Review

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Current status in outpatient parenteral antimicrobial therapy: a practical view

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ABSTRACT

Outpatient parenteral antimicrobial therapy (OPAT) programs are a current and widely spread trend in clinical practice because of it´s a cost-effective option, it´s associated with a greater comfort for the patient, a lower risk of nosocomial complications and an important cost saving for the health care system. OPAT is used for treating a wide range of infections, including skin and soft tissue infections, osteoarticular infections, bacteraemia, endocarditis and complex intra-abdominal and urinary tract infections, even in presence of multiresistant microorganisms. Correct choice of antimicrobial agent and adequate patient selection are crucial for reaching therapeutic success and avoiding readmissions, treatment prolongation or treatment-related toxicity. The optimal antimicrobial for OPAT must be highly effective, have a long half-life and an adequate spectrum of action. Ceftriaxone and teicoplanin are currently the most prescribed antibiotics for OPAT, though daptomycin and ertapenem are also on the rise, due to their high efficiency, safety and wide spectrum of action. Antibiotics that are stable at room temperature can be administered through a continuous perfusion, though self-administration is preferable although it requires training of the patient or the caregiver. Factors that are most frequently associated with OPAT failure include advanced age, recent hospitalization and isolation of multiresistant microorganisms.

Key words: Outpatient parenteral antimicrobial therapy (OPAT), benefits, indications, antimicrobial strategies, treatment failure.

Situación actual del tratamiento antimicrobiano domiciliario endovenoso: una visión práctica

RESUMEN

Los programas de tratamiento antibiótico domiciliario endovenoso (TADE) son una tendencia actual ampliamente extendida en la práctica clínica habitual, puesto que son coste-efectivas, se asocian a mayor comodidad para el paciente, conducen a evitar el riesgo de las complicaciones derivadas del ingreso hospitalario y producen importantes ahorros para el sistema sanitario. El TADE se usa para el tratamiento de un amplio espectro de infecciones, incluidas las de piel y tejidos blandos, osteoarticulares, bacteriemia, endocarditis, intra-abdominales y urinarias complicadas e incluso puede utilizarse en infecciones por microorganismos multirresistentes. La selección adecuada, tanto del antibiótico como del paciente candidato, es crucial para alcanzar el éxito terapéutico y evitar reingresos hospitalarios, tratamientos prolongados y toxicidad relacionada con éstos. El antimicrobiano óptimo debe ser potente, tener una vida media prolongada y un adecuado espectro de acción. La ceftriaxona y la teicoplanina son actualmente los antimicrobianos más habitualmente prescritos para el TADE, incrementándose recientemente la utilización tanto de daptomicina como de ertapenem debido a su alta eficacia, seguridad y amplio espectro de acción. Los antibióticos que son estables a temperatura ambiente pueden administrarse a través de perfusión continua. No obstante, la auto-administración es preferible aunque requiere el entrenamiento del paciente o del cuidador. Los factores que se asocian con mayor frecuencia a un fracaso del TADE incluyen la edad avanzada, la hospitalización reciente y el aislamiento de microorganismos multirresistentes.

Palabras clave: tratamiento antibiótico domiciliario endovenoso (TADE), beneficios, indicaciones, estrategias de tratamiento, fallo terapéutico.

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INTRODUCTION

According to the definition proposed by Alan Tice et al., the term OPAT refers to the "provision of parenteral antimicrobial therapy in at least 2 doses on different days without intervening hospitalization", where "parenteral" encompasses intravenous, subcutaneous and intramuscular routes of administration[1]. Seriously ill patients and infections caused by multiresistant pathogens require continuous monitoring of the patient and of the drug exposure and therefore need hospitalization[2]. However, in certain circumstances parenteral antimicrobial treatment can be safely and efficiently administered in outpatient settings, increasing care quality and patient satisfaction and saving costs for the health care system. Such therapeutic approach, which was initially developed in the USA in the context of Home Hospitalisation Units (HHU), has been expanding rapidly over the globe during the last decade and has become an essential part of antimicrobial therapy in many countries. Its main benefits include increase of patient's wellbeing, lower risk of hospital-acquired infections (due to reduced hospital stay) and sustainability for the health care system. Two following conditions have to be met for the patient to be eligible for an OPAT programme in a HHU: existence of a precise diagnosis based on clinical and microbiological criteria and absence of oral treatment options, in which case, if not for OPAT, hospitalisation would be mandatory. These two requirements shape the OPAT definition given by Tice et al.[1], and their fulfilment is crucial for the safety, quality and cost-benefit balance of the outpatient parenteral treatment service.

In this review, we focus on the practical aspects of OPAT, such as patient selection, choice of the antimicrobial agent and dosing regimen, and OPAT service organization. We also revise the latest clinical evidence on OPAT efficacy and safety and analyse risks and benefits associated with this therapeutic modality.

PERSONNEL AND RESOURCES NECESSARY FOR AN OPAT PROGRAMME

Three models for providing OPAT services have been described, each of them requiring different health care resources: a model where a nurse visits the patient at their home, the self-administration model and a model where the patient visits a specialized centre, such as a infusion centre or an emergency room[3-7]. The first model has the advantage of the administration being supervised by a health care professional, but demands a lot of nurse time, which can be expensive. In the self-administration model the patient or the caregiver administrates the drugs intravenously using a gravity infusion system or an automatic infusion device. This model requires time for the patient's or caregiver's training, but the overall costs are low and nurse time resources can be minimal. In the third model, a nurse administers the drugs, and, therefore, the necessary patient training would be limited to reminding him/her about the possible adverse effects and the catheter

care. On the other hand, this model has the inconveniency of patient's need for daily trips to the centre of administration. In the first and in the third model, the patient is evaluated daily, which allows for rapid detection of adverse effects, catheter-associated complications, infection progression and other clinically important signs.

