**The impact of Pediatric Outpatient Parenteral Antibiotic Therapy (p-OPAT) implementation at a tertiary children's hospital in the United Kingdom**

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**ABSTRACT**

Background: Recent advances in outpatient parenteral antibiotic therapy (OPAT) have largely focused on adult practice, and there are few published data on the safety and effectiveness of pediatric OPAT (p-OPAT).

Methods: During a 3-year-period (2012 to 2015), data were prospectively collected on patients managed within the p-OPAT service at Southampton Children’s Hospital, a tertiary pediatric hospital in the South of England.

Results: A total of 130 p-OPAT episodes were managed during this period. The most frequently managed pathologies were bone and joint infections (44.6%), followed by ENT (10.7%), respiratory (10.0 %) and CNS (10.0 %) infections. The most frequently used antimicrobial agent was ceftriaxone (n=103;79.2%). For the majority of p-OPAT episodes, antimicrobials were delivered in pre-filled syringes (n=109; 83.8%); 24-hour infusions administered by elastomeric devices were used less commonly (n=16;12.3%). The median duration of p-OPAT treatment was 9.2 days (interquartile range: 7.6 – 19.0 days). With regard to patient outcomes, 113 (86.9%) p-OPAT episodes resulted in cure and 12 (9.2%) in improvement; treatment failure occurred in 5 (3.9%) episodes.Intravenous catheter-related complications were rare. A total of 1683 bed days were saved over the 3-year-period.

Conclusions: Our data suggest that p-OPAT is safe and effective, with the potential to offer considerable savings for the healthcare economy through reduced length of inpatient stay.

**Background**

Data from adult practice provides strong rationale for managing children and young people on intravenous antimicrobial therapy at home whenever possible. ([1](#_ENREF_1)) Potential benefits include greater parent and patient satisfaction, enhanced psychological wellbeing, earlier return to school or employment, reductions in healthcare-associated infections and substantial cost savings. Recent advances in outpatient parenteral antibiotic therapy (OPAT) have largely focused on adult practice,([2](#_ENREF_2)) and there are few published data on the impact of pediatric OPAT (p-OPAT) services. While it has been estimated that more than one in 1.000 adults in the U.S. receive OPAT annually,([3](#_ENREF_3)) there are no reliable estimates regarding the use of OPAT in children.

In the U.K. a joint collaboration between the British Society for Antimicrobial Chemotherapy (BSAC) and the British Paediatric Allergy, Immunity and Infection Group (BPAIIG) has proposed the formalisation of clinical practice and governance of p-OPAT through good practice recommendations.([4](#_ENREF_4)) The aim of this initiative was to promote the delivery of safe and effective p-OPAT services in order to enhance patient experience, deliver healthcare closer to or at home, 6 reduce length of inpatient stay in order to deliver cost savings,7 and to embed antimicrobial stewardship into clinical practice.8

This prospective service evaluation aimed to describe the effectiveness and safety of p-OPAT treatment at a tertiary children’s hospital in the South of England over a 3-year period.

**Methods**

We prospectively collected data on patients managed by the p-OPAT service at Southampton Children’s Hospital, University Hospital Southampton NHS Foundation Trust between July 2012 and June 2015. The hospital serves a regional population of approximately 500,000 children, has a total of 124 inpatients beds (excluding neonatal care) and has more than 9,000 pediatric admissions per year. A p-OPAT service was introduced in July 2012, specifically designed to manage children with complex infections requiring prolonged intravenous antibiotic therapy of at least five days duration once discharged from the hospital. The p-OPAT team consisted of a pediatric infectious diseases consultant and a full-time p-OPAT nurse supported by an part time clinical/part time academic pediatric infectious diseases consultant and pediatric medical junior staff. These staff members not only delivered the p-OPAT service but also ran the paediatric infectious diseases service, antimicrobial stewardship service and the PICC Line service. Patients suitable for p-OPAT were identified by the pediatric infectious diseases team on routine antibiotic stewardship ward rounds conducted three times a week, or via direct referral from pediatric subspecialty teams.

