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REVIEW

Outpatient parenteral antimicrobial therapy and antibiotic stewardship: opponents or teammates?

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Abstract

Purpose This narrative review aims to describe barriers of outpatient parenteral antimicrobial therapy at home (OPAT), potentially compromising general standards of antibiotic stewardship (ABS) and facilitators of OPAT for ABS.

Methods After a literature review, five authors determined the barriers and facilitators to discuss in this review.

Results Sixty-six publications were included in the narrative review and seven barriers and five facilitators are discussed in this article. The impracticability of multiple daily dosing during OPAT, the impact of real-life temperature variations, deviations of the infusion rates of elastomeric devices, access to prolonged intravenous antibiotic therapy, not administering loading doses before the initiation of extended or continuous infusions and the transmural nature of care associated with OPAT, can lead to deviations of recommended treatment regimens and sub-optimal clinical and laboratory follow-up, with a risk of inferior clinical outcomes, adverse events, drug-resistance and higher costs. On the other hand, OPAT provides access to treatments with intravenous antibiotics and simultaneously avoids prolonged hospitalization.

Conclusion Implementing ABS guidelines in OPAT programs, e.g., by using a multidisciplinary team approach and facility-specific protocols for OPAT with patient selection criteria and instructions for selection, storage, preparation and administration of antibiotics, can improve appropriate antibiotic use. Additionally, further research should examine the effectiveness of these interventions on outcomes of OPAT.

Keywords Antibiotics · Antimicrobial stewardship · Infectious diseases · Outpatient parenteral antimicrobial therapy · Home care

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Introduction

Outpatient parenteral antimicrobial therapy (OPAT) is defined as the provision of parenteral antimicrobial therapy in at least two doses on different days without the need for hospitalization [1]. OPAT is predominantly used in patients requiring prolonged intravenous (IV) antibiotic therapy such as, amongst others, patients suffering from cystic fibrosis (CF), bone- and joint infections (BJI), infective endocarditis (IE), skin and soft tissue infections (SSTI) and complicated urinary tract infections (UTI) [1, 2]. Three major models for OPAT are described in literature: preparation and administration of parenteral antimicrobial therapy (1) at an ambulatory care center; (2) at home by the patient himself or (3) at home by home care nurses (HCN) [1]. Over the years, in the USA, the third model seems to be evolved to primarily self-administration by patients and once weekly support of a visiting nurse [3]. In Europe, on the contrary, this model can still be interpreted as a model in which general HCNs visit the patient not only once weekly for home care support, but also several times a day for the preparation and/or administration of each dose of the antibiotics at the patient's home [2, 4, 5].

A recent systematic review concluded that OPAT is more cost-effective than inpatient care with favorable patient satisfaction [2]. On the other hand, it has been debated in previous publications that OPAT might compromise general standards of antibiotic stewardship (ABS), potentially leading to adverse events, development of resistance and higher costs [2, 6, 7]. Gilchrist et al. (2015) called this the "ABS vs. OPAT dilemma" [7].

ABS is defined as the coordinated approach to improve and to measure appropriate use of anti-infective agents by promoting the selection of the optimal antibiotic drug including dosing, duration of therapy and route of administration [8]. The purposes of ABS are to optimize the clinical outcomes and to minimize unintended consequences, such as the occurrence of adverse drug events, development of drug-resistance or *Clostridium difficile*-associated diarrhea (CDAD) and higher costs, all associated with inappropriate antibiotic use, including underuse, overuse and misuse [8].

The guidelines on implementation of ABS published by the Infectious Diseases Society of America (IDSA) primarily focus on acute and long-term care settings, but also recommend the expansion of ABS to outpatient settings [8]. The uptake of ABS-interventions in OPAT protocols, and consequent implementation in the home care setting, can resolve the ABS vs. OPAT dilemma and can even improve ABS [7]. The objective of this paper is to give an overview of the barriers underlying OPAT potentially compromising ABS and of the facilitators of OPAT stimulating ABS. This is based on a literature review and our experience with the development and implementation of an OPAT program in University Hospitals Leuven in Belgium.

