Delivering Outpatient Parenteral Antimicrobial Therapy (OPAT) in a Changing National Health Service (NHS): Benefits, Risks, Challenges, and Future Prospects

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) by Publication

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Division of Clinical Medicine
School of Medicine and Population Health

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''There is nothing like staying at home for real comfort.''

Jane Austen

*''The happiest moments of my life have a been the few which I have passed at home in the bosom of my family***.''**

Thomas Jefferson

"Seek home for rest, for home is best."

Thomas Tusser

"The NHS is broken but not beaten."

Wes Streeting

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Reverence to Almighty God for His grace and sustenance.

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I am also grateful to my co-authors for their collaboration and the opportunity to work together to advance knowledge in the field of OPAT. I would especially like to thank Professor Evangelos Kritsotakis of the School of Health and Related Research, Sheffield, and the Laboratory of Biostatistics at the University of Crete in Greece, for his significant contributions as well as for the statistical advice and support he provided in most of the published works.

Finally, and most importantly, I want to thank my loving wife, Foluke, and our three children, Ayomide, Ikeoluwa, and Inioluwa, for their support and understanding while I wrote this thesis, often being away from home and busy in the evenings.

Abstract

This thesis presents a comprehensive investigation into the practice of administering intravenous antimicrobials outside inpatient settings—known as Outpatient Parenteral Antimicrobial Therapy (OPAT)—within the UK National Health Service (NHS) context. Drawing on ten published studies employing diverse methodologies, in which I served as the lead author and primary contributor, this body of work critically examines OPAT's benefits, risks, challenges, and innovations, with the overarching aim of providing evidence-based approaches for optimising service delivery.

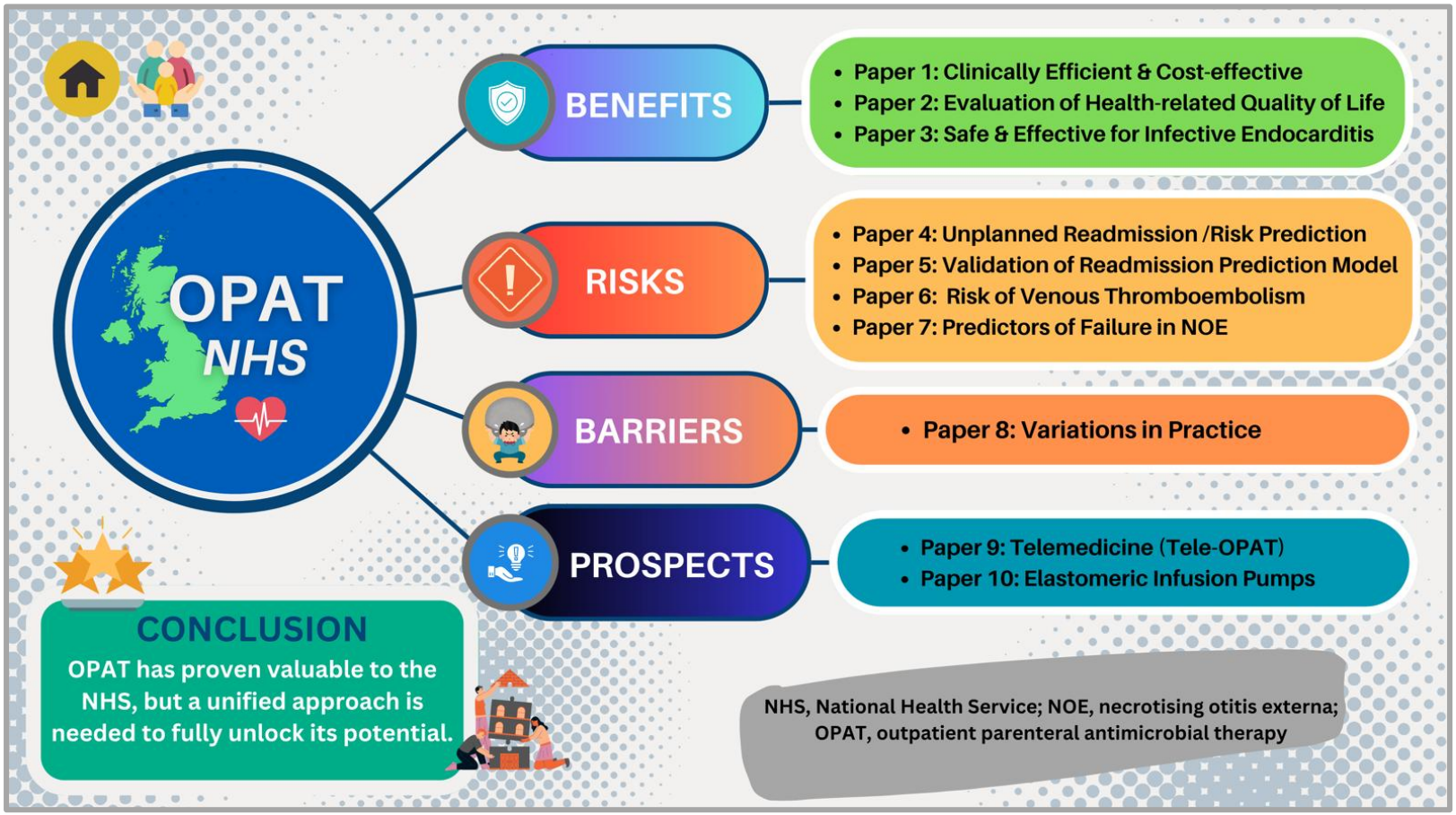
The studies explore multiple facets of OPAT practice. A retrospective evaluation of a decade of service delivery in Sheffield demonstrated its clinical efficacy, cost-effectiveness, and patient acceptability. A cost-consequence analysis indicated that OPAT incurred approximately 39% of national average cost for equivalent inpatient care. Additional studies assessed health-related quality-of-life among OPAT recipients in Derby and identified predictors of outcomes in complex infections, such as infective endocarditis and necrotising otitis externa. Two studies reported the development and validation of a risk prediction model for unplanned hospitalisation, offering a pragmatic tool for improving patient selection.

Safety-related concerns were further addressed through a systematic review and meta-analysis on venous thromboembolism, which revealed low rates of non-catheter-related (0.2%) and catheter-related (1.1%) thrombosis in the OPAT setting, thereby informing future thromboprophylaxis recommendations. A national cross-sectional survey identified significant variation in OPAT practices and service provision, highlighting systemic challenges and opportunities for standardisation. Finally, two recent studies examined innovative approaches—telemedicine-supported OPAT and elastomeric infusion devices—demonstrating their potential to enhance accessibility and efficiency, particularly in underserved populations.

Collectively, the studies provide robust evidence that OPAT is a safe, clinically effective, and cost-efficient use of NHS resources. However, its full potential remains constrained by inconsistent implementation and geographical variation. Realising OPAT’s full benefits will require a coordinated national approach encompassing innovative delivery methods, a standardised funding framework, and comprehensive commissioning policies.

Graphical Abstract

Figure 1. Graphical Abstract



A synthesis of ten key studies evaluating the role of OPAT within the NHS highlights its clear benefits—including clinical effectiveness, cost savings, and improvements in quality of life—while also acknowledging associated risks such as treatment failure, hospital readmissions, and venous thromboembolism. The thesis identifies key barriers, notably the variation in practice and service provision, and explores promising prospects such as telemedicine and elastomeric infusion pumps. The conclusion underscores that while OPAT offers substantial value, a more unified and standardised national approach is required to optimise its impact across the healthcare system.

Abbreviations

AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AUC	Area under the curve
BDS	Bed-days saved
BJI	Bone and joint infection
BSAC	British Society for Antimicrobial Chemotherapy
CDI	*Clostridioides difficile* infection
cIVI	Continuous intravenous infusion
CN	Community nursing
COpAT	Complex outpatient antimicrobial therapy
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
EI	Endovascular infection
EQ-5D-3L	European quality of life 5-Dimension 3-Level version
GPRs	Good practice recommendations
HaH	Hospital-at-Home
HCAIs	Healthcare associated infections
HITH	Hospital-in-the-home
HIV	Human immunodeficiency virus
HIVAT	Home intravenous antibiotic therapy
HRQoL	Health-related quality of life
IC	Infusion centre
ICBs	Integrated care boards
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
IE	Infective endocarditis
IV	Intravenous
IVOST	Intravenous to oral switch therapy
LAPAs	Long-acting parenteral antimicrobials
LP	Linear predictor

LRTI	Lower respiratory tract infection
MDR	Multidrug-resistant
MDR-TB	Multidrug-resistant tuberculosis
MDT	Multidisciplinary team
MDT	Mixed methods appraisal tool
NHS	National Health Service
NIPIV	Non-inpatient intravenous antibiotic therapy
NOE	Necrotising otitis externa
NORS	National outcomes registry system
OHPAT	Outpatient and home parenteral antibiotic therapy
OPAT	Outpatient parenteral antimicrobial therapy
OPIVAT	Outpatient intravenous antibiotic therapy
OSCAT	Outpatient subcutaneous antimicrobial therapy
OT	Other indications
OVIVA	Oral versus intravenous antibiotics for bone and joint infection
PICC	Peripherally inserted central catheter
PJI	Prosthetic joint infection
PK/PD	Pharmacokinetic/pharmacodynamic
POET	Partial oral treatment of endocarditis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PWID	People who inject drugs
QALY	Quality-adjusted life-years
QoL	Quality of life
RCT	Randomised control trial
RD	Respiratory disease
REC	Research Ethics Committee
SAB	*Staphylococcus aureus* bacteraemia
SC	Self/carer administration
SSTI	Skin and soft tissue infection
STH	Sheffield Teaching Hospitals NHS Foundation Trust
TB	Tuberculosis
Tele-OPAT	Telemedicine in outpatient parenteral antimicrobial therapy
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

UGI	Urogenital infection
UHDB	University Hospitals of Derby and Burton
UK	United Kingdom
US	United States
UTI	Urinary tract infection
VTE	Venous thromboembolism

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List of Published Works (including Contributions) Incorporated within the Thesis

The articles presented in this thesis were produced during my role as an Infectious Diseases (ID) physician with a special interest in OPAT at Sheffield Teaching Hospitals NHS Foundation Trust (STH) and the University Hospitals of Derby and Burton (UHDB) NHS Foundation Trust. The thesis includes ten (10) peer-reviewed published papers, listed below, for which I am the first author and primary contributor. These publications are the result of collaborative efforts involving multiple co-authors. The findings from these papers will be synthesised and linked to the central themes of the thesis in the subsequent chapters.

Paper 1: Durojaiye OC, Bell H, Andrews D, Ntziora F, Cartwright K. Clinical efficacy, cost analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service. *International Journal of Antimicrobial Agents* 2018; 51(1): 26-32 [1].

I conceived and designed the study, collected and analysed the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-author HB conducted the economic evaluation. All co-authors reviewed the final manuscript and provided feedback.

Paper 2: Durojaiye OC, Kritsotakis EI. Evaluation of health-related quality of life in patients receiving outpatient parenteral antimicrobial therapy (OPAT) in a UK setting. *Expert Review of Anti-infective Therapy* 2024; 22(11): 987-95 [2].

I was the Chief Investigator for the study. I conceived and designed the study, obtained approval from the Health Research Authority (IRAS Project ID: 316619; REC reference: 22/NW/0299), provided direct clinical care to the patients, collected and analysed the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-author EIK contributed to the study by curating and analysing the data, as well as revising the final manuscript.

Paper 3: Durojaiye OC, Morgan R, Chelaghma N, Kritsotakis EI. Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antibiotic therapy (OPAT). *Journal of Infection* 2021; 83(6): 644-9 [3].

I conceived and designed the study, collected some of the data, analysed the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-authors RM and NC also collected some data, while co-author EIK analysed the data. All co-authors reviewed the manuscript and provided feedback.

Paper 4: Durojaiye OC, Slucka A, Kritsotakis EI. Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa. *European Journal of Clinical Microbiology & Infectious Diseases* 2022; 41(6): 941-9 [4].

I conceived and designed the study, collected the majority of the data, provided direct clinical care to the patients, analysed the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-authors AS and EIK contributed to the study by collecting and analysing the data, respectively, and both revised the final manuscript.

Paper 5: Durojaiye OC, Kritsotakis EI, Johnston P, Kenny T, Ntziora F, Cartwright K. Developing a risk prediction model for 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy. *Clinical Microbiology and Infection* 2019; 25(7): 905.e1-905.e7 [5].

I conceived and designed the study, collected some of the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-author EIK analysed the data, while co-authors PJ, TK, and FN also contributed to data collection. All co-authors reviewed the manuscript and provided feedback.

Paper 6: Durojaiye OC, Morgan R, Chelaghma N, Palit J, Keil C, Omer R, Cartwright K, Kritsotakis EI. External validity and clinical usefulness of a risk prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy. *Journal of Antimicrobial Chemotherapy* 2021; 76(8): 2204-12 [6].

Co-author EIK and I conceived and designed the study. Additionally, I collected some of the data and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-authors RM, NC, JP, CK, and RO also contributed to data collection, while co-author EIK analysed the data. All co-authors reviewed the manuscript and provided feedback.

Paper 7: Durojaiye OC, Cole J, Kritsotakis EI. Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): a systematic review and meta-analysis. *International Journal of Antimicrobial Agents* 2023; 62(3): 106911 [7].

I conceptualised and designed the study. Additionally, I screened the reviewed articles, extracted and analysed the data, and wrote the paper. As the corresponding author, I managed the submission and revision process. Co-author JC also screened the reviewed articles and extracted the data, while co-author EIK extracted and analysed the data. All co-authors reviewed the manuscript and provided feedback.

Paper 8: Durojaiye OC, Cartwright K, Ntziora F. Outpatient parenteral antimicrobial therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards. *Diagnostic Microbiology & Infectious Disease* 2019; 93(1): 58-62 [8].

I conceived and designed the study. In addition, I administered the survey questionnaires, collected and analysed the data, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-authors KC and FN reviewed the manuscript and provided feedback.

Paper 9: Durojaiye OC, Jibril I, Kritsotakis EI. Effectiveness of telemedicine in outpatient parenteral antimicrobial therapy (Tele-OPAT): A systematic review. *Journal of Telemedicine & Telecare* 2024;30(8): 1230-1237 [9].

I conceptualised and designed the study. Additionally, I screened the reviewed articles, extracted the data, and wrote the paper. As the corresponding author, I managed the submission and revision process. Co-author JI also screened the reviewed articles and extracted the data. Co-author EIK extracted and analysed the data. All co-authors reviewed the manuscript and provided feedback.

Paper 10: Durojaiye OC, Cole J, Kritsotakis EI. Effectiveness and safety of a disposable elastomeric continuous infusion pump for outpatient parenteral antimicrobial therapy (OPAT) in a UK setting. *Journal of Chemotherapy* 2024; 36(2): 119-126 [10].

I conceived and designed the study, collected and analysed the data, provided direct clinical care to the patients, and wrote the paper. As the corresponding author, I oversaw the submission and revision process. Co-author EIK also analysed the data. All co-authors reviewed and provided comments on the manuscript.

Declaration

I, *Oyewole Christopher Durojaiye*, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of unfair means (www.sheffield.ac.uk/ssid/unfair-means). This work has not previously been presented for an award at this, or any other, university.

Structure of the Thesis Report

This thesis will be organised into several key chapters, each featuring a collection of closely related peer-reviewed publications that I designed, led, and co-authored as the primary contributor. These publications explore various aspects of the history, advantages, risks, barriers, and opportunities associated with OPAT in the United Kingdom (UK). A review and synthesis of the key findings from the publications outlined in the previous section (page 13) will be presented within the relevant chapters.

Chapter 1 will provide an overview of OPAT, including its definition, historical development, delivery methods, and clinical indications. It will also examine the provision of OPAT in the UK, highlighting its growth, key drivers, and comparisons with international practices.

Chapter 2 will outline the benefits of OPAT, with a focus on its efficacy, safety, and cost-effectiveness. It will also examine the advantages of OPAT for both patients and healthcare systems.

Chapter 3 will review the risks associated with OPAT and outline the key predictors of treatment failure and unplanned hospitalisations among patients receiving OPAT.

Chapter 4 will examine the persistent barriers and challenges that hinder the equitable and effective delivery of OPAT services across the UK.

Chapter 5 will explore promising developments, highlighting innovations and potential opportunities within OPAT to enhance accessibility and optimise the utilisation of NHS resources.

Finally, *Chapter 6* will summarise the key findings of the thesis, discuss their implications for OPAT practice in the UK, and outline potential areas for future research, including my planned research directions in the field of OPAT.

CHAPTER 1

Introduction

1.1 Chapter Overview

This first chapter will provide a comprehensive introduction to the topic of OPAT from both research and clinical perspectives, drawing on national UK perspectives as well as broader international literature and practices. The chapter will begin by defining OPAT and outlining its historical development, followed by a summary of its clinical indications and key areas of application. This overview will highlight the widespread and successful implementation of OPAT across various healthcare settings. The discussion will then shift to the UK context, exploring key trends and, importantly, the policies and guidelines that have shaped OPAT practice at the national level. This will be complemented by a synthesis of key evidence related to UK OPAT practice and a comparison with international approaches. The chapter will conclude with a clear articulation of the overall thesis aims and objectives.

1.2 What is Outpatient Parenteral Antimicrobial Therapy?

The administration of parenteral antimicrobials outside of inpatient settings has been described using various terms, including outpatient and home parenteral antibiotic therapy (OHPAT) [11], home intravenous (IV) antibiotic therapy (HIVAT) [12], community-based parenteral anti-infective therapy [13], hospital-in-the-home (HITH) therapy [14], non-inpatient IV (NIPIV) antibiotic therapy [15], and outpatient IV antibiotic therapy (OPIVAT) [16]. However, *outpatient parenteral antimicrobial therapy* (OPAT) is the most widely used and accepted term.

OPAT involves providing parenteral (usually IV) antimicrobials in outpatient or community settings as an alternative to inpatient care. The Infectious Diseases Society of America (IDSA) defines OPAT as ‘‘the administration of parenteral antimicrobial therapy in at least two doses on different days without intervening hospitalisation’’ [17].

OPAT is intended for patients who require parenteral antimicrobial therapy when no suitable and effective oral agents are available but are well enough not to need hospitalisation. It aims to facilitate

early hospital discharge (i.e., reduce the duration of hospital stay) or avoid hospitalisation for selected patients with infections. OPAT has proven to be cost-effective and provides significant benefits to both local healthcare services and patients [17,18] (see Chapter 2). While increasingly used for a range of infections, OPAT should complement other interventions (e.g., surgical or radiological) and be guided by clear treatment goals, including suppression or palliation in chronic infections [18].

1.3 The History of OPAT

Outpatient administration of IV antimicrobials was first described in 1974 by Rucker *et al*. [19], who treated infectious exacerbations of cystic fibrosis in 62 children and young adults in the United States (US). Several other North American studies in the 1970s also reported use of OPAT in small patient cohorts [20-22]. The development of OPAT in the US was partly driven by gaps in medical insurance coverage, which resulted in excessively high costs for inpatient IV antimicrobial therapy [23].

The 1980s and 1990s witnessed significant growth in OPAT, as reflected by the increasing number of published articles describing its use and documenting its practicality, safety, cost-effectiveness, and clinical efficacy in Australia, Canada, the US, the UK, and other European countries [12,15,16,23,24]. Rising healthcare costs prompted hospitals to explore more cost-effective alternatives to inpatient care [12,23,24]. Early OPAT programmes primarily aimed to facilitate the early discharge of clinically stable patients who still required prolonged parenteral antibiotic therapy [24]. Initially focused on treating cellulitis and osteomyelitis, the scope of OPAT later expanded to include more severe and complex infections, such as infective endocarditis (IE) and bacteraemia, in both adult and children [12,16,23].

Historically, prolonged courses of IV antimicrobials—often extending for six weeks or longer—were routinely prescribed for many serious infections, including bone and joint infections (BJIs), even in the absence of high-quality evidence. This approach reflected both clinical caution and the prevailing conservative treatment culture prevalent in many countries at the time. As clinical practice evolved, some centres pragmatically shortened IV durations, although considerable variation persisted. Within this context, the development of OPAT was driven not only by pressures on healthcare resources and hospital capacity but also by the established norm of extended IV therapy [24]. Introducing OPAT *de novo* today might face greater challenges, given the growing evidence supporting early oral switch strategies and the shift toward less conservative antimicrobial approaches.

By the late 1990s, practice guidelines had been developed to support OPAT implementation across various outpatient settings [13]. While economic factors and the need for cost containment initially drove the development of OPAT programmes, their expansion over the past two decades has been accelerated by recognised benefits to both patients and local healthcare systems. OPAT is now widely implemented across multiple countries and clinical settings and has become the standard of care for selected patients with infections in nations such as Australia [25] and the US [26]. OPAT is also incorporated into management guidelines for many infection syndromes, including IE [27-29], bacterial meningitis [30], prosthetic joint infections (PJIs) [31], and skin and soft tissue infections (SSTIs) [32]. The continued growth of OPAT programmes has been further supported by advances in clinical, technological, and pharmaceutical research, including the development of antimicrobials with convenient dosing schedules (e.g., daily, weekly, or continuous infusions) and improvements in infusion and IV access devices [18,26].

The practice of OPAT has evolved significantly over time. Initially introduced to facilitate early hospital discharge ('step-down'), it is now also used to prevent hospitalisation entirely ('step-up') [24]. OPAT has been successfully provided to a diverse group of patients, including the otherwise healthy and terminally ill [33], those with simple and complex infections [34], the very young [35] and the very old [36,37], the homeless [38], marginalised [39], and hard-to-reach populations [40]. The range of antimicrobials available for OPAT has also expanded, aligning with hospital formularies [26]. However, the choice of agent varies across countries due to differences in licensing regulations and healthcare models. The selection of appropriate antimicrobials for specific infections is typically guided by local guidelines, clinical requirements, or availability [41]. In the UK, for example, ceftriaxone (a cephalosporin), teicoplanin (a glycopeptide), and ertapenem (a carbapenem) are preferred due to their once-daily dosing schedules [42]. In contrast, teicoplanin is not currently licensed for use in the US by the Food and Drug Administration and, therefore, is not available, likely due to a lack of clear benefits over vancomycin (another glycopeptide) [43].

Overall, the history of OPAT reflects continuous evolution and growth, driven by the demand for more efficient and cost-effective infection management strategies, alongside ongoing medical advancements. From its early days as an experimental treatment approach to its current established role, I would argue that the *practice of administering parenteral antimicrobials outside of inpatient settings* has significantly transformed the way infections are managed.

1.4 OPAT Delivery and Indications

1.4.1 Model of Delivery

Intravenous antimicrobial treatment, once a barrier to hospital discharge, can now be initiated or completed through OPAT. The literature describes various methods of delivering OPAT [44,45], highlighting differences in settings and the personnel responsible for administering antimicrobial therapy. OPAT can be provided in diverse settings, including hospital outpatient clinics, ambulatory care units, skilled nursing facilities, primary care centres, community clinics, and even patients' homes. Additionally, administration can be performed by a range of individuals, including healthcare professionals in clinics, specialist OPAT nurses at home, private healthcare providers, district or community nurses, or patients and their carers through self-administration [26,46,47]. The choice of OPAT care model depends on several factors, including local healthcare resources and expertise, patient-specific considerations (e.g., mobility or dexterity for self-administration), personal preferences, access to local resources (e.g., transportation) and insurance coverage [17,26].

In general, OPAT can be delivered through three basic models: infusion centres, visiting healthcare professionals (primarily nurses), and self-administration. Each model has distinct benefits and drawbacks (Table 1). In practice, most OPAT services combine features of each of these models based on local resources and logistical considerations. For instance, the Sheffield (UK) OPAT service offers all three models, whereas the Derby (UK) service initially focused on home administration by visiting nurses [1,5].

In the 'infusion centre model,' patients receive therapy at healthcare facilities. These infusion centres may be specialist OPAT clinics, part of other hospital services (e.g., outpatient clinics, day-care units, or acute assessment units), or community treatment centres. Efficient for treating multiple patients simultaneously, this model is best suited for mobile patients requiring once-daily infusions who live near the facility [24,48].

The 'visiting nurse model' involves home administration by trained healthcare professionals. A UK study suggests that this model may be the most cost-effective for treatment courses of up to seven days and is highly preferred by patients [49]. Similarly, another UK study found that most patients favoured the visiting nurse model over other approaches [50]. However, it may not suit those requiring frequent dosing or those living in remote areas, as it relies on regular travel by healthcare professionals.

Table 1. Pros and Cons of Various Models of Outpatient Parenteral Antimicrobial Therapy (OPAT) Delivery [24,48].

Model	Pros	Cons
Infusion Centre	• Relatively efficient in terms of staff time • Reduced nursing travel costs • Supervised administration • Allows regular in-person monitoring • Readily available healthcare staff	• Cost of clinic facility and staff • Travel requirement for patients • Least convenient for patients • Not ideal for multiple daily dosing • Highest carbon footprint
Visiting Nurse	• Provides medical supervision • Patient travel is minimised • Most suitable for patients with mobility limitations • Most preferred by patients	• Least efficient for staff time • Travel cost for staff • Not ideal for multiple daily dosing • Safety of staff may present a concern • Challenging where community nursing is not readily available
Self- or Carer-Administration	• Patient autonomy and convenience • Most cost-effective • Ideal for patients requiring prolonged or multiple treatment courses • Lowest carbon footprint	• Requires training and competence; infection control vigilance; ongoing monitoring • Patient must possess dexterity and training to perform necessary tasks • Potential clinical risks including non-compliance due to less supervision • Potential burden on carer • Convenience may be limited for multi-daily dosing

Patients and/or their caregivers can be trained to self-administer therapy at home, eliminating the need for nursing visits or hospital travel. The 'self- or carer-administration model' is particularly beneficial for patients requiring prolonged or repeated treatment but may be unsuitable for those who lack the necessary manual dexterity or require only a short treatment course (e.g., for SSTIs), as training can take several days. Moreover, convenience may be limited when multiple daily doses are required, as this can impose a substantial burden on patients and their caregivers in terms of time, technique, and adherence. Self- or carer-administration is increasingly incorporated into modern OPAT services

[24,25]. However, this model necessitates careful patient selection and ongoing support, including regular monitoring and review by the OPAT team to ensure safety and treatment efficacy. Evidence indicates that self-administration is the most cost-effective approach, especially for patients needing extended treatment, provided they receive appropriate training [49,51].

OPAT programmes typically involve designated clinical or nursing staff responsible for service delivery, defined patient selection criteria, and treatment monitoring protocols [17,18,45]. Patients may transition between care models depending on their condition—for example, moving from home nursing to clinic visits as mobility improves, or vice versa. The overarching goal of OPAT is to provide high-quality, patient-centred care that is safe, cost-effective, and easily accessible. There is no 'one-size-fits-all' approach; therefore, I would suggest that UK OPAT services offer a range of care models. This would maximise the benefits of each model, accommodate the diverse needs of eligible patients, and minimise variation in service delivery and inequity in access to OPAT care (see Chapter 4).

1.4.2 Route of OPAT Administration

Safe and reliable intravascular access is critical to the success of OPAT. In its early years, antimicrobials were primarily administered via peripheral venous catheters, such as butterfly needles and IV cannulas [19-22]. Today, a wider range of devices is employed, with the choice depending on various factors, including the practice setting, frequency and anticipated therapy duration, prescribed antimicrobial agent, patient-specific considerations (e.g., vascular status, comorbidities, and preferences), and the need for long-term vascular access beyond antimicrobial therapy [26,52]. The primary goal is to use the least invasive device that minimises complications and remains functional throughout treatment or requires minimal replacements [26]. In the UK, vascular access devices used for OPAT include peripheral venous catheters (typically for short treatment courses), midline catheters, and peripherally inserted central catheters (PICCs), which are preferred for vesicant antimicrobials and prolonged treatment. Tunnelled catheters (e.g., Hickman lines) and implanted ports are also utilised.

1.4.3 Indications for OPAT

A wide range of infections have been effectively managed via OPAT (Table 2), with SSTIs and BJIs being the most common indications [42,44]. However, not all infections are suitable for outpatient IV antibiotic therapy; for example, pneumonia is generally treated with oral agents in mild infections or with inpatient IV therapy in more severe cases [53]. OPAT eligibility should be based on thorough assessment and careful patient selection to optimise outcomes and minimise risk of treatment failure and complications. Over time, the spectrum of infections referred for OPAT has become increasingly

complex [18,42], with the decision to pursue outpatient treatment influenced by several factors, including local commissioning and funding, institutional protocols, resource availability, the patient's condition and preferences, as well as the prescribing clinician's judgement, experience, and approach to care [17,18,26].

Table 2. Types of Infections Successfully Treated with Outpatient Parenteral Antimicrobial Therapy (with Supporting Literature References)

BSAC NORS (2015–19) Ranking[a] [42]	Infection Category	References	Number (%) of Patient Episodes Treated at the Sheffield OPAT Service Over a Decade (2006–2016)[b] [1]	Number (%) of BDS at the Sheffield OPAT Service Over a Decade (2006–2016)[b] [1]
1	Skin and soft tissue infection (including cellulitis & wound infection)	[15,56,57]	2183 (57.3)	15973 (32.0)
2	Bone & joint infection[c]	[20,21,25,39,58]	351 (9.2)	13934 (27.9)
3	Respiratory infections (predominantly bronchiectasis)	[19,59]	151 (4.0)	2188 (4.4)
4	Complex urinary tract infection	[23,60]	295 (7.7)	3530 (7.1)
5	Diabetic foot infection[d]	[61]	-	-
6	Intra-abdominal infections	[62]	59 (1.5)	1411 (2.8)
7	Bacteraemia	[21,38,63]	94 (2.5)	1210 (2.4)
8	Endovascular infection (including endocarditis)	[22,34,37,64]	160 (4.2)	3759 (7.5)
9	Central nervous system infections	[35,65]	364 (9.5)	3233 (6.5)
10	Necrotising otitis externa	[66]	40 (1.0)	1646 (3.3)

[a] Top ten infection categories treated in adult OPAT services in the UK, ranked by number of patient episodes [42].
[b] Data extracted from Paper 1. The total number of patient episodes and bed-days saved were 3,812 and 49,854, respectively [1].
[c] Includes osteomyelitis, prosthetic joint infection, and discitis/vertebral osteomyelitis
[d] In Paper 1, diabetic foot infections were classified as either soft tissue infections or bone and joint infections, depending on the predominant site and severity of infection.
BDS, bed-days saved; BSAC, British Society for Antimicrobial Chemotherapy; OPAT, outpatient parenteral antimicrobial therapy

Over my decades of experience within the Sheffield and Derby OPAT services, I have observed a steady increase in the complexity of referred patients—a trend that has become particularly pronounced since the COVID-19 pandemic. Patients with significant comorbidities (e.g., immunosuppressive conditions), complex infections such as multidrug-resistant (MDR) tuberculosis, and those requiring prolonged treatment, including for palliative care, are being referred with increasing frequency. This trend can be attributed to a heightened focus on out-of-hospital care, the rising prevalence of MDR infections, and the growing number of patients with multimorbidity [18,42]. Consequently, OPAT care now demands greater clinical expertise, enhanced coordination among healthcare professionals, and individualised treatment plans [18].

A brief overview of three common OPAT indications in the UK is presented below. SSTIs and BJIs are the most frequent indications [8,42]. IE is also highlighted as an exemplar condition with strong clinical evidence supporting the safety and efficacy of outpatient management [27-29].

1.4.3.1 Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTIs), primarily cellulitis, account for 1-2% of hospitalisations in the UK [54]. Patients with moderately severe cellulitis (Eron Class II; see Supplementary Table 1) were previously admitted for IV antibiotics. However, with the advent of OPAT, such patients can now either be discharged early on IV antibiotics or avoid hospitalisation altogether, transitioning to oral agents as the infection resolves [32]. Although hospitalisation remains necessary for patients classified as Eron Class III and Class IV, they may transition to OPAT or oral therapy once systemic signs of infection subside and comorbidities are stabilised. Increasingly, nurse-led approaches are being adopted to manage cellulitis in non-inpatient settings [55].

A review of the UK national OPAT registry (2015–2019) (see Section 1.5.4) identified SSTIs as the most common adult indication for OPAT. Although their proportion remained stable over the four-year period, SSTIs accounted for 7,294 episodes, with an average treatment duration of 6.5 days and a success rate >90%, resulting in the saving of over 45,000 inpatient bed-days across participating sites [42]. A randomised controlled trial (RCT) comparing home-based IV therapy for cellulitis to inpatient care found no significant differences in treatment duration, patient outcomes, or adverse events; but reported higher patient satisfaction with home treatment [67]. OPAT for SSTIs is estimated to cost 23-51% of inpatient care, ranging from £566 (self-administration) to £1,266 (single-dose dalbavancin), compared with £2,476 for inpatient treatment [51]. Despite OPAT's benefits for cellulitis, factor such as female sex, diabetes, and teicoplanin therapy have been associated with treatment failure [56].

Consequently, it may be reasonable to suggest that careful patient selection and close monitoring of individuals deemed at high risk could improve outcomes and reduce the likelihood of OPAT failure.

1.4.3.2 Bone and Joint Infections

The management of BJIs often requires prolonged antibiotic treatment, making OPAT an attractive treatment approach. Several retrospective studies have demonstrated the clinical efficacy and safety of OPAT for BJIs [68,69]. However, the multicentre UK OVIVA (Oral Versus Intravenous Antibiotics for BJI) trial suggests that oral antibiotics may be an effective alternative during the initial six weeks of treatment [70]. Applying OVIVA criteria to an OPAT cohort, Marks *et al*. [71] found that 80% of patients could have been managed with oral agents, generating significant cost savings.

While further research is needed before oral therapy can be established as the standard treatment for BJIs (particularly spinal infections), OPAT offers a safe and effective alternative to inpatient care when oral therapy is unsuitable due to toxicity, poor oral absorption, nonadherence, intolerance, drug interactions, or antimicrobial resistance (AMR). Additionally, OPAT services often support the use of complex oral regimens (e.g., linezolid) by enabling close monitoring of adherence and toxicity [72].

1.4.3.3 Infective Endocarditis

Studies indicate that selected patients with IE, including those considered at high-risk of complications, can be safely managed with OPAT [73,74]. Following initial hospitalisation, OPAT is typically used to consolidate antimicrobial therapy and is now recommended in national guidelines [27-29]. However, factors, such as glycopeptide therapy and cardiac or renal failure have been associated with an increased risk of OPAT failure [75,76]. Therefore, careful patient selection and close monitoring are crucial for achieving optimal clinical outcomes. For uncomplicated IE, sequential oral therapy may be preferable to OPAT, as demonstrated in the POET (Partial Oral Treatment of Endocarditis) trial [77]. Nevertheless, OPAT remains appropriate for patients with IE complications (e.g., cardiac or embolic abscesses) requiring prolonged parenteral treatment or for those who cannot tolerate oral therapy (as discussed in the previous section).

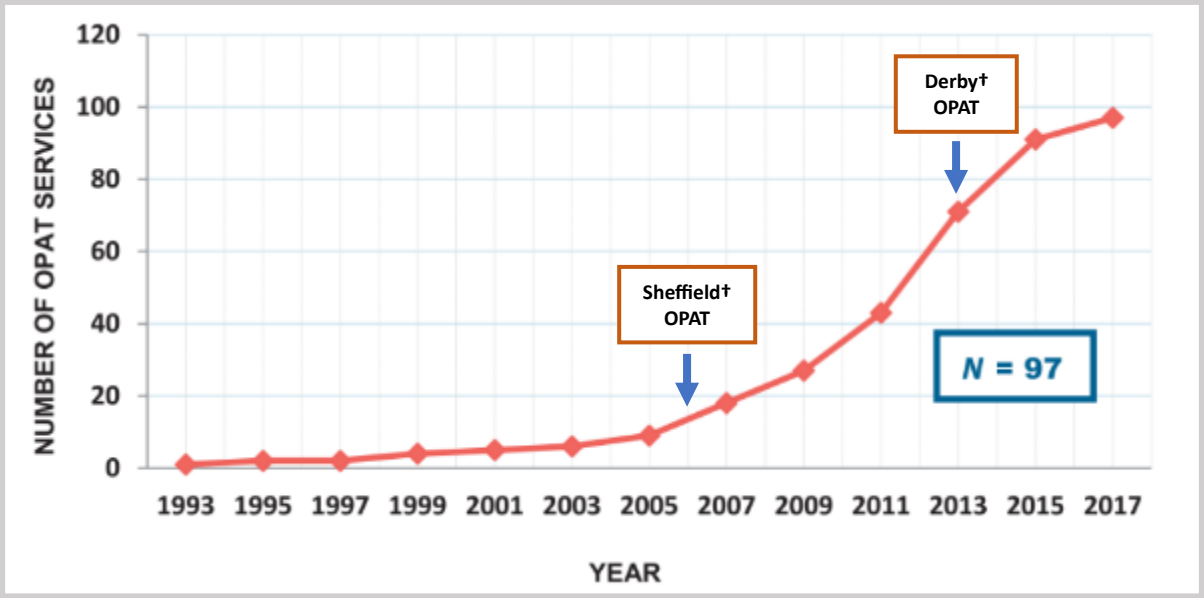
1.5 OPAT in the UK

1.5.1 Overview

The use of OPAT in the UK began in the early 1990s and was initially limited to a few specialist centres [8,18,78,79]. Despite its gradual and ad hoc expansion, OPAT is now implemented across both NHS and

private healthcare sectors. Figure 2 illustrates the cumulative number of OPAT services established in the UK between 1993 and 2017 (as reported in Paper 8 [8]). With further expansion of service—accelerated by pressures associated with the COVID-19 pandemic—it is reasonable to conservatively estimate that over 110 hospital-based OPAT services are currently operating across the country. This estimate is further supported by the presence of more than ten OPAT centres listed in the national OPAT directory [80] that were not captured in a national cross-sectional study I led and co-authored in 2017, which surveyed OPAT practice in UK acute hospital trusts (Paper 8 [8]).

Figure 2. Cumulative Number of OPAT Centres (N = 97) Established in the UK by Year, 1993–2017* (Extracted from Paper 8) [8]



*** The number of OPAT services currently operating in the UK is estimated to exceed 110**
† The Sheffield and Derby OPAT services were formally established in 2006 and 2013, respectively.

Figure 3 shows annual OPAT patient-episodes and treatment days recorded in the UK national OPAT Registry (2015–2019) [42] (see Section 1.5.4). The expansion of OPAT services in the UK can be attributed to several factors, including economic pressures and an increasing focus on delivering healthcare closer to home [18]. Key drivers are summarised in Figure 4. With the growth of OPAT in the UK, services are now delivered across diverse clinical and non-clinical settings. However, unlike in countries such as the US, OPAT in the UK is not provided within skilled nursing facilities, where nurses typically oversee infusion therapy alongside other care services, such as physical therapy or wound management for patients requiring additional support or lacking home infusion insurance coverage [17]. In the UK, antimicrobial therapy may be administered entirely in the community or initiated in hospital and completed through a community-based OPAT service [46].

Figure 3. Annual Number of OPAT Patient Episodes and Treatment Days in 57 UK Healthcare Organisations, 2015-2019 (Generated from Data Presented in [42])

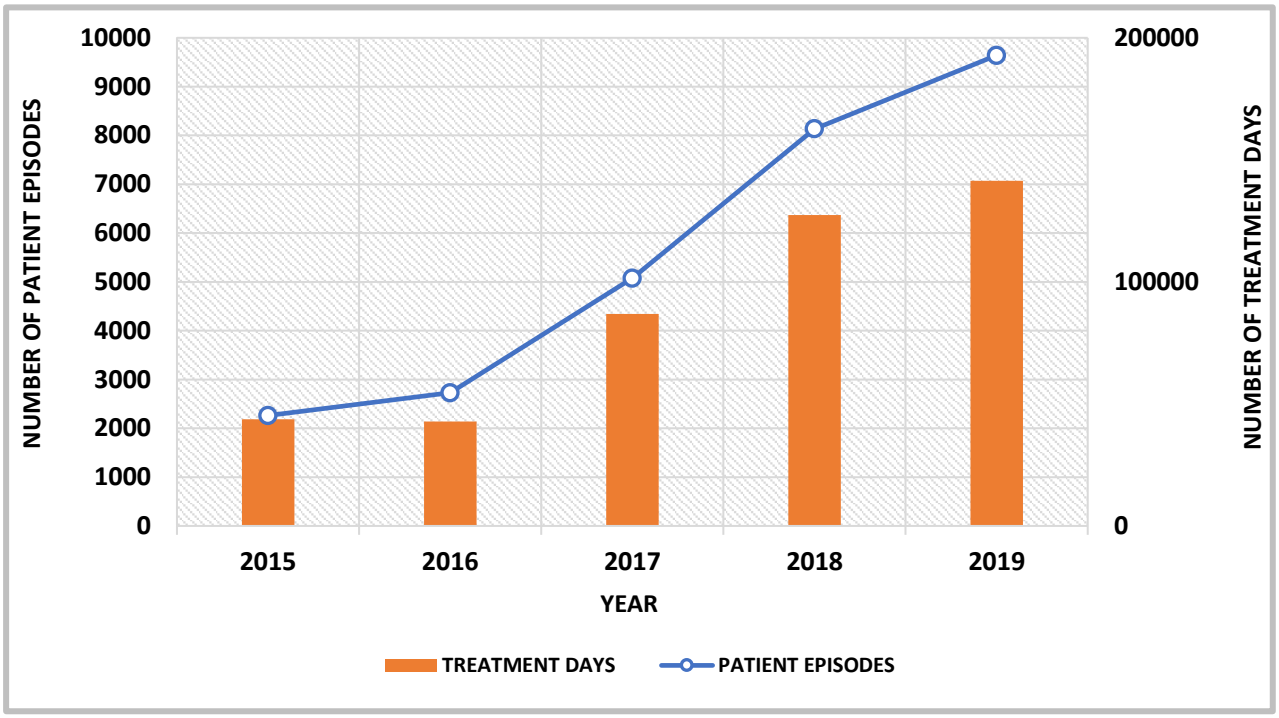
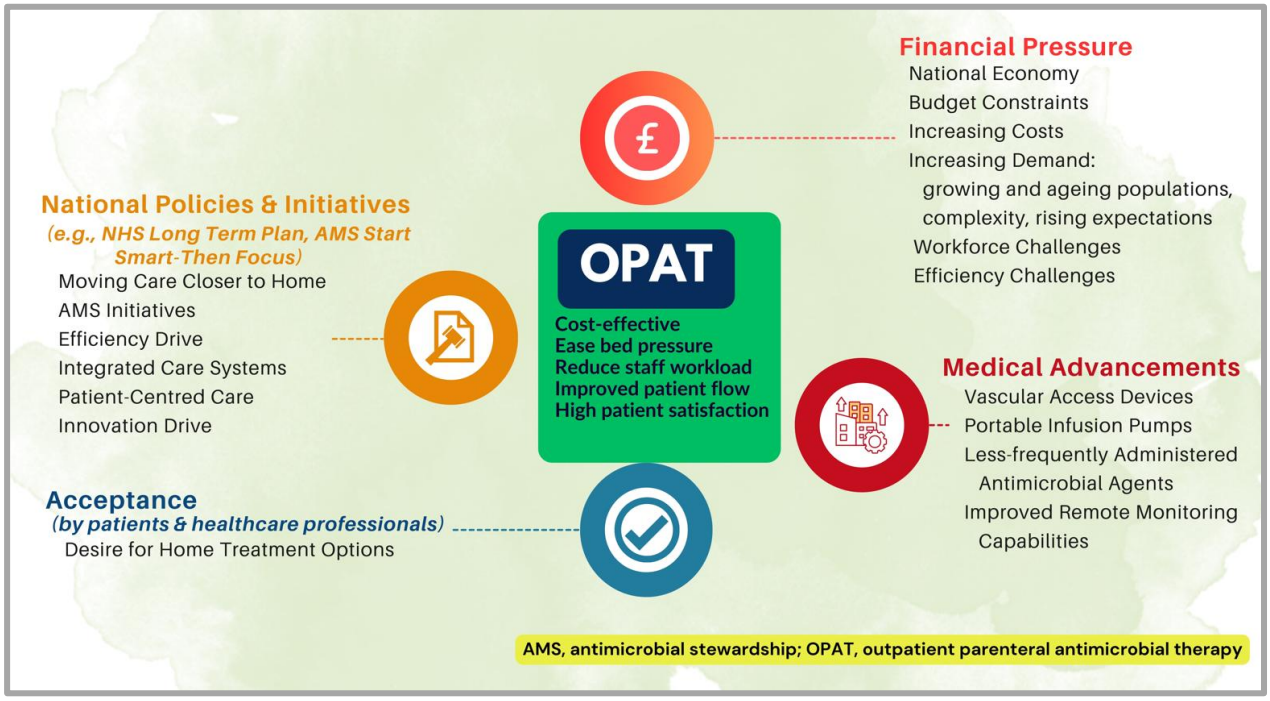


Figure 4. Key Drivers of OPAT in the UK



UK OPAT services reflect international trends and are managed by a diverse range of healthcare professionals—including acute and general physicians, advanced nurse practitioners, specialist nurses, and clinical pharmacists—rather than exclusively by infection specialists [8,18]. Currently, there is no defined national strategy for the provision or expansion of OPAT within the UK healthcare system [37]. In the absence of a centralised programme (as seen in some European countries; see Section 1.6), oversight and governance lie with individual hospitals and healthcare networks offering OPAT care. The diversification in service delivery, therefore, underscores the need for robust governance structures to optimise the quality of care.

1.5.2 The Changing NHS

The NHS is the world's largest publicly funded health system, providing free, comprehensive, and accessible healthcare to millions of UK residents. Since its inception in 1948, it has undergone numerous reforms to address the evolving needs of the UK population. However, it now faces unprecedented challenges, including chronic underfunding by successive governments, workforce shortages, and outdated infrastructure [81-83]. Furthermore, rising demand—driven by an ageing population, increasingly complex healthcare needs, and growing public expectations—has resulted in longer waiting times, while healthcare workers contend with burnout [81-83]. The COVID-19 pandemic has further exacerbated the strain on the NHS [82,84]. Consequently, there is a growing focus on improving efficiency and maximising the value of available resources through various measures, including out-of-hospital care (e.g., virtual wards), patient-centred care, and service innovation [81,84]. While the current UK government and some commentators have described the NHS as 'broken' and advocated for radical reforms [85,86], others contend that it is weakened but salvageable with adequate investment [87]. In response, the UK government has outlined a 10-Year Health Plan to reform the NHS in England. This plan focuses on three core 'shifts': transferring more care from hospitals to community settings, leveraging technology (e.g. telemedicine), and prioritising the prevention of illness [81,88]. Additionally, the government intends to dissolve NHS England—which currently oversees the health service in England—within two years, transferring its functions to the Department of Health and Social Care to streamline operations and reduce costs [89].

With advances in healthcare, rising AMR, and a growing population with increasingly complex needs, the burden of hospital-managed infections is expected to rise. Consequently, the continued development and evolution of OPAT within the NHS may be necessary to meet these challenges [18,90]. OPAT has potential to improve efficiency [90] and support key healthcare objectives, such as those outlined in *Start Smart-Then Focus* [91], and the new *10-Year Health Plan for England* [81]. By

expanding access to and the capabilities of OPAT, the NHS can foster safer, more sustainable, and patient-centred care pathways, ultimately bolstering the health system resilience [47,49]. However, there is currently no national commissioning strategy or policy framework for OPAT in the UK; instead, services are often established locally through agreements with integrated care boards (ICBs) [92].

I am convinced that the development of OPAT in the UK represents a notable success story for the NHS. As the healthcare system continues to evolve, OPAT is expected to play an increasingly significant role in service delivery. However, to maximise its benefits within the NHS and uphold the founding principles of universal and equitable care, a coordinated national approach is essential to ensure that OPAT services are accessible, effective, and sustainable. Such an approach should include the creation of supportive financial frameworks and nationwide service development [90,92].

1.5.3 Review of Existing Evidence on OPAT Delivery within the NHS

This section will provide a brief overview of the key areas of evidence and debate surrounding OPAT delivery in the UK, focusing on its benefits, risks, and opportunities.

1.5.3.1 Benefits

UK studies examining the benefits of OPAT are limited and predominantly consist of single-centre investigations [93,94]. Most in-depth analyses of OPAT's benefits—encompassing clinical efficacy, safety, cost-effectiveness, patient acceptability, and delivery models—have been conducted overseas [23,25,95-98], particularly in the US and Australia [93,98]. Given the substantial differences in healthcare system structure, funding, and delivery across countries [99,100], I would argue that UK-based studies are more relevant to the NHS context, as it better reflects its structure, policies, and patient population. While international evidence provides valuable insights, relying on UK-specific studies ensures that decisions regarding OPAT implementation within the NHS are grounded in data that more accurately reflect the local healthcare environment.

Only a few studies have evaluated the clinical efficacy and cost-effectiveness of OPAT within the NHS. An analysis of the UK national OPAT registry data (2015-2019) reported a positive infection outcome rate (cured or improved) of 92.4% and a positive OPAT outcome rate (success or partial success) of 90.7% across 27,841 treatment-episodes [42]. Most economic evaluations are based on inpatient bed-day cost savings [101,102]. For instance, Acuram *et al.* [102] estimated annual savings of £1–2 million by avoiding 9,516 inpatient bed-days for 391 patients over a two-year period (2022–2024) at King's College Hospital, London—based on inpatient costs of £300-600 per day.

Although OPAT is often presented as a cost-effective alternative to inpatient care, the interpretation of such metrics requires careful consideration. Reductions in inpatient bed-days are frequently used as a proxy for economic benefit but do not necessarily translate into financial savings within the NHS. Hospital expenditure is largely fixed—driven by staffing, infrastructure, and overheads—so shorter hospital stays rarely yield proportional cost reductions. The principal economic value of OPAT instead lies in opportunity cost and system efficiency: releasing capacity to treat acutely unwell patients, reduce elective cancellations, and alleviate bed pressures during periods of high demand. Accordingly, the economic impact of OPAT should be evaluated beyond simple cost-per-bed-day metrics. More refined approaches, such as marginal cost analysis, cost-utility evaluation, and system-level modelling, are required to capture its broader organisational and societal value, including indirect benefits, such as patient satisfaction, productivity gains, and improved access to hospital care.

Only two comprehensive economic evaluations have assessed OPAT's potential to generate cost savings for the NHS. One cost-minimisation analysis found that all OPAT delivery models were consistently less expensive than equivalent inpatient care across various infections. For example, OPAT treatment of diabetic foot infections was estimated at 24%–42% of the cost of inpatient equivalents [51]. Another study, using a decision-analytic model, assessed the cost-effectiveness of different OPAT delivery approaches and concluded that 'specialist nurse home visit' was the most cost-effective option for shorter treatments, while 'self-administration' was more cost-effective for long-term care [103]. Nevertheless, it is important to note that both studies were based on modelled assumptions rather than actual costs of establishing and operating OPAT services. Variations in staffing, infrastructure, patient case-mix, and local operational practices mean these projections may not be directly applicable to all NHS OPAT settings.

Published studies on the benefits of OPAT have primarily focused on cost savings and clinical outcomes, with limited attention to patient-centred factors such as overall quality of life (QoL). A more thorough understanding of OPAT's impact on health-related QoL (HRQoL) could inform patient selection and improve the overall patient experience within the NHS [18,104]. HRQoL data can also be used to calculate quality-adjusted life years (QALYs) in cost-effectiveness analyses of OPAT care, with one QALY equating to one year of life in perfect health [105].