Explicit eligibility criteria were used to assess p-OPAT suitability, with regards to clinical, social and caregiver factors.([4](#_ENREF_4)) If there were any concerns regarding potential patient / parent adherence or suitability of the home environment for p-OPAT, p-OPAT was not initiated. All p-OPAT patients included in this study were initially managed as inpatients by the referring team. The ability to administer antibiotics at home depended on the availability of local community pediatric nurses. In some cases, parents/carers administered their child’s antibiotics at home after being trained appropriately. The choice of the antibiotic regimen was made by the p-OPAT consultant, taking the underlying pathology and the microbiological test results into account. Prior to discharge home, parents or carers were provided with information on central line care by the p-OPAT nurse, and taught about the recognition of potential complications by the p-OPAT nurse. Parents were able to directly contact the OPAT team 24 hours per day while being managed within the p-OPAT service.

Laboratory tests were performed weekly (comprising full blood count, renal function tests, liver function tests and C-reactive protein in all patients; in addition, creatine kinase was determined in 5 children receiving daptomycin). The patients and the laboratory results were reviewed weekly in the hospital-based p-OPAT clinic.

Outcomes were determined in all patients discharged from the p-OPAT service, defined as at the point when intravenous antibiotics were stopped. Treatment outcomes were classified according to previously published consensus definitions, ([4](#_ENREF_4)) with minor modifications. Complications were identified either by parents or community based nurses and communicated directly to the OPAT team or by the OPAT team at the weekly face-to-face clinic review. Concerning *patient infection outcome* an p-OPAT episode was classified as either a) cure: p-OPAT therapy was completed and/or an oral-step-down was decided for a defined duration, with resolution of infection and no requirement for long-term antibiotic therapy; b) improvement: completed p-OPAT therapy with partial resolution of infection requiring long term oral step-down/escalation of antibiotics *or* cure requiring escalation of antibiotics (without admission); or c) failure: progression or lack of clinical response despite p-OPAT, resulting in admission, surgical intervention or death. Concerning *p-OPAT outcome* an p-OPAT episode was classified as either a) success: p-OPAT therapy was completed without line complications or antimicrobial side effects requiring a change in antibiotics or line removal; b) partial success: p-OPAT therapy was completed without readmission to hospital but required a change of antibiotics or line removal due to a line complication or antimicrobial side effects; or c) failure: readmission or death due to line complications or antimicrobial side effects. Regarding weekly blood test monitoring, only abnormalities that required action (i.e. stop/switch antimicrobials), were regarded as a drug complication.

***Data collection and statistical analyses***

All data were collected prospectively in Excel (Microsoft; Redmond, Virginia, WA, U.S.) as part of routine p-OPAT case management. The statistical analyses were performed and figures were constructed with Prism V6 (GraphPad; La Jolla, CA, U.S.).

***Institutional Board Approval***

The project was assessed by University Hospital Southampton NHS Foundation Trust to be a formal service evaluation under the UK Research Governance Framework (<http://www.hra-decisiontools.org.uk/research/glossary.html#S>)

 **Results**

A total of 130 p-OPAT episodes in 123 patients were managed by the p-OPAT service over the 3-year-period. The age distribution was as follows: 0 to 12 months (n=8; 6.2%), 1 to 5 years of age (n=50; 38.5%), 5 to 12 years (n=43; 33.1%), and 12 to 18 years (n=29; 22.3%). The male to female ratio was 1.2:1 (males: n=66, females: n=57). The most frequently managed pathologies were bone and joint infections (44.6%), followed by ENT (10.7%), respiratory (10.0 %) and central nervous system (CNS) (10.0 %) infections (Figure 1).

***Causative organisms***

A causative pathogen was identified in 87 episodes (66.9%; Figure 2). *Staphylococcus aureus* was the most commonly isolated pathogen. Two patients had infections caused by Panton-Valentine leukocidin-producing *S. aureus* isolates*.* There were no cases with methicillin-resistant *S. aureus* (MRSA) infection.

***Antimicrobial agents used***

The most frequently used antimicrobial agent was ceftriaxone (n=103; 79.2%). Other agents used were flucloxacillin (n=6; 4.6%), piperacillin/tazobactam and teicoplanin (n=6; 4.6%, each), daptomycin (n= 5; 3.8%) and ceftazidime combined with inhaled tobramycin (n=4; 3.1%) (Figure 3).