Methods

Pubmed and Embase were searched with combinations of the following search terms and synonyms of these terms: outpatient parenteral antimicrobial therapy, OPAT, COPAT, OHPAT, hospital at home, ambulatory, outpatient, home infusion therapy, intravenous, intravascular, infusion, injection, parenteral, antimicrobial stewardship, appropriate(ness), pharmacokinetics, antibiotic, antimicrobial, anti-infective, anti-bacterial, administration, dosage, continuous, intermittent, elastomeric device, stability, follow-up, (drug) monitoring, resistance, susceptibility, betalactam, glycopeptide and each individual molecule in the latter two classes of antibiotics available in Europe, for example vancomycin, teicoplanin, flucloxacillin, ceftriaxone. The search was limited to glycopeptides and betalactams as these are the most frequently used antibiotics in OPAT programs [1, 7, 9]. In the first phase, titles and abstracts were screened (ES) to select relevant manuscripts. In a second phase, full texts were read by two independent authors before final inclusion (ES and CQ). In case of disagreement, consensus was reached by discussing the eligibility of the publication with a third author (IS). Reference lists of eligible studies were manually screened for additional articles. The search was limited to Dutch or English papers published in peer-reviewed journals between 01/01/2000 and 31/12/2017. Manuscripts focusing on pediatric patients, case reports, congress abstracts, study protocols and animal studies were excluded. If original studies were included in a systematic review or meta-analysis, only the review or meta-analysis and not all the individual studies were included in this study. Retrospective or prospective original research articles, reviews and expert opinions with online access to full texts were included. Studies only evaluating the efficacy and safety of OPAT programs without describing effects of ABS standards on efficacy and safety were excluded as this review did not aimed to comprehensively review the safety and efficacy of OPAT programs and reviews answering this research question were recently published [2, 9]. Two researchers (ES, CQ) extracted data on factors associated with OPAT, on the one hand compromising ABS standards and on the other hand facilitating the implementation of ABS. Five experts (WP, ID, IS, CQ and ES) decided on the final barriers and facilitators to be discussed in this review taking into account (1) the results of the review; (2) the European health care context and (3) their experience with the development and implementation of OPAT in University Hospitals Leuven (Belgium). In our own and several other European OPAT programs, IV antibiotics are prepared and/or administered at patients' homes by HCNs, following hospital admission [2, 5]. In University Hospitals Leuven the treating physician (e.g., urologists, orthopedic surgeons) prescribes the antibiotics and remains responsible for the therapy during the whole OPAT course but also general practitioners (GPs) and HCNs are involved in daily follow-up during OPAT. This paper only focusses on OPAT at home and not on OPAT in ambulatory care centers, nursing homes, physician offices and mainly on antibiotics marketed in Belgium and other European countries. Barriers and facilitators of OPAT for ABS were defined according to the definition of ABS of Barlam et al. (2016) as factors associated with OPAT that may either hamper or stimulate the prescription, use and adequate follow-up of therapy with the most optimal drug, dosing, duration of therapy via the most optimal route of administration [8].

Results

Literature search

Fifty-eight papers were included in this narrative review: 25 prospective and 8 retrospective original studies, 13 (systematic) literature reviews, 4 guidelines and 8 expert opinions (Fig. 1). Twenty-one European, 27 American, 8 Australian and 2 Asian manuscripts were included. Thirty publications specifically addressed OPAT, 13 publications discussed elastomeric devices, including stability of antibiotic solutions, 2 publications described the susceptibility of staphylococci and in 13 publications antimicrobial pharmacokinetics and/or pharmacodynamics, including effectiveness and safety of alternative dosing strategies, were discussed.

