg, vancomycin, gentamicin, or ceftriaxone). An hour before infusion, they can be taken out and warmed to room temperature. Recommendations for stability of compounded solutions may be found in the US Pharmacopeia, *Extended Stability for Parenteral Drugs* handbook by the American Society of Health-System Pharmacists (ASHP),[45] or in *Trissel's Stability of Compounded Formulations* textbook.[44]

It is important to note that drugs requiring three or more times daily-dosing may hinder patient compliance and truncate sleep patterns.[47] One solution for drugs that are stable at room or body temperature is the use of programmable ambulatory pumps

that can function for up to several days without a change in medication reservoir (see Chapter 7). This is ideal for continuous or multiple-daily infusion delivery. If feasible (ie, covered by insurance), delivery via programmable wearable pumps should be considered for drugs stable for ≥24 hours at room temperature (eg, nafcillin, penicillin G, or piperacillin-tazobactam). Taking into account their limited stability at room temperature after reconstitution and dilution, β-lactam agents, such as ampicillin, ampicillin-sulbactam, meropenem, or imipenem-cilastatin, are not suitable for delivery via programmable ambulatory pumps (Table 5.7). In cases where these drugs are indicated, changing to alternative therapy (eg, ertapenem instead of meropenem), or alternative dosing strategies (eg, meropenem at 1 g IV q8h instead of 500 mg IV q6h), can be considered.

Antimicrobials with shorter half-lives (eg, nafcillin, penicillin, or meropenem) can be given via intermittent infusion if the patient or caregiver is willing and able to learn how to mix them just before use, ideally with a simplified system for drug reconstitution immediately prior to administration. A few example of these are: Add-Vantage® adapters (Abbot Laboratories), Mini-Bag Plus® adapters (Baxter Healthcare Corporation), or Vial mate® adapters (Baxter Healthcare Corporation). These simplified "do-it-yourself" options add to the purchase cost, but avoid the need to warm the agent to room temperature, and will save time and the cost of pharmacy mixing. Another very simple, but somewhat costly method of delivery of frequently administered agents, is the use of elastomeric devices.

SAFETY

Given the reduced ability to monitor patients during OPAT, antimicrobials proven to be safe and effective are preferred. Agents with questionable efficacy, or with potential safety concerns, require careful and close observation of the first administration, ideally in the inpatient setting. Clinical evidence estimates that ≥25% of patients undergoing OPAT will experience adverse events, ranging from antibiotic-associated diarrhea to serious, potentially fatal, CLABSIs.[4,48-51] Antimicrobials that have high toxicity rates may not be suitable for initial administration at home. For example, patients who need amphotericin B are often hospitalized to monitor tolerability prior to discharge. Other centers will administer amphotericin B at an infusion center, with daily evaluation and more frequent laboratory testing. For example, the University of California, Davis Medical Center, has initiated an OPAT clinic (the Acute Infections Management Service [AIMS]) that is suitable for administration of more toxic antimicrobials with once-daily dosing.[52] Commonly reported antibiotic-associated complications include rash, neutropenia, drug fever, diarrhea, or hepatotoxicity.[5,15,51,53-56] Table 5.2 outlines the frequency of adverse events observed in the OPAT Outcomes Registry through 2002,[57] as well as more recent studies. The risk of adverse events increases over time, often appearing 2 to 3 weeks into the outpatient course, and is higher with more complicated infections (eg, infective endocarditis).[2,5,51] Thus, surveillance must be vigilant throughout the OPAT procedure.

Medical observation of patients is recommended during initial

administration of drugs associated with immediate, anaphylactic reactions (eg, β-lactams), or infusion-related reactions (eg, vancomycin). If a first dose cannot be given in an inpatient or infusion center setting, an anaphylaxis kit, containing injectable diphenhydramine and epinephrine, should be available to the supervising infusion nurse. Notably, in a study of serious adverse reactions associated with OPAT conducted by the OPTIVA Study Group, the incidence of delayed anaphylactoid reactions was approximately 0.5%, and could occur up to 2 weeks after initiation of therapy.[58] All such reactions were controlled with discontinuation of therapy and use of antihistamines. Approximately 5% of patients had a drug reaction of any kind, severe enough to warrant change in antimicrobial therapy. More recent studies have found similar rates of severe adverse drug reactions, necessitating adjustments in antimicrobial therapy.[2,5,51,55]

Catheter-related complications are a common reason to discontinue OPAT. Prolonged IV antimicrobial therapy is typically administered via a central line, most commonly a peripherally inserted central catheter (PICC). These devices may be subject to various issues, such as infection, venous thrombosis, occlusion, migration, fracture, catheter tip dislodgement, pulmonary emboli, or erosion of the catheter through the vein.[54] The OPAT plan should be in place before the central catheter is placed. A recent study evaluated a multidisciplinary approach to OPAT, including formal review of the OPAT plan by the infectious disease pharmacists prior to PICC placement.[2] This study prevented inappropriate placement of central venous catheters in 48 of 569 (8.4%) of OPAT referrals during the study period, possibly preventing catheter-associated complications and associated costs.[2] Two other recent studies found that many OPAT referrals were considered inappropriate, resulting in prevention of central-line placement in many cases.[15,51] Attention should be paid to the number of lumens as well. To minimize catheter associated complications, a central venous catheter with the minimum number of ports or lumens essential for the management of the patient should be selected.[8] However, patients receiving multiple infusions per day of different agents (ie, other antimicrobials, hydration, or other parenteral therapy), may require multiple lumens purely for practical purposes.

LABORATORY MONITORING

In order to minimize the risk of antibiotic and line-related adverse effects, regular clinical and laboratory monitoring is strongly recommended (see Chapter 4). No definitive studies are available to inform the exact requirements for monitoring drug toxicity on OPAT. The frequency and type of laboratory monitoring depends on the specific antimicrobial and regimen used, but should be done systematically. Most authors, in describing their OPAT programs/policies, recommend weekly complete blood cell count (CBC) and serum creatinine, with the addition of chemistries for some antimicrobials (Table 4.1).[59,60] Clinical evidence indicates that between 4% and 12% of antimicrobial courses are stopped early as a result of adverse reactions (Table 5.2).[5] Common adverse reactions leading to discontinuation include drug- and line-related complications, with possibly higher rates for patients

with more complex infections (eg, infective endocarditis).[2,5,51] For selected agents, it may be prudent to monitor renal function and chemistry more frequently than once weekly. Such agents include amphotericin B, aminoglycosides, cidofovir, and foscarnet, especially when other nephrotoxic agents are being coadministered and/or in high risk patients (eg, elderly or patients with renal impairment at baseline).

Drug-induced hepatitis is associated with some agents utilized in OPAT, and weekly liver function tests are recommended for these agents (Table 4.1). In addition, among patients receiving warfarin, antimicrobials may have direct effects on vitamin K stores through depletion of bowel flora, or inhibition of Cytochrome P450 metabolism, and thus more frequent monitoring of the patient's international normalized ratio (INR) may be indicated.[61]

Leukopenia is commonly reported in the OPAT literature and is associated with β-lactam therapy, particularly with the cephalosporins, but also with the semi-synthetic pencillins (eg, nafcillin and piperacillin), linezolid, or vancomycin.[62-68] White cell dyscrasias appear to be much more common with larger doses and/or extended courses of therapy (ie, ≥2 weeks), during which time patients may seem otherwise stable.[3,69,70] This delayed toxicity further emphasizes the need for routine periodic laboratory monitoring during OPAT (See Chapter 4).

Due to the risk of rhabdomyolysis, patients receiving long-term daptomycin therapy should have creatine kinase (CK) levels measured regularly, both at baseline and weekly.[71,72] More frequent monitoring may be indicated in patients with renal impairment, or those receiving HMG-CoA reductase inhibitors (statins) therapy.[73,74] The manufacturer recommends discontinuing daptomycin if CK is above 1,000 U/L in asymptomatic patients, or if CK is higher than 2,000 U/L, regardless of the presence of symptoms.[72] While some clinicians stop daptomycin at lower CK elevations, post-marketing analysis suggests that the risk for rhabdomyolysis is low, even with high-dose daptomycin therapy, or among obese patients.[74,75] Similarly, while the manufacturer also suggests considering withholding statins during daptomycin therapy, post-marketing analysis suggests this practice may not be necessary.[72,73,76-78]

The new second-generation lipoglycopeptides, dalbavancin and oritavancin, can be administered either as single-dose (dalbavancin; one 30-minute IV infusion), or once weekly, with no requirements for monitoring established by the manufacturer.[12,13]

The literature on therapeutic drug monitoring for vancomycin and aminoglycosides is evolving. Based on current information and guidelines, most authors recommend monitoring renal function and trough levels, at least once weekly in patients being treated with these agents.[79] "Red man syndrome" is a common, infusion-related adverse reaction to vancomycin, which can be managed by increasing the duration of infusion from the standard 60 to 90 minutes, to 120 minutes, in particular for higher doses (500 mg/30 minutes), or by preadministering antihistamines.[79,80]

Finally, it should be recognized that patients vary in their likelihood to experience adverse reactions, as well as their ability to tolerate them. For example, some may persistently experience red man syndrome despite all attempts to prevent its occurrence. Others may complain of bad taste, anorexia, diarrhea, lethargy,

or other symptoms. Although these reactions may not be emphasized in drug labeling, they occur with some frequency and may even require a change in choice of antimicrobial therapy (see Chapter 4).

SPECIAL CONSIDERATIONS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE RECEIVING INTERMITTENT HEMODIALYSIS

Patients with end-stage renal disease receiving hemodialysis should receive OPAT in coordination with their dialysis schedule; ideally via central dialysis access to obviate the need for an additional catheter solely to deliver OPAT (see Chapter 2). For example, cephalosporins (eg, cefazolin, cefepime, or ceftazidime), commonly dosed at 1 g IV daily, can be adjusted to 2 g IV post-dialysis thrice weekly. Similarly, the β-lactams, meropenem or imipenem, usually dosed at 500 mg IV once daily, can be adjusted to 1 g IV postdialysis thrice weekly.[81-83] For dalbavancin, the recommended two-dose regimen is 1 g IV infusion over 30 minutes, followed one week later by 500 mg IV, usually administered without regard to the timing of hemodialysis.[12] For the treatment of a systemic infection after an adequate vancomycin loading dose (eg, 20 mg/kg), patients receiving high-flux intermittent hemodialysis generally require 500 to 750 mg IV postdialysis thrice weekly, or 750 to 1000 mg IV thrice weekly if receiving antimicrobial treatment intradialytically, to maintain predialysis vancomycin goal levels.[83,84] Predialysis vancomycin levels should be monitored at least weekly and the dose should be adjusted as needed to maintain therapeutic target concentrations. An extensive review of vancomycin dosing in the hemodialysis setting has recently been published.[84]

THE UNIQUE ROLE OF PHARMACISTS IN OPAT

Clinical pharmacists, including infectious disease trained pharmacists, can apply their knowledge of antimicrobial PK/PD to suggest optimal antimicrobials under supervision of infectious disease physicians. The pharmacist can help simplify OPAT by recommending more convenient once daily regimens when possible, changing time-dependent agents with frequent dosing to continuous infusion, and/or switching intravenous therapy to oral for agent(s) with good bioavailability (Table 5.4 and 5.5). Pharmacists can suggest appropriate monitoring parameters consistent with the IDSA OPAT guidelines (Table 4.1). The pharmacist can play an active role in OPAT delivery by monitoring therapy and consulting with the infectious disease physician, when needed (eg, laboratory test results, drug concentrations outside of normal limits, drug toxicity, drug interactions, or inadequate patient response to therapy).

Home infusion nursing/pharmacy can assess and assure patient competence and home safety, and document patient monitoring.

BASIC CRITERIA FOR OPAT ANTIMICROBIALS

In the hospital, acquisition, storage, handling, preparation, and dispensing of medications, are carefully controlled and well documented. Standards in the inpatient suite are being developed to assure the quality and safety of medications (see Chapter 11). Recently the American Society of Health-Systems Pharmacy (ASHP) developed Guidelines on Home Infusion Pharmacy Services.[85] It is critical that accepted standards of practice be observed in acquiring, storing, preparing, and delivering, antimicrobial agents for OPAT. It is essential for infusion suites to purchase antimicrobials from suppliers with good quality assurance, and for prescribers of in-home OPAT to utilize home infusion companies with skill and experience in OPAT, and ideally, some form of accreditation. While such certification is voluntary, most commercial payers require infusion pharmacies to be accredited in order to serve their patients. There are a number of accrediting organizations that certify home infusion pharmacies, including the Joint Commission, Community Health Accreditation Partner, Pharmacy Compounding Accreditation Board, Healthcare Quality Association on Accreditation, Accreditation Commission for Healthcare, and Medicare.[85] State health departments also certify home pharmacy services.

Once an antimicrobial solution has been prepared by a knowledgeable professional, it must be clearly labeled with a drug name, patient name, date of mixing, expiration date, and storage requirements. Date and time of anticipated administration are helpful. The label should also contain information regarding the type of infusion device and rate of administration. The initials of the pharmacist preparing the mixture and the home infusion pharmacy's name, address, telephone number, as well as the prescription number and the prescribing physician's name, are normally required by state boards of pharmacy.

PLANNING FOR OPAT

A mandatory infectious disease consultation should be considered, to review the proposed OPAT plan. As noted earlier, this consultation may prevent unnecessary OPAT courses, either through discontinuation of unwarranted antimicrobial therapy or through a transition to oral therapy. An infectious diseases consultation can prevent unnecessary PICC placements, as well as reduce healthcare expenditures without jeopardizing patient outcomes.[2,17,18,60,86-88]

The central catheter placement (eg, PICC), should be ordered once the decision to initiate OPAT is made. It is worthwhile to plan ahead and make arrangements before the day of discharge. Such planning can include teaching patients and/or family members, assessing their competency, ordering laboratory tests, scheduling nursing visit appointments, identifying who will be responsible for care post discharge (eg, who will monitor laboratory results), and arranging for PICC removal after completion of therapy (see Chapter 2). Ideally, the choice of antimicrobial therapy should be finalized before discharge, and tolerability should be assessed. In reality, dose adjustments occur frequently following discharge and for many agents (eg, aminoglycosides or vancomycin), therapeutic drug monitoring still remain a critical component of care (see Chapter 4).

The final plan should also consider the overall treatment complexity of other healthcare activities in the outpatient setting, including parenteral nutrition, hemodialysis, tube feedings, wound dressing changes, and drug-drug interactions with other medications. The identity and contact information for the supervising OPAT physician should be established prior to discharge. Decision-making algorithms for OPAT are summarized in Figure 1.1 and 2.1. Recent reviews have proposed an outline of key elements of an OPAT program, including utilization of an OPAT coverage bundle and check lists, to which the reader is referred.[59,60,88-90]

FIGURES AND TABLES

Table 5.1. Antimicrobial agents commonly used for OPAT-managed infections

OPAT Network (1996-2002)[a]		Children's Hospital San Diego (2000)[b]		UK National Health Service (2006-2008)[c]		University of California, Davis Medical Center (2009-2010)[d]		Cleveland Clinic (2013-2014)[e]	
Type of infection (primary), ranked by frequency (% of OPAT courses; also see Chapter 3)									
Skin and soft tissue	23	Bacteremia	16	Skin-soft tissue	59	Osteomyelitis	33	Bone-joint	27
Osteomyelitis	15	Pyelonephritis	13	CNS	8	Bacteremia	23	Cardiovascular	15
Septic arthritis/bursitis	5	Meningitis	13	Cardiovascular	7	Cellulitis	14	CRBSI	13
Wound	4	Intra-abdominal	8	Intra-abdominal	6	Pneumonia	14	Intra-abdominal	13
Pneumonia	4	Cellulitis	7	Bone-joint	5	UTI	14	Skin-soft tissue	10
Pyelonephritis	3	Osteomyelitis	7	Bacteremia	5	Endocarditis	6	Pneumonia	7
		Wound	7	Genitourinary	4	CNS	4	Genitourinary	7
				Pneumonia	2	Intra-abdominal	3	CNS	6
				Other	5	Other	1	Other	2
Antimicrobial agents administered parenterally, ranked by frequency of use (% of OPAT courses)									

CRBSI, catheter-related bloodstream infections and other primary disseminated infections; UTI, urinary tract infection; CNS, central nervous system.
a. Data from OPAT Outcomes Registry[57]
b. Data from John Bradley, MD, personal communication
c. Data from Chapman et al, 2009[1]
d. Data from Heintz et al, 2011.[2] Note that the frequency exceeds 100% as some patients had more than one site of infection (eg, mixed infection), or received more than one antimicrobial agent
e. Data from Nabin K Shrestha, MD, personal communication. Percentage of infections not recorded

Table 5.2. Frequency of adverse events in OPAT: Summary of 20 reports

Reference	Source of infection or pathogen	Antimicrobial agent(s)	Courses (n)	Adverse drug reactions (%)[a]										Line-related reactions
				Total	Stopped/ Changed[b]	Rash	GI	AKI	BMS	Fever	Hepatic	Vestibular	Anaphylaxis	Infusion related	
Amodeo 2009[91]	Endocarditis	Various	100	16	10	3	2	0	0	5	1	1	0	3	11
Berman 2001[92]	Various	Various	302	25	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cheong 2008[93]	Various	Various	714	5.3	0.7	1.2	1.1	0.6	0.3	0.2	0.1	0	< 0.1	0.6	NR
Dahlgren 1997[94]	Various	Nafcillin or oxacillin	105	24.2	12.4	9.5	1.2	0.9	3.8	4.8	0	0	0	5.7	NR
Dargan 2007[95]	Various	Various	66	15.2	7.5	1.5	6.1	4.5	1.5	0	0	0	0	4.5	18.2
Duncan 2013[96]	Endocarditis	Various	80	8.8	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.75
Esposito 2007[97]	Bone-Joint	Various	239	11	< 1%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Heintz 2011[2]	Various	Various	494	2.2	1.2	1	0.2	0.6	0.4	0	0	0	0	0	NR
Hitchcock 2009[98]	Various	Various	303	1.7	0.7	NR	0.3	NR	NR	NR	NR	0.7	NR	NR	0.7
Hoffman-Terry 1999[4]	Various	Various	291	NR	6.9	4.1	9.6	7.9	6.9	1.7	0	0.3	NR	10.6	10.1
Kieran 2009[99]	Various	Various	60	6.7	3.3	3.3	0	0	1.7	0	1.7	0	0	1.7	8.3
Lai 2013[55]	Various	Various	393	10.2	2.5	2.5	NR	2.8	1.8	NR	NR	NR	NR	NR	6.4
Malani 2005[49]	Various	Amphotericin	113	71.7	24.7	NR	NR	40.7	NR	NR	NR	NR	NR	11.5	10.6

AKI, acute kidney injury; BMS, bone marrow suppression (leukopenia, neutropenia, thrombocytopenia, anemia); CNS, central nervous system; GI, gastrointestinal toxicity (nausea, vomiting, diarrhea); MSSA, Methicilin Susceptible Staphylococcus aureus; NR, not reported.

a. Percentages may add up to more than the total % of adverse reactions as patients may present with more than one adverse reaction. Excludes central-line related reactions which are listed separately

b. Antimicrobial therapy stopped or changed related to an adverse drug reactions and/or line-related reactions

c. 1.5% of patients developed clinically significant elevations in creatine kinase

d. Adverse reactions per 1000 OPAT days

e. 2.5% of patients developed clinically significant elevations in creatine kinase

Table 5.3. Recommended duration of antimicrobial therapy for selected infections

Disease-condition	Recommended duration of therapy	Strength of recommendation
Skin and skin structure infection[28]		
Uncomplicated, culture negative cellulitis	5-7 days	Strong/high
Complicated	7-14 days (based on patient's response)	Strong/high
Pneumonia[20,22]		
CAP	≥5 days. Should be afebrile for 48–72 h and have no more than 1 associated sign of clinical instability before discontinuation	B-I/II
HAP/VAP/HCAP	7-8 days, unless NFGNB (eg, *Pseudomonas*)	A-I
Diabetic foot infections[27]		
Mild DFI	1-2 weeks	A-II
Moderate to severe DFI (without osteomyelitis)	2-4 weeks	A-II
DFI with osteomyelitis	4-6 weeks	B-II
Catheter-related bloodstream infections, if catheter removed[23]		

CAP, community-acquired pneumonia; DFI, diabetic foot infection; HAP, hospital-acquired pneumonia; HCAP, health care–associated pneumonia; MIC, minimum inhibitory concentration; N/A, not available; NFGNB, non-fermenting Gram-negative bacilli; UTI, urinary tract infections; VAP, ventilator-associated pneumonia.

Please refer to references for complete details, as duration of therapy depends on particular antimicrobial agents selected. Adapted from Hayashi Y, et al. *Clin Infect Dis*. 2011;52(10):1232-1240, with permission.[14]

Table 5.4. Four strategies to simplify antimicrobial therapy in OPAT[46]

Consolidation (broad spectrum)	Once daily	Employ programmable ambulatory pump for continuous or intermittent infusion of q4-6h drugs	IV-PO Switch (orally with excellent bioavailability)
Piperacillin-tazobactam	Ceftriaxone	Nafcillin	Fluoroquinolones
Carbapenems	Ertapenem	Penicillin	Tetracyclines
Ampicillin/sulbactam	Daptomycin	Piperacillin	TMP/SMX
Tigecycline	Antifungals	Piperacillin-tazobactam	Metronidazole
Moxifloxacin	Levo/moxifloxacin	Not ampicillin or carbapenems	Linezolid, rifampin
Cefoxitin, cefotetan	Aminoglycosides		Triazole antifungals

IV, intravenous; PO, oral administration [from Latin: *per os*]; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 5.5. Oral bioavailability of selected antimicrobial agents[46]

Antimicrobial agent	Oral bioavailability
Amoxicillin/cephalexin	75-95%
Doxycycline	90-100%
Metronidazole	95%
Azithromycin	35-50%
Clarithromycin	50-60%
Clindamycin	70-85%

Table 5.6. Antimicrobial pharmacodynamics and dose optimization[37,106-109]

Pattern of activity	Antibiotics	Goal of therapy	PK/PD parameter
Concentration-dependent killing and prolonged PAE	Aminoglycosides	Maximize concentrations (high dose, once daily, except ciprofloxacin) ↑ Dose = ↑ C_{max} = ↑ Kill	C_{max}/MIC
	Daptomycin		TDM: peak
	Fluoroquinolones		Bactericidal agents
	Ketolides		
	Amphotericin B		
	Echinocandins		
Time-dependent killing and minimal PAE	β-lactams	Maximize duration of exposure (shorter interval, extended infusion, or continuous infusion)	Time > MIC
	Penicillins		TDM: trough
	Carbapenems		Bactericidal agents
	Cephalosporins		
	Clindamycin		24h-AUC/MIC
	Linezolid		TDM: AUC/MIC calculation

AUC, area under the curve; C_{max}, maximum concentration/peak concentration; MIC, minimum inhibitory concentration; PAE, post-antibiotic effect; PK/PD, pharmacokinetic/pharmacodynamic; TDM, therapeutic drug monitoring.