**Devices used**

For the majority of p-OPAT episodes, antimicrobials were delivered in pre-filled syringes (n=109; 83.8%). 24-hour infusions administered via an elastomeric device were used in 16 patients (12.3%), for the administration of flucloxacillin (n=6), piperacillin/tazobactam (n=6) and ceftazidime (n=4). Daptomycin was dispensed as vials and reconstituted within the p-OPAT setting in 5 patients (3.9%).

***Duration of treatment***

Overall the median duration of p-OPAT treatment was 9.2 days (interquartile range: 7.6 – 19.0 days). The longest p-OPAT treatment duration was observed in cases with pyomyositis (n=3, median 37 days), CNS infections (n=13, median 18 days) and bacterial endocarditis (n=6, median: 17 days), shown in Figure 4. In most types of infections, p-OPAT treatment courses were longer than the duration of inpatient treatment prior to discharge home (mean 9 days (IQR 6-14) compared to 6 days (IQR 4-8.5)), see Figure 4. The only patient group in which the duration of inpatient treatment was longer than the duration of p-OPAT treatment was the group with bacterial endocarditis (mean 20.5 days (IQR 16-24) compared to 17 days (IQR 12-22)).

***Inpatient bed days saved***

A total of 1683 bed days were saved over the period studied. These patients would otherwise have remained in hospital receiving intravenous antibiotics. The largest numbers of bed days saved were observed in the groups of patients with osteomyelitis and CNS infections, where p-OPAT treatment saved a total of 433 and 358 bed days respectively. Other types of infections in which large numbers of bed days were saved included septic arthritis, bacterial endocarditis, and respiratory infections (Figure 5).

***Type of intravenous access***

In the majority of p-OPAT episodes, patients received antimicrobial treatment via a peripherally inserted central catheter (PICC) (n=105; 80.8%). Ten patients (7.6%) had a pre-existing tunnelled central venous catheter *in situ* (eight oncology patients, one patient with chronic granulomatous disease, one patient with structural congenital cardiac anomalies). Peripheral cannulas were rarely used (n=15, 11.5 %).

***Service structure***

For the majority of p-OPAT episodes, intravenous antibiotics were administered at home by pediatric community nurses (n=103; 79.2%) and at home by parents/carers in 3 episodes (2.3%). 24 episodes (18.5%) involved administration on an ambulatory basis at the hospital local to the family, usually the original referring hospital, due to the lack of local community nursing provision.

***Intravenous catheter-related complication***

No catheter-related complications occurred in children with pre-existing tunneled central venous catheters. 12 (11.4%) PICC-related complications occurred during p-OPAT therapy. Mechanical complications (n=9, 75%) comprised line migration / dislodgement (n=5), line blockage (n=3) and line fracture (n=1). Infective complications (n=3, 25%) comprised suspected exit site infections (n=2) and presumed central line-associated bloodstream infection (n=1; not culture-proven).

Three suspected drug-related complications (2.3%) were observed. One patient with osteomyelitis developed a generalised skin rash after 14 days of treatment with piperacillin/tazobactam treatment. After treatment was discontinued the rash resolved. One patient with septic arthritis developed a generalised rash following two days of treatment with ceftriaxone. After switching to teicoplanin the rash resolved. One patient with endocarditis developed a widespread rash, fever and neutropenia after three weeks of treatment with ceftriaxone. Delayed type IV hypersensitivity was diagnosed and the rash resolved after the antimicrobial agent was changed.

***Treatment outcomes***

113 (86.9%) p-OPAT episodes resulted in cure and 12 (9.2%) in improvement, in terms of patient infection outcomes. Treatment failure occurred in 5 (3.9%) episodes. One patient with chronic granulomatous disease who had a persistent lower respiratory tract infection developed pyrexia after 14 days of treatment with piperacillin/tazobactam. Following readmission liposomal amphotericin B was added, which led to resolution of his fever within 2 days. The second patient had septic arthritis caused by Panton-Valentine leukocidin-producing *S. aureus* treated with ceftriaxone. Re-admission was required for further surgical intervention. The three remaining patients were subsequently found to have non-infectious pathologies (inflammatory arthropathy, oesteosarcoma and acute lymphoblastic leukaemia).