1.5.3.2 Risks

The delivery of OPAT is inherently complex and involves certain risks due to the limited clinical supervision and monitoring compared to inpatient care. OPAT patients are at risk of adverse events,

which can result in treatment failure and unplanned hospitalisations [41]. Several UK studies have examined the risk of OPAT failure (i.e., the inability to complete a prescribed course of therapy), particularly in relation to specific infections [56,75,106]. For example, Seaton *et al*. [56] identified female sex, diabetes and teicoplanin use as risk factors for OPAT failure (defined as hospitalisation, adverse events, or infection progression requiring treatment modification) in 963 cases of SSTIs managed by the Glasgow (Scotland) OPAT Service over a seven-year period (2001-2008). Despite their findings, the overall failure rate was relatively low at 13%.

Overall, evidence from the literature suggests that OPAT does not pose a greater risk of treatment failure or complications compared to inpatient care [93,98]. While significant risk factors for unplanned hospitalisation during OPAT have been reported, these findings have primarily emerged from studies conducted outside the UK [107-114]. Identifying and mitigating these risks may improve outcomes, reduce readmissions, and facilitate more cost-effective, personalised care through appropriate patient selection

1.5.3.3 Opportunities

The growing focus on shifting care from hospitals to community settings, supported by a substantial body of evidence, is expected to drive the expansion of OPAT across the UK [18]. It could be argued that this growth will create opportunities for innovative delivery models and novel healthcare applications within NHS settings. Changing patient demographics, medical advancements, and new antimicrobial agents underscore the need for UK OPAT services to evolve beyond 'traditional' practices by integrating technologies, such as telemedicine [115] and elastomeric devices [116] for antibiotic administration. For instance, the use of telemedicine in healthcare delivery has increased sharply since the COVID-19 pandemic, offering benefits such as enhanced efficiency, and is now becoming integral to routine care [117]. There is also potential to extend OPAT beyond curable infections to long-term suppression or palliation (palliative OPAT) [33,118]. However, evidence supporting these expanded applications and delivery methods remains limited, underscoring the need for further research within NHS settings.

1.5.3.4 Conclusion on Existing Literature

In summary, current evidence on OPAT delivery within the NHS highlights a promising yet underexplored area of healthcare innovation. While international research offers valuable insights, UK-specific studies—particularly those examining real-world costs and patient-centred outcomes such as QoL—remain limited. Existing data suggest that OPAT can be both clinically effective and cost-saving

compared to inpatient care; however, these findings are weakened by methodological limitations and a reliance on modelling. Although OPAT appears to carry no greater risk than inpatient treatment, careful patient selection and ongoing monitoring are essential. Looking ahead, the NHS could benefit significantly from expanding OPAT, especially through technological integration and novel applications. However, this potential depends on robust UK-based research to address current evidence gaps and support safe, cost-effective implementation.

1.5.4 National OPAT Initiatives

As previously noted, the UK lacks a centralised OPAT programme. To support OPAT services across the UK, the British Society for Antimicrobial Chemotherapy (BSAC) established a national OPAT Initiative in 2009. This Initiative has achieved several notable accomplishments, including publication of good practice recommendations (GPRs) for adults and children [119]; an OPAT service directory [80]; development of national and international networks; delivery of national and regional educational meetings; antimicrobial stability testing; and establishment of a national outcomes registry system (NORS) to collect outcome data from UK OPAT services [42].

The UK NORS, established in 2015, was discontinued in 2020, primarily due to poor engagement from OPAT services. It has since been replaced by a national service directory, which aims to provide an overview of OPAT services and key personnel across the UK and Ireland [80]. Although participation in NORs was voluntary, the registry captured data from 57 OPAT centres, encompassing 27,841 patient-episodes and 442,280 treatment-days [42]. Such registries provide a comprehensive overview of national OPAT provision and serve as valuable tools for benchmarking, standardising, and quality improvement [42]. The discontinuation of the UK NORS has hindered national outcome assessments, and its reintroduction would be highly beneficial [120].

Figure 5 outlines the BSAC OPAT strategy for 2022 to 2025. The strategy focuses on providing high-quality care closer to home, based on peer-reviewed best practices, optimal use of antimicrobials and devices, and the measurement of specific patient outcomes [121].

Figure 5. OPAT Strategy 2022 – 2025 [121]

1. Establish a modern working definition of OPAT.
2. Secure the establishment and expansion of OPAT services wherever the clinical need exists.
3. Establish OPAT-accredit, a global accreditation scheme for OPAT services.
4. Promote and embed OPAT as a core component of antimicrobial stewardship through the provision of a continuous programme of education and training.
5. Secure a global consensus on drug stability testing, working with licencing and standard setting authorities to amend current standards as and where applicable, and secure an expansion in the number of agents tested.

I have contributed to several national OPAT Initiatives. I have presented at both regional and national OPAT meetings (see Appendix 3) and have co-authored a review of NORS [42]. I am also a member of an expert group currently reviewing the national OPAT GPRs.

1.5.5 National OPAT Guidelines

A UK consensus statement on OPAT delivery was first published in 1998 [122] and was later superseded by separate adult (2012) [123] and paediatric (2015) [124] guidelines. In 2019, the BSAC updated these guidelines, incorporating new evidence and expert consultation to produce combined GPRs for both adult and paediatric services [18]. These GPRs were designed to guide OPAT implementation and provide benchmarks for service evaluation and improvement. The updated recommendations address various aspects of OPAT care, including team and service structure, antimicrobial management, patient selection, outcome monitoring, and clinical governance. Despite the comprehensive review, several evidence gaps were identified, highlighting areas requiring further research [18]. **This thesis seeks to address several of these gaps, including investigations into OPAT outcome predictors, the role of telemedicine in OPAT care (tele-OPAT), the risk of venous thromboembolism (VTE) during OPAT, and the evaluation of QOL indices.**

1.6 OPAT in Other Countries

This section explores international OPAT practices through comparative analysis, highlighting structural differences, common challenges, and best practices that may inform the development of UK services.

OPAT has been widely adopted around the globe. It has been successfully implemented in North America (e.g., the US, Canada) [125,126], Europe [45], South America (e.g., Brazil, Mexico) [127,128], the Middle East (e.g., Saudi Arabia, Bahrain) [129,130], Asia (e.g., Singapore, Japan) [131,132], and Oceania (e.g., Australia, New Zealand) [96,133,134]. However, its use in Central America and Africa is infrequently reported in the literature [120,135,136].

Similar to the UK, many other countries have developed national OPAT registries [44,137,138] and guidelines [17,138-140]. Nonetheless, OPAT availability, organisation, delivery, and utilisation vary significantly within and across countries due to several factors, including healthcare infrastructure, delivery systems, regional policies, geography, and funding models [44,45,120]. For example, a 2004 comparison of OPAT services in the US, UK, and Italy found substantial disparities in infections treated, delivery models, treatment durations, vascular access devices, and administered antimicrobials Notably, self-administration was common in the US, whereas hospital-based models predominated in the UK and Italy, with Italy also favouring intramuscular delivery and longer courses [34]. Similarly, a more recent survey identified considerable heterogeneity in OPAT delivery across Europe, often due to weak organisational structures and the absence of formal guidelines. The study's authors called for European guidelines to enhance and standardise OPAT delivery across the region [45].

Unlike the UK, the Irish national OPAT programme is centralised [120]. A centralised OPAT programme enables streamlined coordination, standardised protocols, reduced variation in patient care, and more effective use of resources by consolidating expertise and monitoring within a cohesive system. Additionally, it allows for systematic evaluation of services and facilitates the implementation of audit and quality improvement systems [120]. In Australia and Spain, OPAT is embedded within broader 'Hospital-at-Home' (HaH) or 'HITH' models—which provide other complex medical therapies, including IV fluids, parenteral nutrition, chemotherapy, and palliative care [120,137,141,142]. This integration appears to support OPAT uptake [120].

As in the UK, the adoption of OPAT in countries such as Ireland, which have comparatively fewer hospital beds per capita, may be largely driven by the imperative to conserve bed days [120]. In contrast, countries like Germany, with relatively lower bed occupancy rates, may face less pressure to expand hospital capacity. Cost-saving is also a key driver for OPAT, particularly in publicly funded systems such as those in the UK and Australia, where financial and ethical incentives promote efficient resource utilisation [120]. Cost savings are likely to be more substantial in countries where inpatient care is relatively expensive, such as the US.

Drawing on these international perspectives, I argue that UK OPAT services could benefit from greater centralisation—potentially at regional levels—and improved integration with community-based services, such as drug addiction programmes and 'virtual wards' (HaH), to support wider adoption and address the barriers identified in Chapter 4.

1.7 Aims and Objectives

This chapter has provided a comprehensive overview of the *practice of administering parenteral antimicrobials outside inpatient settings,* including its history, clinical indications, growth, and implementation within the NHS, alongside international perspectives on OPAT. A review of the literature, however, reveals a notable paucity of evidence-based information to guide decision-making and policy development regarding OPAT within the NHS. Accordingly, the purpose of this thesis is to address some of these gaps.

1.7.1 Research Questions

To guide healthcare providers and commissioners in the UK in designing, delivering, and commissioning OPAT services, as well as to support national guideline developers in formulating best practice recommendations, this thesis seeks to address the following research questions:

- Is OPAT clinically effective, cost-effective, and safe within the NHS?
- What risks are associated with outpatient IV antimicrobial therapy?
- What factors predict these risks?
- What barriers hinder OPAT implementation in the NHS?
- What evidence supports innovative approaches to OPAT delivery?

1.7.2 Research Aims and Objectives

This thesis aims to make original contributions to the understanding of OPAT delivery within the NHS. It seeks to address key knowledge gaps concerning OPAT's benefits for NHS hospitals and patients, factors associated with an increased risk of treatment failure, and potential innovations in OPAT delivery.

The specific objectives are to:

1. Assess the clinical efficacy, cost-effectiveness, and patient benefits of OPAT in a UK hospital (Papers 1 & 2) [1,2].

2. Examine the safety and feasibility of OPAT for various infection syndromes (Papers 3 & 4) [3,4].

3. Develop and validate a predictive risk model for unplanned hospital readmission to support patient selection for OPAT (Papers 5 & 6) [5,6].

4. Conduct a systematic literature review to evaluate the risk of VTE in OPAT (Paper 7) [7].

5. Evaluate OPAT practices across UK healthcare provider organisations (Paper 8) [8].

6. Review the literature to inform integration of telemedicine into UK OPAT practices (Paper 9) [9].

7. Evaluate the safety and effectiveness of continuous antibiotics delivery via disposable elastomeric devices in a UK OPAT setting (Paper 10) [10].

CHAPTER 2

Benefits of OPAT

2.1 Chapter Overview

This chapter will present and contextualise three published studies, which I led and co-authored, within the existing body of scholarly literature on the advantages of OPAT. As will be outlined in Section 2.2, these studies employed diverse methodological approaches, analytical frameworks, and data sources collected over various time periods from two main patient cohorts in Sheffield and Derby hospitals. The studies incorporate quality of life assessments, economic evaluations, patient satisfaction surveys, and measures of morbidity and mortality associated with OPAT in these two healthcare settings. The ensuing discussion will centre on clinical effectiveness, safety, cost-effectiveness, and patient-related outcomes, concluding that OPAT may offer significant benefits for both the NHS and its patients.

2.2 Published Papers

Paper 1: **Durojaiye OC,** Bell H, Andrews D, Ntziora F, Cartwright K. Clinical efficacy, cost analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield (UK) OPAT service. *International Journal of Antimicrobial Agents* 2018;51(1):26-32 [1].

Paper 2: **Durojaiye OC,** Kritsotakis EI. Evaluation of health-related quality of life in patients receiving outpatient parenteral antimicrobial therapy (OPAT) in a UK setting. *Expert Review of Anti-infective Therapy* 2024;22(11):987-95 [2].

Paper 3: **Durojaiye OC,** Morgan R, Chelaghma N, Kritsotakis EI. Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antibiotic therapy (OPAT). *Journal of Infection* 2021;83(6):644-9 [3].

2.3 What are the Benefits of OPAT?

The primary benefits of OPAT lie in its capacity to facilitate early hospital discharge (i.e., reduce inpatient bed days) and prevent hospitalisation [46,48,95]. However, definitive evidence of its clinical

superiority over inpatient IV antibiotic therapy remains limited, largely due to a scarcity of RCTs directly comparing the two approaches [67,98,143,144], as highlighted in several published systematic reviews [93,145,146]. The potential benefits of OPAT for patients, hospitals, and healthcare systems are summarised in Table 3 and discussed below.

Table 3. Potential Benefits of Outpatient Parenteral Antimicrobial Therapy (OPAT)

Admission Avoidance or Shortened Inpatient Stay	
Patient Benefits	**Benefits to Hospitals/Healthcare Systems**
• Improves patient convenience and privacy	• Reduces congestion in emergency departments
• Improves patient experience and satisfaction	• Enhance inpatient capacity and eases bed pressure
• Improves quality of life and sense of wellbeing	• Allows bed reduction and reconfiguration
• Less disruptive to family life	• Streamline patient flow within the hospital system
• Reduces social/psychological stress	• Improves efficient use of inpatient resources
• Allows choice of therapy to suit individual needs	• Reduces hospital staff workload
• Reduces family's costs of visiting patients in hospital	• Provides significant cost savings
• Possibility of an earlier return to work or school	• Reduce carbon footprint
• Reduces risk of healthcare-associated infections	• Consistent infection specialist input into patient care

2.3.1 Clinical Effectiveness and Safety

The first published paper in this thesis [1], was undertaken to provide a comprehensive evaluation of the Sheffield OPAT service during its first decade of operation (2006-2016). It aimed to address a critical gap in the literature regarding long-term clinical outcomes, economic sustainability, and patient-centred acceptability of OPAT delivery models within the NHS. While previous studies [56,69,147] had demonstrated the short-term safety and feasibility of OPAT, there was limited evidence on the performance of these services over extended periods in routine clinical settings. By analysing real-world data, this study assessed the clinical efficacy of OPAT across a range of infections, evaluated cost implications relative to inpatient care, and explored patient perspectives on acceptability and satisfaction.

Drawing on a decade of OPAT data and patients' medical records, the study employed a retrospective, descriptive quantitative design alongside a cost-consequence analysis [1]. Outcomes were assessed using the BSAC NORS definitions (Table 4) [148]. A wide range of infections were successfully managed over the 10-year period, with cure or improvement achieved in 88% of the 3,812 patient-episodes, resulting in a total of 49,854 bed-days saved (Table 2, Chapter 1). There were two deaths (0.05%), both due to cardiac causes unrelated to OPAT, and the rate of line-related infections was low (0.3 per 1,000 OPAT patient-days).

Table 4. BSAC NORS Definitions of OPAT Outcomes [148].

Infection outcomes	
Cure	Completed OPAT therapy +/- oral step down for defined duration with resolution of infection and no requirement for long term antibiotic therapy (usually relates to less severe infections e.g., SSTI, UTI unless prosthetic material removed).
Improved	i. Completed OPAT therapy +/- oral step down with partial resolution of infection but need for further follow up OR ii. Completed OPAT therapy but required escalation of antimicrobial therapy during OPAT (without admission) +/- oral step down with ultimate cure or partial improvement (as above) e.g., osteomyelitis, any infections where prosthetic material has not been removed.
Failure	Progression or non-response of infection despite OPAT, required admission, surgical intervention or died for any reason.
OPAT outcomes	
Success	Completed therapy in OPAT with no change in antimicrobial agent, no adverse events, cure or improvement of infection and no readmission
Partial Success	Completed therapy in OPAT with either change in antimicrobial agent or adverse event not requiring admission
Failure of OPAT	Readmitted due to infection worsening or due to adverse event. Death due to any cause during OPAT
Indeterminate	Readmission due to unrelated event e.g., chest pain

BSAC, British Society for Antimicrobial Chemotherapy; NORS; national outcomes registry system; OPAT, outpatient parenteral antimicrobial therapy; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

Paper 3 focused on the management of IE within the NHS [3]. This study sought to address a significant evidence gap concerning predictors of clinical outcomes in this complex patient population. The rationale was informed by the findings from Paper 5 [5] (see subsection 3.3.2), which identified that patients with endovascular infections—predominantly IE—who were treated via OPAT had an increased risk of unplanned hospital readmission. Management of IE within the Sheffield OPAT

programme followed locally developed multidisciplinary guidelines consistent with national practice standards but established before the POET trial [77]. OPAT eligibility required clinical stability, microbiological control, and absence of complications warranting inpatient care. Patients received continued IV antimicrobials under specialist supervision, with routine monitoring—including weekly blood tests and clinical reviews—and predefined criteria for escalation or readmission. Oral switch therapy, as evaluated in the POET trial, was not adopted during the study period.

The retrospective analysis identified 168 cases of IE managed by the Sheffield OPAT service over a 13-year period (2006-2019), revealing low one-year mortality (2%) and recurrence (8%) rates. Notably, patients traditionally considered at increased risk of complications—and often deemed unsuitable for OPAT—such as those with aortic or prosthetic valve disease, or *Staphylococcus aureus* IE [149], were successfully treated. The finding that inpatient cardiac surgery was associated with favourable long-term outcomes likely reflects the benefits of early, definitive source control, and optimised antimicrobial therapy prior to discharge. These results underscore the importance of careful patient selection and pre-OPAT clinical optimisation, suggesting that surgically treated patients may experience fewer complications and better outcomes during outpatient antibiotic therapy. Overall, Paper 3 contributes to the evolving evidence base underpinning best practice guidelines for OPAT use in IE [74,150], informs risk stratification, and complements broader efforts to enhance patient-centred care. A key strength of this paper, as well as Paper 1, lies in their reflection of the real-world complexity of managing a large OPAT cohort over an extended period, particularly relative to comparable studies.

Similar to other UK studies [79,94,151], international research from Australia [25,96] and the US [23,97], has demonstrated that OPAT is both safe and clinically effective. Some of these studies have focused on the safety of OPAT for specific conditions—such as endocarditis [76], cellulitis [152], or tuberculosis [153]—or for particular population groups, including neonates [35], children [154], older adults [155], and people who inject drugs (PWID) [156]. Others have evaluated different antimicrobial agents [157-160]. These studies assess the safety and effectiveness of OPAT using a range of indicators, including cure rates, treatment success and failure rates, mortality, adverse events, and rehospitalisation rates. In the UK, outcomes are often assessed using the BSAC NORS definitions [147] and the national GPRs guidelines (Supplementary Table 2) [18].

A limited number of systematic reviews have evaluated OPAT's safety and clinical effectiveness, primarily based on single-arm observational studies [74,93,146]. Meta-analyses by Pacheco *et al*. [161] and Mohammed *et al.* [98] of RCTs comparing OPAT with inpatient care found no significant differences

in mortality, treatment failure, or adverse events. While Mohammed *et al.*, drawing on 13 RCTs, concluded that OPAT is a safe and effective alternative to inpatient care, Pacheco *et al.*, based on six RCTs, reported low-quality evidence supporting OPAT's advantages. The review by Mohammed *et al*. was methodologically stronger, incorporating a broader evidence base, clearer inclusion criteria, and formal assessment of publication bias, as well as sensitivity analyses to address heterogeneity. In contrast, Pacheco *et al*. applied stricter risk-of-bias criteria and limited inclusion to home-based OPAT in adults, resulting in most evidence being rated as low or very low quality. Both reviews were constrained by the small number and modest size of available RCTs, variation in OPAT models, and inconsistent outcome definitions. Consequently, while both support the non-inferiority of OPAT relative to inpatient care, the strength their conclusions is limited by methodological heterogeneity and sample size, underscoring the need for high-quality pragmatic RCTs to strengthen the evidence base.

A further systematic review by Mitchell and colleagues examined the effectiveness, safety, and acceptability of OPAT in adult patients as part of a broader evaluation of OPAT service delivery in the NHS [93]. Their review encompassed 128 studies, of which 29 were comparative, and found that OPAT was associated with higher cure or improvement rates, but similar treatment durations, drug-related complications, and mortality compared to inpatient care. However, the authors concluded that evidence remains insufficient to support the clinical superiority of OPAT over inpatient care, primarily due to a lack of high-quality comparative studies. Another review, which included observational studies evaluating the safety and effectiveness of OPAT and HITH programmes across different age groups, reported cure or treatment success rates exceeding 80% in over 88% of studies [146].

When assessing the clinical effectiveness of OPAT, it is essential to define an appropriate baseline for comparison. Although inpatient care represents the conventional standard, identical outcomes may not always be expected given differences in patient selection, monitoring, and care environments. The goal for OPAT should therefore be to demonstrate clinically meaningful **non-inferiority** to inpatient treatment while maintaining patient safety, convenience, and service efficiency. This perspective recognises OPAT not as a replication of inpatient care, but as a pragmatic, patient-centred alternative that maintains high standards of clinical effectiveness. Overall, the demonstrated clinical effectiveness and safety of OPAT, relative to inpatient care, support the conclusion that hospital discharge with a transition to OPAT is a safe and viable option for clinically stable patients requiring parenteral antimicrobial therapy.

2.3.2 Cost-effectiveness

Paper 1 also presented a cost-consequence analysis comparing the expenses of the Sheffield OPAT services during its first decade of operation (2006-2016) with the estimated costs of equivalent inpatient care [1]. The analysis found that OPAT costs were approximately 39% of the national average for equivalent inpatient care. Actual cost savings may be higher, as indirect benefits—such as reduced risk of healthcare-associated infections (HCAIs), improved patient productivity, and QoL—were not included. The analysis assumed that all patients would otherwise remain hospitalised for the full duration of OPAT therapy, which may not always reflect practice. Although bed-days saved is commonly used to estimate OPAT impact, it can overstate benefits. Some patients may transition early to high-bioavailability oral therapy or receive partial inpatient treatment (e.g., dalbavancin) without subsequent OPAT, reducing actual number of bed-days saved. The analysis also assumed that complications occurring during OPAT would have occurred at similar rates in inpatients and were therefore excluded from cost calculations. While this pragmatic approach avoided double-counting, it may have overestimated the financial benefits of OPAT, as inpatient tariffs typically account for the costs of managing such events. It should also be noted that the comparator for OPAT has evolved. Modern strategies, including early oral switch regimens or long-acting parenteral antibiotics, can achieve similar clinical outcomes with reduced hospital resource use. Consequently, while historical cost-effectiveness analyses remain informative, contemporary evaluations should account for these evolving treatment pathways to provide a more accurate assessment of OPAT's economic and clinical value. These limitations should be considered when interpreting the magnitude of the reported cost savings in Paper 1.

Several other studies have demonstrated that OPAT is more cost-effective than inpatient care, particularly for prolonged antimicrobial therapy or for patients at low risk of complications. While most economic evaluations focus on daily inpatient costs [101,102] or use economic modelling [51,103] (see Section 1.5.3.1), my co-authored study presents a more precise estimate of financial savings within the NHS, based on the actual costs of establishing and running the Sheffield OPAT service.

Systematic reviews cited in Section 2.3.1 also included economic evaluations of OPAT alongside assessments of its clinical effectiveness and safety [93,145]. Bryant *et al*. [145] reported that home-based therapy for children was 30-75% cheaper than hospital care, while Mitchell *et al.* [93] found similar cost benefits in adults. Psaltikidis *et al*'s [162] meta-analysis of 35 studies estimated average savings of 57.2% with OPAT, although the poor methodological quality and heterogeneity of the included studies reduced certainty of this estimate.

Economic evaluations should be interpreted alongside other outcomes, including treatment completion, readmission rates, and patient-centred endpoints. It is worth noting that the potential cost savings from OPAT are influenced by local funding mechanisms and the relative cost of inpatient care [113]. In some settings, such as in the US, OPAT delivers substantial cost savings, particularly where inpatient care is relatively more expensive, [120,162]. In other contexts, its primarily benefit is increased flexibility in managing hospital beds and responding to surges in demand.

2.3.3 Patient and Social Aspects

2.3.3.1 Patient Experience and Acceptability

Patient experience and satisfaction are increasingly recognised as key indicators of healthcare quality [163]. Patients now receive information about their health conditions and treatment options, enabling them to participate more actively in their care. The ability to choose where they receive treatment is a valuable aspect of enhancing overall patient experience [81]. Paper 1 also included a patient satisfaction survey conducted over a one-year period (2014-2015) [1]. The survey found that 97% (143/147) of respondents felt that OPAT care met their expectations, 99% rated it as very good or excellent, and 98% indicated they would prefer OPAT over inpatient care if required in the future.

Other studies have also reported high levels of satisfaction and acceptance of OPAT, emphasising improvements in patient autonomy and choice [164,165]. The systematic review by Mitchell *et al.* [86] found that patients valued the flexibility offered by OPAT, including the ability to continue work or school and greater control over their care. Many preferred home-based treatments for its convenience and opportunity to remain with family [86]. Several qualitative studies also support these findings [50,166-168]. For example, Twiddy *et al.* [50] conducted 28 semi-structured interviews and a focus group to examine adult patients' experiences with OPAT in NHS England, revealing high levels of satisfaction. Participants highlighted the importance of responsive healthcare professionals and cited key benefits such as avoiding hospitalisation, remaining at home, and minimising disruptions to daily routines. Similar themes emerged in other qualitative studies [166–168].

2.3.3.2 Health-Related Quality of Life

HRQoL is a crucial component of patient-centred care, encompassing various dimensions of physical, mental, emotional, and social functioning [169]. Infections can significantly impact HRQoL [170-172]. However, OPAT, by preventing prolonged hospitalisation, can enhance QoL by enabling patients to continue daily routines and social engagements—thereby promoting overall well-being. Despite its

importance, only a limited number of studies have explored OPAT's impact on HRQoL, particularly within the NHS context. This gap has also been highlighted in national GPRs guidelines [18].

Paper 2 presents a prospective, before-and-after quasi-experimental study involving 162 adult patients who received OPAT at Derby Hospital between 2022 and 2023 [2]. This study was motivated by the need for patient-centred evidence to inform OPAT service design, the recognition that clinical success alone does not equate to overall patient well-being, and the understanding that quality of care extends beyond infection management to encompass broader health outcomes that are meaningful to patients. In the study, participants completed paired EuroQoL 5-Dimensions 3-level (EQ-5D-3L) questionnaires before starting OPAT and at treatment completion or 30 days after initiation. The study revealed significant improvements in patients' HRQoL scores, particularly in four of the five EQ-5D dimensions: mobility, self-care, usual activities, and pain/discomfort. The lack of improvement in anxiety and depression scores suggests that, while OPAT supports physical recovery and certain aspects of QoL, it may not fully address the psychological burden of infection, prolonged treatment, or underlying mental health issues. This underscores the need for routine screening and referral to appropriate psychosocial support within OPAT services.

The mean utility (index) score increased by 0.2 (P <0.001). However, nearly 50% of patients experienced no change, deterioration, or mixed changes in overall HRQoL, highlighting the heterogeneity of patient experiences. Factors such as baseline health, comorbidities, social support, and treatment burden may influence HRQoL trajectories and should inform individualised care planning and service design. Of the 37 employed participants, 16 (43%) returned to work during OPAT, and both student participants were able to continue their education. To the best of my knowledge, this study represents the first comprehensive assessment of OPAT-related HRQoL in a UK setting. The findings may inform QALY estimations for cost-effectiveness analyses of OPAT within the NHS (QALY = utility score × duration of time; for example, if a patient's health state has a utility score of 0.2, and they remain in that state for one year, the QALY would be 0.2 × 1 = 0.2 QALYs) [105]. While QoL scores improved, Paper 2 was a non-comparative study; therefore, these improvements cannot be directly attributed to OPAT relative to inpatient care and may instead reflect natural recovery.

A few non-UK studies have also examined the impact of OPAT on HRQoL [173-175]. Consistent with the findings from my co-authored publication, these studies demonstrated that patients receiving OPAT have a lower HRQoL than the general population. As such, OPAT patients represent a clinically stable yet functionally vulnerable population whose care requires a more holistic, patient-centred approach

that extends beyond infection management alone. A Canadian study conducted in the early 2000s, which used the Short Form-36 (SF-36), found significant improvements in physical functioning, bodily pain, emotional well-being, and mental component scores after four weeks of OPAT treatment [173]. Similarly, a study from Singapore using the EQ-5D-3L questionnaire reported that higher baseline HRQoL was associated with fewer complications, a lower risk of early OPAT termination, and an increased likelihood of returning to work during treatment [174].

2.3.3.3 Other Patient Benefits

The preference of patients with infections for home treatment over hospital care has been repeatedly demonstrated [50,93,176]. Home-based care addresses common hospital-related challenges, including unfamiliar and potentially intimidating environments, social isolation from friends and family, and limited privacy. Hospitalisation presents particular challenges for children, who often struggle to adapt and may feel overwhelmed by hospital settings [26]. Recovery at home also facilitates the resumption of normal routines, such as work and education, thereby supporting emotional well-being and financial stability. Additionally, OPAT reduces costs by decreasing the need for regular hospital visits and associated transportation expenses.

Various OPAT delivery models enable treatment to be tailored to patients' lifestyles, functional status, family structures, and financial circumstances. Evidence also suggests that OPAT is associated with a lower risk of HCAIs, including *Clostridioides difficile* infection (CDI) and *S. aureus* bacteraemia (SAB) [26]. Despite the widespread use of broad-spectrum antibiotics such as ceftriaxone and ertapenem in OPAT [42], the risk of CDI remains low [177-179]. For example, a UK study analysing OPAT and hospital microbiology databases over a five-year period (2006-2011) identified six cases of "definitely OPAT-attributable CDI" per 100,000 OPAT-days—substantially lower than the national inpatient rate of 54 per 100,000 bed-days during the same period [180]. The lower incidence of CDI and SAB among OPAT patients likely reflects several interrelated factors. OPAT recipients are typically clinically stable and managed in non-acute settings, thereby reducing exposure to nosocomial pathogens. Adherence to aseptic technique, limited line manipulation, and regular specialist monitoring further mitigate the risk of catheter-related bloodstream infections. Additionally, the use of targeted antimicrobial regimens may lower CDI risk, while hospital discharge facilitates the restoration of normal gut and environmental microbiota [179].

To provide a more comprehensive understanding of OPAT's benefits, I argue that patient-reported outcomes—such as HRQoL and patient experiences—should be routinely included in the evaluation of

OPAT programmes. These outcomes capture aspects of care that are most important to patients and facilitate a more patient-centred approach. Moreover, the systematic collection and analysis of patient-reported data can help identify service gaps, inform quality improvement initiatives, and support shared decision-making between clinicians and patients.

2.3.4 Benefits to Healthcare Systems

The COVID-19 pandemic underscored the need for flexible and adaptable hospital capacity. OPAT optimises hospital resource utilisation by reducing staff workload and freeing inpatient beds, thereby enabling increased admissions or planned reductions in bed numbers [48,95,181]. It also prioritises inpatient care for those with higher clinical needs, while stable patients can receive appropriate care at home or in lower-acuity settings. OPAT can enhance patient flow within the hospital system—a process that is often complex and involves multiple stages, such as transitioning from primary care to emergency departments, admissions units, and specialised inpatient beds. Each stage requires coordination among different clinical teams and involves repeated administrative tasks. Access to OPAT from primary care or emergency departments can significantly streamline these transitions. Lastly, most OPAT services are overseen by, or receive input from, local clinical microbiologists or ID physicians [8,182]. Consequently, OPAT promotes consistent infection specialists' involvement in patient care, contributing to improved adherence to care standards, appropriate antimicrobial use, and better patient outcomes [183,184].

2.4 Conclusion

In conclusion, the three published papers discussed in this chapter suggest that OPAT offers a range of distinct yet interrelated benefits. The findings indicate that OPAT is a safe and effective treatment option for a diverse array of infections—including complex cases such as IE—delivered in the comfort of patients' homes or outpatient settings. High levels of patient acceptance and satisfaction were reported, alongside improvements in patient-reported QoL during treatment. OPAT was also associated with an earlier return to work or education; however, as these were non-comparative observations, the improvements in QoL cannot be directly attributed to OPAT relative to inpatient care. Concurrently, hospitals and healthcare systems benefit from reduced inpatient admissions and overall healthcare costs. Supported by corroborating evidence from the broader literature, these findings suggest that OPAT represents a clinically sound, cost-efficient use of NHS resources and a patient-centred model of care that warrants further integration within infection services and broader UK healthcare policy.

CHAPTER 3

Risks of OPAT

3.1 Chapter Overview

In this third chapter, four additional peer-reviewed publications from my body of work—including a systematic review and three retrospective analyses involving key patient cohorts from Sheffield and Derby—will be presented. The discussion will focus on treatment failure, venous thromboembolism in OPAT, unplanned rehospitalisations, and their associated risk factors. By situating the findings of these studies within the broader empirical literature, the chapter will aim to demonstrate how evidence-based practices may help mitigate the risks associated with OPAT and support the continued expansion of services.

3.2 Published Papers

Paper 4: **Durojaiye OC,** Slucka A, Kritsotakis EI. Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa. *European Journal of Clinical Microbiology & Infectious Diseases* 2022;41(6):941-9 [4].

Paper 5: **Durojaiye OC,** Kritsotakis EI, Johnston P, Kenny T, Ntziora F, Cartwright K. Developing a risk prediction model for 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy. *Clinical Microbiology & Infection* 2019;25(7):905.e1-905.e7 [5].

Paper 6: **Durojaiye OC,** Morgan R, Chelaghma N, Palit J, Keil C, Omer R, Cartwright K, Kritsotakis EI. External validity and clinical usefulness of a risk prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy. *Journal of Antimicrobial Chemotherapy* 2021;76(8):2204-12 [6].

Paper 7: **Durojaiye OC,** Cole J, Kritsotakis EI. Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): a systematic review and meta-analysis. *International Journal of Antimicrobial Agents*. 2023;62(3):106911 [7].

3.3 What are the Risks of OPAT?

Despite the findings in the previous chapter regarding the benefits of OPAT for patients and healthcare systems, its delivery is inherently complex and carries risks due to limited clinical supervision and monitoring compared to inpatient care [18,123,185]. OPAT patients are vulnerable to adverse events, including treatment failure, antimicrobial toxicity, and complications related to vascular access, the underlying infection, or pre-existing comorbidities. These adverse events can result in unplanned rehospitalisations. Overall, at least 25% of OPAT patients experience complications, ranging from mild antibiotic reactions to severe bloodstream infection related to vascular access devices [18]. Nevertheless, the overall risk profile and treatment failure rates have been shown to be comparable to those observed in inpatient care, as demonstrated by several comparative systematic reviews [93,98,145,161].

Table 5 summarises the most frequently reported complications associated with OPAT. It is important to acknowledge that some complications may be unavoidable in certain patients, owing to the complexity of the underlying infections, the potential toxicity of antimicrobial agents, the use of vascular access devices, and the often prolonged duration of therapy. Five publications from my body of work—each contributing to the broader literature on treatment failure, unplanned hospital readmission, and thrombosis risk in the context of OPAT—will be discussed in the following sections.

3.3.1 Failure of OPAT

OPAT, like any medical treatment, carries a risk of failure, which can have significant consequences for patients, healthcare costs, and AMR [186]. However, comparative systematic reviews suggest that OPAT does not confer a higher failure risk compared to inpatient care [98,145]. Paper 4 analysed the determinants of OPAT failure—defined as unplanned readmission, infection recrudescence, or mortality within 30 days post-OPAT completion—as well as prolonged therapy duration (IV antimicrobials >8 weeks) in a cohort of 46 patient-episodes with necrotising otitis externa (NOE) managed by the Derby OPAT service between 2018-2022 [4]. NOE, a rare and potentially life-threatening ear infection, often presents management challenges due to the absence of established treatment guidelines. It typically requires a prolonged course of parenteral antimicrobials, which may necessitate extended inpatient stays, thereby incurring substantial costs and risks for patients. The rationale for Paper 4, a retrospective cohort study, stemmed from the limited published real-world evidence on the safety and effectiveness of OPAT in treating this serious infection. Given the rarity of NOE, retrospective analysis presents a practical and efficient approach for exploring risk factors, evaluating treatment outcomes, and informing clinical management strategies.

In the study, OPAT failure and extended therapy occurred in 9 (20%) and 23 (50%) episodes, respectively. Dementia, higher Charlson comorbidity scores, facial nerve involvement, and elevated C-reactive protein (CRP) levels were associated with treatment failure, while extensive disease, facial nerve palsy, and high CRP levels predicted prolonged therapy. These findings highlight the impact of disease severity, comorbidity burden, and cognitive impairment on OPAT outcomes. Dementia may impair adherence, symptom recognition, and timely reporting of relapse or adverse effects, while higher comorbidity scores reflect greater medical complexity and vulnerability to complications. Recognising these factors is essential for appropriate patient selection and individualised care planning.

Findings from Paper 4 have informed local practice at Derby Hospital, resulting in stricter OPAT eligibility criteria and, for patients with complicated or extensive disease, consideration of prolonged or combination antimicrobial therapy and enhanced monitoring. This approach was informed by observed poorer outcomes in patients with severe disease, supported by published evidence and multidisciplinary consensus, rather than by direct evidence of benefit from combination therapy within the study.

Table 5. Common OPAT-related Complications

Vascular Access Complications	Drug-Related Complications	Infusion Device Related	Others
Allergy to dressing Breakage Dislodgement Line infection Line migration Line occlusion Thrombophlebitis Thrombosis	Antibiotic-induced diarrhoea Blood dyscrasia *Clostridioides difficile* infection Electrolyte disturbances Gastrointestinal disturbance Hepatitis Rash Renal impairment	Battery failure (electronic pumps) Flow rate irregularities Incomplete infusion Leaking device Malfunction	Non-adherence Treatment failure Unplanned readmission

OPAT, outpatient parenteral antimicrobial therapy

Paper 3, discussed in subsection 2.3.1, examined not only the effectiveness of OPAT in treating IE but also reported on treatment failure—defined as unplanned readmission or death within 30 days following OPAT completion [3]. OPAT failure occurred in 44 (26%) of the 168 cases of IE, with chronic renal disease and high Charlson comorbidity scores identified as independent risk factors.

Both Papers 3 and 4 contribute to the broader aims of this thesis by exploring the risks and safety of OPAT and providing novel data to support evidence-based decision making in the outpatient management of complex infections. Their findings may improve OPAT outcomes by informing patient selection criteria, particularly through the early identification of those most likely to benefit from this treatment approach. Rather than serving as strict exclusion criteria, these factors can guide the level of monitoring and support required for higher-risk patients. For example, individuals with multiple comorbidities or frailty may remain suitable for OPAT but could benefit from more frequent reviews, structured follow-up, or greater caregiver involvement. Incorporating risk predictors into clinical pathways may enhance safety, optimise resource utilisation, and define priorities for future research, including the development and validation of risk prediction models in unselected inpatient populations and their impact on OPAT outcomes.

Other studies in the literature have also examined OPAT failure in relation to specific diseases [56,75,187] or patient populations [188,189], using a range of indicators to define OPAT failure. Commonly used indicators include one or more of the following: worsening infection, unplanned readmission, failure to complete the initial antimicrobial regimen, prolonged therapy, mortality, infection relapse, and the BSAC NORS definition criteria [147] (Table 4, Chapter 2). For example, Veillette *et al.* [189] investigated risk factors for OPAT failure in the management of SAB, defining treatment failure as ''incomplete therapy, therapy extension, infection relapse, or hospitalisation or surgical intervention within 60 days of therapy completion''. Across the literature, numerous factors have been associated with OPAT failure, with pre-existing comorbidities frequently identified as a key predictor [56,75,187,190].

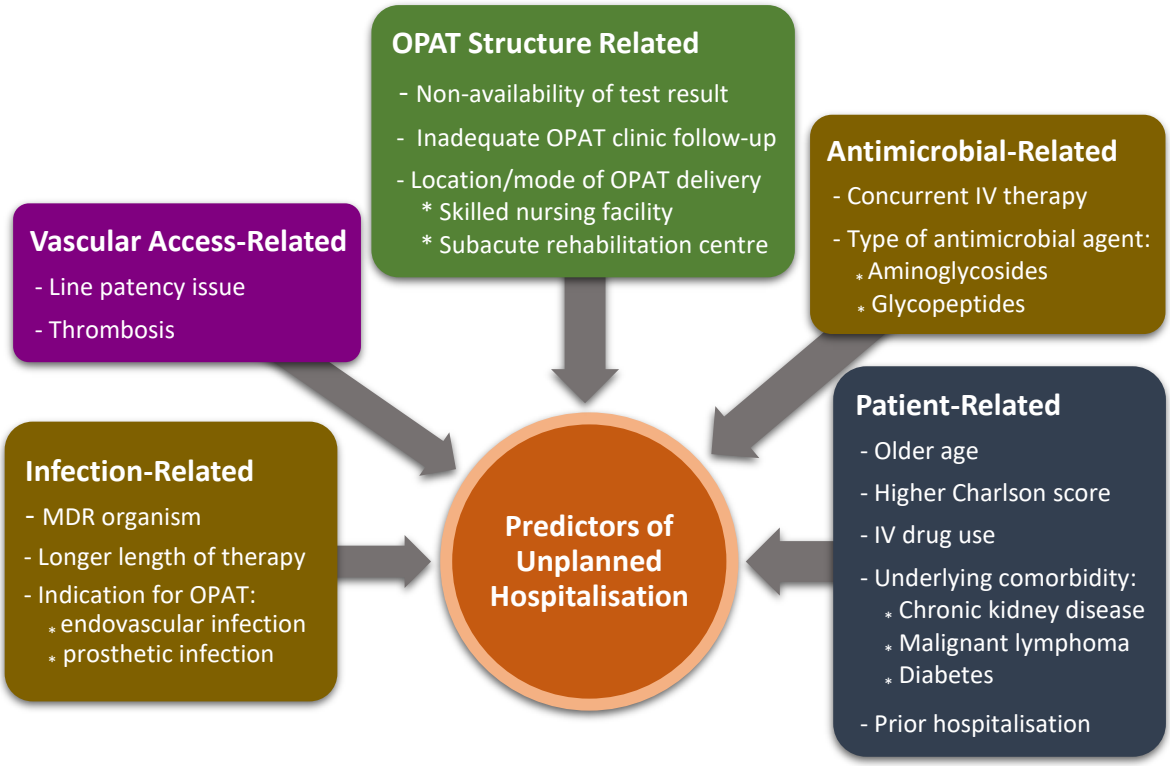
3.3.2 Unplanned Rehospitalisation

Unplanned hospitalisation may result from treatment failure, therapy-related complications, or unrelated events such as falls [107-114,191-193]. Hospital readmission rates, commonly used to assess OPAT outcomes, range from 1% to 26% [107-114,146,191-193]. The primary cause is typically infection progression or an inadequate treatment response [108,109,112,113,191]. Most studies in the literature on unplanned readmissions have been conducted outside the UK [107-114,192-194].

Reported predictors include patient- and infection-specific factors, therapy-related complications, and OPAT service structures (Figure 6), with pre-existing comorbidities being the most consistently identified factor [108,194].

Although OPAT aims to deliver care equivalent to inpatient treatment, its benefits may be compromised if early discharge leads to high readmission rates. Therefore, accurate prediction and prevention of readmissions can improve patient outcomes and reduce healthcare costs by identifying high-risk patients who may benefit from more personalised OPAT care. Research into predictive factors for OPAT outcomes is a recognised gap in the UK national OPAT GPRs guidelines [18].

Figure 6. Predictors of Unplanned Hospitalisation in Patients Receiving OPAT

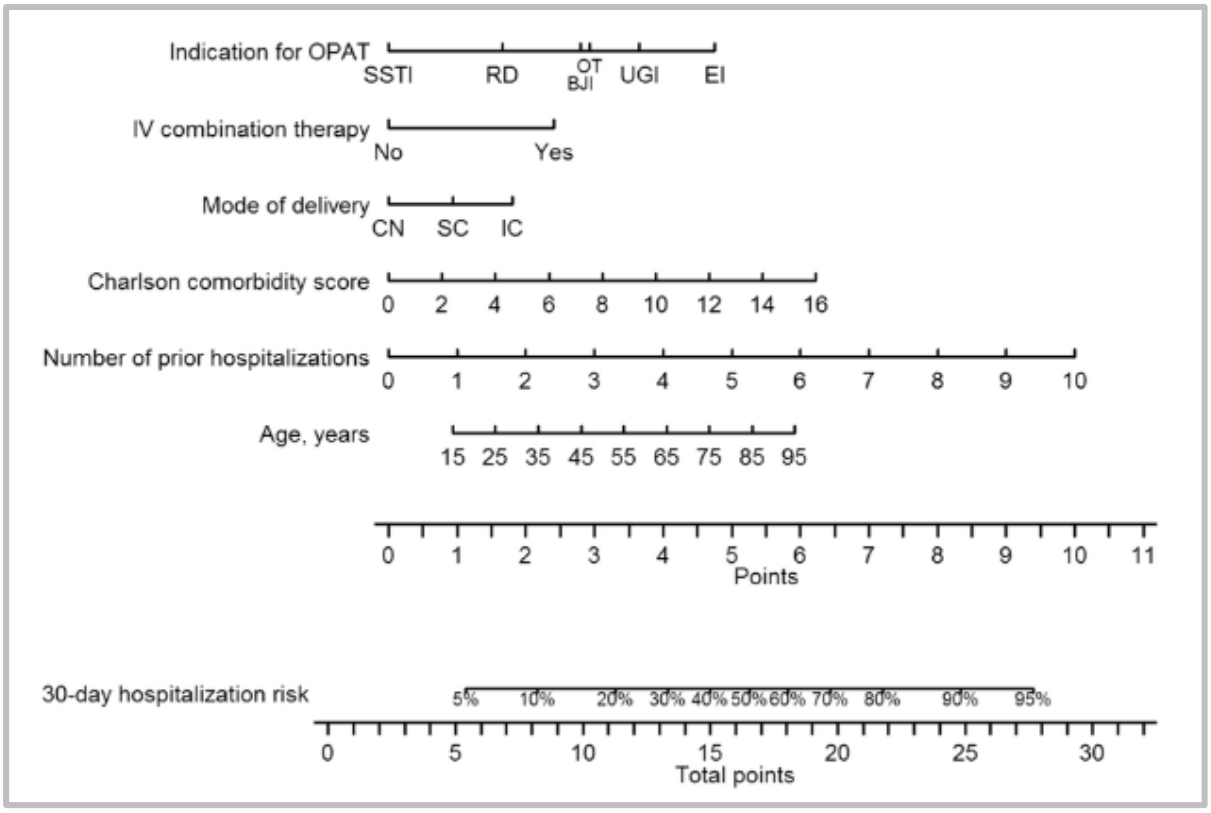


IV, intravenous; MDR, multidrug resistant; OPAT, outpatient parenteral antimicrobial therapy.

Accordingly, I designed, led, and co-authored an observational study (Paper 5) to develop a risk prediction model for 30-day unplanned hospitalisation among patients treated with OPAT within the NHS [5]. The model, derived from a retrospective review of a cohort of 1,073 patients treated at the Sheffield OPAT service between 2015 and 2017, revealed a 30-day unplanned hospitalisation rate of

11%, with worsening or non-improvement of infection being the primary reason for readmission (42%). The model (Figure 7) incorporates six easily accessible variables—age, prior hospitalisations in the preceding 12 months, Charlson comorbidity score, treatment with multiple IV antimicrobials, infection type, and OPAT delivery mode—and demonstrates adequate discrimination (c-statistic 0.7), indicating it can reasonably distinguish between patients who will be readmitted and those who will not. Among the OPAT indications, endovascular infection (predominantly IE) was most strongly associated with unplanned readmission. Consequently, the risk factors for poor outcomes in IE patients via OPAT were further explored in Paper 3 [3] (see subsections 2.3.1 and 3.3.1).

Figure 7. Predictive Nomogram for Assessing the Risk of 30-Day Unplanned Hospitalisation [5]



BJI, bone and joint infection; CN, community nursing; EI, endovascular infection; IC, infusion centre; IV, intravenous; OT, other indications; RD, respiratory disease; SC, self/carer administration; SSTI, skin and soft tissue infection; UGI, urogenital infection

The linear predictor (LP) for patients was calculated as:

LP = -3.628 + (0.016 x age) + (0.264 x number of prior hospitalisations) + (0.103 x Charlson comorbidity score) + (0.248, if self/carer administration) + (0.479, if infusion centre) + (0.635, if IV combination therapy) + (0.480, if endovascular infection) - (0.337, if respiratory disease) + (0.189, if urogenital infection) - (0.037, if bji) - (0.776, if SSTI).

The 30-day unplanned hospitalisation probability was derived using the logistic function:

$$Probability = 1/ [1 + exp(-LP)]$$

The 30-day unplanned hospitalisation rate was selected as the primary outcome because it is a validated and standardised measure of OPAT performance. This timeframe is widely used in healthcare outcomes research, as it captures the period most directly related to the index OPAT episode—when adverse events or infection relapse are most likely and plausibly attributable to OPAT management. Events beyond 30 days are increasingly confounded by comorbidities and unrelated healthcare encounters (e.g., new infections), making causal attribution to OPAT more difficult. Furthermore, a 30-day measure allows comparability across studies and facilitates benchmarking with national audit data. Future research could extend follow-up to 60 or 90 days to assess longer-term outcomes, such as infection relapse and antimicrobial resistance, providing a more comprehensive evaluation of OPAT effectiveness and safety.

The external validity and clinical utility of the model were subsequently examined in Paper 6 [6]. This published study included two cohorts of patients who received OPAT care between 2018 and 2020 at the Derby (external validation, n = 418) and Sheffield (temporal validation, n = 1,087) OPAT services. Thirty-day unplanned hospitalisation rates were 13% and 25% in the temporal and external validation cohorts, respectively. The higher readmission rate observed in the broader validation (Derby) cohort likely reflects greater infection severity, older patient age, and higher comorbidity burden. The demographic and clinical differences between the development and validation cohorts were intentional and reflect the natural heterogeneity of OPAT populations across clinical services. This variability provides a rigorous test of the model's robustness and generalisability.

The model demonstrated reproducible predictive performance, broad clinical transportability, and practical utility. Decision curve analysis showed increased net benefit across a range of clinically relevant risk thresholds, supporting its value in identifying high-risk patients most likely to benefit from targeted interventions. Discrimination was adequate on temporal validation (c-statistic = 0.8) and acceptable on the external validation (c-statistic = 0.7), with excellent calibration between observed and predicted risks in both cohorts, indicating that the predicted readmission risks closely matched actual readmission rates across all risk strata. The slightly lower performance in the external validation cohort highlights the challenges of applying predictive tools across heterogeneous OPAT populations and service contexts, where differences in patient characteristics, infection severity, and antimicrobial regimens may influence model calibration and discrimination.

To the best of my knowledge, this is the first UK-based predictive model for unplanned hospitalisation among OPAT patients. The model has the potential to enhance clinical decision-making by enabling early identification of high-risk patients during initial OPAT assessment within the NHS. This would allow higher-risk patients to receive more frequent reviews, proactive monitoring, or enhanced multidisciplinary support, while lower-risk patients follow standard protocols. Such an approach promotes safe and equitable access to OPAT while optimising resource use.

Multicentre prospective recalibration and validation are required to evaluate the model's performance across other UK OPAT centres, particularly those managing broader patient populations than the Sheffield and Derby services. While its practical value lies in supporting patient management rather than restricting OPAT access, it is important to note that the model was developed using data from patients already enrolled in OPAT; therefore, its predictive performance may not be directly generalisable to inpatient populations or the pre-selection phase of OPAT decision-making. The model is most appropriately applied post-enrolment to identify patients at higher risk of unplanned hospitalisation, thereby supporting targeted monitoring and early intervention. Prospective validation in inpatient cohorts is required before the tool can be implemented for pre-OPAT eligibility assessment.

3.3.3 Venous thromboembolism (VTE) in OPAT

Successful OPAT administration depends on reliable vascular access devices, which are susceptible to complications, including thrombosis (Table 5). VTE can disrupt therapy, lead to unplanned readmissions, increase healthcare costs, and result in significant morbidities such as pulmonary embolism [195,196]. The risk of VTE in OPAT is further heightened by the presence of infection and restricted mobility [197,198]. Although VTE prophylaxis is an established standard of care for hospitalised patients [205], there is currently no consensus on the optimal approach to thromboprophylaxis in OPAT patients due to limited evidence [18]. Consequently, VTE prophylaxis practices vary across UK OPAT centres. This gap is highlighted in the UK OPAT GPRs guidelines, which call for further research into VTE risk [18].

