Clinical Infectious Diseases

IDSA GUIDELINE

2018 IDSA Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy[a]

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A panel of experts was convened by the Infectious Diseases Society of America (IDSA) to update the 2004 clinical practice guideline on outpatient parenteral antimicrobial therapy (OPAT) [1]. This guideline is intended to provide insight for healthcare professionals who prescribe and oversee the provision of OPAT. It considers various patient features, infusion catheter issues, monitoring questions, and antimicrobial stewardship concerns. It does not offer recommendations on the treatment of specific infections. The reader is referred to disease- or organism-specific guidelines for such support.

Keywords. OPAT; parenteral antimicrobial therapy; treatment guideline; IV antimicrobial.

EXECUTIVE SUMMARY

Outpatient parenteral antimicrobial therapy (OPAT) is defined as the administration of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization. Recommendations made in the updated guideline for the prescription and management of OPAT are summarized below. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the strength of the recommendation and quality of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Figure 1) [2–5]. This revision focuses on systematically reviewing the literature to answer specific OPAT practice questions using published evidence. Readers are referred to the 2016 IDSA OPAT eHandbook for a more in-depth discussion of background and hands-on advice on the practice of OPAT [6]. Best practice tables that address pharmacokinetic features, administration options, and potential adverse effects of selected antimicrobials are included in this guideline. The guideline is not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found online in the full text of the guideline.

PATIENT CONSIDERATIONS

I. Should patients (or their caregivers) be allowed to self-administer OPAT?

Recommendation

1. Patients (or their caregivers) should be allowed to self-administer OPAT (strong recommendation, low-quality evidence).

II. Should patients (or their caregivers) be allowed to self-administer OPAT at home without visiting nurse support?

Recommendation

2. Patients (or their caregivers) may be allowed to self-administer OPAT at home without visiting nurse support as long

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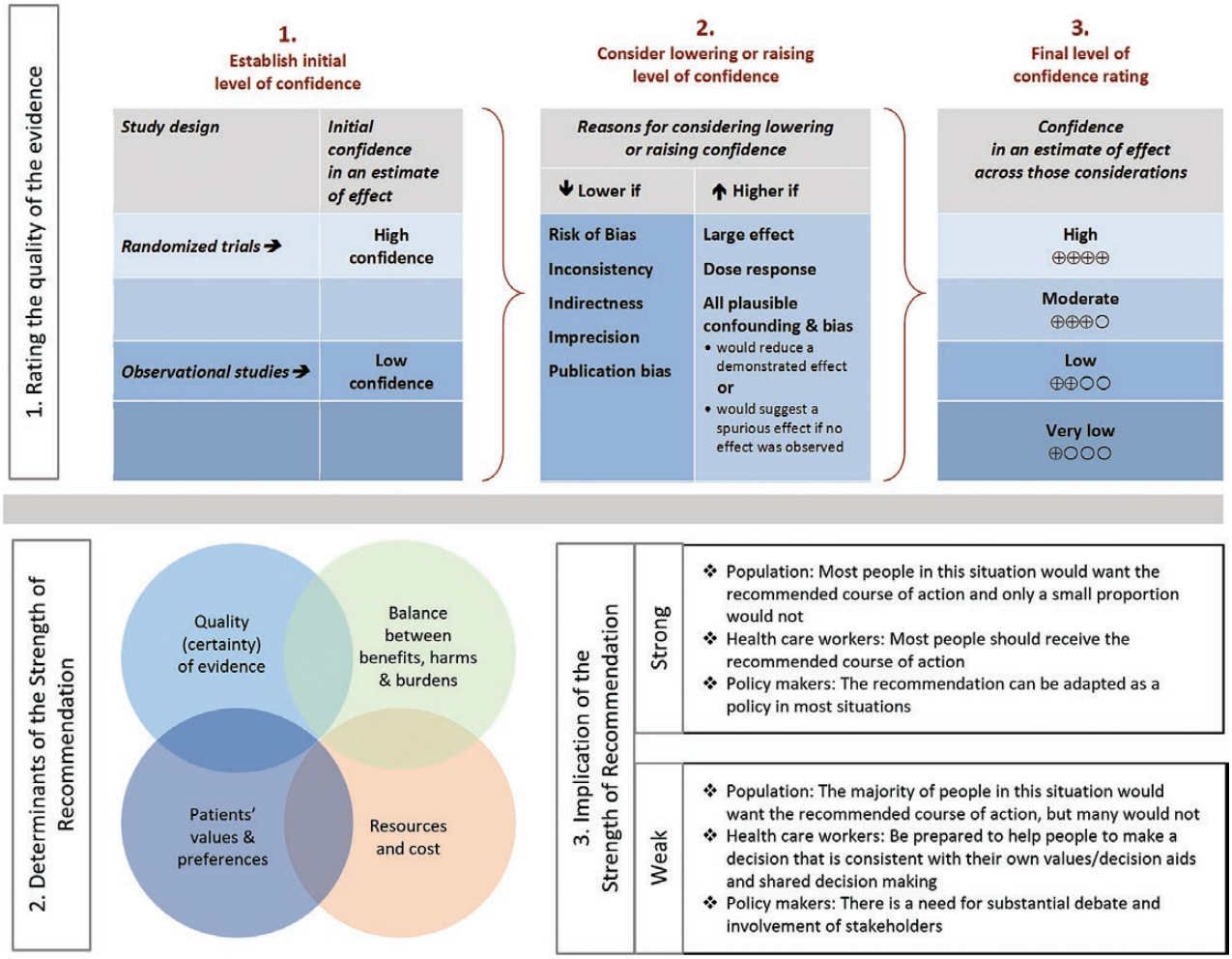

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Unrestricted use of the figure granted by the USA GRADE Network.

as there is a system in place for effective monitoring for vascular access complications and antimicrobial adverse events (weak recommendation, low-quality evidence).

III. Can persons who inject drugs (PWID) be treated with OPAT at home?

Recommendation

3. No recommendation can be made about whether PWID may be treated with OPAT at home (no recommendation, low-quality evidence). Decisions should be made on a case-by-case basis.

IV. Should elderly patients be allowed to be treated with OPAT at home?

Recommendation

4. Elderly patients should be allowed to be treated with OPAT at home (strong recommendation, low-quality evidence). This recommendation assumes that potential challenges to OPAT in the elderly, such as cognition, mobility, and dexterity, have been duly considered and that the patient or caregiver is able to communicate with the treatment team if necessary.

V. Should infants aged <1 month be treated with OPAT at home?

Recommendation

5. No recommendation can be made regarding whether infants aged <1 month may be treated with OPAT at home (no recommendation, very low-quality evidence). Decisions should be made on a case-by-case basis.

ANTIMICROBIAL UTILIZATION

VI. Is it safe and appropriate to administer the first OPAT dose of a new antimicrobial at home?

Recommendation

6. In patients with no prior history of allergy to antimicrobials in the same class, the first dose of a new parenteral antimicrobial may be administered at home under the supervision of healthcare

personnel who are qualified and equipped to respond to anaphylactic reactions (weak recommendation, very low-quality evidence).

VASCULAR ACCESS DEVICES

VII. In patients needing short courses of OPAT, is it acceptable to use a midline catheter (MC) instead of a central venous catheter?

Recommendation

7. In adult patients needing short courses of OPAT (less than 14 days), a MC may be used rather than a central venous catheter (weak recommendation, very low-quality evidence). No recommendations can be made regarding the use of MCs in pediatric patients.

VIII. Should vesicant antimicrobials (medications associated with tissue damage caused by extravasation) be administered via central catheters vs noncentral catheters only?

Recommendation

8. Mandatory use of a central catheter over a noncentral catheter for OPAT with vancomycin is not necessary (weak recommendation, very low-quality evidence). No recommendation can be made for choice of vascular catheter for OPAT with other vesicant antimicrobials such as nafcillin and acyclovir (no recommendation, very low-quality evidence).

IX. Should patients with chronic kidney disease (CKD) requiring OPAT have a tunneled central venous catheter (t-CVC) for vascular access rather than a peripherally inserted central catheter (PICC)?

Recommendation

9. For patients with advanced CKD requiring OPAT, a t-CVC is recommended rather than a PICC (strong recommendation, low-quality evidence).

X. Should patients requiring frequent OPAT courses have a long-term central catheter (LTCC) inserted with the intention of leaving it in place between courses?

Recommendation

10. No recommendation can be made about whether patients who require frequent courses of OPAT should have a LTCC left in place between courses (no recommendation, no evidence).

XI. Should the vascular access device be removed if a patient develops symptomatic catheter-associated venous thromboembolism (CA-VTE) while on OPAT?

Recommendation

11. It is not necessary to remove a vascular access device if CA-VTE develops during OPAT, as long as the catheter remains well positioned and arm pain and swelling decrease with anticoagulation (weak recommendation, very low-quality evidence).

XII. Should patients with prior CA-VTE be treated with prophylactic anticoagulation while on OPAT?

Recommendation

12. No recommendation can be made regarding the need to treat patients with a history of prior CA-VTE with prophylactic oral anticoagulation while on OPAT (no recommendation, no evidence).

XIII. Should children receive OPAT through a PICC or a LTCC?

Recommendation

13. For most children requiring OPAT, a PICC should be placed rather than a LTCC (strong recommendation, very low-quality evidence).

MONITORING

XIV. Should patients receiving OPAT have laboratory test monitoring while on therapy? If so, which tests should be done and how often?

Recommendation

14. Serial laboratory testing should be monitored in patients receiving OPAT (strong recommendation, high-quality evidence). Data are insufficient to make evidence-based recommendations about specific tests and specific frequencies of monitoring for individual antimicrobials used in OPAT.

XV. For patients receiving vancomycin as part of OPAT, should vancomycin serum levels be measured regularly throughout the course of treatment?

Recommendation

15. Vancomycin blood levels should be measured regularly throughout the course of OPAT treatment (strong recommendation, very low-quality evidence). The optimal frequency of measurement is undefined, but the general practice in the setting of stable renal function is once weekly.

XVI. How frequently should patients on OPAT have scheduled physician office visits for monitoring of treatment?

Recommendation

16. No generalized recommendation on frequency of outpatient follow-up can be made for patients treated with OPAT (no recommendation, no evidence). The treating physician should dictate the frequency of office visits, giving consideration to patient characteristics, the nature of the infection, the patient's tolerance of and response to therapy, and individual patient social factors.

ANTIMICROBIAL STEWARDSHIP

XVII. Should all patients have infectious diseases (ID) expert review prior to initiation of OPAT?

Recommendation

17. All patients should have ID expert review prior to initiation of OPAT (strong recommendation, very low-quality evidence).

INTRODUCTION AND BACKGROUND

The first description of successful administration of OPAT was published in 1974, where the safety and efficacy of its use to treat chronic bronchopulmonary infections in children with cystic fibrosis was reported [7]. Since then, numerous studies have detailed the benefits of using OPAT in various populations and settings, including private practices, traditional

academic programs, and Veteran's Affairs medical centers [8–13]. Potential benefits to the healthcare system include shorter or avoided hospital stays [14, 15], prevention of hospital-associated conditions [16], and significant cost savings [8, 16–23]. Advantages of OPAT to patients include the ability to return to work or school faster, care for children or dependents, and, generally, resume activities of daily living with minimal interruption in their lives [24, 25]. An in-depth discussion of the following OPAT considerations can be found in the 2016 IDSA OPAT eHandbook [6].

Models of Care Delivery

Three basic models of outpatient parenteral antimicrobial therapy (OPAT) delivery exist, each with inherent advantages and drawbacks: home based, infusion center based, and skilled nursing facility (SNF) based. The various features of these models are outlined in Table 1. A 2006 Emerging Infections Network (EIN) survey of infectious diseases (ID) physicians in North America noted that 89% of respondents reported their patients receiving OPAT at home, with the remaining 11% distributed among hospitals, infusion clinics, offices, and long-term care facilities [26]. A follow-up EIN survey in 2014 confirmed the ongoing majority of OPAT occurring in the home [27].

In the home-based models of OPAT, all medications are administered in the home by the patient, patient's family member, or a home health nurse. The most common application of OPAT at home incorporates oversight by home infusion nursing, which provides initial home training and periodic home visits, generally weekly but frequently more often. Home-based infusion without home nursing offers another model of self-administered OPAT (S-OPAT). Here, a physician's office provides training and supervision, either in private practice or in a clinic setting. Typically, patients make weekly visits to the office to collect supplies and undergo assessment and catheter dressing changes. Critical to the success of home-based OPAT is the presence of a competent and adherent patient and/or caregiver. Minimal features required for safe home infusion include adequate refrigeration and storage and the presence of at least 1 adult who can reliably learn and perform sterile infusion technique and communicate with the treatment team. A modified version of the home OPAT model is the Hospital at Home, commonly used in Australia and some European countries and in some US Veteran's Affairs programs. Here, antibiotics are infused in the home, but a visiting nurse rather than the patient or caregiver performs each administration.

The infusion center model delivers OPAT in physicians' offices or free-standing infusion centers. Healthcare workers administer medications. This model works well for patients who are physically incapable or unwilling to infuse themselves and for Medicare patients (who lack a home infusion insurance benefit). Since intravenous (IV) antimicrobials administered in outpatient clinics are a covered benefit of Medicare part B, the infusion center model tends to minimize a patient's out-of-pocket expense. This model is resource intensive, requiring reliable transportation, availability of a skilled nurse to infuse antimicrobial agents, and all the accompanying office resources but offers additional oversight with daily in-person visits.

Another model of OPAT administration occurs in the SNF. Patients with additional nursing needs or no home infusion insurance benefits are typically admitted to a SNF, where on-site nurses perform all infusion functions and other activities such as physical therapy or wound care. Since a SNF is a healthcare facility, patients are more likely to encounter resistant organisms, including *Clostridium difficile*. Overall, this option is significantly more expensive to the healthcare system compared to any of the other OPAT models [17] but may minimize the patient's out-of-pocket expense.

In addition, an unknown proportion of OPAT occurs in dialysis units, where advantage can be taken of preexisting vascular access and impaired renal function allows less-frequent dosing.

When OPAT programs were first introduced, great emphasis was placed on appropriate patient selection. Currently in the United States, patients rarely remain hospitalized solely to complete a course of parenteral antimicrobial therapy. Except for some persons who inject drugs (PWID), most patients are eligible for some form of OPAT. The current focus is on identifying the appropriate setting for OPAT, that is, whether patients will receive their antimicrobials at home, in an infusion center, or in a SNF. The exact delivery model chosen for an individual patient is typically determined based on a variety of elements, including payer factors (Medicare covers virtually no home infusion care), available resources (competent home nursing is not always accessible; hospital-based infusion suites may not be open on weekends), as well as patient preference, competencies, and supports. Despite pressure to control inpatient costs, financial concerns related to the setting in which IV antimicrobials are delivered should not take precedence over patient well-being and safety. For some patients, treatment in hospital may be safer than OPAT.

General Considerations in the Choice and Administration of Antimicrobials in OPAT

Tables 2 and 3 outline selected features of a variety of antimicrobials used for OPAT. Advances in infusion device technology have made it possible to administer medications in the outpatient setting that would previously not have been practical. Given appropriate resources, almost any antimicrobial can now be administered as part of OPAT. The choice of antimicrobial now depends more on the OPAT model than on the pharmacokinetic properties of the drug. For instance, for OPAT given in infusion centers, it is impractical to use medications that require more frequent administration than once daily. Drug

Table 1. Models of Care

Model	Infusion Location	Who Performs Administration	Patient Training Location	Nursing Location	Comments	Advantages	Disadvantages
Home	Home	Self/Caregiver	Home	Home[a]	*Home Infusion:* Weekly home nursing visits for supplies, line care, labs[b]	Patient convenience; regular skilled clinical assessments; opportunity for home inspection; availability of a registered nurse on 24-hour basis	Requires patient/caregiver competence and compliance; requires reliable home infusion nursing; increased cost to patient in the absence of home infusion insurance benefit; may entail substantial co- pays
	Home	Self/Caregiver	Office	Office	*Teach and Train:* Weekly office visits for supplies, line care, labs, nursing	Patient convenience; regular skilled clinical assessments	Requires patient/caregiver competence and compliance
	Home	HCW	No training	Home	*Hospital at Home:* Twice-daily home nursing visits and once-daily home physician visits	Cost savings for patient who would otherwise be hospitalized; potential for reduced hospital-acquired conditions and increased patient satisfaction	Not reimbursed by traditional fee-for-service payors; limited uptake in United States, but may be expanding
Infusion center	Office based	HCW	None	ID office	*In-Office Infusion:* Daily visits with nursing staff	High degree of clinical oversight; usually covered by Medicare; minimizes out-of-pocket costs to patient; potential for weekly office visits with ID physician	Patient must be able to travel daily; requires extensive infrastructure and weekend office staffing; limited to once-daily dosing of antimicrobials
	Nonoffice based[c]	HCW	None	Hospital based	*Nonoffice Infusion:* Daily visits with nursing staff	High degree of clinical oversight; usually covered by Medicare; minimizes out-of-pocket costs to patient	Patient must be able to travel daily; requires extensive infrastructure and weekend office staffing; limited to once-daily dosing of antimicrobials
SNF	SNF	HCW	None	SNF	Nursing on site	Usually covered by payers/ Medicare; other skilled nursing needs (eg, physical therapy, wound care) can be met; may be less labor intensive for supervising physicians when treating patients with multiple comorbid conditions; minimizes out-of-pocket costs to patient	Variable levels of clinical oversight; patients may dislike staying in SNF; may exhaust patient's SNF benefits; most expensive for overall healthcare system

Abbreviations: HCW, home care worker; ID, infectious diseases; SNF, skilled nursing facility.

[a]Some training may occur in hospital prior to discharge.

[b]More frequent nursing visits may be possible.

[c]May be hospital based, free standing, or emergency room.