Table 5.7. Practical considerations for selected antimicrobial agents utilized in OPAT[44,55]

Antimicrobial agent	Normal dosing interval (hours)	Central line recommended[c]	Duration of stability by storage temperature after reconstitution[f]		Continuous infusion suitable based upon PK/PD properties and stability[g]
			5°C	25°C	
Acyclovir	8[a]	X	24 hours	24 hours	
Amikacin	24[a]		30 days	24 hours	
Amphotericin B (AmBisome)	24	X[d]	24 hours	24 hours	
Ampicillin	4-6[a]		48 hours	8 hours	
Ampicillin-sulbactam	6[a]		48 hours	8 hours	
Aztreonam	8-12[a]		7 days	48 hours	
Caspofungin	24	X	48 hours	24 hours	
Cefazolin	8[a]		10 days	24 hours	X

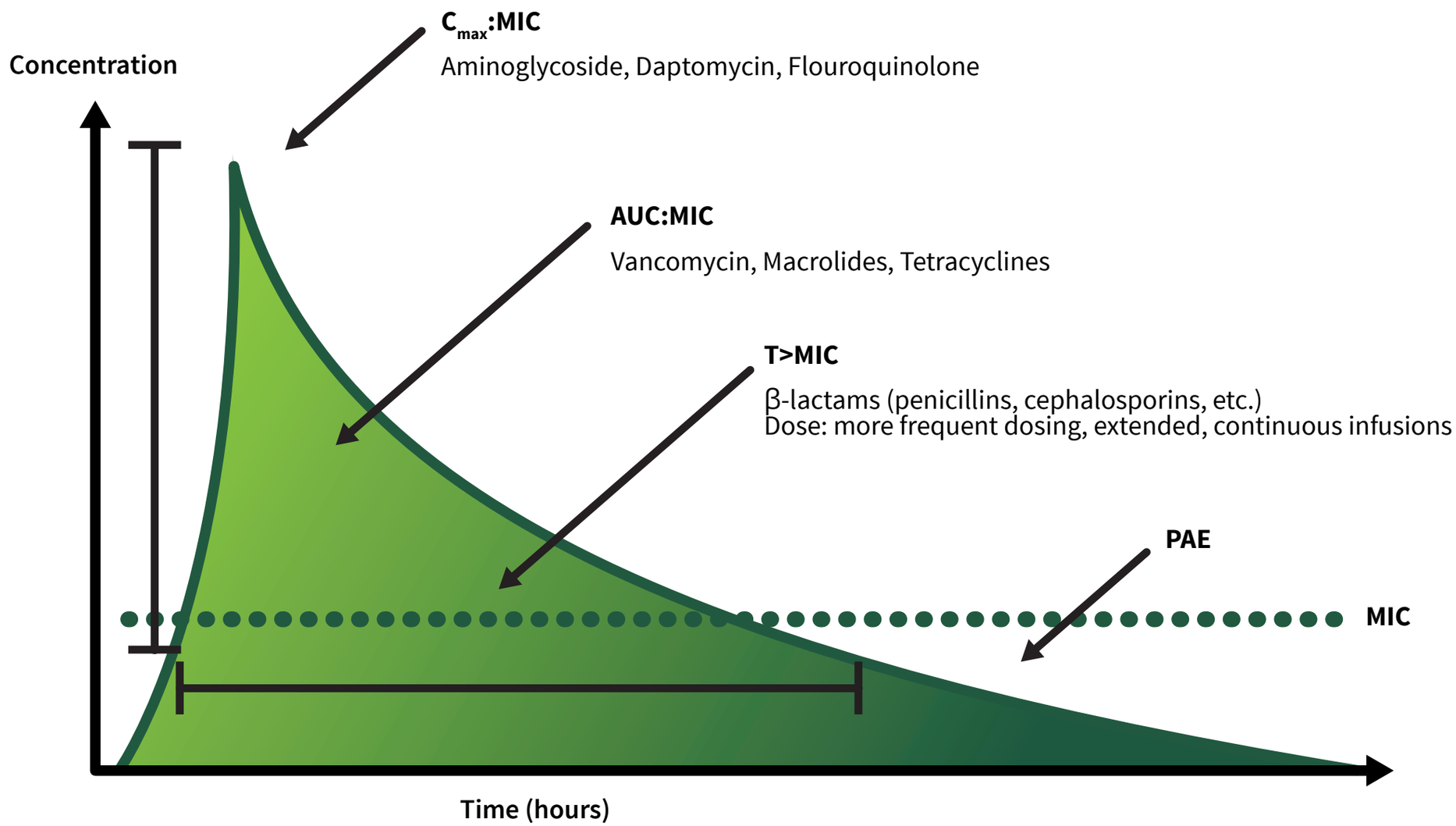
a. Assumes normal renal function, standard infusion delivery, and severe/systemic infection. Interval may be longer in renal impairment
b. Recommended 8 hour dosing interval for synergy against severe/systemic enterococcal infections
c. Use central line, when possible, for drugs associated with venous irritation (phlebitis) and/or pH <5 or >9
d. High risk for phlebitis, thus a central line is strongly recommended
e. Recommended maximum concentration in a peripheral line and central line = 5 mg/mL and 10 mg/mL, respectively
f. Duration of stability may vary depending on the final drug concentration, diluent, and other variables
g. Pharmacokinetic, pharmacodynamic, and stability data support continuous infusion delivery (eg, antimicrobial agents with every eight hour or more frequent dosing, time dependent pharmacodynamic killing profile, stability at room temperature for ≥24 hours, and ideally with an optimal dilution allowing a total volume suitable for administration by a programmable pump)

Figure 5.1. Pharmacokinetics of antimicrobial agents: hydrophilicity vs lipophilicity[38,109,110]

Antimicrobial agents	Pharmacokinetic features	Clinical significance
Hydrophilic agents Beta-lactams Aminoglycosides Glycopeptides Daptomycin Colistimethate	1) Small volume of distribution 2) Renal elimination 3) Does not achieve intracellular concentrations 4) Increased clearance and/or distribution in sepsis 5) Poor-moderate bioavailability	1) Poor tissue penetration 2) Nephrotoxicity (ATN, AIN) 3) Not active against atypical (intracellular) pathogens 4) Consider loading doses and aggressive dosing in sepsis 5) < 1:1 with PO to IV ratio
Lipophilic agents Fluoroquinolones Macrolides Rifampin Linezolid Tetracyclines Chloramphenicol	1) Large volume of distribution 2) Hepatic metabolism 3) Achieves intracellular concentrations 4) Clearance/distribution not altered by sepsis 5) Excellent bioavailability	1) Excellent tissue penetration 2) Hepatotoxicity and DDI 3) Active against atypical (intracellular) pathogens 4) Dose adjustment generally not needed in sepsis 5) 1:1 with PO to IV ratio

ATN, acute tubular necrosis; AIN, acute interstitial nephritis; PO, oral administration [from Latin: per os]; IV, intravenous; DDI, drug-drug interaction.

Figure 5.2. Antimicrobial pharmacodynamic targets[37]



AUC, area under the concentration-time curive; C_{max}, maximum plasma concentration; MIC, minimum inhibitory concentration; PAE, postantibiotic effect; T, time.

Adapted from Roberts JA, et al. *Crit Care Med*. 2009;37(3):840-851.

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6 Models of OPAT

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OPAT is delivered effectively and safely in a variety of settings.[1-4] Extensive experience over a period of thirty years has led to increased standardization and consolidation into five basic models of OPAT delivery:

- Office-based infusions
- Hospital-based infusion centers
- Home -based infusions
- Home-based infusions; teach/train
- Skilled nursing facilities

Each of these models has both clinical and economic advantages and disadvantages (Table 6.1 and 6.2). To determine which model best suits an individual patient, several factors should be considered, including the patient's ability and willingness to self-administer IV medications at home; the patient's mobility; the availability of transportation; the distance from home to the healthcare facility; a history of substance abuse; the payer source; and personal preference (see Chapter 2).

OFFICE-BASED INFUSIONS

Many physicians have expanded their infectious disease practices to provide office-based infusion services (see Chapter 11).[4-6] In addition, freestanding infusion suites, not affiliated with physician practices, provide similar services.[4,6,7] In this model, all medications are administered in either a physician's office, or a freestanding infusion suite, by nurses at the facility. No patient training is required since the office-based nurses can access and/or maintain the intravenous line and infuse all medications.

Expansion of a physician's practice to include office-based OPAT provides several advantages: close supervision of the patient; the ability to rapidly identify side effects or problems with vascular access; and the opportunity to frequently reassess treatment response, enabling prompt modification of therapy if needed.[1,4] Office-based centers are often more accessible to patients than hospital-based infusion centers, and thus offer increased convenience.[1,6] This model also allows the physician to be directly involved in performance improvement activities, outcomes assessment, and enhancement of patient satisfaction.

Patients qualifying for the office-base infusion model of OPAT are often physically incapable or unwilling to infuse themselves through an indwelling catheter in the home setting.[4,5] Many of these patients are elderly, disabled, or without home support that would allow for or predict successful management.[4,5] Another group that requires in-office treatment are Medicare patients who do not have a part D plan, or are unable or unwilling to pay the out-of-pocket doughnut hole expense.[8]

Patients who need daily supervision owing to anticipated noncompliance issues may also benefit from the office-based infusion model.[4] Patients who have a history of injection drug use may be treated at the physician's office and undergo insertion and removal of IV devices at each visit, thus mitigating the risk of manipulation of indwelling intravascular devices.[9]

This model has several benefits. In-office infusion provides the opportunity to exercise maximal control over the delivery of infusion services. Medicare guidelines require a physician or midlevel provider to be physically present during the infusion; the patient is evaluated daily by the office nursing staff and supervising healthcare provider, and therapy can be adjusted quickly if needed.[4,5,8] Adverse reactions may be more rapidly identified, laboratory tests procured, and hospitalizations frequently avoided.[10] Since the administered IV antimicrobials are covered by Medicare part B, this model tends to minimize the patient's out-of-pocket expenses and is more cost-effective than infusions in a hospital-based outpatient infusion centers.[11,12]

Satisfaction is high, as daily contact with the infusion nurse is enjoyable and reassuring for patients and their families, who often appreciate receiving the extra attention.[5] Further, a sense of community often develops among the group of patients being treated, creating an informal support group.[6,7]

Conversely, there are some challenges associated with office-based infusion operations (see Chapter 11: Office-Based Infusion Operations). Patients must access the physician's office

daily and therefore require available transportation. From a physician's standpoint, this model is the most demanding in terms of infrastructure requirements. To optimally treat patients, a physician's office must be open and staffed for infusion services 7 days per week, which is a burden on smaller office practices. A skilled nurse must be available to infuse the medications.[8] Preferably this nurse would be trained specifically in outpatient infusion therapy and would have achieved or be working toward a Certified Registered Nurse Intravenous (CRNI) qualification.[13] While this may translate into a higher level of quality and clinical support for patients and physicians, a nurse with CRNI qualifications will command a higher level of financial remuneration.[13] In the office, space needs to be allocated for the infusion operation. In general, approximately one hundred square feet is needed for each infusion chair, to allow for patient comfort and healthcare worker access.[14]

Supplies must also be available, such as infusion rate control devices (or infusion pumps), intravenous catheters, wound dressings, saline vials for flushes, and the antibiotic agent to be infused. For these, a number of national companies, such as Coram (a division of CVS Health), Option Care (affiliated with Walgreens/Duane Reade), HHI Infusion, Healix, and BioScrip, Inc., are available to provide antibiotics and supplies on an as-needed basis, minimizing extensive and costly overhead. In addition, the National Home Infusion Association (NHIA) provides a searchable database of local provider resources (see Chapter 11).[15]

HOSPITAL-BASED INFUSION CENTERS

Many hospitals offer infusion centers where once-daily intravenous antimicrobials can be administered. Such infusion centers may be dedicated to antimicrobial treatment or may be shared with other service lines, such as chemotherapy for oncology patients.[13,16] From the hospital administration's perspective, the benefit of establishing an infusion center is that existing space and personnel can be used and the costs of constructing and maintaining a new facility are eliminated.[1,17]

The hospital's Emergency Department (ED) may also serve as an infusion center where single daily doses of parenteral antibiotics can be administered. In this setting serial evaluation of patients during their treatment can be performed.[18] Infusion therapy may be scheduled and can be administered during "slow" hours. Some ED infusion centers have incorporated observation units, allowing the administration of parenteral treatment with a greater level of safety, avoiding hospitalizations.[1]

Patients who are candidates for treatment at a hospital-based infusion center are identical to the office-based infusion patients described above.[1] Some hospitals also offer infusion services to indigent hospitalized patients who otherwise would be unable to afford OPAT.[4] Transition of such inpatients to hospital-based outpatient infusion centers enables more rapid throughput. The benefits of this model are similar to those described for the office-based infusion patients above.[4,5] Qualified nursing staff are immediately available to evaluate a patient and the response to treatment, and scheduling is usually not difficult.[13]

A potential downside is that patient transportation issues may be cumbersome.[1,4] Hospital campuses are much larger and may be more difficult to navigate than physicians' offices, particularly if the infusion center is located in an area of the hospital that is difficult to access. Many hospitals have begun to open off-site facilities that minimize this problem. Hospital infusion centers are able to bill for Medicare Part A services, which may result in increased facility fee expenses for the patient and make this model less palatable.[11] There are also gaps in Medicare part B and part D, which cover some but not all aspects of OPAT, that may be a consideration for some patients (see Chapter 10).[19] Weekend availability for hospital-based infusion centers varies, with some offering limited or no weekend hours.

HOME-BASED INFUSIONS

For individuals who require IV antibiotics, but are well enough to return to work, school, or community activities, IV therapy can be safely administered in the home setting. In this model, all medications are administered in the home by the patient, a family member, caregiver, or a home health nurse.[1,4] If children are too young, or adults have physical or cognitive limitations that preclude self-administration, a family member or other caregiver usually can be trained in OPAT administration.[1,20]

Patients who are candidates for the home infusion model should be clinically stable, compliant with medication administration, and willing to travel to physician office visits.[1,20,21] In addition, these patients should possess the necessary cognitive and physical abilities to administer and manage their own OPAT, or have a family member or caregiver available to do so.[1,4]

A potential challenge is the need for all medications and supplies to be delivered to the home; in the absence of home health support, the patient, family member, or other caregiver must be responsible for the appropriate storage of medication and usage of supplies.[1,4,20,22] If home health support is used, the patient should be comfortable allowing healthcare workers in the home. There is less supervision and less frequent evaluation in this model, necessitating more stringent patient selection (see Chapter 2).[22,23]

A common misperception is that a nurse will come to the patient's home to administer each infusion. In fact, the role of the home care nurse is primarily that of clinical educator, who provides instruction on proper self-administration of OPAT.[22] Some patients will receive the initial doses of their antimicrobials in the hospital or a physician's office to ensure

that their medications are well tolerated,[1,4] but an increasing number of home infusion companies will give the first dose of antimicrobial in the home, in the presence of an infusion nurse. Once the patient is deemed competent, the infusion nurse will visit weekly to re-assess, draw laboratory samples, and change the dressing on the line. Vascular access is generally established in the hospital or an infusion center, although some home infusion companies offer home insertion of midline or peripheral intravenous catheters.

For patients receiving OPAT at home, around-the-clock telephone support is necessary to handle questions regarding basic vascular access issues, adverse drug reactions, or proper infusion technique, which can usually be managed by a skilled nurse, pharmacist, or physician over the phone.[4,21] Ideally, patients should visit a healthcare provider regularly for examination and assessment of efficacy and side effects (see Chapter 4).[4] Access to test results is one of the challenges to maintaining consistent patient care and preventing readmissions.[24]

TEACH/TRAIN

This model is a subset of home infusion, with all of the nursing services, supervision, and initial training provided by the outpatient facility – either physician's office or hospital-based infusion center.[1,4,20,22] All medications are administered in the patient's home by the patient, a family member, or caregiver. Potential candidates for teach/train are identical to those described for the infusion models above. A benefit of this model is the elimination of the expense of home health support, and may be favored by insurance companies.

SKILLED NURSING FACILITIES

Many patients are admitted to a skilled nursing facility (SNF) for OPAT services. All medications are administered in the facility by SNF nurses and therefore no patient training is necessary, since the SNF nursing staff manages the infusion operation.[1,4,24]

Several subsets of patients qualify for this model.[25] Patients who do not have the ability to access a physician's office on a daily basis because of lack of transportation may be best served in a SNF.[1,4] If Medicare is the only insurance provider, many patients will not have the financial resources to pay the 20% cost of home infusion expenses mandated by their Medicare agreement after the deductible in Part B.[26] These patients are typically admitted to a SNF, even if they have transportation. Lastly, patients with significant debility who require 24-hour care and would be

unsafe at home are frequently treated in an SNF.

A major benefit of this model is that most insurance companies provide coverage for antibiotic therapy in a SNF. Accordingly, the patient's out-of-pocket expenses are minimized. However, there are now substantial copays for stays exceeding 20 days.[26] Another benefit is the ongoing evaluation and care by nurses, the SNF medical staff, or the patient's physician.[1,4] This allows for increased medical supervision compared with the home or the teach/train models above, nearly eliminating transportation needs for physician office visits.

The major disadvantage of the SNF model is that if OPAT is the primary indication for admission, patients may not return home until the therapy is completed. Also, since an SNF is a health care facility, a patient is at greater risk to encounter resistant organisms, including *Clostridium difficile* or carbapenem-resistant Enterobacteriaceae (ie, Gram-negative rod bacteria).[27-29] Overall, this option is significantly more expensive compared with any of the other models, but the patient's out-of-pocket expense may be minimal.

In summary, several well-designed OPAT options are available. By choosing the appropriate model for an individual patient, satisfaction can be maximized and expense minimized, enabling the safe delivery of effective antimicrobial therapy outside the inpatient setting.

FIGURES AND TABLES

Table 6.1. OPAT models

Model	Office-based	Hospital-based infusion center	Home-based	H
Patient training	None	None	Home	
Infusion location	Office	Facility	Home	
Nursing support	Office	Facility	Home	

OPAT, outpatient parenteral antimicrobial therapy; SNF, skilled nursing facility.

Table 6.2. Advantages/disadvantages of various OPAT models

Model	Advantages	Disadvantages
Hospital-based infusion center	Expert resources available	Cost of clinic facility and staff
	Direct supervision	Patient must travel to clinic
	May combine with physician visits	
Home-based	Patient autonomy	Lack of on-site clinical expertise
	Potentially decreased cost	Need for home-based support

OPAT, outpatient parenteral antimicrobial therapy.

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7 Vascular Access and Infusion Administration Methods

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Along with the proper diagnosis and appropriate drug selection, successful OPAT depends upon choosing the right site for OPAT administration, choosing the best vascular access device (VAD) to meet patient needs and the requirements of the prescribed infusion, and selection of the best infusion administration method. For patients who receive OPAT in the home setting and learn to self-administer, the administration method and effective patient and caregiver education are critically important in ensuring patient safety and adherence.

VASCULAR ACCESS DEVICE SELECTION

The first step in planning for any type of infusion therapy is selection and placement of a VAD. The fundamental VAD choice is between a peripheral intravenous catheter (PIV) and a central vascular access device (CVAD). The overarching goal is to use the least invasive VAD with the lowest risk of complications and one that will last for the duration of the therapy or will require minimal replacements.

A variety of factors guide the decision-making process, such as the characteristics of the prescribed infusate, expected duration of treatment, the integrity of the patient's veins, patient mobility requirements, and patient preference. For OPAT patients, support systems and resources must be considered (see Chapter 2). Even for patients who are attending an outpatient or ambulatory clinic for their infusions, it is recognized that they still require at least some involvement in VAD care and maintenance at home. The Infusion Therapy Standards of Practice recommend that selection of the most appropriate VAD occurs as a collaborative process among the interprofessional team, the patient, and the patient's caregivers.[1] A brief description of each type of VAD is presented and Table 7.1 highlights and summarizes indications, advantages, and disadvantages.

Peripheral Intravenous Catheters

In general, the PIV catheter is indicated for relatively short courses of OPAT, usually less than 7 days, in patients who have adequate venous access. Historically, a PIV catheter was removed and replaced (ie, site rotation) based on a time frame, typically every 72 to 96 hours. Current recommendations are to rotate the site "when clinically indicated".[1] A recently published Cochrane study concluded that there was no increase in the rate of complications with this practice and patient satisfaction is improved when a functioning PIV catheter with no evidence of phlebitis or infiltration is not removed and replaced merely based on protocol.[2] Venipuncture skill, adherence to aseptic technique with insertion, and vein selection (eg, avoiding areas of flexion; the forearm is preferred) are important aspects of care when leaving PIV catheters in place for longer periods of time.