To address this, Paper 7—a systematic review and meta-analysis—was conducted to assess the risk of VTE in OPAT, with the aim of informing future thromboprophylaxis recommendations. The pooled risk estimates were 0.2% for non-catheter-related VTE and 1.1% for catheter-related thrombosis—lower than hospital-associated VTE rates but comparable to those in very low-risk hospitalised medical patients, for whom thromboprophylaxis is not indicated [199,200]. The peer-reviewed study suggests that universal thromboprophylaxis and routine application of inpatient VTE risk assessment models

may not be appropriate in OPAT, given the overall low thrombosis risk. The study was recognised as one of the *Top Ten OPAT Publications of the Year* at the 2024 UK National OPAT conference [201] and may inform future updates to UK OPAT practice guidelines on thromboprophylaxis.

It should be noted, however, that most studies included in the meta-analysis (86%) were rated as having moderate or high risk of bias, reflecting heterogeneity in study design, outcome reporting, and VTE surveillance. Although VTE appears uncommon, the overall certainty of evidence is limited, and pooled estimates should therefore be interpreted with caution. Based on my clinical experience, the true incidence of VTE in OPAT is likely much lower than in inpatient care. Future research should prioritise large, prospective, multicentre studies with standardised definitions and systematic monitoring, and explore OPAT-specific VTE risk assessment protocols to support targeted prevention and safe prescribing.

3.4 Conclusion

While OPAT carries inherent risks, such as treatment failure and unplanned rehospitalisation, the publications from my body of work—alongside the broader empirical literature discussed in this chapter—suggest that these risks can be minimised, particularly through the identification of relevant risk factors to guide patient selection and treatment decisions. Furthermore, the risk of thrombosis in the OPAT setting appears to be low. These findings provide a foundation for future research and quality improvement initiatives aimed at refining eligibility criteria for OPAT, enhancing clinical outcomes, and informing national policies. I conclude that the safety profile of OPAT supports its continued use in appropriately selected patients, provided that robust systems are in place to mitigate the associated risks.

CHAPTER 4

Barriers and Challenges

4.1 Chapter Overview

This chapter will critically examine the key obstacles and challenges to the equitable and effective delivery of OPAT services in the UK. Drawing on findings from a study that I led and co-authored, it will explore the provision and accessibility of OPAT services across the country. By integrating insights from this study with relevant literature and policy documents, the chapter will aim to identify priority areas for improvement and suggest potential strategies to address these challenges. It will conclude by advocating for a nationally coordinated approach to optimise OPAT delivery within the NHS.

4.2 Published Paper

Paper 8: **Durojaiye OC,** Cartwright K, Ntziora F. Outpatient parenteral antimicrobial therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards. *Diagnostic Microbiology and Infectious Disease.* 2019;93(1):58-62 [8].

4.3 What are the Barriers and Challenges of OPAT Delivery?

While the previous chapters have explored the benefits and risks associated with OPAT, its delivery globally faces significant challenges that vary according to local healthcare systems, resource availability, and other contextual factors [41,45,202,203]. For example, a 2013 survey of 555 ID physicians in the US identified the lack of a dedicated OPAT team, the dispersion of patients across multiple treatment sites, poor communication between healthcare professionals, and the burden of managing large volumes of laboratory results, as major barriers to the safe delivery of OPAT [204].

Despite growing interest in OPAT in the UK, comprehensive national-level data on its implementation were limited. To address this gap, I led a descriptive cross-sectional survey in 2017 of all 178 acute hospital trusts and health boards in the UK at the time (Paper 8) [8], aiming to map the extent and nature of OPAT service provision. Using an electronic questionnaire, the survey examined adherence

to national GPR guidelines [123], team structures, delivery models, clinical monitoring protocols, and governance frameworks. A notable strength of the study was its high response rate of 93%, likely facilitated by the increasing relevance of OPAT, the brevity of the electronic questionnaire, and repeated follow-up reminders. Overall, the study provided a comprehensive snapshot of OPAT service provision across the UK at that time. In the subsequent subsections, I will situate this study within the broader literature to explore the barriers and challenges specific to OPAT services in the UK and to propose potential solutions.

4.3.1 Variation in Practice

The study (Paper 8) identified wide variability in practice and adherence to national guidelines, including differences in team composition, service leadership, delivery models, clinical monitoring protocols, and governance frameworks [8]. Service structures ranged from well-established, dedicated centres to more ad hoc models. Notably, 10% of OPAT services operated without an infection specialist, contrary to guideline recommendations. These services typically lacked dedicated ID departments but may have received intermittent support from local clinical microbiology teams. Additionally, 35% were led by acute physicians, specialist nurses, or clinical pharmacists, demonstrating the feasibility of non-specialist-led services when ID input is limited. Although the survey did not systematically capture funding barriers, responses suggested that resource constraints could restrict service delivery. In one instance, a hospital trust was unable to provide formal microbiology support due to staffing shortages, though microbiologists continued to informally recommend the service to clinicians.

It should be noted that OPAT landscape has evolved considerably since the study was conducted. The COVID-19 pandemic accelerated virtual monitoring, telemedicine, and community-based care, improving accessibility and efficiency. Wider use of long-acting agents, particularly dalbavancin, and complex outpatient oral antimicrobial therapy (COpAT) have further influenced practice. Despite these advances, service variability persists, and national data on activity, outcomes, and workforce remain limited. A contemporary follow-up survey is warranted to characterise post-pandemic service models, identify emerging challenges, and inform future NHS policy and resource planning for OPAT.

The ad hoc expansion of OPAT programmes to meet local demands may have contributed to the observed variations in service delivery across the country [18,49]. For instance, a 2013 study by Minton *et al*. [49], which involved interviews with 35 OPAT healthcare professionals (from a pool of 120 potential respondents) in England, identified substantial differences in service organisation and modes of care delivery. Some participants reported difficulties in establishing or sustaining OPAT services,

citing unclear directives from commissioning authorities and limited support from hospital management. By mapping the variations in service delivery and highlighting areas of inconsistency, Paper 8 offers some insights to inform national policy, promote service standardisation, and support the development of safe and effective OPAT delivery across the country.

Variation in OPAT practices is not unique to the UK; substantial discrepancies have also been reported in Saudi Arabia [129], Ireland [182], the US [204,205], the Netherlands [206], Belgium [207], and France [208]. These differences may be attributed to several factors, including knowledge gaps, funding and resource limitations, institutional management approaches, local priorities and guidelines, availability of specialists, and geographic coverage [18,44,45,49]. For example, patients in remote areas often have limited access to home-based visiting nursing OPAT care [49]. In contrast, hospitals with established ID departments and dedicated clinical teams tend to deliver more robust OPAT programmes, bolstered by comprehensive guidelines and specialised nursing staff.

Although the impact of these variations in OPAT practice on its effectiveness and safety remains underexplored, I argue that greater standardisation could improve efficiency, reduce costs, and enhance patient outcomes [209,210]. Collaboration among healthcare providers—such as through regional OPAT networks—can facilitate knowledge sharing and the adoption of best practices, thereby supporting both new and established services and ultimately promoting the standardisation of OPAT delivery across the UK. An OPAT service certification or accreditation programme could also enhance adherence to national guidelines, thereby enhancing patient safety and the overall quality of care [211]. Nonetheless, while standardisation is a desirable goal, it is important to strike a balance between its potential benefits and the need for local adaptability.

4.3.2 Inequity of Access

Paper 8 also found that approximately two-fifths of acute hospital trusts in the UK lacked an OPAT service in 2017. In addition, only six paediatric OPAT services—one ad hoc and five dedicated services—were identified nationwide, all of which were confined to tertiary hospitals [8]. Although OPAT availability has increased since then [80], national coverage remains inadequate. Given the NHS's commitment to equitable healthcare [212], these gaps raise significant concerns regarding health equity.

A 2021 policy review of OPAT in Scotland similarly reported the absence of dedicated paediatric OPAT services within NHS Scotland, all well as considerable geographical variation in access to and uptake of

adult services [213]. A study within a large Scottish health board further highlighted these inequities, showing that individuals from socioeconomically disadvantaged backgrounds and women were less likely to be referred for OPAT [214]. UK OPAT programmes often exclude homeless patients, PWID, and other hard-to-reach groups due to concerns about safety, vascular device misuse, treatment adherence, and complex social circumstances [118,185].

However, recent studies and service evaluations from other countries indicate that, with appropriate patient selection and structured support, OPAT can be delivered safely and effectively in these populations [156]. Successful models integrate addiction medicine, social support services, and close multidisciplinary oversight, reflecting a harm-reduction rather than exclusionary approach [156,215].

From an ethical perspective, systematically excluding hard-to-reach groups may perpetuate health inequities and conflict with principles of patient-centred, equitable care. Eligibility decisions should balance clinical risk with respect for autonomy and fairness, guided by transparent criteria and multidisciplinary consensus. Geographical and socioeconomic disparities further create a 'postcode lottery', where access is determined more by location than clinical need. Consequently, some hospitals fail to realise the full benefits of OPAT, and patients who could be treated at home may remain hospitalised simply because OPAT is unavailable in their area.

Healthcare inequality and postcode lotteries within the NHS are not unique to OPAT services [216,217]. Contributing factors include local policies, financial constraints, resource limitations (including workforce capacity), limited clinician awareness of OPAT, and patient-related barriers such as transport challenges or individual preferences) [45,214]. Nevertheless, the expansion of OPAT services in the UK necessitates targeted strategies to prevent the further exacerbation of existing inequalities.

To fully realise OPAT's potential and support the shift from hospital to community care while ensuring equitable OPAT provision across the UK, I argue for a coordinated package of measures. These include the use of telemedicine to support patients in remote areas [218] (see Section 5.3.1), transport and financial assistance for those in need, and enhanced workforce education. Optimising highly bioavailable oral therapies and using longer-acting parenteral antimicrobials (e.g., dalbavancin and rezafungin) can reduce reliance on indwelling vascular access devices and daily adherence, providing safe frameworks for including PWID and other vulnerable groups [185]. By investing in infrastructure, fostering collaboration, and improving accessibility, the UK can advance equitable OPAT delivery and the broader goal of care closer to home [88].

Furthermore, challenges related to the funding and commissioning of OPAT services must be addressed. NHS England—the organisation responsible for leading and overseeing the NHS in England—has recently published guidance for ICBs (which are responsible for planning and commissioning most local healthcare services) and providers on the development of OPAT services [219]. However, this guidance lacks enforceable standards and dedicated funding mechanisms, offering recommendations without mandating implementation. I propose the development of a national commissioning framework or policy that includes minimum service specifications, mechanisms for service evaluation and continuous improvement, and a standardised tariff for OPAT care. Such a tariff, designed to equitably distribute cost savings between OPAT commissioners and providers, would explicitly fund provider expertise and services, thereby incentivising efficient planning and implementation [92]. A national OPAT tariff would also allow commissioners greater flexibility in procuring necessary expertise, whether from individual or collaborative providers [220]. In rural areas, a hub-and-spoke model—similar to those used in cancer care networks—could link tertiary units, district hospitals, and primary medical centres to facilitate equality access to OPAT services [49].

4.4 Conclusion

As discussed in this chapter, Paper 8 suggests that OPAT delivery in the UK is characterised by fragmentation, inconsistent clinical governance, and inequitable access. Although recent NHS England guidance provides a framework for the development of OPAT services, the absence of dedicated funding and national oversight limits its practical impact. I argue for a coordinated national strategy that includes a clear commissioning policy, supportive financial frameworks, and minimum service specifications. Only through a nationally led, locally delivered approach can OPAT services achieve the scale, quality, and equity required to meet the growing demands of modern healthcare.

CHAPTER 5

Future Prospects and Opportunities

5.1 Chapter Overview

This fifth chapter will examine the evolving landscape of OPAT through the lens of the final two of ten peer-reviewed studies within my body of scholarly works. It will aim to explore innovations with the potential to transform service delivery within the NHS and considers how these developments may improve OPAT accessibility, enhance patient care, and support antimicrobial stewardship (AMS) efforts. The discussion will focus on telemedicine and disposable continuous infusion devices, advocating for the integration of digital health technologies and novel OPAT delivery models to optimise patient outcomes and promote the effective use of NHS resources.

5.2 Published Papers

Paper 9: **Durojaiye OC,** Jibril I, Kritsotakis EI. Effectiveness of telemedicine in outpatient parenteral antimicrobial therapy (Tele-OPAT): A systematic review. *Journal of Telemedicine and Telecare*. 2024;30(8):1230-7 [9].

Paper 10: **Durojaiye OC,** Joby C, Kritsotakis EI. Effectiveness and safety of a disposable elastomeric continuous infusion pump for outpatient parenteral antimicrobial therapy (OPAT) in a UK setting. *Journal of Chemotherapy.* 2024;36(2):119-126 [10].

5.3 What are the Opportunities for OPAT in the UK?

The number of patients eligible for OPAT is expected to rise, partly due to the increasing prevalence of MDR infections for which no viable oral treatment options are available [221]. Despite the challenges outlined in the previous chapter, OPAT is likely to continue expanding in the UK, as it has in many other countries [41]. This growth is likely to be driven by a growing body of evidence supporting its clinical and cost-effectiveness, patient preference, and the post-COVID-19 push for more care to be delivered outside of hospital settings [81,88].

The growth of OPAT presents significant opportunities for innovative healthcare delivery and expanded clinical applications. Evolving patient demographics, increasing infection complexity, ongoing medical advancements, and the emergence of COpAT and novel long-acting antimicrobials—such as dalbavancin [222] and rezafungin [223]—underscore the need for services to adopt emerging technologies and move beyond traditional OPAT models [118].

Although growing evidence supports oral step-down regimens for infections traditionally managed with prolonged IV therapy, such as osteomyelitis [70] and infective endocarditis [77], conventional OPAT remains essential when oral therapy is unsuitable due to antimicrobial resistance, drug interactions, intolerance, poor adherence, limited absorption, or complex comorbidities requiring close monitoring. Classic OPAT also provides a structured framework for adherence support and adverse event surveillance. I expect the future of OPAT in the UK to be more targeted and integrated, combining conventional IV delivery, long-acting formulations, and complex oral therapy within a patient-centred, evidence-based approach. Additional infection-related services, such as elective lumbar puncture (e.g., for neurosyphilis) and penicillin allergy de-labelling programmes, are also expected to expand within OPAT services, particularly as the focus shifts towards oral therapies [185].

The subsections below introduce two peer-reviewed studies from my body of research that explore innovations with the potential to transform OPAT service delivery.

5.3.1 OPAT and Telemedicine

With technological advancements, telemedicine has become increasingly prevalent in healthcare, particularly since the COVID-19 pandemic [115,117]. It has been shown to enhance patient-provider communication, ensure continuity of care, reduce travel burdens, and optimise resource utilisation in non-OPAT settings [115,117]. Although OPAT guidelines acknowledge the potential of telemedicine—particularly for delivering care in remote areas [7,8]—its implementation (Tele-OPAT) has been relatively slow and limited, especially in the UK [224]. Tele-OPAT refers to the delivery and oversight of OPAT through telecommunication technologies, enabling patients to receive IV antimicrobial therapy at home under remote clinical supervision. This model typically integrates scheduled video consultations, remote monitoring of vital signs or infusion devices, and secure digital patient-provider communication. It is best suited for clinically stable patients with adequate home support and technological literacy.

To objectively evaluate the potential of Tele-OPAT, I led a systematic review and meta-analysis to critically examine its clinical efficacy, safety, acceptability, and cost-effectiveness (Paper 9) [9]. The meta-analysis included 2,572 OPAT patients, of whom over 1,245 received telemedicine interventions. Findings indicate that Tele-OPAT is a safe, effective, and cost-efficient method to delivering OPAT, particularly for patients in remote or geographically isolated areas. It was associated with high patient satisfaction and complication rates comparable to traditional models. Notably, the risk of rehospitalisation was significantly lower in the Tele-OPAT group (risk ratio, 0.58; $P = 0.01$), likely reflecting enhanced monitoring, early detection of complications, and greater patient engagement through telemedicine.

However, included studies were predominantly non-randomised, often with small cohorts and limited matching or adjustment of patient characteristics. Such imbalance could introduce confounding, potentially biasing the reported outcomes in favour of Tele-OPAT or masking true differences, as patients selected for Tele-OPAT may have been inherently lower risk due to clinical stability, technological literacy, or home support. Consequently, while the review highlights the potential of telemedicine in OPAT, the non-randomised design and lack of balanced comparison groups limit causal inferences and underscore the need for larger, well-controlled studies to more accurately assess its impact and account for confounders.

By synthesising findings from multiple studies, Paper 9 has the potential to inform best practices and guide future implementation strategies for Tele-OPAT services, aligning with broader NHS digital transformation goals [81,88]. As telemedicine continues to expand, I advocate for wider adoption of Tele-OPAT in the UK, particularly for underserved populations in rural areas, nursing homes, and those facing socioeconomic challenges.

Despite its advantages, Tele-OPAT presents several potential drawbacks. It relies on patient digital literacy and stable internet access, making technical issues a barrier to effective communication and engagement. Remote management may limit direct clinical assessment, potentially delaying detection of complications such as catheter-related infections or adverse drug reactions. Patients with complex comorbidities or limited self-care capacity may be less suitable for telecare, and telemonitoring may inadvertently increase carers' burden. Effective implementation also requires robust organisational infrastructure, clear escalation protocols, and integration with healthcare records. These considerations highlight the importance of careful patient selection and comprehensive support systems to ensure safe and effective Tele-OPAT delivery.

Future research should explore specific telemedicine modalities—such as video consultations, remote monitoring devices, artificial intelligence-driven decision support systems, and mobile health applications—and their optimal integration within Tele-OPAT pathways. Studies should also examine facilitators and barriers to implementation from both patient and healthcare provider perspectives, addressing issues such as digital literacy, access to technology, and regulatory frameworks to support equitable, patient-centred, and sustainable models of care.

5.3.2 Continuous Antimicrobial Infusions and Infusion Devices

Frequent dosing presents a major challenge when using narrow-spectrum beta-lactam antibiotics in OPAT. Generally, antimicrobial selection for OPAT is often restricted to agents that require once-daily or less frequent administration for dosing convenience. The ease of administering once-daily broad-spectrum agents—such as ceftriaxone and ertapenem—often results in their overuse, even when narrower-spectrum agents like flucloxacillin (which requires more frequent dosing) would be more appropriate [225,226]. This practice conflicts with AMS objectives.

Such trade-offs necessitate careful patient selection, multidisciplinary oversight, and periodic therapy review to ensure treatment remains clinically appropriate and stewardship principles are upheld. AMS principles in OPAT settings should focus on minimising unnecessarily prolonged IV therapy, using the narrowest-spectrum antimicrobials possible, promoting early transition from IV to oral treatment, and continually evaluating the need for source control [185].

Portable continuous infusion pumps and elastomeric devices offer a practical solution by enabling the extended infusion of narrow-spectrum antimicrobials, such as penicillins, which exhibit time-dependent killing and short half-lives. This approach eliminates the need for multiple daily doses while supporting AMS principles [227].

Elastomeric devices are increasingly utilised in OPAT and other clinical settings globally, including pain management and cancer immunotherapy [164,228-235]. To evaluate their safety and effectiveness in real-world NHS practice, I designed and led a retrospective analysis of patients who received either flucloxacillin (131 patient-episodes) or piperacillin/tazobactam (301 patient-episodes) as continuous infusions via elastomeric devices for a wide range of infections over a five-year period (2018-2022) at the Derby OPAT service (Paper 10) [10]. A successful outcome (defined as cure or clinical improvement) was achieved in 84% of cases. The adverse drug event rate was 3.2 per 1,000 OPAT-days, and only one line-related infection was reported (0.1 per 1,000 OPAT-days). Although not a primary outcome of the

study, self/carer-administered OPAT was associated with lower rates of treatment failure and readmission, likely reflecting careful patient selection, stronger engagement, and better adherence among those deemed suitable for self-administration. These findings emphasise the role of patient empowerment and structured support in OPAT success. Incomplete infusion from elastomeric devices —rarely reported in the wider literature—was frequently observed in the study, with 38% of patient-episodes experiencing at least one such incident. However, no significant difference in success rates was noted between patients with and without incomplete infusions (P = 0.42). The occurrence of incomplete infusions highlights a potentially widespread yet under-recognised issue in OPAT, underscoring the need for enhanced device monitoring, standardised documentation, and further research into its clinical impact.

Continuous or extended infusion therapy using elastomeric pumps may enhance pharmacokinetic/pharmacodynamic (PK/PD) outcomes in OPAT by maintaining antimicrobial concentrations above the minimum inhibitory concentration for longer periods. This approach optimises bacterial killing for time-dependent antibiotics and may reduce the emergence of resistance. Evidence from inpatient studies, such as BLING III [236], supports potential clinical benefits over intermittent dosing in ambulatory patients, particularly for infections requiring sustained antimicrobial exposure or in those with variable pharmacokinetics. By reducing the frequency of device changes, elastomeric devices promote patient-centred care, enhance autonomy, and reduce the need for nursing visits [230]. Their use in OPAT has also been associated with high patient satisfaction [164], improved QoL [227], and lower costs compared with conventional inpatient therapy [231]. Furthermore, they may reduce line-related complications by limiting the frequency of vascular access interventions.

Paper 10 suggests that disposable elastomeric continuous infusion pumps are both effective and safe in a real-world UK OPAT setting, supporting their broader adoption as a viable alternative to traditional infusion methods. Furthermore, the study contributes to the growing body of evidence needed to inform national OPAT guidelines and procurement decisions, particularly in the context of AMS and resource optimisation.

For selected patients who self-administer antibiotics using elastomeric pumps, telemedicine provides an effective strategy for remote monitoring, enabling timely identification and appropriate management of complications or concerns as they arise. Within Tele-OPAT, both continuous infusion and intermittent self-administration present distinct advantages and limitations. Continuous infusion

minimises line manipulation and facilitates remote monitoring but is constrained by drug stability, flow variability, and cost. Intermittent administration allows greater flexibility in antibiotic selection and scheduling but requires more frequent line access and additional training. Future studies should evaluate patient experience, safety, and cost-effectiveness across these models as Tele-OPAT becomes more integrated into clinical practice.

Continuous infusion via elastomeric devices is not suitable for all antimicrobials due to variability in stability over extended periods, which can affect efficacy and increase the risk of toxicity. The BSAC Drug Stability Group has identified flucloxacillin [237], piperacillin/tazobactam [238], and temocillin [239] as suitable for continuous infusion using elastomeric devices. As OPAT continues to expand in the UK, further research on antimicrobial stability is needed to broaden the range of antibiotics appropriate for extended infusion with elastomeric devices. Wider adoption of this approach is encouraged, particularly to support AMS goals.

5.4 Conclusion

The future of OPAT in the UK presents significant opportunities for growth and evidence-based innovation, including the adoption of Tele-OPAT and disposable continuous infusion devices. The two co-authored peer-reviewed papers presented in this chapter suggest that such innovative delivery methods can enhance accessibility, optimise patient outcome, and improve the efficiency of NHS resource utilisation while aligning with the NHS's ambition for more sustainable and patient-centred care. It is therefore argued that OPAT services in the UK should embrace digital health tools and novel delivery approaches to fully realise their potential benefits. Nonetheless, widespread implementation will require robust infrastructure, clearly defined clinical governance frameworks, and equitable funding mechanisms.

CHAPTER 6

Conclusions

6.1 Chapter Overview

This final chapter will provide an overview of the thesis. It will begin with a summary of the key findings from the ten peer-reviewed publications discussed herein and consider their implications for OPAT practice in the UK. This will be followed by a reflection of the thesis's main strengths and limitations, the identification of priority areas for future research, and an outline of my intended research trajectory within the OPAT field. The chapter will conclude by advocating for the formal recognition of OPAT as a mandated care modality where clinically appropriate.

6.2 Summary and Clinical Implications

This thesis, comprising ten peer-reviewed publications that I designed and co-authored as principal investigator at both Sheffield and Derby hospitals, presents a comprehensive analysis of the clinical, operational, economic, and patient-centred aspects of OPAT within the NHS. Collectively, these works contribute novel insights into the optimisation of OPAT services and inform the development of evidence-based policies and clinical pathways in the UK and beyond.

Paper 1 establishes the clinical effectiveness, economic benefits, and patient acceptability of OPAT, drawing on real-world data from a decade of service delivery in Sheffield. The findings reinforce the role of OPAT as a safe and effective treatment modality for a range of infections in patients suitable for ambulatory care, demonstrating high levels of patient satisfaction and acceptability. Moreover, the study strengthens the case for expanding OPAT services as a cost-saving alternative to hospitalisation within the NHS, with OPAT costing approximately 39% of equivalent inpatient care.

Paper 2 demonstrates that patient-reported QoL improves during OPAT treatment and that OPAT facilitates an earlier return to work or education. It draws attention to the importance of patient-centred evidence in shaping service design, guiding clinical decision-making, and evaluating OPAT services.

Paper 3 highlights the clinical effectiveness of OPAT in the treatment of endocarditis, including in cases considered at increased risk of complications, with low rates of mortality and recurrence. The study identifies clinical predictors of adverse outcomes and underscores the importance of personalised risk stratification, careful patient selection, and close monitoring to optimise clinical outcomes

Paper 4 reports on predictors of clinical outcomes in a cohort of NOE patients treated with OPAT at Derby, demonstrating high success rates and significant inpatient bed-day savings. Similar to Paper 3, this study reinforces the wide range of complex infections that can be safely managed in the outpatient setting and underscores the critical importance of judicious patient selection in optimising outcomes.

Papers 5 and 6 present a validated predictive model for identifying patients at high risk of unplanned hospitalisation within 30 days of OPAT completion, based on real-world data from service delivery in Sheffield and Derby. The model incorporates six easily accessible variables—age, prior hospitalisations, Charlson comorbidity score, treatment with multiple IV antimicrobials, infection type, and delivery mode—enabling early identification of high-risk patients during their initial OPAT assessment. Both papers highlight the need to move away from rigid selection criteria based solely on infection parameters and social factors, advocating instead for a more individualised approach that accounts for comorbidities and recognises that certain patient groups may be more or less suited for OPAT. The prediction model serves as a risk-stratification tool that can be integrated into electronic health records to proactively identify patients requiring intensified monitoring or additional support during OPAT, thereby optimising resource allocation, reducing preventable readmissions, and lowering health costs.

The systematic review and meta-analysis presented in Paper 7 address a previously underexplored aspect of OPAT: the risk of VTE. The findings suggest that universal thromboprophylaxis and the routine application of inpatient VTE risk assessment models may not be appropriate in OPAT settings, given the overall low risk of thrombosis. The work provides a foundation for future recommendations on assessment strategies for OPAT-related thromboprophylaxis and supports safer prescribing practices.

Paper 8 explores OPAT service provision across the UK. A national survey of acute trusts revealed considerable variability in the implementation and practice, highlighting disparities in patient access and service quality. At the policy level, this inter-trust variability underscores the urgent need for national commissioning standards and a unified funding framework to promote equity and ensure long-term sustainability. NHS England (or its future successor) should lead the development of a national OPAT commissioning specification, analogous to those established for specialised services.

This should involve collaboration with the BSAC OPAT initiative to define minimum service standards and clinical governance requirements, while integrating OPAT within national antimicrobial stewardship and integrated care frameworks. Furthermore, incorporating OPAT into the NHS Payment Scheme through a dedicated tariff or bundled payment model would incentivise delivery without financial disadvantage. Mandated reporting of OPAT activity to a central registry (e.g., via NHS Digital) would support benchmarking, quality improvement, and equitable resource allocation.

The systematic review presented in Paper 9 suggests that telemedicine can enhance the safety and cost-effectiveness of OPAT, particularly for patients in remote or geographically isolated areas. This provides promising evidence for improving accessibility to OPAT services without compromising care quality, while also facilitating remote patient monitoring—an increasingly relevant approach in the context of rising health system pressures and ongoing digital transformation.

Paper 10 demonstrates the safety and effectiveness of elastomeric infusion pumps for administering selected antimicrobials—especially narrow-spectrum agents, where drug stability permits—in the OPAT setting. The study underscores the value of integrating appropriate delivery technologies into OPAT services to optimise clinical outcomes, enhance patient experience, and support AMS practices.

Within the limitations of the ten publications, their combined findings suggest that OPAT is a generally safe, effective, and patient-centred alternative to hospitalisation for a broad range of infections, even in the presence of potential risks. However, its full potential within the NHS is constrained by geographical variability in the implementation and practice of OPAT across the country. The implications of this body of work are threefold. First, it provides a robust empirical foundation to inform the development and refinement of national and local guidelines, thereby supporting policymakers, healthcare commissioners, and clinicians in delivering consistent, high-quality, and equitable OPAT care for patients requiring prolonged IV antimicrobial therapy. Second, it delineates key risk domains and highlights emerging innovations—such as remote monitoring technologies, predictive analytics, and novel delivery methods—that should shape clinical decision-making and service configuration. Third, it identifies priority areas for future research, including equity of access and the systematic incorporation of patient-reported outcome measures into OPAT evaluation frameworks.

I propose that all acute hospital trusts in the UK implement OPAT services to ensure equitable access for all patients, regardless of socioeconomic status or geographic location. Furthermore, I argue that all OPAT services should routinely evaluate their practices and consider adopting innovative delivery

methods to enhance accessibility, improve patient outcomes, and ensure long-term sustainability. The principles and demonstrated benefits of OPAT—including cost savings, high levels of patient satisfaction, and effective clinical outcomes—underscore its potential as a blueprint for other healthcare services that may benefit from decentralised or home-based delivery models. In this context, emerging delivery approaches such as telemedicine and other digital health technologies should be explored and integrated, where appropriate, to optimise clinical outcomes and resource utilisation. For example, telemedicine-enabled, community-based care models could be extended to chronic disease management—such as home haemodialysis, diabetes, and chronic obstructive pulmonary disease—particularly in remote or underserved areas, where regular monitoring, remote consultations, and timely interventions may reduce hospitalisations and enhance patient outcomes.

6.3 Reflection

6.3.1 Scholarly Development

This PhD by publication presents a coherent body of work examining multiple facets of OPAT within the UK healthcare context, including clinical outcomes, patient experiences, service delivery models, risk prediction, and innovations in care. The ten papers demonstrate a systematic progression of research—from foundational assessments of national service configurations, OPAT effectiveness, economic impact, and acceptability (Papers 1, 3, 4, 7, and 8) to advanced analyses encompassing predictive modelling (Papers 5 and 6), patient-reported outcomes (Paper 2), systematic reviews (Papers 7 and 9), and evaluations of novel technologies (Paper 10).

Together, these studies provide a substantial contribution to understanding OPAT as a complex, evolving intervention that intersects clinical effectiveness, patient safety, health economics, and service innovation. Each study built upon preceding findings to refine research questions, enhance methodological rigour, and contextualise OPAT-related challenges in real-world practice. The work integrates clinical expertise with epidemiological and statistical approaches, supported by multidisciplinary collaboration, to inform evidence-based improvements in patient care. Its originality lies in linking clinical outcomes, patient perspectives, and predictive analytics to advance both practice and policy in OPAT delivery.

6.3.2 Methodological Overview

A key feature of this PhD by publication is its use of diverse yet complementary quantitative methodologies to address questions on OPAT delivery, outcomes, and service evolution in the UK.

While the methods are described succinctly within each published paper, this subsection offers a reflective synthesis of the approaches, their assumptions, and potential constraints.

6.3.2.1 Logistic Regression Analyses

Several papers in this thesis (Papers 3–5) employed logistic regression to identify factors associated with clinical outcomes and unplanned hospitalisation. Logistic regression was appropriate due to the binary nature of the outcomes (e.g., success vs. failure). Univariate models initially explored crude associations between independent variable (e.g., comorbidities, infection type, antimicrobial class) and outcomes of interest (e.g. unplanned hospitalisation). Variables meeting a pre-specified significance threshold or considered clinically relevant were then included in multivariate models, adjusting for potential confounders to estimate the independent effects. Key assumptions—independence of observations, linearity in the logit for continuous predictors, and absence of multicollinearity—were assessed and addressed where feasible. Residual confounding and information bias remain potential limitations of retrospective datasets; nonetheless, multivariate regression strengthened causal inference within the constraints of observational data, consistent with established epidemiological practice in health outcomes research.

6.3.2.2 Systematic Review and Meta-Analysis

Two studies (Papers 7 and 9) employed systematic review methodologies to synthesise evidence on VTE risk and Tele-OPAT, respectively. Both followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [240], applying predefined eligibility criteria, multi-database searches, and independent study selection and data extraction by at least two reviewers. Citation searching complemented database searches to identify additional relevant studies, enhancing completeness and methodological rigour. Study quality and risk of bias were assessed using the Mixed Methods Appraisal Tool (MMAT) [241], appropriate for diverse study designs. Studies of low methodological quality were identified; as their exclusion is discouraged, findings should be interpreted with consideration of potential bias. Publication bias was possible, particularly due to the exclusion of non-English studies. Inclusion of non-peer-reviewed conference abstracts may have affected robustness. Nevertheless, methodological rigour was maintained through transparent reporting, consistent appraisal, and sensitivity analyses where feasible.

Both papers included meta-analyses to estimate pooled VTE risk and readmission rates associated with Tele-OPAT. Fixed-effects and random-effects models were considered: the former assumes a common effect size, while the latter accounts for between-study heterogeneity. Observed heterogeneity

(quantified by the I^2 statistic) justified the use of random-effects models to provide conservative, generalisable estimates. Sensitivity analyses evaluated the influence of individual studies, though biased or low-quality studies could distort pooled results ("garbage in, garbage out"). Variability in study design, outcome definitions, and reporting standards limited subgroup and meta-regression analyses, and the small number of eligible studies constrained precision in heterogeneity and publication bias assessments. Despite these limitations, the analytic approach followed best-practice standards for quantitative evidence synthesis, enhancing the reliability of pooled estimates.

6.3.2.3 Prediction Model Development and Validation

Papers 5 and 6 described the development and external validation of a risk prediction model for 30-day unplanned hospitalisation in OPAT patients. The derivation model employed multivariate logistic regression with backward stepwise selection to retain the most informative predictors, guided by clinical plausibility and statistical significance. Model performance was evaluated in terms of discrimination and calibration. Discrimination, quantified using the area under the receiver operating characteristic curve (AUC), measures the model's ability to distinguish patients who experienced unplanned hospitalisation from those who did not. Calibration, assessed using the Hosmer–Lemeshow goodness-of-fit test, reflects the agreement between predicted probabilities and observed outcomes across different risk levels.

External validation in an independent OPAT cohort assessed the reproducibility and overall performance. The modest reduction in AUC observed was expected, reflecting real-world variability among patient populations, as well as the inherent challenges in model generalisability. Adherence to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement ensured methodological transparency and reproducibility. Future work could explore extending the model using machine learning techniques or recalibration with larger multicentre datasets to improve validity, accuracy, and applicability across diverse clinical settings.

6.3.2.4 Overall Methodological Reflection

These methodological approaches collectively demonstrate a coherent research trajectory, encompassing local service evaluation, national survey, predictive modelling, and systematic evidence synthesis. Integrating these complementary methods provided a robust framework for addressing complex clinical and policy questions regarding OPAT delivery in the UK. Each approach was carefully selected and applied, with attention to underlying assumptions, statistical validity, and generalisability. Multiple comparisons were managed by restricting analyses to predefined hypotheses and clinically

relevant variables. Multivariable models adjusted for potential confounders, and interpretation focused on effect sizes and confidence intervals rather than statistical significance alone. Findings were evaluated for consistency across studies, minimising the risks of spurious associations. Together, the use of regression analyses, predictive modelling, and systematic evidence synthesis constitutes a rigorous body of work that advances understanding of OPAT safety, efficiency, and implementation in contemporary UK healthcare.

6.3.3 Strengths of the Work

A principal strength of this body of work is its methodological diversity and complementarity, encompassing a wide range of study designs — including observational cohort studies (Papers 1-6, and 10), a cross-sectional survey (Paper 8), and systematic reviews and meta-analyses (Papers 7 and 9) (Table 6). Collectively, these studies exemplify a rigorous, triangulated approach to evaluating OPAT services. This methodological breadth enabled comprehensive appraisal of OPAT from multiple perspectives, including real-world assessments of service efficacy, cost-effectiveness, patient experience, and disease-specific outcomes. The integrative and complementary nature of the individual studies further enhanced the coherence and robustness of the research portfolio.

Another notable strength is the clinical and translational relevance of the findings. For instance, the risk prediction model for unplanned readmission (Papers 5 & 6) provides a practical tool for identifying high-risk patients and tailoring monitoring strategies. The cost-effectiveness analysis (Paper 1) offers context-specific estimates of financial savings to the NHS, grounded in real-world service costs. These findings support evidence-informed policy, resource allocation, and commissioning decisions. Furthermore, the national cross-sectional survey (Paper 8), with a 93% response rate, provided a comprehensive overview of OPAT provision across the UK at the time of data collection. Evaluations of emerging care models—including Tele-OPAT (Paper 9) and elastomeric pumps use (Paper 10)—deliver timely, policy-relevant insights into the scalability, safety, and sustainability of OPAT services in modern healthcare systems.

The collaborative, multidisciplinary approach underpinning this work constitutes an additional strength. Engagement with other infection specialists, pharmacists, specialist nurses, a statistician, and a health economist enriched the analytical processes and enhanced the external validity of the findings. Incorporating external validation (Paper 6) demonstrates methodological rigour and a commitment to reproducibility and scientific transparency.

Table 6. Methodological Strengths and Limitations.

Paper	Study Type	Methodological Strengths	Limitations
Paper 1 [1]	Retrospective cohort (10-year OPAT service review)	Large sample size; Real-world dataset; Combined clinical, economic, and patient acceptability outcomes	Retrospective; Single-centre; Potential missing or incomplete data; Unmeasured confounding factors
Paper 2 [2]	Prospective observational (HRQoL assessment)	Prospective design; Use of validated HRQoL measures; Captures patient-reported outcomes	Single-centre; Modest sample size; Potential selection bias
Paper 3 [3]	Retrospective cohort (infective endocarditis outcomes)	Focused clinical cohort; Statistical analysis to identify predictors; Clinically relevant outcomes	Retrospective; Limited generalisability; Risk of residual confounding
Paper 4 [4]	Retrospective cohort (necrotising otitis externa outcomes)	Addresses a rare infection; Real-world clinical outcomes; Detailed clinical data	Small sample; Retrospective; Single-centre; Limited statistical power
Paper 5 [5]	Development of a predictive risk model	Methodological rigorous; Use of multivariable analysis; Clinically applicable tool	Single-centre derivation; Need external validation; Potential overfitting
Paper 6 [6]	External validation of predictive risk model	Multi-cohort validation; Assesses generalisability and clinical utility	Limited to specific populations; Retrospective nature of validation cohort
Paper 7 [7]	Systematic review and meta-analysis (VTE risk in OPAT)	Comprehensive literature synthesis; Quantitative assessment; Evidence-based summary	Heterogeneity in included studies; Potential publication bias; Limited by quality of primary studies
Paper 8 [8]	Cross-sectional survey (UK hospital trusts)	National scope; Captures organisational practices; Structured survey design	Survey response bias; Self-reported data; Snapshot in time (no longitudinal assessment)
Paper 9 [9]	Systematic review (Tele-OPAT effectiveness)	Comprehensive synthesis; Identifies evidence gaps; Structured review methodology	Limited by small number of studies; Heterogeneity in interventions and outcomes; Potential publication bias
Paper 10 [10]	Retrospective cohort (disposable elastomeric pump evaluation)	Real-world dataset; Practical clinically relevance; Patient safety and efficacy outcomes measured	Retrospective; Single-centre; Relatively small sample; Short follow-up period

HRQoL, Health-related quality of life; OPAT, outpatient parenteral antimicrobial therapy; Tele-OPAT, telemedicine in OPAT; VTE, venous thromboembolism

Finally, this research makes a substantive contribution to the international OPAT evidence base by addressing key knowledge gaps identified in national guidelines, including BSAC and IDSA recommendations. Collectively, the body of work has informed clinical practice, supported evidence-based guidance, and reinforced the relevance and impact of OPAT in contemporary infectious diseases management.

6.3.4 Limitations of the Papers

While the co-authored studies presented in this thesis provide valuable insights into the clinical, economic, and organisational dimensions of OPAT, several limitations warrant consideration (Table 6). These reflect both the inherent challenges of applied health services research and the practical constraints of conducting studies in routine clinical settings.

First, several studies within this body of work (particularly Papers 1, 3, 4, 5, 6, and 10) employed observational or retrospective cohort designs based on prospectively maintained databases and clinical records. Although such data enable real-world service evaluation and minimise recall error, these studies remain susceptible to biases, including incomplete documentation, residual confounding (e.g., unmeasured differences in illness severity, comorbidities, treatment duration, or healthcare access), and selection bias (e.g., preferential enrolment of patients more suitable for OPAT or with stronger social support, potentially influencing treatment completion, readmission, or adverse events). Variability in the quality and completeness of routinely collected clinical data—particularly regarding comorbidities, antimicrobial indications, and clinical outcomes—may also have influenced findings. Despite statistical adjustments, causal inferences should therefore be interpreted cautiously.

Second, the generalisability of findings is constrained by the healthcare contexts in which the studies were undertaken. Several analyses (notably in Papers 1-6, and 10) were derived from one or two large NHS trusts and may not capture the diversity of OPAT delivery models, resource availability, and patient demographics across other regions or international settings. Nevertheless, it is important to note that the Sheffield and Derby services share key structural and operational characteristics with many UK OPAT centres. Similarly, the cross-sectional survey (Paper 8), despite an excellent response rate, represents a self-reported snapshot of OPAT provision at a single time point and may not reflect subsequent developments, particularly following the COVID-19 pandemic and the expansion of telemedicine and home infusion technologies. Reporting and information biases are also possible, as respondents may have provided incomplete or selectively positive accounts, potentially overestimating service quality or coverage.

Third, while some papers (Paper 1 and 2) incorporated patient-reported outcomes and feedback, these measures were not consistently explored across all studies, limiting the depth of understanding of patient experience. Moreover, the studies span more than a decade of OPAT research, during which clinical practice, antimicrobial stewardship policies, and healthcare technologies have evolved substantially. Consequently, some findings should be interpreted within their temporal context, acknowledging that certain models of care or technologies may have since advanced or been superseded.

Although bed-days saved is frequently used to assess OPAT's impact, this measure has inherent limitations. It assumes all patients would otherwise remain hospitalised for the full course of therapy, whereas in practice some may have transitioned earlier to high-bioavailability oral antibiotics or received partial inpatient treatment with long-acting agents such as dalbavancin. Consequently, analyses based solely on bed-days saved may overestimate OPAT's benefits. Interpretation should therefore incorporate additional outcomes—such as treatment completion, readmission, and patient-centred clinical measures—to provide a more comprehensive assessment of efficacy and cost-effectiveness.

Finally, the absence of direct comparisons with inpatient care remains a major limitation. As OPAT becomes more established in the UK and its benefits more widely recognised, conducting a definitive RCT against inpatient care may be both challenging and ethically complex.

Despite these limitations, the cumulative evidence generated by this body of work provides a robust and contextually relevant foundation for ongoing OPAT development, evaluation, and policy formulation. Recognising these methodological and contextual constraints highlights key opportunities for future research, including the need for multicentre prospective studies, standardised outcome metrics, and greater integration of patient-centred measures to strengthen the evidence base for OPAT practice in the UK.

6.3.5 Personal Reflection

Conducting this research programme has been both professionally rewarding and intellectually challenging. The progression from service evaluation to advanced analytical approaches and systematic reviews has deepened my understanding of clinical epidemiology, data science, and translational research. Collaboration with multidisciplinary colleagues not only enhanced the quality and rigour of

the work but also strengthened my appreciation of the complexities inherent in translating evidence into clinical practice.

Throughout this research journey, I have developed skills in critically appraising evidence, recognising methodological limitations, and balancing scientific aspirations with operational feasibility. Beyond service improvement, the collective outputs of the ten publications presented in this thesis have contributed to guideline development and provided a replicable framework for quality assurance, representing a substantive contribution to both clinical practice and healthcare policy.

Ultimately, this body of work demonstrates originality in applying advanced analytical methods to real-world clinical challenges and reflects the evolution of a maturing research identity that integrates clinical expertise, analytical rigour, and translational impact. It underscores a sustained commitment to advancing patient care, enhancing service quality, and optimising health system performance.

6.4 Recommendations for Future Research

While this thesis has provided valuable insights into the clinical, economic, and operational dimensions of OPAT within the NHS, notable evidence gaps remain regarding patient-centred aspects, health system determinants, implementation barriers, and emerging applications—such as palliative OPAT, outpatient subcutaneous antimicrobial therapy (OSCAT), and COpAT [118,185]. To strengthen OPAT services and optimise their potential benefits, future research should prioritise the following areas:

6.4.1 OPAT Implementation and Inequities in Access

Future research should explore the organisational, financial, and regulatory barriers to OPAT delivery and scalability. Perspectives from policymakers, healthcare administrators, and patients could inform context-specific solutions for integrating OPAT into routine care. A mixed-methods approach—including qualitative interviews and quantitative assessments of health system performance indicators—is recommended. Comparative case studies across regions or institutions may identify best practices as well as contextual challenges.

Additionally, research must address structural, geographic, and socioeconomic disparities in service availability, particularly in paediatric OPAT provision. Strategies to improve referral pathways and expand eligibility criteria—especially for hard-to-reach populations like homeless individuals and PWID—warrant further exploration. Spatial analysis of service distribution and access (e.g. using

geographic information systems), combined with qualitative insights from providers, patients, and other stakeholders, could support NHS goals to deliver care closer to home and reduce inequalities.

6.4.2 Economic and Patient Perspectives

Further investigation is required to address existing gaps in understanding the economic benefits and patient experiences associated with different OPAT delivery models, including various drug delivery devices and therapeutic regimens, using real-world data. A mixed-methods approach, combining retrospective clinical outcomes analysis with prospective cohort studies, may be particularly valuable. Comparative evaluations of treatment strategies (e.g., elastomeric devices, long-acting parenteral agents such as dalbavancin and rezafungin, and COpAT) should access costs, clinical outcomes, and patient-reported experiences. Additionally, qualitative interviews with patients and clinicians could further elucidate the acceptability, feasibility, and perceived value of these approaches.

Understanding the QoL of patients—particularly those receiving OPAT palliative— in comparison to inpatient care is essential for optimising patient selection and improving the overall care experience. Although RCTs comparing OPAT with inpatient care may be challenging to conduct, large-scale, multicentre, prospective observational studies could yield robust and informative data.

6.4.3 Innovative Approaches

Integrating innovative approaches and novel applications—such as OSCAT and palliative OPAT—into OPAT across diverse clinical settings warrants thorough investigation to optimise patient outcomes and enhance cost-effectiveness. Robust, context-sensitive research methodologies—such as longitudinal cohort studies, pragmatic observational designs, and qualitative methods—can elucidate patient and provider perspectives, alongside implementation science approaches to assess feasibility, acceptability, and scalability within real-world contexts.

Given the increasing use of continuous infusion and elastomeric devices, research should also evaluate the stability of a wide range of antimicrobials under real-world conditions, particularly in scenarios where devices may be exposed to prolonged near-body temperatures. Such evidence is essential to ensure the safety and efficacy of OPAT care.

6.5 Future Steps

Looking ahead, my future research will focus on strengthening the evidence base for the clinical applicability and benefits of OPAT within the NHS, while also building upon the work presented in this thesis. Over the next two to four years, I intend to concentrate on the following key areas:

6.5.1 Implementing a Risk Prediction Model for Readmission in OPAT Patients

The validated risk prediction model (Figure 7, Chapter 3) outlined in Paper 5 has the potential to improve OPAT outcomes by identifying high-risk patients and predicting adverse events. Integrating this model into clinical practice may facilitate more personalised and structured care. My planned studies will focus on developing a scoring system to categorise OPAT patients into low-, moderate-, or high-risk groups based on rehospitalisation probability. This will involve prospective, multicentre validation and potential model recalibration through re-estimation of regression coefficients, incorporation of additional predictors (e.g., frailty score) and evaluation of performance across diverse OPAT centres—particularly those with broader case mixes than the original derivation and validation cohorts.

6.5.2 Safety and Feasibility of OPAT for Various Infection Syndromes

The UK National OPAT guidelines [8] recommend a broader approach to patient selection, considering not only infection parameters and social circumstances but also additional risk factors for treatment failure or complications. Planned studies will aim to identify predictors of poorer outcomes in patients with various infections, particularly spinal infections, diabetic foot infections, and bronchiectasis. Enhancing risk prediction in these groups may improve clinical outcomes and reduce healthcare costs.

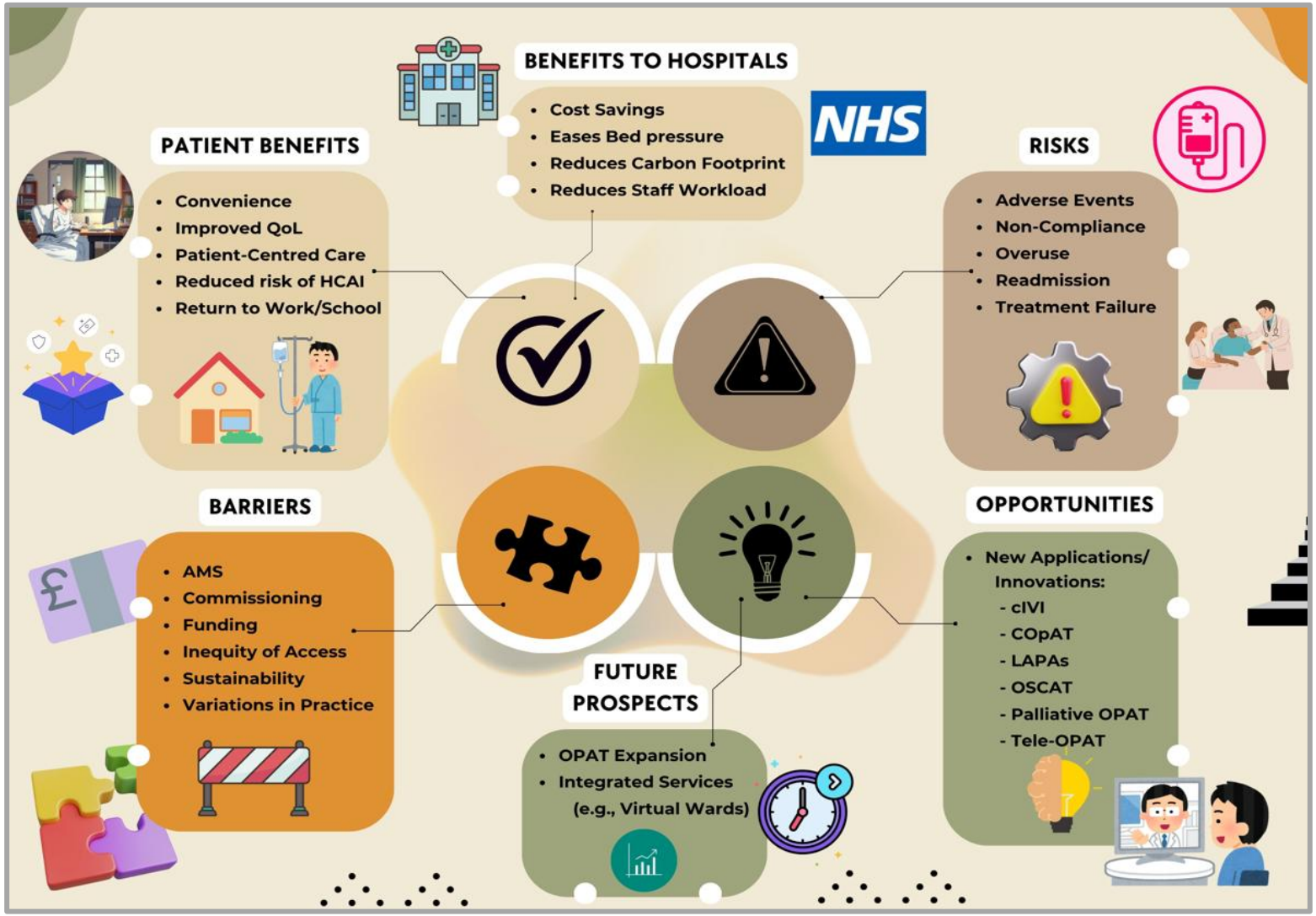
6.5.3 Patient Experiences and Satisfaction with Different Models of OPAT Care

As OPAT services continue to evolve, it is essential to understand how different models of care affect patient outcomes, engagement, and satisfaction. Using a mixed-methods approach, I plan to conduct quantitative surveys and qualitative in-depth interviews with patients receiving care through various delivery models (e.g., self-administration via elastomeric devices). The aim is to explore patient-centred outcomes, including perceptions of accessibility, convenience, involvement in treatment monitoring, and overall satisfaction. I will also investigate potential disparities in patient experiences and elucidate key determinants of positive outcomes. I anticipate that the findings will provide valuable insights into the strengths and limitations of current OPAT models, inform service improvements, and support the development of more responsive, equitable, and patient-focused care pathways within the NHS.

