Current Infectious Disease Reports (2019) 21: 17
https://doi.org/10.1007/s11908-019-0669-6

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Outpatient Parenteral Antimicrobial Therapy in Children

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Published online: 16 April 2019

Abstract

Purpose of Review Over recent years, there has been a marked increase in the number of centres delivering paediatric outpatient parenteral antimicrobial therapy (pOPAT). Various factors have fuelled this drive, including the significant economic pressures faced by high-income countries to contain the cost of healthcare, resulting in a significant reduction of in-patient beds over the past 20 years. It is essential that pOPAT services have formal clinical governance structures in place to ensure the safe and effective management of children being ambulated on intravenous antibiotics. They also require oversight of antimicrobial decisions by a medically qualified infection specialist to ensure that the principles of antimicrobial stewardship are adhered to. This review aims to provide an evidence-based framework for delivering pOPAT services.

Recent Findings There is increasing data supporting the implementation of admission avoidance strategies for children with cellulitis and pyelonephritis. In addition, recent data supports the management of a subset of children with febrile neutropenia within pOPAT services. Above all, there is a clear recognition that embedding antimicrobial stewardship within pOPAT services reduces duration of intravenous antibiotics (IVAbs) and improves patient management.

Summary pOPAT services are safe, cost-effective and associated with high levels of parent/patient satisfaction. Further research is required to develop risk prediction models for children being considered for pOPAT. Further data about the use of elastomeric devices in children and the acceptability of parental administration of IVAbs are also required.

Keywords Outpatient parenteral antimicrobial therapy · Antimicrobial stewardship · Antibiotic stewardship · pOPAT · Hospital at home · Ambulatory antibiotics · Children · Paediatrics

Introduction

Paediatric outpatient parenteral antibiotic therapy (pOPAT) is defined as the parenteral administration of antimicrobials for at least two consecutive days without an intervening hospitalisation. Although children have been managed in this way since the mid-1970s and continue to do so in settings across the world, it has only recently been recognised that such services require formal clinical governance structures to ensure the safe and effective management of children being ambulated on intravenous antibiotics (IVAbs) [1••]. The term pOPAT refers to such services and forms the basis of this review.

There is compelling evidence to support the rationale for managing children under pOPAT services and recent data demonstrate that pOPAT is safe, effective, associated with high levels of patient/parent satisfaction and can offer significant economic savings for healthcare systems [2]. Over recent years, there has been a marked increase in the number of centres delivering pOPAT. This rise has been influenced by several factors (Table 1), including the significant economic pressures faced by high-income countries to contain the cost of healthcare, resulting in a significant reduction of in-patient beds over the past 20 years [3].

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

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Table 1 Factors driving the expansion of pOPAT services

•Increased focus of moving care out of acute hospitals
•Increasing evidence supporting the safety and efficacy of pOPAT
•Advances in antimicrobial administration
•Recognition of OPAT as a vehicle for delivering antimicrobial stewardship

Service Structure

pOPAT can be delivered across a variety of clinical settings, utilising a variety of delivery models:

- Home administration by paediatric nurse (hospital or community-based nurse)
- Infusion centre or ambulatory care provision (in healthcare facility)
- Home administration by parent or carer

In addition, OPAT can be effectively delivered as part of a wider *hospital in the home* programme, in which a wider range of pathologies can be managed, including non-infectious presentations. pOPAT tends to be responsible for most of the activity within such services [4].

Two main cohorts of children can be managed within pOPAT services; those with complex infections requiring prolonged courses of parenteral antimicrobials, often through a central line (tertiary pOPAT patients) and those with common infections requiring short courses of parenteral antimicrobials (ambulatory pOPAT patients). In general, ambulatory pOPAT patients tend to return to a hospital setting each day for review by the pOPAT team and administration of antimicrobials, whilst tertiary pOPAT patients are managed predominantly at home, either with nursing staff (community-based nurses or pOPAT nurses) or parents/carers administering their antimicrobials. Tertiary pOPAT patients should be discussed in a weekly multidisciplinary meeting/virtual ward round to discuss their progress and ongoing management plan. They should also have blood tests performed at least weekly; prolonged use of parenteral antimicrobials is associated with an increasing risk of adverse drug effects.

One of the key roles of an ambulatory OPAT service is to promote admission avoidance for children whose infections can be safely managed at home without admission to hospital. The development of consensus-based local, regional or national clinical pathways for common infections may facilitate this process.

The staffing and expertise required to deliver a pOPAT service depends on the number of cases being managed and their complexity, and the service structure in place. There is no clear consensus on staffing of pOPAT services, but as a minimum, the pOPAT team should include a medically qualified clinician (paediatrician with an interest in infection or paediatric infectious disease consultant), a medically qualified infection specialist (medical microbiologist or paediatric infectious disease consultant), a specialist nurse with expertise in parenteral drug administration and intravenous access device selection and placement, and a clinical antimicrobial pharmacist.