A number of antimicrobial drugs are irritating to veins; resultant medication phlebitis can limit the extent of catheter dwell time. For short courses of irritating antibiotics, placement of the PIV catheter in a larger vein in the forearm may reduce the risk of phlebitis and reduce the need for a midline catheter or a peripherally inserted central catheter (PICC). Vancomycin, a commonly administered OPAT medication, is often of cited as an irritant. However, several studies have found that peripherally infused vancomycin, causes no more phlebitis than other antibiotics.[3-5] Recommendations for short courses vancomycin via a PIV include the use of a small gauge catheter in a large vein.[6] Because peripheral vein preservation is a concern for all patients, a course of therapy intended to extend beyond one week is best managed with a midline peripheral or a CVAD as addressed in the following sections. Care and management of PIV catheters includes:

- Ongoing assessment for complications (eg, phlebitis, infiltration) and prompt removal and replacement as needed
- Stabilizing the catheter to reduce the risk of catheter movement within the vein and accidental dislodgement
- Maintaining an intact dressing over the site
- Flushing with saline to maintain patency after each drug administration or at least daily
- Protection of the site from water exposure
- Prompt removal of the PIV when it is no longer needed

Midline Catheters

The midline catheter is a peripheral catheter. As defined by the Infusion Nurses Society (INS), it is a catheter inserted into the upper arm via the basilic, cephalic, or brachial veins (Figure 7.1), with the internal tip located level at or near the level of the axilla and distal to the shoulder.[1] Midline catheters are inserted into veins above the antecubial fossa to avoid infiltration, dislodgement, or venous thrombosis associated with an area of flexion. Ultrasound is commonly used for vein identification when placing a midline catheter. Because the catheter tip lies in a larger diameter vein, there is greater drug hemodilution, thus reducing the risks of phlebitis and infiltration, which can prolong catheter dwell time. Midline catheters are placed by specially trained and competent OPAT team members.

Recently published research based on a sophisticated analysis of best available evidence and expert opinion concludes that midline catheter placement be considered for peripherally compatible infusion therapies expected to last for 14 days or less.[7] Investigators analyzing a large retrospective European cohort suggest midline use for duration of up to 4 weeks.[8] Antimicrobial therapy is a typical indication for placement of a midline catheter. The 2016 INS Standards[1] recommend cautious use of noncontinuous (or intermittent) vesicant antimicrobial administration because there is the risk of undetected extravasation due to the deeper vein placement. The administration of vancomycin for a median of 5 days through a midline catheter was found to be safe in one study, with complication rates not significantly different than administration using peripherally inserted central catheters (PICCs).[9] For a given limb, midline catheters should be avoided when the patient has a history of thrombosis, hypercoagulability, decreased venous flow to the extremity, or end-stage renal disease (ESRD) requiring vein preservation.

The use of midline catheters is well described in OPAT clinical reports and descriptive studies; there is an overall trend towards increased use of midline peripheral catheters.[8,10,11] Care and management of midline catheters is the same as listed above in relation to PIV catheters. Site care and dressing changes are performed routinely at least every 7 days during the dwell time.

Central Vascular Access Devices

The most common type of CVAD used in OPAT is the PICC. Selection of a PICC is recommended for infusion therapies for more than 15 days for peripherally compatible infusates and at any proposed duration for non-peripherally compatible infusates.[7] PICCs should be avoided when possible, in patients

with chronic kidney disease (stage 3B or greater), as arm veins should be preserved for a potential arteriovenous fistula.[7] Other CVAD options include the subcutaneously tunneled cuffed catheter (eg, Hickman catheter), tunneled small bore central catheter or an implanted vascular access port (Figures 7.2 and 7.3). These types of CVADs are generally placed for other infusion needs (eg, parenteral nutrition or chemotherapy) and may be used for OPAT therapy. One exception is a patient with cystic fibrosis, whose implanted ports may be placed specifically for OPAT, due to the need for long-term, repeated, and intermittent IV antimicrobial therapy and hydration. A Cochrane systematic literature review found that the use of ports in patients with cystic fibrosis is generally safe and effective, but randomized, controlled trials to assess the efficacy and potential adverse events associated with ports are needed.[12]

Care and management of CVADs include:

- Ongoing assessment for complications; while relatively low complication rates are reported, longer duration dwell time is associated with increased risk for complications including infection;[8,13] venous thrombosis is a risk with CVADs in general, and a particular risk associated with PICCs, due to insertion into smaller diameter veins and more upper extremity movement[1,7]

- Stabilizing external catheters to reduce the risk of catheter migration, accidental dislodgement, and to reduce the risk of infection/phlebitis due to catheter movement at insertion site

- Maintaining an intact dressing over the site

- Flushing with saline/heparin to maintain patency after each drug administration; occlusion is a common complication associated with PICCs;[13] one study of home care patients found a trend towards less use of tissue plasminogen activator (tPA) for de-clotting when PICCs were flushed with low concentration heparin (10 units/mL)[14]

- Protecting the site from water exposure

- Prompt removal of the CVAD when no longer needed

INFUSION ADMINISTRATION METHODS

OPAT infusion methods vary from the simple such as IV push or gravity drip infusion to the complex, such as the electronic infusion device (EID). Each infusion method is briefly described below. Key points are summarized in Table 7.2.

Gravity Drip

This is the common and classic method used to deliver intermittent medications. It is cost effective, using simple IV tubing and a Minibag that contains the medication. Commonly used in the infusion center model, it is also used for home care patients. It requires more training than other methods, including: spiking the minibag, priming the IV tubing, and managing the infusion rate by counting the drops in the drip chamber of the IV tubing over a set period of time – all while maintaining aseptic technique. Manual dexterity, adequate eyesight, and good cognitive function are required.

IV Push

The administration of IV medication in a syringe directly into the patient's VAD is increasingly used for selected antimicrobials, including some in the cephalosporin group (eg, ceftriaxone) and daptomycin. While this is an easy and time saving administration method, it is important to understand the risks associated with IV push medications, particularly with administration that is too rapid. "Speed shock" is a systemic reaction that occurs with rapid IV push administration into the circulation. Symptoms include dizziness, facial flushing, headache, and medication-specific symptoms. These can progress to chest tightness, hypotension, irregular pulse, and anaphylaxis. It is critical to administer IV push medications over the appropriate time frame. It is important that the pharmacy place a label on the medication syringe to indicate the administration rate (eg, "administer over 3 to 5 minutes"). For clinicians as well as patients or caregivers who learn to use this technique, the importance of using a watch or other timepiece to make sure the medication is administered at the right rate is critical.[15] Again, manual dexterity, adequate eyesight, and good cognitive function are required.

Syringe Pumps

Syringe pumps use a traditional syringe as the solution container, which is filled with prescribed medication and positioned in a special pump designed to hold it (Figure 7.4). Syringe pumps are piston-driven infusion pumps that provide precise infusion by controlling the rate by drive speed and syringe size, thus eliminating the variables of the drop rate. These pumps are used most frequently for delivery of antibiotics and small-volume parenteral therapy. The volume of the syringe pump is limited to the size of the syringe; a 60-mL syringe is usually used. However, the syringe can be as small as 5 mL. The tubing is usually a single, uninterrupted length of kink-resistant tubing. Use of a syringe pump is helpful to patients as the issue of rate monitoring is avoided. Nevertheless, patients need to learn the steps to load the syringe and use the pump correctly.

Elastomeric Balloon Pumps

These are portable devices that consist of an elastomeric

reservoir, or balloon (Figure 7.5). The balloon is made of a soft rubberized material capable of being inflated to a predetermined volume and is encapsulated inside a rigid, transparent container. When the reservoir is filled, the balloon exerts positive pressure to administer the medication; control over fluid flow rate is maintained by IV tubing with varying tubing diameters. This system requires no batteries or electronic programming and is disposed of after each use. It is important to recognize that the flow rate at the beginning is faster than the rate at the end of the infusion, due to variations in pressure within the stretched elastomeric membrane.[16] This variation may be clinically acceptable the majority of the time; however, for patients with sensitivity to rate, this could be a concern. For example, red man syndrome can be associated with the rate of vancomycin administration. Also important is the fact that temperature can affect performance; flow rate is slower when the infusate is cold.[16] Patients should be instructed to remove the filled device from the refrigerator several hours before the infusion, based on manufacturer's directions for use.

Elastomeric balloon devices are used most often in home OPAT. They are very easy to use, do not depend on gravity to infuse, and are portable. They are ideal for active patients or children who continue to work or go to school during the course of OPAT. Patients who have difficulty with learning a more complex procedure, such as a gravity infusion, will often be successful with an elastomeric device, because rate monitoring is not a concern, due to the predetermined flow rate based on specific elastomeric device used. These devices may be used to deliver a variety of infusion therapies, including IV antibiotics, chemotherapy, and analgesics. Volumes range from 50 to 250 mL. Elastomeric pumps can infuse at rates from 0.5 to 500 mL/h. The additional cost of such drug delivery devices may not be reimbursed by insurance.

Ambulatory Electronic Infusion Devices (EIDs)

EIDs are compact infusion pumps (Figure 7.6). ranging in size and weight, and are capable of delivering most infusion therapies. Favorable features include medication delivery, delivery of several different dose sizes at different intervals, programmable memory, and safety alarms. One disadvantage of ambulatory pumps is a limited power supply; they function on a battery system that requires recharging or replacement of disposable batteries. These pumps can be programmed for either intermittent or continuous infusion of antibiotics. Rates of infusion can be adjusted from 0.10 to 500 mL/h. For intermittent antimicrobial infusions, a "keep vein open rate" is programmed to maintain flow between drug infusions. Many patients previously considered ineligible for self-administration of antimicrobials in the home can be safely and effectively managed using EIDs. Examples include patients who require frequent (every 4- to 6-hour) dosing or even continuous infusion, who lack manual dexterity, who have impaired cognitive function, who are unwilling or unable to learn the necessary techniques for self-administration, and those who lack a support person at home. Patient education must address how to safely live more or less continuously connected to an infusion pump, including basic understanding of its function, alarms, and whom to call for assistance. The patient needs to be trained in how to manage activities of daily living, such as dressing and bathing, while protecting the pump and the VAD (see Chapter 2).

Decision Making: The Best Infusion Method

Depending upon the setting and the types of personnel involved, the decision regarding the best infusion method or device for the type of infusion therapy for OPAT is made in collaboration with the patient, caregiver, physician, pharmacist, and/or nurse.

Factors that drive infusion administration method choice include:

- Drug
    - Compatibility with infusion device (eg, elastomeric)
    - Need for accurate rate control (eg, continuous infusion requiring an EID)
    - Safety of rapid infusion (eg, IV push)
- Frequency of administration
    - High frequency drug administration (eg, 3 or more doses per day) may be a burden for the patient; the use of an ambulatory EID that is programmed to administer the dose at the scheduled times can ensure adherence with OPAT
- Drug stability in solution
    - An issue for OPAT at home when an ambulatory, programmable pump is used because the infusion container is generally prepared for a 24-hour infusion
    - Some agents are not stable for more than a few days after compounding (ie, ampicillin/sulbactam). Many home infusion companies will only deliver once a week and therefore do not offer such agent.
- Patient safety and lifestyle concerns and patient preference
    - An issue for OPAT at home is the need to consider mobility and ability to manage the infusion administration method
- Cost/reimbursement
    - Some insurance companies may have restrictions (eg, some will not cover an elastomeric device)
    - For ambulatory/outpatient OPAT administration by clinicians, the simplest and most cost-effective choice will be made; gravity drips or IV push are more common administration methods, but a stationary infusion pump may be used if stricter rate control is needed

In home care, a unique and non-clinical setting for OPAT patients, the home care nurse may make additional recommendations. Upon assessing the patient and home situation, the home care nurse may advocate for a more complex infusion method. For example, an elastomeric pump may be recommended over a gravity drip infusion to facilitate patient independence, mobility, and ability to return to work. Collaboration between the physician, home care nurse, and home infusion pharmacist is an important and ongoing component of home OPAT. Written instructions, including illustrations, should be provided to the patient as an integral component of patient education.

Risks associated with use of medical technologies in the home are increasingly addressed in the literature. Safe use and operation of infusion pumps, for example, may be affected by temperature extremes, presence of children and pets, dirt and dust, poor lighting, and limited space.[17] Patient safety is ensured by teaching the patient and family how to administer the infusion therapy, how to identify

potential problems, and how to manage activities of daily living. This is particularly a concern when the patient is receiving a continuous infusion and is "hooked up" to an infusion pump 24 hours a day.

Appendix: Infusion Pump Risk Reduction Strategies for Patients Using Infusion Pumps at Home

The Food and Drug Administration (FDA)[18] has provided guidance to both clinicians and patients related to safe infusion pump use. Nurses and physicians can refer patients to the FDA website or print out this information to guide patient education:

Reduce Risk – Plan Ahead

- Work with your home health nurse (or other OPAT team member) to develop a back-up plan in case of an infusion pump failure
- Know if your plan includes calling 911
- Know where your infusion pump back-up battery is located and how to access an emergency power supply, if applicable
- Refer to Home Healthcare Medical Devices: Infusion Therapy - Getting the Most out of Your Pump for more information

Learn about your infusion pump and medication. Ask your home health care provider:

- About the infusion pump
    - What is the name of my infusion pump?
    - Is this infusion pump already set up?
    - Do I need to look at anything on the infusion pump to make sure it is correct? If so, what?
    - How do I start and stop the infusion pump?
    - Do I need training to use this infusion pump?
    - Will any electrical items in my home interfere with my pump?
- About your medication
    - What is the name of my medication?
    - What does the medication do? How should it make me feel?
    - What are the side effects?
    - What is the dose of my medication?
    - How long should my medication take to complete?
    - Can there be medication left in my tubing or in my bag when the infusion pump stops?
- What to do when there are problems
    - What should I look for if I'm getting too much medication too fast?
    - What should I look for if I'm getting too little medication?
    - Who should I call with questions or problems?
    - What should I do if the power goes out?

Check

Make sure you can read the infusion pump's displays and hear the alarms, if applicable

Verify the settings when starting or changing the rate of a medication or fluid, if applicable

If they are not correct, or if you have questions, call your home health provider

Report Problems

Call your home healthcare provider to obtain further instructions if:

The infusion pump appears broken or damaged or has small chips or cracks

An unfamiliar alarm sounds or is displayed

An alarm is unable to be cleared that you have been trained to respond to

You are also encouraged to file a voluntary report with the FDA for any problems you may encounter with the infusion pump.

FIGURES AND TABLES

Table 7.1. Comparison of CVADs used in OPAT [1, 7, 19]

Type of CVAD	PIV catheter	Peripheral mi
Indications	• Short duration (usually <7 days) or intermittent infusion • Non-irritating infusate	• Expected duration of IV therapy: 2 - 4 weeks • Non-irritating infusate
Advantages	• Low risk of infection • Low cost • Placed by nurses	• Low risk of infection • Improved dwell time compared to PIV catheter due t • Less costly than CVAD
Disadvantages	• Short-term • Limitations in types of medications and solutions that may be infused • Site may need to be replaced/rotated	• Must be placed by specially trained OPAT team mem • Some patients may find location difficult in relation t • Signs of infiltration/phlebitis may be more difficult t • Risk of vein thrombosis

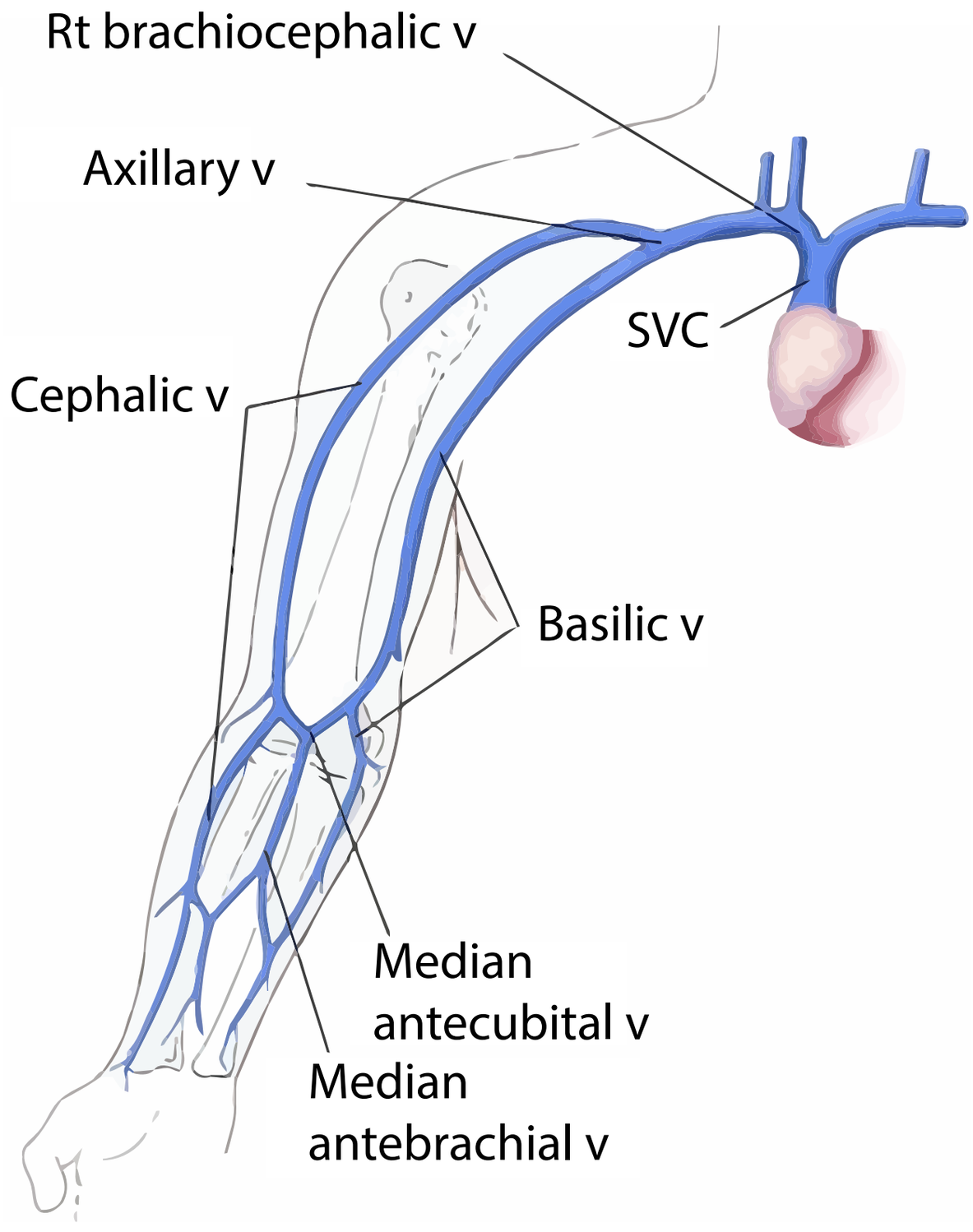
CVAD, central vascular access device; OPAT, outpatient parenteral antimicrobial therapy; PICC, peripherally inserted central catheter; PIV, peripheral intravenous catheter.

Table 7.2. Comparison of OPAT administration methods[1, 7, 19, 20]

Administration Method	IV Push	
Indications	• Limited antimicrobial drugs (eg, some cephalosporins, daptomycin)	• Most antimicrobials unle
Advantages	• Simple • Cost effective: fewer supplies required and shorter home care visits/clinic time. • High patient satisfaction: short infusion times/may increase home care patient adherence	• Simple • Cost effective • Flow regulators can be u
Disadvantages	• Relatively few home infusion drugs appropriate for IV push • Potential for rate-related reactions if pushed in too rapidly	• Requires IV pole or for h • Less patient mobility du • Need to calculate "drip r
Patient Education Issues	• Home care: simpler teaching procedure, but high degree of patient teaching in relation to rate management and risk for reactions	• Home care: more proced • Need to monitor or calcu • Troubleshooting to main

OPAT, outpatient parenteral antimicrobial therapy; IV, intravenous.

Figure 7.1. Possible veins for midline catheter placement



OpenStax College Circulatory Pathways. Version 1.3: June 19, 2013.

