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Delivery models, efficacy, safety, and cost reduction of outpatient parenteral antimicrobial therapy in British Columbia

For nearly 50 years, outpatient parenteral antimicrobial therapy has been proven to benefit both the health care system and patients with severe infections.

ABSTRACT: Outpatient parenteral antimicrobial therapy is an important medical service that allows for the treatment of complex infections outside acute care hospitals. In BC, the practice has evolved over many decades to include both hospital-based and outpatient infusion centres, as well as home intravenous programs. Numerous publications demonstrate the safety, efficacy, and cost reduction of outpatient parenteral antimicrobial therapy, while reducing congestion in emergency departments. With increasing strain on inpatient facilities due to increased numbers of drug-resistant organisms and high-risk immunosuppressed patients with complex infections, outpatient parenteral antimicrobial therapy is a treatment modality that improves patient care and flow through the health care system.

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The practice of administering IV antibiotics in an outpatient setting was first described in Houston, Texas, in 1974, when an indwelling IV infusion set was used to treat chronic bronchopulmonary infection associated with cystic fibrosis in a pediatric population.[1] Numerous Canadian and international studies have evaluated the benefit of outpatient antimicrobial therapy in a variety of settings, including home administration and outpatient infusion centres.[2-4] In 1978, Dr Grant Stiver reported on the first Canadian IV antibiotic therapy at-home model, which involved 23 patients in Winnipeg over 12 months. Once infection had begun to resolve, patients who no longer required hospitalization could safely receive treatment through a home care program. The therapeutic efficacy and considerable cost savings of the model were also demonstrated.[5] In 1995, BC formally incorporated outpatient antimicrobial therapy into the regional home care program at the Vancouver Hospital and Health Sciences Centre.[6] These models have provided many benefits to health care systems, including reducing the length of hospital stay and avoiding unnecessary hospitalization, minimizing the risk of nosocomial complications, and improving patient quality of life.[2] Over the decades, the use of outpatient antimicrobial therapy has become a routine practice, with infectious diseases specialists expanding its application in managing increasingly complex infectious diseases.

The Infectious Diseases Society of America defines outpatient parenteral antimicrobial therapy (OPAT) as the administration of at least two doses of antimicrobial on different days without intervening hospitalization.[3] Over time, three main models of OPAT have been created: infusion centre, home-based administration, and skilled nursing facility. These different settings facilitate the delivery of medication and minimize the duration of patient hospitalization for antimicrobial therapy. Each modality operates under different criteria: some require patients to return to a health care facility such as a hospital clinic or outpatient centre for antimicrobial therapy, while in others, patients can receive antimicrobial treatment at home.

Delivery models

In the infusion centre model, antimicrobial therapy can be delivered in outpatient health care facilities. This model involves the greatest degree of clinical oversight by a multidisciplinary care team, which includes regular assessments by infectious diseases specialists and other physician groups, nursing administration of antimicrobial therapy and wound care, and