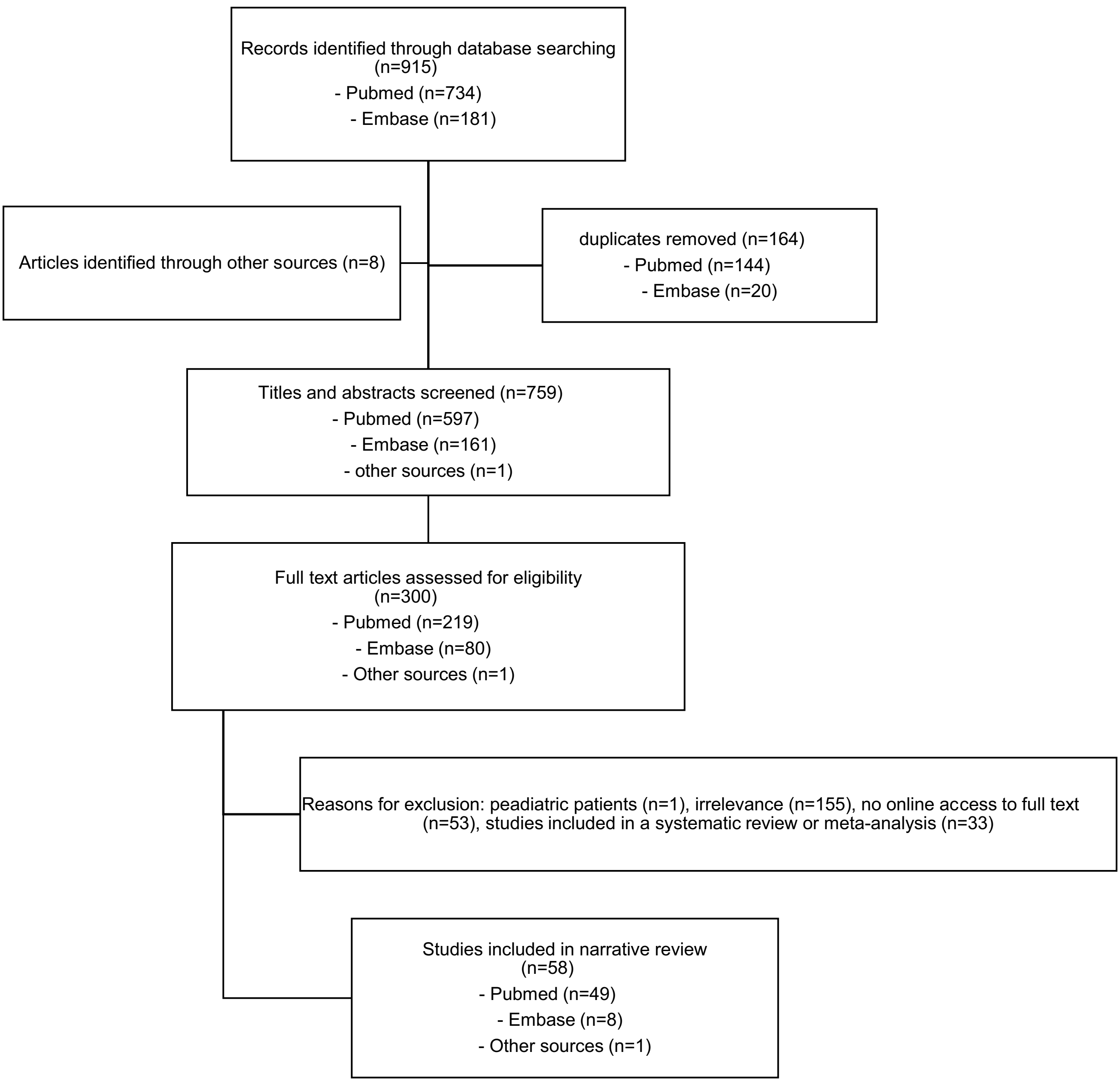

Fig. 1 Flow diagram of the literature search

Barriers associated with OPAT potentially compromising ABS standards

Multiple daily dosing during OPAT can hamper pharmacokinetic/pharmacodynamic target attainment

Multiple daily dosing of antibiotics, especially of betalactams, is required to attain pharmacokinetic/pharmacodynamics (PK/PD) targets associated with a high likelihood of clinical success. For betalactams, bacterial killing is optimized by time-dependent antimicrobial exposure corresponding to (free) drug concentrations exceeding (4- or 5-fold) the MIC for at least 40 up to 100% of the dosing interval, depending on the population in which PK/PD was studied [10]. However, most of the betalactam antibiotics are characterized by a short half-life ($t_{1/2}$) and a short post-antibiotic effect [10]. Consequently, multiple daily dosing and correct dosing intervals are typically required to maximize the time above the MIC; this is for example the case for meropenem (q8h), amoxicillin/clavulanic acid (q6–8 h) and flucloxacillin (q4–6 h) [10]. Ideally, antibiotics are administered with a constant dosing interval, including giving doses overnight.

Consequently, when HCNs prepare and/or administer the betalactam antibiotics during the entire OPAT course, as in several European OPAT programs, multiple home visits a day are needed. When patients self-administer the antibiotics, multiple daily dosing may interfere with their daily activities, e.g., going to work and with their quality of life [11]. In other words, intermittent infusions (II) are impracticable for both HCNs and patients, especially for administering doses at night, leading to sub-optimal dosing regimens throughout the day and possibly sub-optimal PK/PD target attainment [12]. Next to a higher probability of clinical failure, also resistance might be induced when antimicrobial concentrations drop below the MIC of the infecting pathogen [13, 14].

Drug instability

The impracticalities of multiple daily dosing and consequent sub-optimal dosing regimens during OPAT are often avoided at home by using alternative administration strategies such as prolonged (PI) or extended (EI) infusions defined as II infusions lasting 3 to 4 h or continuous (CI) infusions defined as administration over 24 h at a constant flow rate [15–18]. However, the use of PI, EI or CI might be hampered by instability of antibiotics [11, 12, 16, 19–22]. Instability, observed for meropenem and amoxicillin/clavulanic acid and defined as loss of > 10% of initial concentration, might lead to insufficient antimicrobial activity, development of potentially toxic metabolites and adverse events [19–21, 23, 24].

Temperature, one of the determinants of drug stability, is mostly studied under laboratory conditions (at − 5 °C and + 25 °C). For some antibiotics, stability data at body temperature (37 °C) are available but under real-life conditions, solutions are susceptible to non-negligible temperature variations. Voumard et al. (2017) showed that the temperature of antibiotic solutions in elastomeric pumps increased gradually up to 30.9 °C under a blanket during the night and up to 45.4 °C following exposure to sunlight [19]. Furthermore, this study observed a mean decrease in flucloxacillin concentration (8 g/240 ml) of 11% after 24 h under real-life conditions, while cefazolin, cefepime and piperacillin–tazobactam seemed to be stable over 24 h [19]. Degradation of flucloxacillin of > 10% after 24 h under real-life conditions was already shown in other analysis [22, 25, 26]. Other antibiotics susceptible to increasing temperatures (up to 37 °C) are cephalosporins (e.g., ceftazidime, cefepime) and carbapenems (e.g., imipenem and meropenem) [24]. Ceftazidime (4 to 12%) stability is found acceptable for 24 h if kept at room temperature (maximum 25 °C), conversely stability decreases to less than 12 h at body temperature [27]. Cefepime seems to be stable for a maximum of 24 h at 25 °C but for less than 10 h at 37 °C [28]. A Belgian study group has reported stability of meropenem (4 g/100 ml) of 12 h at 25 °C and 6 h at 37 °C [28, 29]. Documentation of the stability of antibiotic solutions should be further carried out in well-designed broad scale studies mimicking real-life conditions in order to avoid the risk of degradation leading to decreased effect [19, 30].