6.6 Concluding Statements

I am convinced that the development of OPAT in the UK has been a notable success for the NHS. The ten selected peer-reviewed papers—based on research that I designed, led and co-authored—constitute significant contributions to the field and enrich the broader OPAT literature. Collectively, this body of work demonstrates that OPAT is a safe, clinically effective, and cost-efficient use of NHS resources (Figure 8). Although complications can occur, its overall safety profile supports continued use in appropriately selected patients, provided that robust systems are in place to mitigate associated risks. While the NHS is often characterised as 'broken' amidst ongoing reform, I anticipate that OPAT will play an increasingly significant role in healthcare provision. However, its full potential is hindered by inconsistent implementation and substantial geographical variation in service delivery. To maximise its benefits, a cohesive and coordinated national approach is required—one that includes the adoption of innovative treatment methods, expansion of OPAT applications, a standardised funding model, and scaling up services at a national level. Future directions should focus on novel models of care and address inequities in access, in order to support evidence-based service expansion and ensure healthcare sustainability. Ultimately, OPAT in the UK should transition from a discretionary 'nice-to-have' service to a mandated 'must-have' modality of care for managing infections where there is a clear clinical need.

Figure 8. Overview of Benefits, Risks, Barriers, and Prospects of OPAT



AMS, antimicrobial stewardship; cIVI, continuous intravenous infusion; COpAT, complex outpatient antimicrobial therapy; HCAI, healthcare associated infections; LAPAs, long-acting parenteral antimicrobials; OPAT, outpatient parenteral antimicrobial therapy; OSCAT, outpatient subcutaneous antimicrobial therapy; QoL, quality of life; Tele-OPAT, telemedicine in OPAT

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APPENDIX

Appendix 1: Supplementary Tables

Supplementary Table 1. Eron Classification of Cellulitis.

Class	Patient Description
Class I	patients have no signs of systemic toxicity, have no uncontrolled co-morbidities and can usually be managed with oral antimicrobials on an outpatient basis.
Class II	patients are either systemically ill or systemically well but with a co-morbidity such as peripheral vascular disease, chronic venous insufficiency or morbid obesity which may complicate or delay resolution of their infection.
Class III	patients may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or may have unstable co-morbidities that may interfere with a response to therapy or have a limb threatening infection due to vascular compromise.
Class IV	patients have sepsis syndrome or severe life-threatening infection such as necrotising fasciitis.

Supplementary Table 2. Updated UK Good Practice Recommendations for Treatment Aims and OPAT Service Outcomes [8].

Treatment aim	
Cure	To complete an agreed OPAT duration of therapy on either intravenous and/or complicated oral antimicrobials[a] with no requirement for long-term antimicrobial therapy
Improvement	To complete an agreed OPAT duration of therapy on either intravenous and/or complicated oral antimicrobials (a) as part of an agreed surgical infection management plan with further surgery planned or (b) where there is a requirement for subsequent long-term or an extended course of oral suppressive antimicrobial therapy, or (c) where potentially infective prosthetic material is still *in situ.*
Palliation	To undertake a course of OPAT on either intravenous and/or complicated oral antimicrobials where there are agreed ceilings of care due to comorbidities, with death being the likely outcome.
OPAT outcome	
treatment aim attained—uncomplicated	Completed OPAT therapy as per treatment aim with: • no unplanned changes in antimicrobial agent. • no adverse events. • no planned or unplanned readmission related to the current OPAT episode. • no readmission of ≥ 24 h for unrelated event (i.e. day case/overnight stay for another medical problem allowed).
treatment aim attained—complicated	Completed OPAT therapy as per treatment aim but with one or more of the following: • unplanned changes in antimicrobial agent. • any adverse event including readmission for < 24 h related to the current OPAT episode.
treatment aim not attained	• failure to complete planned OPAT therapy for any reason other than readmission due to unrelated event. • worsening of infection requiring readmission. • readmission for ≥ 24 h for any cause related to OPAT, including adverse events.
indeterminate	Readmission for ≥ 24 h due to unrelated event
death	Death due to any cause, except palliation.

OPAT, outpatient parenteral antimicrobial therapy
[a] Complicated oral antimicrobials refers to oral regimens that require specific monitoring or are associated with particular risk of toxicity

Appendix 2: Published Papers

Paper 1

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

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

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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 administered between January 2006 and January 2016 were retrieved from a prospectively maintained electronic database. This study compared the real costs of the OPAT service with estimated costs of conventional inpatient care for these patient episodes, and analysed patient feedback questionnaires that were administered randomly 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 49,854. A successful outcome (cure or improvement) was found in 3357 (88%) episodes. Re-admission 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 for an infectious diseases unit, national average costs, other departments (non-infectious diseases unit), and the minimum national average costs for each diagnostic category, respectively. 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.

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1. Introduction

Intravenous (IV) antimicrobials are administered increasingly 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 IV antibiotics was first described in the USA 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 it is now becoming widespread as the benefits to patients and local healthcare systems are being recognized [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 2 years of this service [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 multi-disciplinary 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

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specialist nurse, either directly or by telephone. Patients are enrolled into the service if they meet a number of predefined criteria: age >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 the patient's home; and administration by a district nurse in the patient's home. 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 plans are reviewed weekly at a multi-disciplinary virtual ward round. The ward round is attended by a microbiologist, a pharmacist, and the OPAT nurses and physicians. Anonymous feedback questionnaires are sent to patients periodically 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 IV access, clinical outcome, complications and mode of transportation. Using the database, all patient episodes for 10 years from January 2006 were reviewed retrospectively. Case notes were reviewed where necessary. In addition, this study analysed the patient feedback questionnaires that were administered at random between January 2014 and January 2015.

2.3. Economic evaluation

A cost–consequence analysis was performed; in this, 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. This enables decision makers to form their own opinions regarding the relevance and relative cost-effectiveness of the alternative outcomes. This approach was chosen because there was no single outcome measure capable of capturing all the consequences of the OPAT service.

The total costs of the OPAT service were compared with 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 re-admissions 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 2011–2012 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, it was 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. An appropriate healthcare resource group (HRG4) code was identified for each diagnosis (Table 1), and the associated 2011–2012 unit cost was obtained from the NHS resource costs. The Sheffield Teaching Hospital's (STH's) Directorate of Communicable Diseases average costs per day, and the lowest unit cost for each diagnosis across all other STH departments, were used for the unit costs. The average costs per day for infectious diseases units are often higher than the costs in other

Table 1
Number of patient episodes, patient-days in outpatient parenteral antibiotic therapy (OPAT) (bed-days saved) and estimated costs of inpatient care for patients receiving OPAT.

Diagnostic category	HRG4 codes	n (%) of patient episodes	n (%) of bed-days saved	STH ID unit cost (£)	Minimum STH cost (£)	National cost (£)	Minimum national cost (£)
Bacteraemia	WA09Y, WA03Y, FZ36C	94 (2.5)	1210 (2.4)	703,559	316,391	274,967	271,656
Bone and joint infections (spinal infections)	HD25C, HD21C	180 (4.7)	7302 (14.6)	4,968,813	3,693,715	1,741,649	1,707,738
Bone and joint infections (others)	HD31C	171 (4.5)	6632 (13.3)	1,610,794	1,403,306	1,443,507	1,427,028
Cardiovascular system infections	EB01Z, EB02Z, QZ20Z	160 (4.2)	3759 (7.5)	758,933	375,698	937,679	875,636
Central nervous system infections	AA22B, WA07Z	364 (9.5)	3233 (6.5)	3,163,005	257,282	869,873	568,123
ENT infections	CZ22Y, CZ21Y, WA09Y	40 (1.0)	1646 (3.3)	1,240,109	423,582	395,149	369,541
Intra-abdominal infections (hepatobiliary)	GC15D, GC16D	32 (0.8)	904 (1.8)	774,597	166,119	205,127	205,065
Intra-abdominal infections (other)	FZ45B, FZ47B, FZ36C, LA04F, LB06F, WA06Y	27 (0.7)	507 (1.0)	400,466	107,319	129,291	116,832
Invasive fungal infections	WA09Y	24 (0.6)	303 (0.6)	142,565	55,325	68,026	68,026
Leishmaniasis	WA07Z	20 (0.5)	250 (0.5)	117,628	59,783	43,932	43,932
Lyme disease	CZ21Y	23 (0.6)	595 (1.2)	457,948	161,679	142,955	142,955
Respiratory tract infections	DZ10C, DZ11C	151 (4.0)	2188 (4.4)	1,233,793	528,539	509,697	436,959
Skin and soft tissue infections	HD21C, JD02C, JD04C, WA09Y	2183 (57.3)	15,973 (32.0)	13,300,000	2,505,355	4,187,729	3,586,003
Tuberculosis (including MDR-TB)	DZ14B	22 (0.6)	1499 (3.0)	922,440	701,157	391,232	391,232
Urogenital infections	LB37B, LB28B, LB35B, MB04B	295 (7.7)	3530 (7.1)	2,615,305	1,121,921	839,392	767,137
Unrecorded	WA09Y	2 (0.1)	20 (0.1)	9410	3652	4490	4490
Others[a]	WA09Y, FZ47B, CZ21Y, CZ22Y, WA07Z, WA08Z, DZ29B, SA12F, JD03C	24 (0.6)	303 (0.6)	296,628	80,258	79,693	63,426
Total		3812	49,854	32,715,992	11,961,081	12,264,388	11,045,779

ENT, ear nose and throat; HRG, healthcare resource group; ID, infectious diseases; MDR-TB, multi-drug-resistant tuberculosis; STH, Sheffield Teaching Hospital.
[a] Others include dental infections ($n = 6$), malaria ($n = 4$), ophthalmic infections ($n = 4$), zoster infections ($n = 3$), Whipple's disease ($n = 2$), sarcoidosis ($n = 2$), thrombocytopenia ($n = 2$) and intravenous prophylaxis ($n = 1$).

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, the same method to calculate the costs of conventional inpatient care was used with national average non-elective inpatient costs per day. The lowest national average non-elective cost per day in each diagnostic category was applied 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

Over 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 49,854 (range <1 to 533 days; mean 13.1 days). The longest course of treatment was administered to a patient with multi-drug-resistant tuberculosis requiring parenteral capreomycin and meropenem. The number of episodes per year increased from 158 in 2006–2007 to 607 in 2015–2016. The total number of OPAT patient-days also increased gradually over the 10-year period (Fig. 1).

A wide range of infections was managed (Table 1). SSTIs accounted for the largest number of bed-days saved (15,973 of 49,854; 32%) and patient episodes (2183 of 3812; 57%; median 5 days; range 0–89 days). The longest antibiotic course for an 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 (13,934 of 49,854; 28%). Over the 10-year period, the proportion of episodes due to non-SSTIs rose moderately from 41% to 46% (Fig. 2).

Ceftriaxone was the most frequently prescribed parenteral antimicrobial agent (65%; 2565 of 3936). Table 2 shows the 10 most common agents used. SSTI was the recorded indication for ceftriaxone in 78% (1989 of 2565) of cases. In addition to parenteral antimicrobials, oral agents were used concurrently with parenteral agents in 246 patients.

Vascular access data were recorded for 3581 episodes (Table 2). Peripheral IV catheters (butterfly needles and peripheral venous cannula) accounted for the majority of vascular devices (2579 of 3581; 72%). The intramuscular (IM) route was used in 14 patients (mainly 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; 14,844 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 of 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 recorded infrequently because most patients continued on oral antimicrobial therapy after discharge from the OPAT service. Re-admission was recorded in 265 (7%) episodes. The main indication for re-admission was progression or non-response of infection. SSTI patients who had a poor response or clinical deterioration accounted for the majority of the re-admissions (55 of 265; 21%). Two patients were re-admitted 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

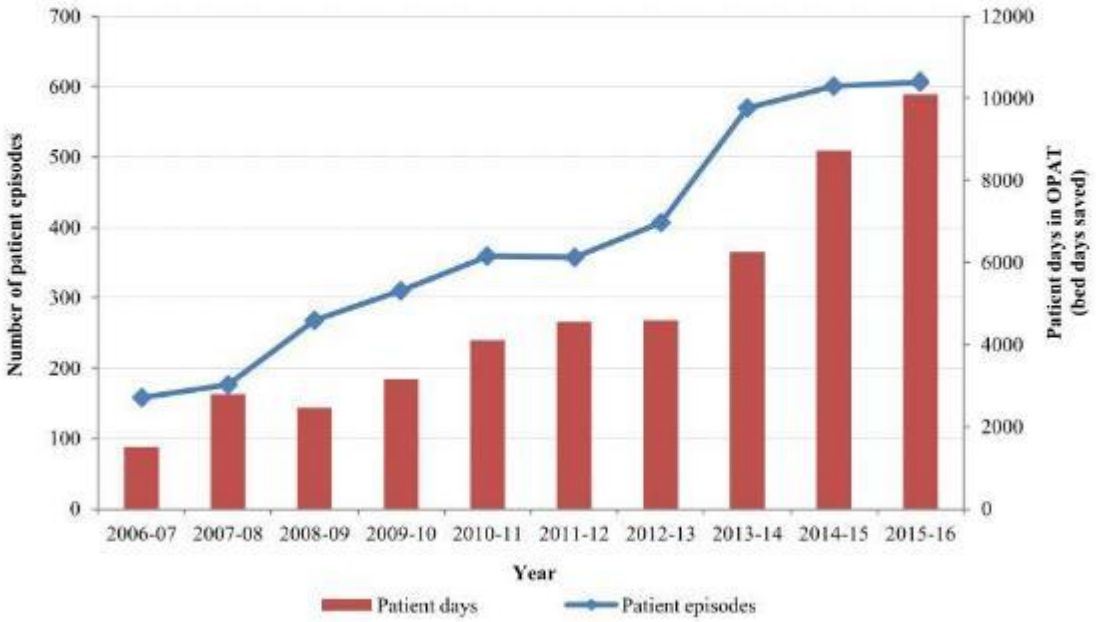

Fig. 1. Number of outpatient parenteral antibiotic therapy (OPAT) patient episodes and patient-days by year: 2006–2016.

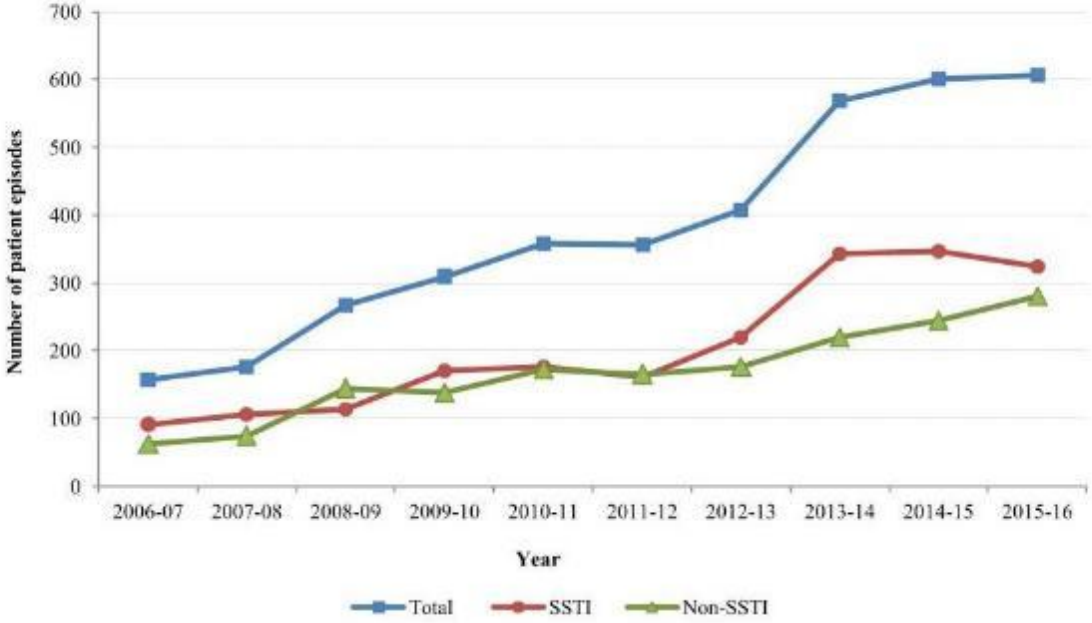

Fig. 2. Trends in number of outpatient parenteral antibiotic therapy (OPAT) patient episodes by diagnostic category: 2006–2016. SSTI, skin and soft tissue infection.

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).

Table 2
Characteristics of outpatient parenteral antimicrobial therapy (OPAT).

	n (%)
Model of antimicrobial administration (n = 3812)	
Daily attendance at OPAT unit	2948 (77.3)
Self/carer administered at home	458 (12.0)
Community nurses administered at home	305 (8.0)
Not recorded	101 (2.6)
Mode of transportation to OPAT (n = 3812)	
Taxi[a]	2054 (53.9)
Self	1592 (41.8)
Ambulance[b]	88 (2.3)
Not recorded	78 (2.0)
Antimicrobial agent (n = 3936)[c]	
Ceftriaxone	2565 (65.2)
Ertapenem	328 (8.3)
Teicoplanin	228 (5.8)
Flucloxacillin	202 (5.1)
Ceftazidime	150 (3.8)
Amphotericin B	67 (1.7)
Daptomycin	64 (1.6)
Meropenem	55 (1.4)
Piperacillin/tazobactam	44 (1.1)
Vancomycin	26 (0.7)
Other agents	205 (5.2)
Type of vascular access device (n = 3581)[d]	
Butterfly needle	2188 (61.1)
Peripheral intravenous cannula–Venflon	391 (10.9)
Peripherally-inserted central catheter	897 (25.0)
Hickman	98 (2.7)
Portacath	7 (0.2)

[a] Free taxi provided by the OPAT unit.
[b] Includes both National Health Service and private ambulance services.
[c] Some patient episodes involved more than one parenteral antimicrobial agent. Therefore, the total number of agents is greater than the total number of patient episodes.
[d] Some patients had no vascular device (e.g. intramuscular route).

3.3. Patient satisfaction survey

Of 279 questionnaires sent out to patients (including those who failed OPAT therapy) between January 2014 and January 2015, 147 were returned (53%). One hundred and forty-six respondents (99%) rated the service as very good or excellent, 143 (97%) stated that the treatment received met their expectations, and 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 2011–2012 prices, the cost was £4,729,071.

Table 3
Clinical outcomes and reasons for re-admission in outpatient parenteral antimicrobial therapy (OPAT) episodes.

Variable	n (%) of patient episodes
Outcome (n = 3812)	
Improved	3327 (87.3)
Cure	30 (0.8)
Re-admitted	265 (7.0)
No change	27 (0.7)
Change of plan	34 (0.9)
Death	2 (0.1)
Not recorded	127 (3.3)
Reasons for re-admission (n = 265)	
Elective admission	17 (6.4)
Inappropriate referral	17 (6.4)
Clinical deterioration/no improvement	115 (43.4)
New event, not related to infection	73 (27.5)
Adverse drug reaction	24 (9.1)
Line-related complications	3 (1.1)
CDAD	2 (0.8)
Logistics/transport	4 (1.5)
Not recorded	10 (3.8)

CDAD, *Clostridium difficile*-associated diarrhoea.

Table 4
Outpatient parenteral antimicrobial therapy (OPAT) patient satisfaction survey: 2014–2015 (n = 147).

Variable	n (%) of responses
Model of antimicrobial delivery	
Daily attendance at OPAT unit	117 (79.6)
Self/carer administration	13 (8.8)
Community nurse	14 (9.5)
Not completed	3 (2.0)
Use the help/advice line	
Yes	10 (6.8)
No	130 (88.4)
Not completed	7 (4.8)
Expectations met	
Yes	143 (97.3)
No	1 (0.7)
Not completed	3 (2.0)
Would choose the service again	
Yes	144 (98.0)
No	1 (0.7)
Not completed	2 (1.3)
Overall rating of the OPAT service	
Poor	0 (0)
Good	0 (0)
Very good	16 (10.9)
Excellent	130 (88.4)
Not completed	1 (0.7)

Set-up costs of the service mainly consisted 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 re-admission and set-up costs) based on the reference cost profile for the infectious diseases outpatient department.

This study identified four re-admissions due to complications that 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 re-admitted to stabilize her fracture and for social reasons. The second patient cut off the end of her PICC line while self-administering antibiotics. She was re-admitted for line replacement and to complete her treatment. The third and fourth patients, who self-administered antimicrobials, were re-admitted with line-related infections. The other 261 re-admissions were excluded from the cost analysis as they were considered 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 who had already been admitted. The estimated cost of these four re-admissions was £95,436 based on 2011–2012 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 2011–2012 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 the 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 (Table 1).

4. Discussion

In the UK, OPAT has evolved relatively slowly, but it is now becoming more common as the benefits to patients and local healthcare systems are being recognized [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 to be manageable in an outpatient setting. It also expanded to the emergency admission area to prevent unnecessary hospital admissions, taking some pressure off emergency care.

The high success rate, high levels of patient satisfaction, and low complication and re-admission rates reflect other UK-based studies [17–20]. Use of once-daily broad-spectrum antimicrobials (e.g. 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

Table 5
Direct costs of the outpatient parenteral antimicrobial therapy (OPAT) service from January 2006 to January 2016.

Year Jan/Feb–Jan[a]	Total staff costs (£)	Consumables and equipment (£)	Drugs (£)	Overhead and support[b] (£)	Total non-staff costs (£)	Total (£)	Total at 2011/2012 prices[c] (£)
Set-up	21,745	–	–	–	1092	22,837	19,474
2006–2007	68,236	15,247	7154	40,605	63,006	131,242	116,051
2007–2008	178,785	11,422	37,950	102,214	151,586	330,371	300,550
2008–2009	134,157	3518	10,233	66,263	80,014	214,171	202,420
2009–2010	192,834	41,925	28,541	117,958	188,424	381,258	362,499
2010–2011	326,767	64,439	5389	177,675	247,503	574,270	562,479
2011–2012	282,921	68,701	10,787	162,359	241,847	524,768	524,768
2012–2013	266,182	71,046	9617	155,387	236,050	502,232	510,765
2013–2014	318,402	72,443	12,121	180,529	265,093	583,495	600,019
2014–2015	360,786	71,427	13,447	199,656	284,530	645,316	669,529
2015–2016	449,069	99,575	20,840	255,129	375,544	824,613	860,516
Total	2,599,884	519,743	156,079	1,457,775	2,134,689	4,734,573	4,729,071

[a] Year 2006–2007 represents costs from OPAT service commencement (20th January 2006) to end of January 2007. All other years represent costs from start of February to end of January.
[b] Overhead and support costs at 44.8% of total cost of the service excluding the re-admission and set-up costs (based on cost profile for the infectious diseases outpatient department).
[c] Costs adjusted for inflation/deflation using the hospital and community health services pay and price index.

infections, two patients were re-admitted because of CDAD. It is difficult to determine the relative contribution of OPAT as both patients were hospitalized and received antimicrobial therapy prior to referral to OPAT. Aberdein et al performed a retrospective review of 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 six cases of CDAD per 100,000 OPAT-days. Generally, the rates of healthcare-associated infections in OPAT are lower than in hospitalized patients [22]. However, the impact of OPAT on the emergence of antibiotic-resistant organisms has been poorly studied and requires urgent attention.

This study shows that a wide variety of conditions in a complex group of patients are 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 (e.g. amphotericin B, caspofungin and anidulafungin) were used to treat invasive fungal diseases with successful outcomes. OPAT has enabled older agents to be used in novel ways [6]. IV fosfomycin, temocillin and aztreonam were used successfully in this 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 reduces costs further 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 manage vascular access problems urgently. 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 infusion 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 minimize potential risks and optimize 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, this study found that the service has delivered substantial cost savings over its 10 years of operation. It was assumed that the number of patient-days in OPAT is the same as the number of days that patients would have been hospitalized. This assumption seems reasonable as both the inpatient infectious diseases and OPAT services are managed by the same group of infectious diseases specialists. The duration of therapy for patients is often predefined and would have been the same irrespective of whether they were treated as inpatients or in OPAT. Using the costs of managing patients in the STH infectious diseases unit, the OPAT service was found to cost 15% of the equivalent inpatient cost. The authors also estimated the costs of managing the patients in other STH departments, 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 that OPAT cost 40% of inpatient care. National average costs were included to make the findings applicable to other acute hospitals in the UK. Average daily costs of infectious diseases units are often higher than national average costs and costs in other units due to the specialist nature of the service and the requirement for isolation facilities. Using the national average costs, OPAT was found 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 the relative costs in the present study 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, the present study assigned an appropriate HRG4 code for each diagnosis rather than the diagnostic categories to give 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, this study showed that OPAT is associated with significant cost savings. Cost savings could be maximized if OPAT patients are monitored closely to prevent complications and hospital re-admissions. It is worth mentioning that OPAT has many indirect benefits and cost savings for patients and healthcare systems (such as reduction in the cost of nosocomial infections, patient satisfaction, increased productivity and quality of life) [4,15] that were not considered in this study as this would require complex mathematical modelling beyond the scope of the study. With the growing interest in OPAT in the UK, novel studies such as the Community Intravenous Antibiotic Study could provide more insight into the cost-effectiveness and patient preference for the different models of OPAT [27]. It will be of interest to examine the causes of, and risk factors for, re-admissions in this large cohort in more detail. 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, organizations 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 IV 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 found that OPAT is suitable for a wide range of infections in an increasingly complex patient group, provided that measures are in place to minimize clinical risks.

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Paper 2

Evaluation of health-related quality of life in patients receiving outpatient parenteral antimicrobial therapy (OPAT) in a UK setting

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ORIGINAL RESEARCH

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Evaluation of health-related quality of life in patients receiving outpatient parenteral antimicrobial therapy (OPAT) in a UK setting

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ABSTRACT

Background: Studies assessing the benefits of outpatient parenteral antimicrobial therapy (OPAT) have paid less attention to patient-centered factors such as patients' experiences and their health-related quality of life (HRQoL).

Research design and methods: Prospective before-and-after quasi-experimental study enrolled adult patients receiving OPAT at a tertiary hospital in Derbyshire, UK, between October 2022 and October 2023. Consenting patients completed paired EQ-5D-3 L questionnaires before OPAT initiation and upon completion of therapy or 30 days after its commencement (whichever occurred first). Changes and predictors of change in HRQoL indicators and associations with clinical outcomes (treatment failure, adverse events, and 30-day unplanned readmission) were examined.

Results: Health state index and visual analogue scale (EQ VAS) scores of 162 enrolled patients at baseline were significantly lower than the UK population averages, but the patients experienced significant improvements in both scores and in four EQ-5D dimensions (mobility, self-care, usual activities, and pain/discomfort). Baseline health index and EQ VAS scores were significant independent predictors of positive changes in HRQoL scores.

Conclusions: OPAT is associated with improved patient-reported quality of life and facilitates early return to work or school. Nevertheless, it is crucial to closely monitor patients with a lower baseline quality of life to optimize their overall OPAT experience.

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EQ-5D-3L; OPAT; outpatient parenteral antimicrobial therapy; patient-centered outcomes research; quality of life

1. Introduction

Intravenous (IV) antimicrobial agents are increasingly administered in home and outpatient settings to treat a wide range of infections [1–3]. Outpatient parenteral antimicrobial therapy (OPAT) has proven to be a safe and effective alternative to inpatient care, offering substantial benefits to both patients and healthcare systems [4,5]. Published studies evaluating the benefits of OPAT have primarily focused on clinical outcomes and cost savings, with less attention given to patient-centered factors, including patients' experiences and perspectives on OPAT, as well as their overall quality of life [6].

Health-related quality of life (HRQoL) is a crucial aspect of patient-centered care; it encompasses various dimensions related to the physical, mental, emotional, and social well-being of individuals [7]. It also takes into account how one's states of heath impact their quality of life. Infections can severely impact HRQoL [8–10]. Thus, a comprehensive understanding of the HRQoL in patients receiving OPAT can aid better patient selection for OPAT and enhance the overall patient experience [11]. Additionally, HRQoL measures can be used to calculate quality-affected life years (QALYs) for cost-effectiveness studies of OPAT, where one QALY is equivalent to one year of life in perfect health [12].

In our present study, we examine the HRQoL in patients who received OPAT care at a large tertiary referral teaching hospital in Derbyshire, England, UK. The primary objective of the study was to assess changes in self-reported HRQoL and determine which patient groups experienced the most significant improvements in terms of HRQoL. A secondary objective was to examine HRQoL indicators at baseline as prognostic factors for subsequent clinical outcomes during OPAT treatment. To the best of our knowledge, there are no published studies evaluating the HRQoL of adult patients treated via OPAT within the UK National Health Service.

2. Patients and methods

2.1. Study design and recruitment

We conducted a one-group before-and-after quasi-experimental study involving adult patients referred to the OPAT service at University Hospitals of Derby and Burton (UHDB) in Derbyshire, England, UK, between October 2022 and October 2023. The OPAT service has been previously described [13,14]. It is managed by a multidisciplinary team comprising infectious diseases specialists, specialist nurses, clinical antimicrobial pharmacists, and community nurses.

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The choice of antimicrobial therapy is limited to agents that can be administered once daily or less frequently for dosing convenience. Antimicrobials were administered through three distinct pathways: delivery in the patient's home by a visiting nurse, daily attendance at the OPAT clinic, and self/carer administration in the patient's home (after appropriate training). The OPAT service utilizes electronic databases to prospectively record patient demographics, clinical diagnoses, the method and duration of OPAT administration, clinical outcomes, and any associated complications.

Participants were eligible for the study if they were older than 18 years of age, capable of giving informed consent, and planned to receive a course of parenteral antimicrobial therapy lasting more than three days. We excluded patients from the study if they had previously received OPAT care.

2.2. HRQoL instrument

The three-level version of EQ-5D (EQ-5D-3 L) questionnaire was used to assess participants' HRQoL (detailed in Supplementary Figure S1). Developed by the EuroQol Group, EQ-5D is a standardized and validated instrument for measuring health status, offering a generic assessment of health for clinical and economic appraisal [15]. The EQ-5D is the preferred UK National Institute for Health and Care Excellence (NICE) measure of HRQoL in adults [16], and the most extensively evaluated HRQoL instrument internationally [17]. EQ-5D-3 L consists of two components: (1) a descriptive system that assesses health in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels of response (no problems, some problems, extreme problems) denoted as 1 to 3; and (2) a visual analogue scale (EQ VAS), that records patients' overall assessment of their health on a scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). The descriptive system element of the EQ-5D questionnaire generates a 5-digit health state profile that represents the level of reported problems on each of the five dimensions of health (e.g. 12213). Using country-specific value set [15,18], each participant's health profile can be converted into a singular summary number, known as an index score, which may range from less than 0 (where 0 signifies a health state equivalent to death; negative values are considered worse than death) to 1 (perfect health) [15].

2.3. Sample size determination

A minimally important difference (MID) of 0.074 units was defined a priori as a clinically relevant change of the EQ-5D index score [19]. With an expected standard deviation (SD) of 0.29 [19], an MID of 0.074 corresponds to an effect size of 0.25, which is regarded as a small to medium effect. We calculated that approximately 160 patients were required to detect a change of 0.074 units in mean EQ-5D index scores from baseline to the final assessment, with power of 90% and a 5% significance level in a paired *t*-test. This sample size allows for reliable estimation of 16 predictors in a multiple linear regression model, based on the "rule-of-thumb" of 10 subjects per variable [20].

2.4. Data collection

Patient sociodemographics, comorbidities, treatment indications, antimicrobial regimens, mode of OPAT delivery, duration of OPAT care, OPAT outcomes, complications experienced, and hospital readmission data were extracted from the OPAT databases and hospital electronic health records. Age (in years) and Charlson Comorbidity Index (CCI) scores [21] were determined at the commencement of OPAT.

Before initiating OPAT (at baseline), consenting patients were asked to complete an EQ-5D-3 L questionnaire. A second (follow-up) questionnaire was administered at the conclusion of OPAT treatment or 30 days after commencing OPAT (whichever occurred first). For the purposes of comparison, UK EQ-5D population norms for self-rated health status were obtained from published studies [22,23]. Patients who were employed or in education before their illness were asked, at the follow-up assessment, to self-report whether they had returned to work or school during OPAT.

2.5. Outcomes and definitions

Clinical outcomes (cure, improvement, or failure) were determined at the conclusion of OPAT treatment using the definitions provided in the BSAC National Outcomes Registry System (see Supplementary Table S1) [24]. Adverse drug reactions (i.e. events possibly related to administered medications) included diarrhea, rash, blood dyscrasia, renal and hepatic dysfunction. Vascular access-related complications encompassed infection, line migration, occlusion, thrombosis, and allergic reactions to dressing. Thirty-day unplanned hospitalization was defined as an unplanned inpatient admission to an acute care hospital for any reason during or within 30 days of the completion of OPAT treatment.

2.6. Data analysis

Descriptive statistics were used to summarize sociodemographic, clinical, and OPAT outcome data. To present the EQ-5D-3 L descriptive system, we calculated the numbers and percentages of patients reporting each level of problems on each of the dimensions at both the baseline and final assessments. Additionally, we determined the means (with SDs) of EQ VAS and EQ-5D-3 L index scores at these two time points. The observed baseline mean scores were compared with published mean scores for the UK general population using one-sample *t*-tests. The mean health state index and EQ VAS scores for the UK general population have previously been reported as 0.86 and 82.5, respectively [22,23].

To assess the magnitude and statistical significance of changes between the two time points, we calculated 95% confidence intervals (CIs) for the differences in the proportion of patients reporting improvements in each dimension and performed McNemar's test. For the summary EQ-5D-3 L index and EQ VAS scores, we calculated 95% CIs for mean differences and paired *t*-test statistics. To aid in the interpretation of the estimated changes, we computed standardized effect sizes using Cohen's g and d statistics for proportion and mean differences, respectively [25]. Following Cohen's benchmarks,

we identified effect sizes as negligible ($g < 0.05$, $d < 0.2$), small ($0.05 \leq g < 0.15$, $0.2 \leq d < 0.5$), medium ($0.15 \leq g < 0.25$, $0.5 \leq d < 0.8$), or large ($g \geq 0.25$, $d \geq 0.8$) [25].

Changes in EQ-5D-3 L were also analyzed using the Paretian Classification of Health Change (PCHC) approach [26]. Patients were classified as 'improved' if they demonstrated improvement in at least one dimension without worsening in any other dimension of the EQ-5D-3 L system; 'worsened' if they worsened on at least one dimension and did not show improvement in any other dimension; and 'no change' if they exhibited the same response in each dimension at baseline and the final assessment. Patients who improved in one or more dimensions and worsened in others were classified as 'mixed change.' PCHC summarizes overall changes in patients' self-reported health without relying on preference weights (utility scores) from the general public, thereby avoiding potential inference bias [27]. We estimated the proportion of patients in each PCHC class by calculating 95% CIs using Wilson's score method.

Analysis of covariance with ordinary least squares estimation was employed to identify groups of patients that derived heterogeneous effects from OPAT treatment in terms of improvements in HRQoL. EQ VAS and EQ-5D-3 L health index scores at the follow up assessment were examined as response variables in two separate multiple linear regression models. A set of a priori selected baseline covariates were examined, including patient characteristics (age, sex, CCI, and clinical frailty score) and therapy-related variables (combination antimicrobial therapy, indication for OPAT, mode of delivery, and type of vascular access device). In these models, we controlled for imbalances in baseline EQ VAS and EQ-5D-3 L scores to estimate the direct causal effects of baseline exposures [28]. Covariate-specific effect sizes were assessed using Cohen's f^2 statistic and were interpreted as small ($f^2 \geq 0.02$), medium ($f^2 \geq 0.15$), or large ($f^2 \geq 0.35$) effects, respectively. Multicollinearity of predictor variables was ruled out by examining variance inflation factors (Supplementary Table S2). Graphical inspection of residuals indicated deviations from normality and homoscedasticity (Supplementary Figures S2 and S3). Therefore, bootstrapping was performed (1,000 replications) to estimate the standard errors and *P*-values. CIs were constructed using the bias-corrected and accelerated bootstrap method.

Multivariable Poisson regression with a log-link function and robust variance estimation was performed to estimate relative risks (RR) with 95% CIs [29]. This analysis aimed to quantify the associations between self-reported HRQoL indices at baseline (EQ-5D-3 L dimensions, full health state, EQ-5D-3 L index score, and EQ VAS score) and subsequent patient outcomes (complications during OPAT, treatment failure, and 30-day unplanned hospitalizations). The models were adjusted for sex, age, and CCI. The log-linearity of continuous variables was examined using restricted cubic splines (Supplementary Figures S4 and S5).

No missing values were observed for any of the study variables. Two-sided *p*-values were reported for all analyses, and statistical significance was considered at $p < 0.05$. All analyses were performed using Stata version 18 (Stata Corporation, College Station, Texas, U.S.A.).

2.7. Ethical approval

The study was approved by the North West – Greater Manchester South (UK) Research Ethics Committee (REC Reference number 22/NW/0299). The study also received organizational approval and support from the Research and Development department at the study institution. All patients agreed to participate in the study by signing an informed consent form.

3. Results

3.1. Baseline characteristics of the study cohort

A total of 162 eligible patients were enrolled in the study and completed the paired EQ-5D questionnaires. Figure 1 shows the flowchart of the study. Table 1 shows the participants' sociodemographic and clinical characteristics. At baseline, 8.0% (13/162) of the participants reported being in a state of perfect health (i.e. a health state index score of 1.0) while 2.5% (4/162) reported being in the best imaginable health (i.e. an EQ VAS score of 100). There was a significant moderate positive correlation between the baseline EQ-5D VAS and index scores ($r = 0.61$, $p < 0.001$) (Supplementary Figure S6). Compared to the UK population averages, the study patients had significantly lower baseline EQ-5D VAS scores (mean 57.9 *vs.* 82.5; $p < 0.001$) and EQ-5D index scores (mean 0.5 *vs.* 0.9; $p < 0.001$). Out of the 37 patients who self-reported being employed before their illness, 43.2% (16/37) were able to return to work while receiving OPAT. Additionally, two patients were students, both of whom were able to continue their education while on OPAT.

3.2. Change in HRQoL scores

The mean increase in the health state index score was 0.2 ($p < 0.001$). The respective Cohen's effect size value ($d = 0.51$) suggested a medium improvement in the mean EQ-5D-3 L index value (Table 2). There was also statistically significant but small gain in mean EQ-VAS score (difference of 7.5; $p < 0.001$; $d = 0.33$) (Table 2). Additionally, there were significant and large increases in the proportion of patients who reported being in perfect health (increase by 7.4%; $p = 0.008$; $g = 0.33$); who had no problems walking about (+10.5%; $p = 0.003$; $g = 0.27$); no problems with self-care (+15.4%; $p < 0.001$; $g = 0.28$); no problems performing daily activities (+19.2%; $p < 0.001$; $g = 0.34$); and no pain/discomfort (+19.2%; $p < 0.001$; $g = 0.28$) (Table 2; Supplementary Figure S7). However, there was no significant change in the proportion of patients with no anxiety/depression (increase of 4.9%; $p = 0.341$; $g = 0.07$). Using the PCHC principle [25], 18.5% (30/162) had no change, 51.9% (84/162) had improved health, 12.3% (20/162) had worse health, and 17.3% (28/162) had a 'mixed' change (Figure 2).

3.3. Predictors of change in HRQoL and association with clinical outcomes

Table 3 shows the results of linear regression analysis examining factors associated with changes in HRQoL scores. No heterogeneous changes in follow up HRQoL scores were detected in relation to patient age, sex, CCI, or treatment-related variables measured at baseline. In multivariable analysis, there was no

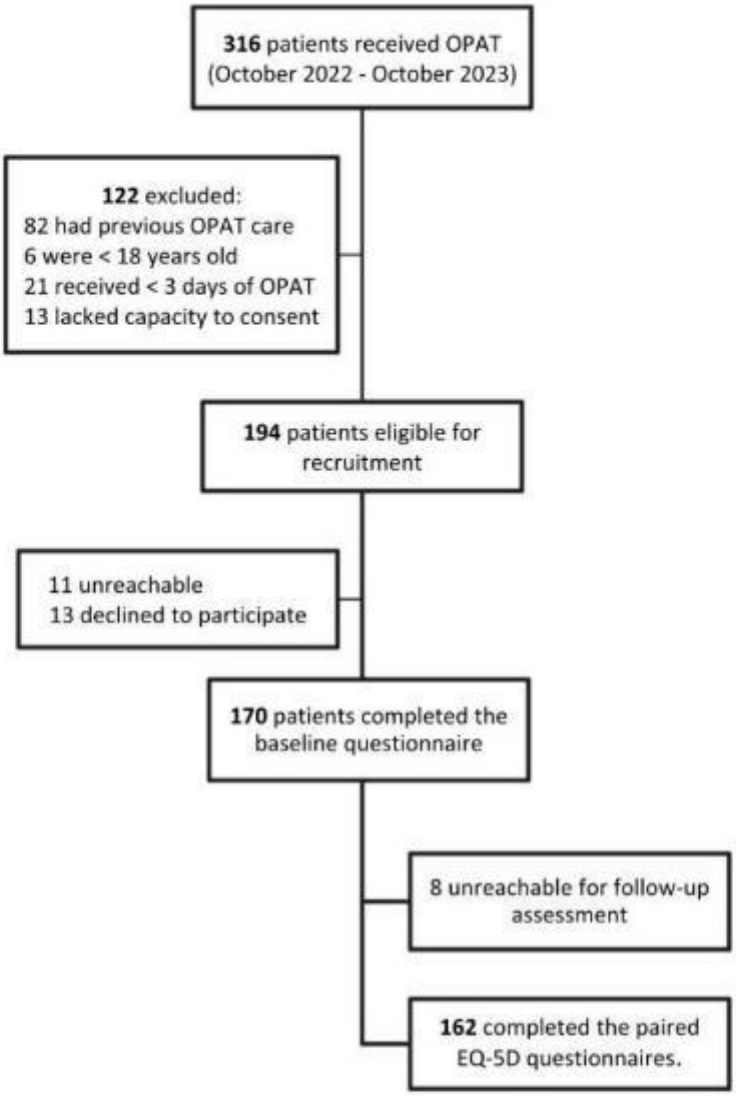

Figure 1. Screening and eligibility flow chart.

significant association between follow-up HRQoL scores and the baseline clinical frailty score analysis ($I^2 = 0.02$; $p = 0.07$). Only baseline EQ VAS (adjusted mean difference (aMD), 3.96 per 10 units increase; 95% CI, 2.09–5.72) and EQ-5D-3 L index (aMD, 0.04 per 0.1-unit increase; 95% CI, 0.03–0.06) scores were significant predictors of a positive change in follow up HRQoL scores.

The association between baseline HRQoL scores and clinical outcomes is presented in Table 4 (the respective univariate analysis is presented as Supplementary Table S3). Accounting for patients' age, CCI, and clinical frailty score in multivariable regression analysis, there were no statistically significant associations between baseline HRQoL scores and the risk of 30-day unplanned readmission, treatment failure, or adverse events.

4. Discussion

Internationally, very few studies have examined the quality of life in patients receiving OPAT. To our knowledge, this study represents the first comprehensive assessment of HRQoL in a UK population of OPAT patients. In this longitudinal pre-post study, we investigated the HRQoL of patients treated with OPAT at a tertiary hospital in the UK. We included patients who received more than three days of OPAT care, as we had previously observed clinical improvement after 48 hours of IV antimicrobial therapy in our settking. Patients with prior OPAT experience were excluded to avoid response bias in their expectations and, consequently, in self-reported HRQoL [30,31].

Similar to studies conducted in Canada by Goodfellow *et al.* and in the United States by Keller *et al.*, we found that OPAT patients have a lower quality of life compared to the general population [32,33]. The reduced HRQoL can be attributable not only to the need for OPAT but also to the presence of underlying comorbidities. It is well documented that HRQoL can be impaired in patients with infections, such as bacteremia [8], infective endocarditis [10], and osteomyelitis [34], which are commonly treated with OPAT. Consequently, OPAT patients should receive adequate support to enhance and optimize their HRQoL.

Table 1. Sociodemographic and clinical characteristics ($N = 162$).

Characteristic	n (%)
Age (years), median [IQR]	67 [54–75]
Male sex	98 (60.5)
Charlson comorbidity index score, median [IQR]	1 [0–3]
Clinical frailty score, median [IQR]	3 [3,4]
Marital status	
Married/Domestic partnership	119 (73.5)
Single	19 (11.7)
Widowed	12 (7.4)
Divorced/Separated	12 (7.4)
Employment status	
Retired	100 (61.7)
Employed	37 (22.8)
Unemployed	16 (9.9)
Homemaker	7 (4.3)
Student	2 (1.2)
Indication for OPAT	
Bone and joint infection (excluding spinal infection)	66 (40.7)
Respiratory infection	34 (21.0)
Endovascular infection	14 (8.6)
Malignant otitis externa	10 (6.2)
Urinary tract infection	10 (6.2)
Spinal infection	7 (4.3)
Skin and soft tissue infection	7 (4.3)
Other indications[a]	14 (8.6)
Mode of antimicrobial (OPAT) delivery	
Visiting nurse	97 (59.9)
Self/carer administration	58 (35.8)
Daily attendance	7 (4.3)
Duration of inpatient (pre-OPAT) stay (days)[b], median [IQR]	11 [6–17]
Duration of OPAT care (bed days saved), median [IQR]	12 [8–27]
Total bed days saved[c]	3337
Complications during OPAT	
Antimicrobial-related adverse events	13 (8.0)
Vascular access related adverse events	10 (6.2)
Antimicrobial and vascular related adverse events	1 (0.6)
Infection Outcomes	
Cure/Improved	135 (83.3)
Failure	27 (16.7)
30 days unplanned hospitalization[d]	37 (22.8)

Data are presented as n (%) for categorical variables and median [interquartile range] for continuous variables.
IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy.
[a]Other indications included bacteremia ($n = 1$), central nervous system infection ($n = 4$), intra-abdominal abscess ($n = 4$), and hepatobiliary infection ($n = 5$).
[b]15 patients had no preceding inpatient admission (admission avoidance pathway).
[c]Total duration of OPAT care for the cohort.
[d]Defined as unplanned inpatient admission for any reason during or within 30 days of OPAT discharge.

We observed a significant improvement in the EQ-VAS and health state index scores at follow-up compared to the baseline assessment. While the gains in the VAS and index scores were small and moderate, respectively, it is essential to note that these are weighted means designed to reflect the preferences of the general public rather than patients [26]. Additionally, we observed significant and large improvements in patients' mobility, self-care, their ability to perform daily activities, and a large reduction in pain or discomfort. Goodfellow *et al.* also documented marked improvements in various domains of self-perceived health among a cohort of OPAT patients four weeks after hospital discharge [32]. By promoting early hospital discharge and averting hospitalization, OPAT can effectively enhance patients' quality of life by enabling them to sustain their daily activities and social interactions, contributing to their overall well-being. Interestingly, we found only a small non-significant improvement in the proportion of patients experiencing no anxiety or depression. Although the exact reasons for this remain unclear, it is important to acknowledge that anxiety and depression are chronic conditions that may not be effectively addressed by antimicrobial therapy.

Forty-six percent of the participants in our cohort, who were employed or in education before their illness, managed to return to work or school while receiving OPAT. This finding is comparable to a similar study in Singapore by Wee *et al.*, who reported that half of OPAT patients returned to work while on treatment [35]. The ability of eligible patients to resume school or work and maintain their income while receiving OPAT may help reduce the financial strain that could result from prolonged absence from work. It can contribute to financial stability, job security, preserve educational progress, and prevent interruptions in career advancement and educational attainment.

Using the Short Form-36 [36] as a measure of HRQoL in a cohort of 82 OPAT patients, Goodfellow *et al.* [32] found that non-orthopedic infection and prolonged hospital stay were associated with a positive change in the physical component summary and mental component summary scores, respectively. Meanwhile, these summary scores at baseline were negative predictors of changes at follow up assessments. In our cohort, we observed that baseline HRQoL scores were the sole predictors of a positive change in HRQoL scores – in other words, the higher the baseline HRQoL scores, the higher the follow-up scores. We noted some evidence for a weak association between baseline clinical frailty score and a subsequent negative change in HRQoL scores ($p = 0.07$). Our findings remained consistent when using the EQ VAS or health index scores, which may capture somewhat different aspects of HRQoL; and suggest that patients with high baseline quality of life are likely to benefit most from OPAT in terms of HRQoL, while frail patients may experience the least benefit. These improvements of HRQoL were otherwise homogenous, irrespective of baseline patient characteristics (age, sex, CCI) or OPAT-related variables measured at baseline (combination therapy, indication, mode of delivery, type of vascular access device). Differences in our findings compared to those of Goodfellow *et al.* [32] may stem from variations in methodology and the case-mix of patients. The most common indications for OPAT in our cohort were respiratory infections and bone and joint infections. For our regression analyses, we excluded other indications for OPAT due to a limited number of events. Additionally, we omitted the length of hospital stay as it is an intermediate variable in the causal pathway between baseline covariates (e.g. CCI, clinical frailty score) and HRQoL.

Unlike Wee *et al.* [35], we observed small and statistically non-significant decreases in the risks of clinical outcomes (treatment failure, complications, and 30-day unplanned readmission) associated with increasing HRQoL scores at baseline. In addition, there was limited evidence in our cohort for an association between being in a full health state upon OPAT initiation and lower risk of subsequent treatment failure and complications. The small numbers of events in our cohort did not allow for precise estimates of the respective relative risks for the clinical outcomes.

Our study is limited by a number of factors, including its confinement to a single hospital, and as a result, our findings may not accurately reflect experiences in other UK

Table 2. Changes in self-reported health-related quality of life indication of patients ($N = 162$), from baseline to final assessment.