Table 2. Features of Selected Antibacterials Used in Outpatient Parenteral Antibiotic Therapy

Antiinfective	Oral Bioavailability, %[a]	Doses per day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly)			Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
					CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil			
Antibacterials										
Amikacin	NA	1–3	30–60 min depending on dose	Grav, Elas	1	2	…	Nephrotoxicity; ototoxicity		See aminoglycoside monitoring[f]
Ampicillin	50	4–6	3–5 min push or 10–15 min infusion	Grav, EID, IVP	1	1	1	Hypersensitivity including anaphylaxis		Stable once reconstituted for only 3 days; see stability footnote[g]
Ampicillin-sulbactam	NA	3–4	10–15 min push or 15–30 min infusion	Grav, EID, Elas, IVP	1	1	1	Hypersensitivity including anaphylaxis		Stable once reconstituted for only 3 days; see stability footnote[g]
Azithromycin	28–52	1	60 min	Grav	1	…	…		Known	Consider change to po
Aztreonam	NA	2–4	3–5 min push or 20–60 min infusion	Grav, EID, Elas, IVP	1	1	1			Rare cross-allergenicity with other beta-lactams
Cefazolin	NA	3–4	3–5 min push or 30–60 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		Dialysis-only dosing possible
Cefepime	NA	2–3	5 min push or 30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		Dialysis-only dosing possible
Cefoxitin	NA	3–4	3–5 min push or 20–30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis		
Ceftaroline	NA	2–3	5 min push or 5–60 min	Grav, IVP	1	1	…	Hypersensitivity including anaphylaxis		
Ceftazidime	NA	3	3–5 min push or 15–30 min infusion	Grav, Elas, IVP	1	1	…	Hypersensitivity including anaphylaxis	NA	Dialysis-only dosing possible
Ceftazidime-avibactam	NA	3	120 min	Grav, EID	1	1	…	Hypersensitivity including anaphylaxis		…
Ceftolozane-tazobactam	NA	3	60 min	Grav, EID	1	1	…	Hypersensitivity including anaphylaxis		…
Ceftriaxone	NA	1–2	1–4 min push or 30 min infusion	Grav, Elas, IVP	1	1	1	Hypersensitivity including anaphylaxis		See monitoring footnote[d]
Ciprofloxacin	50–85	2–3	60 min	Grav, Elas	…	…	…	Tendonitis/tendon rupture; peripheral neuropathy	Known	Consider change to po; see monitoring footnote[d]
Clindamycin	90	3–4	10–60 min (not to exceed 30 mg/min)	Grav, Elas	1	1	1			Consider change to po; see monitoring footnote[f]
Colistin	NA	2–4	3–5 min IVP; 30 min for infusion	Grav, IVP	1	2	…	Nephro- and neurotoxicity		Inhaled colistin may be an option for respiratory tract infections
Daptomycin	NA	1	2 min push or 30 min infusion	Grav, Elas, IVP	1	1	…	Myopathy; rhabdomyolysis		Baseline and weekly CK, discontinue if symptomatic and CK >1000 U/L (~5× ULN) or asymptomatic and CK >2000 U/L (~10× ULN); dialysis-only dosing possible
Dalbavancin	NA	Once per week	30 min	Grav	…	…	…	Hypersensitivity including anaphylaxis		Red man syndrome more likely if infusion <30 min; monitoring requirements unknown for treatment duration greater than 2 weeks

Table 2. Continued

Antiinfective	Oral Bioavailability, %[a]	Doses per day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly)			Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
					CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil			
Ertapenem	NA	1	30 min	Grav, Elas	1	1	1	Hypersensitivity including anaphylaxis	NA	See stability footnote[g]
Gentamicin	NA	1–3	30–120 min depending on dose	Grav, EID, Elas	1	2	…	Nephrotoxicity; ototoxicity		See aminoglycoside monitoring[f]
Imipenem	NA	3–4	20–60 min depending on dose	Grav	1	1	1	Hypersensitivity including anaphylaxis; seizures		See stability footnote[g]
Levofloxacin	90	1	60–90 min depending on dose	Grav	…	…	…	Tendonitis/tendon rupture; cardiac arrhythmias; peripheral neuropathy	Known	Consider change to po; see monitoring footnote;[d] dialysis-only dosing possible
Linezolid	100	2	30–120 min	Grav, EID	1	…	1	Thrombocytopenia; leukopenia; anemia; peripheral neuropathy; optic neuritis		Consider change to po; monitor for neuropathy, optic neuritis in prolonged use; see monitoring footnote;[d] potential for drug interactions
Meropenem	NA	3–4	30 min	Grav, Elas	1	1	1	Hypersensitivity including anaphylaxis		Dialysis-only dosing possible; see stability footnote[g]
Metronidazole	100	2–4	30–60 min	Grav, EID, Elas	1	…	…	Peripheral neuropathy	Conditional	Consider change to po
Nafcillin	NA	4–6	30–60 min	Grav, EID	1	1	1	Hypersensitivity including anaphylaxis		Central line commonly used because of concern for phlebitis risk
Oritavancin	NA	Once	180 min	Grav	…	…	…	Hypersensitivity including anaphylaxis; infusion related		Red man syndrome more likely if infusion <60 min; monitoring requirements unknown for treatment duration greater than a single dose
Oxacillin	NA	4–6	10–30 min	Grav, Elas	1	1	1	Hypersensitivity including anaphylaxis; hepatotoxicity		Central line commonly used because of concern for phlebitis risk
Penicillin G	25–73	4–6	15–30 min	Grav, EID	1	1	1	Hypersensitivity including anaphylaxis		Oral penicillin V K is not a substitute for IV treatment of most clinical conditions requiring IV penicillin, eg, syphilis
Piperacillin-tazobactam	NA	3–4	30–240 min (extended infusion)	Grav, EID	1	1	1	Hypersensitivity including anaphylaxis		
Polymyxin B	NA	1	60–90 min	Grav	1	2	…	Nephro- and neurotoxicity		Monitor for nephrotoxicity, neurotoxicity
Rifampin	70–90	1–3	30 min	Grav	1	1	1	Hepatitis; hypersensitivity	NA	Potential for drug–drug interactions; consider change to po
Tedizolid	91	1	60 min	Grav	1	…	1	Thrombocytopenia; leukopenia; anemia; peripheral neuropathy; optic neuritis		Consider change to po; monitor for neuropathy, optic neuritis in prolonged use; potential for drug interactions; see monitoring footnote[d]

Table 2. Continued

Antiinfective	Oral Bioavailability, %[a]	Doses per day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly)			Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
					CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil			
Telavancin	NA	1	60 min	Grav	1	2	…	Nephrotoxicity; hypersensitivity including anaphylaxis; infusion-related prolongation of QTc	Possible	High rate of renal injury in patients aged >65 years, with preexisting renal impairment or other nephrotoxins; red man syndrome more likely if infusion <60 min
Tigecycline	NA	2	30–60 min	Grav	1	1	1	Nausea/ vomiting		
Tobramycin	NA	1–3	30–120 min depending on dose	Grav, EID, Elas	1	2	…	Nephrotoxicity; ototoxicity		See aminoglycoside monitoring[f]
Trimethoprim/ sulfamethoxazole	85	2–4	60–90 min	Grav	1	1	1	Hyperkalemia; rash; nephrotoxicity; Stevens Johnson syndrome	Special	Consider change to po; potential for drug–drug interactions; high fluid requirement; spurious increase in serum creatinine
Vancomycin	NA	1–2	60–120 min depending on dose	Grav, EID, Elas	1	1	…	Nephrotoxicity; infusion-related reactions		Dialysis-only dosing possible; vancomycin trough levels or area under the curve/minimum inhibitory concentration weekly and with dose changes; red man syndrome more likely if infusion <60 min

This table has been adapted from the OPAT eHandbook 2016 [6]. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Abbreviations: ADR, adverse drug reaction; ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMP, basic metabolic profile; BUN, blood urea nitrogen; CBC, complete blood cell count; CK, creatine kinase; Cr, creatinine; EID, electronic infusion device; Elas, elastomeric; Grav, gravity; IV, intravenous; IVP, intravenous push; K, potassium; LFT, liver function tests; NA, not applicable/no oral formulation; po, by mouth; QTc, corrected QT-interval; Tbil, total bilirubin; ULN, upper limit of normal.

[a]Bioavailability: changing to oral medications when possible is part of good antimicrobial stewardship. Clinicians should consider the full clinical situation, including the appropriateness of oral antimicrobials for the condition being treated. Potential for interaction with foods and other medications as well as concomitant illnesses and the potential for impaired gut absorption must also be considered.

[b]Doses per day: assumes normal renal and hepatic function. More than 2–3 doses per day may be impractical for pediatric outpatient parenteral antimicrobial therapy (OPAT) that requires adult infusion assistance for every dose. Dosing more frequently than once daily is typically not practical for patients who receive care in infusion centers.

[c]Devices: very limited published information on the use of these devices in OPAT. Individual infusion pharmacies have variable policies and device availability. Not all drugs are compatible with all delivery options. EIDs can be programmed to automatically deliver multiple doses per day but they require that the patient be connected to a small device virtually continuously and are not covered by all insurance carriers. Elas are very simple to use but also are not covered by all insurance carriers. Gravity delivery (infusion without a pump, using a roller clamp) is less expensive but also less convenient due to longer infusion times and complexity for patients to learn. Depending upon care setting, use of a traditional infusion pump may be selected in lieu of gravity for rate control. IVP is very convenient because of rapid infusion time.

[d]These are recommendations based on frequency and seriousness of reported adverse events. The monitoring plan for an individual patient may be different based on the comorbid conditions and anticipated duration of OPAT. For instance, for shorter courses of linezolid, ceftriaxone, or clindamycin, it may not be necessary to monitor LFTs and/or renal function. Alternatively, for longer courses of fluoroquinolones, weekly lab monitoring may be appropriate. For patients with normal baseline labs, less intense monitoring may be appropriate.

[e]Risk of Torsades de Pointes (TdP): known, known to prolong QTc interval and cause TdP even when taken as recommended; possible, can cause QTc prolongation but not known to cause TdP when taken as recommended; conditional, associated with TdP but only under certain conditions (ie, excessive dose, with hypokalemia, with other interacting drugs) or by creating conditions that induce TdP (inhibiting metabolism of QTc prolonging drugs); special, high risk of TdP in patients with congenital long QT syndromes due to other actions. Source for TdP risk [28].

[f]Aminoglycoside monitoring: monitor concentrations minimum weekly. Goal aminoglycoside trough values differ according to the drug, infection, and dosing strategy.

[g]For medications with limited stability, home delivery more frequently than once weekly will be required. Some drugs may be reconstituted in the home using a use-activated container, if available.

cost and insurance coverage frequently influence the model of care and, in some instances, the selection of antimicrobial agents for OPAT. For instance, Medicare patients without a secondary infusion benefit are typically required to choose between self-pay and receipt of antimicrobials in a SNF or infusion center, if available. Despite the availability of a number of dialysis-friendly agents [29], patients who receive their parenteral antimicrobials during dialysis sessions may be limited to a choice of vancomycin, cefazolin, or aminoglycosides only, depending on what their dialysis center is willing to pay for.

Therapeutic Considerations

Correct treatment begins with the correct diagnosis. Before embarking on a course of treatment, it is essential to identify the infection being treated. This includes gaining an understanding of the primary site of infection, the extent of infection around the primary site, and distant sites seeded secondarily. Additionally, treatment is always more effective if adequate source control is achieved, such as debridement of necrotic tissue, drainage of abscesses, and removal of infected prosthetic devices. Whenever possible, control at the primary site of infection should be addressed appropriately early in treatment.

The selected antimicrobial agent should have activity against the identified or presumptive causative pathogen(s), known distribution to the site of infection, and proven therapeutic efficacy in the infection being treated. Patient factors that may impact efficacy must be considered, including comorbidities, concomitant therapies (drug and non-drug), patient age, and organ function. Programmable infusion pumps and elastomeric devices (disposable balloons that push medication through tubing) have made it more convenient to use drugs that require multiple infusions a day. In general, for OPAT, drugs that allow for infrequent dosing and rapid/bolus infusions are preferred. However, if the resources exist to administer multiple doses of antimicrobials at home daily, efficacy should not be sacrificed for convenience.

Safety Considerations

While the types of adverse events observed with various antimicrobials would not be expected to differ in OPAT patients vs inpatients, the incidence of such reactions may differ. The cumulative incidence of adverse events to a variety of antimicrobial classes increases with length of treatment [29–33]. For some patients, OPAT courses may extend for weeks or months. Monitoring for adverse events while on treatment has been standard of care [1]; the particular tests required depend on the potential adverse event profile of the antimicrobials being administered. Additionally, some antiinfective agents require plasma concentration monitoring to ensure that they are in the desired therapeutic/nontoxic range (eg, vancomycin, aminoglycosides, and voriconazole). Occurrence of adverse events is a common reason for a change in antimicrobial agent or a complete discontinuation of OPAT [31, 33–36].

Administration Considerations

A suitable antimicrobial for OPAT should have favorable physical and chemical characteristics. The agent should have adequate stability, once reconstituted, in common IV solutions, in a variety of containers (plastic bags, syringes, elastomeric containers), and under various storage/use conditions. For example, ampicillin-sulbactam is only stable for 3 days once formulated, so more than once weekly delivery of medications will be required for home infusion. Stability may vary with diluent, final concentration to be administered, infusion container type, and storage conditions (eg, refrigerated vs room temperature). The pH and osmolality of solutions prepared for IV administration directly affect tolerability and may influence the type of vascular access device (VAD) needed.

Drugs are prepared and supplied to the patient/caregiver in a variety of delivery devices suitable for administering antimicrobials in the outpatient setting. Each method has advantages and disadvantages but should be selected based upon patient preferences and capabilities, drug characteristics (concentration/solubility, stability, infusion time), VAD, and cost/insurance coverage. Intravenous push is a rapid and convenient delivery method for many cephalosporins but may need a dexterity beyond some patients' or caregivers' comfort level or physical ability. Electronic infusion devices can be programmed to improve ease of use by automatically delivering multiple doses per day but they require the patient to be connected to a small device virtually continuously and are not covered by all payers. Elastomeric devices are very simple to use but may not be reimbursed by all insurance carriers. Gravity delivery is the simplest to use and least expensive but is less convenient than other methods due to longer infusion times.

The Role of the Physician and the OPAT Team

Regardless of the OPAT model chosen, it is the responsibility of the treating physician to manage and direct the patient's care. The treating physician addresses the indication for OPAT, selection of antimicrobial agent, duration of therapy, and subsequent medical evaluations. In the modern healthcare system, however, the physician does not work alone. He or she is supported by vascular access teams, social workers, nurses, and pharmacists, all working in collaboration to support the patient. Recognition of the contributions of multiple healthcare professionals and roles has led to the proposal of an OPAT bundle, which identifies several components that require attention when planning an OPAT program [37].

Emerging Trends in OPAT

The role of remote-access delivery of OPAT oversight is currently under investigation [38]. The use of telemedicine to support OPAT in geographically isolated locations is appealing but challenged in the United States by reimbursement models and interstate regulatory requirements. Also unknown, but promising, are the roles of the long-acting semisynthetic lipoglycopeptides

Table 3. Features of Selected Antivirals and Antifungals Used in Outpatient Parenteral Antibiotic Therapy

Antiinfective	Oral Bioavailability, %[a]	Doses per Day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly)			Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
					CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil			
Antifungals										
Amphotericin B	NA	1	Liposomal: 2 hours Deoxycholate: 2–4 hours	EID (including pole pump) Elas	1	2	1	Rates >10%; hypotension, rigors, nausea, vomiting, diarrhea, anemia, thrombocytopenia, electrolyte abnormalities (K, Mg, Ca), renal failure, hypoglycemia, LFT abnormalities	Conditional	Sodium loading recommended; chemistry 10 preferred[f]
Anidulafungin	NA	1	1.5 hours	Grav	1	1	1			
Caspofungin	NA	1	1 hour	Grav, EID, Elas	1	1	1			
Fluconazole	≥90	1	1–2 hours (not to exceed 200 mg/h)	Grav, Elas	…	…	1		Known	Consider change to po; watch for drug-drug interactions
Isavuconazole	98	1–3	≥1 hour	Grav (with pump)	…	…	1			Consider change to po; watch for drug–drug interactions
Micafungin	NA	1	1 hour	Grav	1	1	1			
Posaconazole	Highly dependent on gastric pH	1–2	90 min with in-line filter	Grav	1	1	1		Conditional	Consider change to po; watch for drug–drug interactions
Voriconazole	96	2	1–2 hours	Grav	1	1	1	Hallucinations; auditory/visual disturbances; skin changes; fluorosis with prolonged use	Conditional	Consider change to po; watch for drug–drug interactions; monitor plasma concentrations; avoid intravenous formulations if CrCl <50 unless benefits clearly outweigh risks (accumulation of cyclodextrin vehicle)
Antivirals										
Acyclovir	10–30	3	1 hour	Grav, Elas	1	1	…	Crystalluria; acute renal injury		Hydration critical in preventing nephrotoxicity; consider change to po valacyclovir, famciclovir, or acyclovir
Cidofovir	NA	1	1 hour	EID (including pole pump)	1	2	1	Rash; anemia; neutropenia; iritis; uveitis; decreased intraocular pressure; nephrotoxicity; metabolic acidosis		Hydrate with NS before and after dose; consider probenecid; urinalysis weekly; chemistry 10 preferred[f]
Foscarnet	NA	1–3	1–2 hours (not to exceed 1 mg/kg/min)	EID, Elas	1	2	1	Nephro- and neurotoxicity; anemia; granulocytopenia; electrolyte disturbances		Hydrate with NS or D5W prior to first dose; chemistry 10 preferred[f]

Table 3. Continued

Antiinfective	Oral Bioavailability, %[a]	Doses per Day[b]	Infusion Time	Delivery Device[c]	Monitoring Frequency[d] (Weekly)			Most Common Potentially Serious ADRs	Torsades de Pointes Risk[e]	Other Comments
					CBC-diff	BMP: including K, Cr, BUN	Liver profile: ALT, AST, ALK, Tbil			
Ganciclovir	5–10	1–2	1 hour	Grav, Elas	2	1	…	Dose-dependent myelosuppression		Consider change to po valganciclovir

This table has been adapted from the OPAT eHandbook 2016 [6]. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Abbreviations: ADR, adverse drug reaction; ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMP, basic metabolic profile; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood cell count; CK, creatine kinase; Cl, chloride; Cr, creatinine; D5W, 5% dextrose; EID, electronic infusion device; Elas, elastomeric; Grav, gravity; IV, intravenous; IVP, intravenous push; K, potassium; Mg, magnesium; NA, not applicable/no oral formulation; NS, normal saline; po, by mouth; Tbil, total bilirubin; ULN, upper limit of normal.

[a]Bioavailability: changing to oral medications when possible is part of good antimicrobial stewardship. Clinicians should consider the full clinical situation, including the appropriateness of oral antimicrobial for the condition being treated and potential for interaction with foods and other medications as well as concomitant illnesses and the potential for impaired gut absorption that may decrease serum levels.

[b]Doses per day: assumes normal renal and hepatic function. More than 2–3 doses per day may be impractical for pediatric OPAT that requires adult infusion assistance for every dose.

[c]Devices: very limited published information on the use of these devices in OPAT. Individual infusion pharmacies have variable policies and device availability. Not all drugs are compatible with all delivery options. EIDs can be programmed to automatically deliver multiple doses per day but they require that the patient be connected to a small device virtually continuously and may not be covered by all insurance carriers. Elas are very simple to use but also may not be covered by all insurance carriers. Gravity delivery (infusion without a pump, using a roller clamp) is less expensive but also less convenient due to longer infusion times and complexity for patients to learn. Depending upon care setting, use of a traditional infusion pump may be selected in lieu of gravity for rate control. IVP is very convenient because of rapid infusion time.

[d]These are recommendations based on frequency and seriousness of reported adverse events. The monitoring plan for an individual patient may be different based on the comorbid conditions and anticipated duration of OPAT.

[e]Risk of Torsades de Pointes (TdP): known, known to prolong QTc interval and cause TdP even when taken as recommended; possible, can cause QTc prolongation but not known to cause TdP when taken as recommended; conditional, associated with TdP but only under certain conditions (eg, excessive dose, with hypokalemia, with other interacting drugs) or by creating conditions that induce TdP (inhibiting metabolism of QTc prolonging drugs); special, high risk of TdP in patients with congenital long QT syndromes due to other actions. Source for TdP risk [28].

[f]Chemistry 10 includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, and phosphate.

dalbavancin and oritavancin, currently approved narrowly, but offering potential promise because of their very long half-lives and infrequent dosing requirements. The role of these expensive agents, particularly in PWID, remains to be defined. Additionally, one source of complications during OPAT is the VAD. Delivery of antimicrobials by subcutaneous administration has the potential to avoid the need for a VAD. Subcutaneous antimicrobials have been used in other countries for some time [39–41] but their use in the United States is still investigational. Finally, newer models of care delivery for PWID, homeless patients, and other challenging populations have shown promise in the potential to deliver OPAT for patients who were previously required to either remain in hospital for IV antibiotic therapy or forgo IV antimicrobial treatment [42–45].

METHODOLOGY

Panel Composition

The last version of the IDSA OPAT Guideline was published in 2004 [1]. For the current update, 1 of the chairs assembled 11 ID physicians from both academic and private practice settings, including 3 pediatric ID physicians who are members of the Pediatric Infectious Diseases Society. Also included were an experienced ID pharmacist, a member of the Infusion Nursing Society, and a guideline methodology expert. Two professional health sciences librarians performed literature searches.

Evidence Review and Formulation of Recommendations

The panel followed a process used in the development of other IDSA guidelines that includes a systematic review of the relevant evidence and the formulation of recommendations from that evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Figure 1) [2–5, 46, 47]. The evidence informing a given question began as "high" quality if it included randomized, controlled trials and began as "low" quality if it only included nonrandomized clinical trials or observational studies. Specific features of the evidence base (such as risk of bias or large effect size) warranted decreasing or increasing the rating of the quality of the evidence, as outlined in Figure 1. The strength assigned to a recommendation reflected the net benefits and net harms or trade-offs resulting from that recommendation, in addition to the level of evidence available.