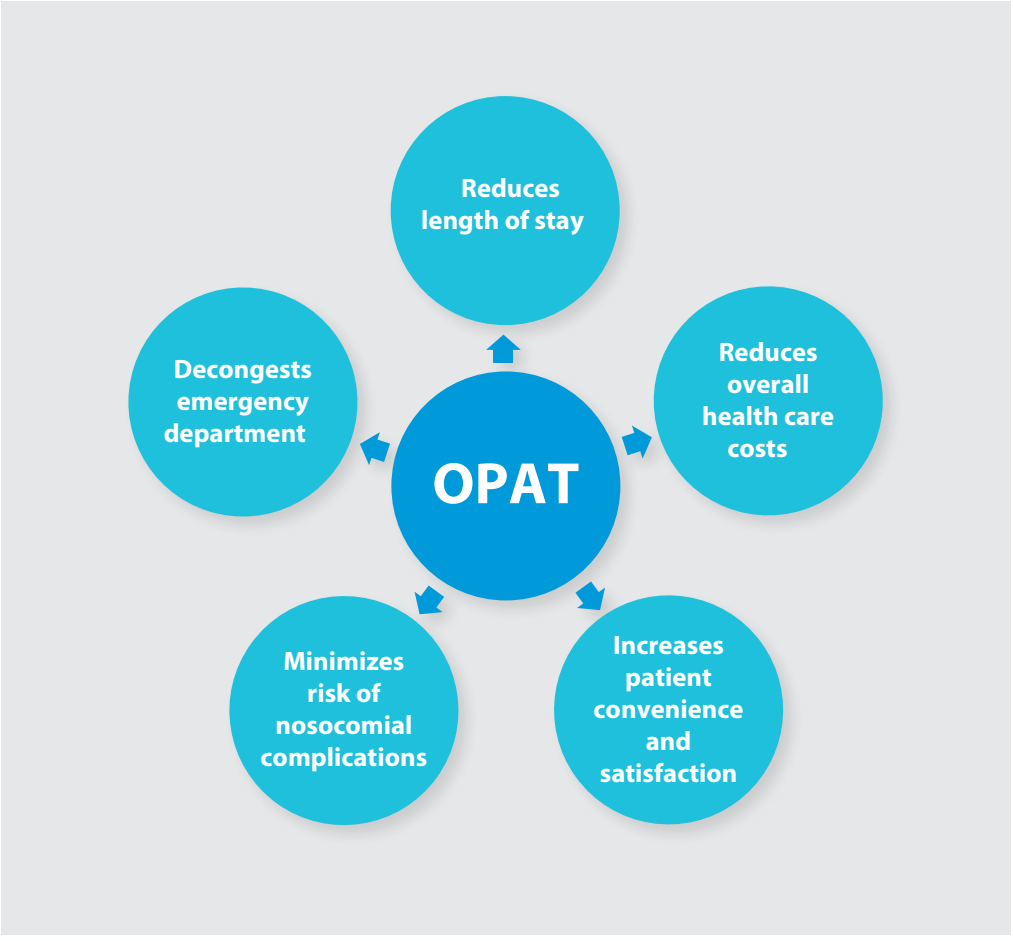

FIGURE 1. Outpatient parenteral antimicrobial therapy (OPAT) model for treating infections.

TABLE 1. Common antimicrobials used in outpatient parenteral antimicrobial therapy.

Common antimicrobial therapy	
Infusion centre	**Home IV therapy**
Amphotericin B	Amikacin
Cefazolin + Probenecid	Amphotericin B
Ceftriaxone	Ampicillin
Daptomycin	Cefazolin
Ertapenem	Ceftazidime
Ganciclovir	Ceftriaxone
Gentamicin	Cloxacillin
Micafungin	Daptomycin
Vancomycin	Ertapenem
	Ganciclovir
	Gentamicin
	Meropenem
	Penicillin G
	Piperacillin-Tazobactam
	Tigecycline
	Tobramycin
	Vancomycin

clinical pharmacist support for patient education and monitoring. The infusion centre can also be part of the acute care hospital setting, as an extension of the emergency department.[3]

The nurse administration model was developed for patients who are eligible to receive antimicrobial therapy at home.[3] In this setting, patients can receive visits from home nursing staff once or twice a day to administer antimicrobial therapy and conduct clinical assessments, or select patients can also be educated about aseptic techniques for antimicrobial self-administration at home. This model requires a certain level of patient or caregiver competency.

In the skilled nursing facility model, registered nurses administer antimicrobial therapy and provide other nursing needs, such as wound care.

The outpatient approach to antimicrobial therapy is highly cost-effective for the health care system.[2] At Surrey Memorial Hospital and the Jim Pattison Outpatient Care and Surgery Centre, the infectious diseases specialist-led infusion centre model with connections to the community for home IV therapy was originally created by Dr Yazdan Mirzanejad in 2005 and serves as a successful model for treating outpatient infections **[Figure 1]**. Patients are referred from the emergency department and inpatient wards and directly from the community for infectious diseases consultation. Following assessment, the infectious diseases physician determines a care plan that is carried out with the support of a multidisciplinary team in the most appropriate setting.

Antimicrobials

A wide range of antimicrobial therapy is used in OPAT; **Table 1** lists common antimicrobials that are used. The choice of antimicrobial agent depends on the OPAT model and the pharmacokinetic properties of the antimicrobial. For example, in infusion centres, due to specific hours of operation, it is practical to use only antimicrobials that require administration once or twice a day. Consequently, the home IV therapy model is a favorable option because a greater variety of antimicrobial therapies can be administered via a programmable pump with different dosing frequencies and narrower spectrums of activity.