	Baseline	Final	Difference (95% CI)	*P* value	Cohen's ES[a]
EQ-5D-3 L dimensions[b]					
Mobility	51 (31.5%)	68 (42.0%)	10.5% (3.3% to 17.7%)	0.003	0.27 (large)
No problem	111 (68.5%)	94 (58.0%)			
Some problems					
Self-care	90 (55.6%)	115 (71.0%)	15.4% (7.1% to 23.8%)	<0.001	0.28 (large)
No problem	72 (44.4%)	45 (29.0%)			
Some problems					
Usual activities	24 (14.8%)	55 (34.0%)	19.2% (11.0% to 27.3%)	<0.001	0.34 (large)
No problem	138 (85.2%)	107 (66.0%)			
Some problems					
Pain/discomfort	60 (37.0%)	91 (56.2%)	19.2% (10.0% to 28.2%)	<0.001	0.28 (large)
No problem	102 (63.0%)	71 (43.8%)			
Some problems					
Anxiety/depression	90 (55.6%)	98 (60.5%)	4.9% (−4.5% to 14.4%)	0.34	0.07 (small)
No problem	72 (44.4%)	64 (39.5%)			
Some problems					
Summary indices					
EQ-5D-3 L full health state[c], *n* (%)	13 (8.0%)	25 (15.4%)	7.4% (1.8% to 13.0%)	0.008	0.33 (large)
EQ-5D-3 L index score, mean (SD)	0.5 (0.3)	0.7 (0.3)	0.2 (0.1 to 0.2)	<0.001	0.51 (medium)
EQ VAS score, mean (SD)	57.9 (20.7)	65.4 (21.4%)	7.5 (3.9 to 11.1)	<0.001	0.33 (small)

Data are presented as n (%) unless otherwise specified.
CI, confidence interval; ES, effect size; SD, standard deviation; VAS, visual analogue scale.
[a]Effect sizes were calculated with Cohen's *g* for categorical variables and Cohen's *d* for continuous variables.
[b]No problem = level 1; some problems = levels 2 + 3.
[c]Full health state was defined as EQ-5D-3 L level "11111" (no problems in all five dimensions).

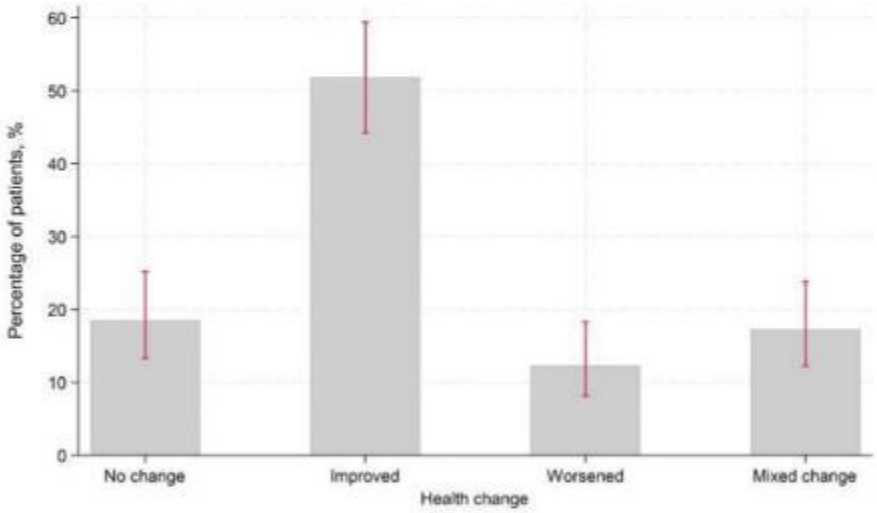

Figure 2. Paretian Classification of Health Change (PCHC) from baseline to final assessment for $N = 162$ patients. Vertical lines are 95% confidence intervals.

OPAT services. We used a validated questionnaire (EQ-5D-3 L) to measure HRQoL, which is limited to three levels of response categories. Compared to the five-level EQ-5D version, the three-level version exhibits a more pronounced ceiling effect and diminished discriminatory power [37]. Therefore, using the five-level version could have provided greater granularity in our data analysis. We also used either 'end of treatment' or '30 days of treatment' as endpoints, depending on which occurred first. This approach was adopted because, based on previous experience [38,39], OPAT patients could develop complications unrelated to OPAT after completing their therapy (but within 30 days), which could negatively affect their HRQoL. However, substantial changes in HRQoL may occur after 30 days of therapy [9,10,34]. Consequently, it is possible that we have not fully captured the impact of OPAT on the quality of life in some patients. Another important limitation is the absence of a comparison with inpatient care. It is possible that the improvements in HRQoL scores observed in our study could have also occurred if the cohort had been treated as inpatients [40]. As OPAT is firmly established in many countries, including the UK, and its benefits are widely recognized, conducting a definitive randomized controlled trial to compare HRQoL in OPAT with inpatient care is not likely to be feasible and may pose ethical challenges. Nonetheless, OPAT offers several potential advantages over inpatient care, including lower healthcare costs and a reduced risk of nosocomial infections, among others [4]. Furthermore, using a control group comprising inpatients in a non-randomized study would require accounting for several

Table 3. Results of linear regression analysis to identify baseline covariates that derived the greatest changes in the HRQoL ($N = 162$).

	EQ-5D-3 L index score					EQ VAS score				
	Univariate analysis		Multivariable analysis			Univariate analysis		Multivariable analysis		
Baseline covariate	MD (95%CI)	*P* value	aMD (95%CI)	*P* value	Cohen's f^2	MD (95%CI)	*P* value	aMD (95%CI)	*P* value	Cohen's f^2
Age, per 10 years	−0.02 (−0.05, 0.00)	0.10	−0.01 (−0.04, 0.02)	0.48	<0.01 (negl.)	−1.98 (−3.92, −0.03)	0.04	−1.40 (−3.59, 0.71)	0.22	0.01 (negl.)
Male sex	−0.05 (−0.14, 0.05)	0.33	−0.06 (−0.14, 0.04)	0.22	0.01 (negl.)	0.40 (−5.94, 7.21)	0.90	−3.58 (−10.24, 3.63)	0.31	0.01 (negl.)
Charlson comorbidity index, per unit	−0.03 (−0.06, −0.00)	0.05	−0.00 (−0.03, 0.03)	0.91	<0.01 (negl.)	−1.64 (−3.60, −0.17)	0.05	0.16 (−1.62, 1.97)	0.86	<0.01 (negl.)
Clinical frailty score, per unit	−0.06 (−0.10, −0.03)	<0.001	−0.02 (−0.07, 0.02)	0.28	0.01 (negl.)	−4.51 (−7.12, −2.43)	<0.001	−2.56 (−5.42, 0.05)	0.07	0.02 (small)
Bone and joint infection	0.02 (−0.06, 0.11)	0.62	0.06 (−0.04, 0.16)	0.23	0.01 (negl.)	2.85 (−3.58, 9.80)	0.40	1.66 (−4.68, 8.43)	0.63	<0.01 (negl.)
Respiratory infection	−0.02 (−0.19, 0.10)	0.78	−0.02 (−0.17, 0.10)	0.79	<0.01 (negl.)	−5.83 (−17.12, 3.93)	0.26	−1.76 (−12.49, 7.86)	0.74	<0.01 (negl.)
Combination antimicrobial therapy	0.02 (−0.09, 0.12)	0.69	−0.02 (−0.14, 0.08)	0.72	<0.01 (negl.)	0.56 (−7.05, 8.16)	0.89	−2.43 (−9.07, 3.83)	0.48	<0.01 (negl.)
Mode of OPAT delivery										
Visiting nurse	Reference	.	Reference	.		Reference	.	Reference	.	
Self/carer administration	0.10 (0.01, 0.19)	0.03	0.01 (−0.09, 0.11)	0.87		6.87 (0.71, 13.17)	0.04	−1.24 (−8.31, 6.20)	0.74	
Daily attendance	0.20 (0.09, 0.33)	0.001	0.02 (−0.14, 0.14)	0.77	<0.01 (negl.)	10.36 (−6.13, 23.31)	0.16	4.64 (−15.23, 14.52)	0.50	<0.01 (negl.)
Vascular access type										
Midline	Reference	.	Reference	.		Reference	.	Reference	.	
PICC line	0.01 (−0.10, 0.10)	0.87	0.05 (−0.05, 0.15)	0.35	<0.01 (negl.)	−4.61 (−12.55, 3.32)	0.25	−2.96 (−10.61, 4.65)	0.44	<0.01 (negl.)
Baseline EQ-5D-3 L score, per 0.1 unit	0.04 (0.03, 0.06)	<0.001	0.04 (0.03, 0.06)	<0.001	0.25 (med.)	-	-	-	-	
Baseline EQ VAS score, per 10 units	-	-	-	-		4.18 (2.33, 5.92)	<0.001	3.96 (2.09, 5.72)	<0.001	0.15 (med.)

aMD, adjusted mean difference; CI, confidence interval; MD, mean difference; med., medium; negl., negligible; PICC, peripherally inserted central catheter; VAS, visual analogue scale.

Table 4. Association between health-related quality of life (HRQoL) indicators and clinical outcomes ($N = 162$).

	30-day readmission [a] ($n = 37$)			Treatment failure [b] ($n = 27$)			OPAT adverse event [c] ($n = 24$)		
HRQoL indicator at baseline	aRR	95% CI	*P* value	aRR	95% CI	*P* value	aRR	95% CI	*P* value
EQ-5D-3 L dimension (level 1 *vs.* 2 + 3)									
Mobility	1.17	0.59–2.36	0.65	1.03	0.47–2.28	0.94	0.82	0.37–1.80	0.61
Self-care	0.91	0.50–1.64	0.75	0.47	0.23–0.97	0.04	0.68	0.31–1.49	0.34
Usual activities	1.74	0.88–3.45	0.11	0.79	0.25–2.47	0.68	0.66	0.23–1.93	0.45
Pain/discomfort	1.00	0.55–1.80	0.99	1.18	0.60–2.34	0.63	0.89	0.39–2.03	0.78
Anxiety/depression	1.00	0.58–1.74	>0.99	0.93	0.47–1.83	0.84	0.85	0.40–1.78	0.66
In full health state[d]	1.71	0.73–3.98	0.22	0.44	0.05–3.61	0.45	0.41	0.07–2.55	0.34
EQ-5D-3 L index score, per 0.1 units	0.97	0.89–1.06	0.54	0.99	0.90–1.08	0.76	0.94	0.84–1.04	0.22
EQ VAS score, per 10 units	0.92	0.80–1.05	0.22	1.01	0.88–1.16	0.90	0.91	0.75–1.09	0.30

aRR, adjusted risk ratio; CI, confidence interval; OPAT, outpatient parenteral antimicrobial therapy; VAS, visual analogue scale.
[a]Defined as unplanned inpatient admission for any reason during or within 30 days of OPAT discharge.
[b]Progression or non-response of infection, readmission during OPAT or death for any reason.
[c]Antimicrobial- and vascular access-related adverse events.
[d]Full health state was defined as EQ-5D-3 L level "11111" (no problems in all five dimensions).

non-health-related confounding factors (e.g. income, lifestyle, sleeping patterns) as health is neither the exclusive nor the most crucial contributor to quality of life.

5. Conclusions

While OPAT patients generally experience a lower quality of life compared to the general population, OPAT is associated with improvements in patient-reported quality of life measures and facilitates an early return to work or school for some patients. Identifying patients with low baseline quality of life is essential for providing closer monitoring and sufficient support to optimize their HRQoL and enhance their OPAT experience. Patient-reported outcomes, such as HRQoL, should be included in the evaluation of OPAT programmes.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethics

The study was approved by the North West – Greater Manchester South (UK) Research Ethics Committee (12/09/2022; REC Reference number 22/NW/0299; IRAS 316,619).

Data availability statement

Dataset generated or analyzed during this study is not available due to ethical restrictions.

Author contributions

Conceptualisation, O.C.D.; methodology, E.I.K. and O.C.D.; software, E.I.K.; validation, E.I.K.; formal analysis, E.I.K. and O.C.D.; investigation, O.C.D.; data curation, O.C.D. and E.I.K.; writing – original draft preparation, O.C.D. and E.I.K.; visualization, E.I.K. and O.C.D. All authors have read and agreed to the final version of the manuscript.

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Paper 3

Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antibiotic therapy (OPAT)

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Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antibiotic therapy (OPAT)

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SUMMARY

Objectives: Outpatient parenteral antimicrobial therapy (OPAT) is increasingly used to treat infective endocarditis (IE) with documented success. This study aims to identify risk factors for treatment failure and poor outcomes in patients with IE treated through OPAT.

Methods: We conducted a retrospective analysis of all episodes of IE treated over 13 years (September 2006 - September 2019) at a large teaching hospital in Sheffield, UK. We defined OPAT failure as unplanned readmission or death within 30 days of discharge from the OPAT service. Major adverse cardiac events (MACE) were defined as a composite of IE-related death, cardiac surgery, and recurrence of IE within the first year of completion of OPAT.

Results: Overall, 168 episodes of IE were reviewed. OPAT failure and MACE occurred in 44 episodes (26.2%) and 29 episodes (17.3%) respectively. On multivariable analysis, pre-existing renal failure (adjusted odds ratio [aOR], 3.00; 95% confidence interval [CI], 1.08–8.30; $P = 0.034$) and Charlson comorbidity score (aOR, 1.29 per unit increase; 95% CI, 1.06–1.57; $P = 0.011$) were associated with increased risk of failure. Previous endocarditis (aOR, 3.60; 95% CI, 1.49–8.70; $P = 0.004$) and cardiac complications (aOR, 3.85; 95% CI, 1.49–9.93; $P = 0.005$) were risk factors for MACE, whereas cardiac surgery during the initial hospitalisation for IE (aOR, 0.34; 95% CI, 0.12–0.22; $P < 0.001$) was a protective factor.

Conclusions: Our findings suggest that OPAT is safe and effective for completing antibiotic treatment for IE, including cases deemed to be at increased risk of complications. However, careful patient selection and monitoring of patients with pre-existing comorbidities and cardiac complications are recommended to optimise clinical outcomes.

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Introduction

Infective endocarditis (IE) is a serious and potentially fatal infection that often requires prolonged parenteral antimicrobial therapy. The efficacy and safety of outpatient parenteral antimicrobial therapy (OPAT) in the management of IE have been demonstrated in several observational studies.[1–7] OPAT is often used to consolidate antimicrobial therapy after initial inpatient treatment. Despite its benefits, OPAT is potentially associated with increased clinical risk due to reduced clinical supervision and monitoring. Even with careful patient selection and multidisciplinary team-driven therapeutic plans, the use of potentially toxic antimicrobial agents and duration of treatment imply complications including treatment failure, and readmission for some patients managed through OPAT are inevitable. Predicting and preventing treatment failure could improve patient outcomes and reduce healthcare costs. Nevertheless, the predictors of failure and poor outcomes in patients with IE treated with OPAT are not totally clear.[7,8]

This study aimed to identify factors that might be associated with increased risk of treatment failure and poor outcomes in patients with IE treated at an OPAT service based in a large tertiary referral teaching hospital in Sheffield, UK.

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Materials and methods

Patient population and setting

We conducted a retrospective cohort study of all episodes of presumed or definite IE treated with OPAT between September 2006 and September 2019 at Sheffield Teaching Hospitals, South Yorkshire, England, UK. Cases of IE were defined according to the modified Duke criteria.[9] Patients with an implantable cardiac electronic device (ICED) infection but without evidence of endocarditis were excluded. The Sheffield OPAT service, established in January 2006, is one of the largest in the United Kingdom. The OPAT service, patient selection criteria and a prospectively maintained database have been previously described.[10] Patient selection, antimicrobial regimen and mode of OPAT delivery were the responsibility of the OPAT physicians. Patients with IE were offered OPAT when deemed clinically stable on careful assessment by cardiology and infectious diseases physicians. They were required to have at least a 2-week period of inpatient care prior to starting OPAT, since the risk of complications is greatest during this period. Patients were reviewed in person at least once a week during their OPAT treatment and regularly by their cardiology team. Individual patient's progress was discussed at a weekly multidisciplinary meeting.

Data collection

The OPAT databases, hospital electronic clinical and laboratory databases were reviewed. Data extracted included patient demographics, comorbidities, risk factors for IE, microbiology culture results, echocardiographic findings, associated ICED infection, inpatient cardiac surgery, complications of IE, antimicrobial regimen, duration of inpatient and OPAT therapy, mode of OPAT delivery, type of vascular access, OPAT outcome, hospital readmission, and reason for and length of hospitalisation. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT was commenced.[11] Chronic kidney disease was based upon an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2.[12] Drug-resistant organisms included methicillin-resistant *Staphylococcus aureus* and penicillin-resistant streptococci. The study was approved by the Trust's clinical effectiveness unit.

Outcomes and definitions

The outcomes were OPAT failure at 30 days and one-year major adverse cardiac events (MACE). 30-day OPAT failure was defined as unplanned cardiac surgery during OPAT, unplanned readmission to an acute care hospital for any reason or death within 30 days of discharge from the OPAT service. MACE were defined as a composite of IE-related death, cardiac surgery and recurrence of IE within the first year of completion of OPAT. IE-related death included cardiac death and death caused by complications of endocarditis. Deaths unrelated to IE (e.g. death from malignant disease) were excluded. A recurrence (relapse or reinfection) was defined as a new episode of IE caused by the same or a different microorganism occurring within one year after completion of OPAT.

Statistical analysis

Categorical data were presented as counts and percentages. Numerical data were summarised as mean with standard deviation or median with interquartile range (IQR) depending on the degree of skewness in the distributions. Logistic regression was used for the analysis of risk factors of 30-day OPAT failure and one-year MACE. A set of 20 potential risk factors were examined, including patient-related, infection-related and treatment-related variables selected by clinical judgment and literature review. None of the candidate risk factors had missing values. An initial multivariable logistic regression model for each outcome was constructed with forward stepwise selection of variables with $P < 0.30$ on univariate analysis. Variables that were identified as risk factors in other studies but did not enter the initial model were forced one-by-one into the initial model to examine the possibility of negative confounding. The final model retained variables with a two-sided $P < 0.05$. The ratio of cases to variables was maintained to at least 10:1 during the model building process. Multicollinearity among model predictors was ruled out by examining Spearman correlations and variance inflation factors. Linearity in the log (odds) for continuous variables (age and Charlson score) was assessed using restricted cubic splines. Potential within-patient correlation caused by having different OPAT episodes in the same patient was taken into account by performing cluster-robust variance estimation relaxing the assumption of independent observations. Analyses were performed using STATA v.14 (StataCorp, College Station, TX, USA).

Results

Cohort characteristics

Over the 13-year study period, we recorded 168 episodes of IE in 146 individual patients. Table 1 shows the demographic and clinical characteristics of the cohort. The mean age of the patients was 60 (range, 16–91) years; 78% (131/168) were male and 68% (115/168) had native valve endocarditis. 109 (65%) episodes were classified as definite IE by modified Duke criteria. The most common causative pathogens isolated were viridans group streptococci (26%; 43/168), *S. aureus* (21%; 36/168), and coagulase-negative staphylococci (14%; 23/168). The median duration of inpatient antimicrobial therapy was 21 days (IQR, 16–30; range, 7–65 days). Patients with complications of IE such as cardiac or embolic events received longer inpatient treatment. The median length of OPAT therapy was 23 days (IQR, 17–31; range, 1–61 days).

Clinical outcomes

OPAT failure was recorded in 44 (26%) episodes – mostly due to unplanned readmission (93%; 41/44). The reasons for unplanned readmission are shown in Supplementary Table 1. MACE occurred in 29 (17%) episodes. Heart valve surgery was the main cause of MACE (59%; 17/29). One-year mortality was 2% (4/168). Four episodes of recurrence occurred within 6 months of completing OPAT (relapse). All recurrences were caused by microorganisms of same species that caused the initial episode Table 2.

Risk factor analysis

The results of the logistic regression analyses of predictors of OPAT failure and MACE are shown in Table 3. Chronic kidney disease (adjusted odds ratio [aOR], 3.00; 95% confidence interval [CI], 1.08–8.30; $P = 0.034$) and Charlson comorbidity score (aOR, 1.29; 95% CI, 1.06–1.57; $P = 0.011$) were independently associated with increased risk of 30-day OPAT failure. Previous IE (aOR, 3.60; 95% CI, 1.49–8.70; $P = 0.004$), cardiac complications (aOR, 3.85; 95% CI, 1.49–9.93; $P = 0.005$) and cardiac surgery during the initial hospitalisation for IE (aOR, 0.34; 95% CI, 0.12–0.22; $P < 0.001$) were independent predictors of one-year MACE.

Discussion

Our study highlights the fact that patients with IE treated with OPAT are at risk of treatment failure and poor outcomes. We have

Table 1
Baseline characteristics of patients and episodes of infective endocarditis ($N = 168$).

Characteristic	n (%)
Age (years), mean ± SD (range)	60 ± 17.6 (16–91)
Male sex	131 (78.0)
Comorbidities	
Pre-existing renal failure[a]	32 (19.0)
Heart failure	35 (20.8)
Charlson comorbidity score, median (IQR)	1 (0–2)
Predisposing factors	
Any predisposing factor	95 (56.5)
Congenital cardiac abnormality	42 (25.0)
Previous endocarditis	31 (18.5)
Rheumatic heart disease	4 (2.4)
Intravenous drug use	3 (1.8)
Diagnostic criteria (modified Duke criteria)	
Possible	59 (35.1)
Definite	109 (64.9)
Cardiac structure involved	
Aortic valve	71 (42.3)
Mitral valve	58 (34.5)
Tricuspid valve	20 (11.9)
Pulmonary valve	4 (2.4)
Multivalvular	9 (5.4)
Other cardiac structures[b]	6 (3.6)
Type of endocarditis	
Native	115 (68.5)
Prosthetic	53 (31.5)
Size of vegetation	
< 10 mm	81 (48.2)
≥ 10 mm	30 (17.9)
Affected side	
Left-sided	140 (83.3)
Right-sided	26 (15.5)
Double-sided	1 (0.6)
aetiology	
Streptococci	62 (36.9)
Viridans group streptococci	43 (25.6)
Beta-haemolytic streptococci	10 (6.0)
S. gallolyticus	4 (2.4)
Nutritionally variant streptococci	2 (1.2)
Other streptococci	3 (1.8)
Staphylococci	59 (35.1)
Staphylococcus aureus	36 (21.4)
Meticillin-sensitive *S. aureus*	35 (20.8)
Meticillin-resistant *S. aureus*	1 (0.6)
Coagulase-negative staphylococci	23 (13.7)
Enterococci	17 (10.1)
Culture negative	14 (8.3)
Gram-negative bacilli	10 (6.0)
HACEK organisms	7 (4.2)
Non-HACEK	3 (1.8)
Fungi	1 (0.6)
Other organisms[c]	5 (3.0)
Multidrug resistant organism	3 (1.8)
Associated ICED infection	22 (13.1)
Embolic complications	47 (28.0)
Cardiac complications	72 (42.9)

Data are presented as n (%) unless otherwise indicated.
HACEK, Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella and Kingella species.
ICED, implantable cardiac electronic device; IQR, interquartile range; SD, standard deviation.
[a] Estimated glomerular filtration rate < 60 ml/min/1.73 m^2.
[b] Other cardiac structures included: atrial septal defect ($n = 1$), mural endocardium ($n = 3$), ventricular septal defect ($n = 1$) and Waterston shunt ($n = 1$).
[c] Other organisms included: Actinomyces, *Lactococcus*, *Propionibacterium*, *Tropheryma* species and mixed culture (1 each).

previously found that patients with endovascular infection (including IE) treated with OPAT are at increased risk of unplanned readmission.[13] In this study, we explore factors associated with 30-day OPAT failure and one-year poor outcomes. Our definitions of OPAT failure and MACE are supported by previous studies.[14–16] We found two factors, which are readily available at the time of commencing

Table 2
Treatment characteristics and outcomes ($N = 168$).

Characteristic	n (%)
Pre-OPAT (inpatient) cardiac surgery	46 (27.4)
Duration of pre-OPAT (inpatient) antimicrobial therapy (days), median (IQR)	21 (16–30)
Duration of OPAT (days), median (IQR)	23 (17–31)
Mode of antimicrobial (OPAT) delivery	
Self/carer administration	79 (47.0)
Visiting nurse	56 (33.3)
Daily attendance	33 (19.6)
Class of antimicrobial (OPAT) agent[a]	
Cephalosporin	76 (40.4)
Penicillin	44 (23.4)
Glycopeptide	33 (19.6)
Cyclic lipopeptide	22 (11.7)
Aminoglycoside	9 (4.8)
Other agents[b]	4 (2.4)
Concurrent IV antimicrobial therapy	19 (11.3)
Use of central venous access	160 (95.2)
Outcomes	
30-day OPAT failure	44 (26.2)
Unplanned readmission	41 (24.4)
Cardiac surgery	2 (1.2)
Death	1 (0.6)
One-year MACE	29 (17.3)
Cardiac surgery	17 (10.1)
IE-related death	4 (2.4)
Recurrence	8 (4.8)

Data are presented as n (%) unless otherwise indicated.
IE, infective endocarditis; IQR, interquartile range; IV, intravenous; MACE; major adverse cardiac events; OPAT, outpatient parenteral antimicrobial therapy.
[a] Some patients received more than one parenteral antimicrobial agent. Thus, total number of antimicrobial agents is greater than total number of patient episodes.
[b] Other agents included: antifungal ($n = 1$) and carbapenem ($n = 3$).

OPAT, to be important predictors of OPAT failure: pre-existing renal failure and Charlson comorbidity index score. In addition, patients with a history of previous IE and those who developed cardiac complications, such as severe valvular insufficiency, perivalvular abscess or intracardiac fistula, were more likely to have worse long-term outcomes. However, patients who had cardiac surgery prior to OPAT were found to have favourable long-term outcomes.

The rates of unplanned readmission (24%) and one-year mortality (2%) in our cohort were comparable to other OPAT studies.[3,4,7,14,17–19] Renal failure and multimorbidity have been shown to be associated with OPAT failure in patients with IE.[14,15] Patients with multimorbidity were likely to be readmitted due to the underlying comorbidities and related complications.[20] For some patients, the risk of OPAT failure may be a direct consequence of their non-cardiac comorbidities rather than cardiac pathology. In non-OPAT related studies, recurrent endocarditis and cardiac complications have been associated with long-term adverse cardiac outcomes.[21–25] Hence, these risk factors observed in our study may not be directly related to the OPAT therapy. In our cohort, antibiotic dosing was appropriately adjusted according to renal function based on established guidelines. Although we did not explore the effects of antimicrobial concentration on clinical outcomes in patients with impaired renal function, serum drug levels were closely monitored to ensure therapeutic levels were achieved where required (i.e. aminoglycoside and glycopeptide therapy). We did not find any association between an antimicrobial agent and OPAT failure.

Similar to Pericăs et al., we found that cardiac surgery during the initial hospitalisation for IE is independently associated with favourable long-term outcomes.[1] Although we did not assess the timing of cardiac surgery, a number of non-OPAT related studies have shown that early valve surgery improves the prognosis of IE in certain groups of patients.[16,22,25] In our study, four patients were readmitted during their OPAT treatment for cardiac surgery.

Table 3
Risk factors for 30-day outpatient parenteral antimicrobial therapy failure and one-year major adverse cardiac events ($N = 168$).

Variable	30-day OPAT failure Univariate		Multivariable		1-year MACE Univariate		Multivariable	
	OR (95% CI)	P	aOR (95% CI)	P	OR (95% CI)	P	aOR (95% CI)	P
Age, per 10 years	1.14 (0.9 – 1.37)	0.172	–	–	0.98 (0.72 – 1.33)	0.883	–	–
Age, restricted cubic splines[a]								
Spline 1, per 10 years	1.25 (0.85 – 1.84)	0.251	–	–	0.76 (0.52 – 1.10)	0.147	–	–
Spline 2, per 10 years	0.88 (0.59 – 1.30)	0.516	–	–	1.46 (0.78 – 2.74)	0.239	–	–
Male sex	0.80 (0.37 – 1.69)	0.553	–	–	2.81 (0.79 – 9.93)	0.109	–	–
Comorbidities								
Pre-existing renal failure	6.49 (2.84 – 14.81)	<0.001	3.00 (1.08 – 8.30)	0.034	0.44 (0.10 – 2.01)	0.288	–	–
Heart failure	1.65 (0.78 – 3.48)	0.191	–	–	1.58 (0.51 – 4.92)	0.429	–	–
Charlson comorbidity score, per unit	1.50 (1.26 – 1.78)	< 0.001	1.29 (1.06 – 1.57)	0.011	0.74 (0.49 – 1.12)	0.157	–	–
Predisposing factors								
Congenital cardiac abnormality	0.59 (0.25 – 1.40)	0.231	–	–	3.70 (1.47 – 9.30)	0.005	–	–
Previous endocarditis	1.19 (0.51 – 2.79)	0.685	–	–	3.64 (1.51 – 8.76)	0.004	3.60 (1.49 – 8.70)	0.004
Cardiac structure involved								
Aortic valve	0.93 (0.47 – 1.83)	0.828	–	–	1.34 (0.53 – 3.43)	0.537	–	–
Mitral valve	0.97 (0.48 – 1.98)	0.943	–	–	1.00 (0.37 – 2.68)	0.997	–	–
Tricuspid valve	0.46 (0.13 – 1.67)	0.238	–	–	0.23 (0.03 – 1.80)	0.160	–	–
Prosthetic valve endocarditis	1.34 (0.68 – 2.67)	0.398	–	–	1.41 (0.52 – 3.79)	0.495	–	–
Left-sided IE vs. right-sided IE	0.74 (0.30 – 1.81)	0.513	–	–	0.54 (0.16 – 1.82)	0.322	–	–
aetiology								
Streptococcus species	0.64 (0.32 – 1.29)	0.216	–	–	0.88 (0.35 – 2.20)	0.785	–	–
Staphylococcus aureus	1.84 (0.82 – 4.13)	0.138	–	–	0.95 (0.33 – 2.76)	0.922	–	–
Enterococcus species	0.85 (0.30 – 2.40)	0.764	–	–	3.04 (0.70 – 13.11)	0.137	–	–
Associated ICED infection	1.07 (0.35 – 3.21)	0.910	–	–	–[b]	–	–	–
Embolic complications	1.29 (0.63 – 2.65)	0.493	–	–	0.98 (0.31 – 3.12)	0.968	–	–
Cardiac complications	1.02 (0.52 – 2.00)	0.959	–	–	3.08 (1.14 – 8.31)	0.026	3.85 (1.49 – 9.93)	0.005
Other sites of infection	1.37 (0.66 – 2.82)	0.393	–	–	0.91 (0.29 – 2.90)	0.874	–	–
Pre-OPAT (inpatient) cardiac surgery	0.60 (0.27 – 1.37)	0.228	–	–	0.50 (0.18 – 1.41)	0.189	0.34 (0.12 – 0.22)	<0.001
Mode of antimicrobial (OPAT) delivery								
Self/carer administration	1.00	–	–	–	1.00	–	–	–
Visiting nurse	0.83 (0.38 – 1.85)	0.658	–	–	0.89 (0.30 – 2.61)	0.831	–	–
Daily attendance	1.20 (0.53 – 2.72)	0.661	–	–	1.03 (0.28 – 3.76)	0.962	–	–
Class of antimicrobial (OPAT) agent								
Cephalosporin	0.79 (0.40 – 1.53)	0.483	–	–	0.58 (0.23 – 1.44)	0.243	–	–
Penicillin	1.26 (0.59 – 2.67)	0.549	–	–	1.09 (0.39 – 3.08)	0.871	–	–
Glycopeptide	1.07 (0.46 – 2.48)	0.872	–	–	0.83 (0.22 – 3.12)	0.778	–	–
Concurrent IV antimicrobial therapy	1.35 (0.47 – 3.88)	0.579	–	–	0.53 (0.12 – 2.43)	0.416	–	–

aOR, adjusted odd ratios; CI; confidence interval; IECD, implantable cardiac electronic device; IV, intravenous; MACE; major adverse cardiac events; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio.

[a] Age was modelled using restricted cubic splines with slopes defined at quartiles (47, 62 and 73 years).

[b] None of the patients with associated ICED infection experienced a 1-year MACE.

Two of the cardiac surgeries were pre-planned and were not considered as OPAT failure. The optimal timing of surgery in IE is not fully understood.[26] Studies are required to optimise the use of surgery, especially in higher risk patients.

OPAT has been shown to be safe and effective for intravenous drug users (IVDUs).[27,28] However, the number of IVDUs in our study is too small to draw meaningful conclusions. Active IVDUs are often excluded from our OPAT service due to a number of challenges including vascular access and social issues. Nevertheless, carefully selected and closely monitored IVDUs with IE may be safely treated with OPAT. Long-active antimicrobial agents, such as dalbavancin and oritavancin, which could be administered once a week, may offer a novel outpatient treatment option for IE in IVDUs and other hard-to-reach groups.[29,30] In our study, one patient was successfully treated (sequential treatment) for *Streptococcus* IE with dalbavancin.

There has been increasing interest in oral therapy for infections traditionally treated with prolonged courses of parenteral antibiotics.[31] Sequential oral antimicrobial therapy may be a suitable alternative to OPAT in carefully selected patients with uncomplicated left-sided IE caused by staphylococci, streptococci and enterococci (POET study).[32] Whilst further works are required before recommending routine use of oral antimicrobials for IE, OPAT remains a safe and effective alternative to inpatient treatment, especially when oral therapy is not appropriate due to drug interactions, intolerance, poor adherence, antibiotic resistance or poor oral absorption. In addition, patients with complications of IE such as embolic or cardiac abscess may require prolonged parenteral therapy. It is possible that oral antibiotic therapy for IE could be administered within an OPAT setting to allow close monitoring and timely follow-up.[33]

OPAT failure and poor long-term outcomes have been associated with *S. aureus* IE and glycopeptide therapy.[3,14,15,34] However, we did not identify these risk factors as significant. In our study, poor outcomes were also not associated with most of the factors (e.g. aortic valve disease, prosthetic value disease and IE caused by

virulent organisms) deemed to be associated with increased risk of complications and preclude use of OPAT by Andrews and von Reyn.[35] As a general rule, it seems logical to consider OPAT for all medically stable patients without major IE complications after an initial period of inpatient therapy. During OPAT therapy, patients should be carefully monitored for early detection of complications, treatment failure, or clinical deterioration, which may necessitate further interventions including readmission.

This study has limitations that should be acknowledged. This was a single-centre, retrospective analysis with no hospitalised comparators. The data were originally collected prospectively, which reduces the risk of measurement bias or poor accuracy of data records. Despite extensive analysis of factors previously reported to be associated with OPAT failure in IE, we cannot be certain that we have not missed other important risk factors or the influence of unrecorded confounders on our findings. Although our epidemiologic data are comparable to other cohort studies, the relatively low incidence of IE suggests that large multicentre studies are needed to confirm our findings and comprehensively explore risk factors for poor outcomes in IE treated with OPAT.

Conclusions

Our study adds to the growing evidence that OPAT for IE is a safe and effective alternative to inpatient treatment. It also demonstrates that patients deemed to be at higher risk of complications, such as prosthetic valve IE or *S. aureus* IE, may be successfully treated in outpatient settings. However, careful patient selection and monitoring of patients with pre-existing comorbidities and cardiac complications are recommended to optimise clinical outcomes.

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Declarations of Competing Interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Oyewole Chris Durojaiye: Visualization, Data curation, Writing – original draft. **Robin Morgan:** Data curation, Writing – original draft. **Naziha Chelaghma:** Data curation, Writing – original draft. **Evangelos I Kritsotakis:** Formal analysis, Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.09.021.

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Paper 4

Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa

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ORIGINAL ARTICLE

Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa

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Abstract

Necrotising otitis externa (NOE) is an uncommon but life-threatening infection that requires prolonged systemic antimicrobial therapy. This study aims to identify factors associated with treatment response and outcome in patients with NOE treated through outpatient parenteral antimicrobial therapy (OPAT). We performed a retrospective analysis of patients with NOE treated over a 4-year period (January 2018–January 2022) at a tertiary referral hospital in Derbyshire, UK. We defined OPAT failure as unplanned readmission within 30 days of discontinuation of OPAT. Prolonged duration of therapy was defined as length of parenteral antimicrobial treatment of more than 8 weeks. A total of 46 cases of NOE were reviewed. OPAT failure and prolonged therapy were recorded in 9 (19.6%) and 23 (50.0%) episodes respectively. Facial nerve involvement (odds ratio [OR], 14.54; 95% confidence interval [CI], 2.76–76.60; $p=0.002$), dementia (OR, 7.65; 95% CI, 1.23–47.46; $p=0.029$), Charlson comorbidity score (OR, 1.41 per unit increase; 95% CI, 1.00–2.00; $p=0.049$) and peak CRP level (OR, 1.03 per unit increase; 95% CI, 1.00–1.06; $p=0.027$) were associated with increased risk of treatment failure. Facial nerve involvement (OR, 16.30; 95% CI, 2.60–102.31; $p=0.003$) and peak CRP level (OR, 1.04; 95% CI, 1.01–1.07; $p=0.016$) were also associated with an increased need for prolonged antimicrobial therapy. In addition, extent of disease (based on imaging findings) was linked to prolonged therapy (OR, 22.89; 95% CI, 3.62–144.76; $p=0.001$). NOE could be effectively managed as outpatient via OPAT. However, vigorous antimicrobial treatment and close monitoring of patients with pre-existing comorbidities, facial nerve paralysis, extensive disease and markedly elevated inflammatory markers are essential to optimise clinical outcomes.

Keywords Malignant otitis externa · Necrotising otitis externa · Outcomes · Outpatient parenteral antimicrobial therapy · Risk factors · Treatment failure

Introduction

Necrotising otitis externa (NOE) (also termed malignant otitis externa) is an uncommon and potentially fatal infection of the external auditory canal and surrounding structures, which typically occurs in elderly diabetic and immunocompromised patients. Although there are currently no established treatment guidelines for NOE, it is often treated with prolonged courses of parenteral antimicrobials which may necessitate lengthy inpatient stays. Outpatient parenteral antimicrobial therapy (OPAT) has been shown to be a safe and effective alternative to hospitalisation for treatment of a wide range of infections [1, 2]. However, studies on OPAT for NOE are very limited.

We aimed to identify factors that might be associated with increased risk of treatment failure and prolonged antimicrobial therapy in patients with NOE treated at an OPAT

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service based in a large tertiary referral teaching hospital in Derbyshire, UK.

Materials and methods

Patient population and setting

This study is a single-centre, retrospective cohort study of all episodes of confirmed NOE treated with OPAT at Royal Derby Hospital (Derbyshire, England, UK) between January 2018 and January 2022. Cases of NOE were clinically and radiologically confirmed (with computed tomography (CT) and/or magnetic resonance imaging (MRI) scan) and referred for OPAT by their Ear, Nose and Throat (ENT) specialist following initial inpatient management. The Derby OPAT service, established in 2013, is run by a multidisciplinary team of infection specialists, clinical pharmacists and specialist nurses. The OPAT service maintains an electronic database to prospectively record patient demographics, clinical diagnosis, antimicrobial agents and duration of antimicrobial treatment. The clinical responsibility for patients receiving OPAT and their follow-ups were shared between the referring clinicians and the OPAT team, unless otherwise agreed. Patients were regularly reviewed in person during their OPAT treatment, and their progress was discussed at a weekly multidisciplinary meeting. Patient selection and individualised OPAT treatment plans were the responsibility of the OPAT infection specialists. In summary, patients with confirmed NOE received 6 to 8 weeks course of intravenous (IV) antimicrobial therapy and had repeat imaging (usually gallium scan) to assess for resolution of infection. Patients with active infection after the 6–8 weeks of treatment received extended courses of therapy with modification of the antimicrobial regimens. Follow-up examinations and radiological imaging were repeated as required until disease resolution.

Data collection

We reviewed the OPAT, hospital electronic clinical and laboratory databases. Data extracted included patient demographics, comorbidities, microbiology culture results, peak white cell count (WCC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, imaging findings, complications of NOE, antimicrobial regimens, duration of inpatient and OPAT therapy, mode of OPAT delivery, OPAT outcomes, hospital readmission, and reasons for and length of hospitalisation. In patients with diabetes mellitus, mean blood glucose levels and haemoglobin A1c (HbA1c) were also analysed. Poor diabetes/glycaemic control was defined as HbA1c above 53 mmol/mol (7%) and required inpatient diabetes team review [3]. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT was commenced [4]. Clinical cure was defined as complete resolution of clinical symptoms, normalisation of inflammatory markers and negative findings on follow-up imaging. Chronic kidney disease was based upon an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2 [5]. All patient data were anonymised prior to analysis. The study was approved by the local clinical audit/effectiveness unit as part of ongoing commitment to service development and clinical governance.

Outcomes and definitions

The outcomes were 'OPAT failure' at 30 days and 'prolonged duration' of IV antimicrobial therapy. OPAT failure was defined as unplanned readmission to an acute care hospital for any reason, recrudescence of infection or death within 30 days of discontinuation of OPAT. Prolonged duration of therapy was defined as length of IV antimicrobial treatment of more than 8 weeks.

Statistical analysis

Numerical data were summarised as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the degree of skewness in the distributions. Categorical data were presented as frequency counts and percentages. Risk factors of OPAT failure and prolonged IV antimicrobial therapy were assessed using logistic regression with penalized maximum likelihood estimation (Firth's method) to account for small sample size [6]. A set of 30 potential risk factors were examined, including patient-related, infection-related and treatment-related variables, based on clinical judgement and literature review. None of the candidate risk factors had missing values. Non-linearity in the log (odds) for continuous variables was examined using lowess smoothed logit plots and was modelled with restricted cubic splines [7]. Due to the small effective sample size, multivariable analysis was not possible. Data were processed and analysed using STATA v.17 (StataCorp, College Station, TX, USA).

Results

Cohort characteristics

We identified 46 episodes of NOE treated through OPAT during the study period with a mean age of 81 (range, 56–96) years. Thirty-three percent (15/46) were female. Table 1 shows the demographic and clinical characteristics of the cohort. Sixty-seven percent (31/46) were diabetic;

Table 1 Baseline patient characteristics ($n = 46$)

Characteristic	n (%)
Age (years), mean ± SD (range)	80.7 ± 9.7 (56–96)
Male sex	31 (67.4)
Diabetics	31 (67.4)
Diabetic control [based on HbA1c (mmol/mol)]	
Good control (HbA1c < 53.0)	11 (23.9)
Poor control (HbA1c > 53.0)	20 (43.5)
HbA1c (mmol/mol), mean ± SD (range)[a]	64.3 ± 17.6 (33.0–106.0)
Random blood glucose (mmol/L), mean ± SD (range)[a]	30.1 ± 26.4 (1.0–99.0)
Duration of diabetes (years), mean ± SD (range)	10.5 ± 4.2 (4.8–20.3)
Previous NOE	4 (8.7)
Charlson comorbidity index score, mean ± SD (range)	2.9 ± 2.1 (0–7)
Comorbidities	
Congestive heart failure/coronary artery disease	15 (32.6)
Peripheral vascular disease	5 (10.9)
Cerebrovascular disease	4 (8.7)
Dementia	5 (10.9)
Chronic obstructive pulmonary disease	5 (10.9)
Diabetes without complication	13 (28.3)
Diabetes with complications	18 (39.1)
Moderate or severe renal disease	18 (39.1)
Tumour without metastasis	4 (8.7)
Moderate or severe liver disease	1 (2.2)
Microbiology result	
No growth/normal skin flora	10 (21.7)
Pseudomonas aeruginosa	34 (73.9)
Other pathogens[b]	2 (4.3)
Polymicrobial culture[c]	10 (21.7)
Extent of Disease	
EAC/SF	31 (67.4)
JF/PA	15 (32.6)
Facial nerve involvement	13 (28.3)
Skull base osteomyelitis	5 (10.9)
Intracranial complications	3 (6.5)
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)
Peak CRP (mg/L), mean ± SD (range)	30.1 ± 26.4 (1.0–99.0)
Peak WCC ($\times 10^9$/L), mean ± SD (range)	9.3 ± 2.9 (4.7–17.0)
Peak ESR (mm/hr), mean ± SD (range)[d]	30.4 ± 29.1 (1.0–73.0)

Data are presented as mean ± SD for continuous measures, and n (%) for categorical measures unless otherwise indicated

CRP, C-reactive protein; *EAC*, external auditory canal; *ESR*, erythrocyte sedimentation rate; *HbA1c*, haemoglobin A1c; *JF*, jugular foramen; *NOE*, necrotising otitis externa; *PA*, petrous apex; *SD*, standard deviation; *SF*, stylomastoid foramen; *WCC*, white cell count

[a]HbA1c and random blood glucose were only recorded in patients with diabetes mellitus ($n = 31$)

[b]Other pathogens included: *Staphylococcus aureus* and *Klebsiella pneumoniae*

[c]Polymicrobial culture included: *P. aeruginosa* with one or more other organisms (anaerobes, *Candida* spp., *Cutibacterium acnes*, *Enterococcus faecalis*, *Streptococcus agalactiae* and *Streptococcus anginosus*)

[d]ESR was recorded in only 8 patient episodes

20 (65%) of them had poor glycaemic control. The mean diabetes duration was 21 (SD, 16; range, 5–76) years. The mean blood glucose and HbA1c levels at presentation were 10 (SD, 4) mmol/L and 64 (SD, 18) mmol/mol respectively. *Pseudomonas aeruginosa* was the most common causative pathogen isolated (74%; 34/46). All but three *P. aeruginosa*

isolates were sensitive to ciprofloxacin. Fungi were isolated in four episodes; they were all established to be commensal organisms and antifungal therapy was not required. Details of peak CRP, WCC and ESR levels are shown Table 1. ESR was checked in only 8 (17%) episodes. Elevated inflammatory markers were recorded in 39 (85%) episodes.

CT or MRI findings were categorised according to extent of the disease. All 46 episodes had external auditory canal (EAC) involvement. The petrous apex was also involved in 14 (30%) episodes. Facial nerve palsy was observed in 13 (28%) episodes; other cranial nerves were not affected. Eleven percent (5/46) had skull base osteomyelitis. Other intracranial complications of NOE (brain abscess and thrombus) occurred in 3 (7%) episodes. Piperacillin/tazobactam was the most frequently prescribed parenteral antimicrobial agent (59%; 27/46). Combination antimicrobial therapy was prescribed in 18 (39%) episodes.

The mean duration of inpatient antimicrobial therapy was 10 (SD, 5; range, 2–25) days. The total number of days of patient care (bed-days saved) delivered through OPAT was 2802 (median 48 days; IQR, 33–86; range, 12–260 days), with an estimated saving of £996,500 (one hospital bed day on an ENT unit is approximately £356).

Clinical outcomes

Follow-up imaging showed complete resolution of infection in 39 (85%) episodes. In six (13%) episodes follow-up scans were not performed. Three of these patients died from other causes (not related to MOE) before the imaging. Two could not tolerate the scans due to chronic back pain and claustrophobia, and treatment discontinuation was based on clinical improvement and normalisation of inflammatory markers. The treatment characteristics and clinical outcomes are presented in Table 2. OPAT failure was recorded in 9 (20%) episodes — mostly due to unplanned readmission. The reasons for unplanned readmission are shown in Online Resource 1. Infection persisted beyond the initial 6–8 week treatment period in half (50%) of the episodes which necessitated additional antimicrobial treatment. Despite prolonged course of antimicrobial therapy, two patients had

Table 2 Treatment characteristics and outcomes ($n=46$)

Characteristic	*n* (%)
Duration of pre-OPAT (inpatient) antimicrobial therapy (days), mean ± SD (range)	9.5 ± 4.8 (2–25)
Duration of OPAT (days), median (IQR)	47.5 (33–86)
Total length of IV antimicrobial therapy (weeks), median (IQR)	8.9 (7.0–15.1)
Mode of antimicrobial (OPAT) delivery	
Self/carer administration	43 (93.5)
Visiting nurse	3 (6.5)
Use of central venous access	23 (50.0)
Antimicrobial regimen	
Antipseudomonal penicillin-based	
IV piperacillin/tazobactam monotherapy	19 (41.3)
IV piperacillin/tazobactam plus oral ciprofloxacin	7 (15.2)
IV piperacillin/tazobactam plus oral metronidazole	1 (2.2)
Cephalosporin-based	
IV ceftazidime monotherapy	6 (13.0)
IV ceftazidime plus oral ciprofloxacin	8 (17.4)
IV ceftazidime plus oral amoxicillin	1 (2.2)
Carbapenem-based	
IV meropenem monotherapy	2 (4.3)
IV meropenem plus IV teicoplanin	1 (2.2)
Cyclic lipopeptide (IV daptomycin)	1 (2.2)
Outcomes	
OPAT failure	9 (19.6)
Prolonged IV antimicrobial therapy	23 (50.0)
Recurrence within follow-up period	4 (8.7)
Duration of follow-up for recurrence (months), mean ± SD (range)	16.7 ± 15.1 (1–46)

Data are presented as mean ± SD and median (IQR) for continuous measures, and n (%) for categorical measures unless otherwise indicated

IQR, interquartile range; *IV*, intravenous; *OPAT*, outpatient parenteral antimicrobial therapy; *SD*, standard deviation

disease progression. Both were deemed unfit for surgical management by their ENT specialist due to underlying comorbidities. One of them was referred for hyperbaric oxygen therapy (HBOT), and the second succumbed to the disease. The mean follow-up duration was 17 (SD, 15; range 1–46) months. During the follow-up period, recurrence of disease was observed in four (7%) cases after a mean of 4 months. The survival rate was 67% (31/46), with 2% disease-specific mortality and 30% mortality from other causes.

