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TITLE PAGE

Article Title:

Clinical efficacy, cost-analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service

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Short Running Title:

Clinical efficacy and cost-analysis of OPAT in Sheffield (UK)

ABSTRACT

Outpatient parenteral antimicrobial therapy (OPAT) has evolved relatively slowly in the UK. This study describes the OPAT service based in a large UK teaching hospital in Sheffield, and examines the clinical efficacy, patient acceptability and costs saved over a 10-year period. Data on 3812 episodes of OPAT treatment administered between January 2006 and January 2016 were retrieved from a prospectively maintained electronic database. We compared the real costs of the OPAT service with estimated costs of conventional inpatient care for these patient episodes. We also analysed patient feedback questionnaires that were randomly administered between January 2014 and January 2015. A wide range of infections were managed during the 10-year period. Skin and soft tissue infections accounted for 57% of OPAT episodes. The total number of bed days saved was 49854. A successful outcome (cure or improvement) was found in 3357 (88%) episodes. Readmission occurred in 265 (7%) episodes. The rates of healthcare-associated infections were low: 15 intravenous line-related infections were recorded (0.3 per 1000 OPAT patient days). Patient acceptance and satisfaction with OPAT were high. OPAT cost 15%, 39%, 40% and 44% of inpatient costs respectively for an infectious diseases unit, national average costs, for other departments (non-infectious diseases unit), and the minimum national average costs for each diagnostic category. This study shows that OPAT is safe, clinically efficacious and acceptable for treating a wide range of infections with high levels of patient satisfaction and substantial cost savings.

Keywords:

Outpatient parenteral antimicrobial therapy (OPAT), home intravenous antibiotics, cost effectiveness

TEXT

Clinical efficacy, cost-analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service

1. Introduction

Intravenous antimicrobials are increasingly administered in outpatient settings to treat a wide range of infections in patients who need parenteral therapy but are well enough not to require hospital admission. Outpatient administration of intravenous antibiotics was first described in the United States in 1974 for patients with cystic fibrosis [1], and has become widely accepted as the standard of care in many parts of the world for patients with low risk infections requiring long-term IV antibiotics [2,3]. In the UK, outpatient parenteral antimicrobial therapy (OPAT) has evolved relatively slowly but is now becoming widespread as the benefits to patients and local healthcare systems are being recognised [4].

The Sheffield OPAT service was established in January 2006 and is one of the largest in the UK. Chapman et al reviewed the first two years [5]; this study reviews the changes in the OPAT service over the last decade and examines the clinical efficacy and cost savings from the use of OPAT within the UK National Health Service (NHS).

2. Materials and methods

2.1. The OPAT service

The Sheffield OPAT service was established in January 2006, based in a regional Infectious Diseases Unit within a large teaching hospital in South Yorkshire, England. The service grew

from a two to 16 bed (-equivalent) outpatient 'infusion centre' in 10 years and the nursing team increased from 1.4 to 8.6 whole-time equivalents. The service is run by a multidisciplinary team of infectious diseases physicians, specialist nurses, and clerical support staff with sessional inputs from microbiology and clinical pharmacy teams.

Patients are referred to OPAT from the emergency admission units, inpatient wards, outpatient clinics and primary care. A small number of patients self-referred having previously received treatment in the OPAT unit. Referred patients are assessed by the OPAT physician or specialist nurse, either directly or by telephone. Patients are enrolled into the service if they meet a number of pre-defined criteria: aged >16 years, suitable antibiotic regimen identified, adequate venous access, medically and psychologically stable, and safe social circumstances.

Vascular access devices are inserted by the OPAT nurses. Antimicrobials are delivered by three distinct pathways: daily attendance at the infusion centre; self or carer administration in patient's own home; and administration in patient's home by a district nurse. Self/carer administration is often used in patients on longer treatment courses (e.g. endocarditis and orthopaedic infections) and those on multiple daily doses of antimicrobials. Patients on short-term antibiotics for skin and soft-tissue infections (SSTIs) attend the unit once daily for treatment and review. Patients on prolonged antimicrobial courses are reviewed at least once weekly by the medical team. Free transport is available for all patients - using local taxis or the ambulance service. All patients have 24-hour access to medical advice via the on-call infectious diseases team. Patient progress and management plan are reviewed weekly at a multidisciplinary virtual ward round. The ward round is attended by a

microbiologist, pharmacist, and the OPAT nurses and physicians. Anonymous feedback questionnaires are periodically sent to patients after completion of treatment. The last survey was conducted between January 2014 and January 2015.