Although there is no paediatric data to support decision making about which service structure to adopt, quantitative preference analysis and economic modelling has been conducted based on a systematic review of adult OPAT data [5]. This supports a specialist OPAT nurse model, although parent administration should be considered for patients on prolonged courses of parenteral antimicrobials (> 7 days). Formal training in the safe administration of parenteral antimicrobials and assessment of competencies is required prior to discharge home. It is recommended that parent administration is only used if a child has secure intravenous access in situ (central line). The role of telemedicine in managing these patients should be considered [6].

Clear lines of communication for parents to contact the pOPAT team are essential for reducing parental anxiety. The creation of "trustful alliances", in which the parents are made aware of the continued input of the OPAT team in their child's management, can avoid parents feeling an overwhelming sense of responsibility when at home [7].

In addition, data on pOPAT patients should be recorded prospectively for monitoring purposes. A dataset that includes standardised outcome criteria should be used, to enable benchmarking between pOPAT services. Such an approach is likely to improve patient safety and facilitate service improvement.

The majority of the pOPAT literature describes tertiary pOPAT services. This is likely to reflect the fact that such services are often set up in children's hospitals, where specialists in paediatric infectious diseases, antimicrobial pharmacists and specialist nurses are available to support such services. On the other hand, staffing levels and expertise in secondary care hospitals managing general paediatric patients make the implementation of such services more challenging and there are currently no clear service models for delivering pOPAT in secondary care hospitals. However, our analysis of local data from the South of England suggests that the number of children potentially managed within ambulatory pOPAT services would far exceed those in tertiary pOPAT services, resulting in a significant impact on flow of patients through admission avoidance and bed days saved, as well as improved antimicrobial stewardship (presented at BSAC OPAT conference 2018 https://vimeo.com/311854525). Further research is urgently required to inform people setting up pOPAT services in secondary care hospitals.

Importance of Embedding Antimicrobial Stewardship Principles into pOPAT Services

There is an evolving evidence base negating the use of prolonged parenteral antimicrobial courses for specific

pathologies, assuming the child can tolerate/absorb oral antimicrobials and adherence to oral treatment regimens without regular oversight is not a concern (Table 2). Embedding AS principles within OPAT services has been shown to reduce the duration of IVABs though earlier cessation of Abs or switching from IV to oral Abs, compared to children being ambulated outside of pOPAT services [14•, 15]. This is especially relevant when children are being ambulated directly from the emergency department or paediatric assessment unit as part of an admission avoidance strategy [16]. Increasing evidence demonstrates that in the absence of oversight by a medically qualified infection specialist, children managed within pOPAT services also have higher rates of bug/drug mismatches, drug dosing errors and readmission rates and less rigorous laboratory monitoring of drug side-effects [17, 18].

For this reason, formal oversight of antimicrobial decisions by a medically qualified infection specialist and routine prospective data collection to facilitate benchmarking is essential to ensure that the principles of antimicrobial stewardship (AS) are adhered to [19, 20]. Staff working within pOPAT services should be up to date with the current evidence about duration of IVABs and optimal timing of IV to oral switch [21••]. OPAT clinicians should consider the use of highly bioavailable oral antimicrobials where possible. Failure to switch when effective oral alternatives are available not only increases IV antimicrobial exposure and results in higher healthcare costs but increases the risk of potential adverse events without therapeutic benefit, with 25% of OPAT complications deemed avoidable in one study due to a highly bioavailable oral alternative being available prior to discharge on OPAT [22].

Table 2 Evidence for management with oral antibiotics

Diagnosis	Evidence for treatment choices	References
Osteoarticular infections	•Increasing evidence that the majority of children should be managed with an early IV to PO switch •pOPAT is only indicated in the minority of children	[8–10]
Pyelonephritis	•No increase in duration of fever or increased renal scarring in children aged 1 to 36 months with their first case of acute pyelonephritis with no known uropathy and a normal renal ultrasound when managed with oral versus IVAbs	[11]
Complicated appendicitis	•No difference in readmission or post-operative complication rates between children with perforated appendicitis discharged home with IV or PO Abs	[12]
Pleural empyema	•Complications related to pneumonia or due to antibiotic therapy were comparable in children discharged home on IVAbs and those discharged on oral Abs.	[13]

However, where high-quality evidence supporting the optimal timing of switching from IV to oral Abs in children is lacking, comparing duration of Ab therapy between pOPAT centres for specific pathologies may provide useful information to guide clinical practice where formal clinical trials in children are either not feasible or unlikely to provide information for some time [23].

Patient Selection and Indications for pOPAT

In order to evaluate the appropriateness of a patient for management within a pOPAT service, clinical, social and caregiver criteria must be assessed [1••]. Although risk prediction models have been developed to calculate the risk of 30-day unplanned hospitalisation in patients receiving OPAT, no such models have been developed for pOPAT [24, 25]. Developing risk prediction models for children being considered for pOPAT should be a research priority.

There is a large body of evidence supporting the use of OPAT in children with a number of infective presentations including fever in the young infant, infective endocarditis, meningitis, lymphadenitis, pyomyositis, pneumonia, lymphadenitis, osteoarticular infections, bacteraemia, central line infections and brain abscesses [1••]. There has recent evidence further supporting the use of pOPAT in the management of children with cellulitis (admission avoidance) [26], pyelonephritis (admission avoidance) [27] and mastoiditis [28].