The success of OPAT programme relies on having adequately trained personnel. According to international guidelines[1,8], an OPAT team should include at least one infectious disease physician, a pharmacist specialized in antimicrobial agents or a clinical microbiologist and several specialised nurses. However, each hospital may form a medical team adapted to its particular needs, as long as it has a multidisciplinary focus and includes experts in antimicrobial therapy. Nowadays, HHU personnel are usually trained in prescribing antimicrobial agents for intravenous administration in the home, dealing with the same problems that physicians and nurses face in the hospital-based practice[9]. In many cases, the prescription responsibility lies with the clinicians and nurses of the HHU, in coordination with a clinical microbiologist, infectologist or even a pharmacist, and forms part of their daily duties.

Including a patient in an OPAT programme requires previous assessment of the usual factors, such as presence of allergies, possible drug interactions, comorbidities and, of course, evidence of clinical efficacy of the prescribed antimicrobial agent against the given infection. Treatment safety and tolerability are essential for OPAT carried out in home settings. Though not mandatory, it is advisable to seek once- or twice-per-day posology with a single antimicrobial agent to guarantee maximal safety and adherence.

It is necessary to establish a plan allowing coordination of the referring physician, the OPAT team and the patient. This implies assigning a physician in charge of the patient's treatment and ambulatory follow-up. It is advisable that the responsible physician sees the patient at least 2 times per week, though individual adjustments should be made based on the patient's characteristics, type of infection, chosen antimicrobial agent and infection severity. The plan should also include the frequency of meetings with a nurse in case of self-administration, and the frequency of laboratory tests and catheter change. Factors that may lead to more frequent laboratory controls include advanced age, comorbidities or specific types of treatment. An efficient communication line must be established between the OPAT team and the patients or their caregivers. The key to success of an OPAT programme is to make the care plan as simple as possible[10].

CANDIDATES FOR AN OPAT PROGRAMME

OPAT may be applied in a wide spectrum of infections (table 1), and the profiles of the selected patients are increasingly complex[11-13]. Success will depend on the careful selection of patients who could benefit from the treatment, the correct choice of the antimicrobial agent, and the

Table 1	Main types of infection treated in OPAT units.

Type of infection	Clinical picture
Cardiovascular infections	Native and prosthetic valve endocarditis; endovascular device infection
Respiratory infections	Worsening of COPD; infected bronchiectasis; community-acquired and nosocomial pneumonia; lung abscess
Intra-abdominal infections	Cholecystitis, diverticulitis, intra-abdominal collections
Urinary tract infections	Pyelonephritis; perirenal abscesses; prostatitis; complicated cystitis in catheterized; urinary tract infections in patients with ureteral devices (pigtails, or double J stents)
Skin and soft tissue infections	Primary infections (cellulitis, pyomyositis), secondary infections (surgical wound infection, diabetic ulcers, pressure ulcers)
Osteoarticular infections	Bursitis; septic arthritis; primary osteomyelitis and spondylodiscitis; osteomyelitis and spondylodiscitis in patients with osteosynthesis material
Bacteraemias	Febrile neutropenia (MASSC low risk), bacteraemia from any source
Neurological infections	Meningitis, brain abscess

OPAT: outpatient parenteral antimicrobial therapy. COPD: chronic obstructive pulmonary disease, MASSC: Multinational Association for Supportive Care in Cancer

programmed and adaptable clinical monitoring and results evaluation. Several studies have demonstrated the usefulness and safety of OPAT in treating a variety of infections.

As for the causing microorganisms, the predominant pathogens are Gram-positive bacteria, especially *Staphylococcus aureus* (including those resistant to methicillin and coagulase-negative staphylococci in device-carrying patients) and streptococci[14,15]. Infections caused by Gram-negative bacteria that are most often included in OPAT programmes are intra-abdominal and urinary tract infections and sometimes severe infections by *Pseudomonas aeruginosa* and other multiresistant Gram-negative bacteria, such as extended spectrum beta-lactamase (ESBL) producing enterobacteria. The spectrum of antimicrobials that can be used in OPAT programmes is now very broad, and almost any infection can be treated outside the hospital[16].

The types of infection most often treated with OPAT include skin and soft tissue infections, bone and joint infections and surgical wound infections[3,17], although patients with bacteraemia, endocarditis and intra-abdominal or urinary tract infections have been included in OPAT programs. Several studies have shown the usefulness of OPAT even in patients with associated neoplastic diseases, neutropenia or hematologic malignancies and MASCC (Multinational Association for Supportive Care in Cancer) scores suggesting low risk of complications, who successfully received intravenous treatment at home[18-21]. As the experience grows, many patients can start OPAT directly without prior hospitalisation. There have been reports on the efficacy and safety of patient referral from emergency departments directly to OPAT units[22].

Choice of patients – candidates for OPAT has many homologies with the requirements set forth in the HHU. The most important ones are that OPAT is necessary and there is no option of oral antibiotics treatment, that the patient is clinically stable and knows the risks and the benefits of

this treatment strategy, that the patient or the caregiver are mentally and physically able to work with the health care professionals and that the home meets minimum requirements that make OPAT service feasible, including a phone for communicating with the OPAT team[10]. The diagnosis and management of complications may be delayed in patients' homes, which may increase morbidity in case of adverse effects. Therefore, it is recommended that the first dose of the antimicrobial be administered in the hospital. As we will see later, an appropriate selection of patients for OPAT could lead to a similar (or even better) clinical evolution, compared to conventional hospitalization[14]. However, we must remember that the candidates included in the OPAT-HHU programmes are more clinically stable, which may confound results.