Risk factor analysis

Tables 3 and 4 show the results of the logistic regression analyses of the risk factors for OPAT failure and prolonged IV therapy, respectively. Facial nerve involvement (odds ratio [OR], 14.54; 95% confidence interval [CI], 2.76–76.60; $p = 0.002$), dementia (OR, 7.65; 95% CI, 1.23–47.46; $p = 0.029$), Charlson comorbidity score (OR, 1.41 per unit increase; 95% CI, 1.00–2.00; $p = 0.049$) and

Table 3 Association between clinical, infection and therapy-related factors and 30-day outpatient antimicrobial therapy failure ($n = 46$)

Risk factor	No. (%) of patients or mean ± SD			Bivariate association measure		
	Total cohort ($n = 46$)	OPAT success ($n = 37$)	OPAT failure ($n = 9$)	OR	95% CI	p-value
Age (years), linear RCS term	80.7 ± 9.7	79.3 ± 9.6	86.7 ± 8.2	0.94	0.80–1.11	0.054
Age (years), non-linear RCS term				1.17	0.98–1.40	
Male sex	31 (67.4)	25 (67.6)	6 (66.7)	0.91	0.21–3.94	0.900
Diabetic patient	31 (67.4)	24 (64.9)	7 (77.8)	1.65	0.34–8.01	0.532
Diabetes control						
No diabetes	15 (32.6)	13 (35.1)	2 (22.2)	1.00	-	0.694
Well-controlled	11 (23.9)	8 (21.6)	3 (33.3)	2.22	0.35–13.94	
Poorly controlled	20 (43.5)	16 (43.2)	4 (44.4)	1.47	0.27–8.10	
Diabetes duration (years), linear RCS term	14.4 ± 16.5	13.6 ± 16.9	17.4 ± 15.5	1.08	0.93–1.26	0.529
Diabetes duration (years), non-linear RCS term				0.91	0.74–1.12	
Previous NOE	4 (8.7)	3 (8.1)	1 (11.1)	1.74	0.22–13.58	0.597
Charlson comorbidity score, per unit	2.9 ± 2.1	2.6 ± 2.0	4.2 ± 2.1	1.41	1.00–2.00	0.049
Comorbidities[a]						
Congestive heart failure/coronary artery disease	15 (32.6)	13 (35.1)	2 (22.2)	0.60	0.12–2.93	0.532
Peripheral vascular disease	5 (10.9)	3 (8.1)	2 (22.2)	3.29	0.54–19.98	0.196
Dementia	5 (10.9)	2 (5.4)	3 (33.3)	7.65	1.23–47.46	0.029
Chronic obstructive pulmonary disease	5 (10.9)	4 (10.8)	1 (11.1)	1.31	0.18–9.66	0.789
Moderate or severe renal disease	18 (39.1)	12 (32.4)	6 (66.7)	3.79	0.88–16.40	0.075
Polymicrobial culture	10 (21.7)	9 (24.3)	1 (11.1)	0.53	0.08–3.49	0.508
Extent of disease, EAC/SF vs JF/PA	15 (32.6)	10 (27.0)	5 (55.6)	3.20	0.76–13.44	0.112
Facial nerve involvement	13 (28.3)	6 (16.2)	7 (77.8)	14.54	2.76–76.60	0.002
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)	31 (83.8)	8 (88.9)	1.17	0.17–8.06	0.874
Peak CRP (mg/L)	30.1 ± 26.4	25.5 ± 22.6	49.2 ± 33.3	1.03	1.00–1.06	0.027
Peak WCC ($\times 10^9$/L), linear RCS term	9.3 ± 2.9	9.0 ± 2.8	10.4 ± 3.2	0.92	0.44–1.93	0.356
Peak WCC ($\times 10^9$/L), non-linear RCS term				1.32	0.56–3.12	
Use of central venous access	23 (50.0)	20 (54.1)	3 (33.3)	0.46	0.11–1.95	0.293
Combination antimicrobial therapy	18 (39.1)	16 (43.2)	2 (22.2)	0.43	0.09–2.08	0.297
Antibiotic agent[b]						
IV ceftazidime	15 (32.6)	11 (29.7)	4 (44.4)	1.89	0.45–7.84	0.383
IV piperacillin/tazobactam	27 (58.7)	23 (62.2)	4 (44.4)	0.50	0.12–2.06	0.341
Oral ciprofloxacin	7 (15.2)	7 (18.9)	0 (0.0)	0.21	0.01–4.11	0.306

CI, confidence interval; *CRP*, C-reactive protein; *EAC*, external auditory canal; *ESR*, erythrocyte sedimentation rate; *IV*, intravenous; *JF*, jugular foramen; *NOE*, necrotising otitis externa; *OPAT*, outpatient parenteral antimicrobial therapy; *OR*, odds ratio; *PA*, petrous apex; *RCS*, restricted cubic splines; *SD*, standard deviation; *SF*, stylomastoid foramen; *WCC*, white cell count

[a]Comorbid conditions that occurred in at least 5 patients (10%) were examined. [b]The 3 most frequently used antibiotic agents were examined

Table 4 Association between clinical, infection and therapy-related factors and prolonged intravenous antimicrobial therapy ($n=46$)

Risk factor	No. (%) of patients or mean ± SD			Bivariate association measure		
	Total cohort ($n=46$)	Expected duration ($n=23$)	Prolonged duration ($n=23$)	OR	95% CI	p-value
Age (years)	80.7 ± 9.7	80.0 ± 9.4	81.5 ± 10.2	1.02	0.96–1.08	0.598
Male sex	31 (67.4)	14 (60.9)	17 (73.9)	1.76	0.52–5.95	0.360
Diabetic patient	31 (67.4)	14 (60.9)	17 (73.9)	1.76	0.52–5.95	0.360
Diabetes control						0.661
No diabetes	15 (32.6)	9 (39.1)	6 (26.1)	1.00	-	
Well-controlled	11 (23.9)	5 (21.7)	6 (26.1)	1.73	0.38–7.83	
Poorly controlled	20 (43.5)	9 (39.1)	11 (47.8)	1.77	0.47–6.60	
Duration of diabetes (years)	14.4 ± 16.5	9.8 ± 10.2	19.0 ± 20.2	1.04	0.99–1.08	0.105
Previous NOE	4 (8.7)	2 (8.7)	2 (8.7)	1.00	0.16–6.37	1.000
Charlson comorbidity score, per unit	2.9 ± 2.1	2.3 ± 2.0	3.5 ± 2.0	1.33	0.98–1.79	0.064
Comorbidities[a]						
Congestive heart failure/coronary artery disease	15 (32.6)	5 (21.7)	10 (43.5)	2.62	0.75–9.11	0.131
Peripheral vascular disease	5 (10.9)	0 (0.0)	5 (21.7)	13.97	0.73–269.23	0.081
Dementia	5 (10.9)	1 (4.3)	4 (17.4)	3.46	0.50–24.20	0.211
Chronic obstructive pulmonary disease	5 (10.9)	1 (4.3)	4 (17.4)	3.46	0.50–24.20	0.211
Moderate or severe renal disease	18 (39.1)	9 (39.1)	9 (39.1)	1.00	0.31–3.18	1.000
Polymicrobial culture	10 (21.7)	5 (21.7)	5 (21.7)	1.00	0.26–3.84	1.000
Extent of disease, EAC/SF vs JF/PA	15 (32.6)	1 (4.3)	14 (60.9)	22.89	3.62–144.76	0.001
Facial nerve involvement	13 (28.3)	1 (4.3)	12 (52.2)	16.30	2.60–102.31	0.003
Presence of elevated inflammatory markers (CRP, WCC or ESR)	39 (84.8)	17 (73.9)	22 (95.7)	5.57	0.85–36.59	0.074
Peak CRP (mg/L)	30.1 ± 26.4	19.2 ± 16.2	41.0 ± 30.2	1.04	1.01–1.07	0.016
Peak WCC ($\times 10^9$/L)	9.3 ± 2.9	8.5 ± 2.7	10.0 ± 3.0	1.20	0.97–1.49	0.089
Use of central venous access	23 (50.0)	10 (43.5)	13 (56.5)	1.65	0.53–5.17	0.388
Combination antimicrobial therapy	18 (39.1)	6 (26.1)	12 (52.2)	2.93	0.88–9.76	0.081
Antibiotic agent[b]						
IV ceftazidime	15 (32.6)	8 (34.8)	7 (30.4)	0.83	0.25–2.76	0.760
IV piperacillin/tazobactam	27 (58.7)	12 (52.2)	15 (65.2)	1.68	0.53–5.34	0.381
Oral ciprofloxacin	7 (15.2)	1 (4.3)	6 (26.1)	5.57	0.85–36.59	0.074

CI, confidence interval; *CRP*, C-reactive protein; *EAC*, external auditory canal; *ESR*, erythrocyte sedimentation rate; *IV*, intravenous; *JF*, jugular foramen; *NOE*, necrotising otitis externa; *OR*, odds ratio; *PA*, petrous apex; *SD*, standard deviation; *SF*, stylomastoid foramen; *WCC*, white cell count

[a]Comorbid conditions that occurred in at least 5 patients (10%) were examined

[b]The 3 most frequently used antibiotic agents were examined

peak CRP levels (OR, 1.03; 95% CI, 1.00–1.06; $p=0.027$) were associated with increased risk of 30-day OPAT failure. Extent of disease based on imaging findings (OR, 22.89; 95% CI, 3.62–144.76; $p=0.001$), facial nerve involvement (OR, 16.30; 95% CI, 2.60–102.31; $p=0.003$) and peak CRP level (OR, 1.04; 95% CI, 1.01–1.07; $p=0.016$) were associated with an increased need for prolonged IV antimicrobial therapy.

Discussion

NOE is a complex and potentially fatal infection with many associated complications. In the UK, its incidence is increasing probably due to ageing population and increasing comorbidities [8]. The diagnosis and management of NOE present several unique challenges. Treatment often involves prolonged courses of parenteral antimicrobials

which may necessitate lengthy inpatient stays with associated cost and risk to both the patient and hospital.

In non-OPAT related studies, a number of factors have been purported to affect the clinical outcome of NOE [9]. In the current study, we explore factors associated with treatment failure and prolonged parenteral antimicrobial therapy in patients with NOE treated with OPAT. Our definitions of OPAT failure and prolonged antimicrobial therapy are supported by previous studies [9–11]. We identified pre-existing comorbidities, facial nerve involvement and CRP level, which are readily available at the time of commencing OPAT, to be associated with OPAT failure. We also found that patients with extensive disease (based on imaging findings), facial nerve palsy and high CRP were more likely to require prolonged courses of antimicrobial therapy.

Facial nerve involvement, pre-existing comorbidities, CRP levels and extent of disease have been associated with poor outcomes in several non-OPAT related studies [9, 10, 12–14]. Hence, these risk factors observed in our study may not be directly related to the OPAT. The rate of unplanned readmission in our cohort was similar to other OPAT studies [15, 16]. However, most of the observed readmissions were non-OPAT related. Our relapse rate is also comparable to other studies [17, 18]. All four recurrences occurred within a year of completion of OPAT and were treated with extended courses of broad-spectrum antimicrobial agents. Thus, it is essential to follow up patients with NOE for at least 1 year after therapy [9, 19]. We did not explore the risk factors for these disease recurrences due to the relatively small number of events. Fifteen patients died during the follow-up period; all but one death were unrelated to NOE.

We have previously identified pre-existing comorbidities to be associated with increased risk of unplanned hospital readmission from OPAT [20]. Patients with multimorbidity were likely to be readmitted due to the underlying comorbidities and related complications. For some patients in our cohort, the risk of readmission, and thus, OPAT failure may be a direct consequence of their underlying comorbidities rather than as a consequence of NOE. Although a number of staging systems for NOE have been proposed based on extent of disease or neurologic complications, none has yet been widely adopted [21, 22]. Similar to Lee et al., we classified the extent of disease according to the expected course of infection [14]. As reported by Nadol, the disease process typically starts in the EAC and spreads to the middle cranial fossa via the stylomastoid foramen, jugular foramen and petrous apex [23]. In our cohort, all patients had CT and/or MRI imaging prior to treatment to confirm the diagnosis and assess location and extent of disease. Patients who had more extensive disease (i.e. jugular foramen and petrous apex involvement) were more likely to have received longer courses of antimicrobial treatment. We recommend CT and/or MRI scans for all patients with suspected NOE — not only to confirm the diagnosis but also to guide duration of antimicrobial treatment.

Cranial nerve palsy is a sign of disease progression and a controversial prognostic factor in NOE [14, 24]. The facial nerve is the most commonly affected cranial nerve due to its proximity to the EAC. Similar to Arsovic et al. and Stern Shavit et al., we found facial nerve paralysis to be associated with treatment failure and prolonged therapy [10, 25]. Our findings support the view that facial nerve involvement may affect the prognosis of NOE. We did not identify skull base osteomyelitis and other intracranial complications of NOE as risk factors for OPAT failure and prolonged therapy, probably due to the relatively small number of these complications in our cohort.

We also observed associations between peak CRP and both OPAT failure and prolonged therapy. CRP correlates closely with disease progression and may serve as an indicator of disease severity. Elevated CRP levels have been linked to longer time to disease resolution and poor outcomes [12, 14]. We advise regular monitoring of CRP and other inflammatory markers until complete resolution of the disease is achieved.

The optimal duration of treatment for NOE is uncertain. However, treatment depends on prolonged administration of systemic antimicrobial therapy with antipseudomonal activity. Surgical management is reserved for refractory cases that fail to resolve with appropriate antimicrobial therapy. None of the patients in our cohort underwent surgery. Current IV antipseudomonal antibiotics require frequent dosing which may preclude their use in outpatient settings. Similar to other studies, piperacillin/tazobactam was the most frequently prescribed parenteral antimicrobial agent in our cohort [8, 26]. We often reserve ceftazidime and meropenem for patients with a definite history of non-urticarial rash allergy to penicillin or evidence of antimicrobial resistance to piperacillin/tazobactam. In our cohort, piperacillin/tazobactam was administered by continuous infusion using elastomeric devices since it allows for once daily community nurse visits and ease of patient teaching and use. Elastomeric pumps and devices allow for continuous and prolonged antimicrobial infusions in OPAT. This helps to optimise the pharmacokinetic/pharmacodynamic ratio (percentage of the time between two injections during which the antibiotic is superior to the minimum inhibitory concentration of the bacteria under consideration) of time-dependent antibiotics (such as penicillins, carbapenems and cephalosporins) and reduces risk of failure and resistance emergence during treatment [27]. In our cohort, antibiotic dosing was appropriately adjusted according to renal function based on established guidelines. Although we did not explore the effects of antimicrobial concentration on clinical outcomes in patients with impaired renal function, we did not find any association between antimicrobial agents and OPAT failure.

Oral antimicrobial therapy (e.g. oral ciprofloxacin) may be a suitable alternative to OPAT in selected patients with NOE. However, OPAT remains a safe, cost-effective and efficacious alternative to inpatient treatment when oral therapy is not appropriate due to antimicrobial resistance, drug interactions, intolerance, poor adherence or poor oral absorption. Furthermore, patients with advance disease and complications such as intracranial complications may require prolonged parenteral therapy. Fluoroquinolones (FQs) are the only available oral treatment for *P. aeruginosa* infections, but resistance is becoming increasingly prevalent. In our cohort, ciprofloxacin-resistant *P. aeruginosa* strains were isolated in three cases which precluded use of oral therapy. There is increasing concerns regarding prolonged use of FQs due to potential serious adverse effects such as tendon rupture, aortic aneurysm and dissection, cardiac arrhythmia (QTc prolongation), hypoglycaemia and *Clostridium difficile* infection. Consequently, oral antimicrobial treatment for uncomplicated NOE could potentially be administered within an OPAT setting to allow close monitoring for compliance and side effects, and timely intervention [28].

Evaluating treatment response in NOE can be challenging. Treatment discontinuation is often based on clinical and radiological improvement, and normalisation of inflammatory markers. Gallium citrate Ga-67 scan is the imaging of choice for follow-up in our centre since it can identify areas of residual infection and often returns to normal once inflammation subsides [29]. A small number of patients in our study had normal inflammatory markers (i.e. CRP, ESR and WCC) at diagnosis, and treatment discontinuation was based on clinical and radiological improvement. We did not find an association between presence of elevated inflammatory markers and clinical outcome. However, changes in inflammatory can help to monitor response to antimicrobial therapy.

Although we did not carry out a cost-effectiveness analysis, we observed considerable cost savings by treating our cohort of patients outside the hospital setting. It is worth mentioning that OPAT provides several indirect benefits and cost savings (e.g. reduction in the cost of nosocomial infections, increased productivity and quality of life) for patients and healthcare systems [2].

Our study is limited by its retrospective design, relatively small sample, and restriction to single-centre experience. The data were initially collected prospectively, which reduces the risk of measurement bias or poor data accuracy. Despite extensive analysis of previously reported risk factors for poor outcomes in patients with NOE, we cannot be certain that we have not missed other important risk factors or the influence of unrecorded confounders. Although our epidemiological data are comparable to other cohort studies, the relatively low incidence of NOE suggests that large multicentre studies are required to confirm our findings and comprehensively explore prognostic factors in NOE treated with OPAT. Novel studies such as the IONOE study could provide more insights into the optimal management of NOE [30].

Our study provides an insight into the duration of therapy for NOE and risk of treatment failure. It shows that patients with NOE could be safely and effectively treated in outpatient settings with substantial cost savings. However, some patients may be at risk of treatment failure and prolonged treatment. Careful patient selection for OPAT, vigorous antimicrobial treatment and close monitoring of patients with pre-existing comorbidities, facial nerve paralysis, extensive disease and very high inflammatory markers are recommended to optimise clinical outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10096-022-04455-y.

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Author contribution OCD conceived the study, collected and analysed data, and wrote the manuscript. AS collected data and revised the manuscript. EIK analysed data and revised the manuscript.

Declarations

Ethics approval This study was approved by the local clinical audit/effectiveness unit as part of ongoing commitment to service development and clinical governance.

Consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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Paper 5

Developing a risk prediction model for 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy

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Original article

Developing a risk prediction model for 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy

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ABSTRACT

Objectives: Outpatient parenteral antimicrobial therapy (OPAT) is increasingly used to treat a wide range of infections. However, there is risk of hospital readmissions. The study aim was to develop a prediction model for the risk of 30-day unplanned hospitalization in patients receiving OPAT.

Methods: Using a retrospective cohort design, we retrieved data on 1073 patients who received OPAT over 2 years (January 2015 to January 2017) at a large teaching hospital in Sheffield, UK. We developed a multivariable logistic regression model for 30-day unplanned hospitalization, assessed its discrimination and calibration abilities, and internally them validated using bootstrap resampling.

Results: The 30-day unplanned hospitalization rate was 11% (123/1073). The main indication for hospitalization was worsening or nonresponse of infection (52/123, 42%). The final regression model consisted of age (adjusted odds ratio (aOR), 1.18 per decade; 95% confidence interval (CI), 1.04–1.34), Charlson comorbidity score (aOR, 1.11 per unit increase; 95% CI, 1.00–1.23), prior hospitalizations in past 12 months (aOR, 1.30 per admission; 95% CI, 1.17–1.45), concurrent intravenous antimicrobial therapy (aOR, 1.89; 95% CI, 1.03–3.47) and endovascular infection (aOR, 3.51; 95% CI, 1.49–8.28). Mode of OPAT treatment was retained in the model as a confounder. The model had adequate concordance (*c*-statistic 0.72; 95% CI 0.67–0.77) and calibration (Hosmer-Lemeshow p 0.546; calibration slope 0.99; 95% CI 0.78–1.21), and low degree of optimism (bootstrap optimism corrected *c*-statistic, 0.70).

Conclusions: We identified a set of six important predictors of unplanned hospitalization based on readily available data. The prediction model may help improve OPAT outcomes through better identification of high-risk patients and provision of tailored care. **O.C. Durojaiye, Clin Microbiol Infect 2019;25:905.e1–905.e7**

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Introduction

Intravenous (IV) antimicrobial agents are increasingly administered in outpatient settings to treat a wide range of infections in patients who require parenteral therapy but who are otherwise well enough not to need hospitalization. Outpatient parenteral antimicrobial therapy (OPAT) has been shown to be safe, clinically efficacious and cost-effective, with high levels of patient satisfaction and acceptability [1–8]. Despite its benefits, OPAT is potentially associated with increased clinical risk due to reduced monitoring and supervision. Even with careful patient selection and multidisciplinary team–driven therapeutic plans, the nature of the infections treated and duration of treatment mean readmission for some patients is inevitable. Thirty-day readmission rates have been used in the United Kingdom and internationally as a marker of healthcare quality [9]. Predicting and preventing unplanned hospitalization could improve patient outcomes and reduce healthcare costs. Few studies have assessed risk factors for unplanned hospitalization in OPAT [10–12]. To our knowledge, no risk prediction models for hospitalization have been developed for patients receiving OPAT within the UK National Health Service.

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This study aimed to identify factors that might be associated with increased risk of hospital readmission in an OPAT service based in a large tertiary referral teaching hospital in Sheffield, UK, and to develop a predictive model for 30-day unplanned hospitalization. The development of an accurate prediction rule may help identify high-risk patients and provide personalized care and support.

Methods

Patient population and setting

We performed a retrospective analysis of all patients who received OPAT between January 2015 and January 2017 at Sheffield Teaching Hospitals, South Yorkshire, England, UK. The Sheffield OPAT service, established in January 2006, is one of the largest in the United Kingdom. The OPAT service, patient selection criteria and a prospectively maintained database have been previously described [13]. Patient selection, antimicrobial regimens and mode of OPAT delivery were the responsibility of the OPAT physicians.

Data collection

The OPAT database, hospital electronic clinical and laboratory databases were reviewed. Data extracted included patient demographics, comorbidities, hospitalization at Sheffield Teaching Hospitals in the previous 12 months, treatment indication, microbiology culture data, antimicrobial regimen, mode of OPAT delivery, type of IV access, length of OPAT stay, OPAT outcome, prior OPAT stay, hospital readmission, and reason for and length of hospitalization. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT commenced [14]. Drug-resistant organisms were defined as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, multidrug-resistant tuberculosis, extended-spectrum β-lactamase–producing bacteria and multidrug-resistant *Candida*.

The primary outcome was 30-day unplanned hospitalization, defined as unplanned inpatient admission to an acute care hospital for any reason within 30 days of discharge from the OPAT service.

Sample size

To ensure a reliable prediction model, we adhered to the accepted rule of having at least ten events per regression coefficient estimated [15]. We planned for 15 predictor degrees of freedom. Using an anticipated hospitalization rate of 10% with approximately 750 OPAT episodes per year, we chose to review 2 years' worth of OPAT records to ensure adequate sample size for formulating the model.

Statistical analysis

Because some patients had more than one episode of OPAT treatment during the study period, we performed individual-level analysis by taking a simple random sample of one OPAT episode per patient. Univariate analysis was performed to describe differences between patients with 30-day unplanned hospitalization and those without and to confirm expected predictive relations from previous studies. Crude associations were quantified using odds ratios with 95% confidence intervals (CI) calculated by binary logistic regression.

A multivariable logistic regression model was developed to predict the risk of unplanned hospitalization within 30 days of discharge from OPAT. We initially considered 13 predictor variables based on review of the literature, clinical relevance and data availability at time of OPAT initiation. These included patient sex, age, number of prior hospitalizations in the past 12 months, Charlson comorbidity score, mode of antimicrobial delivery, drug-resistant organisms, concurrent intravenous antimicrobial therapy, four antimicrobial classes (penicillin, cephalosporin, carbapenem and glycopeptide), indication for OPAT and type of vascular access (peripheral vs. central) (Larraza AV et al., 'Unplanned 30-day hospital readmission of patients receiving outpatient parenteral antimicrobial therapy,' poster presented at the 27th European Congress of Clinical Microbiology and Infectious Diseases meeting, 22–25 April 2017, Vienna, Austria) [10–12,16–22]. None of the candidate predictor variables had missing values in our database. To minimize the risk of overfitting, no exploratory search beyond the prespecified set of predictors was carried out.

To limit collinearity and ensure a parsimonious prognostic model, we examined Spearman correlations and variance inflation factors among the 13 initial predictors. Of the four antimicrobial classes examined, we retained only cephalosporin in the analysis because it had strong negative correlations with other classes and is the most commonly prescribed antimicrobial class in OPAT [1,5,12] (thus limiting candidate predictors to ten variables). We assessed nonlinear effects of continuous variables using restricted cubic splines. A linear relationship with the log odds of 30-day unplanned hospitalization was found to be a good approximation for age, Charlson score and number of prior hospitalizations.

After the fit of the logistic regression model with the preselected set of ten predictors, those that did not retain statistical significance (at the alpha level of 0.05) were tested for confounding and predictive contributions by dropping them one at a time, starting from the least significant. Predictors that caused substantial confounding (change in model coefficient by at least 10%) or improved prediction (nonzero difference in *c*-statistic of nested models) were retained in the model. We also considered changes in the Bayesian information criterion during this process. To provide a graphical depiction of all variables in the final risk-prediction model and enable an approximate computation of output probabilities, we constructed a Kattan-style nomogram in which the length of the line corresponding to a given predictor is indicative of its importance. Points were assigned to each predictor variable, and total points corresponded to an absolute predicted risk for 30-day unplanned hospitalization.

The validity of the final model was assessed by estimating its concordance and calibration ability. Model calibration (agreement between observed outcomes and predictions) was assessed by the Hosmer-Lemeshow goodness-of-fit test and by evaluating how much the slope of the calibration line (plotting the predicted probabilities against the observed probabilities) deviates from the ideal of 1.0. Discrimination ability (the extent to which the model distinguishes patients with unplanned hospitalization from those without) was assessed using the concordance statistic (*c*-statistic). Internal validation was carried out by calculating the *c*-statistic with correction for 'optimism' overfitting using 200 bootstrap samples.

Data were processed and analysed by STATA/IC 3.1 (StataCorp, College Station, TX, USA). The nomolog programme was used to produce the nomogram [23].

Ethical approval for this study was not deemed necessary because the data were routinely collected and analysed for clinical governance, service development and service evaluation activities. The study complied with the transparent reporting of studies developing multivariable prediction models for individual prognosis (TRIPOD) statement [24].

Results

Cohort characteristics

Over the 2-year study period, we recorded 1324 episodes of OPAT in 1073 individual patients. To develop the risk prediction

model, a random sample of one episode per patient was selected. Table 1 shows the demographic and clinical characteristics of the cohort. The mean age of the patients was 56 (range, 16–95) years, and 57% (611/1073) subjects were male. Skin and soft tissue infection (SSTI) was the most common indication for OPAT (616/1073, 57%) and use of cephalosporins (577/790, 73%). Most patients received intravenous therapy by attending the infusion centre daily (767/1073, 71%). The median duration of OPAT was 7 days (interquartile range, 4–19 days; range, <1 to 261 days).

Hospitalization within 30 days of discharge from the OPAT service was recorded in 14% (145/1073) patients. The majority of these hospitalizations were unplanned (123/1073, 11%; 95% CI, 9.6–13.4). Seventy-eight (63%) of the 123 patients with unplanned hospitalization were admitted during OPAT treatment. Half of these patients (38/78, 49%) were admitted within the first week of treatment. More than a third of the patients (17/45, 38%) who required hospitalization after completion of OPAT were admitted 2 weeks after OPAT therapy. Reasons for the unplanned hospitalization are shown in Table 2. The leading indication for hospitalization was progression or nonresponse of infection (52/123, 42%). The median length of hospitalization was five days (interquartile range, 2–10; range, <1 to 114 days).

Table 1
Patient characteristics

Characteristic	With 30-day unplanned hospitalization (n = 123), n (%)	Without 30-day unplanned hospitalization (n = 950), n (%)	OR (95% CI)[a]
Male sex	67 (54.5)	544 (57.3)	0.89 (0.61–1.30)
Age (years), mean (SD)	60.8 (17.1)	55.5 (17.5)	1.02 (1.01–1.03)
Comorbidities			
Chronic pulmonary disease	34 (27.6)	163 (17.2)	1.84 (1.20–2.83)
Diabetes with complications	21 (17.1)	88 (9.3)	1.42 (1.10–1.84)
Peripheral vascular disease	19 (15.4)	68 (7.2)	2.37 (1.37–4.10)
Diabetes without complications	9 (7.3)	98 (10.3)	0.69 (0.34–1.40)
Tumour without metastasis	16 (13.0)	74 (7.8)	1.33 (1.00–1.77)
Moderate or severe renal disease	20 (16.3)	62 (6.5)	1.67 (1.27–2.19)
Connective tissue disease	12 (9.8)	59 (6.2)	1.63 (0.85–3.13)
Myocardial infarction	19 (15.4)	60 (6.3)	2.71 (1.56–4.72)
Cerebrovascular disease	7 (5.7)	42 (4.4)	1.30 (0.57–2.97)
Congestive heart failure	12 (9.8)	41 (4.3)	2.40 (1.22–4.70)
Peptic ulcer disease	7 (5.7)	33 (3.5)	1.68 (0.72–3.88)
Moderate or severe liver disease	8 (6.5)	17 (1.8)	1.56 (1.17–2.08)
Metastatic solid tumour	1 (0.8)	20 (2.1)	0.85 (0.61–1.19)
Lymphoma	1 (0.8)	7 (0.7)	1.05 (0.37–3.01)
Leukaemia	1 (0.8)	10 (1.1)	0.88 (0.31–2.46)
Haemiplegia	0	6 (0.6)	—
Dementia	1 (0.8)	5 (0.5)	1.55 (0.18–13.37)
AIDS	0	2 (0.2)	—
Mild liver disease	0	0	—
Charlson comorbidity score, median (IQR)	2 (0–3)	1 (0–2)	1.23 (1.13–1.34)
Indication for OPAT			
Skin and soft tissue infection	48 (39.0)	568 (59.8)	1.00 (Ref.)
Bone and joint infection	22 (17.9)	115 (12.1)	2.26 (1.31–3.90)
Urogenital infection	13 (10.6)	57 (6.0)	2.70 (1.38–5.28)
Respiratory disease	6 (4.9)	39 (4.1)	1.82 (0.73–4.52)
Endovascular infection	11 (8.9)	34 (3.6)	3.83 (1.82–8.03)
Other indication	23 (18.7)	137 (14.4)	1.99 (1.17–3.38)
Multidrug resistant organism	15 (12.2)	71 (7.5)	1.72 (0.95–3.11)
Mode of antimicrobial delivery			
Infusion centre	75 (61.0)	692 (72.8)	1.00 (Ref.)
Self/carer administration	15 (12.2)	90 (9.5)	1.54 (0.85–2.79)
Community nurse	33 (26.8)	168 (17.7)	1.81 (1.16–2.82)
Type of vascular access			
Central line	54 (43.9)	261 (27.5)	2.07 (1.41–3.03)
Peripheral access	69 (56.0)	689 (72.5)	1.00 (Ref.)
Antimicrobial agent[b,c]			
Penicillin	19 (15.4)	74 (7.8)	2.16 (1.26–3.72)
Cephalosporin	66 (53.7)	724 (76.2)	0.36 (0.25–0.53)
Carbapenem	22 (17.9)	82 (8.6)	2.31 (1.38–3.85)
Glycopeptide	21 (17.1)	77 (8.1)	2.33 (1.38–3.94)
Other	8 (6.5)	43 (4.5)	1.47 (0.67–3.20)
Concurrent intravenous antimicrobial therapy	21 (17.1)	60 (6.3)	3.05 (1.78–5.23)
Oral antibiotic included	8 (6.5)	114 (12.0)	0.51 (0.24–1.07)
Duration of OPAT (days), median (IQR)	9 (4–20)	7 (4–19)	1.00 (0.98–1.01)
No. of prior hospitalizations, median (IQR)[d]	1 (0–3)	0 (0–1)	1.38 (1.26–1.52)
Prior OPAT stay in past 12 months	23 (18.7)	150 (15.8)	1.23 (0.75–1.99)
Initiation of OPAT as inpatient	87 (70.7)	615 (64.7)	1.32 (0.87–1.98)

Data are presented as n (%) unless otherwise indicated. CI, confidence interval; IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio; SD, standard deviation.

[a] ORs for numerical variables refer to unit increases.

[b] Reference category for each antimicrobial agent is receipt of any other antibiotic (e.g. receipt of penicillin vs. no penicillin).

[c] Some patients received more than one parenteral antimicrobial agent. Thus, total number of antimicrobial agents is greater than total number of patients.

[d] In 12 months preceding current OPAT episode.

Univariate (unadjusted) analysis

Patients with unplanned hospitalization were older (mean, 61 vs. 56 years), had higher Charlson comorbidity scores (median 2 vs. 1) and had more prior hospital admissions in the past 12 months (median 1 vs. 0) compared to patients without 30-day unplanned hospitalizations (Table 1). Unplanned hospitalization was also more likely to have occurred in patients who had received OPAT by a community nurse as opposed to an infusion centre, patients with central vascular access devices as opposed to peripheral access and patients treated for endovascular, urogenital or bone and joint infections as opposed to SSTI. Regarding antimicrobial class, unplanned hospitalization was positively associated with receipt of penicillin, carbapenem and glycopeptide, but negatively associated with use of cephalosporin. Patients who had an unplanned hospitalization were also more likely to have been treated simultaneously with multiple parenteral antimicrobial agents.

Multivariable model

Results of logistic regression analysis are shown in Table 3 for the full set of the ten preselected predictors (model 1) and for the model that retained only predictors with important predictive contribution or confounding effects (model 2). Age, prior non-OPAT hospitalization in the past 12 months, endovascular infection and receipt of concurrent intravenous antimicrobial therapy were independently and significantly associated with increased risk of 30-day unplanned hospitalization. Receipt of intravenous cephalosporin therapy was significantly associated with decreased risk of 30-day unplanned hospitalization. Charlson comorbidity score and mode of OPAT delivery had high p values. However, both variables were retained in the model because the former made an important predictive contribution and the latter was an important confounder. By contrast, patient sex, type of vascular access device or multidrug-resistant organism had no predictive contribution in the risk of hospitalization. Because antimicrobial treatment may reflect local practices that may limit generalizability of the prediction model to different OPAT settings, we examined the possibility of removing the cephalosporin variable from the model. Model discrimination and calibration were affected only slightly, but the Bayesian information criterion improved slightly, supporting the removal of cephalosporin from the final model (Table 3).

Independent predictors of the risk of 30-day unplanned hospitalization in the final model (model 3) were age (adjusted odds ratio (aOR), 1.18 per decade; 95% CI, 1.04–1.34), Charlson comorbidity score (aOR, 1.11 per unit increase; 95% CI, 1.00–1231), prior non-OPAT hospitalization in the past 12 months (aOR, 1.30 per prior admission; 95% CI, 1.17–1.45), receipt of concurrent intravenous antimicrobial therapy (aOR, 1.89; 95% CI, 1.03–3.47), treatment for endovascular infection (aOR, 3.51; 95% CI, 1.49–8.28) and urogenital infection (aOR, 2.62; 95% CI, 1.27–5.43) and bone and joint infection (aOR, 2.09; 95% CI, 1.06–4.12) as opposed to SSTI. Mode of OPAT delivery was retained in the final model as an important confounder. Fig. 1 provides a nomogram of the model's predicted risks for 30-day unplanned hospitalization.

The final model's discrimination ability was adequate (*c*-statistic 0.72; 95% CI 0.67–0.77), and internal validation indicated a low degree of overfitting (bootstrap optimism-corrected *c*-statistic, 0.70). Model predicted probabilities ranged 1.8% to 83.4%. The Hosmer-Lemeshow test (p 0.546) and the calibration slope (0.99; 95% CI 0.78–1.21) indicated a good agreement between predicted and observed probabilities. In addition, the calibration plot did not indicate a pattern of either over- or underestimation (Fig. 2).

Table 2
Reasons for 30-day unplanned hospitalization ($n = 123$)

Reason for hospitalization	Patient episodes, *n* (%)
Worsening of existing infection/no improvement	52 (42.3)
Non-OPAT related	50 (40.7)
New infection	8 (6.5)
Adverse drug reaction	7 (5.7)
Intravenous line–related complications	3 (2.4)
Clostridium difficile–associated diarrhoea	2 (1.6)
Unknown	1 (0.8)

OPAT, outpatient parenteral antimicrobial therapy.

Discussion

Our study highlights the fact that patients treated with OPAT are at risk of unplanned hospital readmission. The rate of unplanned hospitalization (123/1073, 11%) in our cohort is comparable to other OPAT studies (Larraza AV et al., 'Unplanned 30-day hospital readmission') [20]. Worsening response or nonresponse of infection was the main indication for unplanned hospitalization. These patients were readmitted for further management, including change in antimicrobial therapy and source control. We found the following factors, which are readily available at the time of commencing OPAT, to be important predictors of unplanned hospitalization: age, prior non-OPAT hospitalizations in past 12 months, Charlson comorbidity index score, concurrent receipt of more than one intravenous antimicrobial agent and indication for OPAT.

Patient age, underlying comorbid conditions and prior hospital admissions have been recognised as important patient-related risk factors for hospital readmission in OPAT patients in previous research (Larraza AV et al., 'Unplanned 30-day hospital readmission') [12,16,17,19,22]. We estimated a relative increase in the odds of 30-day hospitalization of about 18% per decade increase in age and of about 30% per prior admission of patients attending our OPAT service, which are close to those reported in a comparable study in Tufts Medical Center in Boston [12]. Patients with prior hospital admissions were more likely to be hospitalized because they usually have more medical comorbidities and are likely to be readmitted as a result of other conditions. Using the composite Charlson comorbidity index, we additionally identified an important risk increase associated with patient multimorbidity (an increase in the odds of 30-day hospitalization by 11% per unit increase in Charlson score).

The increased risk of hospitalization in patients who were treated simultaneously with multiple parenteral antimicrobial agents (i.e. concurrent antimicrobial therapy) in our cohort may reflect a higher severity of infection, adverse drug reactions or drug interactions. Similar to other OPAT services [1,5,7,10,12,17,18,22], cephalosporins were the most frequently prescribed parenteral antimicrobial agent in our cohort (790/1136, 70%). Patients who received IV cephalosporin were less likely to be hospitalized. We mostly use IV ceftriaxone to treat patients with uncomplicated SSTI. These patients are generally well and are at lower risk of hospitalization. In Glasgow, Scotland, United Kingdom, ceftriaxone therapy was found to be associated with reduced duration of OPAT in patients with skin and soft tissue infections [10]. Nevertheless, we decided to exclude cephalosporin treatment from our risk prediction model because it might reflect our specific OPAT setting and might be a less influential clinical factor in other settings. Future studies should consider examining a potential association between cephalosporin use in OPAT and readmission.

Similar to Kouma et al. [19], we also found a strong association of endovascular infection with unplanned hospitalization.

Table 3
Multivariable logistic regression models for risk of 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy ($n = 1073$)

Predictor	Model 1			Model 2			Model 3 (final)		
	aOR	95% CI	p	aOR	95% CI	p	aOR	95% CI	p
Male sex	0.77	0.51–1.17	0.217	—	—	—	—	—	—
Age, per 10 years	1.19	1.04–1.35	0.010	1.18	1.03–1.34	0.012	1.18	1.04–1.34	0.012
Prior hospitalizations	1.29	1.16–1.44	<0.001	1.28	1.15–1.43	<0.001	1.30	1.17–1.45	<0.001
Charlson comorbidity score	1.10	0.99–1.22	0.065	1.09	0.99–1.21	0.082	1.11	1.00–1.23	0.045
Mode of delivery									
Infusion centre	1.00	—	—	1.00	—	—	1.00	—	—
Self/carer administration	0.76	0.36–1.62	0.484	0.75	0.37–1.53	0.426	0.79	0.39–1.62	0.525
Community nurse	0.60	0.33–1.10	0.098	0.60	0.33–1.07	0.083	0.62	0.35–1.11	0.108
Multidrug-resistant organism	0.71	0.35–1.44	0.342	—	—	—	—	—	—
Concurrent IV antimicrobial therapy	2.15	1.15–4.01	0.017	2.01	1.09–3.70	0.026	1.89	1.03–3.47	0.041
Receipt of intravenous cephalosporin	0.49	0.28–0.84	0.010	0.55	0.33–0.91	0.020	—	—	—
Indication for OPAT									
Skin and soft tissue infection	1.00	—	—	1.00	—	—	1.00	—	—
Bone and joint infection	1.65	0.75–3.62	0.212	1.46	0.69–3.07	0.318	2.09	1.06–4.12	0.032
Urogenital infection	1.84	0.79–4.30	0.160	1.74	0.77–3.91	0.180	2.62	1.27–5.43	0.009
Respiratory disease	1.28	0.46–3.56	0.642	1.22	0.45–3.35	0.695	1.55	0.58–4.14	0.382
Endovascular infection	3.19	1.22–8.31	0.018	2.74	1.13–6.65	0.026	3.51	1.49–8.28	0.004
Other indication	1.96	0.97–3.95	0.061	1.78	0.93–3.42	0.084	2.17	1.16–4.06	0.015
Central line access	0.85	0.45–1.61	0.610	—	—	—	—	—	—
Model performance statistics									
Calibration slope	1.01	0.77–1.25	—	0.96	0.68–1.25	—	0.99	0.78–1.21	—
HL goodness of fit, χ^2 (*df*)	7.83 (8)	—	0.450	11.79 (8)	—	0.161	6.91 (8)	—	0.546
C statistic	0.74	0.69–0.79	—	0.73	0.69–0.78	—	0.72	0.67–0.77	—
C statistic, BOC	0.70	—	—	0.71	—	—	0.70	—	—
BIC	793.1	—	—	774.9	—	—	773.3	—	—

Initial model (model 1) contains full set of candidate predictors. Model 2 retains only predictors with substantial predictive contribution and/or important confounders. Final model (model 3) excludes cephalosporin variable (based on lowest BIC). aOR, adjusted odds ratio; BIC, Bayesian information criterion; BOC, bootstrap optimism corrected; CI, confidence interval; df, degrees of freedom; HL, Hosmer-Lemeshow; IV, intravenous; OPAT, outpatient parenteral antimicrobial therapy.

Endocarditis accounted for more than two thirds of endovascular infections treated in our cohort. These patients were properly selected for OPAT in line with national guidelines. Larraza et al. ('Unplanned 30-day hospital readmission') additionally reported respiratory and post–intra-abdominal surgery infections as risk factors for readmission in their cohort. However, the indication for OPAT (infection treated) was not identified as a risk factor for readmission in other comparable studies [12,16–18].

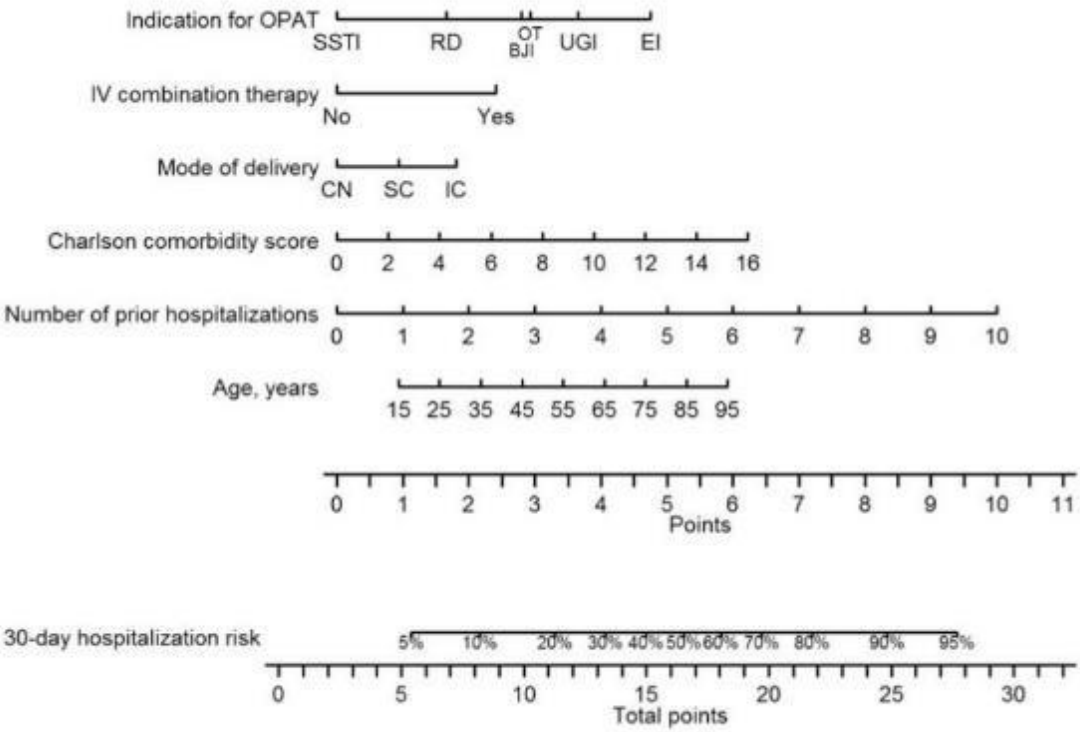

Fig. 1. Prediction rule nomogram for risk of 30-day unplanned hospitalization after outpatient parenteral antimicrobial therapy. BJI, bone and joint infection; CN, community nurse; EI, endovascular infection; IC, infusion centre; IV, intravenous; OT, other indication; RD, respiratory disease; SC, self/carer administration; SSTI, skin and soft tissue infection; UGI, urogenital infection.

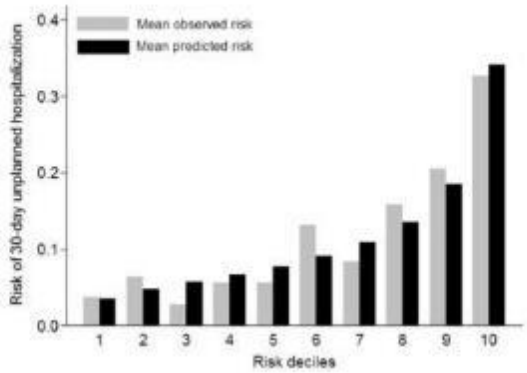

Fig. 2. Calibration plot for final model of risk of 30-day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy.

Unlike other OPAT studies [12,16–18], we did not identify aminoglycoside use, presence of drug-resistant organisms or length of treatment as predictors of unplanned hospitalization. In our cohort, aminoglycosides were administered in only eight patients. We seldom use aminoglycosides in our OPAT service because of the toxicity of these agents and challenges in therapeutic drug monitoring in an outpatient setting. Although OPAT administered at home by community nurses appeared to be associated with an increased risk of hospitalization in univariate analysis, the association diminished after adjusting for other predictors. Nevertheless, we retained mode of OPAT treatment in our risk prediction model as an important confounder.

Some limitations of this study should be acknowledged. This was a single-centre study. Although our epidemiologic data are consistent with those reported in different settings in the United Kingdom and the United States [10–12,16,17], our risk prediction model needs to be externally validated to assess its generalizability to patients treated in other settings. Our analysis was retrospective, but the data were originally collected prospectively, which reduces the risk of measurement bias or poor accuracy of data records. However, we cannot be certain that we have not missed some patients who were readmitted to other hospitals. The potential for undocumented hospital readmissions might result in an underestimate of the actual risk of 30-day hospitalization. Nevertheless, most patients' interactions with healthcare systems are documented in their clinical records, and they were usually reviewed 4 to 6 weeks after completion of OPAT. Despite extensively analysing factors previously reported to be associated with hospitalization, we cannot be certain that we have not missed other important predictors or that unrecorded confounders may have influenced our findings. We did not explore factors (such as therapeutic drug levels, frequency of monitoring or follow-up visits) that are not readily available before OPAT but that are plausible readmission risk factors; our aim was to develop a risk prediction model based on data available on presentation to the OPAT service. Our risk prediction model produced excellent agreement (calibration) between observed and predicted probabilities of 30-day hospitalization, and the bootstrap internal validation suggests only a small degree of bias from overfitting the model to our data. However, our model should be prospectively validated in an independent diverse patient population before use in actual patient care. We intend to continue the project and are currently planning for quasi-external validation of the model in future patients in our centre and external validation in patients from other UK centres.

This study adds to existing literature by showing that patients receiving OPAT are at risk of unplanned hospitalizations, some of which may be preventable. Averting unnecessary hospitalization depends on understanding which patients are likely to be readmitted. The predictive model for 30-day unplanned hospitalization developed in this study is based on six easily obtainable variables and has adequate prediction metrics. This model has the potential to identify high-risk patients upon presentation to the OPAT service at a large tertiary referral teaching hospital, thereby informing evidence-based interventions and personalized care, and support to prevent hospital readmissions. Further research is required to assess how this model may perform in different settings and to elucidate how it may be incorporated into clinical practice to improve the care of patients receiving OPAT.

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Transparency declaration

All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2018.11.009.

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Paper 6

External validity and clinical usefulness of a risk prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy

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External validity and clinical usefulness of a risk prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy

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Objectives: Outpatient parenteral antimicrobial therapy (OPAT) is increasingly used to treat a variety of infections. However, hospital readmissions remain relatively common. We examined the external validity and clinical usefulness of a previously derived risk prediction model for 30 day unplanned hospitalization in patients receiving OPAT.

Methods: A retrospective cohort study was conducted at two large teaching hospitals in the UK. The design comprised quasi-external temporal validation on patients from the same OPAT setting as the model development, and broader external validation on patients from a different setting. The model predictors were age, prior hospitalizations in the preceding 12 months, Charlson comorbidity score, concurrent IV antimicrobial therapy, type of infection and mode of OPAT treatment. Discriminative ability, calibration and clinical usefulness were assessed.

Results: Data from 2578 OPAT patients were analysed. The rates of 30 day unplanned hospitalization were 11.5% (123/1073), 12.9% (140/1087) and 25.4% (106/418) in the model derivation, temporal validation and broader external validation cohorts, respectively. The discriminative ability of the prediction model was adequate on temporal validation (*c*-statistic 0.75; 95% CI: 0.71–0.79) and acceptable on broader validation (*c*-statistic 0.67; 95% CI: 0.61–0.73). In both external cohorts, the model displayed excellent calibration between observed and predicted probabilities. Decision curve analysis showed increased net benefit across a range of meaningful risk thresholds.

Conclusions: A simple risk prediction model for unplanned readmission in OPAT patients demonstrated reproducible predictive performance, broad clinical transportability and clinical usefulness. This model may help improve OPAT outcomes through better identification of high-risk patients and provision of tailored care.

Introduction

IV antimicrobial agents are increasingly administered in outpatient settings to treat a variety of infections in patients who need parenteral therapy but are well enough not to require hospitalization.[1,2] The efficacy and safety of outpatient parenteral antimicrobial therapy (OPAT) have been well documented.[3–6] Despite its benefits, OPAT is potentially associated with increased clinical risk due to the reduced level of clinical supervision and monitoring compared with inpatient care. Even with careful patient selection and multidisciplinary team-driven therapeutic plans, the nature of infections treated, the use of potentially toxic antimicrobial agents and the duration of treatment imply that complications, including readmissions for some patients, are inevitable. Thirty-day readmission rates have been used in the UK and internationally as a marker of healthcare quality and OPAT outcome.[7–9] Predicting and preventing unplanned hospitalization could improve patient outcomes and reduce healthcare costs. We previously developed a risk prediction model for 30 day unplanned hospitalization in patients receiving OPAT at a large teaching hospital in Sheffield, UK.[10] The model predictors were: age; Charlson comorbidity score; prior

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hospitalizations in the preceding 12 months; concurrent IV antimicrobial therapy; type of infection; and mode of OPAT treatment. The performance of clinical prediction models can vary due to changing outcome rates, shifting patient mix and evolving clinical practice. Before a prediction model can be used in clinical practice, it is essential to evaluate its ability to produce accurate predictions as well as its usefulness to support clinical decision-making on new subjects from the same source population (reproducibility) and in different clinical settings (transportability).[11–13]

This study aimed to evaluate the external validity and clinical usefulness of a previously published model for predicting the risk of 30 day unplanned hospitalization in patients receiving OPAT,[10] by selecting more recently treated subjects in the OPAT setting where the model was derived (reproducibility) and subjects from a different OPAT setting (transportability).

Patients and methods

Study design and setting

We conducted a retrospective cohort study of adult patients (aged >18 years) who received OPAT at two large teaching hospitals in the UK (Sheffield Teaching Hospitals and Royal Derby Hospital). The design comprised quasi-external validation on patients (Sheffield cohort) having temporal characteristics different from those of the model development (temporal validation) and broader external validation on patients from a different OPAT setting (Derby cohort) with expected differences in case mix.

The Sheffield and Derby OPAT services were formally established in 2006 and 2013, respectively. Both services are run by a multidisciplinary team of infection specialists, specialist nurses and clinical antimicrobial pharmacists. In the Sheffield OPAT centre, antimicrobials were delivered by three distinct pathways: daily attendance at the 'infusion centre'; self or carer administration in the patient's home; and administration by a district/community nurse in the patient's home. However, in the Derby OPAT setting, antimicrobials were primarily delivered in the patient's home by visiting nurses. Both OPAT centres maintain electronic databases to prospectively record patient demographics, clinical diagnosis, model of delivery, antimicrobial agents, treatment duration, type of vascular access, clinical outcome and complications. Patient selection, antimicrobial regimen and mode of OPAT delivery were the responsibility of the infection specialists at each centre. The clinical responsibility for patients receiving OPAT and their follow-up were shared between the referring clinicians and the OPAT infection specialists, unless otherwise agreed.

The temporal and broader external validation cohorts were made up of data extracted from the OPAT databases and electronic health records of patients who received OPAT between January 2018 and January 2020. Age (years) was determined at the time of commencing OPAT. Weighted Charlson comorbidity score was calculated for each patient and was determined at the time OPAT was commenced.[14]

Original risk prediction model

The original prediction model was developed using data from 1073 patients who received OPAT between January 2015 and January 2017 in Sheffield (derivation cohort).[10] The primary outcome was 30 day unplanned hospitalization, defined as unplanned inpatient admission to an acute care hospital for any reason within 30 days of discharge from the OPAT service. The model consisted of six predictors: age; Charlson comorbidity score;[14] number of prior non-OPAT hospitalizations in the preceding 12 months; concurrent receipt of more than one IV antimicrobial agent; type of infection; and mode of OPAT delivery (infusion centre, community nurse or self/carer administration). The linear predictor (LP) for a patient was given by: LP = −3.628 + (0.016 × age in years) + (0.264 × number of prior hospitalizations) + (0.103 × Charlson comorbidity score) + (0.248, if self/carer administration) + (0.479, if infusion centre) + (0.635, if IV combination therapy) + (0.480, if endovascular infection) − (0.337, if respiratory disease) + (0.189, if urogenital infection) − (0.037, if bone and joint infection) − (0.776, if skin and soft tissue infection). The probability (or risk) of 30 day unplanned hospitalization for the same patient was given by: $1/[1 + \exp(-LP)]$.

