Developments in outpatient parenteral antimicrobial therapy (OPAT) for Gram-positive infections in Europe, and the potential impact of daptomycin

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Parenteral antimicrobial therapy is traditionally offered in the inpatient setting in many parts of the world. In the USA, the past three decades have seen an unprecedented increase in the delivery of these therapies in the non-inpatient setting, and outpatient parenteral antibiotic therapy (OPAT) is now an established standard of care in North America. However, the uptake of OPAT within Europe has been more gradual, owing to a number of clinical, fiscal, logistical and cultural considerations. In particular, physicians who are not currently engaged in OPAT programmes frequently cite concerns over patient safety as a major barrier. However, where OPAT programmes have been established, high levels of satisfaction are reported by both patients and physicians, suggesting that many anxieties concerning the introduction of OPAT stem from a lack of patient and physician education regarding the key potential benefits associated with OPAT. As the burden of serious Gram-positive infections grows, so does the need to offer clinicians, administrators and patients alternative treatment programmes that are equally effective and safe compared with inpatient treatment, while promoting optimal use of limited healthcare resources. This article will review the European experience of OPAT, discussing the associated benefits and the potential antibiotic options, with an emphasis on the evolving experience with daptomycin.

Keywords: cost-effective, hospital-acquired infections, community, reimbursement

Introduction

Parenteral antimicrobial therapy is traditionally offered in the inpatient setting in many parts of the world. The past three decades have seen an unprecedented increase in the delivery of these therapies in the non-inpatient setting, offering a number of potential clinical, economic and quality-of-life benefits to the patient or carer, community-based clinician, administrator and hospital. This type of service has been termed outpatient parenteral antimicrobial therapy (OPAT), outpatient and home parenteral antimicrobial therapy (OHPAT), hospital in the home (HITH) therapy or community-based parenteral anti-infective therapy (Co-PAT). Because all definitions refer to offering patients and carers the ability to access parenteral antimicrobial therapy in settings other than as a hospital inpatient, for the sake of consistency, we will use the term OPAT in this article.

OPAT is an established standard of care in North America, in a recent survey, 94% of infectious disease consultants in the USA reported that patients were frequently discharged on OPAT. It has been adopted in other parts of the world including Australia, parts of Asia and Europe. Notably, despite a predominantly European consensus on how potential barriers to OPAT might be overcome, the extent to which OPAT has been adopted has varied considerably between the different European countries. One of the key drivers for the increased requirement for OPAT services is the rise in serious, hospital-acquired Gram-positive infections, particularly infections such as complicated skin and soft tissue infections (SSTIs), bone, joint and prostatic infections and line-related sepsis (with or without bacteremia). Indeed, bone and joint infections, endocarditis, SSTIs and bacteremia were the four most frequently treated infections in two recent, large US studies of OPAT. Other infections treated in the outpatient setting included prosthetic or orthopaedic device infections, line and endovascular infections and intra-abdominal infections. Both a large, 13 year cohort study based in Oxford, UK, and an overview of experience from Italy, the UK and the USA have demonstrated the use of OPAT to treat a range of infections. With the exception of intra-abdominal infections, the predominant pathogens in such infections are Gram-positive bacteria, many of which can be treated with OPAT for the total or partial duration of their antibiotic course, depending on factors such as patient or carer willingness, adequate support, disease severity, local availability of OPAT services and local fiscal or other incentives.

Increasing numbers of serious Gram-positive infections are due to drug-resistant pathogens such as methicillin-resistant...
Implementation of OPAT in Europe

The uptake of OPAT in Europe has been more gradual than in North America. During 2005, OPAT accounted for >1% of total outpatient antibiotic use in only six out of 20 European countries, with some countries (e.g. the UK and Italy) having more-established OPAT programmes than others. The slow uptake of OPAT is due to a number of clinical, fiscal, logistical and cultural considerations. These include the provision of an appropriate healthcare infrastructure to ensure that the basic models of outpatient care can be provided to ensure safety; payment or reimbursement incentives for care professionals, inhibited a more extensive uptake of OPAT. Physicians who spent a significant proportion of their time (≥60%) in direct patient care and who treated or consulted on at least 10 patients with serious Gram-positive infections per month were eligible for interview. Although this survey was not of rigorous methodology and may not be fully representative of clinicians that are potential users of OPAT, or indeed OPAT experts, such qualitative opinion can be helpful in formulating an early understanding of key potential issues related to the provision of OPAT in Europe. The survey revealed that the countries with more-established OPAT programmes were the UK, Italy and Spain. Although home administration is available in the UK and Spain, the preference was for the initiation of treatment in the inpatient setting with subsequent transfer to outpatient clinics for patients who are responding well to therapy. Physicians suggested that uncertain delineation of fiscal responsibility between the hospital and primary care physicians, as well as a shortage of trained healthcare professionals, inhibited a more extensive uptake of OPAT. Despite an extensive network of outpatient clinics in France, many antibiotic agents are classified for in-hospital use only, and physicians expressed additional concerns over patient safety. In Germany, unfavourable reimbursement arrangements mean that OPAT is limited to specific clinical conditions such as cystic fibrosis.