The OPAT setting can be used to practise antimicrobial stewardship. The optimal practice consists of a timely transition from intravenous to oral antibiotics. This needs to be considered both at the point of referral to OPAT and during the course of therapy. General principles for when to step down from IV to suitable oral options include assessing the patient's clinical condition and ability to absorb oral antibiotic therapy, the pharmacokinetic/pharmacodynamic properties of oral agents, the availability of

an appropriate choice of oral agent, and the potential drug–drug and drug–host interactions.[7] Therefore, patients should be counseled when a change to another intravenous agent is being considered or when transition to oral therapy is deemed appropriate **[Table 2]**.

Efficacy

Emergency department flow and decongestion

Emergency department overcrowding, and prolonged wait times to receive treatment and specialist visits are persistent problems for many hospitals in different countries.[8] Congestion in the emergency department affects flow through the health care system, and in times of global crisis such as the COVID-19 pandemic, it becomes essential to use resources such as infusion centres to help ease congestion. Changes in admitting patterns have been one way of reducing demand for hospital beds.[9] Patients who require IV antibiotics may receive care in infusion centres. In this model, the appropriate specialty services at each facility are responsible for disease management and minimizing the need for general internal medicine physicians or hospitalists to admit patients to hospital and occupy emergency department beds.[8] The initial model of patient referral from the emergency department to infusion centre was created for adults with nonpurulent skin and soft tissue infection, which avoided hospitalization if patients were not septic.[10] Previous emergency department–based studies indicated that IV antibiotics are one of the most frequently administered medications in those settings.[11,12] The infusion centre model benefits the health care system because fewer return visits are made to emergency departments and family physician clinics. It also reduces emergency department overcrowding and helps identify adverse effects or treatment failures in a timely manner, which further reduces repeat presentations to the emergency department. The three main goals achieved by this model are reduced hospital admissions, increased patient convenience, and reduced number of emergency department visits.[13] A 2013 retrospective study of 1900 patients referred from the Surrey Memorial Hospital emergency department to the infusion centre at the Jim Pattison Outpatient Care and Surgery Centre for treatment of a variety of conditions revealed a median stay of 6.1 days, resulting in 3456 patient-days diverted from the emergency department and inpatient beds.[14]

Minimizing extended antibiotic exposure

Advances in infusion centre device technology and drug stability have made it possible to administer a wider range of antimicrobial therapies that previously were not practical in an OPAT setting.[3] However, appropriate treatment begins with the correct diagnosis. Many "infectious mimickers" present in these settings; therefore, it is essential to correctly identify the infection being treated in order to determine appropriate management **[Table 3]**. Timely administration of appropriate antibiotics in the emergency department can be

TABLE 2. Common infectious diseases treated with commonly used intravenous and oral antibiotic therapies.

Infectious disease condition	Home IV/infusion centre antibiotic therapy	Potential oral antimicrobial* (depending on culture results)
Osteoarticular infection		
Septic arthritis (native joint) *Staphylococcus aureus*	Cefazolin/cloxacillin/vancomycin	Cefadroxil/clindamycin/ doxycycline
Septic arthritis (prosthetic joint) *Staphylococcus aureus*	Cefazolin/cloxacillin/vancomycin + rifampin (orally)	(Doxycycline/levofloxacin) + rifampin
Osteomyelitis	Ceftriaxone + vancomycin	Doxycycline/trimethoprim-sulfamethoxazole
Diabetic foot infection	Ceftriaxone + metronidazole/ ertapenem	Amoxicillin clavulanic acid/ doxycycline
Skin and soft tissue infection		
Nonpurulent cellulitis	Cefazolin/ceftriaxone	Cephalexin
Purulent cellulitis/abscess	Daptomycin/vancomycin	Clindamycin/doxycycline/ trimethoprim-sulfamethoxazole
Intra-abdominal infection		
Diverticulitis/liver abscess/ peritonitis	Piperacillin/tazobactam	Amoxicillin clavulanic acid
Genitourinary infection		
Prostatitis/pyelonephritis	Ceftriaxone/ertapenem	Ciprofloxacin/trimethoprim-sulfamethoxazole

* Examples of the most common therapy; other antibiotics may be suitable depending on the microbiological results.

TABLE 3. Frequent "infectious mimickers."