Process Overview

Five overarching topics were identified for review: patient considerations, antimicrobials, VADs, monitoring, and stewardship. Two to 3 panel members were assigned to each section with responsibility to review the literature, assess the risk of bias of the individual studies identified, synthesize the evidence, and formulate recommendations informed by this synthesis. The panel met face-to-face 4 times and conducted numerous conference calls to develop the guideline questions and literature search

strategy and to review and discuss all recommendations, their strengths, and their underlying evidence base. Inconsistencies and differences were discussed and resolved, and all final recommendations represent a consensus opinion of the entire panel.

All recommendations were labeled as either "strong" or "weak" using the GRADE approach [5]. Although there is ongoing need for research on virtually all of the subjects addressed in this guideline, research needs were highlighted in areas the panelists felt were of the highest priority; these are summarized in "Future Directions" at the end of this document. High-quality evidence was lacking for most of the recommendations. Strong recommendations were sometimes made in the setting of low-quality evidence when the panelists believed that most individuals would endorse the recommended course of action and that most well-informed clinicians would agree, despite the low-quality evidence [2, 3].

The panel obtained feedback from 3 external peer reviewers. The guideline was also reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the IDSA Board of Directors.

Literature Search Methodology

Health sciences librarians identified studies using medical subject headings and text words for OPAT (Supplementary Table A). Additional searches were run for the concepts of dialysis, VADs, monitoring, and stewardship (Supplementary Tables B–E). After excluding duplicates, 23 435 citations remained. Results were limited to human studies published between January 1980 and October 2015. All publications in English or containing English abstracts were included, except editorials, letters, and comments. Databases accessed on the Ovid platform included MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE (1946 to present), Embase (1980 to present), Cochrane Central Register of Controlled Trials (1991 to present), Health Technology Assessment Database (2001 to present), and National Health Service Economic Evaluation Database (1995–2015). To supplement the electronic search, members contacted experts and hand-searched journals, conference proceedings, and reference lists. Initial literature searches were done in October 2014, with updates performed 28 October 2015 and 31 January 2017.

Literature Review Methodology

A total of 23 435 citations were divided equally among a panel of 6 reviewers who prescreened them and retained 3102 citations. Using EndNote, citations were divided into topical libraries for each writing group. One to 2 independent reviewers (depending on the writing group) used predetermined inclusion and exclusion criteria to complete a 2-step screening method: the first screen consisted of a title and abstract review to ascertain relevance to OPAT, and the second screen entailed review of the full text to determine if the study addressed any of the questions posed. Twenty-six articles were included in the final evidence tables; numerous others were referenced in discussion sections but did not meet criteria for inclusion in the systematic reviews.

Risk of Bias Assessment of Individual Studies

The Newcastle-Ottawa scale (NOS) was used to assess risk of bias for cohort and case control studies, and the Cochrane Collaboration's Risk of Bias Tool was used to assess risk of bias in clinical trials. Risk of bias was independently checked by 3 reviewers for each study. Discrepancies were addressed through consensus discussion.

A summary assessment of "overall risk of bias" was created by first grouping the criteria in the NOS into 3 domains and the criteria in the Cochrane Collaboration tool into 4 domains based on the nature of their respective threats to validity. The elements examined in each domain are shown in Table 4.

General rules were developed to guide the grading process. Each observational study was evaluated and assigned stars for criteria as laid out in the NOS [48]. An individual study was then considered to be at "high" overall risk of bias if it lacked 1 or more stars in each of the 3 domains or if it lacked all stars in 1 domain and 2 or more stars in other domains. A study was considered to be at medium risk of bias if it lacked all stars in 1 domain or lacked stars in at least 2 domains.

Each clinical trial was examined and rated as introducing "low," "high," or "unclear" risk of bias in each criterion in each domain. A clinical trial was then considered to be at "high" overall risk of bias if it was assigned a "high" risk rating for 1 or more discrete criteria in at least 2 domains. A clinical trial was determined to be at "medium" overall risk of bias if it was assigned a "high" risk rating in only 1 domain or if it was determined to be at "unclear" risk of bias in 1 or more discrete criteria in at least 2 domains.

Data Synthesis

The evidence was synthesized using strength-of-evidence tables. Due to the heterogeneity and small number of included studies in each individual evidence table, data from the studies were not combined quantitatively using metaanalyses.

For each question, clinically relevant outcomes were sought. When available from individual studies, point estimates, confidence intervals, and *P* values were reviewed. If errors were found, corrected values were used. *P* values of <.05 were considered statistically significant.

Strength of the Body of Evidence

The strength of evidence for each outcome was evaluated using the GRADE criteria [5]. This method initially assigns a starting level of evidence strength based on the design of the studies informing that evidence base. The method then evaluates the evidence base for 8 characteristics that may increase or decrease

Table 4. Domains Evaluated in Assessing Risk of Bias

Cohort Study Domains			
Subjects and Exposures	**Comparability**	**Outcome Evaluation**	
• Representative cohort	• Controlled for the most important variable	• Outcome assessment	
• Selection of nonexposed control	• Controlled for any other variable	• Duration of follow-up	
• Exposure ascertained		• Adequate follow-up	
• Not present at outset			
Case Control Study Domains			
Subjects and Exposures	**Comparability**	**Exposure Evaluation**	
• Exposure	• Controlled for the most important variable	• Exposure ascertainment	
• Case definition	• Controlled for any other variable	• Nonresponse rate	
• Representative cases			
• Control selection			
• Control definition			
Clinical Trials Domains			
Participant Enrollment	**Blinding**	**Outcome Data**	**Other Bias**
• Sequence generation	• Blinding of participants and personnel	• Incomplete outcome data	
• Allocation concealment	• Blinding of outcome assessors	• Selective outcome reporting	

the level of evidence to arrive at a final level of evidence strength. Randomized, controlled trials start at a high level of evidence strength, while observational studies (cohort and case-control studies) start at a low level.

General rules were developed to guide the assessment of strength of evidence. The characteristics that have the potential to decrease the strength of evidence are risk of bias, inconsistency, indirectness, imprecision, and publication bias. The characteristics that have the potential to increase the level of evidence strength are large magnitude of effect, dose–response, and a potential increase in effect size when considering unmeasured confounders. For each outcome considered, the starting level of evidence strength was the highest level of evidence strength of any study examining that outcome. Each of the 8 characteristics of the body of evidence for that outcome was then evaluated using the criteria described in the following paragraphs, and the level of evidence strength was downgraded or upgraded accordingly.

Downgrading for risk of bias was done if 50% or more of the studies evaluated for a given outcome were at medium or high overall risk of bias as described above. In these situations, if 50% or more of the studies evaluated for a given outcome were at high overall risk of bias, the level of evidence was downgraded by 2 points, otherwise by 1 point.

Consistency of results for the same outcome among the available studies in terms of the direction and magnitude of effect was examined. Downgrading for inconsistency was done when there was heterogeneity in the effects of an intervention across studies for a given outcome that could not be explained through identifiable differences in study characteristics.

Evidence was considered indirect if the populations, interventions, comparisons, or outcomes used within studies did not directly correspond to the question of interest and this indirectness could realistically result in different findings. For example, some included studies were performed on inpatients; the evidence was considered indirect in this setting because OPAT, by definition, is an outpatient activity. Downgrading for indirectness was done if 50% or more of the studies evaluating the given outcome suffered from indirectness.

Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome and is affected by sample size and number of events; it is most commonly represented by the width of confidence intervals. We considered the evidence to be imprecise when the width of the confidence interval spanned more than 1 logarithm on a base 10 scale. We also downgraded for imprecision when key components of the outcome data provided by studies were not fully reported (eg, measures of variance were not included) or when it was not possible to derive an estimate of effect based on the available data. Downgrading for imprecision was done if 50% or more of the studies evaluating the given outcome suffered from imprecision or if there was only 1 study evaluating a particular outcome.

Reporting bias includes publication bias, outcome reporting bias, and analysis reporting bias. Given the small number of studies, funnel plots were not examined. We downgraded for reporting bias when we detected a likelihood of outcome reporting bias (important clinical outcomes appeared to have been collected but not reported) or analysis reporting bias (important comparisons were not analyzed) in 50% or more of the studies evaluating the given outcome.

The level of evidence was upgraded for large magnitude of effect. If 50% or more of the studies evaluated for a given outcome had an effect size ≥2 or ≤0.5, 1 point was added to the level of evidence. If 50% or more of the studies evaluated for a given outcome had an effect size ≥5 or ≤0.2, the level of evidence was upgraded by 2 points. Upgrading for a dose–response relationship was done if 50% or more of the studies evaluating a given outcome demonstrated a dose–response relationship. Upgrading for confounders was done if in 50% or more of the studies evaluating a particular outcome, the consideration of unmeasured confounders would have been expected to increase the magnitude of the effect reported. For example, if

2 or more out of 3 studies that reported on a particular outcome found a positive effect, and inclusion of residual confounders in 2 or more of these studies would have been expected to increase the magnitude of the effect found, the level of evidence was upgraded.

The gathered evidence was used to draw a summary conclusion for each outcome examined. If the final level of evidence strength was very low, we considered it to be insufficient to draw a conclusion about the outcome of interest.

Formulation of Recommendations

Interventions associated with benefit also often have proven or theoretical harms. Recommendations were made considering the strength of the evidence available and the net benefits, net harms, or trade-offs resulting from those interventions (Figure 1). The bulk of the OPAT literature base is composed of nonrandomized studies that, by their nature, compare groups that have inherent differences, thus limiting the quality of the evidence. For instance, outcomes for patients treated at home might differ from those treated in SNFs, not necessarily due to the care received at the respective sites but because patients selected for treatment at home may be younger and healthier than those selected for treatment in SNFs. Evidence tables are presented for each question. A detailed analysis of the risk of bias for individual studies included in the evidence tables is provided in Supplementary Tables F–H.

Conflicts of Interest

The expert panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that may be construed as constituting an actual, potential, or apparent conflict. Panel members were provided IDSA's conflicts of interest disclosure statement and were asked to identify ties to companies that develop products that may be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. Decisions were made on a case-by-case basis as to whether an individual's role should be limited due to conflict. Potential conflicts of interests are listed in the Notes section at the end of the guideline.

Future Revision Dates

At annual intervals, the panel chairs, Standards and Practice Guidelines Committee (SPGC) liaison advisor, and SPGC chair will determine the need for guideline revisions by reviewing current literature. If necessary, the entire panel will be reconvened. When appropriate, the panel will recommend revisions to the IDSA SPGC, Board, and other collaborating organizations for review and approval.

PATIENT CONSIDERATIONS

I.Should patients (or their caregivers) be allowed to self-administer outpatient parenteral antimicrobial therapy (OPAT)?

Recommendation

1. Patients (or their caregivers) should be allowed to self-administer OPAT (strong recommendation, low-quality evidence).

Evidence Summary

Three observational studies allow for comparison of outcomes among patients treated by self-administered OPAT (S-OPAT) vs healthcare-administered OPAT (H-OPAT) [49–51]. S-OPAT refers to administration of IV antimicrobials by the patient, relative, or caregiver, whereas H-OPAT refers to administration of IV antimicrobials by a healthcare worker. One study compared outcomes between 473 S-OPAT and 1536 H-OPAT patients in the United Kingdom [49]. S-OPAT patients were selected patients who were deemed capable of self-administration. Another study compared outcomes for patients in Singapore, categorized into 1 of 3 groups: self OPAT (379 patients), termed S-OPAT; H-OPAT (156 patients), where infusions were done by a healthcare worker in the patient's home; and hospital OPAT (1694 patients), which was essentially infusion center–based treatment [50]. For this question, only the first 2 groups are relevant. The study reported hazard ratios (HRs) based on hospital OPAT as the reference group. At our request, the HRs were recalculated by the original investigators, changing the reference level to H-OPAT. The third study examined associations of various factors, including self-administration (vs OPAT clinic staff administration), with line infection and with other line event, in a multivariable analysis in a cohort of 2766 patients in the United Kingdom treated with OPAT [51].

Readmission rates for S-OPAT vs H-OPAT were compared in 2 of these 3 studies [49, 50]. S-OPAT was associated with a lower HR of readmission compared to H-OPAT (HR 0.36, 95% confidence interval [CI] 0.24–0.53, $P < .001$) in 1 study [49] and was not associated with an increase (10.5% vs 12.6%, risk ratio [RR] 0.83, 95% CI 0.59–1.14, $P = .30$) in the other [50]. A comparison of complication rates for S-OPAT vs H-OPAT could be obtained from 2 of these studies [49, 51]. Complication rates did not differ for S-OPAT vs H-OPAT in 1 study (24% vs 23%, RR 1.03, 95% CI 0.86–1.24, $P = .80$) [49]. No significant associations were found between OPAT administration group (self vs OPAT clinic staff administration) and vascular access complications in the other study (odds ratio [OR] 0.84, 95% CI not reported [NR], $P = .72$ for line infection; OR 1.32, 95% CI NR, $P = .22$ for other line events) [51]. The evidence from these 3 studies is summarized in Table 5. In addition to these comparative studies, there have been many descriptive studies in the adult and pediatric literature documenting the successful administration of OPAT medications at home by patients or family members, with few complications [8, 52–55].

Rationale for the Recommendation

Readmissions, emergency department (ED) visits, and complications were the critical outcomes. There was moderate-quality evidence for absence of an increase in readmission risk with S-OPAT compared to H-OPAT and low-quality evidence for equivalence in complications. There were no data for ED visits. These findings amount to overall low-quality evidence for equivalence in S-OPAT vs H-OPAT.

When OPAT was originally introduced into medical practice, it involved training patients or their caregivers to administer parenteral antimicrobials at home. In the United States, once the patient has established infusion competency, the home care model generally includes a once-weekly visit by a nurse who performs clinical assessment, changes the VAD dressings, and draws blood for monitoring tests, with the option to visit patients' homes more frequently if needed. In time, other models of care have evolved, including the use of various office or infusion center settings. However, the majority of OPAT in the United States continues to be delivered by patients or their caregivers in the home [27]. Most of these infusions, however they may be labeled, are essentially S-OPAT treatments.

There is vast clinical experience with S-OPAT in the United States. Many descriptive studies of S-OPAT in the United States for different infectious conditions in different settings have reported successful outcomes [8, 52–55]. Allowing people to self-administer their parenteral antimicrobials after appropriate training and with appropriate support mechanisms in place reduces unnecessary burden on the healthcare system and enhances patient satisfaction. These considerations warrant a strong recommendation that patients or their caregivers be allowed to self-administer OPAT.

II. Should patients (or their caregivers) be allowed to self-administer OPAT at home without visiting nurse support?

Recommendation

2. Patients (or their caregivers) may be allowed to self-administer OPAT at home without visiting nurse support as long as there is a system in place for effective monitoring for vascular access complications and antimicrobial adverse events (weak recommendation, low-quality evidence).

Evidence Summary

A direct comparison of S-OPAT at home with vs without visiting nurse support has not been described. However, comparison of outcomes for S-OPAT at home without visiting nurse support vs usual care (which may include some nursing support) has been reported in 1 study. Usual care included S-OPAT at home with visiting nurse support as well as patients whose OPAT was administered at a SNF. This study was done among uninsured patients in the United States, and the analysis used a multivariable Cox proportional hazards regression model that adjusted for the propensity to be included in one or the other group [52]. The patients without visiting nurse support, so-called teach-and-train OPAT (TT-OPAT) patients were instructed to self-administer IV antimicrobials by gravity and were followed at designated intervals in clinic for IV access care, laboratory monitoring, and physician follow-up. Following training, competency was established before discharge through a standardized protocol, requiring patients to repeatedly demonstrate mastery of all the steps in self-administration by gravity. The comparison group included patients who were treated with S-OPAT at home with the support of weekly nurse visits or who were treated in SNFs, so called nurse-administered OPAT (NA-OPAT).

The 30-day readmission rate was significantly lower for the 944 TT-OPAT patients compared to the 244 OPAT patients who

Table 5. Evidence Table: Comparison of Outcomes in Self-Administration of Outpatient Parenteral Antimicrobial Therapy (OPAT) Medications Versus Healthcare Personnel Administration of OPAT Medications

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Readmission	No increase	Lower hazard of readmission[a] for S-OPAT (HR 0.36,[b] 95% CI 0.24–0.53, $P < .001$) in 1 study [50] No difference in readmission rates (10.5% vs 12.6%, RR 0.83, 95% CI 0.59–1.14, $P = .30$) in 1 study [49]	2 cohort studies (n = 2059, 2229) [49, 50]	Low	Large effect (+1)	Moderate
Complications[c]	No increase	Similar overall complication rate (24% vs 23%, RR 1.03, 95% CI 0.86–1.24, $P = .80$) in 1 study [49] S-OPAT at home (vs administration by staff in OPAT clinic) was not associated with line infection (OR 0.84, 95% CI NR $P = .72$) or other line events (OR 1.32, 95% CI NR, $P = .22$) in 1 study [51]	2 cohort studies (n = 2059, 2766) [49, 51]	Low	…	Low

Abbreviations: CI, confidence interval; H-OPAT, administration of IV antimicrobials by a healthcare worker; HR, hazard ratio; NR, not reported; OR, odds ratio; RR, relative risk; S-OPAT, administration of IV antimicrobials by the patient, relative, or caregiver rather than by a healthcare worker.

[a]The outcome reported in the study was "clinical deterioration," which was a composite outcome of readmission or death. There were 2 deaths so, effectively, the outcome could be considered readmission.

[b]Estimates recalculated by original authors at our request after changing the reference level to more directly answer the question posed in this section.

[c]Complications were drug associated, line associated, and other.

received NA-OPAT (16.7% vs 23.7%, HR 0.53, 95% CI 0.35–0.81, P = .003) [52]. The evidence from this study is summarized in Table 6.

Rationale for the Recommendation

Readmissions, ED visits, and complications were considered critical outcomes. There was low-quality evidence for a lower hazard of readmission with TT-OPAT vs NA-OPAT, but no data to determine risk of complications or ED visits.

In traditional home-based infusion models in the United States, patients self-administer their OPAT medications and have a weekly visit by a visiting nurse. In other countries, OPAT at home may mean daily visits by an infusion nurse. In the TT model of home-based OPAT, there are no home visits by a nurse. Patients self-administer their OPAT medications and follow-up in a physician's office or clinic for monitoring.

The study by Bhavan et al provides reassurance that patients or their caregivers can be trained to safely administer OPAT medications at home without the need for visiting nurse support and without an increased risk of readmission if there is a system to follow them regularly [52]. Demonstration of the lack of increase in risk of readmission and the potential advantages of such self-administration allow for a weak recommendation that OPAT may be done at home via self-administration without the need for visiting nurse support. However, such a model requires strict training and monitoring systems that may not be readily available, and all patients may not be able to master the skills to do this.

III. Can people who inject drugs (PWID) be treated with OPAT at home?

Recommendation

3. No recommendation can be made about whether PWID may be treated with OPAT at home (no recommendation, low-quality evidence). Decisions should be made on a case-by-case basis.

Evidence Summary

No studies have directly compared outcomes for OPAT at home between PWID (equivalent term for injection drug use [IDU]) vs people who do not inject drugs. One study examined associations of various factors, including PWID, with vascular access complications in a multivariable analysis in a cohort of 1461 patients, 16 of whom were PWID [55]. IDU was found to be a risk factor for vascular access complications (incidence rate ratio [IRR] 3.32, 95% CI 1.16–7.46, P = .01). The findings are summarized in Table 7.