OPTIMAL ANTIMICROBIAL PROFILE FOR OPAT

As pointed out before, it is essential that the patient requires longer term of parenteral treatment to receive OPAT services and it is imperative to switch to oral therapy as soon as the clinical situation allows. Parenteral antimicrobial treatment can be indicated due to three main reasons. First, the antimicrobial agent may not be absorbed in the gastrointestinal tract, either for structural reasons (i.e., short bowel syndrome) or functional reasons (diarrhoea, nausea, vomiting). Second, the appropriate medicine may have low or no oral bioavailability (i.e., aminoglycosides, carbapenems, gluco- or lipopeptides). Third, because infective microorganism is resistant to antimicrobials that can be administered orally[23].

The optimal antibiotics for OP are those with long half-lives that can be administered only once or twice per day. In case of more frequent dosing regimens (every 8 or 6 hours, or even extended infusions) the molecular stability of the antimicrobial must be taken into account. At the same time, possible treatment-related toxicity should be monitored following clinical and analytical protocols. Finally, care should

Table 2	Characteristics of intravenous antimicrobials potentially useful for OPAT programmes.							
Drug	Dose range	Half-life	Stability at 5°C	Stability at 20-25°C	Infusion pump	Risk of phlebitis	ADRs	Recommended monitoring
Penicillin G sodium	2-4 mU/4h	< 1hour	7 days	24 hours	Yes	I		
Ampicillin	0,5-2 g/4-6h	1 hour	3 days	8 hours	No	I		
Amoxicillin-clavulanic acid	1-2 g/8h	1 hour	24 hours. 7-10 days reconstituted	1 hour	No	I		
Cloxacillin	1-2 g/4-6h	< 1hour	3-7 days	24 hours	Yes	I		
Cefazolin	0,5-2 g/6-8h	1-2 hours	24 hours	6 hours	Yes	L		
Cefoxitin	1-2 g/6-8h	1 hours	4 days	24 hours	ND	L		
Cefuroxime	1-1,5 g/8h	1-2 hours	7 days	24 hours	Yes	L		
Ceftriaxone	2 g/24h	5-10 hours	10 days	3 days	Not recommended	L	M, R, H	CBC, LFT, R and I once per week
Ceftazidime	1-2 g/8h	1,5-2 hours	7 days	24 hours	Yes	L		
Cefepime	0,5-2 g/12h	2 hours	7 days	24 hours	Not recommended	L		
Ceftaroline	1 g/8-12h	2,5 hours	24 hours	6 hours	ND	ND		
Aztreonam	1-2 g/8h	1-2 hours	7 days	2 days	Little experience	L		
Piperacillin-tazobactam	4 g/6h	1 hour	48 hours	24 hours	Yes	I		
Ertapenem	1 g/24h	4 hours	24 hours	6 hours	Not recommended	I		
Imipenem	0,5-1 g/6-8h	1 hour	24-48 hours	1 hour	Not recommended	I		
Meropenem	0,5-2 g/8-12h	1 hour	24 hours	4 hours	Not recommended	L		
Amikacin	10-15 mg/kg/24h	2-3 hours	7 days	24 hours	Not recommended	L		
Tobramycin	5-10 mg/kg/24h	2-3 hours	4 days	24 hours	Not recommended	L	R, N	R twice per week, LFT once per week and hearing test every visit
Gentamycin	5-10 mg/kg/24h	2-3 hours	4 days	24 hours	Not recommended	L		
Streptomycin	15 mg/kg/24h	2-4 hours	24 hours	ND	Not recommended	L		
Azithromycin	500 mg/24h	48-60 hours	1-7 days	24 hours	Not recommended	H	R, H, C, GI	R, LFT and ECG once per week, ask about GI disorders
Tigecycline	100 mg load and 50 mg/12h	40-60 hours	48 hours 5% dextrose or SSF	24 hours	Not recommended	I	H, GI	LFT twice per week, ask about GI symptoms every visit

Table 2	Characteristics of intravenous antimicrobials potentially useful for OPAT programmes.

Drug	Dose range	Half-life	Stability at 5ºC	Stability at 20-25ºC	Infusion pump	Risk of phlebitis	ADRs	Recommended monitoring
Clindamycin	300-900 mg /6-8h	2-3 hours	7 days	24 hours	Yes	L	GI	CBC, R and LFT once per week, ask about diarrhoea every visit
Metronidazole	500 mg/8h	6-12 hours	10 days	24 hours	Yes	L	H, M, GI	LFT and CBC once per week, ask about GI symptoms every visit
Cotrimoxazole	160/800 mg/8-12h	10 hours	Not recommended	24 hours in glucose, 14 hours in NaCl solution	Not recommended	I	GI, D, M, H	CBC, LFT, R and I once per week, ask about GI and D symptoms every visit
Fosfomycin	100-300 mg/kg/day	1,5-2 hours	Not recommended	24 hours	Yes	H	GI, H, M, C	CBC and LFT once per week, I twice per week, ask about GI symptoms, check for blood pressure, oedemas and dyspnoea every visit
Vancomycin	2 g/12h	6 hours	4-7 days	24 hours	Yes	I	R, D, N	R twice per week, slow infusion, ask about ototoxicity every visit
Teicoplanin	6 mg/kg in 3 doses every 12h, then every 24h	50-70 hours	24 hours en API	24-36 hours	Not recommended	I	R, D, N	R twice per week, slow infusion, ask about ototoxicity every visit
Daptomycin	6-10 mg/kg/day	8-9 hours	24 hours	12 hours	Not recommended	L	Myopathy	R and CPK once per week, ask about myalgia every visit
Linezolid	600 mg/12h	5 hours	7 days	7 days	Not recommended	L	H, M, GI	LFT and CBC once per week
Ciprofloxacin	400 mg/8-12h	4 hours	14 days	14 days	Not recommended	L	N, GI, H, C, tendinitis	H once per week, ECG, ask about tendinitis and GI symptoms every visit
Levofloxacin	500 mg/12-24h	7 hours	14 days	3 days	Not recommended	L	N, GI, H, C, tendinitis	LFT once per week, ECG, ask about tendinitis and GI symptoms every visit
Moxifloxacin	400 mg/24h	12 hours	Not recommended	Not recommended	Not recommended	L	N, GI, H, C, tendinitis	LFT once per week, ECG, ask about tendinitis and GI symptoms every visit
Isoniazid	4-6 mg/kg/day	1-2 hours	21 days	24 hours	Not recommended	I	H, N (optic neuritis)	LFT once per week, ask about N (visual disorders) every visit