Infectious diseases	Infectious mimickers
Cellulitis/skin and soft tissue infection	• Contact dermatitis • Deep vein thrombosis of lower or upper extremities • Eosinophilic cellulitis • Lipodermatosclerosis • Lymphedema • Papular urticaria • Pyoderma granulosum • Stasis dermatitis
Intra-abdominal infection	• Acute pancreatitis
Pneumonia	• Eosinophilic pneumonia • Pulmonary embolism • Pulmonary edema • Radiation pneumonitis
Septic arthritis	• Gout (urate crystals) • Pseudogout (calcium pyrophosphate)
Urinary tract infection	• Atrophic vaginitis • Drug-induced cystitis • Interstitial cystitis • Radiation cystitis

lifesaving. At the same time, antibiotics are not benign interventions, and unnecessary or inappropriate therapy can lead to community and patient harm, including antimicrobial resistance or harm associated with adverse effects.[15] In the OPAT setting, regardless of the model chosen, it is the treating physician's responsibility to direct and manage antimicrobial therapy. In the Surrey model and elsewhere around the province, the infectious diseases specialist is responsible for selecting the antimicrobial agent and duration of treatment in OPAT. Patients on IV antimicrobials may be discharged from the emergency department to infusion centres. They subsequently have a visit with the infectious diseases specialist in 1 to 3 days, at which time their treatment is further modified or, in some cases, discontinued if an infection is no longer present. In a study conducted in Queensland, Australia, the pattern of antibiotic prescribing in the emergency department and its overall appropriateness were evaluated by a panel of experts from the fields of infectious disease, microbiology, and emergency medicine, and by a senior antimicrobial stewardship pharmacist. It showed that in 1 in 3 patients who were prescribed an antibiotic regimen, the regimen was assessed as either suboptimal or inadequate. The antibiotic prescription was most commonly deemed to be inappropriate when the agent chosen was too broad, there was an unnecessary overlap of spectrums, or antibiotics were not required at all.[15] In 2013, a single-centre study in an infusion centre in Surrey, BC, showed that infectious diseases specialists modified the initial antibiotic therapy in 373 (66%) episodes of OPAT. The most common interventions were transitioning to oral antibiotic therapy (34%), discontinuation of antibiotic therapy (5%), and other changes including changes to alternative IV antibiotics (27%). This resulted in early antibiotic de-escalation in 211 patients.[14] A similar OPAT study conducted over 10 years with 7000 patients in Victoria, BC, showed that changes to initial antibiotic therapy given in the emergency department were made in 35% of patients.[16]

Safety

Adverse events

Outpatient antimicrobial therapy allows patients to receive parenteral therapy outside acute care settings. While hospitalized, patients have ready access to clinical assessments and laboratory testing to detect potential adverse drug events, whereas in OPAT settings, the frequency of this testing is reduced.[17] The types of adverse events associated with antimicrobials are not expected to be different for OPAT patients compared with hospital patients, but the incidence of reactions may differ.[3] In OPAT settings, patients may require long durations of antimicrobial therapy (weeks or months) because the outpatient service provides an opportunity to treat more complex infections (e.g., prosthetic joint infections and osteomyelitis), which will increase the cumulative incidence of adverse events to a variety of medications as treatment lengths increase. A readmission rate of 14% to 27% is common among OPAT patients.[14,18,19] A patient's readmission to hospital can be related to a variety of factors, including age, history of a drug-resistant organism, prior hospitalization in the past 12 months, and adverse events. In the Surrey, BC, infusion centre study of 2013, treatment failure occurred in 14.0% of patients and consisted of the following: 1.0% worsening infection, 5.2% related hospitalization, 4.0% unrelated hospitalization, 2.6% relapse, 4.6% absconded from therapy, and 0.6% mortality; the total success rate was 82.0%.[14] A study conducted at Tufts Medical Center in Boston showed that the most common reasons for 30-day readmission in 207 patients were not related to infection (30%) or the result of infection worsening (30%); however, 14% of patients were readmitted due to adverse events associated with antimicrobial treatment.[19] In a prospective study of 339 patients in Israel who were discharged to OPAT, 14.5% had significant adverse drug events that required a change in therapy, early termination of therapy, or readmission, or that resulted in *Clostridioides difficile* infection. Patients were at higher risk of developing significant adverse drug events in their first 2 weeks of OPAT, known as the hospital-to-home transition period, which highlights the importance of prudent prescribing of OPAT, ensuring proper dosing of medication, educating patients, and careful monitoring of adverse drug events.[18]

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Even though *Clostridioides difficile* infections are one of the adverse drug events related to readmission, the occurrence of these infections in patients receiving OPAT is rare. A retrospective study of 1514 patients in the UK who received antimicrobial therapy in teaching hospitals from 2006 to 2011 and who completed 16 750 OPAT days reported only seven patients with *Clostridioides difficile* infection; all but one of those patients had other possible causes of *Clostridioides difficile* infection.[20] The detection rate for *Clostridioides difficile* infections among OPAT patients is sufficiently low (2%) that with proper monitoring and clinical assessment, receiving prolonged courses of antimicrobial therapy in an OPAT setting is safe for patients.[21]