Figure 7.2. Typical placement of a Hickman catheter

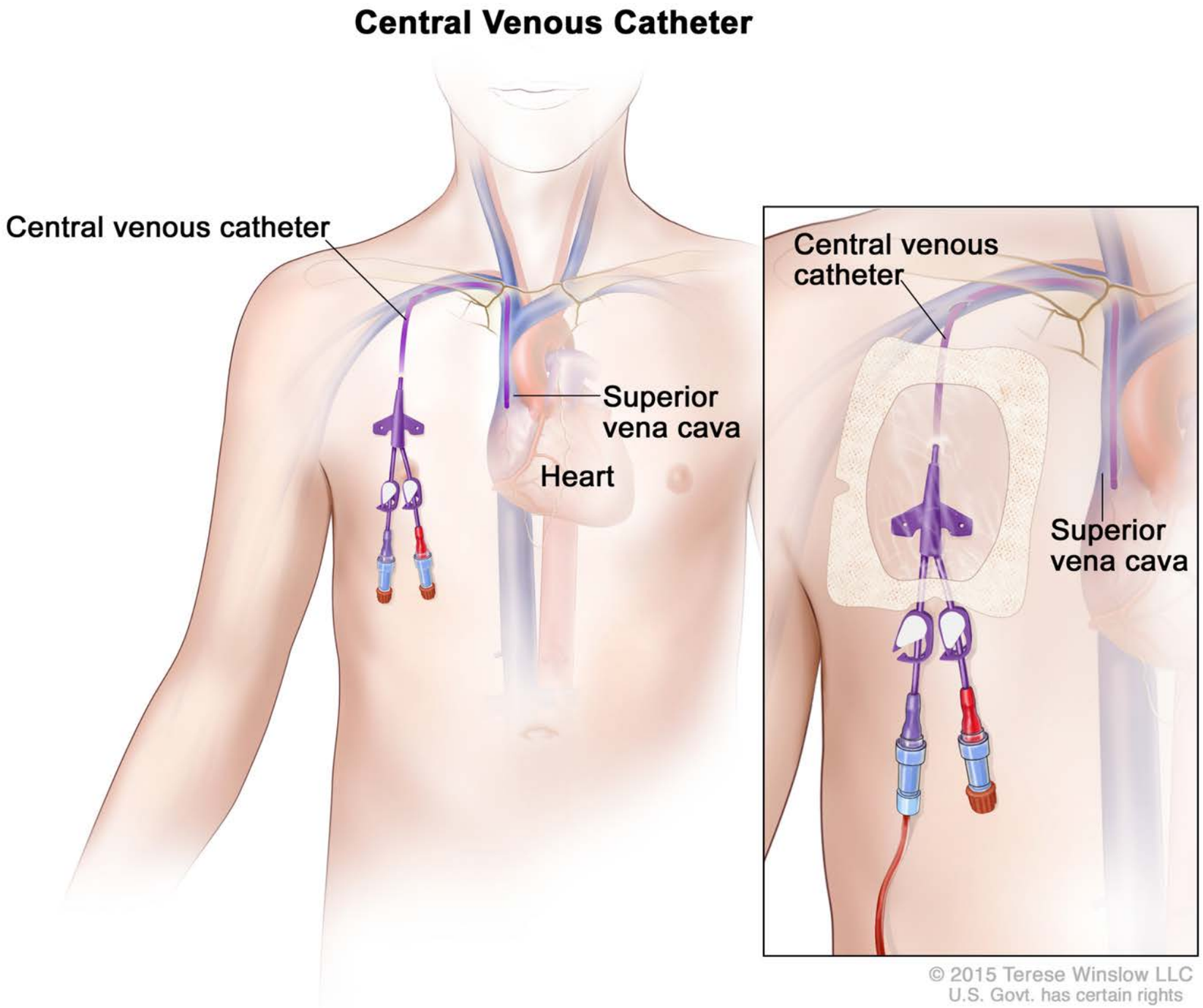


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Figure 7.3. Typical implanted port system

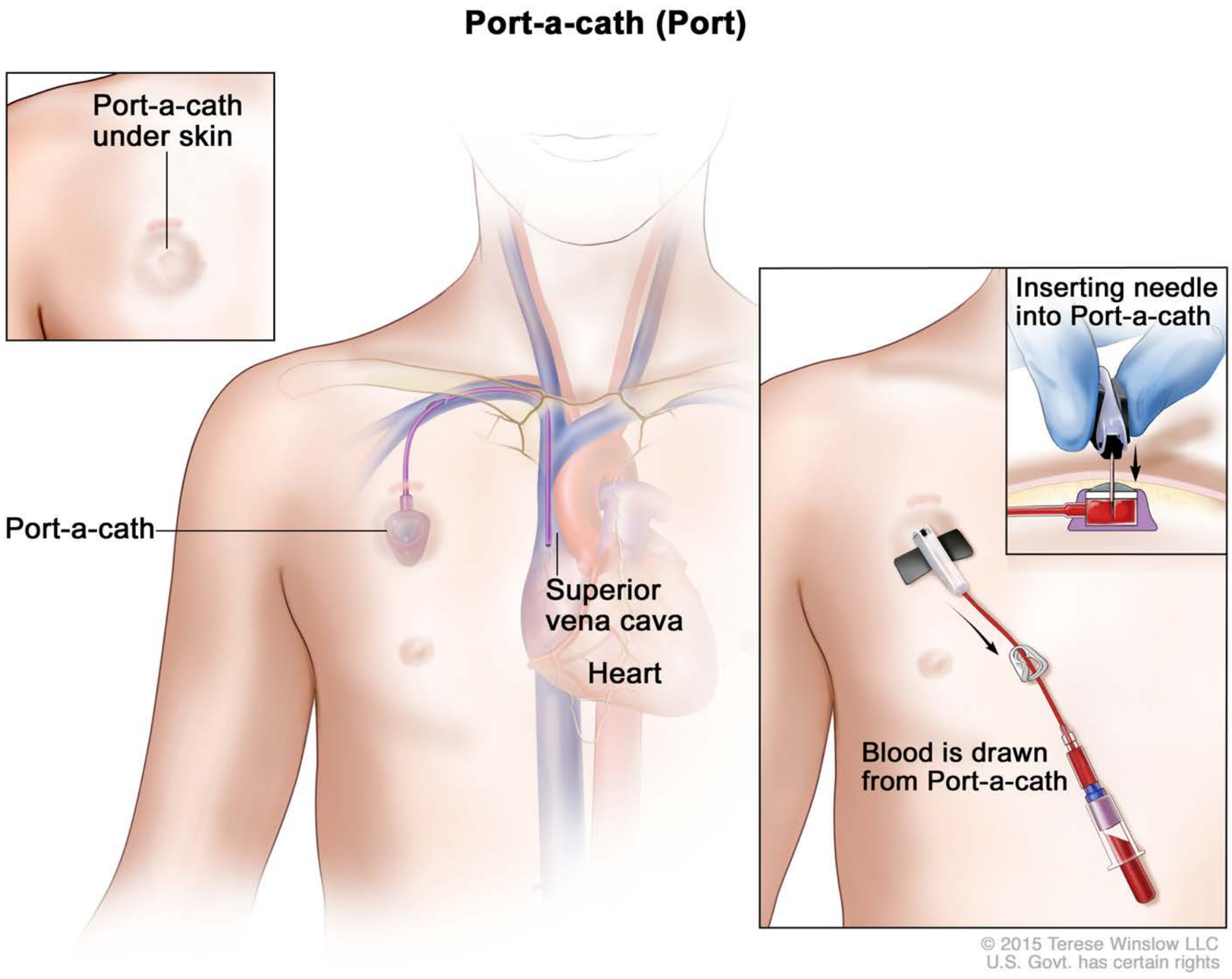

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Figure 7.4. A syringe pump with advanced delivery features that offer safety and accuracy may be required for adult and pediatric care areas where safe delivery of controlled substances are critical

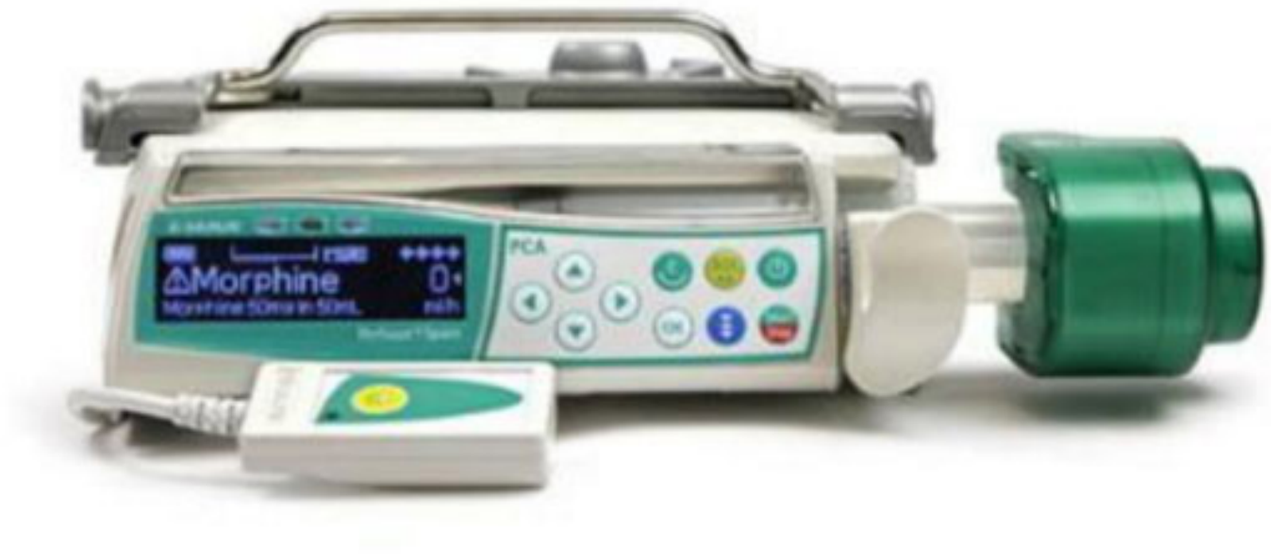
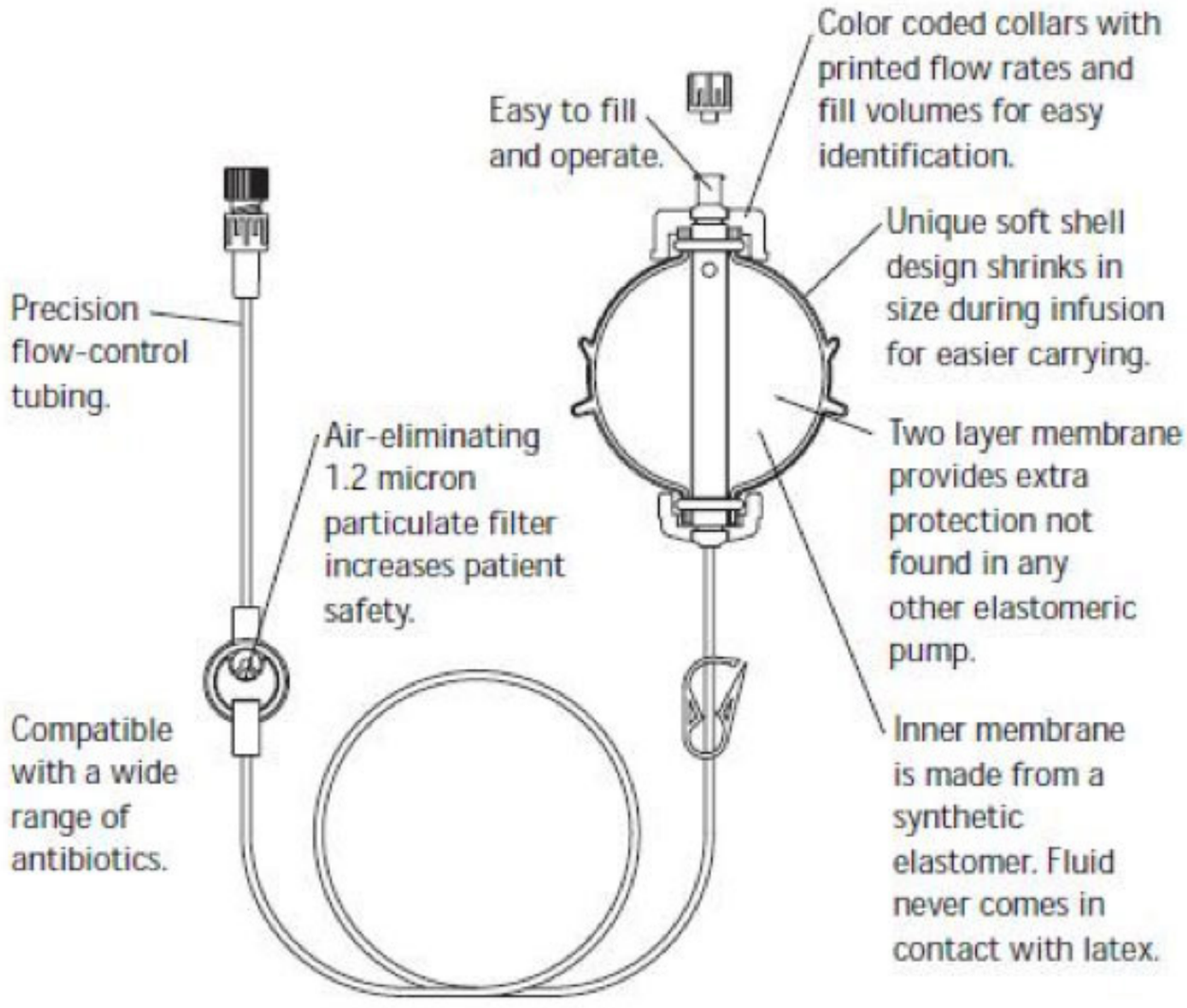


Photo courtesy of B. Braun USA.

Figure 7.5. An elastomeric pump allows mobility for the homecare patient while they're receiving IV infusions. A wide range of flow rates and sizes covers most OPAT infusion protocols.



Adapted from Allegro Medical Supplies Inc.

Figure 7.6. Ambulatory electronic infusion pumps are able to deliver medication while allowing the patient to be mobile.

Photo courtesy of Smiths Medical.

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8

OPAT for Pediatrics

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Infections are the most common cause of hospitalization in pediatrics, both for previously healthy children and those with underlying chronic diseases.[1,2] When children are hospitalized, not only is there a direct cost associated with delivering care to the child, but very often one or both parents have to take time off from work, thereby compounding the expense associated with a child's hospitalization.

Once patients are stable, OPAT allows for the treatment of infections to be completed at home. Improvements in vascular access devices and infusion equipment make it possible for parents or other care providers to accomplish this with minimal training. OPAT permits children to reintegrate in to their social structures, such as school, sports, or other important age appropriate activities, minimizing the disruption caused by medical treatment. This is even more important for patients already affected by chronic illness that impacts their social interaction and educational growth.

New antimicrobial medications with longer half-lives, and new ways of using older medications, allow for safe administration with minimal daily dosing. There are two widely employed models of OPAT care delivery for pediatric patients, as described below.

PEDIATRIC PATIENT SELECTION FOR OPAT

In the case of pediatric patients, the most important feature of eligibility for OPAT relates to the parent or care provider. Regardless of the diagnosis and the model chosen, a child will need the care of a competent and reliable adult to facilitate OPAT. The two modes of OPAT delivery open to pediatric patients are the infusion center model and the home infusion model (see Chapter 6).

Infusion Center

It is common practice for pediatric patients receiving antineoplastic chemotherapy to use hospital- or office-based infusion centers (see Chapter 6). OPAT providers can take advantage of the experience children with cancer have with these facilities, and the personnel working there. Such centers are often affiliated with hospitals, and staffed by clinicians with whom the children are familiar. This environment offers an intermediate location, a more monitored setting than the patient's home, but more welcoming and comfortable than the inpatient venue. This model is most likely to be successful when single daily (or less frequent) dosing regimens are required, since patients still have to be transported to the infusion center by an adult. Other advantages of OPAT, such as preserved school attendance, are also compromised with this model.

Home Infusion

This is the most common means of delivering OPAT to pediatric patients. Children's hospitals typically have established relationships with home infusion companies, either wholly owned by the hospital, or derived via contract. Frequently, it is the payer who dictates which agency may be used. These agencies provide the pharmacy and nursing support, though rarely will nursing visits occur daily, or with every dose (for reimbursement and legal issues, see Chapter 10).

Home infusion nurses are familiar with infusion equipment and vascular access devices (VAD). Visiting nurses evaluate the environment and can provide input regarding safety, cleanliness, access to appropriate refrigeration, electrical power and telephone. These nurses should be trained in evaluating children of all ages, including neonates.[3] Appropriately trained nurses should perform education, clinical evaluation, catheter care, adherence monitoring, and report to the treating physician. They should obtain drug levels for safety and other laboratories to document response to therapy (see Chapter 4). Complications of OPAT, such as VAD malfunction, can often be effectively evaluated by visiting nurses, who can also provide treatment, such as thrombolytic agents, under the guidance of a physician familiar with these medications. When the integrity of the VAD has been compromised, the nurse may refer patient to the emergency room, or contact the treating physician.

Often, adequate nursing support may not be available. For instance, the home may be in a rural area, or in a location that is not safe for nursing visitation. In these circumstances, OPAT may need to be reevaluated. Providers must be attuned to the practicality of home OPAT, particularly in the most vulnerable pediatric situations, such as neonates, and patients with central nervous system infections who may develop late complications (eg, seizures, enlarging head circumference, or feeding problems).

PATIENTS AND INFECTIONS SUITABLE FOR OPAT

OPAT can be used to treat virtually any infection, with appropriate patient selection and clinical monitoring. In accord with earlier reports,[1-5] a recent survey of pediatric infectious diseases clinicians, through the Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN), found that the most common conditions for which OPAT was prescribed were bone and joint infections.[2] Other commonly OPAT- treated infections in pediatric patients include bacteremia, central nervous system, complicated bacterial pneumonia, complicated intra-abdominal, and soft-tissue infections, particularly due to methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2]

Chronic Diseases Amenable to OPAT

While the value of OPAT for pediatric patients has been well established,[3,6] attention has recently been focused on the use of shorter courses of antibiotics and early parenteral-to-oral antibiotic switch. Yet for a number of infectious syndromes lengthy parenteral treatment is still required.[4] Similarly, underlying medical conditions associated with impaired gastrointestinal absorption may make the choice of oral antibiotics a less attractive option.

Gastrointestinal Disease

Children with intestinal failure frequently develop serious infectious, specifically bacteremia.[6] This could be associated with the VAD (eg, central line-associated blood stream infection; CLABSI) placed for nutritional, fluid, and electrolyte support, or related to the underlying condition that resulted in intestinal failure. Intestinal failure is most often secondary to surgical intervention; extensive intestinal resection following necrotizing enterocolitis (NEC) in premature infants is the most common cause of surgical intestinal failure.[7] Other congenital anatomical abnormalities, such as gastroschisis, intestinal atresias, and strictures, require extensive surgical resection and result in prolonged intestinal failure.[8] Dismotility syndromes and metabolic disorders are also frequent causes of protracted intestinal failure. Fortunately, such patients are already experienced in home parenteral alimentation and IV antibiotic therapy, so their care providers are knowledgeable in the management of VADs and infusion devices. Also they already have existing home health support with pharmacy and appropriate nursing involved in their care. If an effort to preserve the line is attempted, therapy focused on the CLABSI pathogen should be infused through the involved catheter for the duration of treatment. Other recommendations for the management of CLABSI can be found in the IDSA 2009 guideline.[9]

Cystic fibrosis (CF)

Children and adolescents with cystic fibrosis (CF) have infectious endobronchitis and require frequent courses of antibiotics,[10,11] and the very first report of successful OPAT utilization was published in 1974.[12] Fairly early in life, these young patients become colonized with *Pseudomonas aeruginosa*, for which oral antibiotic options are limited.[13] In the past these patients were commonly hospitalized for a minimum of 14 days at a time. The introduction of oral quinolones and aerosolized antibiotics has contributed greatly to keeping these children at home, yet they still require hospitalization at times for more intense therapy. After initial stabilization, patients are frequently discharged home on OPAT. They often require a sophisticated team of health care providers and infusion equipment, as some of the antimicrobials destabilize rapidly at room temperature, whereas others may require careful, prolonged infusion times and drug level monitoring (see Chapter 4).

Dialysis

Children on dialysis, either continuous ambulatory peritoneal dialysis or hemodialysis, frequently develop infections associated with their indwelling devices. Infectious disease specialists may take advantage of their impaired renal status to design regimens that are administered infrequently (after hemodialysis). Such courses may be lengthy, lasting 14 to 21 days,[9] but if the patients are otherwise medically stable, they may be ideal candidates for OPAT. In children receiving peritoneal dialysis, the peritoneal dialysate itself may be used to deliver antibiotics, potentially avoiding the need for venous access and parenteral antimicrobial therapy, thus minimizing discomfort for the patient.

Infections Complicating Antineoplastic Chemotherapy

Children receiving chemotherapy often develop serious infections during periods of neutropenia.[14] Typically these patients have a VAD already in place. Among other serious infections, CLABSI are common, as are bacteremias not related to the VAD.[9,14] Traditionally, these infections are treated in the hospital, at least until resolution of neutropenia. Recently, employment of risk stratification models, assessing levels of severity of illness and markers of poor outcome, has resulted in increasingly frequent utilization of OPAT. Clinically stable children can receive antibiotics and chemotherapy at the same infusion center, with daily observation by highly qualified personnel during infusion visits. Increasingly, these children are being transitioned to home therapy, to allow better integration with their regular lifestyles.[14]

Immunocompromised Patients

Pediatric patients with primary or acquired immune suppression often develop serious infections. After initial treatment in hospital to stabilize them, even these patients can be safely transitioned to OPAT. Patients with primary immune deficiencies are surviving longer and are at risk for a variety of infections, depending on the underlying defect. Chronic granulomatous disease, for example, renders patients susceptible to infections with Gram-positive catalase-producing organisms, most prominently *Staphylococcus aureus* and *Nocardia* spp, but also some Gram-negative organisms, such as *Burkholderia cepacia* and *Serratia maercescens*, as well as fungi (most often *Aspergillus* spp and *Candida* spp among others).[15,16] These infections often require prolonged parenteral antibiotics that can be safely delivered at home. Patients with inflammatory bowel disease (eg, Crohn's

disease and ulcerative colitis) are frequently treated with immune suppressive agents, including tumor necrosis factor (TNF) antagonists and steroids.[17] The risk of infection in these patients is compounded by the disruption of the natural barrier offered by an intact intestinal mucosa. Patients with other immune suppressive conditions, such as Wiskott-Aldrich syndrome (common pathogens: cytomegalovirus, fungi), congenital neutropenias (common pathogens: *S. aureus*, *Candida* spp), and transplant recipients (common pathogens: fungi, herpes viruses, *Streptococcus pneumoniae*) among others, survive for long periods of time with substantially increased risk for infections.[18-23] Similar to the oncology patients discussed above, these patients often already have a VAD in place and are familiar with managing medications at home, which greatly facilitates instituting OPAT.

ANTIMICROBIAL AGENTS SUITABLE FOR PEDIATRIC OPAT

There are many factors to consider when selecting an appropriate antimicrobial, including pharmacokinetic and pharmacodynamic parameters (see Chapter 5). A selection of common antibiotics used when treating children are highlighted in Table 8.1. Here we focus on considerations for pediatric patients for use in the home OPAT. These observations are intended as useful guides towards the choice of antimicrobial agents for pediatric patients; providers are referred to full prescribing information and local patterns of susceptibility and resistance for final antimicrobial selection.