Most episodes of p-OPAT therapy were completed without any adverse events due to line complications or side effects of antimicrobial treatment (p-OPAT success, n=114; 87.7 %). In 13 episodes (10.0 %), the p-OPAT course was complicated with an adverse event requiring a change in antibiotic therapy or line removal without the patient requiring readmission to hospital, mainly due to mechanical catheter-related complications and mild drug-related reactions such as minor skin rashes (p-OPAT partial success (appendix 1)). The p-OPAT outcome was considered failed in three cases (2.3%); one patient had to be readmitted for PICC replacement due to a blocked line (failed attempt to clear the line with urokinase) and two cases were readmitted with suspected catheter-related infections (p-OPAT failure). One of these two cases was a child being treated by the p-OPAT service for a central line infection.

**Discussion**

These data are the first description of a formal p-OPAT cohort in Europe, demonstrating that p-OPAT delivered by a dedicated team allowed children with complex infections to be safely managed at home. Robust clinical governance, clear channels of communication and accurate outcome monitoring were an essential component of this work. ([4](#_ENREF_4))

Readmission rates, rates of catheter-related complications and drug-related adverse events were very low. These rates were broadly similar to those described in other p-OPAT centers in the USA and Australia. ([5](#_ENREF_5), [6](#_ENREF_6)) Rates of PICC line complications were far lower than previously reported. ([7](#_ENREF_7), [8](#_ENREF_8))

Bone and joint infections made up the majority of cases within our service. Although there is little clinical trial evidence, clinicians are switching earlier from intravenous to oral antibiotics in osteoarticular infections. ([9](#_ENREF_9), [10](#_ENREF_10)) This is likely to result in such patients representing a smaller proportion of p-OPAT activity in the future. Respiratory cases made up only 10% of our p-OPAT cohort. Although pathologies such as infective exacerbations of cystic fibrosis appear amenable for management within a p-OPAT service, there is a lack of consensus about the safety of this approach. ([11-13](#_ENREF_11)). Our experience is that an increasing number of subspecialist colleagues were prepared to consider the p-OPAT approach for their patients once the service was established and robust safety and family satisfaction data were available.

P-OPAT clinicians need to remain mindful of their antimicrobial stewardship responsibilities and not prolong the duration of intravenous antimicrobial therapy unnecessarily. This is especially relevant given the ease of administering p-OPAT with minimal disruption to families. It is possible that waiting for a weekly review prior to stopping antibiotics may have unnecessarily prolonged the duration of intravenous antibiotics in some of our patients. The mean duration of p-OPAT therapy in our cohort was 9.2 days. This is similar to that reported by other p-OPAT centers. ([5](#_ENREF_5), [6](#_ENREF_6)) As there is little high quality evidence currently supporting the optimal timing of switching from intravenous to oral antibiotics, comparing duration of antibiotic therapy between p-OPAT centers for specific pathologies may provide useful information in future to guide clinical practice where formal clinical trials are not feasible or unlikely to provide information for some time. ([14](#_ENREF_14))

Ceftriaxone was by far the most commonly used antibiotic, due to its once per day ease of administration and excellent side-effect profile. Higher dose (>= 80 mg/kg/day) ceftriaxone has been used widely for once daily dosing in the UK for pediatric infections including those caused mostly by *Staphylococcus aureus* such as bone and joint infections, with apparently low treatment failure rates in or out of hospital. ([15](#_ENREF_15)) Although p-OPAT infection outcomes were extremely good using this approach, clinicians are coming under increasing pressure to use narrow spectrum antibiotics where possible to reduce the evolution of antimicrobial resistance. ([16](#_ENREF_16)) However, no patients within our cohort developed clinical *Clostridium difficile* infection or infection with vancomycin-resistant Enterococcus. Balancing the risks and benefits of using a well-tolerated once daily antibiotic versus a narrow-spectrum agent requiring multiple daily dosing is a genuine challenge for clinicians. However, continuous infusion via elastomeric devices represents a potential alternative that can facilitate the administration of certain antibiotic agents that require multiple daily doses. ([17](#_ENREF_17))

Administration of antibiotics by parents/ carers made up an extremely small proportion of p-OPAT episodes (2.3%). With increasing confidence in the safety of p-OPAT, it is likely that this proportion will increase significantly. Administration using self-infusing elastomeric devices administered via a PICC line occurred in 16 p-OPAT episodes (12.3%). Informal feedback suggested that elastomerics are preferred to syringe drivers due to ease of use.