Experience with OPAT for PWID has been described in several case series. In 1 study, 29 PWID were sent home with an indwelling vascular device but brought to an infusion center for daily antibiotic infusions. Patients were prescreened, counseled, and had standardized measures to detect peripherally inserted central catheter (PICC) abuse, including use of a security seal over the PICC. No deaths or episodes of PICC abuse were noted [43]. Another study reported an intensive treatment program for 83 patients with substance abuse, where patients were managed in a hospital outpatient unit by day and sent to an off-site supervised residential shelter at night. Treatment for 70% of patients included a parenteral antibiotic. No information on choice of vascular access or complications was reported. However, about 70% of patients completed the medical treatment course and 64% transitioned to an outpatient substance abuse treatment program [44]. These descriptive studies cannot be taken as evidence of safety in OPAT in PWID but are examples of how OPAT has been successfully administered in highly structured settings to a very challenging population.

Rationale for the Recommendation

Mortality, clinical cure, readmission, ED visits, and vascular access complications were considered critical outcomes. There were no data to evaluate mortality, clinical cure, readmission, and ED visits. There was low-quality evidence for increased risk of vascular access complications for PWID vs non-PWID, but no data to determine if the risk was lower, the same, or greater than when OPAT for PWID was carried out in a SNF.

PWID are treated with OPAT around the world [42, 43, 55]. However, such treatment at home in PWID is controversial [56, 57]. The theoretical concerns are 3-fold. First, patients could misuse their vascular access, leading to catheter complications. Second, largely due to psychosocial factors, patients may not adhere to the treatment plan, which may result in lower cure rates. Accidental drug overdose is an additional concern, but it is not known if having a VAD for OPAT increases the risk for drug overdose. Typical

Table 6. Evidence Table: Comparison of Outcomes in Teach-and-Train Outpatient Parenteral Antimicrobial Therapy (OPAT) Versus Nurse-Administered OPAT

Outcome	Conclusion	Summary of Findings	Study Design and Sample Size	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Readmission	Lower hazard of readmission	Lower hazard of readmission (HR 0.53, 95% CI 0.35–0.81, P = .003) [52]	1 cohort study (n = 1168) [52]	Low	Large effect (+1) Imprecision (–1)	Low
Mortality	Insufficient evidence	No difference in 1–year mortality (HR 0.86, 95% CI 0.37–2.00, P = .73) [52]	1 cohort study (n = 1168) [52]	Low	Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 7. Evidence Table: Outpatient Parenteral Antimicrobial Therapy at Home in Patients Who Inject Drugs: Comparison of Outcomes in Patients With and Without Injection Drug Use

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Vascular access complications	IDU is a risk factor	IDU was a risk factor for vascular access complications (IRR 3.32, 95% CI 1.16–7.46, $P = .01$) [55]	1 cohort study (n = 1461, 16 with IDU) [55]	Low	Large effect (+1) Imprecision (–1)	Low

Abbreviations: CI, confidence interval; IDU, injection drug use; IRR, incidence rate ratio.

alternatives to OPAT at home include discharging patients to SNFs, sending patients home without a VAD but bringing them to an outpatient facility for each antimicrobial administration, or keeping them in hospital for the duration of their parenteral antibiotic treatment course. It should be noted that there are no data to suggest that the risk of device misuse is any lower in SNFs, where patients have ample opportunity for illicit drug administration. Confirmation about whether PWID are at higher risk of vascular access complications during OPAT and, if so, refinement of the estimate of this risk requires additional studies.

There are other practical considerations that make it difficult to arrange for OPAT at home for PWID. In addition to a serious infection, these patients also have an addiction and often associated mental health disorders that may require treatment. A large proportion of these patients lack insurance. Many such patients are homeless or have a home environment that is unsuitable for the provision of OPAT. Two recent studies have reported successful OPAT administration in homeless patients (some of whom were identified as PWID) using externally funded respite housing for the duration of the OPAT course [44, 45].

In summary, there is insufficient evidence to make a recommendation for or against treating PWID with OPAT at home. In some situations, there may be no safe alternatives to in-hospital treatment. Decisions must be made on a case-by-case basis depending on the patient's unique circumstances and the resources available. Studies examining innovative models of care for this challenging group of patients that involve management of addiction in addition to treatment of infection are needed. The role of long-acting glycopeptides in this population needs to be explored.

IV. Should elderly patients be allowed to be treated with OPAT at home?

Recommendation

4. Elderly patients should be allowed to be treated with OPAT at home (strong recommendation, low-quality evidence). This recommendation assumes that potential challenges to OPAT in the elderly, such as cognition, mobility, and dexterity, have been duly considered and that the patient or caregiver is able to communicate with the treatment team if necessary.

Evidence Summary

Eleven observational studies allow for an evaluation of the effect of age on outcomes associated with OPAT [10, 50, 51, 55, 58–64]. The relevant outcomes examined in these studies were clinical improvement, hospital readmission, adverse events, and healthcare utilization.

Clinical improvement for elderly patients treated with OPAT was examined in 2 observational studies [10, 58]. The first compared outcomes among patients aged ≥60 years with those aged <60 years in a population of military veterans treated with OPAT with a teach-and-train model [10]. The study was limited in that it did not control for confounders. The second study examined risk factors for failure of OPAT in the treatment of infective endocarditis in the United Kingdom, but it was not designed with a specific intent of examining age as a risk factor [58]. The proportion of patients cured, improved, or made stable was similar in older (>60 years) and younger patients in the first of these studies (90% vs 94% of OPAT courses, RR 0.97, 95% CI 0.90–1.05, $P = .4$]) [10]. Similarly, in the other study, older age was not associated with OPAT failure on univariable analysis (OR 1.01, 95% CI 0.98–1.05, $P = .47$) [58]. However, given that both studies suffer from significant risk of bias, the available data provide insufficient evidence to conclude that there is no difference in clinical improvement with OPAT between older and younger patients.

Hospital readmission for older patients treated with OPAT at home was examined in 7 observational studies [50, 59–64]. The first was a direct comparison between older (>70 years) and younger patients, but it was not controlled for factors that differed across the groups [59]. The other 6 reports were observational studies where factors associated with hospital readmission were examined in multivariable analyses [50, 60–64]. No difference in early readmission (8% vs 7% of OPAT courses, RR 1.07, 95% CI 0.33–3.49, $P = .93$) or readmission within 3 months (14% vs 16% of OPAT courses, RR 0.88, 95% CI 0.40–1.93, $P = .75$) was found between older and younger patients in the direct comparison [59]. Age was not found to be associated with unplanned 30-day readmission (OR 1.09 per decade, 95% CI 0.99–1.21, $P = .10$ [60]; HRs 1.27, 1.13, 1.20 for higher age groups vs 18- to 63-year-old age group were not significant [61]; not significantly associated on univariable analysis, not examined in multivariable analysis [62]), readmission while on OPAT (OR 0.99, 95% CI 0.97–1.00, $P = .13$ [63]), or 6-week readmission (OR NR, 95% CI NR, $P = .16$) [64]. However, age >70 years was associated with a higher hazard of

clinical deterioration (readmission or death) in 1 study (HR 1.6, 95% CI 1.1–2.2, P = .008) [50]. Although 1 in 7 studies found increased risk of readmission in patients aged >70 years, the preponderance of evidence suggests that OPAT in older patients is not associated with increased risk of readmission compared to OPAT in younger people.

Adverse events in older patients while on OPAT and association of age and adverse events while on OPAT were examined in 5 studies [10, 51, 55, 59, 62]. Two were direct comparisons of adverse events in older patients vs younger patients [10, 59]. Neither study controlled for other variables that differed between the older and younger patients. Rates of adverse events overall (16% vs 16% of OPAT courses, RR 0.94, 95% CI 0.38–2.35, P = .89) [59], catheter-associated bloodstream infection (0.76 vs 0.23 per 1000 OPAT days, IRR 3.26, 95% CI 0.17–192.10, P = .65 [10], and catheter occlusion (3.03 vs 2.32 per 1000 OPAT days, IRR 1.30, 95% CI 0.45–3.67, P = .74) [10] did not differ between older patients and younger controls in these 2 observational studies. A higher rate of nephrotoxicity in the elderly group (3.03 vs 0.46 per 1000 IV antibiotic days, IRR 6.51, 95% CI 1.30–44.89, P = .02) was found in 1 study [10]. Older age was not found to be a risk factor for vascular access complications on multivariable analyses in 2 observational studies (IRR = 0.99, 95% C.I. 0.98–1.00, P = .04 [55]; OR 1.0, 95% CI 0.99–1.01, P NR [62]) or for line infection (P = .57 on univariable analysis, age not included in multivariable analysis) and other line events (OR 0.997, 95% CI NR, P = .57) in another large observational study [51]. The preponderance of evidence from these studies suggests that OPAT in older patients is not associated with increased risk of adverse events compared to OPAT in younger patients.

Healthcare resource utilization related to administering OPAT to elderly patients at home was examined in 1 observational study comparing older (>60 years) and younger patients [10]. The study did not control for other variables that differed between the older and younger patients. Older patients had lower rates of ability to self-administer (20% vs 41%, RR 0.48, 95% CI 0.31–0.74, P < .001), higher rates of urgent care visits (31.4 vs 14.3 per 1000 OPAT days, IRR 2.20, 95% CI NR, P < .001), higher rates of calls to physicians and pharmacies (14.3 vs 8.57 per 1000 OPAT days, IRR 1.67, 95% CI NR, P = .04), and higher rates of requirement for social work intervention (7.1 vs 2.9 per 1000 OPAT days, IRR 2.45, 95% CI NR, P = .01) than younger patients [10]. Given the substantial risk of bias in this single study, the available data provide insufficient evidence to allow a conclusion that more resources are required to deliver OPAT in the elderly than in younger patients. The evidence from the relevant studies is summarized in Table 8.

Rationale for the Recommendation

Clinical improvement, readmission, and adverse events were considered critical outcomes. There was low-quality evidence for equivalence in readmission and adverse events between older and younger patients on OPAT and very low-quality evidence for comparison of clinical improvement or healthcare utilization.

Many elderly patients are consigned to receive OPAT in SNFs because of lack of insurance coverage for various components of the home OPAT package (medications, supplies, nursing), but most patients prefer to be discharged to home. For some patients, treatment in an infusion center may be an option. For others, this this may not be an option because of the lack of a suitable infusion center in the patient's geographic area or inability to make daily trips to the infusion center. OPAT at home is generally less labor intensive for the healthcare system than OPAT in a SNF.

Accounting for patient's values and preferences, the overall balance of costs, benefits, and harms, the equivalence in critical outcomes, and lack of evidence of harm, there is sufficient evidence to make a strong recommendation that older patients may be treated with OPAT at home. This recommendation assumes that potential challenges to OPAT in the elderly, such as cognition, mobility, and dexterity, have been duly considered and that the patient or caregiver is able to communicate with the treatment team if necessary.

V. Should infants aged <1 month be treated with OPAT at home?

Recommendation

5. No recommendation can be made regarding whether infants aged <1 month may be treated with OPAT at home (no recommendation, very low-quality evidence). Decisions should be made on a case-by-case basis.

Evidence Summary

Treatment failure, adverse events, and hospital readmission have not been directly compared between neonates (aged <1 month) and older infants and children treated with OPAT in any published studies. Successful use of OPAT at home for neonates has been reported in 2 case series. No infectious relapses or treatment complications were noted in 1 study that included 51 neonates treated with ceftriaxone at home (majority intramuscular) [65]. Additionally, few complications were reported in a study that described OPAT care for 95 neonates with an average age at discharge of 5 days [66]. Four patients required an antimicrobial change due to loss of vascular access, and 4 had a change in antimicrobial (ceftriaxone to ampicillin and gentamicin) due to hyperbilirubinemia. Of note, all patients were treated with a peripheral, rather than a central, catheter.

Rationale for the Recommendation

The extremely limited number of reports of use of OPAT for neonates is reinforced by the fact that patient age is reported as among the most important considerations that impact the decision to use OPAT by pediatric ID specialists [67]. Several clinical and logistical factors make OPAT more challenging for neonates than for other children. OPAT use in neonates has generally been

Table 8. Evidence Table: Outpatient Parenteral Antimicrobial Therapy in the Elderly: Comparison of Outcomes in Older Versus Younger Patients

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Clinical improvement	Insufficient evidence	No difference in rate of cured, improved, or stable (90% vs 94% of OPAT courses [RR 0.97, 95% CI 0.90–1.05, $P = .43$]) in 1 study [10] Age was not associated with OPAT failure among patients treated with OPAT for infective endocarditis (OR 1.01, 95% CI 0.98–1.05, $P = .47$) in 1 study [58]	2 cohort studies (n = 231, 80) [10, 58]	Low	Risk of bias (–1) Confounding (+1)	Low
Readmission	No difference in readmission	No difference in rate of readmission during the clinical episode (8% vs 7% of OPAT courses, RR 1.07, 95% CI 0.33–3.49, $P = .93$) or within 3 months (14% vs 16% of OPAT courses, RR 0.88, 95% CI 0.40–1.93, $P = .75$)[a] in 1 study [59] Higher age was not associated with 30-day readmission (OR 1.09 per decade, 95% CI 0.99–1.21, $P = .10$ [60]; HRs 1.27, 1.13, 1.20 for higher age groups vs 18–63 years age group, none significant [61]; not significant on univariable analysis, age not included in multivariable analysis [62]), or readmission while on OPAT (OR 0.99, 95% CI 0.97–1.00, $P = .13$) [63], or 6-week readmission (OR NR, 95% CI NR, $P = .16$) [64], in a total of 5 studies Age >70 years was associated with a higher hazard of clinical deterioration (readmission or death)[b] (HR 1.6, 95% C.I. 1.1–2.2, $P = .008$)[5] in 1 study [50]	7 cohort studies (n = 2229, 420, 145, 782, 379, 400, 96) [50, 59–64]	Low	…	Low
Adverse events	No difference in adverse events	No difference in overall rate of adverse events (16% vs 16% of OPAT courses (RR 0.94, 95% CI 0.38–2.35, $P = .89$)[a] in 1 study [59] Similar rates of catheter-associated bloodstream infection (0.76 vs 0.23 per 1000 OPAT days, IRR 3.26, 95% CI 0.17–192.10, $P = .65$)[a] in 1 study [10] Similar rates of catheter occlusion (3.03 vs 2.32 per 1000 OPAT days, IRR 1.30, 95% CI 0.45–3.67, $P = .74$)[a] in 1 study [10] Increasing age was not associated with more vascular access complications (IRR 0.99, 95% C.I. 0.98–1.00, $P = .04$ [55]; OR 1.0, 95% CI 0.99–1.01, P NR) [62] in 2 studies Increasing age was not associated with line infection ($P = .57$ on univariable analysis, not included in multivariable model) or other line events in a multivariable model (OR 0.997, 95% CI NR, $P = .57$) in 1 study [51] Higher rate of nephrotoxicity in the elderly (3.03 vs 0.46 per 1000 IV antibiotic days, IRR 6.51, 95% CI 1.30–44.89, $P = .02$)[a] in 1 study [10]	5 cohort studies (n = 231, 2638, 1461, 145, 420) [10, 51, 55, 59, 62]	Low	…	Low
Healthcare resource utilization	Insufficient evidence	Lower rate of ability to self-administer (20% of courses vs 41% of courses (RR 0.48, 95% CI 0.31–0.74, $P < .001$)[a] [10] Higher rate of urgent care visits (31.4 vs 14.3 per 1000 OPAT days, IRR 2.20, 95% CI NR, $P < .001$)[a] [10] Higher rate of calls to physicians or pharmacists (14.3 vs 8.57 per 1000 OPAT days, IRR 1.67, 95% CI NR, $P = .04$) [10] Higher rate of requirement for social work intervention (7.1 vs 2.9 per 1000 OPAT days, IRR 2.45, 95% CI NR, $P = .01$)[a] [10]	1 cohort study (n = 231) [10]	Low	Risk of bias (–1) Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NR, not reported; OPAT, outpatient parenteral antimicrobial therapy; RR, relative risk.

[a]Calculated from data reported in the study.

[b]The outcome reported in the study was "clinical deterioration," which was a composite outcome of readmission or death. There were 2 deaths so, effectively, the outcome could be considered readmission.

discouraged for serious infections such as meningitis [68]. For such serious infections, the signs suggestive of treatment failure or clinical worsening may be relatively subtle. Therefore, clinicians may feel that the entire course of treatment must be completed in an inpatient setting where both compliance and continuous clinical monitoring are ensured. However, it should be acknowledged that the consequences of prolonged hospitalization instead of OPAT for neonates may be especially substantial in terms of economic and social costs to the family, as certain infections (eg, bacterial or herpes simplex virus meningitis) require treatment duration of up to 3 weeks. Another important factor is that some home care companies will not provide services for neonates. Additionally, some hospitals may not have the technical capabilities to place a central line suitable for OPAT at home in neonates.

In summary, OPAT use for neonates is extremely limited due to a variety of clinical and technical factors, some of which are unique to this vulnerable patient population. The absence of evidence about the safety and efficacy of OPAT using central catheters in neonates, especially for invasive infections such as meningitis, remains an important research gap for pediatric investigators.

ANTIMICROBIAL UTILIZATION

VI. Is it safe and appropriate to administer the first OPAT dose of a new antimicrobial at home?

Recommendation

6. In patients with no prior history of allergy to antimicrobials in the same class, the first dose of a new parenteral antimicrobial may be administered at home under the supervision of healthcare personnel who are qualified and equipped to respond to anaphylactic reactions (weak recommendation, very low-quality evidence).

Evidence Summary

No studies have compared the outcomes of allergic reactions or other drug-related adverse events in patients treated with OPAT where the initial dose of an antimicrobial was administered outside the healthcare system environment (eg, in the patient's home) to outcomes when administered within the healthcare system (eg, in the hospital inpatient service, ED, infusion center, or physician office).

Reports of anaphylaxis related to administration of OPAT have been rare. No instances of anaphylaxis were reported in a study examining allergic reactions in 770 patients who received 1000 courses of home OPAT with 25 different antimicrobials [69]. Of note, in that study, 90% of antibiotics and virtually all prescribed beta lactam antibiotics or vancomycin were administered via continuous infusion, which may reduce the likelihood of allergic reactions. In another study of 2009 OPAT episodes, 0.2% of courses were complicated by anaphylaxis [49]. The timing of these reactions was not reported. It is recognized that serious adverse events from antimicrobials may occur on subsequent administrations after the first dose has been tolerated. Among 1000 courses of OPAT at home, allergic reactions were noted in 28 courses, with the mean time to allergic reaction being 19.6 days [69]. Of the 3 episodes of perioral angioedema that were noted, onset of symptoms was delayed, ranging from 13 to 33 days after the start of therapy.

Rationale for the Recommendation

For many patients starting OPAT, therapy is continued from hospital discharge to an outpatient setting, and the patient has already demonstrated adequate tolerance to the chosen antimicrobial. However, in some instances, OPAT initiation may involve starting a new or entirely different treatment as an outpatient. The most serious concern about administering the first dose of an antimicrobial at home is the ability to manage an immediate hypersensitivity reaction or anaphylaxis, conditions that can be life-threatening. Due to concerns about patient safety and to ensure the appropriate management of anaphylaxis, the 2004 IDSA Practice Guidelines for OPAT recommended that the first OPAT dose be administered in a supervised healthcare setting before allowing OPAT administration at home [22].

There is increasing recognition that other considerations must inform practice. For some patients (eg, elderly, disabled, hospice), the potential benefit of first-dose observation in a healthcare facility is greatly outweighed by the inconvenience and cost of transport to the facility. The 2012 UK OPAT Good Practice Recommendations assert that the patient's home may be a suitable setting if the first dose is administered in the presence of a person competent to manage anaphylaxis (eg, home care nurse) [70]. This practice has been adopted in some places in the United States and in other countries around the world [71]. Reports related to this practice have not provided reason to suggest that this has been an unsafe undertaking [72]. There are no clear guidelines about how long a patient should be observed after administration of the first dose of a new antimicrobial. The usual practice is 30 minutes [73].