In summary, the survey confirmed many of the findings of AdHOC.5 In particular, it highlighted that the variable extent to which OPAT had been adopted reflected the variable structure of healthcare provision in the five countries, as well as the differing attitudes of physicians towards OPAT. Although only five countries were surveyed, the lessons learned are likely to be broadly applicable to other similar European countries. The concerns raised by physicians in the various countries serve to emphasize the importance of engaging all the stakeholders in careful clinical and fiscal planning if OPAT programmes are to be introduced successfully with good governance. This sentiment is echoed by US experience and in other proposed models of OPAT, which have also highlighted the necessity to undertake meticulous prospective planning and, critically, the need for effective co-ordination and communication so that all stakeholders are working towards a unified vision and goal.14
Key benefits associated with OPAT

A number of potential advantages and disadvantages have been associated with OPAT (Table 1). These have also been well described in the literature. One important perceived advantage of OPAT is as a means of reducing healthcare-acquired infection. Although this seems to be an obvious benefit, data to support this are relatively sparse with the exception that line-related infections are historically less common than those in the healthcare setting. This clearly highlights the need for surveillance of infections associated with outpatient administration of antibiotics.

The aim of OPAT is to offer patients a treatment programme that is equally effective and safe compared with inpatient treatment, while promoting optimal use of limited healthcare resources. The economic benefits have been well described, and there is general agreement that expenditure associated with providing an OPAT service (staff, equipment and drugs) is generally offset by the cost savings resulting from earlier discharge from hospital. For example, the implementation of an OPAT programme in a Canadian teaching hospital resulted in an estimated cost saving of $1730520 over a 3 year period. However, the majority of these studies are primarily from a US hospital (provider) and clinician perspective. Emerging European data have demonstrated substantial cost savings or decreased resource use with OPAT, although the cost of OPAT can vary considerably, depending on various factors such as the choice of antimicrobial agent, the location of administration (i.e. an outpatient clinic, an infusion centre or the patient’s home) and the clinical condition of the patient. The well-established OPAT programme in Oxford, UK, saved over 6200 bed days in one calendar year; the mean cost of care per episode of infection for OPAT was £1749, compared with £11400 for inpatient treatment in a retrospective analysis of 55 episodes of bone and joint infections in the UK. In addition, a study in France reported that treatment of 39 osteomyelitis patients with OPAT resulted in a potential cost saving of US$1873885, compared with conventional therapy.

Other more subjective benefits of OPAT, such as patient satisfaction and quality of life, are difficult to quantify directly; however, there is some evidence to suggest that these are improved greatly compared with inpatient therapy. For example, OPAT allows the early return of patients to the community, enabling them to resume normal activities and, in some cases, return to employment. The SF-36 is a validated 36 question health survey that assesses physical and mental health and well-being. In a 15 month study of patients referred to the OPAT programme of an adult tertiary-care teaching hospital, OPAT resulted in significant improvements in several domains of the SF-36 questionnaire, as well as in the mental component summary score.

Clinician and patient perspectives on OPAT

The poor uptake of OPAT in Europe has been attributed to the reluctance of both patients and clinicians to consider OPAT as a therapeutic alternative. Anecdotal evidence, personal experience
and some clinician user/patient survey data indicate that patients are often uncertain about the benefits of OPAT, thus they are less willing to consider this as a treatment choice, and clinicians express concerns about safety. However, our experience in Tayside, Scotland is that once the risks and benefits of OPAT are clearly explained to patients/carers and attending clinicians there is generally a willingness to consider this option. Various studies have been conducted on the use of OPAT for the treatment of patients with co-morbid conditions such as malignancy or neutropenia. Patients with haematological malignancies were successfully transferred from initial inpatient therapy to self-administration at home. A second study conducted in patients with haematological malignancies found that the response of patients to antimicrobial therapy delivered on a solely outpatient basis was similar to that of patients who were hospitalized initially. Further to this, a study analysing the safety of 2059 patients treated with OPAT over a 13 year period revealed similar rates of complications and re-admissions, regardless of whether OPAT was given in the patient’s home or in a hospital clinic.