Antimicrobial agents that can be used in pediatric OPAT regimens should meet certain criteria to allow safe administration at home, without close supervision by health care personnel. The likelihood of infusion-related side effects should be minimal, such as the frequent infusion-related toxicities associated with amphotericin B deoxicholate.[24] Vancomycin should be avoided in patients who have a history of red man syndrome. The administration is typically performed by a parent or care provider to ensure compliance; dosing more than 3 times a day, or regimens with more than 2 drugs, are often unrealistic. Ideally, dosing should be spaced out enough to allow the child or adolescent to go to school, and participate as much as possible in daily activities.

β-LACTAM CLASS

β-lactam agents, which include cephalosporins, penicillin derivatives, monobactams, and carbapenems, are the most common class of antibiotics used in pediatrics. These medications are generally safe and, when infecting pathogens are susceptible, the bactericidal activity is highly desirable.[25-27]

Ceftriaxone

Ceftriaxone, is frequently active against some of the most common pathogens associated with community acquired infections in children, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Streptococcus pyogenes* (a group A streptococcus; GAS).[28] Although it has activity against methicillin-sensitive *Streptococcus aureus* (MSSA), it is rarely used for this purpose.

It also has excellent activity against *Haemophillus influenzae*, including those producing β-lactamase, or otherwise resistant to ampicillin. It is worth mentioning that this pathogen has been almost eradicated in the US after the introduction of *H. influenzae* type b conjugate vaccine. Ceftriaxone also has excellent activity against *Escherichia coli*, the most common pathogen responsible for complicated urinary tract infections (UTI) and bacteremia in children.[29] Ceftriaxone has proven safe and effective in the treatment of most infections associated with above pathogens, including meningitis; it has convenient once daily dosing and a short infusion time, making ceftriaxone an ideal agent for OPAT.[28,29]

Cefazolin

A first generation cephalosporin with excellent activity against MSSA, cefazolin is frequently used to treat infections proven, or suspected, to be due this pathogen.[30] Complicated skin and soft tissue infections (cSSTI), as well as bone and joint infections, are often due to MSSA and can be adequately treated with cefazolin, after MRSA has been ruled out.[30] Cefazolin has an excellent safety profile; the short infusion time renders the 3 times a day dosing schedule manageable, allowing patients to go to school around dosing times. Cefazolin can also be delivered as a continuous infusion, using a programmable ambulatory pump, which may be more convenient for parents or children with a busy schedule.

Cefepime

Cefepime is a fourth generation cephalosporin with excellent activity against *Pseudomonas aeruginosa*, and other Gram-negative organisms, often seen in children with underlying medical conditions who require frequent hospitalizations.[31] These include *Enterobacter cloacae*, *Serratia marcesens, and Citrobacter* spp, including strains producing AmpC β-lactamases.[27] This agent is particularly useful in CF patients, often in combination with an aminoglycoside. It is also increasingly deployed as monotherapy in children with "low risk" fever and chemotherapy-induced neutropenia, in an attempt to minimize inpatient time and the costs associated with treating these patients. Cefepime also has an excellent safety profile; again, its short infusion time makes the 3 times a day dosing tolerable. In non-neutropenic hosts, who have infections with pathogens other than *P. aeruginosa*, it is sometimes used in an every 12-hours regimen. It can also be used as a continuous infusion, often in CF patients, since it is stable for 24 hours without refrigeration.[31]

Ceftaroline

Ceftaroline is a new cepahlosporin with excellent activity against *S. aureus*, both MSSA and MRSA. While it is approved in adults for cSSTI, its use in pediatrics is currently being evaluated in pharmacokinetic trials. This agent may provide MRSA activity with the safety profile usually expected of this class of agents.[32,33]

Penicillins

Amongst the penicillins, piperacillin-tazobactam is used frequently for OPAT.[34] Typically prescribed every 6 hours, it may be less convenient than other agents dosed less frequently, unless paired with a programmable ambulatory pump. It can also be used every 8 hours via extended (over 4 hours) infusion time, a strategy often employed in CF patients, or those with polymicrobial infections, such as intra-abdominal infections. Although it has a very good safety profile, frequent monitoring

of white blood cell count (WBC) is indicated when used for ≥3 weeks.[34] Semisynthetic antistaphylococcal penicillins, particularly nafcillin and oxacillin, are frequently used for serious, life-threatening infections, especially MSSA endocarditis.[35,36] These may require dosing every 4 hours, or as a continuous infusion. These have a strong safety profile, but frequent monitoring of renal function and WBC (eg, weekly for oxacillin) is indicated when used for >2 weeks.[35,36]

Carbapenem Antibiotics

Carbapenem antibiotics have broad spectrum of activity.[37] Meropenem has a better safety profile than imipenem-cilastatin in pediatric patients, particularly those with meningitis who may have an increased risk of seizures.[38,39] Like piperacillin-tazobactam, meropenem is frequently used in patients with CF and in polymicrobial infections. It crosses the blood-brain barrier well and has been used to treat meningitis and brain abscesses.[11,37] It is dosed 3 times a day, facilitating the patient's return to normal activities.[38] Continuous infusion is impractical, as meropenem loses activity after 4 hours at room temperature. Ertapenem may be used instead of meropenem, when carbapenems are indicated, but it has no activity against *P. aeruginosa* or enterococci.[40] There are no data for meningitis. Dosing is more convenient (twice daily in children <12 years old, and once every 24 hours when older).

AMINOGLYCOSIDES AND GLYCOPEPTIDES

Aminoglycosides have excellent activity against Gram-negative pathogens. In recent years, an improved understanding of the pharmacodynamic properties of these antibiotics has resulted in the use of these agents, particularly tobramycin and gentamicin, in once-daily dosing regimens.[41-43] These medications are frequently utilized in patients with CF and UTI,[25] but drug levels and renal safety laboratory studies need to be monitored frequently. Once-daily dosing is not appropriate for patients who have liver failure, severe renal insufficiency, serious illness, or nutritional deficiency.[41]

Glycopeptides (primarily vancomycin in the US) are often used for severe Gram-positive infections resistant to β-lactam agents.[44,45] These medications are particularly useful in coagulase-negative staphylococci and MRSA infections, such as CLABSI and ventriculoperitoneal (VP) shunt infections,[46-48] but also cSSTI, and bone and joint infections.[45,49] Increased risk of treatment failure has been reported with MRSA pneumonia.[50] In pediatric patients, vancomycin requires dosing every 6 hours and, like aminoglycosides, frequent monitoring of drug levels and safety studies.[44] The safety of vancomycin as a continuous infusion is being evaluated and may become an option in the future.[51]

OTHER ANTIBIOTICS

Daptomycin, a lipopedtide antibiotic, has limited data in children and should be used with caution. It has strong bactericidal activity and has been used successfully in life-threatening, Gram-positive infections, resistant to other antibiotics, particularly MRSA.[32,52,53] It is generally well tolerated, although elevation of creatine kinase of uncertain clinical significance has been observed. Clinical data on long term use is lacking and use for extended periods of time should only be done under infectious diseases consultation. Daptomycin is dosed conveniently once daily.[53] It should not be used for pneumonia because it is inactivated in the lungs by surfactant.[53,54]

Oritavancin, televancin, and dalbavancin, are new agents with potent activity against resistant Gram positive organisms.[55-58] Although there are limited data in children, they are promising agents for OPAT with exceptionally long half-lives, allowing for a single dose regimens with oritavancin (lasting two weeks), once daily dosing for televancin, and once weekly dosing for dalbavancin.[55-58]

Quinolones (eg, ciprofloxacin and levofloxacin), oxazolinidones (eg, linezolid), and clindamycin, have similar bioavailability when used orally or parenterally.[59-62] Oral administration is the superior route unless mitigating circumstances prevail. These medications are used intravenously when oral administration is difficult due to taste, or ineffective, due to impaired absorption. When using quinolones at home, nursing support must be proficient in evaluating for bone or joint toxicity, and report to the physician managing OPAT.

There is extensive data on clindamycin for bone and joint infections, including those due to MRSA, and it can be used in 3- or 4-times daily regimens.[62] Ciprofloxacin and levofloxacin are often used in CF patients or other patients with *P. aeruginosa* infections, particularly UTIs.[63,64] Linezolid has excellent activity against MRSA and vancomycin-resistant enterococci (VRE).[65,66] It has been studied extensively in pediatric patients and must be dosed 3 times a day in children <12 years old.[63] Monitoring for thrombocytopenia should be heightened when linezolid is used for >2 weeks. Peripheral neuritis, including optic neuritis, has been reported when used for >5 weeks.[61] Linezolid has been used for cSSTI, bone and joint infections, pneumonia, and endocarditis, though randomized clinical trials are available only for pneumonia and cSSTI.

ANTIFUNGAL MEDICATIONS

Fungal infections are frequent in patients with compromised immune systems. The echinocandins, micafungin and caspofungin, have been used extensively in pediatrics (safety and efficacy of anidulafungin have not been established for patients ≤16 years old), and are recommended for the treatment of candidiasis in neutropenic patients and other immune compromised hosts.[67-69] In general, both echinocandins are well tolerated, and a once daily infusion is convenient for OPAT. Liposomal amphotericin B has a better infusion-related safety profile than amphotericin B deoxicholate.[24,70] To a great extent, amphotericin has been replaced by oral triazole agents in the treatment of *Aspergillus* infections, but it is still used for treatment of zygomycosis.[71] It is used once daily and infused over 1 to 2 hours. Monitoring of renal function and electrolytes, particularly potassium, is important. Severe hypokalemia may be a limiting factor when considering OPAT with liposomal amphotericin B.[70] The triazoles fluconazole, voriconazole, and posaconazole, have similar bioavailability, either orally or parenterally.[72-74] These are often used parenterally when oral tolerability, due to taste or absorption, is a question. There is also extensive information on fluconazole for the treatment of *Candida* infections in children.[75] The pharmacokinetics of voriconazole in children is highly variable and makes its use, orally or parenterally, difficult.[76]

SUMMARY

In summary, OPAT should be considered an important alternative for pediatric patients in need of prolonged parenteral antibiotic therapy. Children with chronic conditions requiring frequent hospitalization may also find it appealing to spend less time in the hospital. The availability of safe and potent antibiotics with convenient pharmacokinetic characteristics has allowed for an increased use of OPAT, although significant limitations exist. Among these, perhaps the most important is the requirement of a committed care provider to facilitate the treatment at home.

FIGURES AND TABLES

Table 8.1. Common antimicrobial choices for pediatric patients

Antimicrobial agents	Ceftriaxone	Cefazolin	
Frequent indications	Community acquired infections	Osteomyelitis	
Dosing	100 mg/kg/day, divided q8h, may be used as continuous infusion	100 mg/kg/day, divided q8h, may be used as continuous infusion	1
Maximum daily dose	4 g	3 g	
Comments			

CNS, central nervous system; CF, cystic fibrosis; g, gram; h, hours; kg, kilogram; m^2, square meter; mg, milligram; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible *Staphylococcus aureus*; OPAT, outpatient parenteral antimicrobial therapy; q, every [from Latin: quaque].

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9 Quality Assurance & Outcomes

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Providers of OPAT must maintain a certain level of risk management, preferably under the umbrella of a broad quality assurance program. The concept of providing hospital-quality care in outpatient facilities and in the home setting is accompanied by some risk. Improved long-term vascular access and the development of new antimicrobials with more convenient dosing has led to steady growth of OPAT as a viable delivery of care model in an era of increased pressure to avoid or reduce hospitalization and readmissions.

Not every patient who needs IV medication can or should be treated in an outpatient setting. Outcomes measures to test OPAT's safety and quality are essential in the health care reform environment, and standardized monitoring systems should be firmly in place. The IDSA Practice Guidelines for OPAT, published in 2004, updated the previous edition from 1997, with particular emphasis on quality measures and outcomes indicators.[1] An update of IDSA practice guidelines for OPAT is currently underway. The OPAT Outcomes Registry was a national database that aggregated the outcomes of 24 centers and represented over 8,000 patients and 11,000 antibiotic courses, administered between 1997 and 2000.[1-3] Additionally, a survey of Emerging Infectious Network participants reporting on more than 13,000 patients similarly highlighted the need for standardized quality goals.[4] In the absence of published outcomes standards for infections treated with OPAT, funding is needed to develop a new and expanded national registry. Such an effort will require outpatient parenteral antimicrobial therapy centers to collect data on patient outcomes and monitor site specific performance metrics over time.

Quality assurance in health care is an essential part of health care reform (see Chapter 12). The overall quality of care in the outpatient setting should be comparable to that required in the hospital, although clearly many of the risks are different. A better understanding of the nature and importance of these specific risks is required to implement relevant performance improvement measures within the realm of quality assurance.

Protocols and guidelines that have been developed by individual OPAT programs and home infusion companies vary greatly and may be proprietary.[5] Standardization is hindered by the rapid changes taking place in the industry in response to advances in technology as well as changing financial incentives (see Chapter 10). Quality assurance activities required or recommended by accrediting and licensing bodies have generally been focused on compliance with patient care processes and procedures rather than actual clinical outcomes such as readmission to the hospital or excess utilization of emergency department services as indicators of quality.

OPAT ACCREDITATION

In an effort to provide some assurance of quality, many third-party payers currently require that eligible OPAT programs have some kind of formal accreditation. The Joint Commission, has expanded its certification process to include outpatient and home care settings.[6] Accreditation is also available for mental health care, long-term health care, and ambulatory health care,[7] under which an accreditation process for ambulatory infusion centers was initiated in January 1995. Thus, physicians' office-based infusion centers may be eligible for Joint Commission accreditation. In 1997, long-term care pharmacies, which provide infusion and other drug therapy to long-term care facilities, were included for Joint Commission accreditation.[8] Most of the larger home infusion pharmacy provider organizations have earned Joint Commission accreditation. Other providers have been accredited through the Community Health Accreditation Program (CHAP), and some have the imprimatur of both.

The accreditation survey process is costly, with fees based on a provider's gross annual revenue (eg, CHAP), or a base fee plus a variable amount calculated on patient volume and number of sites (eg, Joint Commission). The incentives to pursue accreditation are great, however. The majority of health insurance plans and managed care organizations require it, and once accredited, agencies can receive "deemed status," which allows them to be reimbursed by Medicare and Medicaid without undergoing a separate certification process. The Joint Commission's focus changed in 1995 to emphasize actual performance (not simply the capacity to perform), as well as performance standards focused on quality improvement. Thus, indicators, defined as quantitative outcomes or process measures related to performance, have now become an integral part of the organization's accreditation process.[9,10] In addition, infusion pharmacies are subject to state licensure, the statues of which vary by state.

INDICATORS OF OPAT QUALITY

The American Society of Health-System Pharmacists (ASHP) has written guidelines that define the role of the pharmacist in providing pharmaceutical care to patients in the home or alternate-site setting. An updated ASHP comprehensive guidelines on home infusion pharmacy services was published in 2014.[11] The Infusion Nurses Society (INS) publishes standards of practice that address vascular access device insertion, care and management, and administration of infusion therapy.[12] The Centers for Disease Control and Prevention (CDC) guidelines for "practitioners who insert catheters and for persons responsible for surveillance and control of infections in hospital, outpatient, and home health care settings" was made available in 2011.[13]

The Food and Drug Administration (FDA) has a standing MedWatch System to track problems and adverse events associated with medications and medical devices, such as infusion pumps. The IDSA's 2004 guideline includes the basic criteria for an outpatient program; outlining requirements of key personnel; clinical monitoring of patients to assess treatment success and failure; program outcomes such as, how often a treatment course was completed as planned, treatment complications (vascular access or antibiotic-related issues) and additional measures such as functional outcomes (patient's ability to return to work), morbidity and mortality.[1] A review of the global OPAT literature suggests that, while the above outcomes are useful in monitoring daily practice activities at individual sites, a more expanded approach needs to be developed to capture other relevant measures, including: OPAT-related emergency department utilization and hospital readmissions, adverse events from antimicrobials, PICC line complications–catheter related blood stream infections and thrombosis, and progression of infection.[14-15] Patients and providers now also have access to online resources such as the Centers for Medicare and Medicaid Services (CMS) website to compare individual home health service agencies along standardized outcome measures including, emergency department use and rehospitalization during the first 30 days of home health. Many home infusion nursing agencies are not CMS certified, and therefore not represented in Home Health Compare, so comparative data are limited at this time. Similarly, there is no comparative data available at present to assess quality outcomes for patients receiving OPAT through an infusion center.

OPAT STEWARDSHIP

Improving the use of antibiotics to protect patients and reducing the threat of antibiotic resistance has been declared a national priority by the CDC.[16] Providers of OPAT must have an antibiotic stewardship program in place, supervised by specialists with clinical expertise in infectious diseases and antibiotics. The OPAT stewardship program should include tracking and monitoring for appropriate antibiotic use and outcomes; as well as, education for clinicians, nursing staff, and families, about antibiotic resistance, adverse events (including *Clostridium difficile* associated diarrhea), catheter complications, and opportunities

for improving the use of antibiotics. The stewardship program should also include methods to promote timely switching from IV to PO antibiotics when appropriate; deescalation of broad spectrum antibiotics (choosing the most effective, safe, and narrow-spectrum agent); [17] as well as, prompt discontinuation of antibiotics when not needed. Studies evaluating the impact of mandatory infectious diseases consultation prior to the initiation of OPAT have consistently demonstrated that without specialist consultation there is greater overuse of OPAT for infections that could be treated with oral agents.[18]

INFECTIOUS DISEASES CONSULTATION AND OPAT

The 2004 IDSA OPAT guidelines in the US recommend involvement by an infectious diseases physician (or equivalent) with OPAT experience, to inform patient selection into an OPAT program.[1] Utilizing the expertise of an infectious diseases physician through consultation, prior to discharging the patient into an OPAT program, may have collateral benefits, including: better adherence to standards of care, decreased use of inappropriate therapy, and improved patient outcomes.[19]

Shrestha et al. published their findings on the contribution of infectious diseases consultation toward the care of inpatients being considered for OPAT, and found a positive impact supporting this practice. The investigators specifically describe the increased value provided by improved antimicrobial stewardship, via optimization of recommended antimicrobials prior to discharge, and improved continuity of care.[20] While additional research needs to be done in diverse settings, to better define the overall impact of consultation prior to discharging a patient into an OPAT program; the limited data available to date supports this practice as a means to optimize outcomes for patients receiving treatment in this transition of care model.

MONITORING OUTCOMES

As OPAT grows, objective measurements of its value must be developed. To accomplish this, providers must agree on criteria by which to measure program quality, based on practical clinical outcome indicators. Ongoing monitoring of outcomes offers the additional advantage of identifying the comparative value of different therapeutic approaches. Today, more than ever, physicians must know about the relative value of almost every therapy, to justify it under the pressures of managed care—when it is appropriate to send the patient home with IV therapy; what the best dosing regimen is; and when oral antibiotics can be used instead.

Outcomes measurements of an OPAT program are a part of the continuous performance improvement process through which health care providers attempt to improve and ensure quality of their care and services. Accrediting bodies require outcomes measurements as a part of their certification process, but do not specify the parameters or indicators to use. Therefore OPAT centers should have an active performance improvement program that can track clinical and program outcomes. Tools with which to judge the quality of OPAT programs objectively were developed in

the OPAT Outcomes Registry, which provided information about the most commonly treated infections (Figure 9.1), the pathogens found, and the primary antibiotics used, as well as outcomes indicators for patients treated with OPAT (Table 9.1).[1]

Table 5.1 outlines additional data on infections and antimicrobials from several more recent programs. An International OPAT Outcomes Registry based on the US project includes data from the United Kingdom, Italy, and Canada. Over the 3 years from 1998 to 2001, 1141 cases have been entered from those countries.[2] These data can be used by OPAT organizations to compare their outcomes with those from their own countries, or from the entire registry database. An OPAT Outcomes Registry can also be used by local OPAT programs to evaluate and track their services. For example, it can be adapted to provide information on issues such as, economics, and patient satisfaction. The introduction of such quality indicators for evaluating one local practice proved valuable in terms of both quality improvement and service development (Table 9.2).

Patient safety and health care-related infections are of particular concern with OPAT.[21] The home environment is rarely constructed for medical safety and application of hospital infection control policies may not be appropriate. Fortunately, the risk of complications and infection related to home care appears to be less than those related to hospitalization, including the risk of acquiring antimicrobial-resistant organisms (Figure 9.2).[22, 23] While there is limited data on outcomes for self-administered OPAT in the US, a large retrospective study from Parkland Hospital (Dallas County, Texas) showed similar results to what has been reported in the UK.[24] The study demonstrated safety and efficacy for patients who were uninsured and able to administer self-OPAT without the assistance of skilled nursing.

In May 2004, the Emerging Infections Network (EIN) of the IDSA sent a survey to its 848 North American members–all infectious diseases consultants–regarding the delivery of OPAT in their practice settings, their involvement in the process, and their observations about its use and safety.[4] A total of 454 (54%) members responded with relevant data. They collectively had followed more than 13,000 OPAT patients during the previous year, treating over 90% at home, using peripherally inserted central venous catheters for 86%. They used a variety of infusion devices. During that year, however, more than 60% of EIN members collectively encountered approximately 1951 infectious and noninfectious complications (Figure 9.3).[4]

The investigators concluded that most hospitals in North America have OPAT services, and infectious diseases consultants frequently participate in the management and follow-up of these patients.