Peripheral line complication

The delivery of antimicrobial therapy in OPAT requires the use of vascular access devices. The type of device used varies based on different practice settings, the anticipated duration of treatment, and the antimicrobial selected.[22] The principal central devices used in OPAT are peripherally inserted central catheters and long-term central catheters. There are two main types of long-term central catheter: tunneled

central venous catheters and ports.[3] Peripherally inserted central catheters are inserted by a clinical nurse specialist; long-term central catheters need to be inserted by the radiology department. Each OPAT model, whether it involves home infusion, a hospital or outpatient facility infusion centre, or community centres, has specific vascular access requirements. Peripherally inserted central catheter lines are the most common type of vascular access used in an outpatient setting. In a large 13-year cohort study in the UK, peripherally inserted central catheter lines were used in 64% of patients who received antimicrobial therapy in infusion centres and in 71% of patients who received therapy at home.[23] Vascular catheters can put patients at risk of complications. Common complications are vascular catheter–related infection, occlusion, and venous thrombosis. Vascular catheter–related infection is defined as positive blood cultures or obvious purulence at the catheter site, which requires catheter removal. Vascular occlusions occur when the patient or caregiver is unable to infuse the IV antimicrobial due to lack of flow. Venous thrombosis is identified by clinical imaging evidence of deep or superficial venous thrombosis in the blood vessels.[22] In a retrospective study of 2766 OPAT patients in Scotland, line infection limited to midlines, peripherally inserted central catheters, and tunneled central venous catheters occurred in 2.3% of all line episodes (0.8 per 1000 line-use days).[24] In another retrospective cohort study in the United States, line complications in 3161 OPAT patient encounters were analyzed. Only OPAT courses that were conducted at home were included. The study identified 131 (9%) patients who had one or more vascular access complications, for a total of 144 complications, with an overall rate of 4.29 complications per 1000 OPAT days.[20] The most common complication was line occlusion, at a rate of 2.26 events per 1000 OPAT days. Thrombosis and line infection each occurred in less than 1% of OPAT courses overall, with only five line infections and 12 thrombotic complications.[22] Line complications can occur in the OPAT setting; however, the rate of severe complications such as line infections and thrombotic events is low in both infusion centres and home IV therapy.

Cost

Cost reduction of outpatient therapy

Outpatient parenteral antimicrobial therapy is associated with a low risk of adverse events such as hospital readmission and line complications, and is an effective model for easing hospital congestion and minimizing extended antibiotic exposure. Cost analysis from a local study conducted at Vancouver General Hospital in 1995 indicated that from a hospital perspective, the cost of therapy through the OPAT program was approximately 13% of the cost estimated if the patient received the same therapy as an inpatient.[25] The estimated cost of providing outpatient antimicrobial therapy in a hospital setting was $1 997 923, of which $1 659 303 was attributed to the cost of hospitalization. The cost of outpatient parenteral antibacterial therapy was $267 403, which included the cost of labor (pharmacy and nurse educator), laboratory blood tests, catheters, and complications.[26] A cost analysis study in the UK that compared the expense of different OPAT models showed that treatment at infusion centres (£973) was more expensive than at-home infusion by a general nurse (£788) or specialist nurse (£710) for short-term treatments of 4 to 7 days. For patients who required a longer duration of antibiotic therapy, the cost associated with infusion centres (£5135) was also greater than that of home infusions by a general nurse (£2957) or specialist nurse (£2379).[26] The analysis showed that home infusion for both long- and short-term therapy was highly cost-effective. Another major economic benefit of OPAT is the reduction in the cost of nosocomial infections associated with hospitalization. In the United States, 5% of hospitalized patients may develop an infection during their hospitalization; each infection is estimated to cost US$2100, with a cumulative annual cost of more than US$2 billion.[27] OPAT settings are