When those clinicians and patients who had previously participated in an OPAT programme were surveyed, interesting results were found. Only 2% of UK clinicians felt that intravenous (iv) antibiotic therapy mandated in-hospital administration. In another study, 71% of physicians and 53% of parents preferred OPAT for paediatric patients with low-risk febrile neutropenia. Furthermore, all patients participating in OPAT as part of a pilot early-discharge strategy in Sweden reported that they would favour OPAT for subsequent antibiotic therapy. In a Scottish series, 75% of patients with SSTIs indicated a willingness to undergo OPAT, and in a study in Canada, 89% of patients receiving OPAT expressed a preference for treatment at home rather than in the hospital clinic. These results suggest that many concerns over the introduction of OPAT stem from a lack of experience. Thus, better education of both patients and physicians on the key benefits and outcomes might serve to expedite the establishment of OPAT programmes in Europe.

**Antibiotic agents and indications for OPAT**

The desired properties of an iv antibiotic agent for use in the ambulatory setting include proven efficacy for specified infections, a good safety and tolerability profile, stability in an ambulatory environment, a long half-life thus requiring infrequent administration and predictable pharmacokinetics to minimize the requirement for therapeutic drug monitoring. For these reasons, and for reasons of convenience, antibiotics given once daily or less, either by a bolus or short infusion, are generally preferred.

According to a 2004 analysis of data reported to the International OPAT registry, ceftriaxone was the most frequently used antimicrobial agent in OPAT in the UK, Italy and the USA, followed by teicoplanin in the UK and Italy, and by vancomycin in the USA. SSTIs were the infections most frequently treated by OPAT in all three countries, followed by bone and joint infections. The relatively short half-life of vancomycin (6–8 h), compounded with limited bone penetration, means that vancomycin is often administered as a continuous infusion when used to treat osteomyelitis. The lack of appropriate infrastructure and limited experience with continuous infusion in the OPAT setting might partially explain why vancomycin is a less popular choice in Europe.

While a systematic review of the outcomes of these established OPAT agents is beyond the scope of this article, the data discussed below provide some indication of the value of these agents in the OPAT setting. For example, 125 patients were treated as part of an OPAT programme in Scotland. Of these, 113 were treated in an outpatient clinic, 7 at home (self-administration or by a caregiver) and 5 by a community nurse. Ceftriaxone (69.6%) and teicoplanin (29.6%) were the most frequently used antimicrobial agents, after which 98% of patients achieved clinical cure or showed improvement. In a single-centre study in France where OPAT was administered to 39 osteomyelitis patients, prolonged administration of iv antibiotics (>4 weeks) was often required. OPAT was administered in the patient’s home by continuous infusion via implanted catheters (self-administered or given by a home-care nurse). The majority of patients were treated with vancomycin (51%) or β-lactams (44%). Of the 30 patients who completed the 12 month follow-up, 28 achieved clinical cure; adverse events were rare and 19 patients returned to work or school during treatment. A pilot study in Italy assessed the safety and efficacy of teicoplanin as outpatient treatment for 10 patients with osteomyelitis. Patients were treated with teicoplanin, administered by a 30 min infusion three times a week, for a mean duration of 48 days. All three of the patients in whom removal of infected hardware had been performed and six of seven patients who did not undergo surgery achieved clinical success. No adverse events were recorded. An analysis of a national OPAT registry set up in Italy in 2003, along with two additional European reports (not published in English), also point towards successful treatment of bone and joint infections using OPAT. A retrospective analysis evaluated 56 episodes of chronic osteomyelitis due to methicillin-resistant staphylococci treated with teicoplanin three times a week or daily administration schemes and adequate surgery. The efficacy was higher when antibiotic therapy was associated with adequate surgery (86% versus 46%; P=0.001), and was similar whether teicoplanin was administered daily or three times a week. Teicoplanin was safe with an adverse event rate of 9%. These and other data support the use of various agents to treat serious Gram-positive infections. The clinical decision-making process for the use of different agents in an OPAT setting is based on a number of clinical and logistical considerations and has been discussed through a consensus statement for managing SSTIs. This publication from 2003 does not contain information on newer agents, but the generic principles outlined should apply to help clinicians assess the risks and benefits associated with any proposed regimen for a given situation.

In light of the limited number of large, controlled clinical studies, registries are an invaluable tool to assess the extent to which OPAT is used, as well as clinical outcomes with this treatment modality. Importantly, registries permit analysis of qualitative as well as quantitative indicators using a larger dataset and a more diverse patient population than could be achieved with clinical trials. In addition to national registries, data from a number of countries are collated in the International OPAT registry. The participation of OPAT centres in local or national registries is vital because they provide a means of monitoring the care process and the clinical, microbiological...
and fiscal outcomes, and importantly underpin the safety and governance of such programmes.