Table 2	Characteristics of intravenous antimicrobials potentially useful for OPAT programmes.							
Drug	Dose range	Half-life	Stability at 5°C	Stability at 20-25°C	Infusion pump	Risk of phlebitis	ADRs	Recommended monitoring
Rifampicin	10-20 mg/kg/day	3-4 hours	72 hours	7 days	Not recommended	I	H, M, D (exanthema, urticaria)	LFT and CBC once per week, ask about D every visit
ANTIFUNGALS								
Fluconazole	50-800 mg/day	30 hours	24 hours	24 hours	Not recommended	I	H, GI, D	LFT once per week, ask about D and GI every visit
Voriconazole	6 mg/kg/day the first day, then 4 mg/kg/day	6 hours	4-6 days	24 hours	Not recommended	I	H, GI, D, visual disorders	LFT once per week, ask about D, visual disorders and GI every visit
Caspofungin	70 mg/kg/day the first day, then 50 mg/kg/day	9-11 hours	48 hours	24 hours	Not recommended	L	D, GI, H	LFT once per week, ask about D and GI every visit
Anidulafungin	200 mg the first day, then 100 mg	26 hours	48-96 hours	24-48 hours	Not recommended	L	D, GI, H	LFT once per week, ask about D and GI every visit
Micafungin	100 mg/day	15 hours	48 hours	24 hours	Not recommended	L	D, GI, H	LFT once per week, ask about D and GI every visit
Ambisome	1-3 mg/kg day	24-30 hours	7 days in glucose, 24 hours in API	3 days in glucose, 24 hours in API	Not recommended	I	R	R and I twice per week
ANTIVIRALS								
Aciclovir	5-15 mg/kg/8h	3 hours	24 hours	8-12 hours	Not recommended	L	R, H, M, D	CBC, LFT and R once per week, ask about D every visit
Ganciclovir	5 mg/kg/12h	3-4 hours	10 days	24 hours	Yes	L	M, H, R, N	CBC, LFT and R once per week, ask about N every visit
Cidofovir	3-5 mg/kg in a single dose every 7 days during 2 weeks	3 hours	1-5 days	24 hours	Not recommended	L	R, M	CBC and R once per week

Risk of phlebitis: H: high, I: intermediate, L: Low. ADRs (Adverse drug reactions): M (myeloid: leukopenia, thrombocytopenia, anaemia), R (renal: deterioration of renal function), H (hepatic: deterioration of liver function), N (Neurotoxicity: ototoxicity), C (Cardio: changes in ECG, signs of CHF), GI (Gastrointestinal: nausea, vomits, diarrhoea), D (Dermatological: photosensitivity, exanthema, urticaria, pruritus). Recommended monitoring: CBC: Hemogram (complete cell count and white blood cell formula), R: renal profile (sediment, urea and creatinine), LFT: Liver function tests (aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, alkaline phosphatase and total and direct bilirubin), I: ionogram (Na and K), CPK: creatine phosphokinase, ECG: electrocardiogram, CHF: congestive heart failure, ND: not determined. Based on references 1,6,26-30.

be given to properly preserve the venous access[1,7] and avoid chemical phlebitis. Between 5 and 25% of all catheter-related complications are associated with infection and thrombosis in hospitalized patients[24]. However in patients receiving OPAT at home less than 1% of patients had vascular catheter infection or thrombosis. In this regard, a recent study by Almirante et al. showed a lower percentage of infection in peripherally inserted central catheters, compared to centrally inserted central catheters, while peripheral catheters had the lowest incidence of infection[25].

The elimination half-life of an antimicrobial ($t_{1/2}$) is the most commonly used parameter, which can be defined as the time necessary for the plasma concentration of a drug to drop by half. Protein binding can influence the half-life length, because the bound fraction acts as a drug reservoir that is released slowly, while the free fraction is metabolized directly. Other factors, such as volume of distribution of the antimicrobial, may also affect the kinetics of drug elimination. Therefore, we conclude that posology of an antibiotic is determined by its half-life, which is influenced by protein binding, among other factors. In OPAT programmes it is preferable to use antibiotics with high protein binding, which ensures long elimination period and allows making the dosing as sparse as possible. This helps to avoid multiple visits per day and, therefore, increases the patient's comfort and preserves the unit's logistics. In addition, the reduced use of venous access implies lower risk of phlebitis-related complications. This explains why drugs such as ceftriaxone, ertapenem, daptomycin or teicoplanin are among the most commonly used in OPAT units.

However, the existing variety of infectious diseases and etiological agents makes it sometimes impossible to use the abovementioned drugs, either because of the infection type, the aetiology or the antimicrobial spectrum. In these cases the physician may choose a different antimicrobial with a shorter half-life and shorter dosing intervals. In these circumstances, to prescribe a drug for administration in the home it is necessary to take into account the infusion type (pulse, continuous), the kind of device (elastomeric pumps, etc.) and physico-chemical properties of the antibiotic, especially its molecular stability at room temperature and when refrigerated.