Lacking loading dose

Administering a loading dose prior to PI, EI or CI is obligatory as it shortens the time needed to reach a steady-state target concentration and subsequently avoids sub-therapeutic dosing early in the course of treatment [31]. For betalactams, the dose normally administered for II is recommended [31]. For vancomycin, a loading dose of 25–30 mg/kg is recommended [32, 33]. Recently, however, it was observed that, in hospitals, a loading dose is not always administered prior to PI, EI or CI, increasing the risk on insufficient antimicrobial activity and sub-optimal treatment outcomes [31, 34].

As it is recommended that the first dose of an antibiotic used during OPAT is administered in a supervised setting, patients usually receive several days of the OPAT antibiotic during hospitalization. In our hospital, as in many European hospitals, IV antibiotics are administered via II during the hospitalization preceding OPAT [5]. CI, used during OPAT, are started at the hospital ward on the discharge day, immediately after administration of the last II, which acts as loading dose for the CI [1].

Deviation in the flow rates of elastomeric devices

Electronic or elastomeric devices are frequently used for PI, EI or CI of antibiotics at home. Compared to electronic devices, elastomeric pumps work independently of an external energy source, have a low weight and are small in size, which promotes the autonomy of patients [35].

In contrast, elastomeric pumps are also characterized by variations in the flow rate, which is determined by a thermoregulatory part called the "flow restrictor" and influenced by the viscosity of the solution, the temperature, the filling volume of the pump, storage condition and the height between the pump and the flow regulator [35–37]. While manufacturers report flow rate variations between 10–15%, different authors report variations up to 40% [35, 38, 39]. These flow rate deviations cause deviations in infusion times and administered doses, putting patients at risk for sub- or supra-therapeutic serum concentrations and adverse treatment outcomes. Seventeen percent of infusions in an OPAT program in Australia, for example, were not completed in time and this may be related to flow rate deviations [38].

B. Braun and Theramed indicate flow rate deviations of their elastomeric pumps (Easypump® and Accufuser®, respectively) up to 15% while Baxter states that the flow rate of Infusor® can deviate with 10% from the nominal flow rate [35]. Few studies compared flow rate accuracy of different brands of these pumps and up till now, results seem to be inconclusive. Ackermann et al. (2007) concluded that the mean flow rate of only one pump (Easypump®) was within the range indicated by the manufacturer and the mean flow rates of the Infusor® and Accufuser® were without the accuracy range indicated by the manufacturers [35]. Furthermore, the infusion duration of the three pumps was shorter than the 24 h specified by the manufacturers with Easypump® most closely matching the 24 h infusion duration and a constant flow rate in all three devices was only reached after 4–5 h [35]. A second study, on the other hand, found no significant difference in flow rate accuracy between Easypump® and Infusor® ($p = 0.01$) [39]. An increased flow rate was observed more frequently in Easypump® but a reduced flow rate was observed more frequently in Infusor® [39]. Thus, further research is needed to study accuracy and consistency of elastomeric pumps.

Non-adherence to follow-up recommendations

Despite the availability of recommendations for clinical and laboratory monitoring, up to 25% of patients develop drug- or line-related adverse events during OPAT [1, 40]. Actual implementation of (laboratory) monitoring in daily practice seems challenging [40–44]. In our opinion, the treating and prescribing physician (e.g., ID physician, orthopedic surgeon, urologist), remains responsible for the therapy during the whole OPAT course. Although, they do not always receive results of requested blood samples during OPAT, e.g., from the GP, which can be associated with hospital readmission and premature withdrawal of antibiotics [45]. Inadequate follow-up, often explained by sub-optimal communication and coordination between the treating physician in the hospital and the primary care team involved in follow-up of the patient (e.g., to draw blood or monitor adverse reactions) as well as unfamiliarity of GPs and HCNs with IV antibiotics used during OPAT, can restrain timely action when the first signs and symptoms of an adverse event arise [1, 4, 15, 46].

Delayed or lacking IV–oral switch

Oral antibiotics should be considered as an alternative for OPAT in patients without gastro-intestinal resorption problems and if appropriate concentrations of the oral antibiotics could be attained at the site of infection [7, 12]. Bioequivalent antimicrobial agents (e.g., clindamycin, rifampin, clarithromycin, linezolid, levofloxacin, moxifloxacin, ornidazole, metronidazole) do reach equal plasma concentrations after oral administration in comparison to IV administration, which means that these antibiotics should not be used intravenously in OPAT except in patients with malabsorption. The availability of OPAT might hamper treating physicians (e.g., orthopedic surgeons, trauma surgeons,…) to critically evaluate the possibility for IV to oral switches, potentially resulting in reduced patient comfort and mobility, line-related adverse events, e.g., catheter-related bloodstream infections (CRBSI), increased nursing time and increased costs [6, 47].