2.2. Data collection

An electronic database has been in place since 2006 to prospectively record patient demographics, clinical diagnosis, model of delivery, antimicrobial agents, treatment duration, type of intravenous access, clinical outcome, complications and mode of transportation. Using the database, we retrospectively reviewed all patient episodes for 10 years from January 2006. Case notes were reviewed where necessary. We also analysed the patient feedback questionnaires that were randomly administered between January 2014 and January 2015.

2.3. Economic evaluation

We carried out a cost-consequence analysis in which the components of incremental costs (e.g. additional therapies) and consequences (e.g. health outcomes) are estimated and presented separately, without combining the results into a cost-effectiveness ratio. It allows decision-makers to form their own opinion regarding the relevance and relative cost-effectiveness of the alternative outcomes. We chose this approach because there was no single outcome measure capable of capturing all the consequences of the OPAT service.

We compared the total costs of the OPAT service to estimated costs of conventional inpatient care. Costs were estimated from the NHS perspective to reflect the fact that the OPAT service works within a fixed NHS budget. The total costs of OPAT were estimated from

the actual costs, and costs of readmissions following adverse events that would not have occurred had the patients been treated as an inpatient. The actual costs were obtained from the annual financial records of the service over the 10-year period. These included set-up costs, staff wages, drugs, equipment, consumables and overheads. All costs were deflated/inflated to 2011/12 prices using the hospital and community health services pay and price index to ensure comparability over the 10-year period.

To estimate the costs of conventional care that would have been incurred had the OPAT patients been treated as inpatients, we assumed that the length of inpatient stay would have been equal to the length of OPAT care, and the diagnosis was the same. Bed days saved were determined by calculating the number of days between the start and end of OPAT care. We identified an appropriate healthcare resource group (HRG4) code for each diagnosis (Table 1) and obtained the associated 2011/12 unit cost from the NHS resource costs. For the unit costs, we used the Sheffield Teaching Hospital's (STH) Directorate of Communicable Diseases average costs per day, and the lowest unit cost for each diagnosis across all other STH departments. Infectious diseases units' average costs per day are often higher than the costs in other departments because of the increased costs of managing patients in single isolation rooms. The theoretical costs of conventional inpatient care were calculated by multiplying the number of bed days saved for each diagnosis by the unit cost associated with the diagnosis. To assess the cost of the service within a national context, we used the same method to calculate the costs of conventional inpatient care using national average non-elective inpatient costs per day. We also applied the lowest national average non-elective cost per day in each diagnostic category to all patients within the category, to

account for the fact that patients who are eligible for OPAT are likely to require minimal inpatient care and incur low inpatient treatment costs per day.

3. Results

3.1. Clinical activity

In the 10-year study period, 3812 OPAT episodes were recorded in 3004 patients. The total number of days of patient care (bed days saved) delivered through OPAT was 49854 (range <1 day to 533 days; mean 13.1 days). The longest course of treatment was administered to a patient with multidrug-resistant tuberculosis requiring parenteral capreomycin and meropenem. The number of episodes per year increased from 158 in 2006/07 to 607 in 2015/16. The total number of OPAT patient days also increased gradually over the 10-year period (Figure 1).

A wide range of infections was managed (Table 1). SSTIs accounted for the largest number of bed days saved (15973/49854; 32%) and patient episodes (2183/3812; 57%; median 5 days; range 0-89 days). The longest antibiotic course for a SSTI case was administered to a patient with *Mycobacterium chelonae* skin infection requiring IV tobramycin and tigecycline. Among the non-SSTI cases, bone and joint infections (including spinal discitis) accounted for the largest number of bed days saved (13934/49854; 28%). Over the 10-year period, the proportion of episodes due to non-SSTI rose moderately from 41% to 46% (Figure 2).