The molecular stability is the ability of an antibiotic to keep its original properties within the existing quality specifications for a determined period of time. Physical (eg. humidity, temperature, light), chemical (eg. degradation) and biological alterations (microbial growth) may cause instability of the drug. This has to be taken into account when prescribing an antimicrobial agent and may lead to a change of the antimicrobial in an OPAT programme. There are differences, particularly in the stability at room temperature and in febrile ranges (less when refrigerated) between various antimicrobials. A study by Viaene et al.[26] explored the stability of a number of antipseudomonal beta-lactams at different temperatures with the objective of evaluating their suitability for administration in HHU using portable pumps. The authors found that, while aztreonam and piperacillin-tazobactam were stable for 24

hours at 37 degrees, ceftazidime or cefepime were stable only for 8 to 13 hours at the same temperature. However, the four drugs were stable at room temperature (22-25°C) for over 24 hours. The same study showed that meropenem and imipenem had a degradation of 10% at 25°C at 3 and 5 hours, respectively, while faropenem remained stable, similarly to aztreonam or piperacillin[26]. Despite knowledge about the degradation of carbapenems, a recent study by Manning et al. on continuous ambulatory infusion of meropenem via elastomeric pump reported similar efficacy at both room temperature and under cooled conditions, especially at doses above 3 grams per day[27]. Degradation of antimicrobial agents could start as soon as they are placed in elastomeric pumps on a feverish patient. In their recent report Valliére et al. communicated that the temperature of portable pumps frequently exceeded 25°C and even raised up to 33°C, which could lead to a substantial degradation of the antimicrobial. The authors recommended to refrain from leaving the pump overnight inside the patient's bed, to avoid sun exposure and, if possible, to place the pump inside an isothermal container for transportation or dispensing[28].

Different sources provide variable data on the molecular stability of antimicrobials, and it could not be guaranteed that all formulations have the standard stability time at room temperature needed for extended or continuous regimens in HHU. This happens primarily with time-dependent antibiotics as betalactams and could be a problem for optimization of antimicrobial therapy at home. Most of the standards that antimicrobials have to meet are logically focused on the activity and bioequivalence; however, its need to guarantee the stability after reconstitution during the time quoted in literature, to avoid emergence in resistance, or treatment failure. It is therefore essential to know the specific molecular stability of antimicrobials in a particular hospital pharmacy. Table 2 summarises the indicative information on dosage and a range of stability at room temperature and under cooled conditions for the main antimicrobials used in OPAT, according to frequently cited sources[1,7,29-33].

A possible solution to this problem would be to preserve multiple reconstituted aliquots in the refrigerator (at +4°C) and to continuously change the infusion bag, charging the full daily dose through self-administration. This measure is often convenient for patients to avoid delays in drug administration, and it also saves caregiver's work[34]. However, it should not be allowed until the patient or the caregiver has successfully and aseptically performed the technique[35]. Errors in the administration procedure or catheter care can cause adverse effects or catheter occlusion. Once it is determined that the patient is an OPAT candidate, he/she or their caregiver should be properly trained by a team member in the administration of the antimicrobial agent. The training should include instructions on how to detect signs or symptoms of infection, catheter-related adverse effects or drug-associated toxicity. The level of the patient-caregiver training can be so high that a study by Cox et al.[35] showed similar rates of complications and re-admissions, regardless of whether OPAT was performed

in the patient's home or in an infusion centre. However, Matthews et al.[14] in a retrospective analysis of a large cohort over 13 years found no difference in rates of re-admission due to catheter-related complications between patients on a self-administration regimen and patients to whom the antibiotic was administered in an OPAT unit. Moreover, in another retrospective cohort study Barr et al.[36] observed lower rates of thrombosis in the self-administration group. Seetoh et al[37] in a prospective study on a large Asian cohort observed that patients included in OPAT programme that were not following self-administration regime were those with greater comorbidity and worse functional or mental status. However, despite the data obtained from clinical studies, the main logistical difficulty in most OPAT programmes is the need to use antibiotics with long half-life, high protein binding and dosing every 12 or 24 hours.

Two glucolipopeptides, dalbavancin and oritavancin, both approved in 2014 by the FDA for skin and soft tissue infections (including those caused by MRSA), could be of potential utility in OPAT programs, because of its easily dosage. A loading dose of 1000 mg dalbavancin followed by a weekly dose of 500 mg was as effective as vancomycin or linezolid for 7-10 days in the treatment of SSTIs[38,39]. The same dose was similar to vancomycin for 10 days in the treatment of catheter related bacteremia[40]. A maintained course for 4 to 6 weeks after the load was effective and well tolerated in the treatment of osteoarticular infection[41]. For oritavancin, a single 1200 mg dose was as effective and safe as 7-10 days of vancomycin treatment in SSTIs[42].