Sample size

For external validation of prognostic models, a minimum of 100 outcome events is recommended to ensure adequate power to detect changes in predictive performance in external datasets.[15] Given our previous experience with the Sheffield OPAT service (about 65 unplanned readmissions per year),[10] we reviewed 2 years' worth of OPAT records to form the external validation cohorts in this study.

Statistical analysis

We conducted external validation in line with the methodological framework proposed by Debray *et al.*[13] We report the study in accordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) recommendations.[12] Because some patients had more than one episode of OPAT treatment during the study period, we performed individual-level analysis taking a simple random sample of one OPAT episode per patient.

The first step in our validation approach was to assess the extent to which the external cohorts are useful for evaluating the model's reproducibility or its transportability.[13] The relatedness between the derivation cohort and the external cohorts was reviewed using two approaches. First, the distribution of context-important patient characteristics, including model predictors and outcomes, were compared. Second, the degree of relatedness in case mix between the development and validation cohorts was quantified by the *c*-statistic [area under the receiver operating characteristic (ROC) curve] of a binary logistic regression (membership) model predicting the probability that an individual patient is a member of the derivation cohort as opposed to the validation cohort.[13] Independent variables in the membership model were the outcome and the six predictors of the original predictive model for unplanned hospitalization. Low values of the concordance *c*-statistic for the membership model (close to 0.5) indicate indistinguishable case mix between the datasets.

In the second step, we examined heterogeneity in predictor–outcome associations by fitting the original set of predictors internally to each validation cohort and by calculating optimism-corrected performance measures using bootstrap resampling with 500 replications.[16] Optimism-corrected measures were reduced by the estimated deterioration that the model is expected to have when applied to new individuals. We then externally assessed the performance of the originally developed model in each validation cohort. For the latter, a logistic regression model with the unplanned hospitalization as the outcome variable and the linear predictor of the original risk model as the only covariate was applied to each validation dataset.

Model performance was evaluated in terms of discriminative ability (to differentiate patients with unplanned hospitalization from those without) and calibration (agreement between predicted probabilities and actual rates of unplanned hospitalization). Discrimination was quantified with the *c*-statistic and was displayed graphically with an ROC curve. Calibration was broadly assessed by the Hosmer–Lemeshow goodness-of-fit test; a non-significant test indicates good calibration. The deviation of the intercept (calibration-in-the-large) and the slope of the calibration line (plotting predicted against observed event rates) from the ideal values of 1 and 0, respectively, were examined.[17] Calibration-in-the-large represents the agreement between the overall observed and the overall predicted risk of hospitalization (by definition this is zero in the development sample).

Calibration slopes >1 typically occur when predicted probabilities do not vary enough (e.g. predicted risks are systematically too low), whereas slopes <1 occur when they vary too much (e.g. low predictions are too low and high predictions are too high).[13,17] Calibration was visually inspected using loess-based calibration plots.[18]

In the third step, we used recalibration methods to improve the performance of the originally developed model in the validation cohorts.[19] Where calibration-in-the-large was significantly different from zero due to different overall risks of hospitalization in the external cohorts, intercept recalibration was performed by fitting a new logistic regression model with an intercept only and an offset term for the linear predictor of the original risk model.

Finally, we performed decision curve analysis to assess the clinical usefulness of the recalibrated model on the external cohorts.[20] This analysis provides insight into the range of predicted risks (decision thresholds) for which the model has a greater net benefit (NB) than an 'intervention for all' strategy (assuming all patients have complications and require hospitalization) or an 'intervention for none' strategy (assuming none have complications). NB combines the benefits of true positives and the harms of false positives on a single scale by weighting false positives by the odds of the chosen risk threshold to select patients for intervention.[20]

All patient data were anonymized prior to analysis. Data were processed and analysed using Stata/MP 14.1 (StataCorp, College Station, TX, USA). The study was approved by the local clinical effectiveness unit as part of ongoing commitment to service development.

Results

A total of 2578 patients were identified, of which 1073 were recorded in the initial model derivation cohort. We recorded 418 and 1087 patients in the temporal validation cohort (Sheffield, 2018–20) and broader external validation cohort (Derby, 2018–20), respectively. Table 1 compares patient characteristics and outcomes between the development and validation stages. The temporal validation (Sheffield) cohort had similar patient characteristics and outcomes as the derivation cohort. Of note, more subjects in the temporal validation cohort received glycopeptides (14.8% versus 9.1%; $P<0.001$) and concurrent oral antibiotic therapy (20.1% versus 11.4%; $P<0.001$) but fewer received cephalosporins (66.0% versus 73.6%; $P<0.001$), prior OPAT treatment (7.5% versus 16.1%; $P<0.001$) and 'infusion centre' administration (66.0% versus 73.6%; $P<0.001$) than the model development subjects. Rates of 30 day unplanned hospitalization were similar in the two cohorts (11.5% versus 12.9%; $P=0.314$). The *c*-statistic for the membership model comparing the respective cohorts was 0.60 (95% CI: 0.57–0.62), indicating similar case mix. This implies that temporal validation in this study merely assesses the model's reproducibility in the same target population rather than transportability in a different setting.

However, the broader external validation (Derby) cohort was different to the model derivation cohort. Subjects in the Derby cohort were older (mean age 68 versus 56 years; $P<0.001$), with more comorbidities (median Charlson score 2 versus 1; $P<0.001$), more MDR organisms (11.7% versus 8.0%; $P=0.026$), more central vascular access (88.8% versus 70.6%; $P<0.001$), more severe indications for OPAT and a higher rate of unplanned hospitalization (25.4% versus 11.5%; $P<0.001$). The *c*-statistic for the membership model was 0.95 (95% CI: 0.94–0.96), indicating highly discordant case mix. This implies that the broader external validation in this study reflects the transportability of the original risk prediction model to more severe patients selected differently to receive OPAT.

The effects of the six predictors in the original risk model were consistent (in direction and magnitude) across the three cohorts (Table 2). Internal validation of the six-predictor model, when separately fitted in each validation cohort, showed adequate discriminative performance with optimism-corrected *c*-statistics at 0.70, 0.78 and 0.74 in the derivation, temporal validation and broader validation cohorts, respectively. The Hosmer–Lemeshow goodness-of-fit test indicated good broad calibration in deciles of predicted risks in all cohorts. There were no significant differences in the calibration intercept and calibration slope from the ideal values of 0 and 1, respectively.

When the originally derived model was externally validated, adequate discriminative ability was retained in the temporal validation cohort (*c*-statistic 0.75; 95% CI: 0.71–0.79) and despite being reduced, discriminative ability was acceptable in the broader validation cohort (*c*-statistic 0.67; 95% CI: 0.61–0.73). There were no significant differences in the calibration slopes from the ideal value of 1 in either external cohort. However, calibration-in-the-large was slightly higher than zero in temporal validation and too high in broader external validation (intercept 0.54; 95% CI: 0.31–0.77; Hosmer–Lemeshow test $P<0.001$). ROC curves and calibration plots are contrasted in Figure 1. Poor calibration-in-the-large was easily overcome by recalibrating the intercept of the model. The intercept-recalibrated model demonstrated excellent calibration performance in the external cohorts (Figure 1).

Decision curve analysis showed that the recalibrated model has greater NB (i.e. clinically useful) than 'intervention for all' or 'intervention for none' strategies in a range of meaningful predicted probability thresholds between approximately 15% and 50% for both external validation cohorts (Figure 2).

Discussion

This study examined the temporal and broader external validity and clinical usefulness of a previously published risk prediction model for 30 day unplanned hospitalization in patients receiving OPAT. The rates of unplanned hospitalization in the model derivation cohort, temporal validation cohort and broader validation cohort (11%, 13% and 25%, respectively) are comparable with other OPAT studies.[8,9,21,22] The higher rate of unplanned hospitalization in the broader validation (Derby) cohort is likely due to the severity of infections treated, older age and high levels of comorbidity among the subjects. The discriminatory performance of the prediction model was retained and good in the temporal validation cohort (*c*-statistic 0.75), meaning that all subjects can be discriminated appropriately between the readmitted and non-readmitted group. The performance was reduced in the broader external dataset (*c*-statistic 0.67; 95% CI: 0.61–0.73), but remained potentially acceptable. In general, a *c*-statistic of 0.5 indicates no discrimination; 0.7 to 0.8 shows acceptable discrimination; 0.8 to 0.9 shows excellent discrimination; and values ≥ 0.9 are considered outstanding discrimination but are rarely seen in practice.[23] In both external validation cohorts, the calibration slopes were very close to the ideal value of 1, suggesting good correlation between observed and predicted risks across the subjects. However, calibration-in-the-large was poor in the broader validation cohort,

Table 1. Characteristics of subjects between development and validation cohorts

Characteristics	Derivation cohort (n = 1073)	Temporal validation cohort (n = 1087)	P value[a]	Broader validation cohort (n = 418)	P value[b]
Male sex, n (%)	611 (56.9)	641 (59.0)	0.340	259 (62.0)	0.078
Age, years, mean (SD)	56 (17.5)	56 (17.7)	0.795	68 (14.4)	<0.001
Age group, years, n (%)			0.702		<0.001
≤30	97 (9.0)	112 (10.3)		9 (2.2)	
31–40	121 (11.3)	108 (9.9)		15 (3.6)	
41–50	177 (16.5)	164 (15.1)		22 (5.3)	
51–60	209 (19.5)	225 (20.7)		58 (13.9)	
61–70	219 (20.4)	228 (21.0)		116 (27.8)	
>70	250 (23.3)	250 (23.0)		198 (47.4)	
Comorbidities, n (%)					
Chronic pulmonary disease	197 (18.4)	111 (10.2)	<0.001	94 (22.5)	0.071
Diabetes with complications	109 (10.2)	123 (11.3)	0.385	100 (23.9)	<0.001
Peripheral vascular disease	87 (8.1)	59 (5.4)	0.014	62 (14.8)	<0.001
Diabetes without complications	107 (10.0)	97 (8.9)	0.405	62 (14.8)	0.008
Tumour without metastasis	90 (8.4)	62 (5.7)	0.015	25 (6.0)	0.119
Moderate or severe renal disease	82 (7.6)	134 (12.3)	<0.001	80 (19.1)	<0.001
Connective tissue disease	71 (6.6)	56 (5.2)	0.149	29 (6.9)	0.824
Myocardial infarction	79 (7.4)	68 (6.3)	0.308	45 (10.8)	0.034
Cerebrovascular disease	49 (4.6)	64 (5.9)	0.169	31 (7.4)	0.030
Congestive heart failure	53 (4.9)	62 (5.7)	0.429	32 (7.7)	0.044
Peptic ulcer disease	40 (3.7)	10 (0.9)	<0.001	7 (1.7)	0.047
Moderate or severe liver disease	25 (2.3)	24 (2.2)	0.849	11 (2.6)	0.733
Metastatic solid tumour	21 (2.0)	20 (1.8)	0.842	12 (2.9)	0.284
Lymphoma	8 (0.7)	6 (0.6)	0.576	4 (1.0)	0.682
Leukaemia	11 (1.0)	12 (1.1)	0.858	6 (1.4)	0.505
Hemiplegia	6 (0.6)	8 (0.7)	0.610	1 (0.2)	0.431
Dementia	6 (0.6)	9 (0.8)	0.455	8 (1.9)	0.022
AIDS	2 (0.2)	0 (0.0)	0.999	0 (0.0)	0.999
Mild liver disease	0 (0.0)	27 (2.5)	0.998	4 (1.0)	0.999
Charlson comorbidity score, median (IQR)	1 (0–2)	0 (0–2)	0.308	2 (1–3)	<0.001
Charlson comorbidity score, n (%)			<0.001		<0.001
0	472 (44.0)	564 (51.9)		104 (24.9)	
1	203 (18.9)	154 (14.2)		83 (19.9)	
2	170 (15.8)	156 (14.4)		83 (19.9)	
3	101 (9.4)	64 (5.9)		49 (11.7)	
4+	127 (11.8)	149 (13.7)		99 (23.7)	
Indication for OPAT, n (%)			0.267		0.000
Skin and soft tissue infection	616 (57.4)	584 (53.7)		4 (1.0)	
Bone and joint infection	137 (12.8)	174 (16.0)		242 (57.9)	
Urogenital infection	70 (6.5)	63 (5.8)		6 (1.4)	
Respiratory disease	45 (4.2)	46 (4.2)		68 (16.3)	
Endovascular infection	45 (4.2)	43 (4.0)		40 (9.6)	
Other indication	160 (14.9)	177 (16.3)		58 (13.9)	
MDR organism, n (%)	86 (8.0)	89 (8.2)	0.883	49 (11.7)	0.026
Mode of antimicrobial delivery, n (%)			<0.001		<0.001
Infusion centre	767 (71.5)	673 (61.9)		3 (0.7)	
Community nurse[c]	201 (18.7)	289 (26.6)		412 (98.6)	
Self/carer administration	105 (9.8)	125 (11.5)		3 (0.7)	
Type of vascular access, n (%)			0.267		<0.001
Central line	758 (70.6)	744 (68.4)		371 (88.8)	
Peripheral access	315 (29.4)	343 (31.6)		47 (11.2)	

Continued

Table 1. *Continued*

Characteristics	Derivation cohort (*n* = 1073)	Temporal validation cohort (*n* = 1087)	*P* value[a]	Broader validation cohort (*n* = 418)	*P* value[b]
Antimicrobial agent, *n* (%)[d]					
Penicillin	93 (8.7)	99 (9.1)	0.719	121 (28.9)	<0.001
Cephalosporin	790 (73.6)	717 (66.0)	<0.001	111 (26.6)	<0.001
Carbapenem	104 (9.7)	121 (11.1)	0.274	59 (14.1)	0.015
Glycopeptide	98 (9.1)	161 (14.8)	<0.001	134 (32.1)	<0.001
Other	51 (4.8)	68 (6.3)	0.127	15 (3.6)	0.328
Concurrent IV OPAT, *n* (%)	81 (7.5)	81 (7.5)	0.932	21 (5.0)	0.085
Oral antibiotic included, *n* (%)	122 (11.4)	218 (20.1)	<0.001	111 (26.6)	<0.001
Duration of OPAT, days, median (IQR)	7 (4–19)	7 (3–21)	0.776	18 (8–32)	<0.001
Number of prior hospitalizations, median (IQR)[e]	0 (0–1)	0 (0–1)	0.096	1 (0–2)	0.011
Prior OPAT stay in past 12 months, *n* (%)	173 (16.1)	81 (7.5)	<0.001	42 (10.0)	0.003
Outcomes					
30 day hospitalization, *n* (%)	145 (13.5)	159 (14.6)	0.457	117 (28.0)	<0.001
30 day unplanned hospitalization, *n* (%)	123 (11.5)	140 (12.9)	0.314	106 (25.4)	<0.001
Reason for 30 day unplanned admission, *n* (%)			0.261		0.042
Worsening of infection/no improvement	52 (42.3)	64 (45.7)		35 (33.0)	
Non-OPAT related	50 (40.7)	40 (28.6)		36 (34.0)	
New infection	8 (6.5)	14 (10.0)		18 (17.0)	
Adverse drug reaction	7 (5.7)	14 (10.0)		12 (11.3)	
IV line-related complications	3 (2.4)	6 (4.3)		5 (4.7)	
Clostridioides difficile-associated diarrhoea	2 (1.6)	2 (1.4)		0 (0.0)	
Unknown	1 (0.8)	0 (0.0)		0 (0.0)	

[a]*P* value refers to the comparison between the Sheffield derivation cohort and the Sheffield validation cohort.
[b]*P* value refers to the comparison between the Sheffield derivation cohort and the Derby validation cohort.
[c]Community nurse refers to administration of antimicrobial therapy in a patient's home by a nurse.
[d]Some patients received more than one antimicrobial agent. Thus, total number of antimicrobial agents is greater than total number of patients.
[e]In 12 months preceding current OPAT episode.

indicating systematic overprediction of the risk of unplanned hospitalization in that cohort.

In external validation studies, decreases in performance of prediction models are common and can be due to differences in case mix of patients between the development and validation cohorts, overfitting of the model to the data used for development, differences in the effect of the model predictors between the development and validation cohorts, or a combination of these factors.[13,24] Prediction model performance can sometimes be improved by recalibration to the new setting, re-estimation of regression coefficients or including more predictors.[19,24] We addressed the poor calibration-in-the-large by recalibrating the intercept of the model to reflect the higher overall risks of unplanned hospitalization in the external cohorts (especially the broader validation cohort) compared with the derivation cohort.

Clinical usefulness is the ability to make a better decision when using a prediction model compared with when not using the model.[20,24] However, it is not clear how good the model's discriminative and calibration performances need to be to warrant clinical use. In this study, we confirmed the clinical usefulness of the recalibrated model by calculating its NB. NB is a simple type of decision analysis; similar to the idea of net profit in business.[20] We found the NB difference (true NB) of using the predictive model to be greater than 0 for all threshold probabilities between 0.15 and 0.50. Thus, our study demonstrates that the model is useful for identifying patients at high risk of unplanned hospital readmission upon presentation to an OPAT service. Based on our results, the model can be used to aid clinicians in managing patients receiving IV antimicrobial therapy in outpatient settings. Once identified as 'high risk', careful forward planning can help to prevent hospital readmissions and optimize clinical outcomes—by careful patient selection, closer monitoring and timely follow-up.[25]

This study has limitations that should be acknowledged. Caution should be applied when using the model. Each OPAT centre may have a different case mix of patients, OPAT structure and mode of delivery from those of the centres in which our study was conducted. Therefore, each OPAT service should compare their case mix and structure with those of the study OPAT services before using the risk prediction model directly. Recalibration of the model should be considered in settings with broader case mix before clinical use. Our analysis was retrospective, but the data were originally collected prospectively, which reduces the risk of

Table 2. Multivariable logistic regression analysis for the risk of 30 day unplanned hospitalization in patients receiving OPAT

	Model derivation cohort (Sheffield) (n = 1073)			Temporal validation cohort (Sheffield) (n = 1087)			Broader validation cohort (Derby) (n = 418)		
Predictors	aOR	95% CI	P value	aOR	95% CI	P value	aOR	95% CI	P value
Age, per 10 years	1.18	1.04–1.34	0.012	0.98	0.86–1.12	0.808	1.00	0.83–1.21	0.998
Prior hospitalizations, per unit	1.30	1.17–1.45	<0.001	1.17	1.05–1.31	0.005	1.05	0.91–1.20	0.511
Charlson comorbidity score, per unit	1.11	1.00–1.23	0.045	1.52	1.37–1.68	<0.001	1.66	1.44–1.90	<0.001
Mode of delivery									
Community nurse[a]	1.00	—	—	1.00	—	—	NA	—	—
Self/carer administration	1.28	0.62–2.64	0.500	0.96	0.50–1.85	0.911	NA	—	—
Infusion centre	1.61	0.90–2.89	0.108	1.37	0.76–2.45	0.298	NA	—	—
Concurrent IV antimicrobial therapy	1.89	1.03–3.47	0.041	1.18	0.61–2.30	0.622	0.78	0.25–2.44	0.671
Indication for OPAT									
Endovascular infection	1.62	0.67–3.88	0.283	0.50	0.17–1.49	0.213	1.75	0.62–4.94	0.291
Respiratory disease	0.71	0.26–1.96	0.513	1.66	0.72–3.82	0.237	2.51	1.02–6.19	0.046
Urogenital infection	1.21	0.54–2.69	0.643	1.43	0.67–3.06	0.359	NA	—	—
Bone and joint infection	0.96	0.49–1.90	0.916	0.67	0.36–1.24	0.202	1.66	0.77–3.61	0.196
Skin and soft tissue infection	0.46	0.25–0.86	0.015	0.39	0.20–0.76	0.006	3.39	0.29–39.46	0.330
Other indication	1.00	—	—	1.00	—	—	1.00	—	—
Performance on bootstrap internal validation (500 replications)									
Discrimination, c-statistic	0.70	0.65–0.74	—	0.78	0.74–0.82	—	0.74	0.69–0.80	—
HL goodness-of-fit statistic (df)	4.20 (8)	—	0.838	3.17 (8)	—	0.923	10.11 (8)	—	0.257
Average predicted (observed) risk, %	12.0 (11.5)	—	—	—	13.3 (12.9)	—	26.2 (25.4)	—	—
Calibration slope	0.87	0.68–1.06	—	0.93	0.78–1.07	—	0.91	0.68–1.15	—
Calibration-in-the-large	0.00	−0.20 to 0.21	—	0.00	−0.21 to 0.22	—	0.00	−0.26 to 0.27	—
Performance of original model on external validation									
Discrimination, c-statistic	—	—	—	0.75	0.71–0.79	—	0.67	0.61–0.73	—
HL goodness-of-fit statistic (df)	—	—	—	10.79 (8)	—	0.214	26.61 (8)	—	<0.001
Average predicted (observed) risk, %	—	—	—	11.4 (12.9)	—	—	17.1 (25.4)	—	—
Calibration slope	—	—	—	1.05	0.84–1.26	—	1.01	0.65–1.37	—
Calibration-in-the-large	—	—	—	0.16	−0.03 to 0.35	—	0.54	0.31–0.77	—
Performance of recalibrated original model on external validation									
Discrimination, c-statistic	—	—	—	0.75	0.71–0.79	—	0.67	0.61–0.73	—
HL goodness-of-fit statistic (df)	—	—	—	7.07 (8)	—	0.529	3.80 (8)	—	0.875
Average predicted (observed) risk, %	—	—	—	12.9 (12.9)	—	—	26.2 (26.2)	—	—
Calibration slope	—	—	—	1.05	0.84–1.26	—	1.01	0.65–1.37	—
Calibration-in-the-large	—	—	—	0.00	−0.19 to 0.19	—	0.00	−0.23 to 0.23	—

aOR, adjusted OR; df, degrees of freedom; HL, Hosmer–Lemeshow. NA indicates that in the broader validation (Derby) cohort, mode of delivery and urogenital infection could not be included as predictors because of complete separation (very few or no subjects with urogenital infection, self/carer administration or treated via infusion centre, none of whom required hospitalization).
[a]Community nurse refers to administration of antimicrobial therapy in a patient's home by a nurse.

measurement bias or poor accuracy of recorded data. However, we cannot be entirely confident that we have not missed some patients who were readmitted to other hospitals. Nevertheless, most patient interactions with healthcare systems are well documented in their clinical records. In the model development, we did not explore factors (such as therapeutic drug levels, frequency of monitoring or follow-up visits) that are not readily available prior to OPAT but are plausible risk factors for readmission. Our aim was to develop a risk prediction model based on parameters available on presentation to an OPAT service.

In conclusion, the prediction model is temporally and externally valid, and clinically useful for the prediction of 30 day

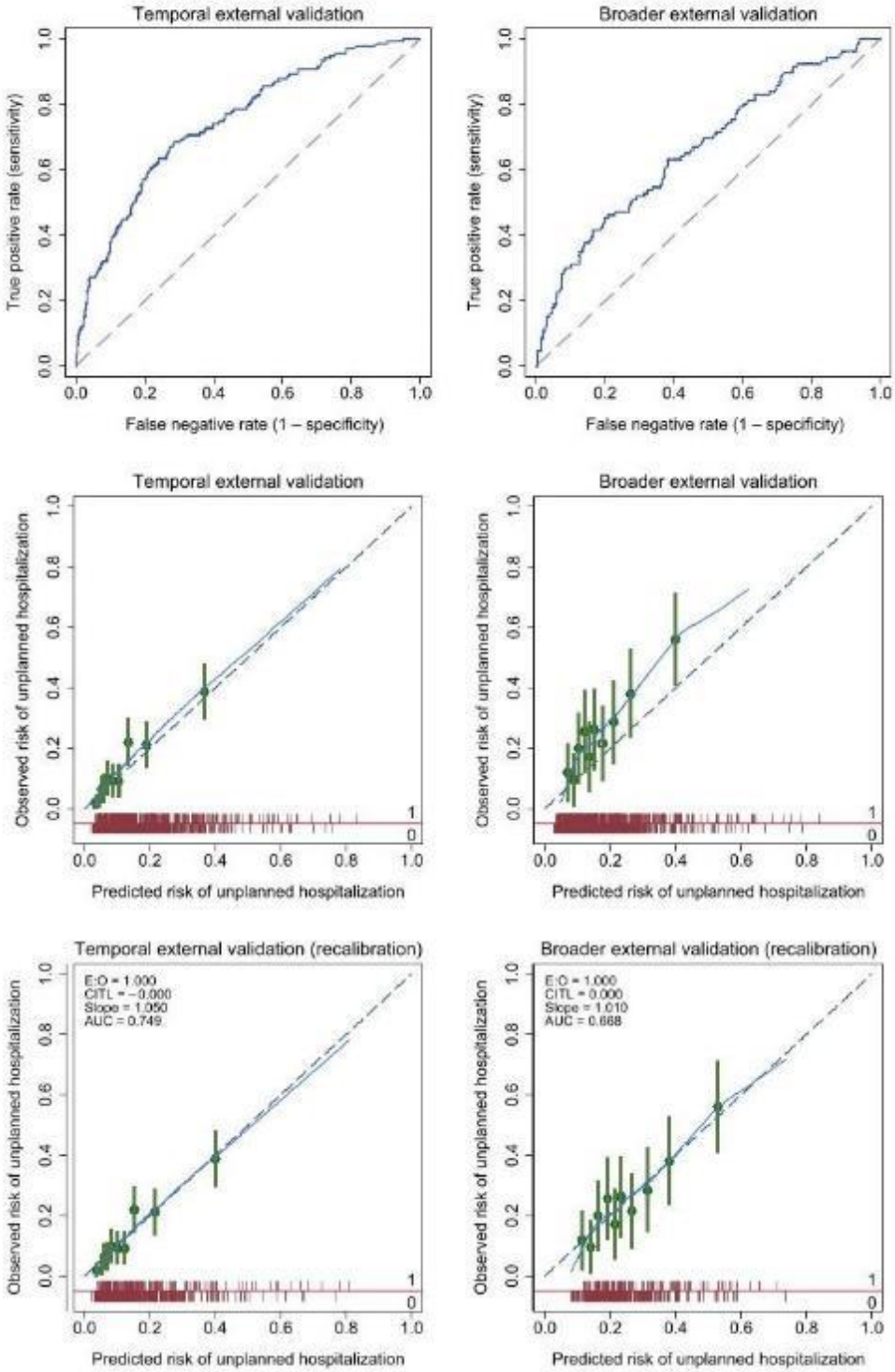

Figure 1. ROC curves and calibration plots of the multivariable prediction model for 30 day unplanned hospitalization when applied to external validation cohorts. On the ROC curves, the diagonal line indicates complete absence of discriminative ability. On the calibration plots, the smoothed line shows the agreement between predicted and observed probabilities of 30 day unplanned hospitalization. The dashed diagonal line indicates perfect calibration. The circled points represent observed proportions of unplanned hospitalization in decile groups of predicted risks, with vertical lines representing 95% CIs. The spike plot on the *x*-axis summarizes the density of patients in the range of predicted risks of unplanned hospitalization.

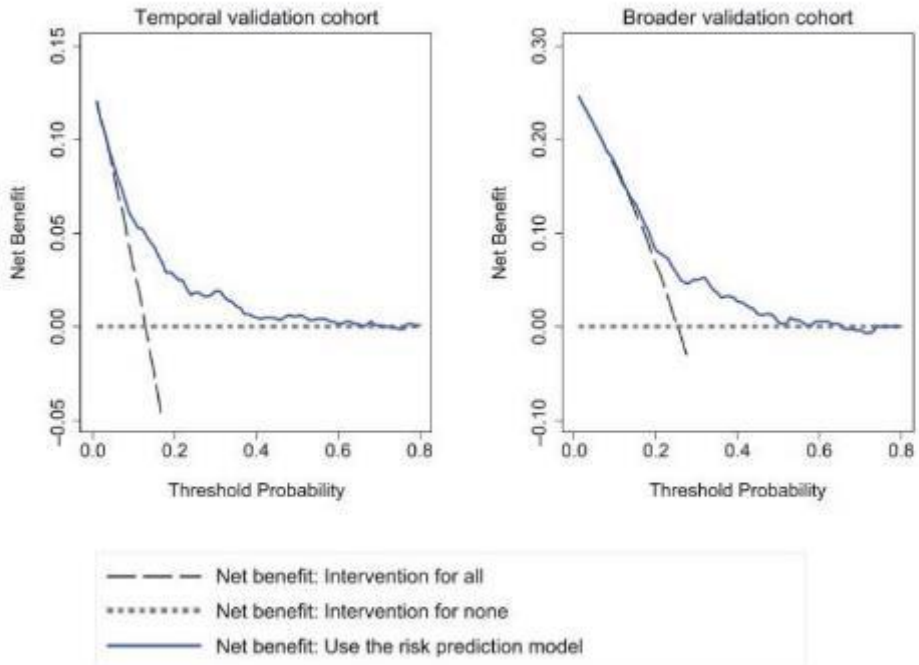

Figure 2. NB curves of the multivariable prediction model for 30 day unplanned hospitalization in patients receiving OPAT when applied to external validation cohorts. The solid blue line represents the NB when using the risk prediction model; the dashed line represents the NB when all patients are administered therapy as inpatients ('intervention for all'); the dotted horizontal line represents the NB with current practice for selecting patients for OPAT ('intervention for none').

unplanned hospitalization in patients receiving OPAT. It may help improve OPAT outcomes through better identification of high-risk patients and provision of tailored care. Future research should focus on recalibration and assessing the model performance in other OPAT centres, especially those with broader case mix from the study cohorts.

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Transparency declarations

None to declare.

Author contributions

O.C.D. and E.I.K. conceptualized and designed the study. K.C. contributed to the conduct of the study. O.C.D., R.M., N.C., J.P., C.K. and R.O. collected and extracted data. E.I.K. performed the statistical analysis. O.C.D. and E.I.K. drafted the manuscript. All authors contributed to the final manuscript.

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Paper 7

Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): a systematic review and meta-analysis

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Review

Risk of venous thromboembolism in outpatient parenteral antimicrobial therapy (OPAT): A systematic review and meta-analysis

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ABSTRACT

The risk of venous thromboembolism (VTE) in outpatient parenteral antimicrobial therapy (OPAT) is not fully understood and the optimal strategy for thromboprophylaxis remains unclear. This systematic review investigated the incidence of VTE in OPAT settings (PROSPERO CRD42022381523). MEDLINE, CINAHL, Emcare, Embase, Cochrane Library and grey literature were searched from earliest records to 18 January 2023. Primary studies reporting non-catheter-related VTE or catheter-related thromboembolism (CRT) events in adults who received parenteral antibiotics in home or outpatient settings were eligible. In total, 43 studies involving 23 432 patient episodes were reviewed, of which 4 studies reported non-catheter-related VTE and 39 included CRT. Based on generalised linear mixed-effects models, pooled risk estimates of non-catheter-related VTE and CRT were 0.2% [95% confidence interval (CI) 0.0–0.7%] and 1.1% [95% CI 0.8–1.5%; prediction interval (PI) 0.2–5.4%]. Heterogeneity was largely attributed to risk of bias by meta-regression (R^2 = 21%). Excluding high-risk-of-bias studies, CRT risk was 0.8% (95% CI 0.5–1.2%; PI 0.1–4.5%). From 25 studies, the pooled CRT rate per 1000 catheter-days was 0.37 (95% CI 0.25–0.55; PI 0.08–1.64). These findings do not support universal thromboprophylaxis or routine use of an inpatient VTE risk assessment model in the OPAT setting. However, a high index of suspicion should be maintained, especially for patients with known risk factors for VTE. An optimised protocol of OPAT-specific VTE risk assessment should be sought.

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1. Introduction

Outpatient parenteral antimicrobial therapy (OPAT) programmes are widely used to administer intravenous (IV) antibiotics via a vascular access device to facilitate early hospital discharge and admission avoidance of patients with infection. The effectiveness and safety of OPAT have been well documented [1–3]. Despite its benefits, patients receiving OPAT remain at risk of adverse events, including antibiotic-related and vascular access-related complications, which could result in unplanned hospital re-admissions [4,5]. Venous thromboembolism (VTE) is a common complication of intravascular access devices and is associated with interruption of antimicrobial therapy, unplanned re-admission, increased healthcare costs, post-thrombotic syndrome and pulmonary embolism (PE) [6,7]. The potential risk of VTE in OPAT is further increased by the presence of infection and restricted mobility [8]. VTE prophylaxis is an established standard of care for hospitalised patients following individualised risk assessment [9]. Appropriate thromboprophylaxis in at-risk hospitalised patients has been shown to reduce the risk of VTE and related mortality [10]. However, the risk of VTE in OPAT is not fully understood and the optimal strategy for thromboprophylaxis for OPAT patients has not been established [11].

To guide strategy for optimal thromboprophylaxis in OPAT, this systematic review aimed to examine the incidence of VTE in adult patients with infection treated with IV antimicrobials in home and outpatient settings.

2. Materials and methods

The protocol for this systematic review was registered with PROSPERO, the international prospective register of systematic reviews (CRD42022381523), and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table A.1) [12].

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2.1. Search strategy and information sources

The search strategy and sources of evidence were developed after an initial review of the existing literature. In this systematic review, a three-step search strategy was utilised. An initial limited search of MEDLINE (PubMed) and CINAHL was undertaken, followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then conducted across CINAHL, Embase (Ovid), Ovid Emcare, MEDLINE (PubMed) and the Cochrane Library. The reference lists of all identified articles were then searched for additional sources. Supplementary searches of clinical trial registries, Web of Science Conference Proceedings, Google/Google Scholar, and the websites of the British Infection Association, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America were conducted to identify relevant unpublished work and grey literature. The search terms were generated based on the two main key terms (i.e. VTE and OPAT) and their corresponding alternative terms. The full search strategy is available in Supplementary Table A.2. The search was not restricted by date of publication but was limited to studies published in English. The last electronic search was undertaken on 18 January 2023.

2.2. Eligibility criteria

Eligibility criteria were based on the PICO framework (population, intervention, comparator and outcome) [13]. Studies were eligible if they reported catheter-related thromboembolism (CRT) and/or non-catheter-related VTE (outcome) in adult patients (>16 years old) with infection (population) who received parenteral antibiotics in home or outpatient settings (intervention). Studies of any research design were considered (with the exception of commentaries, editorials, reviews and guidelines). Studies that did not allow for calculation of the incidence rate of VTE were excluded (Supplementary Table A.3).

Due to limited studies on non-catheter-related VTE in OPAT, conference abstracts as were considered recommended by Scherer et al. [14], who suggested that conference abstracts should be considered in systematic reviews if available evidence is sparse or conflicting. Attempts were made to contact the authors of the abstracts to obtain further information on study methods and results. Conference abstracts meeting the eligibility criteria were included in this systematic review if there were no full-length publications or no response from the author.

2.3. Study selection and data extraction

All publications identified by the searches were imported into EndNote reference management software. After removing duplicate records, all identified articles were screened independently against the eligibility criteria by two reviewers (O.C.D. and J.C.). Disagreements were resolved by consensus or with a third reviewer (E.I.K.). Data were extracted independently from retrieved studies by all reviewers (O.C.D., J.C. and E.I.K.) using a standardised and piloted data extraction spreadsheet. Extracted data included citation details (first author, year and type of publication), location, study purpose, design, sample size, number of CRT and non-catheter-related VTE events, duration of follow-up and main findings. Any discrepancies in data extraction were discussed and resolved.

2.4. Quality assessment

The Mixed Methods Appraisal Tool (MMAT) version 2018 was used to access the methodological quality of the included studies [15]. Quality appraisal was independently performed by two reviewers (O.C.D. and J.C.). Any disagreement was resolved by discussion between the authors, and no studies were excluded based on the results of the evaluation. The developers of MMAT discourage the calculation of an overall numerical score and the exclusion of studies with low methodological quality [16]. Based on MMAT results, the risks of selection bias and information bias were assessed separately and a classification of overall risk as low, moderate or high was produced, as shown in Supplementary Table A.4. The latter was used to examine heterogeneity related to risk of bias in meta-regression and subgroup analyses.

2.5. Meta-analysis

The primary study outcome was incidence of CRT and non-catheter-related VTE. Population-averaged incidence proportions pooled over the studies were estimated using a random intercept logistic regression model with maximum-likelihood estimation [17]. The model assumed a binomial distribution for the observed number of VTE cases in each study, and a normal distribution for the random effects following the logit transformation. This approach correctly incorporates studies reporting zero cases and maintains confidence limits of pooled proportions within the zero to one range. The resulting confidence interval (CI) estimates the expected (average) VTE risk of all possible studies.

Higgin–Thompson's I^2 statistic was used as a summary index of the amount of variability of VTE incidence across studies that cannot be attributed to sampling error. Because I^2 is usually high and may not be discriminative for prevalence or incidence data [18], between-study variance (τ^2) with the respective 95% prediction interval (PI) was additionally reported. The PI describes the range of VTE risk that can be expected in new studies [19]. A forest plot was constructed to illustrate the distribution of VTE incidence across the studies along with 95% CIs calculated by Wilson's score method. To examine potential sources of variation in VTE incidence among the studies, multivariable meta-regression analysis was conducted with a binomial-normal mixed-effects model. Adjusted odds ratios (aORs) with respective 95% CIs summarised the strength and direction of associations between study-level covariates and VTE incidence. For each covariate, a covariate-specific R^2 was calculated as the portion of between-study variance that was reduced after the inclusion of that covariate in the model (in the presence of all other variables). Moreover, for each covariate level, pooled estimates of VTE incidence were calculated based on univariate subgroup analysis. Candidate covariates for the regression analysis were decided a priori in the study protocol [20]. The following variables were examined: publication year; geographical location [World Health Organization (WHO) region]; study design; and risk of bias (classified as either low–moderate or high).

Leave-one-out sensitivity analysis was carried out to assess the robustness of pooled estimates of VTE incidence against excessively influential studies. To address time-dependent confounding due to studies recording VTE incidence over different risk periods, we sought studies reporting OPAT duration statistics, calculated incidence density rates (expressed as number of events per 1000 catheter-days) and estimated population-averaged incidence rates based on a Poisson-normal mixed-effects model. All analyses were carried out using Stata Statistical Software: Release 17 (StataCorp, College Station, TX, USA).

3. Results

3.1. Selection results and characteristics of the studies

The initial electronic search yielded 18 436 different publications, of which 39 met the eligibility criteria. An additional

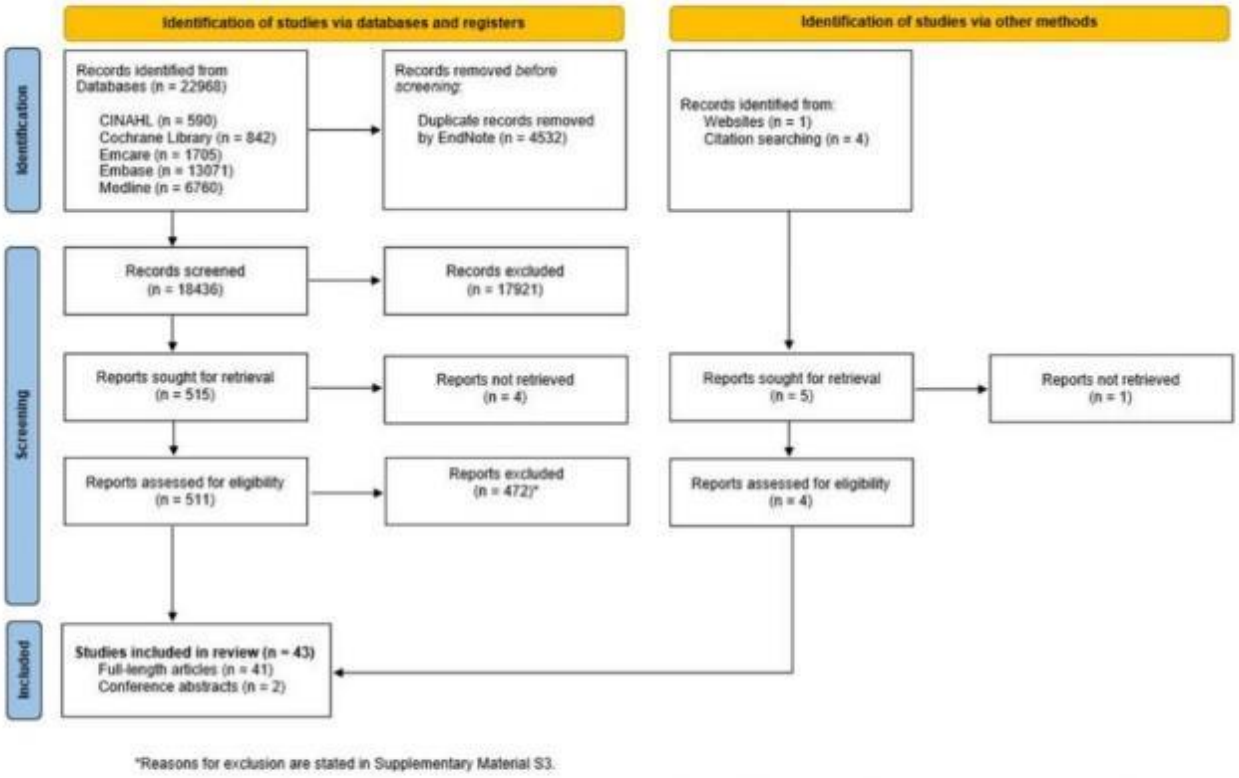

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the systematic review process [13].

four articles were identified through hand-searching of bibliographies and other sources. Hence, a total of 43 publications (2 conference abstracts [21,22] and 41 full-length articles [4,7,23–61]) were included in the review (Fig. 1). Supplementary Table A.5 shows the details of the reviewed studies. The studies were published between 2001 and 2023 and were carried out in the USA ($n = 21$) [25,27,32–34,36,38,40,42–47,50,53–56,58,59], UK ($n = 6$) [21,22,24,28,49,60], Australia ($n = 6$) [7,29,48,51,52,57], New Zealand ($n = 3$) [30,31,61], Switzerland ($n = 3$) [26,37,39], Germany ($n = 1$) [23], Canada ($n = 1$) [35], the Netherlands ($n = 1$) [4] and Japan ($n = 1$) [41]. We did not find any studies conducted in low-income countries. The period under study ranged from 6 months [17,33,36] to 13 years [49]. Study sample sizes ranged from 11 to 4160 [23,29]. Overall, the reviewed studies included 23 432 patient episodes (mean 545; median 231), of which 22 292 (mean 572; median 247) and 1140 (mean 285; median, 154) were enrolled in studies that explored CRT and non-catheter-related VTE events, respectively.

3.2. Quality appraisal

An overview of the quality appraisal is provided in Supplementary Tables A.6. Of the 43 studies, 15 studies (35%) were categorised as quantitative non-randomised studies [4,7,25,31,32,34,37,42–44,49,52–54,56] and 28 (65%) were categorised as quantitative descriptive studies [21–24,26–30,33,35,36,38–41,45–48,50,51,55,57–61]. There were no qualitative or quantitative randomised controlled trials (RCTs). Using the MMAT tool, two studies [22,26] had one 'Yes' answer out of five criteria (weakest), while the strongest one [4] had five 'Yes' answers. Overall, 6 studies (14%) were assessed as having a low risk of bias, 22 (51%) as moderate and 15 (35%) had high risk of bias (Supplementary Table A.7). Inadequate information in the conference articles did not allow the rating questions to be adequately answered. Key quality issues were related to non-response bias, accounting for confounders, and appropriateness of the statistical analysis.

3.3. Incidence of venous thromboembolism

Four studies (two full-length articles [24,52] and two conference abstracts [21,22]) examined the risk of non-catheter-related VTE in OPAT. Barr et al. carried out a retrospective review over a 3-year period of 780 OPAT episodes who did not receive thromboprophylaxis and reported two cases of proximal lower limb deep vein thrombosis (DVT) within 90 days of OPAT, giving a VTE incidence rate of 0.26% (95% CI 0.03–0.92%) [24]. Kenyon and Chapman reported no VTE within 4 weeks of OPAT in their cohort of 94 patients aged >40 years with cellulitis who had no VTE prophylaxis [22]. Another study also reported zero incidence of VTE among 214 patient episodes (who had no thromboprophylaxis) within 90 days of OPAT [21]. Ong et al. compared the outcomes of patients with cellulitis who received IV therapy in a Hospital in the Home (HITH) programme with those treated in the hospital. They recorded one case of PE in the hospital group but no VTE (PE/DVT) in the HITH group [52]. Pooling data from the four studies, the estimated incidence of non-catheter-related VTE was 0.2% (95% CI 0.0–0.7%) (Table 1). Heterogeneity statistics could not reliably be estimated owing to limited sample sizes, but heterogeneity should be considered low as the studies consistently reported near zero events of non-catheter-related VTE.

CRT events were more commonly reported than non-catheter-related VTE. The incidence risk of CRT ranged from 0% to 7.7% among the 39 reviewed studies [4,7,23,25–51,53–61]. Some studies also reported the incidence of CRT in events per OPAT/IV catheter-days [7,29,34,36,42,43,55]. In these studies, the incidence

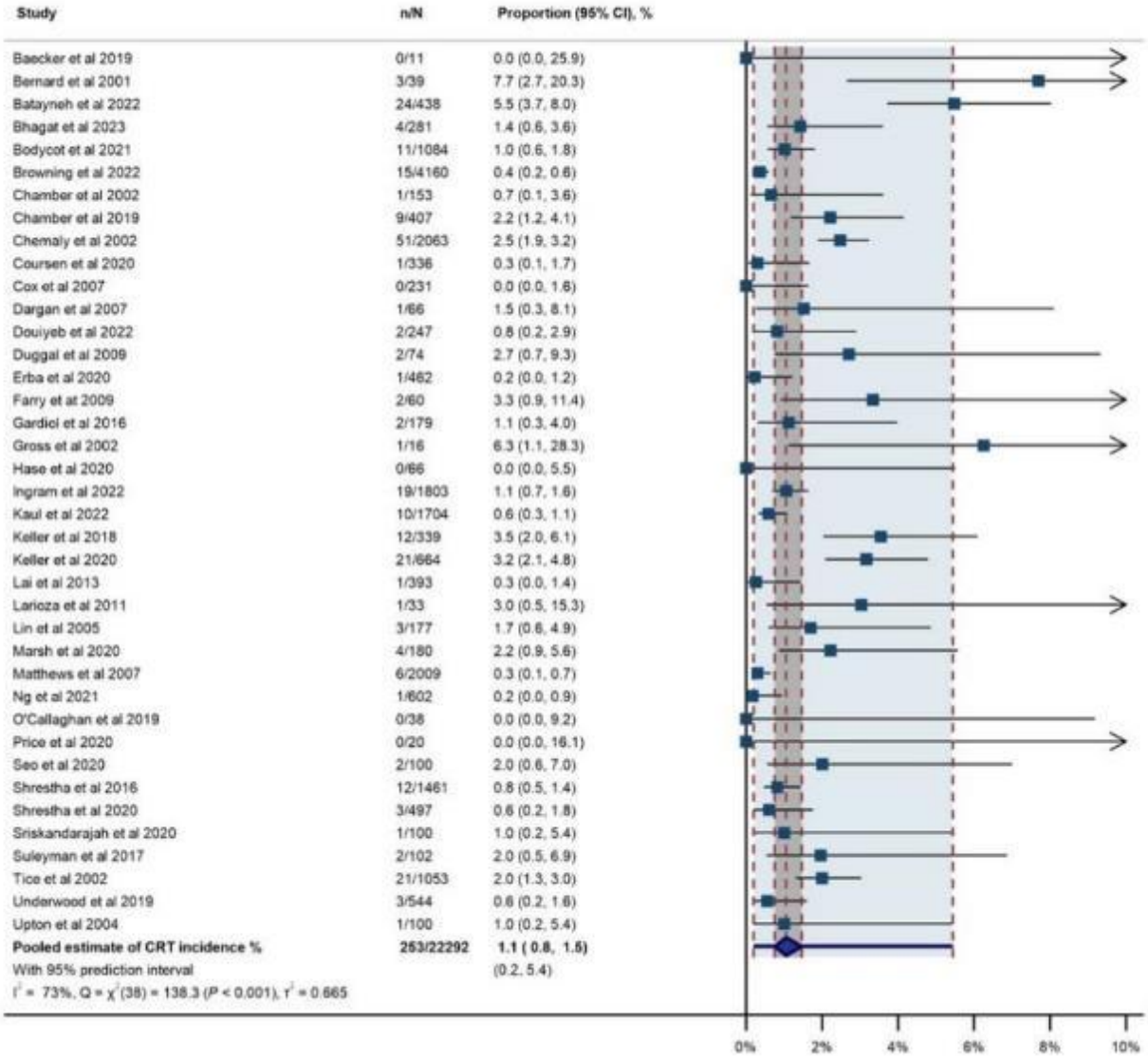

Fig. 2. Forest plot of results of the random-effects meta-analysis of the risk of catheter-related venous thromboembolism (CRT) in outpatient parenteral antimicrobial therapy (OPAT). *n/N* denotes the number of CRT events over the total number of patients at risk in each study. The diamond's centre is the population-averaged CRT incidence proportion. The diamond's length and respective grey vertical area indicate the 95% CI of the pooled average estimate. The extended blue line continuing through the CI and the respective bluish-grey vertical area indicate the 95% prediction interval (PI) of CRT incidence expected in new studies. CI, confidence interval.

Table 1
Results of random-effects meta-analysis of incidence of non-catheter-related thromboembolism (VTE) events in outpatient parenteral antimicrobial therapy.

Study	*n/N*	VTE incidence (%)	95% CI
Barr et al., [24]	2/780	0.3	0.0–0.9
Keeley et al., [21]	0/214	0.0	0.0–1.7
Kenyon and Chapman, [22]	0/94	0.0	0.0–3.8
Ong et al., [52]	0/52	0.0	0.0–6.8
Population-averaged estimate	2/1140	0.2	0.0–0.7

n/N, number of non-catheter-related VTE events over the total number of patients at risk in each study; CI, confidence interval.

rate ranged between 0 and 0.9 events per 1000 OPAT/IV catheter-days. Only three studies directly assessed risk factors for CRT in the OPAT setting [7,25,32]. In other studies, CRTs were reported as an OPAT complication. A case–control study by Ingram et al. found malposition of the catheter tip and complicated catheter insertion as risk factors for thrombosis [7]. Another study identified younger age, history of DVT, discharge to a skilled nursing facility and therapy with amphotericin B as risk factors for peripherally inserted central catheter (PICC)-associated venous thrombosis [32]. Batayneh et al. did not identify a risk factor for PICC-related DVT among their cohorts but observed that patients with diabetic mellitus were less likely to develop DVT. The reason for this finding is unclear and needs further clarification [25]. All but one study differentiated between catheter-related superficial and deep vein thrombosis. Chemaly et al. reported that 44% of upper extremity venous thromboses in their cohort were superficial but found no significant difference in mean time to diagnosis between deep and superficial thromboses [32].

Using the binomial-normal mixed-effects model, the estimated population-averaged risk of CRT was 1.1% (95% CI 0.8–1.5%). However, accounting for heterogeneity, the 95% PI indicated that CRT incidence in future studies can be expected to range between 0.2% and 5.4%, pointing out considerable predictive uncertainty (Fig. 2).