Given the rarity of severe immediate type 1 allergic reactions, it is reasonable to administer the first dose of an antimicrobial in a patient's home under the supervision of a competent healthcare worker in patients with no prior history of allergy to antimicrobials in the same class.

VASCULAR ACCESS DEVICES

For the purposes of uniformity and clarity in this guideline, VADs are referred to as either central or noncentral. In OPAT, the principal central devices are peripherally inserted central catheters (PICCs) and long-term central catheters (LTCCs), of which there are 2 main types: tunneled central venous catheters (t-CVCs) and ports. Noncentral catheters include midline catheters (MCs) which are peripheral lines placed in the larger veins of the upper arm with the catheter tip destination at or below the axillary line, and short peripheral catheters (SPCs) (Table 9).

VII. In patients needing short courses of OPAT, is it acceptable to use a midline catheter (MC) instead of a central venous catheter?

Recommendation

7. In adult patients needing short courses of OPAT (less than 14 days), a MC may be used rather than a central catheter (weak recommendation, very low-quality evidence). No recommendations can be made regarding the use of MCs in pediatric patients.

Evidence Summary

Four studies comparing complications of MCs vs PICCs can be used to address this question in OPAT patients [51, 74–76]. One was a small, randomized, controlled trial (N = 54) that compared outcomes in inpatients expected to be treated with up to 6 days of vancomycin who were randomized to receive either a MC or a PICC [74]. The study was limited by its small size, short duration, and indirectness to OPAT patients since it was an inpatient venue. The second was an observational study that examined vascular access complications in 328 adult patients with cystic fibrosis who received 231 MCs and 97 PICCs, 48% of whom were receiving home-based OPAT [75]. The mean in situ time for MCs was 22 days and that for PICCs was 14 days. A third inpatient observational study compared outcomes among 206 patients who had PICCs vs 200 patients who had MCs for a variety of indications [76]. The fourth was a multivariable analysis that examined factors associated with vascular access complications in a large OPAT cohort [51].

A composite of catheter-related adverse events overall was reported in 3 studies [74–76]. An increased risk of adverse events among patients with MCs compared to patients with PICCs (19.5% vs 5.8%, OR 3.90, 95% CI 1.92–8.48, $P < .001$) was found in 1 study [76], but no significant difference was found in the other 2 studies (19.9% vs 17.9%, RR 1.00, 95% CI 0.35–2.89, $P = 1.0$ [74] and 14 vs 11 per 1000 VAD days, IRR 1.18, 0.62–2.22, $P = .62$ [75]) for MCs and PICCs, respectively.

Occurrence of major complications and minor complications were reported in all 4 studies [51, 74–76]. Vascular catheter infections and deep venous thrombosis (DVT) were considered major complications. More DVTs were reported in MCs (5.96% vs 0.0%) in 1 study [75], but it is not clear if this was a statistically significant difference. There were no line infections with either type of catheter in another study [51]. There was no difference in the occurrence of major complications in the other 2 studies (9.0% vs 4.9%, OR 1.94, 95% CI 0.87–4.47, $P = .12$ [76]; 0% vs 0% [74]). More minor complications were found among patients with MCs in 1 study (11.5% vs 1.5%, OR 8.76, 95% CI 2.84–37.21, $P < .001$ [76]) but not in another (19.9% vs 17.9%, RR 1.00, 95% CI 0.35–2.89, $P = 1.0$ [74]).

Table 10 outlines the evidence from these studies. Taken together, the available evidence provides insufficient information to draw conclusions about the relative safety of MCs vs PICCs.

Table 9. Vascular Access Devices Commonly Used in Outpatient Parenteral Antimicrobial Therapy

Central Catheters	Noncentral Catheters

• Peripherally inserted central catheters
• Long-term central catheters
  • Tunneled central vein catheters
  • Ports
	• Midline catheters
	• Short peripheral catheters

Rationale for the Recommendation

Vascular access complications were considered the critical outcome. There was very low-quality evidence for increased risk of complications with MCs vs PICCs during OPAT. MCs may be preferred by some providers as they provide a longer dwell time compared to SPCs and a less invasive option compared to central lines, as well as faster placement and lower cost. In addition, the fact that MC-associated bloodstream infections are not counted as central line–associated bloodstream infections may have increased the use of MCs for vascular access in hospitalized patients. However, there are limited data on OPAT outcomes in patients with MCs, and the available studies provide insufficient evidence with respect to outcomes for MCs vs PICCs.

A reasonable definition of a short duration of OPAT is a treatment course that lasts less than 14 days. Using an expert consensus method such as a modified Delphi approach (RAND/UCLA Appropriateness Method), appropriateness criteria for use and care of VADs were developed for hospitalized and SNF patients only [77]. Among patients receiving peripherally compatible infusates, this group recommended the use of a MC for infusions anticipated to last 14 or fewer days and preferential use of a PICC for infusions anticipated to last 15 or more days among hospitalized patients [77].

On occasion, a MC may be selected for a course of therapy anticipated to be short but then extended for a longer period. Very limited data suggest that having a MC in place for more than 2 weeks is reasonably safe. In a retrospective cohort study of 92 patients in palliative home care with no comparator group, MCs had a median catheter dwell time of 85 days (range 1–365 days) [78]. Premature MC removal was reported in 7.7% due to mechanical complications, which included obstruction (4.3%, N = 4), accidental dislodgement (2.2%, N = 2), and catheter damage (1.1%, N = 1). There were no reports of infectious complications. In the setting of a well-functioning catheter, there is no compelling argument to exchange a MC for a PICC if an anticipated short OPAT course requires extension.

Lack of evidence of harm when MCs are used for short periods and the increasing willingness of the medical community to use MCs warrants a weak recommendation that it is acceptable to use a MC instead of a CVC for patients requiring courses of OPAT lasting fewer than 14 days. Studies are needed to examine the safety of MCs used for OPAT courses lasting more than 14 days.

Table 10. Evidence Table: Vascular Access Complications During Outpatient Parenteral Antimicrobial Therapy: Comparison for Patients With Midline Catheters Versus Peripherally Inserted Central Catheters

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Vascular access complications overall	Insufficient evidence	More complications overall with MCs (19.5% vs 5.8%, OR 3.90,[a] 95% CI 1.92–8.48,[a] $P < .001$) in 1 study with high risk of bias [76] No difference (19.9% vs 17.9%, RR 1.00, 95% CI 0.35–2.89,[a] $P = 1.0$ [74]; 14 vs 11 complications per 1000 vascular access device days, IRR 1.18, 95% CI 0.62–2.22, $P = .62$ [75]) in 2 studies	1 RCT (n = 54) [74] 2 cohort studies (n = 328, 406) [75, 76]	High	Risk of bias (–2) Inconsistency (–1) Indirectness (–1)	Very low
Major complications	Insufficient evidence	No difference in major complications (0% vs 0%) [74]; 9.0% vs 4.9%, OR 1.94,[a] 95% CI 0.87–4.47[a], $P = .12$ [76]) in 2 studies More DVT in MCs (5.9% vs 0.0%) reported in 1 study (tests of significance not reported [75] MCs not associated with line infections compared to PICCs (no line infections with either) in 1 study [51]	1 RCT (n = 54) [74] 3 cohort studies (n = 2766, 328, 406) [51, 75, 76]	High	Risk of bias (–1) Indirectness (–1) Imprecision (–1)	Very low
Minor complications	Insufficient evidence	More minor complications among patients with MCs (11.5% vs 1.5%, OR 8.76,[a] 95% CI 2.84–37.21,[a] $P < .001$) in 1 study with high risk of bias [76], but not in another (19.9% vs 17.9%, RR 1.00, 95% CI 0.35–2.89, $P = 1.0$) [74] No difference in dislodgement (6.6% vs 14.2%, RR 0.39, 95% CI 0.06–2.33,[a] $P = .40$ [74]; 6.90 vs 2.89 per 1000 vascular access device days, IRR 2.24, 95% CI 0.91–5.56, $P = .08$) [75] in 2 studies No difference in infiltration (10% vs 0%, RR 6.73, 95% CI 0.33–137.02,[a] $P = .24$) in 1 study [74] No difference in leak (3.3% vs 0%, RR 2.68, 95% CI 0.01–68.66,[a] $P = 1.00$) in 1 study [74] Higher odds of "other line events"[b] with MCs compared to PICCs (OR 4.1, $P = .03$) in 1 study [51]	1 RCT (n = 54) [74] 3 cohort studies (n = 2766, 328, 406) [51, 75, 76]	High	Risk of bias (–1) Inconsistency (–1) Indirectness (–1) Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; DVT, deep venous thrombosis; MC, midline catheter; OR, odds ratio; PICC, peripherally inserted central catheter; RCT, randomized, controlled trial; RR, relative risk.

[a]Calculated from data reported in the study.

[b]Other line events were a composite outcome of phlebitis, leakage, extravasation, and occlusion.

There are no published data in the pediatric population addressing the use of MCs in children needing OPAT. MCs have only recently been used for IV access in the inpatient pediatric population, and experience is limited.

VIII. Should vesicant antimicrobials (medications associated with tissue damage caused by extravasation) be administered via central catheters vs noncentral catheters only?

Recommendation

8. Mandatory use of a central catheter over a noncentral catheter for OPAT with vancomycin is not necessary (weak recommendation, very low-quality evidence). No recommendation can be made for choice of vascular catheter for OPAT with other vesicant antimicrobials such as nafcillin and acyclovir (no recommendation, very low-quality evidence).

Evidence Summary

The first question when evaluating the use of vesicant antimicrobials is the safety of vesicant vs nonvesicant antimicrobial administration via peripheral catheters. Two studies have addressed this question [51, 79]. The first, a retrospective cohort study of 153 surgical inpatients with SPCs that compared patients receiving vancomycin to all other antibiotics, found that infiltration scores were significantly higher with vancomycin compared to other antibiotics (mean score 0.20 vs 0.06, $P = .02$) [79]. Of note, MCs, which may be less prone to infiltration than SPCs, were not used in this study. A second study analyzed vascular device outcomes among 2766 OPAT patients [51]. Because only 4 recipients of vancomycin were included, the use of vancomycin was not incorporated in multivariable analyses. The study did, however, find a significant association with the use of flucloxacillin (a presumptive vesicant not used in the United States) and the occurrence of the composite of various line events, when controlled for the type of catheter (MC, t-CVC, PICC), gender, presence of comorbidity, person administering the OPAT, and duration of catheter use (OR 3.01, 95% CI NR, $P = .01$) [51]. The evidence from these studies is summarized in Table 11. Because of a high risk of bias in 1 study [79] and indirectness in the other [51], evidence from these studies is of too low quality to form a conclusion on the safety of vesicant antimicrobials via a peripheral catheter.

A second issue is the safety of vesicant antimicrobial administration via central vs noncentral catheters. One randomized,

controlled trial assessed vascular complications in patients receiving the vesicant antimicrobial vancomycin via a noncentral vs central catheter, specifically MCs vs PICCs, for fewer than 6 days (n = 54) [74]. No differences in rates of vascular access–related adverse events were found. The rate of adverse events was 19.9% among patients with MCs vs 17.9% among patients with PICCs (P = 1.0) [74]. There were no instances of phlebitis or thrombosis in either group. The study was limited by its small size and the very short duration of therapy. Its applicability to OPAT is restricted by the fact that participants were inpatients. The evidence from this study is summarized in Table 12. There have not been other comparisons of outcomes for other vesicant antimicrobials administered via central vs noncentral catheters.

Rationale for the Recommendation

Vascular access complications were considered the critical outcome. The evidence assessing harm from administering vancomycin via a MC rather than a central catheter was of very low quality.

The majority of antibiotics delivered in the OPAT setting are administered through central catheters (eg, PICCs), but increasingly, noncentral catheters, particularly MCs, are used. Therefore, it is important to understand the safety of vesicant antimicrobial agents in these settings.

Different groups have defined vesicants in different ways. One systematic review of the literature sought to identify medications associated with tissue damage caused by extravasation and, thus, characterized as vesicant drugs [80]. Cytotoxic medications (chemotherapy) were excluded. In the category of antimicrobials, 11 drugs were identified: acyclovir, amphotericin B, ampicillin, cloxacillin, gentamicin, metronidazole, nafcillin, oxacillin, penicillin, tetracycline, and vancomycin. The review found 232 extravasation cases, including 21 antibiotic events. Notably, except for nafcillin (9 reports), tetracycline (2 reports), and vancomycin (3 reports), the remainder of the drugs included only a single citation. The Infusion Nurses Society recently published a list of noncytotoxic vesicant drugs, of which only 4 antimicrobials were classified as vesicants: acyclovir, nafcillin, pentamidine, and vancomycin [81].

Despite common perceptions, there is insufficient evidence to state that it is unsafe to administer vancomycin via a noncentral catheter. Of the 3 referenced studies, 1 used SPCs (not commonly used in OPAT) and found increased odds of infiltration with vancomycin [79]; a second had too few patients on vancomycin to analyze this as a risk factor [51]; and the third was a comparison of vancomycin vs other antimicrobials but was limited by its small size, very short duration of therapy, and indirectness to the question of use for OPAT (it was an inpatient study) [74].

Given the lack of evidence for harm in administering vancomycin via a MC, it is unnecessarily restrictive to mandate a requirement of a central catheter for OPAT with vancomycin. There is insufficient evidence to make a blanket catheter recommendation for all vesicant antimicrobials.

IX. Should patients with chronic kidney disease (CKD) requiring OPAT have a tunneled central venous catheter (t-CVC) for vascular access rather than a PICC?

Recommendation

9. For patients with advanced CKD requiring OPAT, a t-CVC is recommended rather than a PICC (strong recommendation, low-quality evidence).

Evidence Summary

Only 1 case-control study has examined the association between a history of PICC use and absence of a functioning arteriovenous fistula (AVF) for dialysis access [82]. A total of 120 patients with a lack of a functioning AVF (cases) were compared to 162 patients with a functioning AVF (controls). A history of having a PICC was found in 44.2% of cases but only in 19.7% of controls. A strong association was found between a history of PICC use and absence of a functioning AVF for dialysis (OR 2.8, 95% 1.5–5.5, P = .002). The evidence from this study is summarized in Table 13.

Table 11. Evidence Table: Vascular Access Complications During Outpatient Parenteral Antimicrobial Therapy Via a Noncentral Line: Comparison for Vesicants Versus Nonvesicant Antimicrobials

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors that Alter the Strength of Evidence	Final Evidence Strength
Vascular access complications	Insufficient evidence	Higher infiltration scores with vancomycin than with other antibiotics administered via SPCs (0.20 vs 0.06, P = .02) in 1 study [79] Flucloxacillin (presumptive vesicant) treatment was associated with increase in OLE[a] (OR 3.01, 95% CI NR, P = .01) in 1 study [51]	2 cohort studies (N = 153, 2766) [51, 79]	Low	Large effect (+1) Indirectness (–1) Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; NR, not reported; OLE, other line events; OR, odds ratio; SPC, short peripheral catheter.

[a]Other line events were a composite outcome of phlebitis, leakage, extravasation, and occlusion.

Table 12. Evidence Table: Outpatient Parenteral Antimicrobial Therapy With Vesicant Antimicrobials: Comparison of Outcomes for Patients Treated via a Midline Versus Those Treated via Central Line

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Vascular access complications	Insufficient evidence	No difference in complications overall (RR 1.00, 95% CI 0.35–2.89, $P = 1.0$) [74] No venous thrombosis or line infection in either group	1 RCT (n = 54) [74]	High	Risk of bias (–2) Imprecision (–1) Indirectness (–1)	Very low

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR = relative risk.

Rationale for the Recommendation

The critical outcome was functioning AVF. There was low-quality evidence for increased odds of a nonfunctioning fistula in patients who had had a PICC in the past. Among patients with CKD who currently need hemodialysis or may need hemodialysis in the future, vein preservation is paramount. The Centers for Medicare and Medicaid Services and the National Kidney Foundation have collaborated through the Fistula First Breakthrough Initiative (fistulafirst.org) and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI 2006 Clinical Practice Guidelines) to promote the prevalence of functioning AVFs in hemodialysis patients. These AVFs have superior patency rates and decreased mortality, morbidity, and cost compared to synthetic grafts and CVCs [82–96]. Specifically, fistulas are favored over central venous dialysis catheters, which have been shown to promote a chronic inflammatory state, create an ongoing risk of bloodstream infection, and increase both mortality and cost of chronic dialysis [83–89, 93–95, 97].

To increase the likelihood that patent vessels are available for placement of AVFs, guidelines have recommended that PICCs be avoided in those with advanced kidney disease, on dialysis, or with kidney transplants [98]. The CKD stage at which PICCs should be avoided has been debated. According to the American Society for Diagnostic and Interventional Nephrology/Association for Vascular Access Joint Clinical Practice Committee, patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or a serum creatinine level ≥2.0 mg/dL should undergo an expert vascular access assessment prior to placement of any VAD [98]. In the Michigan Appropriateness Guide for Intravenous Catheters study, a multidisciplinary panel of experts rated scenarios in which PICCs might or might not be indicated [77]. For patients with CKD stage 3b (eGFR of <45 mL/min/1.73 m^2) or greater or receiving renal replacement therapy, panelists recommended CVCs over PICCs and MCs to maximize upper extremity vein preservation.

The ability to provide effective dialysis is critical to survival for patients with end-stage renal disease. It is important for all medical personnel to preserve options for hemodialysis in patients who may need renal replacement therapy in the near future. In keeping with this goal and consistent with recommendations from other societies [98], a strong recommendation that PICCs be avoided in patients with advanced CKD requiring OPAT is warranted.

X. Should patients requiring frequent OPAT courses have a long-term central catheter (LTCC) inserted with the intention of leaving it in place between courses?

Recommendation

10. No recommendation can be made about whether patients who require frequent courses of OPAT should have a LTCC left in place between courses (no recommendation, no evidence).

Evidence Summary

Neither clinical outcomes nor patient satisfaction have been compared for a strategy of leaving a LTCC in place between courses vs repeatedly placing a new VAD for repeated courses of OPAT.

Table 13. Evidence Table: Comparison of Arteriovenous Fistula Failure Among Patients With and Without Prior Peripherally Inserted Central Catheters

Outcome	Conclusions	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
AV fistula failure	Higher odds of lack of functioning AV fistula	Lack of a functioning AV fistula was associated with having had a PICC in the past (OR 2.8, 95% CI 1.5–5.5, $P = .002$) [82]	1 case-control study (n = 282) [82]	Low	Large effect (+1) Imprecision (–1)	Low

Abbreviations: AV, arteriovenous; CI, confidence interval; OR, odds ratio; PICC, peripherally inserted central catheter.

Rationale for the Recommendation

For patients who are known to require repeated courses of OPAT, the options include leaving an LTCC such as an implanted port or t-CVC in place between episodes or placing a new catheter, typically a PICC, for each event. There are no clinical outcomes data comparing these 2 options.

Two small studies suggest that if the decision is made to place an LTCC for repeated courses of OPAT, patients may prefer a port rather than a tunneled catheter. In a follow-up to a randomized, controlled trial of acute leukemia patients with t-CVCs or implanted ports, 32 adult patients were periodically surveyed about their perceptions of vascular access strategies [99]. Overall, patients were more satisfied with the ports. In another retrospective cohort study of cystic fibrosis patients needing ongoing central venous access for OPAT who had received ports, 28 of 30 patients preferred the ports to the SPCs or CVCs that they had used before [100]. However, both studies involved surveys and only 1 involved OPAT patients, so the quality of the evidence does not allow for the formulation of a recommendation.

XI. Should the vascular access device be removed if a patient develops symptomatic catheter-associated venous thromboembolism (CA-VTE) while on OPAT?

Recommendation

11. It is not necessary to remove a vascular access device if CA-VTE develops during OPAT, as long as the catheter remains well positioned and arm pain and swelling decrease with anticoagulation (weak recommendation, very low-quality evidence).