OPAT PROGRAMME EXPERIENCE IN THE WORLD

Infections that are most frequently treated in OPAT units are skin and soft tissue infections (SSTI) and musculoskeletal infections (MSI). Furthermore, there are increasingly more cases of complicated bacteraemia, intra-abdominal infections, cardiovascular infections and infections caused by Gram-negative multiresistant bacteria (ESBL-producers) that are treated in OPAT units, and it is now considered standard practice, based on medical advice, convenience and cost[3,43]. However, the most important challenge is to identify patients that have an increased risk of OPAT failure, since this could lead to re-admission, prolongation of the antimicrobial treatment or side effects. Allison et al.[44] proposed an interesting statistical model based on patient's demographic parameters, type of infection (bacteraemia, osteomyelitis, pyelonephritis or intra-abdominal infection), class of employed antibiotics and comorbidities. The four independent predictors of OPAT failure identified by the model were age, previous hospitalization, use of aminoglycosides and history of isolation of multiresistant bacteria.
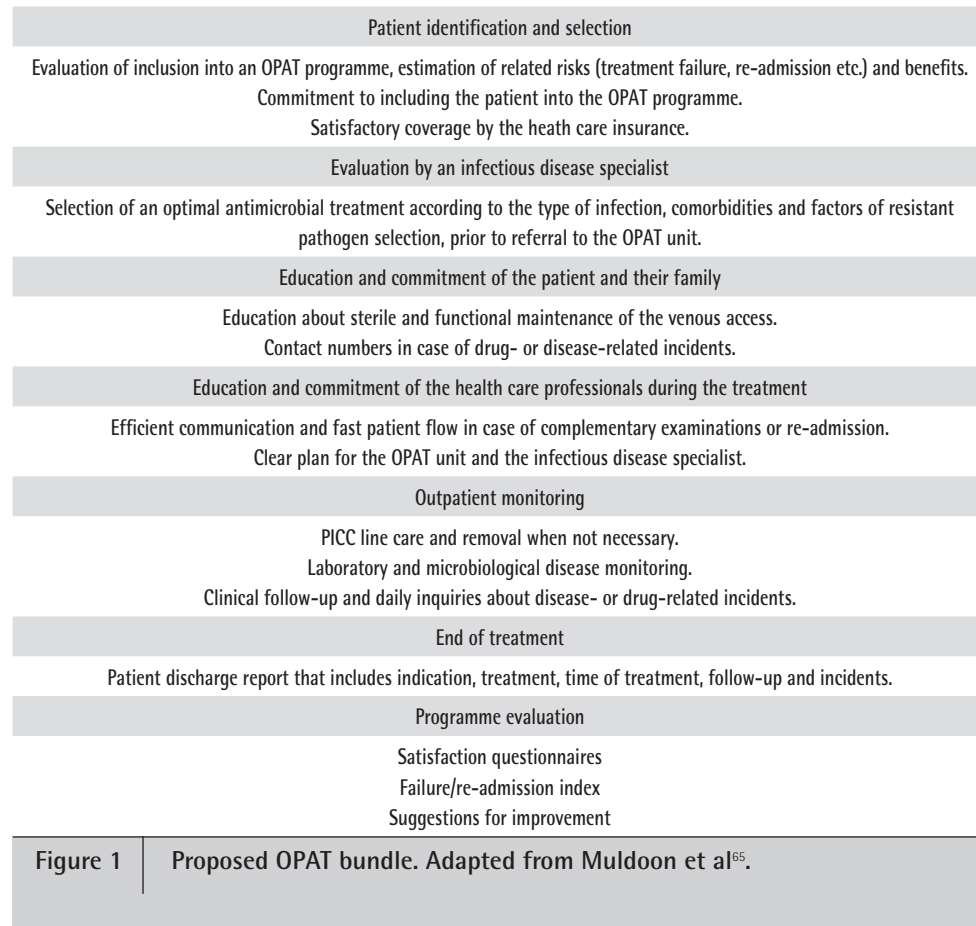
SSTI is one of the three main indications for OPAT, especially in case of non-life-threatening cellulitis or when the patient has comorbidities that make the intravenous route advantageous in terms of clinical outcome, compared to the oral route. The most commonly used drug, as reported

in the most extensive study, is ceftriaxone[43], while teicoplanin is reserved for cases of allergy or history of methicillin-resistant *S. aureus* (MRSA). The usual treatment duration is between 3 and 6 days[45], though it can be longer in elderly patient or in patients with bursitis, vascular disease or in cases of MRSA treated with teicoplanin. Daptomycin, due to its broad spectrum of action and high bactericidal potency, has facilitated home treatment of complicated cases of SSTI in comorbid patients and sometimes is used as a rescue after another antibiotic[3,46,47].

The MSI often require extended infusion therapy and are, therefore, *bona fide* indications for OPAT programmes. The most common infection treated with OPAT is osteomyelitis, often in the diabetic foot and associated with osteosynthesis. The most frequently implicated pathogen is MRSA (>50% of cases), and the treatment time is between 4 and 6 weeks. An indispensable requirement for the success of OPAT in this type of infection is good surgical control of the lesion, and without it chances of recurrence, re-admission or reoperation are high[48]. The choice of antimicrobial depends on *in vitro* susceptibility of the pathogen, presence of comorbidities, drug metabolism and dissemination into the bone. The most utilised drugs are ceftriaxone or cefazolin against methicillin-susceptible *S. aureus* (clindamycin in case of allergy), and vancomycin (including continuous infusion) or teicoplanin against MRSA, although it has been observed that these treatment schemes more frequently fail in elderly patients with infections in the diabetic foot and produced by MRSA.

Toxicity is an important cause of treatment failure and is especially worrisome in case of glycopeptides. It has been reported that in patients treated at home with continuous infusions of vancomycin for approximately two weeks the nephrotoxicity ranged around 15-20%. Older patients, those treated with loop diuretics and especially those who maintained trough concentrations of vancomycin $\geq$ 28 mg/L presented more toxicity[49]. At present, there are very good results obtained with daptomycin in this type of infection, with lower incidence of toxicity compared to glycopeptides[47,50,51].