However, opportunities exist for improving OPAT monitoring and patient safety. A 2012 survey of American infectious diseases physicians engaged in OPAT, revealed that out of 316 respondents, only half had a formal OPAT program. While 52% reported no systematic method of communication between inpatient and outpatient physicians, 49% had no systematic method of lab tracking, and 34% have no method of ensuring patient adherence to clinic visits. All of these patient safety measures were more likely to be present in practice sites with formal OPAT programs.[25] The non-availability of laboratory tests results, for instance, has been shown to correlate with increased risk of readmissions.[26]

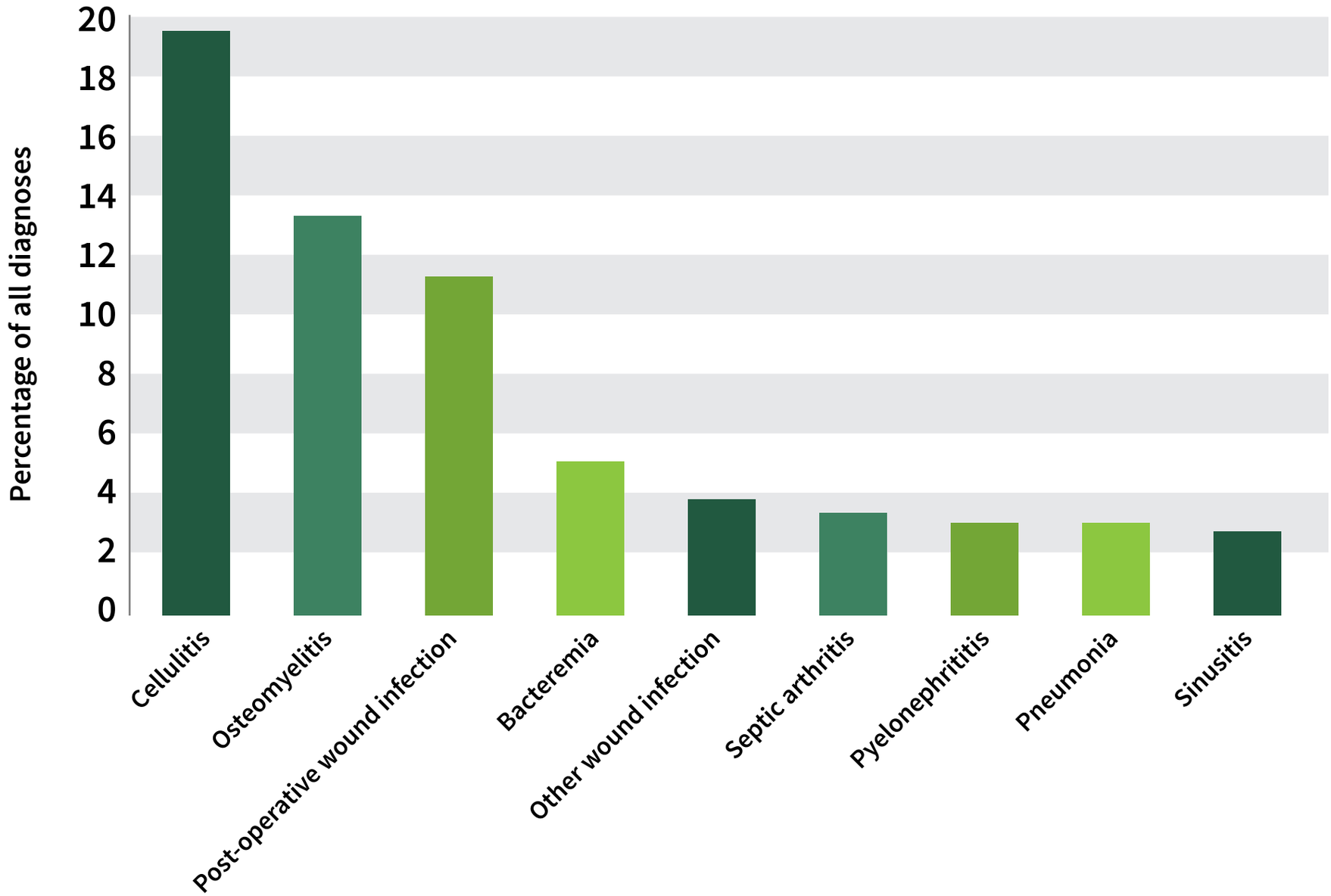
The magnitude of OPAT operations and the frequency of complications suggest that additional investigation is warranted to improve the quality and safety of OPAT services. The need for quality measures and performance indicators will continue to increase as medical care shifts out of the hospital and back into the community. Hospitals have evolved valuable mechanisms to improve patient care and safety under the watchful care of omnipresent medical staff and remarkable resources. Unfortunately, the cost of hospital care may no longer be justifiable. Patients, even those with serious infections, are increasingly being discharged early or not admitted at all. A safety net of providers and systems needs to be established in order to ensure effective therapy with minimal risks.

SELECTING AN OPAT PROGRAM

Factors to be considered by physicians in selecting an OPAT provider agency are outlined in Table 9.3. 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. However, the referring physician must always keep in mind, that he or she remains responsible for the referred patient's care, regardless of who actually administers it (see Chapter 10). The checklist also may be helpful in making comparisons among available programs.

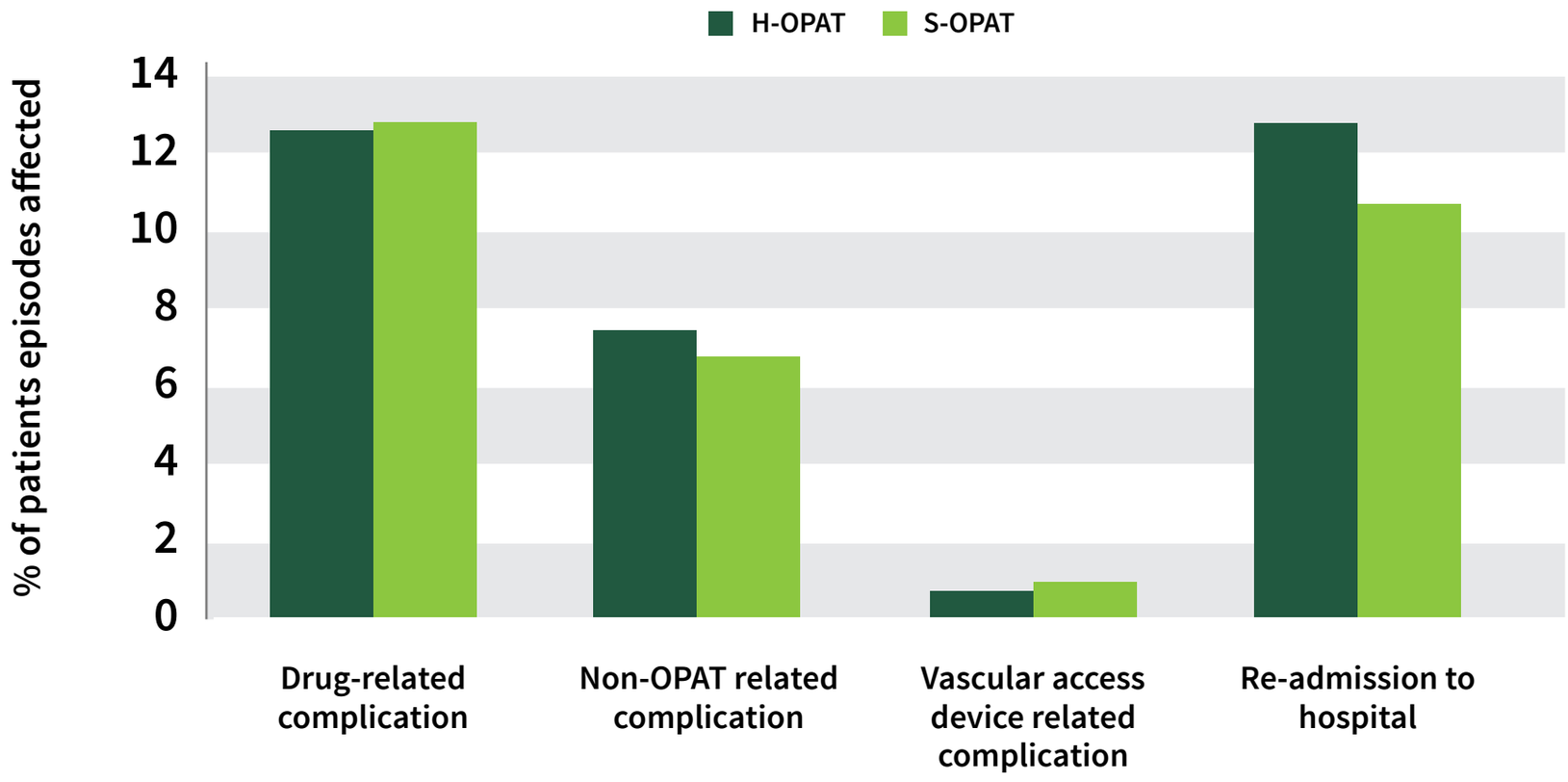
FIGURES AND TABLES

Figure 9.1. Top 10 infections treated in the OPAT Outcomes Registry of 24 sites in the US between 1997 and 2000



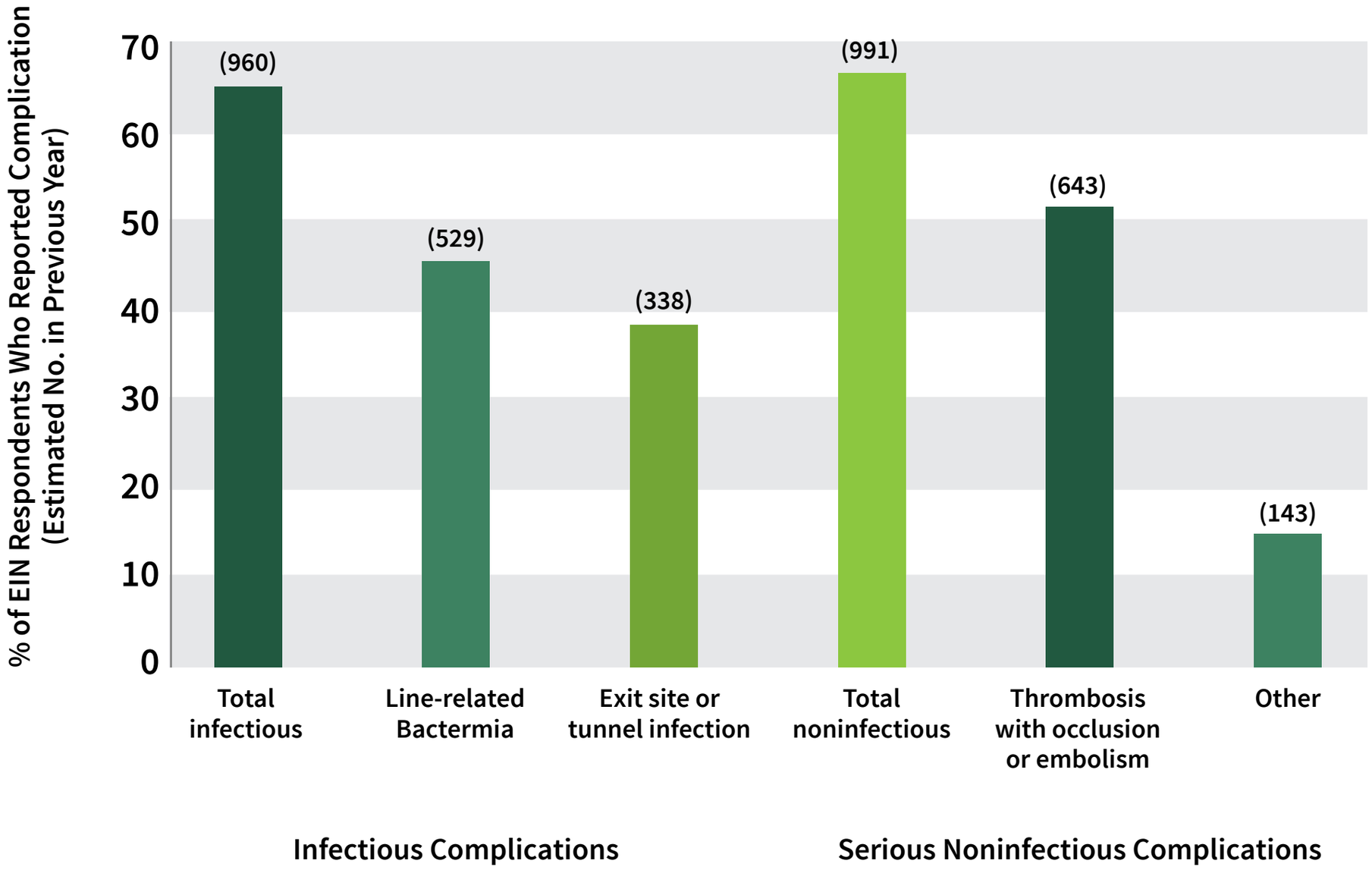
Adapted from Nathwani D, Tice A. Ambulatory antimicrobial use: the value of an outcomes registry. *J Antimicrob Chemother*. 2002;49:149-154, with permission from Oxford University Press.[2]

Figure 9.2. Complications and hospital re-admissions in self-administered OPAT at home vs. hospital OPAT in 2007



Adapted from Matthews PC, et al. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort over 13 years. *J Antimicrob Chemother*. 2007;60(2):356-362, with permission of Oxford University Press.[23]

Figure 9.3. Complications of OPAT



Adapted from Chary A, et al. Experience of infectious diseases consultants with outpatient parenteral antimicrobial therapy: results of an Emerging Infections Network survey. *Clin Infect Dis*. 2006;43(10):1290-1295, with permission from Oxford University Press.[4]

Table 9.1. Outcome measures for OPAT

1. **Clinical Status**
A. Improved
B. Clinical failure
C. No change
2. **Program Outcome**
A. Therapy completed as planned
B. Therapy not completed (give reason)
3. **Complications**
A. Vascular Access
B. Adverse effects from antimicrobials (bone marrow, liver, kidney complications, eg: rhabdomyolysis or acute kidney injury)
C. Allergic response to antimicrobial agent
D. Development of thrombus
E. Catheter related bloodstream infection
4. **Health Care Utilization**

Table 9.2. Quality indicators for infections treated with intravenous antibiotics in the outpatient and home setting between April 1998 and August 2001, Tayside, Scotland, UK

Infections treated[a]	Percentage (%)	Clinical outcomes	Percentage (%)	Microbiological outcomes	Percentage (%)
Skin/soft tissue infections	54.5	Cure	97.2	Positive culture pre-treatment	20
Osteomyelitis/septic arthritis	22	No change	1.8	Positive culture post-treatment	0
Bacterial endocarditis	3.7	Worse	1		
Others	19.6	Adverse drug reactions	2.4		
		Unscheduled re-admission	3		
		PICC complications	1		

[a]These include meningitis, complicated urinary tract infections. methicillin-resistant Staphylococcus aureus wound infections and bacteremia, chest infections, cutancous leishmaniasis, etc.

PICC, peripherally inserted central catheter.

Adapted from Nathwani D, Tice A. Ambulatory antimicrobial use: the value of an outcomes registry. *J Antimicrob Chemother*. 2002;49:149·154, with permission from Oxford University Press.[2]

Table 9.3. Criteria for evaluation and selection of an OPAT provider

1	Medical director or advisor knowledgeable in infectious diseases and OPAT
2	Outlined roles of prescribing physician, medical director, nurse, and pharmacist
3	Standards for nurse, pharmacist, physician, and other patient care personnel regarding training, experience, and licensure
4	Accreditation or certification of infusion pharmacy and nursing agency or program (eg, Joint Commission)
5	Experience providing OPAT
6	Policies regarding • Frequency of physician and nurse clinical assessments • Staffing and on-call policies • Frequency of reports to physicians
7	Reporting of laboratory results to physicians within 24 hours
8	Willingness to share local quality assurance and outcomes information
9	Willingness to share charge information regarding individual patients

Adapted from Tice AD, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. *Clin Infect Dis*. 2004;38(12):1651-1672, with permission from Oxford University Press.[1]

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10 Legal and Reimbursement Issues in OPAT

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LEGAL ISSUES

Since its inception over 20 years ago, treatment of infectious diseases with OPAT has become not only accepted, but expected by third-party payers, patients, and their families. OPAT is no longer a novel concept, and data support safety and clinical outcomes comparable to inpatient care. However, there remain several areas of risk and liability that must be considered by any provider engaged in the delivery of OPAT. Some of these can be generalized; others will be specific to program type, state/local regulations, and/or payer requirements. Infectious diseases physicians need to be educated and aware of what is going on in the home infusion and outpatient hospital-based infusion arena, as many will refer their patients to these site providers and/or will serve as medical directors for these organizations.

Medical Risk

Regardless of the setting where the actual infusion takes place, the medical risks associated with the outpatient setting are different from those in the hospital. Patients and their families should be informed of their risks and responsibilities, prior to initiation of the treatment plan. Patient selection is critical in minimizing risk (see Chapter 2). Patients cannot be as closely monitored at home, and will not have the same access to a physician or nurse. They must take responsibility for monitoring their own symptoms, as well as for identifying and reporting problems. They must comply with the scheduling and travel requirements of the delivery model agreed upon with the physician and the other members of the OPAT team. It is common practice for patients to sign a document that indicates they have been informed of the potential risks and problems involved with outpatient therapy, and that they have had an opportunity to discuss them in full with a physician. Legally, such forms may deter lawsuits and may be helpful in defense, but they do not ensure victory in the courtroom (see Chapter 2).

Confidentiality

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations are now a required part of any outpatient treatment facility and address patient confidentiality as well as electronic information management.[1] As in all other medical care settings, attention must be paid to the privacy and protection of health care records among OPAT patients.

Transparency

Patients may have to make choices among IV therapy providers. The prescribing physician may be helpful in selecting the provider, based on his or her knowledge of the chosen provider's quality of service, as well as his or her ability to work with that provider. Also important is the prescribing physician's willingness to take responsibility for the care provided. Patients should be informed of the mechanism for reporting complaints, both within and outside the provider organization. Information regarding the ownership of the provider organization should be disclosed; particularly, if the referring physician participates in ownership on any level. Medicare beneficiaries are protected by a law that requires all providers to inform them of uncovered services to be rendered, as well as a written estimate of any financial responsibility incurred, including all deductibles and copays, before beginning treatment.[2]

Antitrust Law

Federal antitrust policies, generally developed through court decisions rather than mandated by legislation, have been designed to protect consumers from high prices, price fixing, and limitation of choice among goods or services.[3-5] Physicians and other health care providers cannot form organizations simply to reduce competition or fix prices for medical services. Specific guidelines define acceptable arrangements and situations in which exceptions may apply. In 1996, legislation widened the safety net for physician providers.[3-5] However, any provider considering participation in joint ventures, networks, or integrated delivery systems should consult a qualified antitrust law specialist to minimize the risk of running afoul of these complex regulations.

Professional Liability

The growth of OPAT can largely be attributed to the efforts of pharmacists, nurses, and business entrepreneurs. In the past, physicians often lagged behind in their interest and involvement in outpatient and home therapy, in part, because of the lack of reimbursement for patient care-services in the home or outpatient hospital-based setting. Furthermore, the idea of managing patients in a home-based setting without continuous hands-on assessment and intervention has been difficult for many physicians to embrace. Some infectious diseases specialists do not even have an office in which to see outpatients for follow-up, since they are hospital-based and only provide inpatient consultations.

Thus, in many outpatient infusion programs, a nurse or pharmacist is the person primarily responsible for patient care, with a physician signing forms and providing minimal oversight. The physician may not even be involved in the choice of home care provider or in the day-to-day supervision of the quality-of-care provided to their patients. Nevertheless, although nurses and pharmacists carry a certain degree of risk in terms of professional liability, physicians should be aware that they remain ultimately responsible, and liable, for the patient care, even if they do not deliver it personally. The classic model of the physician as "captain of the ship" has been tested repeatedly, and proven in court. That leaves the ultimate responsibility for patient care to the physician who orders the treatment, selects the OPAT provider(s), and monitors the patient during the course of therapy.

Litigation specifically related to OPAT is hard to track. OPAT problems may be less susceptible to lawsuits because of greater patient participation, as well as general satisfaction with the benefits of the outpatient setting. In a survey of infectious diseases specialists, approximately 4% of respondents reported having been sued in the past with respect to an OPAT matter.[6] As more and sicker patients are being treated in an outpatient setting, an increased number of recorded case law may be seen. So far, the problems have been focused around inadequate availability and follow-up by physicians, and aminoglycoside toxicity.

Physician Conflict of Interest and Self-Referral

Monetary incentives for physicians that may interfere with their clinical judgment and therapeutic parsimony are generally considered unethical and illegal. If, for example, physicians own or have a financial interest in an outpatient-care provider organization, concern has arisen that they may overprescribe services, including home infusion therapy.[7]

On the other hand, if physicians are not involved in overseeing the quality of the services provided, patients may be ill-served and the programs will suffer. It is often difficult to get physicians to spend the time, work, and energy required for such involvement, despite the fact that they are ultimately responsible for patient outcomes. The situation is largely the result of poor, usually absent, payment to physicians for their management of patients being cared for at home. There is little incentive for physicians to discharge patients when they are paid for daily hospital visits, but not for intermittent office visits, despite similar risks and responsibilities.