Evidence Summary

Two uncontrolled clinical trials have evaluated outcomes among patients with CA-VTE in cancer patients who were managed with vascular catheter retention and anticoagulation [101, 102]. In the first study, patients were treated with dalteparin for 5–7 days, followed by warfarin, and were followed for 3 months [101]. In the second study, all patients were treated with rivaroxaban for 12 weeks [102].

Catheter function was 100% at 3 months in both studies [101, 102]. Recurrent thromboembolism occurred in 0% and 1.4% [101, 102], and major bleeding occurred in 4% and 10% [101, 102]. The evidence from these studies is shown in Table 14. In addition, 1 descriptive study found that only 3 of 83 cancer patients (4%) treated with catheter retention and anticoagulation developed catheter dysfunction while on rivaroxaban, and 2 patients had major bleeding [103].

Rationale for the Recommendation

Catheter function, recurrent symptomatic thromboembolism, and major bleeding were considered critical outcomes. There was low-quality evidence for ability to preserve catheter function and very low-quality evidence for risk of recurrent thromboembolism and major bleeding with anticoagulation. In addition, the population studied was that of cancer patients, not OPAT patients. Overall, these amount to very low-quality evidence for a net benefit of catheter preservation with anticoagulation in the setting of PICC thrombosis during OPAT.

The International Society on Thrombosis and Haemostasis [104], the Infusion Nurses Society [81], and the American College of Chest Physicians [105] have suggested that the occurrence of CA-VTE is, by itself, not an absolute reason to remove the catheter as long as the catheter remains well positioned and arm pain and swelling decrease with anticoagulation. The practice of maintaining the VAD when patients develop CA-VTE while on OPAT is being increasingly adopted by physicians; to date, this change in practice has not led to complications that raise concern about patient safety.

Catheter retention and anticoagulation allow continued use of the catheter in most cases. The potential for major bleeding must be factored into a decision regarding catheter retention and anticoagulation. However, if a patient develops CA-VTE while on OPAT and if there is continued need for a vascular catheter, the very low-quality evidence for a net benefit of catheter preservation warrants a weak recommendation that it is not necessary to remove the catheter and place a new one as long as the catheter is functional and arm pain and swelling decrease with anticoagulation.

Table 14. Evidence Table: Outcomes for Vascular Access Retention in the Setting of Catheter-Associated Venous Thromboembolism

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Overall Evidence Strength
Preservation of line function	Line function can be preserved	42/42[a] (100%) [101] and 70/70 (100%) [102] of patients had a functional catheter at 3 months	2 clinical trials (N = 74, 70) [101, 102]	Low	Large effect (+1) Indirectness (–1)	Low
Recurrent symptomatic thromboembolism	Insufficient evidence	0/74 (0%) [101] and 1 (1.43%) [102] had recurrent thromboembolism	2 clinical trials (N = 74, 70) [101, 102]	Low	Risk of bias (–1) Indirectness (–1)	Very low
Major bleeding	Insufficient evidence	3 (4%) and 7 (10%) had major bleeding [101, 102]	2 clinical trials (N = 74, 70) [101, 102]	Low	Indirectness (–1)	Very low

[a]The remaining catheters were removed before the end of the study for other reasons (no longer needed, 21; infection, 2; other reasons not study endpoints, 9).

XII. Should patients with prior CA-VTE be treated with prophylactic anticoagulation while on OPAT?

Recommendation

12. No recommendation can be made regarding the need to treat patients with a history of prior CA-VTE with prophylactic oral anticoagulation while on OPAT (no recommendation, no evidence).

Evidence Summary

Outcomes have not been compared for anticoagulation vs no anticoagulation for prevention of CA-VTE among patients with a prior history of CA-VTE in either inpatient or outpatient settings.

Rationale for the Recommendation

Several groups have recommended against anticoagulation for routine prophylaxis of CA-VTE in cancer patients [104, 106–110]. Guidelines have not addressed other populations. Patients who have had CA-VTE in the past may be at increased risk of CA-VTE with subsequent VADs. However, the use of oral anticoagulation to reduce the risk of CA-VTE in such patients has not been examined.

XIII. Should children receive OPAT through a PICC or a LTCC?

Recommendation

13. For most children requiring OPAT, a PICC should be placed rather than a LTCC (strong recommendation, very low-quality evidence).

Evidence Summary

One cohort study compared complications from PICCs vs LTCCs in children receiving OPAT [111]. Findings from this study are dated, and the evidence is all of low quality, as summarized in Table 15. These published data provide insufficient evidence to draw conclusions about differences in complications between the 2 catheter types.

Seven case series have described the utilization of PICCs in pediatric patients [112–118]. Reported rates of most catheter-related complications were low; line infections ranged from none to 7%, thrombosis ranged from none to 9%, mechanical complications ranged from 7% to 28%, and catheter removal ranged from 8% to 33%.

Rationale for the Recommendation

Vascular access complications were considered the critical outcome. There was very low-quality evidence for increased risk of vascular access complications with PICCs compared to LTCCs in children.

The available literature comparing outcomes of PICCs vs LTCCs in children is very limited. Although the single reported study comparing PICCs to LTCCs found more minor complications with PICCs [111], there are many reasons to consider PICCs to be a safer option in children currently. The study was done at a time when use of PICCs in children was relatively new. Since then, PICCs have been used extensively in children, and with increasing use has come increasing comfort with their use. The collective experience of pediatricians is that PICCs are much safer than appears to be the case from the findings in this study, and PICCs are much more convenient to place than LTCCs.

Mechanical complications in children with PICCs have decreased as experience with their use has accrued, resulting in a decline in reported complication rates from >25% in earlier studies [111, 112, 114] to <10% in more recent studies [115, 116, 118]. LTCCs require placement by an experienced surgeon in the operating room under general anesthesia. In current practice, PICCs are typically placed by trained nurses with the aid of ultrasound at the bedside, though they may also be placed by an interventional radiologist [119]. Given the relative ease of placement of PICCs and declining complication rates

Table 15. Evidence Table: Comparison of Vascular Access Complications Among Pediatric Patients With Peripherally Inserted Central Catheters and Long-Term Central Catheters

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Overall Evidence Strength
Overall complications	Insufficient evidence	No difference in overall complications (36% vs 24%, RR 1.49,[a] 95% CI 1.00–2.23,[a] *P* = .07) [111]	1 cohort study (N = 234, 104 PICC, 130 LTCC) [111]	Low	Risk of bias (–1) Imprecision (–1)	Very low
Major complications	Insufficient evidence	No difference in infectious complications (details not reported) [111]	1 cohort study (N = 234, 104 PICC, 130 LTCC) [111]	Low	Risk of bias (–1) Imprecision (–1)	Very low
Minor complications	Insufficient evidence	More mechanical complications in PICCs (27% vs 15%, RR 1.84,[a] 95% CI 1.09–3.11,[a] *P* = .03) [111]	1 cohort study (N = 234, 104 PICC, 130 LTCC) [111]	Low	Risk of bias (–1) Imprecision (–1)	Very low
Time to first complication	Insufficient evidence	Shorter time to first complication with PICCs (median 41 days vs 61 days, *P* = .003) (HR not reported) [111]	1 cohort study (N = 234, 104) PICC, 130 LTCC) [111]	Low	Risk of bias (–1) Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; HR, hazard ratio; LTCC, long-term central catheter; PICC, peripherally inserted central catheter; RR, relative risk.

[a]Calculated from data reported in the study.

associated with their use, PICCs have become the most common type of VAD selected for pediatric OPAT in the United States [118, 120] and other developed countries [121] in children who do not have a preexisting LTCC in place. Given the widespread adoption of PICCs in children, it is unlikely that any additional studies comparing PICCs and LTCCs in children will be done.

Mechanical complications of PICCs have been noted more often in older children; the risk for these complications has been reported to increase with longer dwell time and when the tip of the catheter is not centrally located [114, 117, 118]. Newer anchoring devices may reduce the risk of dislodgement [122, 123].

Giving due consideration to balancing benefits, harms, burdens, and utilization of resources for pediatric OPAT, a strong recommendation is warranted that insertion of PICCs (by appropriately trained nursing teams or interventional radiologists) is preferable to placement of LTCCs (in an operating room under general anesthesia) in most circumstances. Some pediatricians may prefer LTCCs over PICCs when the anticipated duration of OPAT is unusually long.

MONITORING

XIV. Should patients receiving OPAT have laboratory test monitoring while on therapy? If so, which tests should be done and how often?

Recommendation

14. Serial laboratory testing should be monitored in patients receiving OPAT (strong recommendation, high-quality evidence). Data are insufficient to make evidence-based recommendations about specific tests and specific frequencies of monitoring for individual antimicrobials used in OPAT.

Evidence Summary

Two adult studies and 1 pediatric study have addressed the importance of laboratory test monitoring in patients receiving OPAT [63, 124, 125]. Effective laboratory test monitoring entails the performance of laboratory tests and the availability of results to the physician or team overseeing the OPAT course. One study compared readmission while on OPAT for patients whose laboratory test results were available to the treatment team vs those for whom they were not (total 400 patients) [63]. The second study examined 60-day readmission and ED visits for patients who were seen by an ID transitions service (IDTS), where laboratory test results were available to the treating physicians. These patients were compared to those not followed by the IDTS, where laboratory test results were usually not available (total 488 patients) [124]. The third study was an observational cohort study of outcomes (including readmission while on OPAT) in 407 episodes of pediatric OPAT before and after implementation of a dedicated medical support team [125].

The odds of readmission while on OPAT were lower with effective monitoring (OR 0.40, 95% CI 0.21–0.74, $P = .003$) in 1 adult study [63] and in the pediatric study (OR 0.45, 95% CI 0.24–0.86, $P = .014$) [125], but a statistically significant reduction in risk of readmission was not demonstrated in the other adult study (OR 0.38, 95% CI 0.10–1.52, *P* NR for 30-day readmission and OR 0.45, 95% CI 0.12–1.34, *P* NR for 60-day readmission) [124]. In all studies, residual confounders would have likely decreased the effect of monitoring in reducing odds of readmission. The evidence from these 3 studies is summarized in Table 16. With 2 studies demonstrating a large effect despite confounders that would have the effect of reducing the size of the effect, this constitutes a high level of evidence strength that effective monitoring of OPAT is associated with reduced readmission.

There are no published studies that directly address the question of which laboratory tests should be followed and how often for patients receiving specific antibiotics. One study assessed eosinophilia as a predictor of adverse events in a prospective cohort of 824 patients in their OPAT program [126]; 25% of patients developed eosinophilia

Table 16. Evidence Table: Comparison of Hospital Readmission in the Presence Versus Absence of Effective Outpatient Parenteral Antimicrobial Therapy Laboratory Test Result Monitoring

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Overall Evidence Strength
Readmission	Lower risk of readmission	Lower odds of readmission while on OPAT with effective monitoring (OR 0.40[a] 95% CI 0.21–0.74, $P = 0.003$ [63]; OR 0.45, 95% CI 0.24 to 0.86, $P = .014$ [125]) in 2 studies No statistically significant difference in 30-day readmission (OR 0.38, 95% CI 0.10–1.52, *P* NR) or 60-day readmission (OR 0.45, 95% CI 0.12–1.34, *P* NR) in 1 study [124]	3 cohort studies (n = 400, 488, 407) [63, 124, 125]	Low	Large effect (+1) Confounding (+1)	High

Abbreviations: CI, confidence interval; NR, not reported; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio.

[a]Calculated from data reported in the study.

over a median duration of therapy of 41 days. Treatment with vancomycin, penicillin, rifampin, and linezolid was significantly associated with eosinophilia. In a multivariable analysis, eosinophilia was found to be a predictor of subsequent hypersensitivity reactions (HSRs; rash: HR 4.16, 95% CI 2.54–6.83, $P < .0001$; renal injury: HR 2.13, 95% CI 1.36–3.33, $P = .0009$), although most patients (70%) with eosinophilia did not develop any HSRs.

Rationale for the Recommendation

Readmission and ED visits were considered the critical outcomes. There was high-quality evidence that effective monitoring of OPAT laboratory results was associated with reduced risk of readmission. There were no data on ED visits.

No comprehensive study has systematically explored the incidence of adverse drug events (ADEs) associated with antibiotics used in OPAT. Not surprisingly, some antibiotics are used much more frequently than others in studies of OPAT (eg, vancomycin, ceftriaxone, cefazolin, piperacillin/tazobactam). Consequently, more ADEs have been reported in association with these agents. In addition, ADEs often develop while patients are receiving multiple OPAT antibiotics, making it difficult to accurately attribute such events to one drug vs another. Despite these limitations, evidence shows that adverse reactions while on OPAT are common, occurring at a reported rate of 11.8% to 63.2% [35–37, 124, 127].

Many studies report following the monitoring table from the IDSA guideline published in 2004, which generally advocates for weekly testing for most antibiotics [1]. Serial surveys of the IDSA/Centers for Disease Control and Prevention EIN demonstrated that 98% [27] and 77% [28] of respondents followed the 2004 IDSA guideline monitoring recommendations.

Effective laboratory monitoring requires that appropriate monitoring tests be done and the results be made available to the physician or team overseeing the OPAT course. Effective laboratory monitoring for OPAT appears to be facilitated in institutions by having a dedicated team for management of OPAT. Additional important outcomes noted by Keller et al following introduction of an IDTS for OPAT patients included increased receipt of laboratory test results (increasing from 37.4% to 94.3%), improved attendance at outpatient follow-up appointments (60.9% to 79.6%), and decreased antimicrobial prescribing errors at discharge (18.1% to 1.4%) [124].

In summary, the high-quality evidence that effective laboratory monitoring is associated with lower risk of readmission and the potential to identify problems before they become severe merit a strong recommendation that laboratory tests be monitored for patients on OPAT. The tests required and the frequency of testing vary by the antimicrobial the patient is receiving. Short courses of OPAT may not require laboratory monitoring. Tables 2 and 3 outline the panel's recommendations based on pharmacokinetic properties of antimicrobials, common adverse effects, and implications of potential adverse effects.

XV. For patients receiving vancomycin as part of OPAT, should vancomycin serum levels be measured regularly throughout the course of treatment?

Recommendation

15. Vancomycin blood levels should be measured regularly throughout the course of OPAT treatment (strong recommendation, very low-quality evidence). The optimal frequency of measurement is undefined, but the general practice in the setting of stable renal function is once weekly.

Evidence Summary

No published studies have directly compared outcomes of patients receiving vancomycin in OPAT settings who either did or did not have serial monitoring of vancomycin levels.

A related question is whether it is necessary to follow vancomycin levels throughout the treatment course or whether this test may be avoided for patients who have stable renal function and appropriate vancomycin levels in the early weeks of OPAT. This question can be informed by knowledge of when vancomycin nephrotoxicity has been noted to occur during OPAT. In a US retrospective cohort of 579 OPAT patients receiving vancomycin (not continuous infusion), of the 154 patients who developed nephrotoxicity, 64 (42%) did so after 14 days [127], highlighting that vancomycin nephrotoxicity can occur at any time during the treatment course, even with previously stable renal function.

Rationale for the Recommendation

Given that vancomycin has a narrow therapeutic window, serum vancomycin levels should be monitored during therapy of more than a few days duration. Vancomycin for OPAT appears to be associated with more adverse events than comparator antibiotics. In 1 propensity score-matched cohort study comparing vancomycin and daptomycin used in an OPAT setting, vancomycin-treated patients had a higher incidence of rash and nephrotoxicity than daptomycin-treated patients (7.7 vs 3.2 per 1000 OPAT days, respectively, IRR 2.63, 95% CI 1.16–6.67, $P = .002$) and required a greater number of antimicrobial interventions (27.1 vs 5.6 per 1000 OPAT days, respectively, IRR 4.76, 95% CI 2.78–9.09, $P < .001$) [128]. The narrow therapeutic margin of vancomycin in OPAT has been highlighted in 2 retrospective studies of outpatients receiving continuous vancomycin infusion, where higher vancomycin levels were associated with nephrotoxicity [129, 130]. In both studies, vancomycin steady-state levels were measured at least weekly. Among 102 patients in Singapore, nephrotoxicity was associated with serum concentrations >28 mg/L (OR 21.2, 95% CI 2.7–167.8, $P = .004$) in a multivariable analysis [129]. In an Australian cohort of 155 OPAT episodes, nephrotoxicity was associated with a steady-state level >30 mg/L (OR 8.7, 95% CI 3.1–29.6, $P < .001$) in multivariable analysis [130]. It should be noted that continuous infusion of vancomycin is not commonly done in the United States.

Ample published clinical data link nephrotoxicity to higher vancomycin trough levels that are now commonly utilized in the treatment of methicillin-resistant *Staphylococcus aureus*

infections, particularly deep-seated infections [131–133]. In addition to vancomycin accumulation, other factors that could contribute to nephrotoxicity in OPAT patients include the concomitant use of other nephrotoxins, a high Acute Physiology and Chronic Health Evaluation (APACHE) score, and the use of vasopressors [133]. Based on 1 observational study that found that nephrotoxicity is frequently noted more than 2 weeks into the course of treatment [127] and consistent with the clinical experience of the members of the guideline panel, we recommend that vancomycin drug levels be monitored throughout the course of OPAT, not just during the initial phase of treatment. Whether serial measurement can be useful in averting other manifestations of vancomycin toxicity (eg, leukopenia) remains uncertain due to lack of clinical data.

In summary, vancomycin levels should be monitored throughout the OPAT course to ensure adequate and safe treatment. The reader is referred to a previously published consensus statement for management of vancomycin that addresses appropriate dosing, timing, and monitoring of serum concentrations [134]. This statement, which is widely followed, recommends vancomycin dose adjustments based on serum trough levels. There is emerging consensus that monitoring of the area under the curve/minimum inhibitory concentration ratio may allow more appropriate dosing than monitoring of serum vancomycin trough levels, but this practice has not yet gained widespread adoption.

XVI. How frequently should patients on OPAT have scheduled physician office visits for monitoring of treatment?

Recommendation

16. No generalized recommendation on frequency of outpatient follow-up can be made for patients treated with OPAT (no recommendation, no evidence). The treating physician should dictate the frequency of office visits, giving consideration to patient characteristics, the nature of the infection, the patient's tolerance of and response to therapy, and individual patient social factors.

Evidence Summary

No published studies have compared outcomes in relation to frequency of outpatient follow-up in patients receiving OPAT.

Rationale for the Recommendation

It is important to recognize that there are different models of OPAT, each with unique patterns of nursing and physician oversight and each with their own schedule of follow-up and observation. There is great variability in the frequency with which patients are seen by a physician who is overseeing OPAT. Despite previous IDSA guidelines that recommended weekly outpatient visits for patients receiving OPAT [1], only 29% of respondents in the 2006 EIN Survey of OPAT saw their patients at least weekly [27]. Some programs report physician evaluation as frequently as every 1–2 weeks [8, 52]. Other programs see patients after therapy, with more frequent visits as clinical needs dictate [128]. Regarding nursing oversight, the most common reported site of OPAT is at home (90%) [27], where patients usually have at least weekly nursing visits. Patients who receive OPAT at an infusion center are physically seen daily by nurses who administer their antimicrobial therapy.

The potential benefits of frequent ID physician office visits must be weighed against the practicalities of the patient being able to get to the clinic. For patients who are receiving OPAT in an infusion center, weekly physician visits are a typical component of the oversight program. For patients who are receiving OPAT at home or in SNFs, the physical condition of the patient or availability of transportation services (which may involve traveling great distances) may render frequent ID physician visits impractical. The frequency of ID physician visits for any individual patient should be determined by the treating physician, giving due consideration to patient characteristics, the disease being treated, how the patient is tolerating the treatment, and the socioeconomic conditions associated with the OPAT course.