Febrile neutropenia: the management of children with febrile neutropenia within pOPAT services is challenging. A significant proportion of children with febrile neutropenia are unlikely to be suitable for pOPAT management, such as those with high-risk malignancies and those with evidence of sepsis at the time of presentation. For those in whom pOPAT is considered, high-intensity home nursing input is likely to be required and high readmission rates are likely (30% in one study) [29].

For cystic fibrosis (CF), although the origins of OPAT are based on the management of children with CF, a recent review of the paediatric CF literature confirms the absence of randomised controlled trials comparing inpatient versus OPAT management of this cohort of patients [30••]. Cohort studies have yielded conflicting results in terms of patient/parent satisfaction and clinical outcomes [31–33]. In the absence of a high-quality RCT, it is difficult to offer clear recommendations about the safety and effectiveness of pOPAT in children with CF. The authors suggest that the decision about whether to manage an individual patient with CF within a pOPAT service should be made by weighing up the likely benefits to the child/young person/family against the potential impact of pOPAT on their long-term respiratory function.

Drugs and Devices

Antimicrobial Selection

Due to its ease of administration, dosing convenience and excellent side-effect profile, ceftriaxone is by far the most commonly used antimicrobial for pOPAT. However, debate continues as to whether the convenience of ceftriaxone can be justified against its risk of driving antimicrobial resistance.

Although 24 h continuous infusions using elastomeric devices have been successfully used in children to administer antibiotics (presented at BSAC OPAT conference 2018 https://vimeo.com/311870318), there is a paucity of data confirming the stability of antibiotics in such devices [34•]. This is being addressed through the BSAC drug stability workstream, with data recently published on flucloxacillin and meropenem [35•, 36]. Concerns have been raised about the use of 24-h infusions of ceftazidime in children with CF due to the production of the breakdown product pyridine. It has been suggested that using a twice daily regimen where ceftazidime is administered immediately after reconstitution over 11.5 h whilst avoiding temperatures over 22 °C reduced the production of pyridine significantly [37].

Vascular Access

PICC lines complications in pOPAT patients are far less common than previously reported [38, 39]. Recent studies have described an 8–15% complication rate for PICC lines used for the administration of IVAbs to pOPAT patients; infections are only responsible for less than 25% of these adverse events [2, 40, 41].

More data are required about the rate of adverse events associated with midlines before they can be routinely recommended for use within pOPAT services. A complication rate of 43% has been described in one small study [42].

Adverse Drug Reactions (ADRs)

Significant ADRs requiring readmission are infrequent in pOPAT. Readmissions due to drug side effects only occurred in 0–2.3% of patients described in two recent pOPAT cohorts [2, 42]. However, a retrospective case series of children managed between 2008 and 2015 describes a 13.5% readmission rate due to antimicrobial side-effects [41]. Oxacillin was associated with significantly higher rates of adverse drug events (hepatic transaminitis, fever and rash) compared to ceftriaxone. High rates of adverse drug events have also been described with piperacillin/tazobactam (fever, transaminitis, neutropenia, rising inflammatory markers), with 26% of children readmitted due to drug side effects in that cohort. Adverse events due to piperacillin/tazobactam occurred after a minimum of 14 days of treatment in 93% of cases [43].

Patient Satisfaction

pOPAT is associated with high levels of parent/patient satisfaction and high quality of life scores compared to children managed as inpatients [44]. However, parents occasionally express concern about taking a febrile child home and looking after a child with an in-dwelling catheter in situ [45]. In our experience, parents benefit from being given clear information about the symptoms/signs suggesting clinical deterioration requiring them to seek urgent medical attention, information about the likely duration of antibiotics and likely duration of symptoms. In addition, trusting relationships should be forged between the pOPAT team and family, to avoid them feeling an overwhelming sense of responsibility when their child is managed at home [7]. Parent/patient satisfaction surveys should regularly be undertaken.

Economic Benefits of pOPAT

The ever-increasing financial pressures on healthcare services have driven the current focus on moving care out of hospital settings where possible. pOPAT clearly has the potential to significantly reduce in-patient bed days, which in turn improves flow of patients through hospitals. In addition, optimising management of patients in terms of shortening duration of IVAb courses, avoiding inappropriate central line insertion, avoiding inappropriate ambulation of patients and improved monitoring for adverse events allows care to be delivered more cost-effectively. Although no formal health economic evaluation of pOPAT services has been conducted, calculations based on inpatient bed days saved suggest significant cost savings [26, 27]. A systematic review of pOPAT services suggested that pOPAT management was 30–75% less expensive per episode than hospital-based treatment [30].

Conclusions

pOPAT services are safe, cost-effective and associated with high levels of parent/patient satisfaction. However, they need to ensure that antimicrobial stewardship principles are adhered to, in order to avoid unnecessary prolongation of parenteral antimicrobial therapy. Further research is required to develop risk prediction models for children being considered for pOPAT. Further data about the use of elastomeric devices in children and the acceptability of parental administration of IVAbs are also required.

Compliance with Ethical Standards

Conflict of Interest Sanjay Patel and Helen Green declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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