Although traditionally the intravenous route in case of MSI was chosen because of the poor oral bioavailability of the most utilised drugs, beta-lactams, now there exist oral formulations with good diffusion profile, tolerability and oral availability, such as rifampicin, quinolones and linezolid. Rifampicin is frequently added to quinolone against methicillin-susceptible *S. aureus* and linezolid in case of MRSA[52]. The main aspects to take into consideration when working with rifampicin are not to give it in monotherapy, because of the high rates of resistance-causing mutations, and to monitor liver toxicity and enzyme induction by concomitant medication. Rifampicin is usually incorporated approximately one week after starting the first antibiotic. Linezolid can produce reversible myelotoxicity in treatments longer than 15 days and neuropathy in those longer than one month. Furthermore, it interacts with monoamine oxidase inhibitors and selective inhibitors of serotonin reuptake. A new oxazolidinone antimicrobial, tedizolid, recently marketed in Europe and USA, in clinical

Patient identification and selection
Evaluation of inclusion into an OPAT programme, estimation of related risks (treatment failure, re-admission etc.) and benefits. Commitment to including the patient into the OPAT programme. Satisfactory coverage by the heath care insurance.
Evaluation by an infectious disease specialist
Selection of an optimal antimicrobial treatment according to the type of infection, comorbidities and factors of resistant pathogen selection, prior to referral to the OPAT unit.
Education and commitment of the patient and their family
Education about sterile and functional maintenance of the venous access. Contact numbers in case of drug- or disease-related incidents.
Education and commitment of the health care professionals during the treatment
Efficient communication and fast patient flow in case of complementary examinations or re-admission. Clear plan for the OPAT unit and the infectious disease specialist.
Outpatient monitoring
PICC line care and removal when not necessary. Laboratory and microbiological disease monitoring. Clinical follow-up and daily inquiries about disease- or drug-related incidents.
End of treatment
Patient discharge report that includes indication, treatment, time of treatment, follow-up and incidents.
Programme evaluation
Satisfaction questionnaires Failure/re-admission index Suggestions for improvement

Figure 1	Proposed OPAT bundle. Adapted from Muldoon et al[65].

OPAT: Outpatient parenteral antimicrobial treatment, PICC: Peripherally inserted central catheter.

trials has demonstrated activity similar to linezolid, but has a more convenient dosing regimen (once in 24 hours) and lower myelotoxicity, which make it a potential candidate for OPAT programmes, especially for prolonged treatments[53].

OPAT protocols are implemented in HHU during the defervescence period of bacteraemia, even in complicated cases of bacteraemia. Intravenous administration of drug at home in selected patients allows obtaining comparable and even better results, compared to patients treated in hospital. This has been specifically shown for *S. aureus* bacteraemia[54]. In this type of infection daptomycin is positioned as a useful option, particularly in patients with comorbidities, thanks to its potency, dosing convenience and lower toxicity compared to vancomycin[55]. In bacteraemias caused by Gram-negative bacteria the most utilised antimicrobials are ceftriaxone and ertapenem, the latter being reserved for infections by ESBL-producing enterobacteria, often of urinary tract or abdominal origin. Excellent results have been shown both in cure and in toxicity, including in treatments that lasted longer than three weeks[56-58].

Infective endocarditis is the third most common indication for OPAT. Patients can usually leave the hospital after completing the first 2 weeks of antibiotic treatment in the hospital - a period, during which the greatest number of embolic events occur. Candidates for OPAT include patients with native or prosthetic valve endocarditis and patients with pacemaker wire infection[59-61]. The criteria for admission to an OPAT unit are controlled infection (negative blood cultures over the past three days and apyrexia for at least one week), hemodynamic and electrophysiological stability, absence of cardiac (paravalvular abscesses) or extracardiac complications (septic embolism) and at least one week of treatment[62]. Regarding the aetiology, the cases of endocarditis referred to OPAT units are frequently caused by microorganisms of low pathogenic potential, such as *Streptococcus spp* of *viridans* group, *Streptococcus bovis* or, to a lesser extent, *Enterococcus* sp or, even less frequently, *S. aureus*, with MRSA inclusion only in exceptional cases. The most commonly used antibiotics reported in literature are ceftriaxone and teicoplanin. Cloxacillin is used sometimes in units equipped with elastomeric pumps in extended perfusion mode against sensitive strains because of its high molecular stability at room temperature, although this is not common. The average treatment duration in these cases is 2 weeks, and the factors that best correlate with re-admission are cardiac or renal failure and complications related to the use of glycopeptides[59-61].

Intra-abdominal infections also have their niche in OPAT units. Thus, uncomplicated diverticulitis, biliary tract infections and intra-abdominal abscesses are the most commonly included pathologies. Polymicrobial mixed flora is the most frequently isolated flora, and ertapenem is the most used drug because of its convenient dosing, antimicrobial potency and wide antimicrobial spectrum[56-58]. There are also reports on successful use of ertapenem in uncomplicated cases of cholecystitis during defervescence and after oral tolerance, and in diverticulitis with free fluid and pericolic fat inflammation without signs of perforation. In both reports there were no occurrences of hospital re-admission[63,64].

MONITORING AND DETECTION OF ADVERSE EFFECTS

It is estimated that about 25% of patients experience OPAT-related adverse events, gastrointestinal complications, re-admission and complications of intravenous access being the most frequent ones[9]. To minimize the risk of these events it is important to establish appropriate clinical and laboratory monitoring.

The incidence of reactions that are severe enough to discontinue the antimicrobial therapy varies between 3% and 10%. The most common side effect that leads to therapy discontinuation is rash, while fever, nausea and diarrhoea are less common[18]. Including a pharmacist in planning the therapeutic regimen could help to choose an optimal dose of antibiotic adjusted to the patient's age, weight, renal and/ or liver function, potential drug interactions and type of infection. The recommended analytical and clinical monitoring of drug-related toxicity is provided in table 2[1,6,26-30].