Monitoring While on Aminoglycosides

The Monitoring Section of the Guidelines Committee also considered the question of monitoring OPAT patients receiving aminoglycoside antibiotics. Aminoglycoside use is generally limited in most OPAT settings. There is no published literature that would allow systematic evaluations of various aspects of aminoglycoside OPAT. The known toxicity of aminoglycosides warrants careful monitoring during OPAT, and the narrow therapeutic range warrants dose adjustments based on serum drug levels. However, important questions about frequency of serum drug level monitoring and the optimal schedule of monitoring for both renal and oto-vestibular toxicities (eg, serial audiograms) are currently unanswerable based on the published literature.

ANTIMICROBIAL STEWARDSHIP

XVII. Should all patients have an infectious disease (ID) expert review prior to initiation of OPAT?

Recommendation

17. All patients should have ID expert review prior to initiation of OPAT (strong recommendation, very low-quality evidence).

Evidence Summary

Outcomes of OPAT with and without ID expert review were compared in 3 observational studies [125, 135, 136]. The first compared outcomes in 407 episodes of pediatric OPAT before and after implementation of a dedicated OPAT medical support team, which included a consultant pediatric ID physician and/or a fellow [125]. The second assessed 100 adults discharged on ertapenem, 60 of whom had ID expert review prior to discharge

[135]. The third included 210 pediatric patients, of whom 114 had ID consultation prior to discharge from hospital [136].

Outcomes evaluated in these studies included clinical cure [135], readmissions [125, 135, 136], and ED visits [136]. Clinical cure rates were not found to be different between patients with and without ID consultation in 1 small study (78% vs 80%, OR 0.90, 95% CI 0.34–2.43, $P = 1.00$) [135]. A substantially lower odds of readmission (OR 0.45, 95% CI 0.24–0.86, $P = .014$) was noted in the largest of these studies (n = 407) [125] but not in the 2 smaller studies (15% vs 13%, OR 1.24, 95% CI 0.38–4.00, $P = .96$ [131]; 5.3% vs 2.1%, OR 2.61, 95% CI 0.51–13.25, $P = .41$) [136]. The use of ED visits was no different (7.0% vs 4.2%, OR 1.74, 95% CI 0.51–5.96, $P = .56$) among ID vs no ID consultation patients in 1 of the small OPAT cohorts [136]. The evidence from these studies is summarized in Table 17.

Rationale for the Recommendation

Readmission and ED visits were considered critical outcomes. There was moderate-quality evidence that OPAT with ID expert review was associated with lower risk of hospital readmission than OPAT without ID expert review. There was very low-quality evidence that ID expert review was associated with improvement in clinical cure or reduction in ED visits. These findings amount to overall very low-quality evidence for a benefit of ID expert review in OPAT.

Inappropriate use of antimicrobials (unnecessary parenteral treatment when oral therapy would have sufficed and the unnecessary use of antibiotic treatment entirely) has been widely reported in the adult and pediatric literature. ID stewardship, in the form of expert review, has been credited with the curtailment of unnecessary OPAT in several observational studies [124, 125, 137–141]. In these studies, consultations were provided by either an ID specialist [137, 138, 140] or by "teams" that consisted of ID specialists plus trained pharmacists and discharge planners [124, 125, 139, 141]. A switch from IV to oral administration was achieved in 43 of 263 (16%) [138], 16 of 56 (29%) [137], 66 of 250 (26.4%) [139], and 17 of 44 (39%) [140]. In a recently published pediatric report, a 24% reduction in the rate of OPAT prescribing was realized by the institution of an ID-led OPAT stewardship program [141]. In addition, in various studies, antibiotic therapy was not felt to be necessary at all in a substantial proportion of patients: 6 of 573 (1%) [135], 1 of 44 (2.3%) [140], 38 of 415 (9.2%) [139], 28 of 263 (10.6%) [138], and 10 of 100 (10%) [135]. Other frequently described interventions included changes in the dose, duration, and choice of IV antimicrobial. ID team intervention was credited with enhanced coordination of care after hospital discharge [124].

OPAT administration in nontraditional locations, such as dialysis units, has not been well studied but appears to be particularly susceptible to overuse. One retrospective review of antimicrobial prescribing in hemodialysis units over a 12-month period noted that among 1003 antimicrobial doses prescribed, 276 (29.8%) were classified as inappropriate, unnecessarily broad, or not needed at all [142].

Curtailment of antibiotic use after ID expert review prior to OPAT has not been associated with poor outcomes. In 2 observational studies, adult patients for whom OPAT was denied did well, with none of the OPAT-denied patients having an ED visit or readmission related to infection within 30 days [140, 143]. In a third observational study, readmission rates for pediatric patients discharged on oral antibiotics did not increase after implementation of enhanced OPAT stewardship that resulted in an estimated 24% of patients being discharged on no or oral antibiotics instead of IV antibiotics, suggesting that curtailment of OPAT by ID expert review did not cause harm [141]. In another study of 56 patients denied OPAT, 7 patients

Table 17. Comparison of Outcomes for Patients Who Had Infectious Diseases (ID) Expert Review Versus No ID Expert Review

Outcome	Conclusion	Summary of Findings	Quantity and Type of Evidence	Starting Level of Evidence	Factors That Alter the Strength of Evidence	Final Evidence Strength
Clinical cure	Insufficient evidence	No difference (78%[a] vs 80%,[a] OR 0.90,[a] 95% CI 0.34–2.43,[a] $P = 1.00$[a]) [135]	1 cohort study (N = 100) [135]	Low	Risk of bias (–1) Imprecision (–1)	Very low
Readmission	Lower risk of readmission	Lower odds of readmission in ID intervention cohort (OR 0.45, 95% CI 0.24–0.86, $P = .014$) in 1 study (N = 407) with low risk of bias [125] No difference (5.3%[a] vs 2.1%,[a] OR 2.61,[a] 95% CI 0.51–13.25,[a] $P = .41$[a]) [136];15%[a] vs 13%,[a] OR 1.24,[a] 95% CI 0.38–4.00,[a] $P = .96$[a] [135] in 2 studies with high risk of bias	3 cohort studies (N = 407, 100, 210) [125, 135, 136]	Low	Large effect (+1) Imprecision (–1) Confounding (+1)	Moderate
Emergency Department visits	Insufficient evidence	No difference (7.0%[a] vs 4.2%,[a] OR 1.74,[a] 95% CI 0.51–5.96,[a] $P = .56$[a]) in 1 study [136]	1 cohort study (N = 210) [136]	Low	Risk of bias (–1) Imprecision (–1)	Very low

Abbreviations: CI, confidence interval; ID, infectious diseases; OR, odds ratio.

[a]Calculated from data reported in the study.

(12.5%) had treatment failure. Six of the 7 were noncompliant with their oral medications, and the seventh had infections that were deemed incurable by the ID consult service based on the underlying disease processes, regardless of the route of antibiotic administration [137].

OPAT for pediatric patients remains a safe and effective alternative to prolonged hospitalization for appropriately selected patients to complete therapy for complicated infections such as bacteremia and endocarditis or for patients with cystic fibrosis. The advantages of OPAT relative to prolonged hospitalization are substantial. These include decreased medical costs and an earlier return to usual daily activities at home both for patients and caregivers. For example, some school-aged children may return to school while receiving treatment at home. However, there is mounting evidence that oral therapy can be substituted for OPAT without compromising cure rates. Safety is enhanced by avoiding OPAT-related complications for certain clinical conditions where OPAT has traditionally been the preferred treatment mode. The evidence supporting this practice includes studies comparing oral vs parenteral therapy for osteomyelitis [144, 145], perforated appendicitis [146], and complicated pneumonia [147, 148]. As a result, ensuring that OPAT is only prescribed for patients where an equivalent oral therapy is not available is a high priority for pediatric ID specialists and pediatric antimicrobial stewardship programs.

Estimated cost savings involve reductions in hospital expenses and avoidance of central lines. In the study by Conant et al, the overall cost avoidance of averted OPAT in 56 patients was $3487 per patient [137]. In another retrospective review, after accounting for the cost of pharmacist time, the institution realized a net savings of $620 per OPAT referral [139]. In a report of 44 patients who underwent mandatory ID consultation prior to OPAT, 17 patients were switched from IV to oral therapy, resulting in a cost savings of $1550 per patient [140].

In addition to a demonstration of direct benefit of ID expert review for OPAT, there is indirect evidence for the value of ID specialists in the management of infectious conditions. ID consultation for inpatients with suspected infection has been shown to be associated with lower mortality and readmissions [149]. ID consultation has been shown to reduce mortality in patients with *S. aureus* bacteremia in several studies. Both a systematic review and a metaanalysis of these studies have been published [150, 151].

ID expert review may take different forms, depending on the resources available. It may take the form of traditional ID consultation [137, 138, 140], ID care transition team [124, 125, 139], OPAT stewardship team [141], or an ID pharmacist–managed program in collaboration with an ID physician [152]. Oversight of OPAT by ID physicians can be expected to provide value for the patient. Novel models need to be developed to allow ID support of decision-making about antimicrobial use in dialysis units.

Antimicrobial resistance has been identified as a global health emergency. It is widely recognized that there is large-scale inappropriate antimicrobial prescribing. The current global crisis of antimicrobial resistance demands better stewardship of our antibiotic resources. The body of evidence showing substantial misuse of OPAT, reasonable control of antibiotic misuse when there is ID expert review, and lack of patient harm when ID expert review leads to limitation of antibiotic use and moderate-strength evidence that ID expert review is associated with a reduction in hospital readmissions warrants a strong recommendation that ID expert review be obtained prior to initiation of OPAT.

FUTURE DIRECTIONS

The guideline panel identified areas of specific interest for future research. Given the current opiate addiction crisis in the United States, an area of need is the development of newer models of care for PWID, potentially expanding on nontraditional sites of care and newer technologies, perhaps including telemedicine. Also, in view of the burgeoning application of midline catheters, the safety of their use for OPAT courses of longer than 2 weeks duration should be delineated. The safety of vancomycin delivered through a peripheral catheter should be addressed. Additionally, data on the safety and efficacy of OPAT in younger infants (<1 month) are needed. Finally, an OPAT registry, following in the footsteps of the work of Tice and others, should be reestablished in the United States [153]. This would enable us to capitalize on the tremendous amount of siloed data accumulating at large OPAT sites and answer these and other questions about the care of patients receiving OPAT.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Tice AD, Rehm SJ, Dalovisio JR, et al.; IDSA. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis **2004**; 38:1651–72.
2. Guyatt GH, Oxman AD, Kunz R, et al.; GRADE Working Group. Going from evidence to recommendations. BMJ **2008**; 336:1049–51.
3. Guyatt GH, Oxman AD, Kunz R, et al.; GRADE Working Group. Incorporating considerations of resources use into grading recommendations. BMJ **2008**; 336:1170–3.
4. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ **2008**; 336:995–8.
5. Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ **2008**; 336:924–6.
6. OPAT eHandbook. In: Shah A, Norris A. (https://www.idsociety.org/opat-ehandbook/) CRG Publishing and Infectious Diseases Society of America, **2016**. Accessed 26 October 2018.
7. Rucker RW, Harrison GM. Outpatient intravenous medications in the management of cystic fibrosis. Pediatrics **1974**; 54:358–60.
8. Petrak RM, Skorodin NC, Fliegelman RM, Hines DW, Chundi VV, Harting BP. Value and clinical impact of an infectious disease-supervised outpatient parenteral antibiotic therapy program. Open Forum Infect Dis **2016**; 3:ofw193.
9. Nguyen HH. Hospitalist to home: outpatient parenteral antimicrobial therapy at an academic center. Clin Infect Dis **2010**; 51:S220–3.
10. Cox AM, Malani PN, Wiseman SW, Kauffman CA. Home intravenous antimicrobial infusion therapy: a viable option in older adults. J Am Geriatr Soc **2007**; 55:645–50.
11. Barr DA, Semple L, Seaton RA. Outpatient parenteral antimicrobial therapy (OPAT) in a teaching hospital-based practice: a retrospective cohort study describing experience and evolution over 10 years. Int J Antimicrob Agents **2012**; 39:407–13.
12. Gordon SM, Shrestha NK, Rehm SJ. Transitioning antimicrobial stewardship beyond the hospital: the Cleveland Clinic's community-based parenteral anti-infective therapy (CoPAT) program. J Hosp Med **2011**; 6:S24–30.
13. Madigan T, Banerjee R. Characteristics and outcomes of outpatient parenteral antimicrobial therapy at an academic children's hospital. Pediatr Infect Dis J **2013**; 32:346–9.
14. Rentala M, Andrews S, Tiberio A, et al. Intravenous home infusion therapy instituted from a 24-hour clinical decision unit for patients with cellulitis. Am J Emerg Med **2016**; 34:1273–5.
15. Kayley J, Berendt AR, Snelling MJ, et al. Safe intravenous antibiotic therapy at home: experience of a UK based programme. J Antimicrob Chemother **1996**; 37:1023–9.
16. Martone WJ, Lindfield KC, Katz DE. Outpatient parenteral antibiotic therapy with daptomycin: insights from a patient registry. Int J Clin Pract **2008**; 62:1183–7.
17. Dalovisio JR, Juneau J, Baumgarten K, Kateiva J. Financial impact of a home intravenous antibiotic program on a Medicare managed care program. Clin Infect Dis **2000**; 30:639–42.
18. Antoniskis A, Anderson BC, Van Volkinburg EJ, Jackson JM, Gilbert DN. Feasibility of outpatient self-administration of parenteral antibiotics. West J Med **1978**; 128:203–6.
19. Poretz DM, Eron LJ, Goldenberg RI, et al. Intravenous antibiotic therapy in an outpatient setting. JAMA **1982**; 248:336–9.
20. Rehm SJ, Weinstein AJ. Home intravenous antibiotic therapy: a team approach. Ann Intern Med **1983**; 99:388–92.
21. Tice AD. An office model of outpatient parenteral antibiotic therapy. Rev Infect Dis **1991**; 13 Suppl 2:S184–8.
22. Poretz DM. Evolution of outpatient parenteral antibiotic therapy. Infect Dis Clin North Am **1998**; 12:827–34.
23. Wolter JM, Cagney RA, McCormack JG. A randomized trial of home vs hospital intravenous antibiotic therapy in adults with infectious diseases. J Infect **2004**; 48:263–8.
24. Board N, Brennan N, Caplan GA. A randomised controlled trial of the costs of hospital as compared with hospital in the home for acute medical patients. Aust N Z J Public Health **2000**; 24:305–11.
25. Corwin P, Toop L, McGeoch G, et al. Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital. BMJ **2005**; 330:129.
26. Chary A, Tice AD, Martinelli LP, Liedtke LA, Plantenga MS, Strausbaugh LJ; Infectious Diseases Society of America Emerging Infections Network. Experience of infectious diseases consultants with outpatient parenteral antimicrobial therapy: results of an Emerging Infections Network survey. Clin Infect Dis **2006**; 43:1290–5.
27. Lane MA, Marschall J, Beekmann SE, et al. Outpatient parenteral antimicrobial therapy practices among adult infectious disease physicians. Infect Control Hosp Epidemiol **2014**; 35:839–44.
28. Woosley RL, Heise CW, Gallo T, Tate J, Woosley D, Romero KA. QTdrugs List. Oro Valley, AZ: AZCERT, Inc. Available at: https://www.crediblemeds.org. Accessed 26 October 2018.
29. Cunha CB, D'Agata EM. Implementing an antimicrobial stewardship program in out-patient dialysis units. Curr Opin Nephrol Hypertens **2016**; 25:551–5.
30. Hoffman-Terry ML, Fraimow HS, Fox TR, Swift BG, Wolf JE. Adverse effects of outpatient parenteral antibiotic therapy. Am J Med **1999**; 106:44–9.
31. Gomez M, Maraqa N, Alvarez A, Rathore M. Complications of outpatient parenteral antibiotic therapy in childhood. Pediatr Infect Dis J **2001**; 20:541–3.
32. Ceroni D, Regusci M, Pazos JM, Saunders CT, Kaelin A. Risks and complications of prolonged parenteral antibiotic treatment in children with acute osteoarticular infections. Acta Orthop Belg **2003**; 69:400–4.
33. Pulcini C, Couadau T, Bernard E, et al. Adverse effects of parenteral antimicrobial therapy for chronic bone infections. Eur J Clin Microbiol Infect Dis **2008**; 27:1227–32.
34. Hale CM, Steele JM, Seabury RW, Miller CD. Characterization of drug-related problems occurring in patients receiving outpatient antimicrobial therapy. J Pharm Pract **2017**; 30:600–5.
35. Lee B, Tam I, Weigel B 4th, et al. Comparative outcomes of β-lactam antibiotics in outpatient parenteral antibiotic therapy: treatment success, readmissions and antibiotic switches. J Antimicrob Chemother **2015**; 70:2389–96.
36. Murphy JL, Fenn N, Pyle L, et al. Adverse events in pediatric patients receiving long-term oral and intravenous antibiotics. Hosp Pediatr **2016**; 6:330–8.
37. Muldoon EG, Snydman DR, Penland EC, Allison GM. Are we ready for an outpatient parenteral antimicrobial therapy bundle? A critical appraisal of the evidence. Clin Infect Dis **2013**; 57:419–24.
38. Tan SJ, Ingram PR, Rothnie AJ, et al. Successful outpatient parenteral antibiotic therapy delivery via telemedicine. J Antimicrob Chemother **2017**; 72:2898–901.
39. Forestier E, Gros S, Peynaud D, et al. Ertapenem administered intravenously or subcutaneously for urinary tract infections caused by ESBL producing enterobacteriacea. Med Mal Infect **2012**; 42:440–3.
40. Gauthier D, Schambach S, Crouzet J, Sirvain S, Fraisse T. Subcutaneous and intravenous ceftriaxone administration in patients more than 75 years of age. Med Mal Infect **2014**; 44:275–80.
41. Peeters O, Ferry T, Ader F, et al.; Lyon BJI Study Group. Teicoplanin-based antimicrobial therapy in *Staphylococcus aureus* bone and joint infection: tolerance, efficacy and experience with subcutaneous administration. BMC Infect Dis **2016**; 16:622.
42. Ho J, Archuleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother **2010**; 65:2641–4.
43. O'Toole TP, Conde-Martel A, Young JH, Price J, Bigelow G, Ford DE. Managing acutely ill substance-abusing patients in an integrated day hospital outpatient program: medical therapies, complications, and overall treatment outcomes. J Gen Intern Med **2006**; 21:570–6.