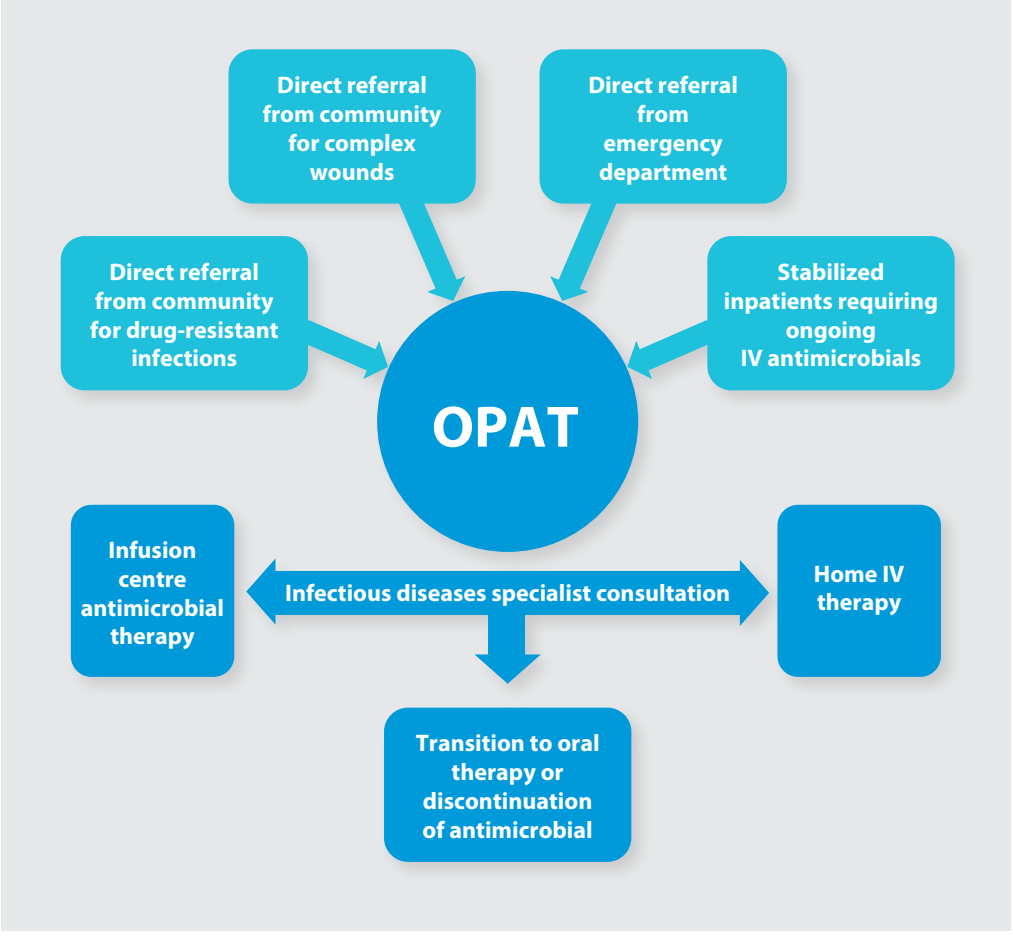

FIGURE 2. Outpatient parenteral antimicrobial therapy (OPAT) benefit of care model.

safe and cost-effective for patients to receive treatment at home or at infusion centres, and minimize the risk of nosocomial infections.

Cost-saving methods

The cost analysis literature in outpatient settings is limited, but with continuous changes in drug delivery systems, there is potential for further cost reduction. There is increasing evidence that self-administration of IV antimicrobial therapy is safe and reduces costs.[28] The use of elastomeric pumps facilitates outpatient management and favors the use of first-line antimicrobial agents.[29] This delivery model reduces the cost associated with nursing and clinic visits, and gives patients more flexibility while being treated.[28] Future research on the cost-effectiveness of OPAT services using different drug delivery devices and the use of resources for facilitating at-home infusions will be essential in order to provide better decision making regarding outpatient treatments.

Summary

For nearly 50 years, OPAT has been proven to be a safe, effective, and cost-saving model of care for patients with severe infections **[Figure 2]**. Infectious diseases specialists play an increasing role in the management of complex infections in the outpatient setting. The increasing number of severe infections, immunocompromised patients, and multidrug-resistant organisms will shape the future of OPAT. The COVID-19 pandemic has placed a strain on acute care hospitals over the past 2 years, and the ability to provide safe and effective care in outpatient settings has never been more critical. Realizing the cost-saving benefits of OPAT requires increasing investments in resources for infusion centres to reduce congestion in the emergency department and for home IV services to allow patients to convalesce at home with their family. ■

Competing interests

None declared.

Future research on the cost-effectiveness of OPAT services using different drug delivery devices and the use of resources for facilitating at-home infusions will be essential in order to provide better decision making regarding outpatient treatments.

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