Ceftriaxone was the most frequently prescribed parenteral antimicrobial agent (65%; 2565/3936). Table 2 shows the 10 most common agents used. SSTI was the recorded

indication for ceftriaxone in 78% (1989/2565) of cases. In addition to parenteral antimicrobials, oral agents were used in 246 patients concurrently with parenteral agents.

Vascular access data were recorded for 3581 episodes (Table 2). Peripheral IV catheters (butterfly needles and peripheral venous cannula) accounted for the majority of the vascular device (2579/3581; 72%). The intramuscular (IM) route was used in 14 patients - mostly IM streptomycin for tuberculosis infection. The model of delivery was recorded in 3711 episodes (Table 2). Most patients attended the OPAT unit daily. In 458 episodes (12% of total OPAT episodes; 14844 OPAT patient days) antibiotics were administered by the patient or a relative at home after formal training. The mode of transportation used by patients attending the OPAT unit was recorded in 3734 patient episodes. Taxis provided by the unit were the main mode of transportation (2054/3812; 54%).

3.2. Clinical outcomes

Clinical outcomes on completion of parenteral therapy were documented in 3685 episodes (Table 3). A successful outcome (cure or improvement) was recorded in 3357 (88%) of the 3812 episodes; 94% of patients with SSTIs had a successful outcome. Cure was infrequently recorded because most patients continued on oral antimicrobial therapy after discharge from the OPAT service. Readmission was recorded in 265 (7%) episodes. The main indication for readmission was progression or non-response of infection. SSTI patients who had poor response or clinical deterioration accounted for the majority of the readmissions (55/265; 21%). Two patients were readmitted with *Clostridium difficile*-associated diarrhoea (CDAD) and three with line-related complications. Of the latter, two had central line-associated bloodstream infections and the third patient cut off the end of her peripherally inserted

central catheter (PICC) line while self-administering antibiotics. Two patients died, both from cardiac causes unrelated to OPAT.

Line-related infections were recorded in 15 patient episodes (0.4%; cumulative risk 0.3 events per 1000 OPAT patient days). Two of the 458 patient episodes where antimicrobials were self-administered, had line-related infections (0.4%; cumulative risk 0.1 events per 1000 OPAT patient days). Other line-related complications (e.g. leakage, chemical/mechanical phlebitis, thrombosis, dislodgement, breakage) occurred in 27 episodes (0.7%; cumulative risk 0.5 per 1000 OPAT patient days).

3.3. Patient satisfaction survey

Of 279 questionnaires sent out to patients (including those who failed OPAT therapy) between January 2014 to January 2015, 147 were returned (53%). 146 respondents (99%) rated the service as very good or excellent. 143 (97%) stated that the treatment received met their expectations. 144 (98%) would choose OPAT again if required (Table 4).

3.4. Cost-analysis

Table 5 shows a summary of the costs associated with delivering the OPAT service. The actual cost of delivering the service over the 10-year period was £4,734,573 (includes staffing, consumables, equipment, drugs, set-up and overhead costs). After adjusting for inflation/deflation to 2011/12 prices, the cost was £4,729,071. Set-up costs of the service consisted mostly of staffing costs and were assumed to be fully attributed to the 10-year period. Staffing costs accounted for 55% of the total costs and were relatively consistent over the 10-year period. The overheads and support costs represent pharmacy,

physiotherapy, laboratory services, transport and other direct costs associated with the OPAT service. The overheads and support costs were assumed to be 44.8% of the total costs of the OPAT service (excluding readmission and set-up costs) based on the reference cost profile for our infectious diseases outpatient department.

We identified four readmissions due to complications that were deemed would not have occurred had the patients been treated as inpatients. One patient sustained a fractured humerus after falling on her way to the OPAT unit and was readmitted to stabilise her fracture and for social reasons. The second patient cut off the end of her PICC line while self-administering antibiotics. She was readmitted for line replacement and to complete her treatment. The third and fourth patients, who self-administered antimicrobials, were readmitted with line related infections. The other 261 readmissions were excluded from the cost analysis as they were deemed to have had complications that would have occurred regardless of method of treatment, and would have resulted in increased length of hospital stay for patients already on admission. The estimated cost of these four readmissions was £95,436 - based on 2011/12 STH unit costs. Thus, the total cost of the OPAT service over the 10-year period was £4,824,507 (i.e. £4,729,071 plus £95,436) at 2011/12 prices.