44. Beieler AM, Dellit TH, Chan JD, et al. Successful implementation of outpatient parenteral antimicrobial therapy at a medical respite facility for homeless patients. J Hosp Med **2016**; 11:531–5.
45. Hernandez W, Price C, Knepper B, McLees M, Young H. Oral parenteral antimicrobial therapy administration in a homeless population. J Infus Nurs **2016**; 39:81–5.
46. Jaeschke R, Guyatt GH, Dellinger P, et al.; GRADE Working Group. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ **2008**; 337:a744.
47. Schünemann HJ, Schünemann AH, Oxman AD, et al.; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ **2008**; 336:1106–10.
48. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 26 October 2018.
49. Matthews PC, Conlon CP, Berendt AR, 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**; 60:356–62.
50. Seetoh T, Lye DC, Cook AR, et al. An outcomes analysis of outpatient parenteral antibiotic therapy (OPAT) in a large Asian cohort. Int J Antimicrob Agents **2013**; 41:569–73.
51. Barr DA, Semple L, Seaton RA. Self-administration of outpatient parenteral antibiotic therapy and risk of catheter-related adverse events: a retrospective cohort study. Eur J Clin Microbiol Infect Dis **2012**; 31:2611–9.
52. Bhavan KP, Brown LS, Haley RW. Self-administered outpatient antimicrobial infusion by uninsured patients discharged from a safety-net hospital: a propensity-score-balanced retrospective cohort study. PLoS Med **2015**; 12:e1001922.
53. Kieran J, O'Reilly A, Parker J, Clarke S, Bergin C. Self-administered outpatient parenteral antimicrobial therapy: a report of three years experience in the Irish healthcare setting. Eur J Clin Microbiol Infect Dis **2009**; 28:1369–74.
54. Pajarón M, Fernández-Miera MF, Allende I, et al.; Hospital Valdecilla Endocarditis Study Group. Self-administered outpatient parenteral antimicrobial therapy (S-OPAT) for infective endocarditis: a safe and effective model. Eur J Intern Med **2015**; 26:131–6.
55. Shrestha NK, Shrestha J, Everett A, et al. Vascular access complications during outpatient parenteral antimicrobial therapy at home: a retrospective cohort study. J Antimicrob Chemother **2016**; 71:506–12.
56. Mallon WK. Is it acceptable to discharge a heroin user with an intravenous line to complete his antibiotic therapy for cellulitis at home under a nurse's supervision? No: a home central line is too hazardous. West J Med **2001**; 174:157.
57. Riazati N. Is it acceptable to discharge a heroin user with an intravenous line to complete his antibiotic therapy for cellulitis at home under a nurse's supervision? Yes: supervised home care ensures continued treatment at lower cost. West J Med **2001**; 174:156.
58. Duncan CJ, Barr DA, Ho A, Sharp E, Semple L, Seaton RA. Risk factors for failure of outpatient parenteral antibiotic therapy (OPAT) in infective endocarditis. J Antimicrob Chemother **2013**; 68:1650–4.
59. Pérez-López J, San José Laporte A, Pardos-Gea J, et al. Safety and efficacy of home intravenous antimicrobial infusion therapy in older patients: a comparative study with younger patients. Int J Clin Pract **2008**; 62:1188–92.
60. Allison GM, Muldoon EG, Kent DM, et al. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. Clin Infect Dis **2014**; 58:812–9.
61. Cramer S, Fonager K. Risk factors of 30-days re-hospitalization after Hospital at Home in a cohort of patients treated with parenteral therapy. Eur J Intern Med **2014**; 25:895–9.
62. Mujal A, Sola J, Hernandez M, et al. Safety and effectiveness of outpatient parenteral antimicrobial therapy in older people. J Antimicrob Chemother **2016**; 71:1402–7.
63. Huck D, Ginsberg JP, Gordon SM, Nowacki AS, Rehm SJ, Shrestha NK. Association of laboratory test result availability and rehospitalizations in an outpatient parenteral antimicrobial therapy programme. J Antimicrob Chemother **2014**; 69:228–33.
64. Ruh CA, Parameswaran GI, Wojciechowski AL, Mergenhagen KA. Outcomes and pharmacoeconomic analysis of a home intravenous antibiotic infusion program in veterans. Clin Ther **2015**; 37:2527–35.
65. Bradley JS, Ching DL, Wilson TA, Compogiannis LS. Once-daily ceftriaxone to complete therapy of uncomplicated group B streptococcal infection in neonates. A preliminary report. Clin Pediatr **1992**; 31:274–8.
66. Wagner CL, Wagstaff P, Cox TH, Annibale DJ. Early discharge with home antibiotic therapy in the treatment of neonatal infection. J Perinatol **2000**; 20:346–50.
67. Banerjee R, Beekmann SE, Doby EH, Polgreen PM, Rathore MH, Hersh AL. Outpatient parenteral antimicrobial therapy practices among pediatric infectious diseases consultants: results of an Emerging Infections Network survey. J Pediatric Infect Dis Soc **2014**; 3:85–8.
68. Rathore MH. The unique issues of outpatient parenteral antimicrobial therapy in children and adolescents. Clin Infect Dis **2010**; 51:S209–15.
69. Dobson PM, Boyle M, Loewenthal M. Home intravenous antibiotic therapy and allergic drug reactions: is there a case for routine supply of anaphylaxis kits? J Infus Nurs **2004**; 27:425–30.
70. Chapman AL, Seaton RA, Cooper MA, et al.; BSAC/BIA OPAT Project Good Practice Recommendations Working Group. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. J Antimicrob Chemother **2012**; 67:1053–62.
71. Thiele H. First dose of intravenous antibiotics in outpatient parenteral antimicrobial therapy/hospital in the home—criteria for administration at home. Journal of Pharmacy Practice and Research **2017**; 47:78–80.
72. Ma G, Annaliese T, Paul T, Dorothy T, Susan M, Gerald E. The safety of first-dose home IV antibiotic therapy. Can J Hosp Pharm **2007**; 60:106–13.
73. Gorski LA, Hadaway L, Hagle M, McGoldrick M, Meyer B, Orr M. Infusion therapy policies and procedures. 5th ed. Norwood, MA: Infusion Nurses Society, **2016**.
74. Caparas JV, Hu JP. Safe administration of vancomycin through a novel midline catheter: a randomized, prospective clinical trial. J Vasc Access **2014**; 15:251–6.
75. Sharp R, Esterman A, McCutcheon H, Hearse N, Cummings M. The safety and efficacy of midlines compared to peripherally inserted central catheters for adult cystic fibrosis patients: a retrospective, observational study. Int J Nurs Stud **2014**; 51:694–702.
76. Xu T, Kingsley L, DiNucci S, et al. Safety and utilization of peripherally inserted central catheters versus midline catheters at a large academic medical center. Am J Infect Control **2016**; 44:1458–61.
77. Chopra V, Flanders SA, Saint S, et al.; Michigan Appropriateness Guide for Intravenous Catheters (MAGIC) Panel. The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC): results from a multispecialty panel using the RAND/UCLA appropriateness method. Ann Intern Med **2015**; 163:S1–40.
78. Giuliani J, Andreetta L, Mattioli M, et al. Intravenous midline catheter usage: which clinical impact in homecare patients? J Palliat Med **2013**; 16:598.
79. Roszell S, Jones C. Intravenous administration issues: a comparison of intravenous insertions and complications in vancomycin versus other antibiotics. J Infus Nurs **2010**; 33:112–8.
80. Le A, Patel S. Extravasation of noncytotoxic drugs: a review of the literature. Ann Pharmacother **2014**; 48:870–86.
81. Gorski LA, Stranz M, Cook LS, et al.; Infusion Nurses Society Vesicant Task Force. Development of an evidence-based list of noncytotoxic vesicant medications and solutions. J Infus Nurs **2017**; 40:26–40.
82. El Ters M, Schears GJ, Taler SJ, et al. Association between prior peripherally inserted central catheters and lack of functioning arteriovenous fistulas: a case-control study in hemodialysis patients. Am J Kidney Dis **2012**; 60:601–8.
83. Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. J Vasc Surg **2003**; 38:1005–11.
84. Oliver MJ, Rothwell DM, Fung K, Hux JE, Lok CE. Late creation of vascular access for hemodialysis and increased risk of sepsis. J Am Soc Nephrol **2004**; 15:1936–42.
85. Ortega T, Ortega F, Diaz-Corte C, Rebollo P, Ma Baltar J, Alvarez-Grande J. The timely construction of arteriovenous fistulae: a key to reducing morbidity and mortality and to improving cost management. Nephrol Dial Transplant **2005**; 20:598–603.
86. Perera GB, Mueller MP, Kubaska SM, Wilson SE, Lawrence PF, Fujitani RM. Superiority of autogenous arteriovenous hemodialysis access: maintenance of function with fewer secondary interventions. Ann Vasc Surg **2004**; 18:66–73.
87. Schon D, Blume SW, Niebauer K, Hollenbeak CS, de Lissovoy G. Increasing the use of arteriovenous fistula in hemodialysis: economic benefits and economic barriers. Clin J Am Soc Nephrol **2007**; 2:268–76.
88. Woods JD, Turenne MN, Strawderman RL, et al. Vascular access survival among incident hemodialysis patients in the United States. Am J Kidney Dis **1997**; 30:50–7.
89. Allon M, Daugirdas J, Depner TA, Greene T, Ornt D, Schwab SJ. Effect of change in vascular access on patient mortality in hemodialysis patients. Am J Kidney Dis **2006**; 47:469–77.
90. Lynch JR, Wasse H, Armistead NC, McClellan WM. Achieving the goal of the Fistula First Breakthrough Initiative for prevalent maintenance hemodialysis patients. Am J Kidney Dis **2011**; 57:78–89.
91. Vassalotti JA, Jennings WC, Beathard GA, et al.; Fistula First Breakthrough Initiative Community Education Committee. Fistula First Breakthrough Initiative: targeting catheter last in fistula first. Semin Dial **2012**; 25:303–10.
92. McGill RL, Marcus RJ, Healy DA, Brouwer DJ, Smith BC, Sandroni SE. AV fistula rates: changing the culture of vascular access. J Vasc Access **2005**; 6:13–7.

93. Wasse H, Kutner N, Zhang R, Huang Y. Association of initial hemodialysis vascular access with patient-reported health status and quality of life. Clin J Am Soc Nephrol **2007**; 2:708–14.
94. Banerjee T, Kim SJ, Astor B, Shafi T, Coresh J, Powe NR. Vascular access type, inflammatory markers, and mortality in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal disease (CHOICE) study. Am J Kidney Dis **2014**; 64:954–61.
95. Solid CA, Carlin C. Timing of arteriovenous fistula placement and Medicare costs during dialysis initiation. Am J Nephrol **2012**; 35:498–508.
96. Navuluri R, Regalado S. The KDOQI 2006 Vascular Access Update and Fistula First Program synopsis. Semin Intervent Radiol **2009**; 26:122–4.
97. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney Int **2001**; 60:1443–51.
98. Hoggard J, Saad T, Schon D, Vesely TM, Royer T; American Society of Diagnostic and Interventional Nephrology, Clinical Practice Committee; Association for Vascular Access. Guidelines for venous access in patients with chronic kidney disease. A position statement from the American Society of Diagnostic and Interventional Nephrology, Clinical Practice Committee and the Association for Vascular Access. Semin Dial **2008**; 21:186–91.
99. Johansson E, Engervall P, Björvell H, Hast R, Björkholm M. Patients' perceptions of having a central venous catheter or a totally implantable subcutaneous port system—results from a randomised study in acute leukaemia. Support Care Cancer **2009**; 17:137–43.
100. Rodgers HC, Liddle K, Nixon SJ, Innes JA, Greening AP. Totally implantable venous access devices in cystic fibrosis: complications and patients' opinions. Eur Respir J **1998**; 12:217–20.
101. Kovacs MJ, Kahn SR, Rodger M, et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (the Catheter Study). J Thromb Haemost **2007**; 5:1650–3.
102. Davies GA, Lazo-Langner A, Gandara E, et al. A prospective study of rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2). Thromb Res **2017**.
103. Laube ES, Mantha S, Samedy P, Wills J, Harnicar S, Soff GA. Treatment of central venous catheter-associated deep venous thrombosis in cancer patients with rivaroxaban. Am J Hematol **2017**; 92:E9–E10.
104. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost **2013**; 11:71–80.
105. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest **2012**; 141: e419S–e96S.
106. Schoot RA, Kremer LC, van de Wetering MD, van Ommen CH. Systemic treatments for the prevention of venous thrombo-embolic events in paediatric cancer patients with tunnelled central venous catheters. Cochrane Database Syst Rev **2013**; 9:CD009160.
107. Kirkpatrick A, Rathbun S, Whitsett T, Raskob G. Prevention of central venous catheter-associated thrombosis: a meta-analysis. Am J Med **2007**; 120:901 e1–13.
108. Lokich JJ, Bothe A Jr, Benotti P, Moore C. Complications and management of implanted venous access catheters. J Clin Oncol **1985**; 3:710–7.
109. Mandala M, Falanga A, Roila F, Group EGW. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol **2011**; 22: vi85–92.
110. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest **2012**; 141: 7S–47S.
111. Hussain S, Gomez MM, Wludyka P, Chiu T, Rathore MH. Survival times and complications of catheters used for outpatient parenteral antibiotic therapy in children. Clin Pediatr **2007**; 46:247–51.
112. Dubois J, Garel L, Tapiero B, Dubé J, Laframboise S, David M. Peripherally inserted central catheters in infants and children. Radiology **1997**; 204:622–6.
113. Thiagarajan RR, Ramamoorthy C, Gettmann T, Bratton SL. Survey of the use of peripherally inserted central venous catheters in children. Pediatrics **1997**; 99:E4.
114. Van Winkle P, Whiffen T, Liu IL. Experience using peripherally inserted central venous catheters for outpatient parenteral antibiotic therapy in children at a community hospital. Pediatr Infect Dis J **2008**; 27:1069–72.
115. Le J, San Agustin M, Hernandez EA, Tran TT, Adler-Shohet FC. Complications associated with outpatient parenteral antibiotic therapy in children. Clin Pediatr **2010**; 49:1038–43.
116. Hodgson KA, Huynh J, Ibrahim LF, et al. The use, appropriateness and outcomes of outpatient parenteral antimicrobial therapy. Arch Dis Child **2016**; 101:886–93.
117. Racadio JM, Doellman DA, Johnson ND, Bean JA, Jacobs BR. Pediatric peripherally inserted central catheters: complication rates related to catheter tip location. Pediatrics **2001**; 107:E28.
118. Kovacich A, Tamma PD, Advani S, et al. Peripherally inserted central venous catheter complications in children receiving outpatient parenteral antibiotic therapy (OPAT). Infect Control Hosp Epidemiol **2016**; 37:420–4.
119. Nichols I, Doellman D. Pediatric peripherally inserted central catheter placement: application of ultrasound technology. J Infus Nurs **2007**; 30:351–6.
120. Maraqa NF, Rathore MH. Pediatric outpatient parenteral antimicrobial therapy: an update. Adv Pediatr **2010**; 57:219–45.
121. Patel S, Abrahamson E, Goldring S, Green H, Wickens H, Laundy M. Good practice recommendations for paediatric outpatient parenteral antibiotic therapy (p-OPAT) in the UK: a consensus statement. J Antimicrob Chemother **2015**; 70:360–73.
122. Krenik KM, Smith GE, Bernatchez SF. Catheter securement systems for peripherally inserted and nontunneled central vascular access devices: clinical evaluation of a novel sutureless device. J Infus Nurs **2016**; 39:210–7.
123. Yamamoto AJ, Solomon JA, Soulen MC, et al. Sutureless securement device reduces complications of peripherally inserted central venous catheters. J Vasc Interv Radiol **2002**; 13:77–81.
124. Keller SC, Ciuffetelli D, Bilker W, et al. The impact of an infectious diseases transition service on the care of outpatients on parenteral antimicrobial therapy. J Pharm Technol **2013**; 29:205–14.
125. Mace AO, McLeod C, Yeoh DK, et al. Dedicated paediatric outpatient parenteral antimicrobial therapy medical support: a pre-post observational study. Arch Dis Child **2017**.
126. Blumenthal KG, Youngster I, Rabideau DJ, et al. Peripheral blood eosinophilia and hypersensitivity reactions among patients receiving outpatient parenteral antibiotics. J Allergy Clin Immunol **2015**; 136:1288–94 e1.
127. Moh'd H, Kheir F, Kong L, et al. Incidence and predictors of vancomycin-associated nephrotoxicity. South Med J **2014**; 107:383–8.
128. Shrestha NK, Mason P, Gordon SM, et al. Adverse events, healthcare interventions and healthcare utilization during home infusion therapy with daptomycin and vancomycin: a propensity score-matched cohort study. J Antimicrob Chemother **2014**; 69:1407–15.
129. Ingram PR, Lye DC, Tambyah PA, Goh WP, Tam VH, Fisher DA. Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy. J Antimicrob Chemother **2008**; 62:168–71.
130. Norton K, Ingram PR, Heath CH, Manning L. Risk factors for nephrotoxicity in patients receiving outpatient continuous infusions of vancomycin in an Australian tertiary hospital. J Antimicrob Chemother **2014**; 69:805–8.
131. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother **2008**; 52:1330–6.
132. Minejima E, Choi J, Beringer P, Lou M, Tse E, Wong-Beringer A. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother **2011**; 55:3278–83.
133. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int J Antimicrob Agents **2011**; 37:95–101.
134. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis **2009**; 49:325–7.
135. Bauer K, Mangino JE, Paolo-Holman D, Goff DA. Outpatient parenteral antimicrobial therapy and antimicrobial stewardship. Infect Dis Clin Pract **2016**; 24: 328–31.
136. Akar A, Singh N, Hyun DY. Appropriateness and safety of outpatient parenteral antimicrobial therapy in children: opportunities for pediatric antimicrobial stewardship. Clin Pediatr **2014**; 53:1000–3.
137. Conant MM, Erdman SM, Osterholzer D. Mandatory infectious diseases approval of outpatient parenteral antimicrobial therapy (OPAT): clinical and economic outcomes of averted cases. J Antimicrob Chemother **2014**; 69:1695–700.
138. Shrestha NK, Bhaskaran A, Scalera NM, Schmitt SK, Rehm SJ, Gordon SM. Contribution of infectious disease consultation toward the care of inpatients being considered for community-based parenteral anti-infective therapy. J Hosp Med **2012**; 7:365–9.
139. Heintz BH, Halilovic J, Christensen CL. Impact of a multidisciplinary team review of potential outpatient parenteral antimicrobial therapy prior to discharge from an academic medical center. Ann Pharmacother **2011**; 45:1329–37.
140. Sharma R, Loomis W, Brown RB. Impact of mandatory inpatient infectious disease consultation on outpatient parenteral antibiotic therapy. Am J Med Sci **2005**; 330:60–4.
141. Hersh AL, Olson J, Stockmann C, et al. Impact of antimicrobial stewardship for pediatric outpatient parenteral antibiotic therapy. J Pediatric Infect Dis Soc **2017**.
142. Snyder GM, Patel PR, Kallen AJ, Strom JA, Tucker JK, D'Agata EM. Antimicrobial use in outpatient hemodialysis units. Infect Control Hosp Epidemiol **2013**; 34:349–57.

143. Shrestha NK, Bhaskaran A, Scalera NM, Schmitt SK, Rehm SJ, Gordon SM. Antimicrobial stewardship at transition of care from hospital to community. Infect Control Hosp Epidemiol **2012**; 33:401–4.
144. Keren R, Shah SS, Srivastava R, et al.; Pediatric Research in Inpatient Settings Network. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. JAMA Pediatr **2015**; 169:120–8.
145. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics **2009**; 123:636–42.
146. Rangel SJ, Anderson BR, Srivastava R, et al.; Pediatric Research in Inpatient Settings (PRIS) Network. Intravenous versus oral antibiotics for the prevention of treatment failure in children with complicated appendicitis: has the abandonment of peripherally inserted catheters been justified? Ann Surg **2017**; 266:361–8.
147. Stockmann C, Ampofo K, Pavia AT, et al. Comparative effectiveness of oral versus outpatient parenteral antibiotic therapy for empyema. Hosp Pediatr **2015**; 5:605–12.
148. Shah SS, Srivastava R, Wu S, et al. Intravenous versus oral antibiotics for postdischarge treatment of complicated pneumonia. Pediatrics **2016**; 138:e20161692.
149. Schmitt S, McQuillen DP, Nahass R, et al. Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. Clin Infect Dis **2014**; 58:22–8.
150. Paulsen J, Solligard E, Damas JK, DeWan A, Asvold BO, Bracken MB. The impact of infectious disease specialist consultation for *Staphylococcus aureus* bloodstream infections: a systematic review. Open Forum Infect Dis **2016**; 3:ofw048.
151. Vogel M, Schmitz RP, Hagel S, et al. Infectious disease consultation for *Staphylococcus aureus* bacteremia—a systematic review and meta-analysis. J Infect **2016**; 72:19–28.
152. Chung EK, Beeler CB, Muloma EW, Osterholzer D, Damer KM, Erdman SM. Development and implementation of a pharmacist-managed outpatient parenteral antimicrobial therapy program. Am J Health Syst Pharm **2016**; 73:e24–33.
153. Nathwani D, Tice A. Ambulatory antimicrobial use: the value of an outcomes registry. J Antimicrob Chemother **2002**; 49:149–54.