Over 30 years ago, one solution was devised by pharmacy-based home infusion providers to encourage more physician involvement in the novel idea of outpatient home infusion of drugs. Payments were made to physicians as direct referral fees per patient, and/or as "advisory board" compensation, sometimes in the form of ownership equity. The practice was widespread in some areas and caused growing concern about overuse of services for Medicare beneficiaries, believed by many to be influenced by financial remuneration. In response to these concerns, Fortney "Pete" Stark, former representative from California's 13th congressional district (1993 to 2012), sponsored legislation that attempted to regulate and restrict physician ownership and other financial arrangements with 12 designated health services (DHS) to which they refer patients.[8,9] While one of these services is home infusion, treatments carried out in a physician's office or at an infusion clinic are not.[8] The final Stark phase III regulations were effective in December 2007; phases I and II have been in effect for many years prior to that time. At this time, federal regulations apply only to Medicare and Medicaid beneficiaries, although some states have passed similar legislation that extends restrictions to patients whose health care is funded through private insurance plans.[9] The assumption is that any ownership interest in, or payments from, provider organizations are inducements to overuse their services, as well as a conflict of interest in terms of a physician's role as patient advocate and judge of quality-of-care. Of note is that there are clearly outlined exceptions to these self-referral situations. Two of these are physician and ancillary services rendered "incident to" physician office visits, as long as other payment criteria are met. As such, a physician who "refers" a Medicare or Medicaid patient to his or her own office-based OPAT program, and provides the direct supervision required, then bills for that service, is not considered to be making a prohibited referral under Stark laws. These laws were never intended to restrict physicians in providing appropriate care, procedures, or related supplies to their own patients.[2,8-11]

The Stark phase III regulations are most likely only of concern to those physicians who choose to serve as a Medical Director for OPAT delivered by a home infusion provider or hospital-based outpatient program. These regulations make distinctions between direct and indirect compensation agreements, and highlight exceptions for each type.[11-13]

Physician Involvement in OPAT

Under current stringent laws, rules, and regulations, there are still four ways for a physician to participate in OPAT:

1. Providing care plan-oversight services (see Chapter 6)
2. As a paid medical director of a hospital, pharmacy, or home health care company-based program
3. Providing infusion services as an extension of his or her medical practice
4. Becoming a member of a physician-network joint venture

Consultation with a competent health care attorney, who is familiar with both state and federal regulations, is an important step before finalizing the structure of any ownership or compensation agreement related to OPAT. However, safe harbors and reasonable exemptions exist whereby physicians

can provide OPAT services as an extension of their practices, while remaining compliant with relevant regulations. A physician who provides actual management services related to all patients of an OPAT provider organization, and is compensated at fair market value for their actual time spent in provision of these services, may continue the relationship even while referring some or all of his/her OPAT patients to that entity.

A physician-network joint venture is defined by the Department of Justice and Federal Trade Commission as a physician-controlled organization in which members collectively agree on prices or other significant terms of competition, and jointly market their services.[3-5,7]

Policy statements by the Department of Justice and Federal Trade Commission describe how antitrust laws apply to such organizations and establish "safety zones," within which their conduct will not be challenged by the federal antitrust agencies. There are, however, significant antitrust risks associated with joint ventures. Qualified antitrust counseling should be sought by any physician considering participation in such a network.

Licensure and Medications

Most requirements for licensure of an OPAT program will be dictated by the state where care and services are provided. Some payers, including Medicare and Medicaid, may require specific licensure, certification, or accreditation in order to contract with a provider. It is best to contact the relevant State Board of Licensing to determine the requirements for a particular model or setting in a given state.

In most states, two aspects of OPAT require licensure, registration, or compliance with published standards. One is the provision of hands-on nursing care in a patient's home, for which a state home-health agency license may be required. The other is preparation and dispensing of medications for patient self-administration at home. The administration of drugs on-site will usually fall under the license of the professional or the facility where the infusion occurs (eg, a physician's office or a hospital outpatient department). Once a drug has been given to the patient to take home, this is considered to be the act of dispensing, and the appropriate state board of pharmacy has full purview in dictating the licensure required or regulations to guide practice. In some states, even a physician's office must include a licensed retail pharmacy in order to dispense medications. Other states require only that the guidelines regarding preparation, labeling, and transportation are followed. All questions about dispensing are best asked of your state board of pharmacy, which can be accessed through the National Association of Boards of Pharmacy.

As of January 1, 2006, a new set of federal regulations govern all preparation of medications that will not be administered immediately. Commonly referred to as USP 797, these regulations were developed in response to a number of cases of contaminated solutions due, at least in part, to the methods and environment for compounding.[14] As a result, even if your own state regulations do not require that a physician's office maintain a pharmacy license in order to dispense medications, these regulations must be followed when parenteral solutions for home administration are dispensed to a patient. Some infectious diseases practices may choose to meet these requirements in

their office, which at minimum involve the training of personnel, purchase of an airflow hood, and/or the creation of a clean room. Other practices may find premixed products that meet their criteria or sign a contract with a pharmacy to prepare solutions for their patients. Of note is that these regulations do not pertain to solutions administered on-site immediately after mixing, and therefore does not apply to Medicare beneficiaries, whose only option is on-site administration.

The Future

If managed care and global capitation become more common, issues of self-referral and conflict of interest may be more focused on concerns regarding underuse, rather than overuse of services. In the managed care environment, non-physicians usually set practice guidelines and parameters. A case in point is a 1986 court decision holding the physician responsible for the loss of a patient's leg from gangrene.[15] The patient had been discharged earlier than the doctor had advised due to pressures from his health maintenance organization (HMO). The court held the physician negligent, however, because he did not more strenuously object to the discharge.

The combination of government and consumer interest in controlling costs and ensuring high quality patient care may continue to foster additional legislative and regulatory initiatives. It is important for anyone involved with medicine to be aware of the regulations, as well as any potential legal and ethical problems. To what extent they will benefit the quality-of-patient care and improve the use of available resources remains to be determined, especially in the outpatient setting.

REIMBURSEMENT ISSUES

The process of billing and reimbursement for OPAT is complex and varies based on type of insurance and location of service delivery.[12] We will attempt to clarify various reimbursement policies for OPAT for the major third party payers: Medicare, Medicaid, and commercial insurers.

The first and most important step related to reimbursement after you identify a patient in need of OPAT is to verify insurance coverage. The next step is to secure a prior authorization, if possible and necessary. This should be done as early in the process as possible, to support treatment planning and so as not to delay patient discharge from the hospital.

Medicare

The Medicare program has three mechanisms for reimbursement: parts A, B, and D (Medicare Advantage Plans or part C plans should be treated like a private payer until specific benefits can be determined).[16] None will give preauthorization for payment, although coverage is outlined by the Centers for Medicare and Medicaid Services (CMS). Summaries of how each part covers OPAT are:

- *Medicare part A* – Covers inpatient hospitalization, home health and skilled nursing facility (SNF) services. Hospitals and SNFs payments are global and as such, individual drugs, supplies, and services provided for infusion of antibiotics are not billed or covered separately. Some designated medical equipment and supplies provided to Medicare patients at home are covered under part A. With some specific exceptions (eg, antiviral medications for patients with AIDS),

infusion supplies, equipment and drugs are not included. Skilled nursing visits to support home antibiotic infusion can be reimbursed if the patient meets homebound criteria and requires other skilled services at home, but antibiotics and supplies are not covered under the part A benefit

- *Medicare part B* – Covers physician services, the procedure of infusion, and antibiotics administered in outpatient infusion suites or office-based infusion operations. Medicare part B will not pay for antibiotics when administered at home, or infused over 24 hours at home via a disposable or durable infusion pump. In a hospital-based outpatient clinic, a procedure code and a code for the drug can be billed and reimbursed. This is not incident to physician services and a physician is not required to be present or supervise the procedure. In a physician office or clinic, outpatient infusion of antibiotics is covered only if performed under physician supervision. The physician must be present, or immediately at hand when the patient is receiving care. Bright line clarifications have made it clear this cannot be in a nearby building or available only by pager. Nurse practitioners, contract MDs, or physician assistants can replace physicians in this supervisory role.[17] To date, telemedicine is not an approved method of supervision of in-office infusion. When covered, the procedure, drug, and some supplies are reimbursed at 80% of the published Medicare allowable fee. The patient is then responsible for the 20% co-payment required. Patients may carry a supplemental (Medi-Gap) insurance policy to cover the 20% co-payment for services covered by Medicare

- *Medicare Part D* – Medicare beneficiaries are eligible for prescription drug coverage if they are enrolled in a part D plan.[18] The Medicare Modernization Act established a standard drug benefit which employs a three-tiered system. Only the cost of the drug is included. As the exact thresholds are calculated on a yearly basis, expect all estimated out-of-pocket expenses to change. Examples using 2013 data:
  - *Tier 1* – Beneficiary must pay a $325 deductible, then a 25% co-pay of drug costs up to $2,970
  - *Tier 2* – Once the tier 1 limit is reached, the beneficiary pays the full cost of the antibiotics up to a total out-of-pocket expense of $4,750 (ie, the “donut hole”)
  - *Tier 3* – Once the beneficiary has reached the total out-of-pocket threshold, the majority of drug costs are covered

Given the cost of a course of IV antibiotics, using the Medicare part D benefits for home IV antibiotics will result in large out-of-pocket expenses for the patient. Some hospitals have an outpatient infusion program. Hospitals can bill a daily procedure code (APC), plus the cost of the drug. The patient is still responsible for deductibles and copays.

Hospital-based infusion centers are billed and paid differently from physician office clinics. Medicare billing for office-based infusions includes office administration codes (Current Procedural Terminology [CPT] codes) for 1st hour of infusion, then additional hours of infusion:

- Antibiotic drug code (HCPCS J Code)
- Infusion procedure code (CPT Code)
- Peripherally inserted central catheter (PICC) line insertion, Mediport access, blood draws, when performed in the office

Attempts to persuade CMS to include home infusion as a Medicare benefit under A, B or D have thus far failed. At this time, the National Home Infusion Association (NHIA) has submitted a white paper to Congress strongly encouraging the enactment

of HR 5435, the Medicare Home Infusion Site of Care Act, which would provide reimbursement and give Medicare beneficiaries the option to receive infusion therapy at home.[19] In addition, a three-year demonstration project was recently launched by CMS which may lead to eventual changes in coverage for OPAT in the patient's home. The study is designed to evaluate the benefits of providing payment for items and services needed for in-home administration of intravenous immune globulin (IVIG) for patients who are not otherwise homebound or receiving home health benefits.[20,21]

Medicaid

Sponsored by both federal and state governments, Medicaid is actually 50 different state-run insurance programs. Prior authorization is generally required for OPAT on a case-by-case basis. As many Medicaid plans transition to managed care via third-party administrators, a physician or hospital-based OPAT site will need to have a provider agreement for OPAT services with each plan. Each provider of OPAT must design programs to meet the state Medicaid or Medicaid third-party administrator requirements for the specific US state where services are administered.

Commercial Insurance

Most private insurance policies have some provision for OPAT, covered either in the patient's home or in an outpatient clinic. However, insurance companies may require the program or physician to have a "preferred provider agreement" in place before authorizing OPAT, especially if it is provided in the patient's home. If the patient has Medicare and a true secondary private insurance policy (not supplemental), the provider of OPAT in the patient's home must bill Medicare first for denial, then bill the secondary insurance for the services provided. Many commercial plans require itemized billing for OPAT, in the office or at home. This may include a list of drugs, supplies, and services rendered. Place of service codes may also be required, such as 11-office or 12-home. Other providers may prefer a per diem payment method for OPAT. This method establishes a set price for each day a patient needs OPAT. The per diem fee usually includes supplies, nursing care, and related overhead with the drug billed separately.

In summary, OPAT is one of the few procedures that lie squarely in the toolbox of the infectious diseases specialist. With attention to federal, state and local legal issues and reimbursement requirements by payer type, compensation for supervising and/or providing this procedure should be forthcoming and straightforward. In addition to IDSA, we have access to additional resources via NHIA, including updates on legal and reimbursement issues in OPAT.

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11 The Infusion Suite/ Office-based Infusion Operations

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This chapter is concerned primarily with the actual physical components and major design elements of an infusion suite, regardless of the setting. Not included here are pharmacy design issues, and regulations, which will be highly individualized based on the size of the practice, the population served, and State Board of Pharmacy regulations governing medication preparation and dispensing. As of November 2, 2015, a substantial revision of the federal regulations developed by the US Pharmacopeia (USP) was published for public comment (until January 31, 2016) before going into effect in the US.[1] The revisions include that sterile medications be administered in accordance with the Centers for Disease Control and Prevention (CDC) Safe Injection Practices.[2]

These regulations are periodically updated and will be enforced by the US Food and Drug Administration (FDA) and Joint Commission for Accreditation of Health Care Organizations, which will target the preparation of dispensed medications, with an exception for those used immediately (defined as use that begins within 1 hour and is completed within 12 hours of noncontaminated preparation). All other sterile preparations, including the puncture of proprietary bag and vial systems (eg, ADD-Vantage® [Hospira], Mini-Bag Plus® [Baxter], and addEASE® [B Braun Medical, Inc]) must meet the requirements outlined. The regulations, proposed revisions, and updates can be accessed on the USP website.

Figure 11.1. Basic components and general design features.

Policy

A printed copy of clinical, administrative, and procedural manuals listing all policies and procedures of the ambulatory infusion suite

Access

Adequate parking, including designated parking for people with disabilities, accessibility ramps and doors

Restrooms

Accessible to patients and persons accompanying them. All restroom fixtures should be in working order. Grab bars and other accommodations should be available as required by law. A call bell should be installed in the patient restroom

Waiting area

Appropriate space, lighting, and seating that is adequate for the number of patients and visitors expected. A fire extinguisher should be available. “No Smoking” signs

THE BASICS

The basic elements of an IV therapy suite are shown in **Figure 11.1** (left). Although the arrangement of these components will depend on the configuration and size of the space available, the major clinical considerations should be safety, efficiency of work flow, patient comfort, and privacy. Needless to say, attention should be given to the needs and comfort of the staff. Some questions that have bearing on spatial organization of any suite include:

- Is there a need for isolation of the patient?
- Should children have special accommodations?
- How should disruptive patients be accommodated?
- Will physicians be using the space for office visits and treatment of patients in addition to infusion therapy?
- Will special procedures, such as peripherally inserted central venous catheter (PICC) line insertion be performed in the room?
- Will there be wound care required with the visit?

A number of factors should be considered for all infusion suites regardless of size. However, since each ambulatory infusion suite (AIS) sees a different patient mix, each AIS may have slightly different supply needs.

TREATMENT ROOMS

The number and kind of treatment rooms within a suite will depend primarily on the size and nature of the patient population. A typical mix of individual rooms might include: (1) a multipurpose room containing a single bed; (2) several small private rooms, each with a single reclining chair for infusions for infusions; and (3) one group treatment room with three or four reclining chairs for infusions.

Amenities such as flat-screen TVs and Wi-Fi access can be offered throughout the treatment rooms to ensure a pleasant infusion experience. Linoleum is preferable to carpet for floor covering because of potential spills during procedures, such as PICC line insertions.

Multipurpose Room With Electrically Controlled Bed

This room may be used for examinations, procedures, infusions, rest and comfort, training more than one caregiver, or for children to have more space to move around and play in during their own or a parent's infusion. Highly emotional or disruptive patients may be treated here. Acoustic privacy and good lighting are critical. Ideally, daylight should be available, with fluorescent light on dimmers, an adjustable procedure lamp, and a wall-mounted reading lamp by the bed. An otoscope and a sphygmomanometer should be mounted on the wall near the bed, along with two additional grounded electrical outlets. This room definitely should have its own sink and storage for procedure supplies.

Private Room With Recliner

A "living room" look is appropriate here with recliners that do not extend when in the reclining position, if the room is particularly small. In suites with more than one private room, physicians should consider setting aside one room for people with physical disabilities, or elderly people. The recliner may be replaced with a hardback chair, which can be moved easily to make room for a wheelchair. This room also can be used for brief patient visits, such as an unplanned peripheral catheter restart.

Group Treatment Room

This room should contain a maximum of four recliners, separated by ceiling-hung cubicle curtains. Most patients who are otherwise healthy can be treated here, and many sicker patients actually prefer to have company during infusions.

NURSES' STATION

This area should be centrally located, with a clear view of the infusion rooms. Although a central island accomplishes this, it lacks acoustic privacy for discussions of patient problems. A better arrangement might be to locate the station at the head of a corridor with the rooms off both sides.

TREATMENT SUPPLY ROOM

Located close to the nurses' station, this room should contain a sink, refrigerator, and a counter for the preparation of equipment and supplies. The area should be large enough for two people to work in at the same time. Ideally, this should be a separate room, inaccessible to unsupervised patients or visitors. It should be designated as "clean" and not be used for storage of any "dirty" items. In some cases, depending on qualified personnel and volume of OPAT infusions, it will make sense to have USP 797 compliant compounding pharmacy capabilities on-site. If this is the case, the treatment supply room will require a variety of additional equipment, such as refrigerators and containment hoods.

STAFF ROOM

This room, which provides a change of atmosphere from the patient care area, can be used for meetings, breaks, and staff education. A secured closet, lockers, or drawers should be available here for storage of staff's personal belongings. Refreshments, food, or coffee may be allowed, but pose a risk in regard to infection control.

BUILDING REGULATIONS

All local building code requirements must be met, including the health department, American with Disabilities Act (ADA), and US Occupational Safety and Health Administration (OSHA). Physicians seeking accreditation by the Joint Commission for Accreditation of Health Care Organizations, the Community Health Accreditation Program (CHAP), or the Accreditation Association for Ambulatory Health Care (AAAHC) should review the relevant organization's physical plant standards for ambulatory care and/or ambulatory infusion centers when designing hallway size, exits, emergency plans, and infection control features (see Chapter 9: OPAT Accreditation).

Finally, in designing an infusion suite, physicians should involve staff members who will be working in the space. Their perspective and ideas will be valuable in developing a facility that is both functional and attractive. Patients are also a good source for suggestions.

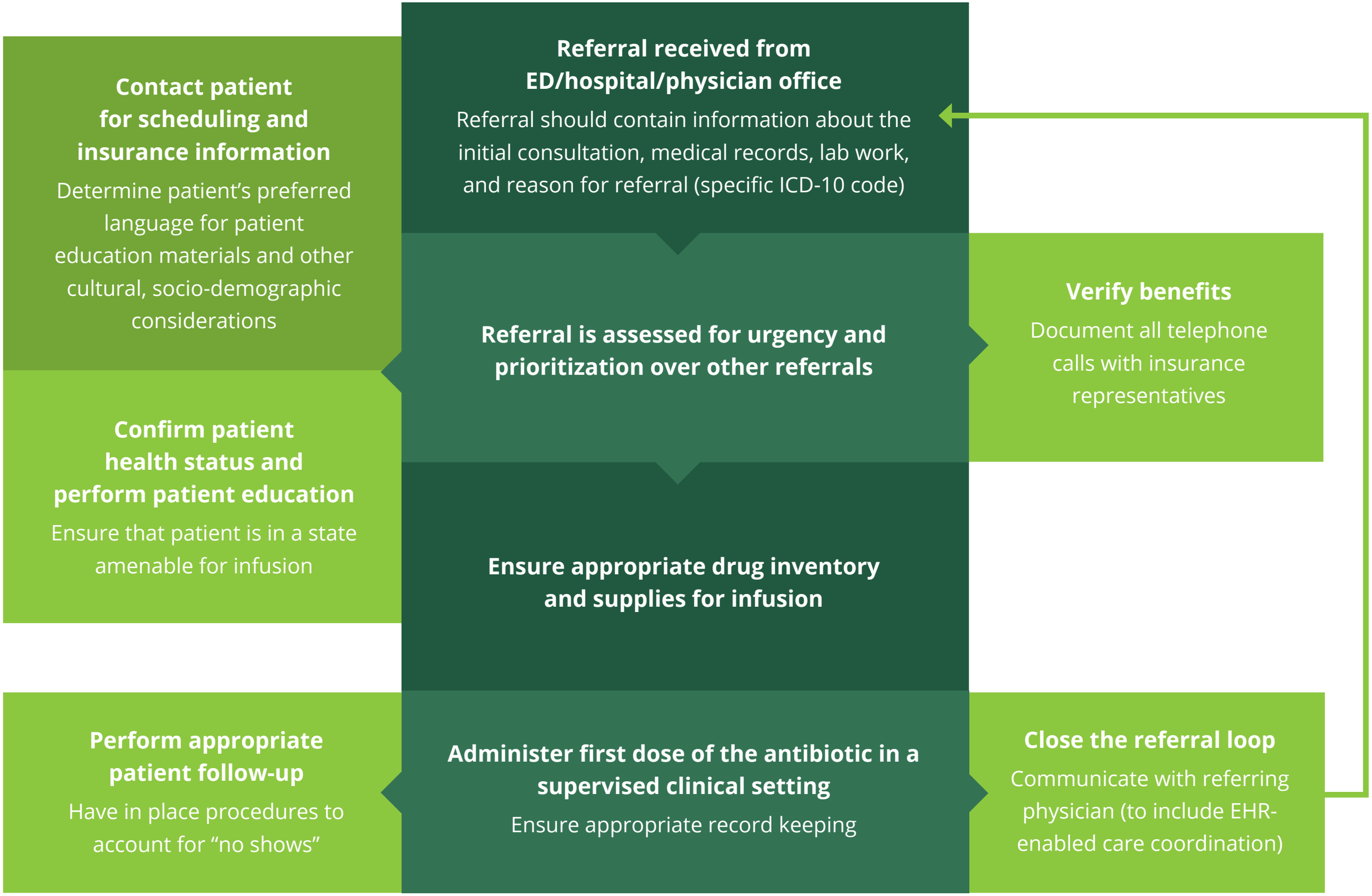
OFFICE-BASED INFUSION OPERATIONS

The infectious diseases specialist that supervises OPAT programs must understand the scope of operations and be comfortable with the associated responsibilities. Operating an infusion suite will require knowledge in staffing, case management, billing, third party reimbursement, health care quality, federal/state regulations related to dispensing drugs, and provider supervision of "incident to" services. The estimated start-up costs for a small, office-based infusion operation begins at approximately $50,000. Start-up costs and ongoing expenses include space rental, staff salaries and benefits, equipment, and drugs. The professional staff involved in infusion operations includes registered nurses, nurse practitioners, or physician assistants, with infusion experience and qualifications, for placement and management of vascular access. A pharmacist is an additional professional staff member that supports the infusion operation.