Facilitators of OPAT programs for ABS

Extended and continuous infusions of betalactams and vancomycin improve the attainment or documentation of PK/PD targets

As discussed earlier, multiple daily dosing (II) as required for betalactams and vancomycin during OPAT, is not feasible in terms of organization; therefore, alternative dosing strategies (PI, EI or CI) are implemented when the patient is discharged.

EI (e.g., meropenem 2 g/30 min loading dose + 1 g q8h/3h) or CI (e.g., flucloxacillin 2 g /30 min loading dose + 6 g q12h/12 h) of betalactams has been concluded to result in better PK/PD target attainment, and for some antibiotics, such as meropenem, also in better clinical cure rates particularly in intensive care unit (ICU) patients [8, 10]. As well in ICU as in non-ICU patients, PI of betalactams had no inferior effect on clinical success, adverse events and mortality [17, 48, 49]. CI results in sustained steady-state concentrations above the MIC consequently avoiding trough concentrations around or below the MIC [10]. Above this, some authors describe a better tissue penetration of CI compared to II [50].

For vancomycin, the most important PK/PD index is the ratio of the area under the plasma concentration time curve over 24 h above the MIC (AUC_{24h}/MIC) [10]. Advantages of CI of vancomycin (q24h) compared to II are lower variability in AUC_{24}, more accurate determination of the AUC $_{24}$ and more correct dose adjustments [51]. Recent reviews and meta-analyses also stated that CI of vancomycin significantly lowers the rate of nephrotoxicity and that CI is at least as effective as II [52, 53]. However, only a small number of studies, predominantly carried out in ICU patients, was included in the meta-analyses and further research is thus needed to evaluate the clinical effects of PI and CI in non-ICU settings [53].

Access to flucloxacillin at home avoids too early switch to clindamycin

In patients infected with methicillin-susceptible *Staphylococcus aureus* (MSSA), OPAT avoids switching the most appropriate antimicrobial anti-staphylococcal therapy (penicillinase-resistant penicillins, e.g., flucloxacillin) to sub-optimal alternative therapies such as (oral) clindamycin or fluoroquinolones (e.g., levofloxacin, ciprofloxacin, moxifloxacin) to promote early discharge, to improve patient comfort and to reduce costs [54–56].

A treatment regimen of 2–6 weeks of IV penicillinase-resistant penicillins therapy (e.g., flucloxacillin) has been recommended to be the preferred treatment for MSSA catheter sepsis and IE [54].

Without the availability of OPAT, early switch to oral alternatives such as fluoroquinolones or clindamycin may be considered by several clinicians to allow hospital discharge [57]. Clindamycin and fluoroquinolones can be given orally and have excellent bioavailability [56, 57]. However, it has bacteriostatic activity and, although recommended for chronic oral antimicrobial suppression in case of prosthetic joint infections with staphylococci, it is not recommended as a first-line treatment regimen for this indication [55, 58]. Furthermore, clindamycin is associated with a higher risk on relapse and thus, is not recommended for IE [54].

Access to vancomycin at home avoids linezolid toxicity

In patients infected with methicillin-resistant staphylococci, including *S. aureus* and coagulase-negative staphylococci (e.g., in case of BJI, prosthesis-related infection, complicated SSTI), the availability of OPAT avoids switching the preferred treatment with vancomycin to oral linezolid [32].

Linezolid has a comparable spectrum as vancomycin and a high oral bioavailability (100%). Therefore, it is a frequently used alternative for vancomycin to allow hospital discharge in hospitals where OPAT is not used [59]. This is the case when other, more appropriate oral antibiotics (e.g., clindamycin, doxycycline, co-trimoxazole) are not an option given their bacteriostatic activity (e.g., clindamycin), their risks on toxicity (e.g., esophagitis and liver insufficiency associated with doxycycline) or on resistance [32]. However, long-term administration of linezolid is also associated with an enhanced risk for adverse effects such as irreversible peripheral and optic neuropathy and lactate acidosis, as well as reversible bone marrow suppression (especially thrombocytopenia) [32, 59]. Also many drug–drug interactions between linezolid, which is a weak monoamine oxidase (MAO)-inhibitor, and serotoninergic drugs, potentially leading to serotonin syndrome, are reported. Implementation of OPAT avoids the use of linezolid and gives the opportunity to discharge patients with vancomycin.

OPAT avoids colonization with multidrug resistant organisms (MDRO) and CDAD

OPAT is assumed to reduce the spread of MDRO and other pathogens between hospitalized patients. One study observed a high prevalence of MDRO (e.g., vancomycin-resistant enterococci (VRE), MRSA) and other pathogens (e.g., *Clostridium difficile*) in OPAT patients [60]. This may be clarified by the prolonged anti-infective therapies these patients receive (e.g., for BJI, IE). Exposure to antibiotics (e.g., vancomycin) is indeed associated with colonization of the GI tract with VRE [61]. However, it is not yet demonstrated that OPAT can diminish the spread of MDRO and other pathogens and reduce the prevalence of nosocomial infections. For example, no (cluster) randomized controlled trial are carried out to compare the prevalence of MDRO infections between hospitals where OPAT is used and hospitals where OPAT is not used [1].