Clinical protocols should be used to reduce the risk of drug-induced toxicity and overall treatment failure. Using protocols increases the quality of health care. The correct execution of protocols, their validation, monitoring, and the analysis of all incidents during follow-up contribute to their improvement. This is the philosophy that lies at the heart of "bundles", or packages of measures employed in many clinical trials. The OPAT programmes are at the vanguard of clinical practice, since they provide hospital services outside the hospital walls. Even when the protocols are fully integrated into the hospital practice, they should be followed carefully, from the selection of patients and cross-consultation with the infectious disease expert to patient/caregiver education and adverse effect monitoring. Automation of these processes confers quality and safety. This is why it has been suggested to implement "bundles" for attending OPAT patients. Figure 1 shows one proposal that could serve as a basis for OPAT programmes[65].

ECOLOGICAL AND ECONOMICAL BENEFITS OF OPAT: RELATION WITH STEWARDSHIP PROGRAMS

The first and most important benefit of OPAT programmes is their contribution to the control of

nosocomial infection. OPAT programmes fit into Antimicrobial Stewardship philosophy in several ways. First, by prescribing antimicrobials with the narrowest spectrum possible, taking into consideration dosage limitations and switching to oral therapy as soon as possible. Besides, the duration of the antibiotic treatment is shortened in OPAT programmes, giving priority to the control of the lesion. Finally, the prescribing patterns are adapted to the objectives of the referral hospital and the clinical process, taking into account the ecological niche and the patient's underlying disease[66]. They contribute to control of nosocomial infection by isolating and treating the patients in their home, despite using procedures of the hospital setting.

It is difficult to reconcile strictly stewardship objectives regarding to restriction of certain antibiotics with both clinical and logistical OPAT´s needs[66]. For example, aminoglycosides are not restricted in stewardship programs, but there are few indications that can be used in monotherapy (uncomplicated urinary tract infections). They are also nephrotoxicity and ototoxic and their use is correlated in multivariate analysis with treatment failure and re-admission into OPAT[44] programs. Semisynthetic penicillins (ampicillin and amoxicillin) are not restricted in stewardship[66] programs. Its indications are confined to osteoarticular and endovascular enterococcal infection. Multiple intravenous doses are required and there is no experience in continuous infusion. The complex logistics associated with its dosage in a hospital at home and the presence of more comfortable and effective alternatives has limited its use in OPAT programs. Cloxacillin is not restricted, but intravenous use is limited by the frequent daily dispensations. Administered orally presents a first-pass effect, which decreases its plasma concentration, affecting the pharmacodynamic profile and activity. There is no evidence of the use of continuous infusion cloxacillin. Experience with cefazolin is scarce, and only in staphylococcal infection[67]. The third-generation cephalosporins, clindamycin and even amoxicillin clavulanate, widely used by OPAT teams are restricted by the potential risk of selection of *C. difficile*[66], however, inclusion of patients in OPAT programmes did not lead to increment *C. difficile* infection, which remained below 1% in a recently published study[68]. Glycopeptides are not restricted. Lipopeptides are restricted by cost reasons. Carbapenems, piperacillin-tazobactam are restricted too by the risk of resistance and *C. difficile* selection, however ertapenem or daptomycin bolus and piperacillin-tazobactam in continuous infusion with elastomeric pumps are safely and effectively used in OPAT teams for treatment of multiresistant pathogens (ESBL *Enterobacteriaceae*, MRSA and multidrug-resistant *P. aeruginosa,* respectively) with low ecological impact.

One of the objectives of OPAT is to avoid hospitalization or to shorten hospital stay facilitating early patient discharge and effectively contributing to the sustainability of the health care system[69]. A hospital programme of antibiotic treatment

optimization could establish therapeutic recommendations to improve the effectiveness and safety of the antibiotic treatment and to reduce costs, and in certain circumstances it can recommend oral treatment alternatives to avoid using OPAT[70]. An expensive treatment that is administered once a day and has excellent tolerability may be preferred over a cheaper alternative if it leads to fewer antimicrobial adverse events or fewer antimicrobial interventions by OPAT team[71]. It is important for drug control spending, but have more expense economic impact the readmission process, the reoperations, the shortening of defervescence period or delays in patient reintegration.

There are multiple publications on economic benefits of OPAT. There is a general agreement that OPAT-associated costs (personal, devices, medication) are offset by the cost savings due to prevention of hospitalization or due to early discharge. OPAT is a recognized quality standard for management of a variety of infections. A study carried out in the UK showed that OPAT programme saved 6,200 hospital bed days per year[14] with an average cost of €1,749 per OPAT patient versus €11,400 per patient treated in hospital[72]. In France, a potential saving of using OPAT programme in patients with osteomyelitis instead of conventional management was estimated to be $1,873,855[73].

Another potential benefit is the reduction of costs related to nosocomial infections, since outpatient treatment reduces exposure to resistant strains, morbidity and mortality as a result of shortening hospital stay. Importantly, about 5% of patients develop an infection during hospitalization[74], and the estimated cost of treating a nosocomial infection is $2,100[7].

Finally, the more subjective benefits of OPAT, such as patients' satisfaction and quality of life, are difficult to measure directly. However, there is some evidence that suggests their strong improvement in OPAT patients compared to hospitalized patients. OPAT allows the patient to return soon to the community and resume normal activities and, in some cases, even return to work.

CONCLUSIONS

In brief, after reviewing all the evidence we conclude that OPAT programmes are an effective and safe alternative to hospitalization in treatment of complex infections. Special attention should be paid to patient and drug selection. When choosing an antimicrobial, it is important to take into account its' half-life, stability at different temperatures, spectrum of action and safety profile. A clear plan of action and efficient communication between the hospital, the OPAT unit and the patient are crucial for the treatment success. When performed properly, OPAT offers greater comfort for the patient, diminishes the risk of nosocomial infections and reduces the cost for the health care system.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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