**Implications of recent therapeutic advances**

Over the past decade, several antimicrobial agents have been approved in Europe for the treatment of Gram-positive infections, including linezolid (2001), tigecycline (2005) and daptomycin (2006). A recent analysis reviewed outcomes of a European cohort of patients receiving OPAT using either linezolid or teicoplanin as part of a multinational study. Treatment was initiated with iv antibiotics, with the option to switch to oral (linezolid) or intramuscular (teicoplanin) therapy. Patients treated with linezolid had a shorter average duration of antibiotic therapy compared with patients treated with teicoplanin (6.3 days versus 9.5 days, respectively). However, certain baseline variables, particularly access to OPAT, had substantial effects on LOS and cost of treatment, and the apparent economic benefits of linezolid treatment over teicoplanin were exclusively found in the subset of patients who had access to OPAT. Minimal data for OPAT with tigecycline are available, e.g. only 1% of 5522 treatment courses in 5017 evaluable patients received tigecycline in a broad-based experience of treating 6318 patients with a variety of infections.

Daptomycin has been used for OPAT in both the USA and Europe. The Cubicin Outcomes Registry and Experience (CORE) is a retrospective post-marketing database of daptomycin (Cubicin) use in the USA. Outcomes for CORE-registered patients who were treated with daptomycin during 2005 were recently reviewed. Of 949 evaluable patients treated with daptomycin, 539 (56.8%) received OPAT and 410 (43.2%) received only inpatient therapy. Of the OPAT patients, 273 (50.6%) also received some inpatient treatment, usually preceding OPAT. Clinical success rates (clinical cure or improvement) for OPAT patients compared with inpatients were 94.6% versus 86.3%, respectively ($P<0.001$). Fifty (9.3%) of 539 OPAT patients and 81 (18.8%) of 410 inpatients experienced at least one adverse event ($P<0.0001$), and 31 (5.8%) of 539 OPAT patients and 34 (8.3%) of 410 inpatients experienced adverse events evaluated as possibly related to daptomycin therapy ($P=0.12$). However, OPAT patients were younger, had fewer underlying diseases and were more clinically stable than inpatients, thus patient selection may have precipitated better outcomes with OPAT patients.

A recent randomized study compared daptomycin with standard therapy for patients with S. aureus bacteraemia and endocarditis. Of the 200 US patients enrolled in this study, 103 received a portion of their treatment on an outpatient basis. Compared with the inpatient group, OPAT patients had a longer mean duration of therapy (25.4 days versus 13.5 days; $P<0.001$; however, they also experienced higher rates of therapy completion (90.3% versus 45.4%; $P<0.001$). A higher rate of clinical success at the test-of-cure visit was observed among the OPAT group than the inpatient group (86.4% versus 55.7%; $P<0.001$). Within the OPAT group, clinical success rates were similar for patients treated with daptomycin and standard therapy (90% and 83%, respectively). Experience in the UK indicates that daptomycin is safe and effective for OPAT. The records of 29 patients treated with daptomycin at a hospital in Scotland were reviewed recently. Nineteen patients were managed through OPAT, 11 without admission. Eleven of the 19 were trained to self-administer or received therapy via a trained carer. Daptomycin was well tolerated for OPAT and there were no unplanned re-admissions. Another study provides an early and interesting insight into the use of different anti-Gram-positive agents in the physician office-based model of OPAT in the USA. In this large experience of treating 6318 patients with a variety of infections, vancomycin remained the first choice antibiotic (70% of 5522 treatment courses) in 5017 evaluable patients, possibly for reasons such as longer extended stability, greater experience and lower drug-acquisition costs. However, daptomycin was by far the most extensively used of all the comparator agents (27% of 5522 treatment courses), although teicoplanin is not available in the USA. These data confirm the potential and evolving role of daptomycin in OPAT for treating Gram-positive infections. Daptomycin is currently administered as a 30 min iv infusion; however, a 2 min iv injection is in development, and early results suggest similar pharmacokinetic and safety profiles to the 30 min iv infusion. The reduced infusion time of the 2 min iv injection has the potential to facilitate greater use of daptomycin in outpatient settings. Additional studies in different healthcare settings (particularly in Europe), including treatment of traditional and evolving Gram-positive infections (e.g. stent and endovascular infections), the use of combination therapy (e.g. with rifampicin), the use of different models of OPAT (e.g. self-administration) and the development of bolus infusions are required to assess fully the true potential value of recently licensed agents in the OPAT setting.

**Conclusions**

OPAT is a recognized standard of care for managing a range of infections, including those due to Gram-positive organisms. As the burden of these infections grows, our ability to mitigate them with existing and new therapies appears to be keeping pace. However, an increasing demand for hospital capacity and the need to offer clinicians, administrators and patients alternative clinical options that are both safe and cost-effective highlight the urgent need for expansion of OPAT services in Europe. Better studies are required to examine the current practice of OPAT throughout Europe, and a collaborative and concerted effort is required to establish European solutions to potential barriers of OPAT development. Despite the recommendations of AdHOC nearly a decade ago, progress has been slow. New therapies such as daptomycin are likely to prove an invaluable OPAT resource, should early promise in this area be fulfilled.

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