There is an extensive workflow process that needs to be in place in order to ensure efficient infusion operations and ensure a satisfactory patient experience. This workflow process encompasses the tracking of referrals, patient engagement, education and care coordination, as well as, quality measurement and performance improvement.

Below, a schematic of the basic workflow process is provided and should be tailored as appropriate to address the variety of circumstances across various facilities (Figure 11.2).

Figure 11.2. Work flow schematic for an infusion suite.



ED, emergency department; EHR, electronic health records.

FACILITY-BASED INFUSION OPERATIONS

Infusion done in a facility such as a hospital outpatient department has similar considerations in terms of resources and operations as in office-based infusions. However, the costs and associated overhead expense are quite different. Infectious diseases specialists who are interested in starting up OPAT operations within a facility, should discuss the finance and operational aspects with hospital administrators. It is likely that the facility would offer infusion services beyond antimicrobials, to include oncology, rheumatology, and other specialties. Accommodation for uninterrupted OPAT administration must be considered, as facility-based infusion suites may not be accessible on weekends and holidays.

WORKING WITH HOME HEALTH CARE PROVIDERS

Depending on the particular circumstances of the care plan and the patient's insurance benefit design, coordination with a home health agency may come into play. The delivery of OPAT should be seamless regardless of the model. To the extent possible, it may benefit the infectious diseases specialist and the infusion administrator to develop a solid professional relationship with local home health organizations that have demonstrated a commitment to patient safety and health care quality. The National Home Infusion Association (NHIA) may serve as a useful resource to aid in the assessment of local home health organizations.

The key aspects that relate to OPAT are as follows:

- **Nurse Training** – Home health and office-based nurses should be knowledgeable in OPAT infusions.

- **Interconnectivity** – A system should be in place to connect the home health nurse with your staff in the event he or she encounters a complication related to OPAT administration. Consider the applications of telehealth and telecare, virtual connectivity that allows communication through the use of video and/or the internet between home health nurse and patient.

- **Billing and Coding** – A keen awareness of the applicable codes that apply to home health care is essential to enabling an efficient partnership with home health providers. On-site personnel with people skills and knowledge in OPAT billing and coding should be strongly considered, when possible. This is a critical, but yet often neglected aspect of treatment, and requires expertise for patient satisfaction/ understanding and reimbursement.

ECONOMIC VIABILITY OF INFUSION OPERATIONS

Regardless of whether the infusion operation is office-based or situated in a hospital facility, the operation needs to perform in a manner that ensures the economic viability and cost-effective health care delivery. The first financial consideration when planning an infusion operation is to determine the initial estimated volume of patients. This will then dictate the associated start-up costs with respect to staffing, "hardware" (eg, chairs and refrigerators), drug inventory, and supply expenses. Additionally, a basic understanding of revenue cycle/cash flow management is necessary and should reflect the typical delay in payments from payers (ie, 60+ days from filing the claim), as well as the inevitable exception handling of denials or underpayments. Foundational to the financial viability of an infusion operation is appropriate, accurate coding of services provided. Given the considerable costs associated with the antimicrobials, one must recognize the financial risk involved with care plans that involve patient self-administration in the home. In some cases, should the drugs become compromised, the third-party payer may not provide reimbursement for the drug loss. Infectious diseases specialists and infusion administrators should discuss these potential risks in advance and have protocols in place to address them. One should understand how prior certifications and prior authorizations work as utilization management tools for payers.

- A *preauthorization* requirement means that the insurance company will not pay for a service unless the provider gets permission. Sometimes this permission is to ensure that a patient has benefit dollars remaining, and at other times it is to ensure that a particular kind of service is eligible for payment under the patient's contract. Authorization can be granted retrospectively after receiving "emergency care".

- A *precertification* requirement means that a payer must review the medical necessity of a proposed service and provide a certification number before a claim will be paid, which is particularly common with infusions.

Preauthorization and/or predetermination are not a guarantee of payment, but without either, a denial of coverage is far more likely for a portion or even the entire claim.

A policy needs to be developed for the purchase of drugs. One possibility is the "assignment of benefits" which means that the drug (eg, an antibiotic) is preauthorized and is covered under the patient's prescription drug plan. A second method is "buy and bill," which requires the center to sign an agreement with a wholesaler, purchase the product, and the billing department will then bill the insurance company of the patient. Unfortunately, sometimes the reimbursement is below the infusion center's cost, causing an appeal process and delay in payment.

For infectious diseases specialists interested in establishing an in-office infusion operation as part of their practice, the start-up financial costs may be prohibitive, and therefore alternative operations may be needed. There are in-office infusion management companies that offer a full portfolio of services under contractual terms, and that operate out of dedicated space in physician offices. For some, engaging these types of companies may be an effective first-step to establishing OPAT services.

BILLING AND CODING FOR INFUSIONS

A billing and coding policy needs to be developed to ensure accuracy. Submission of accurate claims is essential to ensure appropriate reimbursement. Insurance companies usually require identification of the antibiotic to be used, frequency of dosing, duration of therapy, and diagnostic ICD-10 code for approval. Coverage is determined by the patient's individual health plan. The Current Procedural Terminology (CPT® American Medical Association) codes below are for reference purposes only (Table 11.1).

Table 11.1. Current Procedural Terminology

96360	96361	96365	96366	9636
Intravenous infusion, hydration; initial, 31 minutes to 1 hour	Intravenous infusion, hydration; each additional hour (list separately in addition to code for primary procedure)	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (list separately in addition to code for primary procedure)	Intravenous i for therapy, pr or diagnosis substance or additional se infusion of a n substance, up (list separately i to code for p procedu

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STAFFING TEAM

Job roles and responsibilities need to be maintained in writing for each position in the form of a job description; regardless of individual role, a team-based approach to care should be emphasized. The focus of the team is to work collaboratively to provide and enhance the patient infusion experience. Job descriptions are used for a variety of reasons including determining salary levels, conducting performance reviews, establishing titles and pay grades, and maintaining compliance with the Fair Labor Standards Act (FLSA) and the ADA. Regular meetings with individuals involved with patient care are essential.

Other clinical policies that will need to be established for operations:

- Frequency of physicians' and nurses' clinical assessments of the patient
- On-call policies, especially to sustain 7-day-a-week operations
- Frequency of clinical status reports to physicians, which should be at least weekly
- Delivery of laboratory results to physicians within 24 hours
- Prompt reporting of patient problems and critical laboratory values
- Program quality and outcomes information
- Antimicrobial preparation, storage, and dispensing
- Vascular access systems used and site care protocols
- Monitoring of guidelines for physician visits, nurse evaluations, and laboratory studies
- Disposal of waste and needles
- Health care worker safety
- Provision of patient education
- Finally, an ongoing system to monitor quality indicators, including outcomes and complications of therapy, is of utmost importance

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12

OPAT & Health Care Reform

Akshay B. Shah, MD, Nabin Shrestha, MD, and Mark J. Dougherty, MD

The Affordable Care Act (ACA) was signed in 2010 to slow the growth of healthcare spending, while improving the quality of care.[1] Two fundamental programs established by the ACA include the Readmission Reduction Program,[2] which applies increasingly large financial penalties for 30-day readmissions, and Value Based Purchasing (VBP),[3] which provides financial incentives to hospitals for strong performance in processes of care, patient satisfaction, clinical outcomes and efficiency. While these programs are Centers for Medicare and Medicaid Services (CMS) initiatives, private payers have followed suit, with their own pay-for-performance, value-based payment programs and denials of payment for readmissions. Additional pressure on the health care payment landscape has been realized through the proliferation of accountable care organizations (ACOs) and various bundled payment programs which provide one lump payment for an episode of care. Such episodes may span several months of time, multiple providers, including physicians, hospitals and post-acute services, and all of the sites of care, inpatient and outpatient. As payment models change from fee-for-service to fee-for-value, hospitals and health care providers will have to swim or sink in these changing health care waters, and potentially add new care delivery models.[4] OPAT has the ability to add value and/or innovation to the infectious diseases physician practice in the domains of patient care, infection control, and antibiotic stewardship. Many aspects of health care reform revolve around the concept of "value," loosely defined as more quality and less cost (Figure 12.1).[5] More quality will include improvements in outcome measures and patient satisfaction. Lower cost is tied into the many shared savings incentive programs.

The timetable of the implementation of the ACA is from 2010 to 2020, and sweeping reforms are well underway. There remain many uncertainties and obstacles. Numerous pilots and test programs, exploring new models of healthcare delivery are currently ongoing (Figure 12.2). In this challenging paradigm shift, let us look at how OPAT can bring some opportunities for infectious diseases physicians, both in terms of payment reform and care delivery reform.

PAYMENT REFORM

The cost effectiveness of OPAT programs has been fairly well established in the UK.[6] American payment reform features (pay-for-value) in which OPAT can have a profound impact include:

- Pay-for-performance
- Bundled payments (episodes of care)
- Integrated care delivery (shared savings)

Pay-for-performance

Hospitals became subject to the CMS readmission penalties in 2012; these are currently set at 3% of CMS payments, estimated to amount to 420 million dollars in 2016.[2] Infectious diseases-led OPAT programs have the potential to reduce 30-day readmissions by focusing on the transition of care. A prediction model for risk of 30-day readmission among OPAT patients has been proposed.[7] The availability of laboratory result monitoring, for instance, has been correlated with reduced readmissions for OPAT patients.[8] Early reports of the benefit of OPAT for readmission reduction are beginning to appear, largely in the form of abstracts.[9-11] Prospective data on the impact of a robust OPAT program on readmission risk are needed, but it is likely that oversight of therapeutic drug monitoring, toxicity and efficacy are of significant benefit.

The Value-Based Purchasing (VBP) Program adjusts what CMS pays hospitals based on the quality of care they provide to patients, withholding an increasing percentage of payments, which can be earned back by meeting a complex system of measures. The penalty for Fiscal Year 2016 is 1.75% of CMS payments.[3]

Current metrics include:

- 10% – Clinical process of care
- 25% – Patient experience of care (Hospital Consumer Assessment of Healthcare Providers and Systems survey)
- 40% – Outcome (hospital mortality measures for acute myocardial infarction, heart failure, pneumonia; central line-associated bloodstream infection rate; catheter associated urinary tract infection rate; surgical site infection strata, and a composite of patient safety indicators
- 25% – Efficiency (Medicare Spending per Beneficiary measure)

While much of the VBP initiative is inpatient-focused, an infectious diseases physician-led OPAT program can have a substantial impact on efficiency (overall cost) by enabling earlier discharge to a less expensive site of care. Additionally, earlier discharge can reduce the incidence of hospital-acquired conditions (HAC) and improve patient satisfaction.[12]

Bundled Payment

The CMS initiative, Bundled Payments for Care Improvement (BPCI),[13] links payments for the multiple services beneficiaries receive during an episode of care. Developed by the CMS Innovation Center, this program tests the concept of endowing the health care system with responsibility for controlling cost of care by reimbursing a lump sum for a given episode of care. Major cost drivers within BPCI are the inpatient stay, hospital readmissions, and the post-acute setting; with skilled nursing facilities (SNFs) and inpatient rehabilitation facilities (IRFs) making up most of the cost. Home or infusion center models of OPAT have the potential to reduce cost of care by shortening inpatient length of stay, reducing readmissions by excellent care oversight, and avoiding costly post-acute care settings (SNFs or IRFs). Many private payers have launched similar bundle payment test programs of a wide variety. It remains to be seen if this strategy will result in real cost containment, preserving quality and safety. The Acute Infections Management Service (AIMS) OPAT model at the University of California, Davis Medical Center, Sacramento, demonstrates how OPAT can save cost in a single center, observational study, for the diagnosis of cellulitis.[14] Application of a similar concept to the many infectious diagnoses for which OPAT can be used (eg, osteomyelitis, wound infection, septic arthritis, pyelonephritis, or pneumonia), offers the potential of substantial cost savings.[15]

Shared Savings (ACOs)

The CMS Shared Savings Program rewards ACOs that lower growth in health care costs while meeting performance standards on quality of care.[16] In this model, Medicare allows physicians to receive a percentage of the savings if they keep costs below a certain level, indeed a powerful economic incentive. The shared savings bonus can be up to 50% of the traditional fee rate.

An infectious diseases physician-supervised OPAT bundled payment or gain sharing model has yet to be devised. However, the model seems warranted as a tool to reduce hospitalization cost, facilitate timely discharge and transitions of care, decrease readmissions, and improve VBP scores, while improving outcome measures and patient satisfaction.[17]

The VBP system of the future will compensate physicians for patient outcomes, improvements in patient health status, and a favorable patient experience. The Institute for Healthcare Improvement has defined the Triple Aim for Populations, as follows:[18]

- Improving the health of the population
- Enhancing the patient experience and outcomes
- Lowering overall costs

OPAT certainly has the potential to promote these goals. Hopefully OPAT programs will continue to collect and publish data to support this claim.

DELIVERY REFORM

Integrated health care delivery models all seek to coordinate care, avoid duplications, and combine efforts to save costs while improving quality. The many recent mergers in the health care sector underscore movement towards health care integration.

Accountable Care Organizations (ACOs) remain a work in progress,[19] and the role of specialists in ACOs is still evolving. There are a few examples of specialty ACOs who contract treatment out to local specialty practices. Some groups are going a step further, by signing contracts with payers to form their own disease-specific ACOs. Infectious diseases physicians with OPAT services can certainly be of significant value in this model. While likely to face many obstacles, the specialty or disease-specific ACO is slowly gaining in popularity with providers and payers.

Hospitalizations incur substantial costs to the health care system. Technological advances have made it possible to deliver IV antibiotics without hospitalizing patients. It is now the norm to discharge patients from a short hospitalization after stabilization, but while still requiring IV antibiotic therapy. Some infectious diseases physician groups have been able to develop hospital avoidance programs, evaluating patients promptly and starting IV antibiotics in the outpatient setting (if needed). With close monitoring, hospitalization can sometimes be avoided altogether for selected patients.[20]

Creating a New Paradigm

The major recent health care reforms outlined above offer infectious diseases physicians an opportunity to create a new paradigm that produces value and lowers costs for patients, hospitals, insurers, and society. OPAT is a powerful tool to facilitate the care of outpatients who are even more ill than traditional OPAT patients. One new paradigm in acute outpatient care, moves patients, who would otherwise be admitted or remain in the hospital, to a daily visit in the infectious diseases clinic, with adjustments in therapy in lieu of hospitalization. Such an arrangement can deliver inpatient quality care out of the hospital, at a fraction of the cost of hospitalization. A further refinement of this model is demonstrated in the Hospital at Home program,[21] which offers daily home nursing and physician visits to patients who would otherwise be hospitalized. This model has been applied to a variety of conditions, among them community-acquired pneumonia and cellulitis, for which OPAT has been a key element. Formal programs for transition of care and utilization management can be negotiated with hospitals, insurers, and ACOs. These programs entail additional overhead costs for the infectious diseases practitioner because patients will likely require weekend and holiday outpatient visits for care equivalent to that available in the hospital. This can be a winning proposition for patients, hospitals, and insurers, but infectious diseases care providers will need to be appropriately compensated. CMS is working on establishing new guidelines for

shared savings between hospitals and providers, which could enable infectious diseases physicians to realize financial benefits from these types of programs.

Recently the Department of Health and Human Services projected that 85% of Medicare payments will be tied to value and quality by the end of 2016.[22] As we move from fee-for-service to fee-for-value, an infectious diseases physician-led OPAT program has the potential to contribute considerably to readmission reductions, value based purchasing goals, and integrated care delivery.

FIGURES AND TABLES

Figure 12.1. The core principle of healthcare reform-value

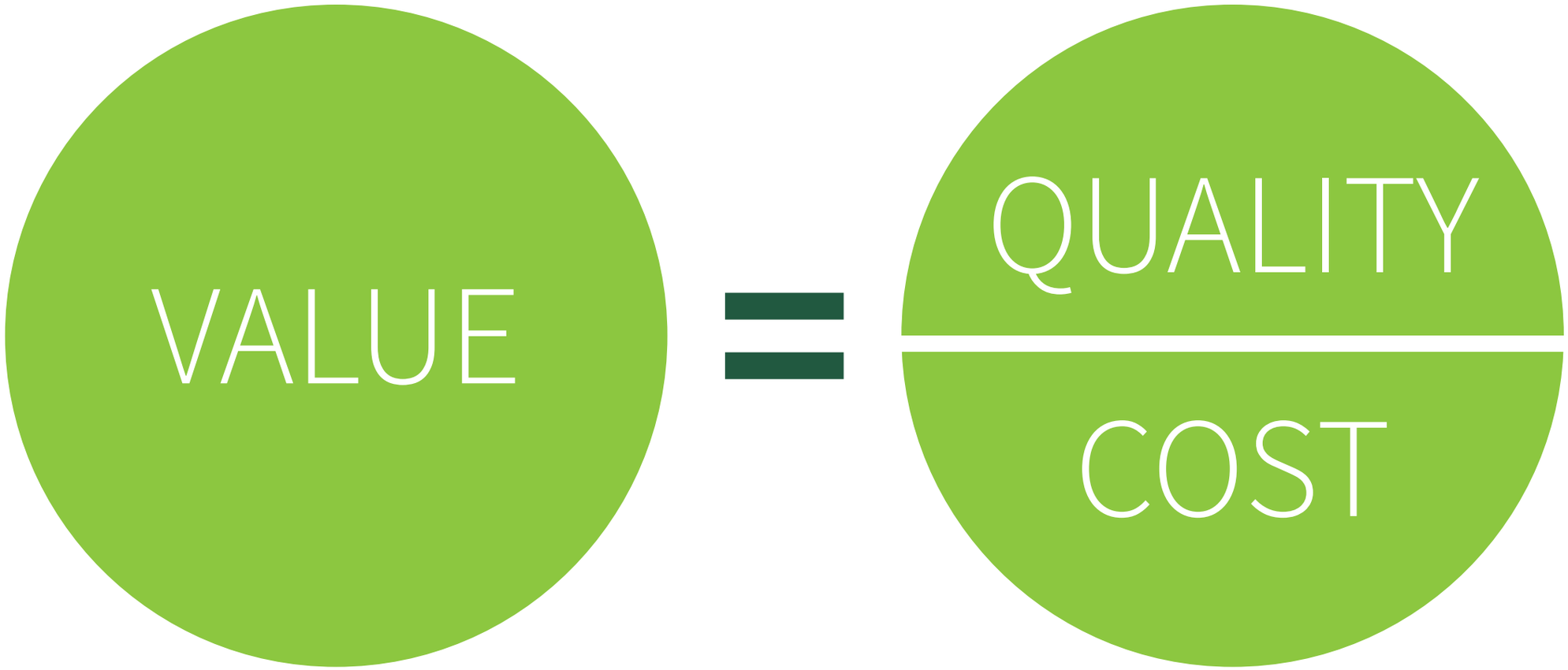
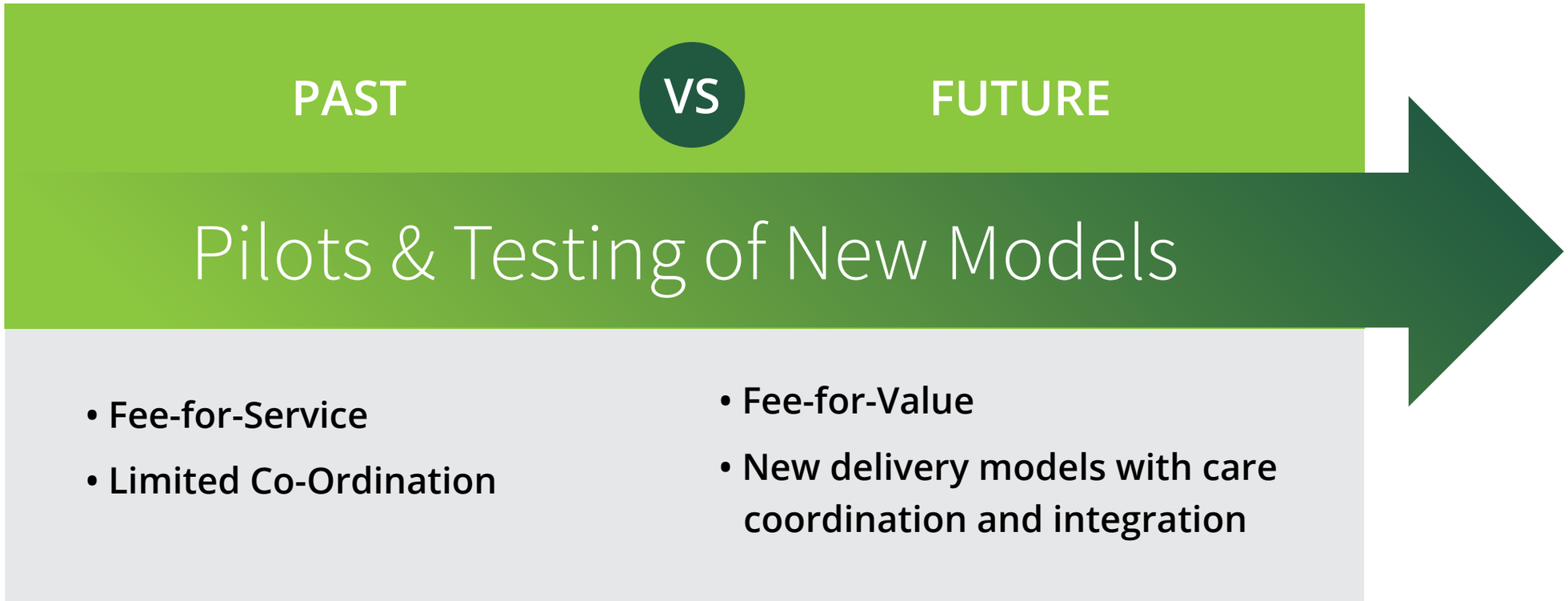


Figure 12.2. The new paradigm (and OPAT)



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