One of the limitations of this study is that it did not include children being ambulated on short courses of intravenous antibiotics (i.e. <5 days). Such patients make up the majority of children receiving intravenous antibiotics and are likely to pose different challenges to the patients described within our cohort. At present, such patients are not managed within the p-OPAT service.

Our data suggest that p-OPAT is safe and effective. Within a dedicated, well-managed p-OPAT service both treatment failures and complications are comparatively rare. Importantly, p-OPAT has the potential to offer considerable savings for the healthcare economy through reduced length of inpatient stay, and free up precious bed spaces at a time when many healthcare systems in Europe and North America are under pressure. ([18](#_ENREF_18), [19](#_ENREF_19))

**Figure 1**. Underlying diagnoses associated with 130 p-OPAT episodes over a 3-year-period.



(\*) ENT infections: mastoiditis, sinusitis, tonsillar abscess and chronic otitis media; (\*\*) Respiratory infections: pneumonia, pulmonary abscess, cystic fibrosis; (§) CNS infections: bacterial meningitis, intracranial abscess / empyema; (§§) Surgical wound infections: mediastinal and spinal infections; (‡) Sepsis: one case of staphylococcal toxic shock syndrome (STSS), one case of multi-focal infections due to Panton-Valentine leukocidin-producing *S. aureus* (endocarditis, septic arthritis, bilateral pneumonia), one case of *Streptococcus pneumoniae* bacteraemia, two cases without identified organism; (‡‡) Infected devices: ventriculoperitoneal shunt infections, vagal nerve stimulation device infection. Abbreviations used: ENT, ear, nose and throat; CNS, central nervous system; CVC, central venous catheter.

**Figure 2.** Causative organisms identified (n=87) in 130 p-OPAT episodes at Southampton Children Hospital



(\*) 2 cases were caused by Panton-Valentine leukocidin-producing *S. aureus* isolates; (\*\*) group F streptococci (n=1), group B streptococci (n=1), non-haemolytic streptococci (n=1), *Streptococcus intermedius* (n=3), *Streptococcus sanguis* (n=1); (§) *Fusobacterium necrophorum* (n=1), remaining isolates not speciated; (§§) *Klebsiella* spp. (n=2), non-lactose fermenting coliforms (n=2); (‡) *Pseudomonas* spp. (n=2), *Pseudomonas aeruginosa* (n=1); (‡‡) *Brevibacterium casei* (n=1), *Bacillus subtilis* (n=1), anaerobic diphteroids (n=1) .

**Figure 3.** Antimicrobial agents used for p-OPAT treatment according to diagnoses. The figures above each bar represent the total number of cases in each category.



(\*) all 4 patients receiving intravenous ceftazidime additionally received intravenous tobramycin.

**Figure 4.** Duration of inpatient and p-OPAT treatment courses according to diagnoses. The bars represent the median; the whiskers represent the interquartile range.



Abbreviations used: ENT, ear, nose and throat; CNS, central nervous system; CVC, central venous catheter.

**Figure 5.** Total number of bed days saved in each category



Abbreviations used: ENT, ear, nose and throat; CNS, central nervous system; CVC, central venous catheter.

**Appendix 1**: p-OPAT partial success cases; reasons for classification (n=13)

 Generalised rash (n=4)

 Peripheral cannula reinsertion (n=2)

 PICC lines left clamped/unclamped incorrectly for 1 day during their treatment (n=2)

 Blocked PICC line - cleared with urokinase (n=2)

 PICC line leak on the final day of treatment (n=1)

 Mild Stevens-Johnson syndrome in the final week of treatment (n=1)

 Neutropenia (<0.5) during the final week of treatment - asymptomatic (n=1)

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