Furthermore, OPAT is associated with a lower incidence of CDAD compared to hospitalized patients even when high-risk antibiotics (e.g., cephalosporins) are used [7, 62]. Less than 1% of OPAT patients develop CDAD, possibly explained by the shorter length of hospital stay [7]. It is, however, not clear if this effect is only observed for CDAD. In other words, further research is needed to compare the incidence of MDRO carriage between OPAT patients and hospitalized patients receiving prolonged antibiotic courses.

Improvement of choice of antibiotic due to preauthorization

Preauthorization, i.e., the approval granted by an ID specialist to prescribe a specific antimicrobial in the OPAT setting, is associated with a reduction in the use of broad-spectrum or inappropriate antibiotics, in the prevalence of CDAD and in costs [8, 63].

Clinical and biochemical evaluation of the patient who is a potential candidate for OPAT by an ID specialist, a microbiologist and/or a clinical pharmacist, gives the opportunity to evaluate the anti-infective treatment before prescribing OPAT [7, 8]. Consultation by an infectious disease specialist and clinical pharmacist has been shown to decrease the number of inappropriate OPAT courses without negative consequences, to enhance early IV–oral switch, to shorten the duration of antibiotic therapy, to optimize safety and to decrease overall costs [6, 63–68]. Preauthorization can be facilitated by computerized decision support systems, a restricted list of antibiotics to use during OPAT and good communication with clinicians about this intervention [7, 8].

Discussion

This article discussed barriers and facilitators of OPAT for appropriate antibiotic use, based on a literature review and our experience with the implementation of an "OPAT at home" program in Belgium.

"Delivering antibiotic therapy, compliant with guidelines, including indication, molecule, duration, dosing and timing" is recently defined as a quality indicator for outpatient antibiotic therapy [69]. In the context of OPAT, the compliance to this indicator can be facilitated by, e.g., giving preference to CI over II of antibiotics, making it possible to choose the most appropriate antibiotic (e.g., flucloxacillin vs. clindamycin) and avoiding colonization with MDRO and CDAD. Otherwise, compliance to this indicator can be reduced during OPAT, e.g., by administering antibiotics with incorrect dosing intervals, drug instability, forgetting loading doses before the initiation of CI, flow rate deviations of elastomeric pumps, suboptimal follow-up and delayed IV–oral switch; all potentially resulting in sub-optimal treatment outcomes, adverse events and resistance [69, 70].

These barriers for appropriate antibiotic use during OPAT support the implementation of a formal OPAT program and local OPAT protocols based on recommendations and quality indicators for both ABS and OPAT [8, 69, 71, 72]. Formal OPAT programs and local OPAT protocols can reduce inappropriate antibiotic use during OPAT [73]. Also in-hospital studies showed that facility-specific protocols improved antibiotic management [1, 8, 40, 72–75]. Although, patients are still discharged with OPAT outside the structure of formal OPAT programs [42, 76].

A formal OPAT program is preferably coordinated by a multidisciplinary team of OPAT experts (ID-physicians, microbiologists, clinical pharmacists, advanced practice nurses) in close cooperation with referring physicians, hospital ward, HCNs and GPs [69, 72]. The role of each of these healthcare professionals is discussed hereafter.

Appropriate antibiotic selection and prescription during OPAT can be improved by incorporating a restrictive list of antibiotics (including dosing schemes and devices) in OPAT protocols [69]. This list is preferably developed in consultation with ABS committees, taking into consideration the antibiotics marketed in the country and—to avoid delays in administration of antibiotics at home—availability of antibiotics or in hospital or community pharmacies [4, 69]. Such a restrictive list can avoid inappropriate prescription of bio-equivalent antibiotics during OPAT as well as the use of CI for unstable antibiotics or for antibiotics of which stability under real-life conditions is not documented [69].

When developing such a restrictive list, OPAT teams must consider alternative dosing strategies (e.g., CI) given the practicability, safety and efficacy [5]. CI of betalactams were, for example, advised in an OPAT program in the UK [70]. Once or twice daily dosing with CI indeed promotes patients' autonomy. Furthermore, alternative dosing strategies allow inclusion of antibiotics in OPAT program that could not have been included if only administration via II was possible. Although it is important to mention that safe and effective use of PI, EI or CI requires (1) the administration of a loading dose prior to initiation of these PI, EI or CI; (2) the use of a drug delivery device with a sufficiently constant flow rate; (3) education about risk factors for flow rate deviations (e.g., temperature, height), about follow-up of the flow rate to detect deviations early and about action to take when flow rate deviations are observed; (4) documentation of the stability of antibiotic solutions under real-life conditions. In other words, using alternative dosing strategies during OPAT requires a formal OPAT team and clear and comprehensive OPAT protocols. Furthermore, both stability of antibiotic solutions as well as safety and efficacy of CI in the OPAT setting need to be further investigated [5, 68]. While a few studies in ICU seem to indicate that CI are at least as safe and effective as II, this is not demonstrated, specifically in the OPAT setting. Therefore, involvement of (clinical) pharmacists in OPAT programs is important given their expertise in PK/PD as well as in drug stability.