The theoretical costs of treating the 3812 OPAT patient episodes as an inpatient were estimated in four ways using: STH's Directorate of Communicable Diseases unit costs, minimum STH unit costs across all departments, national average unit costs, and minimum national average unit costs in each diagnostic category. Using our directorate and minimum STH unit costs, the total estimated costs of equivalent inpatient care for the 3812 patient episodes were £32,715,992 and £11,961,081 respectively. When the national average unit

costs were used, the total estimated cost was £12,264,388. Using the minimum national unit costs within each diagnostic category, the total cost was £11,045,779 (Table1).

4. Discussion

OPAT in the UK has evolved relatively slowly but is now becoming more common as the benefits to patients and local healthcare systems are being recognised [4]. Existing OPAT services have developed uniquely to meet local requirements [6], and have led to variations in practice and model of service delivery. This study reviews the OPAT service based in a regional Infectious Diseases Unit within a large teaching hospital and adds to the growing evidence that OPAT is safe, effective and acceptable to patients [7-16]. The OPAT service used a combination of outpatient 'infusion' centre, self/carer administration and visiting nurse models of OPAT delivery. Over the last decade, the service has expanded to accommodate complex infections such as multi-drug resistant tuberculosis that were previously not deemed manageable in outpatient setting. It also expanded to the emergency admission area to prevent unnecessary hospital admissions, taking some pressure off emergency care.

Our high success rate, high levels of patient satisfaction, and low complication and readmission rates reflect other UK-based studies [17-20]. Use of once-daily broad-spectrum antimicrobials such as ceftriaxone and ertapenem for infections that require narrow spectrum agents could be associated with the emergence of resistant organisms and increase incidence of CDAD. Although the database did not include prospective data on healthcare-associated infections (HAIs), two patients were readmitted because of CDAD. It is difficult to determine the relative contribution of OPAT as both patients were hospitalised

and received antimicrobial therapy prior to referral to OPAT. Aberdein et al retrospectively reviewed patients who attended the Sheffield OPAT service between April 2006 and December 2011, and identified five further cases of CDAD following OPAT, who remained in the community [21]. All but one of these cases had other possible causes for their CDAD. They reported a rate of 6 cases of CDAD per 100,000 OPAT-days. Generally, the rates of HAI in OPAT are lower than in hospitalised patients [22]. However, the impact of OPAT on the emergence of antibiotic resistant organisms is poorly studied and requires urgent attention.

The study shows that a wide variety of conditions in a complex group of patients is amenable to treatment by OPAT. In recent years, the number of patients treated per year by the OPAT service has been stable. However, the proportion of non-SSTI cases and the number of OPAT patient days (bed days saved) per year are rising due to increasing complexity of patients and diversity of case mix. Despite the changes in patient complexity and minimal increase in staffing costs, outcome success was maintained over the 10-year study period. A range of antimicrobial agents was used. For instance, antifungal agents such as amphotericin B, caspofungin and anidulafungin, were used to treat invasive fungal diseases with successful outcomes. OPAT has allowed older agents to be used in novel ways [6]. IV fosfomycin, temocillin and aztreonam were used successfully in our service to treat patients with orthopaedic infections caused by drug-resistant organisms. Novel agents such as dalbavancin (once-weekly) and telavancin (once-daily) are potentially useful in OPAT and require further evaluation.