Next to a restrictive list, also preauthorization by ID-physicians and ID-pharmacists seems to improve antibiotic selection and prescription during OPAT, e.g., by avoiding OPAT when oral antibiotics are available and should therefore be incorporated in OPAT protocols [6, 64, 67]. During preauthorization, also the susceptibility and adverse effects of antibiotics can be considered and discussed with treating physicians [8, 69]. ID-experts can advise OPAT with CI of vancomycin to avoid the use of the more toxic linezolid. Last, preauthorization can also facilitate clinical and biochemical evaluation of OPAT candidates (e.g., assessment of betalactam allergies, therapeutic drug monitoring, renal function, etc.).

Patient selection incorporates the evaluation of patient-specific factors (e.g., self-care abilities, ability to understand OPAT, medication compliance, etc.) [1]. Patients need to be able and willing to comply with several home visits a day or with several self-administrations a day at the right times to allow multiple daily dosing of betalactams that are not stable enough to be administered in CI. To ensure clinical and laboratory follow-up in our own OPAT program, patients need to be able to travel to the hospital every week or every 2 weeks, depending on the clinical condition of the patient [1].

Patient education is another key item of an OPAT protocol. To ensure timely action and to avoid serious adverse events, patients indeed need to be provided with information about side effects of the OPAT antibiotic, about the first actions to take when side effects arise and about contact numbers in case of emergencies [8, 69, 77]. When elastomeric devices are used, the influence of temperature on stability and infusion rate needs to be explained to patients. Above, patients need to know how they can evaluate the infusion rate themselves by looking at the progression lines on the plastic housing of the devices or by weighting the devices [1, 10, 13, 35, 36]. Patients who self-administer antibiotics, need to be informed about the procedures to dose, prepare and administer the antibiotics and about the operation of elastomeric devices or electronic pumps [72, 78]. As several antibiotics (e.g., temocillin) need to be stored in a refrigerator, education on the storage of antibiotics has to be provided [69]. Specialized nurses and advanced practice nurses in the hospital can have an important role in evaluation of patient-specific selection criteria and in patient education [72]. Local OPAT protocols should also define patient eligibility criteria for OPAT and patient information leaflets need to be developed by the OPAT team to support patient education [1, 72].

Together with other stewardship interventions, oral and written education of health care professionals can improve antibiotic use during OPAT [8]. To prevent drug-related adverse events during OPAT, antibiotics must be prepared and administered in accordance with international guidelines and local OPAT protocols. This is especially important when HCNs compound elastomeric devices as this is infrequently performed by them [79]. Although, sub-optimal knowledge of healthcare workers on antibiotic stewardship is reported [8, 80]. Among others, information about the prescribed antibiotic, the dose to administer, the infusion rates, the correct dosing intervals, the used devices, adverse events and actions to take, etc. need to be provided to health care workers. When glycopeptides as vancomycin are prescribed all involved healthcare workers need to be informed about the procedure for TDM and dose adaptations.

When OPAT is started, the treatment plan and responsibilities of each healthcare worker need to be communicated from the hospital's OPAT team to the primary care team. During OPAT, also the administered doses, dose adaptations of vancomycin, adverse events, the weight of the elastomeric devices should be registered and ideally shared with all healthcare workers by using telemedicine. This is important to ensure timely actions when problems arise, e.g., deviations in the flow rate of elastomeric devices, allergic reactions on antibiotics, etc. The organization of follow-up needs to be incorporated in OPAT protocols.

An important limitation of this review is that it is not a systematic review and that our review process started at the same time that our OPAT program was implemented. This means that our personal experience with the implementation might have influenced the review process. Absence of bias in the literature search and in the selection of barriers or facilitators cannot be guaranteed. However, we are convinced that bias was largely avoided since the review was carried out by 5 experts in OPAT and ABS.

Our review focusses on the European health care context and builds upon the article of Gilchrist et al. (2015) that introduced "the ABS vs. OPAT dilemma" [7]. Compared to Gilchrist, our review goes more deeply into several challenges associated with OPAT (e.g., drug stability, lack of antibiotics with convenient (once-daily) dosing regimens) and adds additional challenges (e.g., challenges associated with EI and CI such as stability and deviations in the flow rate of elastomeric devices) and opportunities (e.g., avoiding to switch to suboptimal oral therapies). Above, our review discusses approaches to overcome each specific barrier (Table 1).

In conclusion, during OPAT, there is a risk on the prescription of antibiotics based on dose convenience instead of prescribing the most appropriate antibiotic drug regimen based on indication and spectrum. This has been described as the "ABS vs. OPAT dilemma". On the other hand, OPAT offers patients the possibility to reside in the comfort of their homes or even to resume work with the most appropriate antibiotic treatment regimen, which would possibly not have been feasible without OPAT. Incorporating interventions as patient and provider education, a multidisciplinary team approach and local protocols which define selection criteria for OPAT and procedures for selection, storage, preparation and administration of antibiotics in OPAT programs can improve appropriate use of antibiotics. These interventions can improve clinical outcomes and reduce adverse events and drug-resistance during OPAT [69]. However, the effectiveness of these interventions needs to be evaluated by monitoring OPAT prescriptions and antibiotic use during OPAT [69]. Feedback about the effectiveness need to be provided to all healthcare workers involved in OPAT services. Further research on the effectiveness of these interventions during

Table 1 Summary: barriers and facilitators

Barriers [References]	Summary	Main approaches to overcome these barriers
Multiple daily dosing and PK/PD target attainment [10–14]	Impracticable for HCNs and patients Risk on applying suboptimal dosing regimens Less efficient PK/PD target attainment	Alternative dosing strategies (e.g., PI, EI, CI) Restrictive list of OPAT antibiotics (incl. dosing regimens) Education of patients and HCNs about correct dosing intervals (for CI and II) Comprehensive and clear prescription for HCNs that specifies dosing intervals Shared electronic medical record for registration of medication administration and early detection of incorrect dosing intervals, accessible for hospital and primary care workers
Drug instability [11, 12, 15–25]	PI, EI or CI => not feasible for unstable antibiotics Risk on insufficient antimicrobial activity and toxic metabolites Temperature => determinant of drug stability	PI, EI, CI only for antibiotics, stable under real-life conditions Multidisciplinary cooperation with a (clinical) pharmacist Patient education about influence of temperature on drug stability
Lacking loading dose [1, 26–29]	Risk on sub-therapeutic dosing early in the course of treatment	OPAT protocols and information leaflets Coordination of OPAT by a multidisciplinary team Close cooperation between OPAT team and treating physician/hospital ward
Deviations in the flow rates of elastomeric devices [30–34]	Elastomeric devices User-friendly for PI, EI or CI But susceptible to flow rate deviations Risk on deviations in administered doses and sub- or supra-therapeutic serum concentrations	OPAT protocols and information leaflets Education of patients and HCNs about flow rate Daily registration of weights of elastomeric devices in shared medical records enables early detection of deviations
Non-adherence to follow-up recommendations [1, 4, 15, 35–41]	OPAT => transmural care Risk on sub-optimal communication and coordination between hospital and primary care Risk on inadequate clinical and laboratory follow-up	Procedures for TDM and dose adaptations during OPAT Education of primary care workers (HCNs and GPs) Communication about dose adaptation via electronic medical record
Delayed or lacking IV–oral switch [6, 7, 12, 42]	OPAT can delay IV–oral switches Risk on reduced patient comfort and mobility line-related adverse events, e.g., CRBSI Increased nursing time and costs	Restrictive list of OPAT antibiotics Pre-authorization Close follow-up during OPAT
Facilitators		Main approaches to guarantee that these factors can act as facilitators
Extended and continuous infusions of betalactams and vancomycin improve attainment or documentation of PK/PD targets [8, 10, 17, 43–48]	EI, PI, CI—advantages User-friendly Better PK/PD target attainment, clinical cure rates (e.g., meropenem) and reduced number of adverse events (e.g., vancomycin)	Documented stability of antibiotic solutions under real-life conditions Loading dose prior to PI, EI or CI Drug delivery devices with sufficiently constant flow rate Education of patients and HCNs about deviations in flow rate

Table 1 (continued)

Barriers [References]	Summary	Main approaches to overcome these barriers
Access to flucloxacillin at home avoids too early switch to clindamycin [49–53]	Without OPAT Early discharge with oral clindamycin or fluoroquinolones in MSSA infections OPAT IV flucloxacillin post-discharge (preferred treatment for MSSA catheter sepsis and IE)	Close cooperation of OPAT team with treating physicians Pre-authorization
Access to vancomycin at home avoids linezolid toxicity [27, 54]	Without OPAT Early discharge with linezolid for methicillin-resistant staphylococci infections Linezolid = associated with adverse effects and drug–drug interactions OPAT vancomycin after hospital discharge	Close cooperation of OPAT team with treating physicians Pre-authorization
Avoidance of colonization with multidrug resistant organisms (MDRO) and CDAD [1, 7, 55, 57]	Prolonged AB-courses during OPAT => Risk on MDRO-colonization OPAT => avoidance of dissemination of MDRO in hospitals	Transmural communication Education of primary care workers (e.g., HCNs) prevents transmission of MDRO at home
Improvement of choice of antibiotic due to preauthorization [6–8, 58–63]	Advantages of pre-authorization Decreases the number of inappropriate OPAT courses Enhances IV–oral switch Shortens duration of antibiotic therapy	Multidisciplinary OPAT team with cooperation of ID-physicians and clinical pharmacists Restrictive list of OPAT antibiotics

PK/PD pharmacokinetic/pharmacodynamics, *HCN* home care nurse, *PI* prolonged infusion, *EI* extended infusion, *CI* continuous infusion, *OPAT* outpatient parenteral antimicrobial therapy, *TDM* therapeutic drug monitoring, *GP* general practitioner, *CRBSI* catheter-related bloodstream infections, *MSSA* methicillin-sensitive staphylococci, *IE* infective endocarditis, *MDRO* multidrug-resistant micro-organisms, *ID* infectious disease

OPAT is needed since relatively few studies examined this relationship.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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