This study also adds to the growing evidence that self/carer administration of IV antimicrobial therapy is safe [18,23,24]. This model of delivery has the advantage that it

further lowers costs with fewer nursing and clinic visits. It also gives patients more flexibility and control over their treatment; they can fit treatment around their work schedule and other commitments. However, patients or carers must possess the required dexterity and receive adequate training. Pathways must be in place to urgently manage vascular access problems. Furthermore, the model may not be suitable for antibiotics such as amoxicillin that are unstable in aqueous solution unless patients can personally collect premixed bags of antibiotics for infusions or have them delivered [25,26]. Hence, self/carer administration should be reserved for a carefully selected group of patients. Although OPAT is safe, risk assessment, risk management and quality assurance systems are essential to minimise potential risks and optimise the quality of care, in accordance with existing practice guidelines [2-4].

Comparing the total costs of the OPAT service with estimated costs of equivalent inpatient care, we found that the service has delivered substantial cost savings over its 10 years of operation. We assumed that the number of patient days in OPAT is the same as the number of days patients would have been hospitalised. The assumption seems reasonable since both the inpatient Infectious Diseases and OPAT service are managed by the same group of infectious diseases specialists. The duration of therapy for our patients is often pre-defined and would have been the same irrespective of whether they were treated as inpatients or in OPAT. Using the costs of managing patients in our infectious diseases unit, the OPAT service cost 15% of equivalent inpatient cost. We also estimated the costs of managing the patients in other departments in our hospital because the infectious diseases unit accounts for a very small proportion of the total referrals to the OPAT service and patients may otherwise have been treated in other STH departments where the lowest costs would be incurred. This

comparison found OPAT to cost 40% of inpatient care. We included the national average costs to make the findings applicable to other acute hospitals in the UK. Infectious diseases units' average daily costs are often higher than national average costs and costs in other units due to the specialist nature of the service and requirement for isolation facilities. Using the national average costs, we found OPAT to cost 39% of equivalent inpatient cost. Finally, with the minimum national average costs, OPAT cost 44% of inpatient care.

Chapman et al [5] reported relative costs of 41%, 47% and 61% for the STH infectious diseases unit costs, national average costs and minimum inpatient costs respectively. Although our relative costs are much lower than those reported by Chapman et al, they are not directly comparable due to changes in the structure of the NHS reference costs over the years. Chapman et al used aggregated diagnostic categories for cost allocation based on HRG v3.5 codes. In contrast, we assigned appropriate HRG4 code for each diagnosis rather than the diagnostic categories to give a more accurate cost estimates. HRG4 superseded HRG v3.5 and provides a more accurate reflection of clinical activity. An analysis of the costs per year showed that the ratio of actual OPAT costs to estimated costs of equivalent inpatient care remained fairly stable over the 10-year period.

Without a doubt, even using the minimum possible costs for inpatient care, we have shown that OPAT is associated with significant cost savings. Cost savings could be maximised if OPAT patients are closely monitored to prevent complications and hospital readmissions. It is worth mentioning that there are many indirect benefits and cost savings of OPAT to patients and healthcare systems (such as reduction in the cost of nosocomial infections, patients satisfaction, increased productivity and quality of life) [4,15] which we did not

consider in this study as it would require complex mathematical modelling beyond the scope of our study. With the growing interest in OPAT in the UK, novel studies such as the Community IntraVenous Antibiotic Study (CIVAS) could provide more insight into the cost-effectiveness and patient preference for the different models of OPAT service [27]. It will be of interest to examine in more detail the causes of and risk factors for readmissions from OPAT in this large cohort. For a successful OPAT service, it is essential to align the interests of the major stakeholders - patients, carers, physicians, providers, commissioners etc [16]. For instance, in countries where hospitals are paid according to the number of occupied bed-days, OPAT may be discouraged. Hence, organisations wishing to set up OPAT services should consider the model of delivery and payment system that best suit their local healthcare setting pending a standard OPAT tariff [28].

5. Conclusion

Despite the usual limitations of a retrospective database review with some missing data and potential for bias, as well as the assumptions required for the cost analysis, this large cohort study of 10 years of OPAT experience in Sheffield adds to the growing evidence that administration of intravenous antimicrobials to patients outside a hospital ward setting is safe, clinically efficacious and provides substantial cost savings with high levels of patient acceptance and satisfaction. This study demonstrates that OPAT is suitable for a wide range of infections in an increasingly complex patient group as long as measures are in place to minimise clinical risks.

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Declaration of interests

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