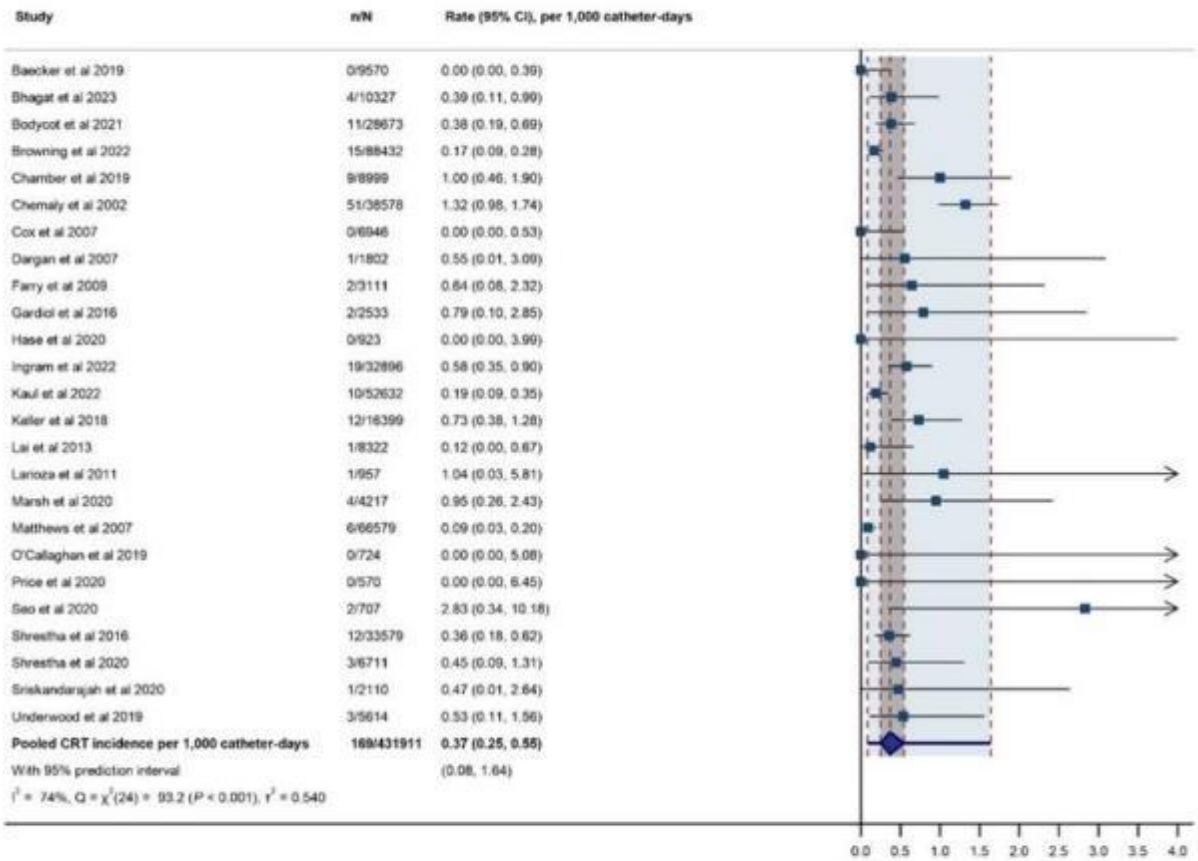

Fig. 3. Forest plot of results of the random-effects meta-analysis of the incidence density rate of catheter-related venous thromboembolism (CRT) in outpatient parenteral antimicrobial therapy (OPAT). *n/N* denotes the number of CRT events over the total number of OPAT/IV catheter-days in each study. The diamond's centre is the population-averaged CRT incidence rate. The diamond's length and respective grey vertical area indicate the 95% CI of the pooled average estimate. The extended blue line continuing through the CI and the respective bluish-grey vertical area indicate the 95% prediction interval (PI) of CRT incidence expected in new studies. IV, intravenous; CI, confidence interval.

Table 2
Multivariable meta-regression analysis of associations between study-level characteristics and incidence of catheter-related venous thromboembolism (CRT) in outpatient parenteral antimicrobial therapy.

Study characteristic	Levels	*n*	CRT incidence (CI; PI) (%)	Adjusted OR (CI)	*P*-value	R^2 (%)
Year of publication	≤2019	22	1.3 (0.8–1.9; 0.3–6.0)	Ref.	0.942	0.0
	≥2020	17	0.9 (0.5–1.4; 0.1–5.6)	0.98 (0.51–1.88)		
Region	Europe	8	0.7 (0.4–0.9; 1.9–3.0)	Ref.	0.657	6.5
	North America	22	1.3 (1.1–1.6; 1.9–2.9)	1.45 (0.66–3.16)		
	Western Pacific	9	0.9 (0.7–1.1; 1.9–3.0)	1.27 (0.52–3.12)		
Study design	Descriptive (single arm)	25	1.0 (0.7–1.4; 0.3–3.6)	Ref.	0.282	9.0
	Comparative non-randomised	14	1.1 (0.6–2.0; 0.1–9.3)	1.39 (0.77–2.49)		
Risk of bias	Low/moderate	26	0.8 (0.5–1.2; 0.1–4.5)	Ref.	0.019	21.2
	High	13	2.4 (1.9–2.9; 1.9–2.9)	2.48 (1.20–5.14)		

n, number of studies; CI, 95% confidence interval; PI, prediction interval; OR, odds ratio.

As seen in Table 2, multivariable meta-regression analysis showed no significant variation in CRT incidence in relation to year of study, region or study design. However, risk of bias was the main driver of heterogeneity, explaining 21% of the between-study variance. Studies with a high risk of bias had significantly greater incidence of CRT than studies classified as low or moderate risk of bias (aOR = 2.48, 95% CI 1.20–5.14; $P = 0.019$). Excluding the high-risk studies, the estimated average risk of CRT was 0.8% (95% CI 0.5–1.2%; 95% PI 0.1–4.5%). Leave-one-out sensitivity analysis did not identify excessively influential (outlier) studies (Supplementary Fig. A.1).

Data on follow-up OPAT/IV catheter-days were retrieved from 25 studies, which reported 169 CRT events over 431 911 catheter-days in total. Based on the Poisson-normal mixed-effects model, the estimated population-averaged incidence rate of CRT was 0.37 events (95% CI 0.25–0.55; PI 0.08–1.64) per 1000 catheter-days. Fig. 3 presents the respective forest plot. Leave-one-out sensitivity analysis did not identify outlier studies (Supplementary Fig. A.2). Meta-regression analysis of the time-adjusted incidence density rates produced compatible results as those from the previous analysis of cumulative incidence proportions (Supplementary Table A.8).

4. Discussion

The risk of VTE in hospitalised patients has been stratified into very low (<0.5%), low (1.5%), moderate (3%) and high (6%) [62]. However, VTE risk in OPAT is not entirely clear. Here we present a systematic review of the current literature to establish the incidence of VTE in OPAT. The comprehensive analysis revealed a low incidence of thromboembolic events among patients who received OPAT. The pooled estimate for non-catheter-related VTE (0.2%) in our study is significantly lower than reported hospital-associated VTE incidence proportions (1.0–1.3%) among hospitalised patients [63–65] but is comparable with the rates in very low-risk hospitalised medical patients for whom thromboprophylaxis is not recommended [10,62,66].

In this review, the incidence of CRT varied among the studies depending on the type of vascular access device, indication for OPAT, antimicrobial agent administered, prior surgical intervention and underlying co-morbidities. IV catheters can cause endothelial injury, vein wall inflammation and haemodynamic flow changes, which can lead to venous thrombosis [67]. The incidence risks of CRT found in this review are lower than the reported risks (5–15%) for critically ill populations and hospitalised patients [6]. The relatively low incidence of CRT in this review supports existing guidelines that do not recommend routine prophylactic anticoagulation or heparin flushes to prevent catheter thrombosis [68]. Nevertheless, RCTs of the risks and benefits of pharmacological prophylaxis for CRT could provide more convincing data. To minimise the risk of CRT in the OPAT setting, careful consideration of modifiable risk factors and non-pharmacological methods such as type of vascular access device, insertion techniques, location of insertion, line care and early switch to oral therapy may be more relevant [6,69].

Most cases of hospital-associated VTE are diagnosed post-hospital discharge [63,64]. In this review, the highest incidence of VTE (7.7%) was observed in a small cohort of patients with osteomyelitis, most of whom had surgical interventions [26]. Surgery is a major risk factor for VTE [70,71]. Extending thromboprophylaxis in the outpatient period for up to 35 days post-operatively is recommended in selected patients who have undergone major orthopaedic surgery [71]. However, extended thromboprophylaxis after hospital discharge in medical patients is not routinely recommended due to increased risk of adverse events and uncertainty about its benefit in preventing major or fatal thromboembolic events [72]. A systematic review of hospitalised medical patients found no significant effect of thromboprophylaxis on mortality but did result in more bleeding events (risk ratio = 1.34; 9 events per 1000 patients treated) [73]. Thus, the low risk of thromboembolic events found in this review indicates that extending thromboprophylaxis for all patients receiving OPAT may cause unnecessary harm. Apart from hospitalised patients, OPAT is also administered to patients with no prior hospitalisation to prevent admission.

The lower rate of non-catheter-related VTE in this review compared with hospital-associated VTE rates reported in literature [63–65] also suggests that validated risk assessment tools for VTE prevention in hospitalised patients may not be appropriate for patients receiving OPAT [24]. Hospitalised patients are often relatively less mobile and sicker than OPAT patients. Hence, there is a need for an OPAT-specific VTE risk assessment protocol based on a robust analysis of the risk–benefit balance. It is possible that thrombotic events, especially CRT, are underdiagnosed in the OPAT settings owing to lack of symptoms or signs to prompt a diagnostic test [32,74]. A high index of suspicion should be maintained, especially in patients with known risk factors, and appropriate diagnostic work-up should be performed. Confirmed cases should be treated promptly according to existing guidelines or standards of care [75] in order to minimise the risk of embolisation and post-thrombotic syndrome without interrupting OPAT treatment.

The main strengths of this systematic review are its robust and iterative methodology approach to identify all relevant literature, the large sample size, and the sensitivity analysis to assess the robustness of pooled estimates of each outcome. However, there are a number of potential limitations. Since the relevant data were not consistently reported in the reviewed articles, we were unable to examine potential risk factors for VTE in OPAT (e.g. patient factors, history of VTE, catheter type and insertion techniques) [6,70], concomitant anticoagulation in patients who had CRT, and CRT occurring after completion of OPAT. Moreover, it can be presumed that in studies with shorter mean follow-up, the number of thromboembolic events would be higher if the patients were followed for a longer duration; as most studies did not clearly report the risk period during which they sought thromboembolic events, our pooled estimates of VTE risk are subject to confounding from this time-dependency. Nevertheless, our analysis of time-adjusted incidence density rates based on approximately 65% of the studies provides assurance that the risk of VTE is low even when considering duration of IV catheter use for OPAT. We were also unable to differentiate between superficial and deep vein catheter-related thrombosis, and between the incidence of VTE in patients with and without prior hospitalisation. We included two conference abstracts due to limited publications on non-catheter-related VTE in OPAT. Conference abstracts are often not peer-reviewed, and reported outcomes are often preliminary and/or based on limited analyses. However, inclusion of conference abstracts can provide a broader overview and reduce the potential impact of publication bias [14]. Non-English language articles were not assessed due to lack of language resources (i.e. professional translators), which may have resulted in some language bias. The existing OPAT-VTE literature comprises mainly observational studies. The lack of high-quality RCTs comparing VTE in OPAT with hospital-associated VTE limits the conclusions of this review. Finally, as is well known, the findings of meta-analyses of observational studies are limited by risk of systematic and random biases, unmeasured confounders and high heterogeneity [76]. The meta-regression and subgroup analyses may have mitigated some of these concerns.

4.1. Implications for research

Further research is needed to develop accurate VTE risk assessment tools appropriate for OPAT. Since a substantial proportion of hospital-associated VTE events occur after hospital discharge [63,64], future studies should also differentiate between the risks of VTE in OPAT patients who had prior admission (early hospital discharge) and those who did not (admission avoidance). We encourage OPAT services (especially those in low-income countries) to publish their experiences in order to provide more prospective data on the risk of VTE. Decision-analytic modelling can be conducted using existing data to compare the benefits, risks and costs of thromboprophylaxis in OPAT. It would help to determine the risk threshold at which prophylaxis provides optimal clinical benefit. The findings from decision-analytic modelling techniques would require validation.

4.2. Implications for practice

The current findings of a low risk of VTE among patients receiving OPAT do not support either universal thromboprophylaxis or anticoagulation and heparin flushes for routine prevention of CRT in this setting. A validated risk assessment model for inpatients identifies one bleeding event in 52 (1.9%) low-risk medical patients who had pharmacological thromboprophylaxis [66]. Thus,

the risk of bleeding may outweigh the benefits of thromboprophylaxis in OPAT settings. Furthermore, in agreement with Barr et al. [24], we suggest that OPAT patients should not be routinely assessed for VTE risk using inpatient risk assessment tools owing to differences in risk profile. Risk assessment models appropriate to OPAT have been proposed [22]. In the interim, as recommended by the UK OPAT guidelines [11], patients deemed at high risk of VTE during hospitalisation (e.g. post major orthopaedic surgery) should be carefully considered for extended thromboprophylaxis during OPAT after an individualised risk–benefit assessment if the risk persists. OPAT clinicians should maintain a high index of suspicion for prompt diagnosis and appropriate treatment of VTE/catheter-related thrombosis, especially in high-risk patients.

4.3. Conclusions

This study gives insight into the risk of VTE in OPAT. Within its constraints, this review suggests that patient receiving OPAT are at low risk of VTE and adds to the growing evidence that OPAT is a safe alternative to inpatient care. The current findings provide a strong rationale and foundation for future studies on the optimal assessment strategy for OPAT thromboprophylaxis. In the interim, a mindful individualised approach that weighs the pros and cons of prophylaxis seems prudent.

CRediT authorship contribution statement

Oyewole Christopher Durojaiye: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Visualization. **Joby Cole:** Investigation, Writing – review & editing. **Evangelos I. Kritsotakis:** Validation, Formal analysis, Writing – review & editing.

Declarations

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Supplementary materials

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Paper 8

Outpatient parenteral antimicrobial therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards

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UK

ABSTRACT

This study reviews the current OPAT service provision in the UK and evaluates concordance with the national OPAT practice guidelines (standards of care). We conducted a survey of acute hospital trusts and health boards in the UK regarding OPAT practices between June and September 2017. 165 (93%) of the 178 acute hospital trusts/health boards that were contacted responded to the survey. 100 (61%) indicated they had an OPAT service. Ten (10%) OPAT services did not involve an infection specialist. Bone and joint infections, and skin and soft-tissue infections were the most common conditions treated. Most OPAT services (74%) hold weekly multidisciplinary meetings/virtual ward rounds to review patient's progress. 73% had a dedicated OPAT database. We identified variations in practice and concordance with the national OPAT good practice guidelines. In an era of increasing demand for home-based care, further studies are required to identify the optimal configuration of OPAT services with regards to quality and patient safety.

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1. Introduction

Outpatient administration of intravenous (IV) antibiotics was first described in the USA in 1974 (Rucker and Harrison, 1974) and has now become part of routine care in many developed countries (Howden and Grayson, 2002; Tice et al., 2004). In the UK, outpatient parenteral antimicrobial therapy (OPAT) has evolved slowly but is now becoming widespread as the benefits to patients and healthcare delivery systems are recognized (Chapman et al., 2012). Despite its benefits, OPAT is potentially associated with increased clinical risk due to reduced level of supervision compared to inpatient care. Several professional bodies have produced recommendations regarding the optimal delivery of OPAT (Gallagher et al., 2010; Tice et al., 2004). The British Society for Antimicrobial Chemotherapy (BSAC) has published good practice guidelines commending evidence-based standards for adult and pediatric OPAT services in the UK, with aim of minimizing risks and optimizing the quality of care (Chapman et al., 2012; Patel et al., 2015). OPAT Service was defined as a clinical team that supervises parenteral antimicrobial therapy in a non-inpatient setting. The BSAC guidelines provide recommendations on service structure, patient selection, antimicrobial delivery, patient monitoring, and clinical governance and outcome monitoring. The BSAC OPAT initiative has produced an electronic patient management system (PMS) that enables OPAT services to manage patients and monitor outcomes (British Society for Antimicrobial Chemotherapy). In addition, the BSAC National Outcomes Registry System (NORS) collates outcome reports from all submitting services, aiming to provide a comprehensive picture of OPAT service provision in the UK (British Society for Antimicrobial Chemotherapy).

This study reviews the current OPAT service provision in the UK and assesses concordance with the BSAC OPAT recommendations.

2. Materials and methods

We conducted a cross-sectional survey of acute hospital trusts and health boards (healthcare organizations) in the UK between June and September 2017. At that time, there were 152 acute trusts in England, 14 regional health boards in Scotland, 7 local health boards in Wales, and 5 regional health and social care trusts in Northern Ireland responsible for the provision of healthcare across the UK.

The questionnaires were sent electronically to infection specialists, antimicrobial pharmacists, OPAT lead nurses, OPAT coordinators, and other clinicians who provide OPAT care. Follow-up emails and telephone calls were made to nonrespondents 4 and 8 weeks after the initial invitation. The survey questions (see appendix) sought to explore characteristics of OPAT practice and aspects of clinical governance. The survey asked respondents questions relating to the following:

- Demographics: respondent details, name of the hospital trust/health boards.

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- OPAT team and service structure: year of establishment, where the service is based, the clinical lead, members of the OPAT team, and model of OPAT delivery.
- Patient selection: the number of patient episodes per year and types of infection treated.
- Antimicrobial management and drug delivery: type of intravascular access devices used.
- Monitoring of patients during OPAT: frequency of clinical and multidisciplinary team reviews
- Outcome monitoring and clinical governance: OPAT follow-up clinic, use of dedicated OPAT database, and registration with the BSAC NORS and PMS systems.
- Any future plans: development of service.

For healthcare organizations with multiple responders, a primary respondent was selected based on who gave the most comprehensive answers. Data were recorded and analyzed using Microsoft Excel (Sheffield, UK). Percentages were calculated on the available responses for each survey question. Hence, the denominator for each question varies.

3. Results

One hundred and eighty-three responses were received from 165 of the 178 healthcare organizations, giving a response rate per organization of 93%. Sixteen responses were excluded from the analysis where the same organization provided multiple responses. One hundred (61%) of the 165 healthcare organizations that responded to the survey reported they had an OPAT service. Most of those reporting they did not have OPAT were in the process of setting up a service. Two trusts reported having both adult and pediatric OPAT services revealing 102 OPAT services. Fig. 1 shows the cumulative number of OPAT services by the year of establishment.

3.1. OPAT teams and service structure

The characteristics of the OPAT services are shown in Tables 1 and 2. Table 1 shows the clinical leads for the 102 OPAT services. Seventy-six (75%) OPAT teams included a clinical pharmacist. Ten (10%) did not include an infection specialist (Table 2). In the majority of services, OPAT treatment was administered in the community by visiting healthcare professionals. Thirty-six (35%) services offered all three main models of care.

3.2. Patient selection

Eight-two OPAT services reported a total of 18,765 patient episodes in the previous year, with an average of 229 (range 5–837) episodes per service. Patients with a variety of infections were treated. Bone and joint infections (BJIs), and skin and soft-tissue infections (SSTIs) accounted for the most frequent use of OPAT (Table 2).

Table 1
Characteristics of OPAT services in the UK: team structure, number of patient episodes, monitoring, and clinical governance.

Variable	Number (%)
OPAT team and service structure	
Clinical lead (N = 102)	
No formal lead	6 (5.9)
Infectious diseases or microbiology consultant	60 (58.8)
Acute physician	13 (12.7)
Specialist nurse	12 (11.8)
Advanced nurse practitioner	4 (3.9)
Consultant pediatrician	2 (2.0)
Clinical pharmacist	2 (2.0)
Others[a]	3 (2.9)
Number of patient episodes in the previous year (N = 82)	
<50	6 (7.3)
50–100	11 (13.4)
100–250	35 (42.7)
250–500	25 (30.5)
500–750	4 (4.9)
>750	1 (1.2)
Monitoring of patient during OPAT	
Multidisciplinary "virtual" ward round (N = 100)	
No	20 (20.0)
Daily	1 (1.0)
Weekly	74 (74.0)
Monthly	1 (1.0)
Others[b]	4 (4.0)
Follow-up clinic post-OPAT (N = 101)	
Yes	41 (40.6)
No	60 (59.4)
Outcome monitoring and clinical governance	
Dedicated OPAT database (N = 100)	
Yes	73 (73.0)
No	27 (27.0)
Registered with BSAC OPAT NORS (N = 99)	
Yes	34 (34.3)
No	65 (65.7)
Currently using BSAC OPAT PMS (N = 101)	
Yes	17 (16.8)
No	84 (83.2)

[a] Others include general practitioner, respiratory consultant, and IV nurse consultant.
[b] Others include variable (1), biweekly (1), and fortnightly (2).

3.3. Antimicrobial management and drug delivery

Peripherally inserted central catheters were the most commonly used vascular access device, followed by peripheral venous catheters

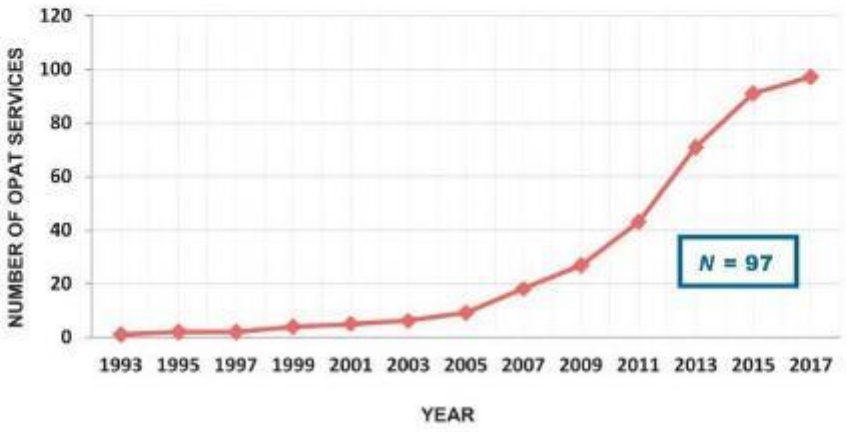

Fig. 1. Cumulative number of OPAT centers by the year of establishment, 1993–2017 (N = 97).

Table 2
Characteristics of OPAT services in the UK: model of delivery, members of OPAT team, diagnosis, frequency of clinical review, and type of vascular access devices.

Variable ($N = 102$)	Number
Model of OPAT delivery	
C-OPAT	94
H-OPAT	67
S-OPAT	48
Combined C-OPAT and H-OPAT	23
Combined C-OPAT and S-OPAT	9
Combined H-OPAT and S-OPAT	3
Combined C-OPAT, H-OPAT and S-OPAT	36
Members of OPAT team	
Infectious diseases or microbiology consultant	92
Acute physician or consultant pediatrician	36
Advanced nurse practitioner	17
Specialist nurse	66
Community nurse	52
Staff nurse	32
Clinical pharmacist	76
Administrative/secretarial support staff	44
Doctors in training	21
Others[a]	7
Infection diagnosis	
Bone and joint infection	97
Skin and soft-tissue infection	96
Respiratory tract infection	90
Spinal infections	87
Urinary tract infection	86
Cardiovascular infection	82
Hepatobiliary infection	74
Central nervous infection	69
Ear, nose, and throat infection	69
Invasive fungal infection	44
Tuberculosis (including MDR-TB)	40
Cystic fibrosis	12
Others[b]	6
Frequency of clinical review during OPAT	
Daily	22
Weekly	55
Monthly	13
Infrequently	28
Others[c]	8
Type of vascular device	
Peripherally inserted central catheter	94
Peripheral venous cannula	81
Midline venous catheter	78
Tunneled central venous catheter	53
Implanted port	33

C-OPAT, community-based OPAT; *H-OPAT*, healthcare-administered OPAT; *S-OPAT*, self-/carer-administered OPAT; *MDR-TB*, multidrug-resistant tuberculosis.

[a] Other members include general practitioner, surgeon, associate specialist, clinical scientist, and podiatrist.

[b] Other commonly treated infections include bacteremia, Lyme disease, and syphilis.

[c] Other include biweekly (3), fortnightly (4), and prior completion of OPAT (1).

(i.e., butterfly needles and peripheral venous cannulae) and midline peripheral catheters (Table 2).

3.4. Monitoring of the patient during OPAT

Most OPAT services reported that patients were reviewed at least weekly by a clinician during their treatment. In 28 (27%) services, patients were not routinely reviewed but only when deemed clinically necessary. The majority of services (74 of 100; 74%) held weekly multidisciplinary meetings/virtual ward rounds to review patients' progress (Table 1). Forty-one (41%) services held follow-up clinics to see patients after completion of OPAT (Table 1).

3.5. Outcome monitoring and clinical governance

Most services (73 of 100; 73%) reported they had a dedicated OPAT database (Table 1). However, majority of OPAT services reported they were not registered with the BSAC OPAT NORS (65 of 99; 66%) and did not use the BSAC OPAT PMS (84 of 101; 83%).

3.6. Pediatric OPAT (p-OPAT) service

Six p-OPAT services were identified — 1 ad hoc and 5 dedicated services. The first p-OPAT was established in 2012. The 5 dedicated services reported 609 patient episodes in the previous year (range 45–190) with an average of 122 patient episodes per service. In most services, OPAT was administered in the community by visiting healthcare professionals.

4. Discussion

This study reflects the growth of UK OPAT in the last few decades and describes some elements of current OPAT practice. Until recently, OPAT was limited to a small number of specialist centers (Chapman et al., 2012). In the last decade, OPAT services have expanded according to local needs and circumstances, resulting in a variety of different service configurations and models of care. OPAT is likely to continue to expand given the economic pressures faced by most healthcare systems and the focus on providing care closer to patients' home (Chapman, 2013). p-OPAT in the UK is relatively small when compared to adult OPAT (Patel et al., 2015). p-OPAT has evolved slowly and is currently limited to tertiary pediatric centers.

Thirty-nine percent of the acute healthcare organizations that responded did not have an OPAT service. Most of them reported that there was a need for a local service and were in the process of setting up one. These findings were similar to the results of the 2013 BSAC survey of OPAT in the UK (response rate of 63%) which found that 32% of 193 health trusts/boards had no OPAT service and 87% of these organizations would like one (Seaton). A range of barriers to service development were identified including lack of nurses and clinicians, and financial constraint. In our study, most of the organizations that did not have an OPAT service used "ad hoc" services such as hospital-based ambulatory care, district nursing team, and private homecare services to deliver IV antibiotics in the community.

Within existing UK OPAT services, our study shows variation in team configuration, service leadership, models of service delivery, types of infections treated, monitoring practice, and governance arrangements. Some OPAT services were "dedicated," while others were part of a wider remit. A number of studies have also shown significant variations in the management and delivery of OPAT services both locally and internationally (Banerjee et al., 2014; Esposito et al., 2004; Lane et al., 2014; Minton et al; Muldoon et al., 2013; Pareja-Cebrian et al., 2014). The delivery of OPAT services may be influenced by a number of factors including, but not limited to, existing local health delivery systems, local needs, geography (inner city vs. rural setting), and available specialist services (Muldoon et al., 2013; Pareja-Cebrian et al., 2014).

The BSAC OPAT guidelines (Chapman et al., 2012) recommend that the OPAT multidisciplinary team should be led by a clinician/infection specialist with OPAT experience and should include, as a minimum, a clinician, an infection specialist [infectious diseases (ID) physician or clinical microbiologist], a specialist nurse, and a clinical antimicrobial pharmacist. We found that OPAT services were predominantly physician led. However, a small number of services had no clearly designated clinical lead. Defining leadership within teams may contribute to improvements in quality of care (West et al., 2015). Moreover, 10% of services did not include an infection specialist. These services did not have a local ID department but may have received ad hoc input from their local clinical microbiology service. Of interest, 1 hospital trust was not able to offer formal microbiology input due to staffing constraints, but microbiologists would recommend the OPAT service to clinicians. Selecting appropriate patients for OPAT is crucial to treatment success. Studies have shown that consultation by an infection specialist prior to commencement of OPAT significantly reduces the need for OPAT via early oral switching or stopping antimicrobial therapy altogether. This

benefits patient safety and convenience, and provides cost savings while maintaining good clinical outcome (Conant et al., 2014; Dryden et al., 2012; Sharma et al., 2005; Shrestha et al., 2012). Twenty-five percent of services did not formally include an antimicrobial pharmacist but presumably relied on ad hoc support. Pharmaceutical care in OPAT should be equivalent to that expected for inpatient care. Pharmacists play a crucial role in the OPAT team in ensuring safe antimicrobial prescribing and high-quality stewardship (Goodall et al., 2013; Heintz et al., 2011; Petroff et al., 2014).

A wide range of infections were treated. BJIs and SSTIs were the most commonly reported. Although we did not explore the number of OPAT episodes due to these infections, SSTIs (mainly cellulitis) are the most common indications for OPAT in the UK (Barr et al., 2012; Chapman, 2013; Durojaiye et al., 2017).

OPAT is potentially associated with increased clinical risk due to reduced levels of clinical supervision. The BSAC guidelines (Chapman et al., 2012) recommend weekly multidisciplinary meeting (MDT)/virtual ward round to discuss progress of patients receiving OPAT, in addition to regular clinical review. In our study, 20% of services did not hold an MDT/virtual ward round, and 59% did not have a follow-up clinic to assess patients following completion of treatment. At least a quarter of patients receiving OPAT will experience an adverse event. These range from mild antibiotic reactions to severe line complications (Chapman et al., 2012). OPAT complications may result in readmission or unplanned healthcare visits with associated morbidity and cost. Adverse events may not be appropriately attributed to OPAT if patients are not followed-up closely.

The BSAC guidelines advocate a local database to facilitate service evaluation and quality assurance. In our study, 27% of the services did not use a local database. The development and expansion of any service require structured quality improvement measures and periodic audit to ensure that patients are receiving safe and effective care (Muldoon et al., 2013). Thirty-four percent of the services reported that they are registered with the BSAC OPAT NORS system. National collection of data on OPAT patients could allow standardization of outcomes and benchmarking.

The effects of these variations in OPAT practices on the clinical efficacy and safety of OPAT are not well studied. However, standardization of practice has the potential to provide significant benefits to patients and healthcare systems (Lehmann and Miller, 2004; Woolf et al., 1999). Formation of regional/geographical networks of OPAT services could support new and existing services, and standardization of practice.

OPAT has been highlighted as 1 of the 5 key antimicrobial stewardship decisions in the Department of Health's antimicrobial stewardship program 'Start Smart – then Focus'. (Public Health England, 2015). Its use is likely to increase. However, there are growing concerns that OPAT is overused especially for patients with mild infections (Brindle, 2013; Goldman et al., 2017). In our study, 4 respondents echoed these concerns. Preliminary results of the OVIVA trial suggest that oral antibiotic therapy is just as effective as IV therapy in treating BJIs (Scarborough et al., 2017). Therefore, it is paramount that the use of IV antibiotics in OPAT and broadly is overseen through a robust antimicrobial stewardship program. Oral antimicrobial therapy may not be appropriate for some infections (e.g., infective endocarditis). OPAT should only be used when there are no suitable alternative oral antimicrobial agents. Patients starting OPAT should have individualized antibiotic plan. The plan should be reviewed regularly and modified based on clinical responses.

A major strength of our study was the high response rate which may be due to the growing interest in OPAT, the relatively short length of our electronic questionnaire, and multiple reminders (Edwards et al., 2009; Van Mol, 2017). However, our study has limitations which may limit the generalizability of the results to OPAT practices in the UK. We did not assess practices in community hospital trusts and private homecare services which also deliver parenteral antimicrobials in the community. Furthermore, responses may be subject to recall bias. Our study did not explore factors that contribute to the decision-making process around commencing OPAT or barriers to OPAT delivery.

5. Conclusions

Our study provides the most comprehensive overview to date of OPAT services in the UK. We demonstrate significant variations in OPAT practices and clinical governance arrangements. The BSAC OPAT recommendations were not completely met. OPAT is predicted to continue to expand. However, it is not without risk. Risk assessment, risk management, and quality assurance systems, including benchmarking, are essential to minimize potential risks and optimize the quality of care, in accordance with existing practice guidelines. Given the variations in practice, further evidence-based studies are required to identify the optimal configuration of OPAT services with regards to patient outcomes and safety.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.07.013.

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Paper 9

Effectiveness of telemedicine in outpatient parenteral antimicrobial therapy (Tele-OPAT): A systematic review

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Effectiveness of telemedicine in outpatient parenteral antimicrobial therapy (Tele-OPAT): A systematic review

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Abstract

Introduction: Telemedicine is increasingly used to deliver healthcare in many clinical specialities. However, the adoption of telemedicine in the delivery of outpatient parenteral antimicrobial therapy (OPAT) has been relatively slow and limited. This study aims to collate current evidence for telemedicine in OPAT regarding clinical efficacy, safety, acceptability and cost-effectiveness.

Methods: We systematically searched the Cochrane Library, CINAHL, EMCARE, EMBASE and MEDLINE databases through 24 July 2022, for relevant studies published in English. Research articles and conference abstracts were included if they involved any form of telephone or video consultation in delivering parenteral antibiotics in the home or outpatient setting. Study findings were synthesised into three main themes: patient outcomes and safety, patient and provider satisfaction and cost-effectiveness. The mixed methods appraisal tool was used to review the methodological quality of the studies. PROSPERO CRD42022342874

Results: The literature search yielded 311 articles, of which 12 (five full-length articles and seven conference abstracts) reporting over 1245 telemedicine interventions were reviewed. The reported outcomes were heterogeneous. Telemedicine was cost-effective and associated with high patient satisfaction and comparable complication rates compared to conventional OPAT. Considering six comparative studies, rehospitalisation risk was lower for telemedicine than conventional OPAT (risk ratio, 0.58; 95% confidence interval, 0.38–0.88; $I^2 = 31\%$).

Discussion: The results of this review demonstrate that telemedicine has a role in delivering safe and cost-effective OPAT care, especially for patients residing in remote and geographically isolated locations. Nevertheless, high-quality studies and publication of existing data and experiences are needed to further validate this model of care delivery.

Keywords

eHealth, home health monitoring, outpatient parenteral antimicrobial therapy, systematic review, telehealth, telemedicine

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Introduction

A wide range of infections is increasingly treated with intravenous (IV) antibiotics in-home and outpatient settings rather than inpatient settings. The effectiveness and safety of outpatient parenteral antimicrobial therapy (OPAT) have been well documented.[1–3] Despite its benefits, OPAT is potentially associated with increased clinical risk compared with inpatient care due to a reduced level of supervision and monitoring.[4] OPAT practice guidelines emphasise the need for close monitoring of patients during treatment and ongoing communication between patients and their care team to optimise clinical outcomes.[5,6] However, monitoring of patients living in remote and rural locations could be challenging.

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The use of telemedicine to support the delivery of OPAT, especially in geographically isolated locations, is recognised by OPAT practice guidelines.[5,6] Telemedicine is the use of telecommunication and information technology to provide remote health assessments and therapeutic interventions.[7] This could include video or voice messaging services on mobile phones, computers and tablets. With advances in technology, telemedicine has been more widely used to deliver healthcare in many clinical specialities, including infectious diseases and across different healthcare settings with associated significant cost savings and high patient/clinician satisfaction.[8–10] The COVID-19 pandemic has further accelerated the growth of telemedicine, and it is likely to be used increasingly in the future.[11]

The adoption of telemedicine in OPAT has been relatively slow and limited.[12] This systematic review aims to collate current evidence for telemedicine in OPAT practice (tele-OPAT) regarding its clinical efficacy, safety, acceptability and cost-effectiveness.

Methods

This systematic review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022342874) and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Material, Table A.1).[13]

Search strategy and information sources

The source of evidence and search strategy were developed after an initial review of existing literature. A three-step search strategy was used in this systematic review. An initial limited search of CINAHL and MEDLINE (PubMed) databases was conducted followed by an analysis of the text words contained in the titles and abstracts of retrieved articles, and of the index terms used to describe the articles. A second search was then performed across the databases of CINAHL, EMBASE (Ovid), Ovid Emcare, MEDLINE (PubMed) and the Cochrane Library, using all identified keywords and index terms. Thereafter, the reference lists of identified articles were searched for additional sources. Supplementary searches of clinical trial registries, Web of Science Conference Proceedings, Google/Google Scholar, WorldCat and the websites of the Infectious Diseases Society of America and British Society for Antimicrobial Chemotherapy were performed to identify relevant grey literature and unpublished studies. The search terms were generated based on the two main key terms (i.e. telemedicine and OPAT) and their corresponding alternative terms. The full search strategy is presented in the Supplementary Material (Table A.2). The search was not limited by years (all articles up to 24 July 2022) but restricted to studies published in English.

Eligibility criteria

Eligibility criteria were assessed using the PICO framework (population, intervention, comparison and outcome).[14] Studies were eligible if they reported any form of video or telephone consultation (intervention) in the delivery of parenteral antibiotics in-home or outpatient settings (population), and measurable outcomes (e.g. readmission rates) evaluating telemedicine (outcome) – with or without conventional OPAT (comparison). Studies of any research design were considered – with the exception of reviews, guidelines, commentaries and editorials. Studies were excluded if they were not specifically related to tele-OPAT (Supplementary Material, Table A.3). Given the sparse research in tele-OPAT, conference abstracts were considered to account for as much existing literature as possible and provide a comprehensive overview of the topic. The authors of the abstracts were contacted to inquire whether the full data were later published in a scientific journal. We included original conference abstracts meeting our eligibility criteria if the full-length articles were not available or no response from the author. The inclusion of conference abstracts follows Scherer and Saldanha[15] recommendations that conference abstracts should be considered for systematic review if the available evidence is sparse or conflicting.

Study selection and data extraction

Duplicate records were removed using endnote reference management software. All identified titles and abstracts were independently reviewed by two reviewers (OCD and IJ). The full texts of potentially eligible studies were then screened independently against the eligibility criteria by both reviewers. Disagreements were resolved by consensus or with a third reviewer (EIK). All reviewers (OCD, IJ and EIK) independently extracted data from retrieved studies using a standardised pro forma. Extracted data included citation details (author, year of publication and title), location, study aim/purpose, design, sample size/population details, duration, type of telemedicine intervention, study outcome and main findings. Discrepancies in data extraction were resolved by discussion.

Data synthesis

We qualitatively classified different applications of telemedicine in OPAT and reported outcomes. Considering the limited number of full-length articles on tele-OPAT and methodological heterogeneities in study design, intervention and outcome definitions, a meta-analysis was only possible for assessing the average risk of all-cause unplanned readmission, but no other outcome could be meaningfully meta-summarised. We estimated the pooled risk ratio (RR) for readmission and the respective 95%

confidence interval (CI) associated with tele-OPAT (as opposed to conventional OPAT) using the random-effects model. The between-study variability parameter (Tau^2) was estimated with the restricted maximum likelihood method. Heterogeneity of intervention effects across the studies was measured using Cochrane's Q statistic and chi-square test, and Higgin's I^2 statistic ($I^2 > 50\%$ indicates substantial heterogeneity).

Quality assessment

We used the Mixed Methods Appraisal Tool (MMAT) version 2018 to access the methodological quality of the included studies,[16] due to differences in study design. The MMAT tool was designed for the appraisal stage of systematic mixed studies reviews (i.e. qualitative, quantitative and mixed methods studies) and allows assessment of quality over five criteria with rating scales of 'Yes', 'No' and 'Can't tell'. The developers of the tool discourage the calculation of an overall numerical score but advise reviewers to provide a detailed presentation of the ratings of each criterion to better inform the quality of the included studies. They also discourage the exclusion of studies with low methodological quality.[17] In our study, the quality appraisal was independently performed by all reviewers. Any disagreement was resolved by discussion, and no studies were excluded based on the results of the evaluation.

Results

Selection results and characteristics of the studies

The search yielded 311 non-duplicate publications, of which 12 met the eligibility criteria and were reviewed (Figure 1). Details of the studies (five full-length articles[18–22] and seven conference abstracts[23–29]) are presented in the Supplementary Material (Table A.4). The findings of the studies were classified into three main themes: patient outcomes and safety, patient and provider satisfaction and cost-effectiveness. The studies were published between 2004 and 2022. Most (10/12; 83%) appeared in the last 5 years,[19,21–29] and were conducted in the United States ($n = 9$)[20,22–29] and Australia ($n = 3$).[18,19,21] Two studies were conducted in paediatric patients.[18,25] Altogether, the studies included 2572 (median, 145) participants, of whom over 1245 (median, 49) had some form of telemedicine intervention, with sample sizes ranging from 2[25] to 636.[26]

Real-time (synchronous) telemedicine was utilised in all but one study. Videoconferencing was most commonly used (8/12; 67%),[18–21,23,25,27,28] followed by telephone calls only ($n = 3$).[22,26,29] The technology used was not specified in one study.[24] The types of services provided via telemedicine included consultation between healthcare professionals,[18,21,24] remote patient monitoring,[20] home support and care,[18,20] patient/caregivers consultation[26] and tele-visit.[19,20,22–25,27–29]

Quality appraisal

Eight (67%) studies were categorised as quantitative non-randomised studies,[18,20–24,28,29] and four (33%) studies as quantitative descriptive studies.[19,25–27] There were no qualitative, randomised controlled trials (RCTs) nor mixed method studies. Using the MMAT tool, the weakest studies[25,28,29] had only one 'Yes' answer out of five criteria, while the strongest one[20,21] had five 'Yes' answers. The key quality issue was related to the insufficient information in most of the conference articles to determine if the criterion was met or not (Supplementary Material, Table A.5).

Patient outcomes and safety

Nine studies reported on patient outcomes or safety of telemedicine.[19–24,27–29] Hospital readmission was the most assessed outcome. Tan et al.[19] reported on the use of telemedicine in the management of OPAT patients over a wide geographical area of Australia and recorded a low unplanned OPAT-related admission rate which was comparable to published non-telemedicine OPAT literature. Treatment was administered by local nursing staff and supported by a weekly videoconference with an infectious diseases (ID) specialist Two other studies also showed similar readmission rates between telemedicine and non-telemedicine groups,[21,23] while four studies showed a significant reduction in rehospitalisation.[22,24,27,29] Vaz et al.[25] demonstrated the feasibility and functionality of telemedicine to conduct OPAT clinic visits in two paediatric OPAT patients with no reported rehospitalisation. Another study also reported no readmission (cf. one rehospitalisation in the control group) in their cohort of 25 patients treated via telemedicine.[20] No study identified significantly higher readmission rates for OPAT patients treated via telemedicine compared to those treated via conventional OPAT. Pooling data from six comparative cohort studies (1051 patients), the risk of readmission was significantly lower for the telemedicine group compared with the conventional OPAT group (RR, 0.58; 95% CI, 0.38–0.88; $p = 0.01$) with moderate heterogeneity of effects across the studies ($I^2 = 31\%$) (Figure 2).

One study demonstrated comparable clinical cure or improvement rates using telemedicine compared with conventional OPAT.[19] Another study also reported that patients treated via telemedicine had satisfactory (comparable) clinical outcomes ($p = 0.30$), shorter length of hospitalisation ($p = 0.02$) and returned to normal function sooner ($p < 0.001$) than hospitalised patients.[20]

Among the studies assessing rates of adverse events, Felder et al.[26] showed that post-hospital discharge telephone

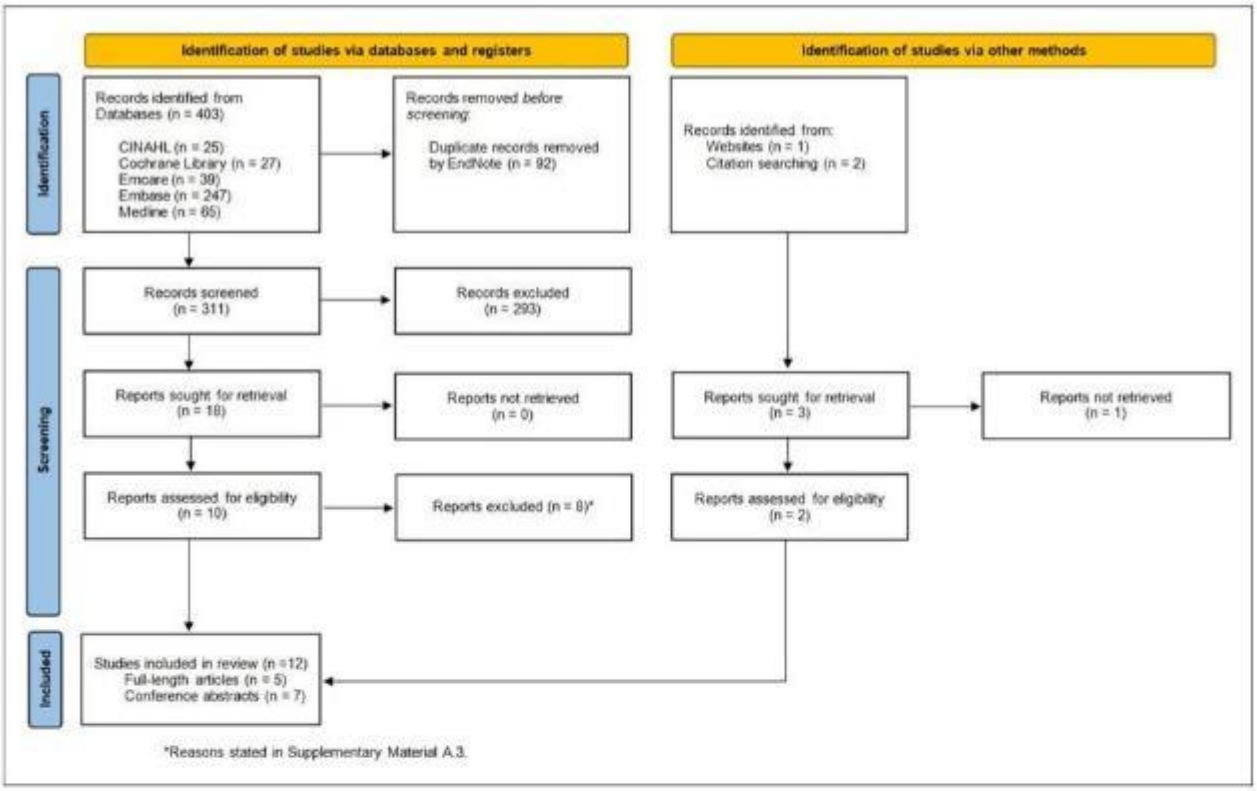

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the systematic review process.[13]

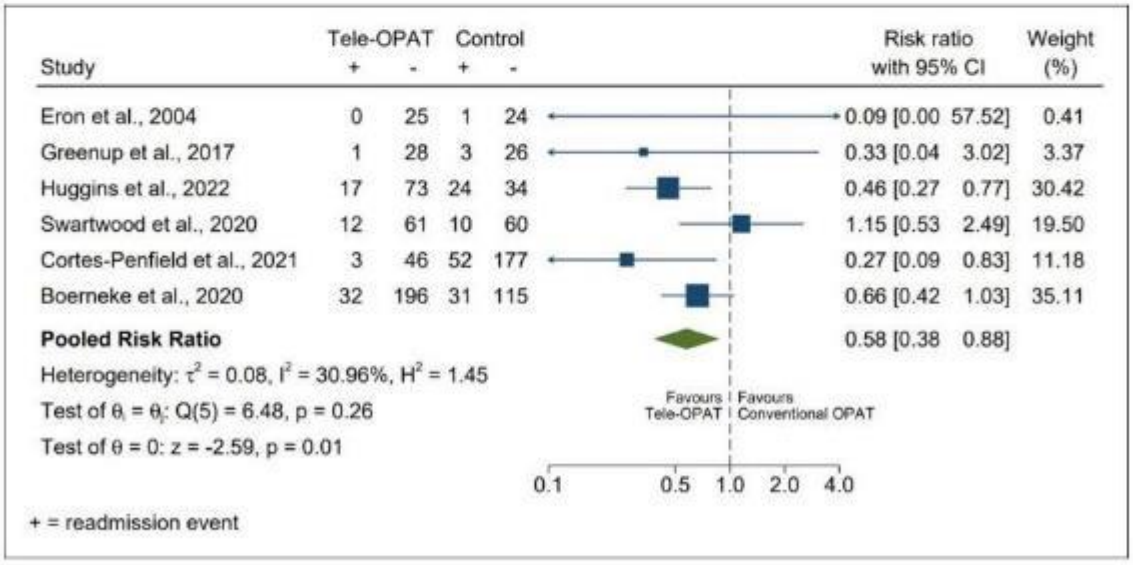

Figure 2. Results of random-effects meta-analysis for the risk of hospital readmission in telemedicine versus conventional OPAT.

calls resulted in early identification of significant concerns and OPAT-related complications. Two additional studies reported comparable adverse event rates between the telemedicine group and the historic OPAT programmes.[19,29] One study reported one case of vascular access-related complication in a cohort of 13 patients managed via telemedicine,[27] but lacked a direct comparison with non-telemedicine OPAT group.

Patient and provider satisfaction

Only one study assessed patient satisfaction with telemedicine, but none reported on provider/clinician satisfaction. Eron et al.[20] reported a higher mean satisfaction score for patients with acute infections managed in the home setting via telemedicine compared with a comparable group of patients treated in the hospital. The telemedicine group was more comfortable at home ($p = 0.35$) but would have felt safer in the hospital ($p = 0.09$). The authors suggested that patient perception will have to be altered before telemedicine is widely accepted.

Cost-effectiveness

Telemedicine was associated with lower cost when compared with the conventional treatment model. A study on telemedicine-supported OPAT reported that over 100,000 km of travel was averted over a 4-year period with associated cost savings from travel, accommodation and early return to work.[19] Another study compared the cost of outpatient treatment via telemedicine with the cost of inpatient treatment and estimated a cost saving of $135,000 to $540,000 over a year.[20] A cost minimisation study compared the costs associated with three different methods of administering IV antibiotic therapy in outpatient settings to paediatric oncology patients and found that service cost in a scenario where antibiotics were prepared in the home setting and checked by a second nurse via a video link was significantly lower than the costs wherein the medications were prepared by an outsourced company or in the hospital (mean costs of a medication episode of $129.91 versus $312.00 and $355.91, respectively).[18]

Discussion

This study presents a systematic review of the literature to summarise data regarding the use of telemedicine in the delivery of OPAT. Based on the available limited evidence, the impact of tele-OPAT on clinical outcomes is comparable to conventional OPAT. In addition, tele-OPAT can be a valid, safe, cost-efficient and acceptable method of delivering OPAT, especially for patients residing in remote and geographically isolated locations. However, we identified a small number of articles reporting on our predefined outcomes, and the majority were conference articles, leading to negative ratings in the quality assessment. It would have been ideal to include RCTs in this review but none of the RCTs identified by the search strategy met the inclusion criteria. Nonetheless, observational studies can provide meaningful insight into 'tele-OPAT' and explore its long-term efficacy, rare complications and clinical outcomes.[30] The lack of RCTs comparing tele-OPAT to conventional OPAT, and of robust high-quality data are significant weakness of the existing literature. Consequently, strong conclusions regarding the clinical efficacy, safety, acceptability and cost-effectiveness of tele-OPAT cannot be made.

In the reviewed studies, the operationalisation of tele-OPAT varied widely. The most commonly reported type of telemedicine was live (real-time) videoconferencing. Also known as synchronous telemedicine, live videoconferencing allows healthcare providers to communicate with patients in real-time. Other forms of telemedicine that could be adopted in OPAT settings include: (a) Asynchronous (store-and-forward) technique, wherein patients' data are collected, stored and later sent to health practitioners for diagnostic and treatment expertise; (b) Remote patient monitoring, which involves continuous evaluation of patients remotely; (c) Mobile health (mHealth), which is the delivery of healthcare services via mobile devices, often incorporating wearable technologies.[31]

The studies within this review demonstrated the effectiveness of telemedicine in OPAT across a range of clinical outcomes. However, only one study reported on and identified high patient satisfaction with tele-OPAT.[20] Whilst the reasons for the high patient satisfaction were not assessed in the study, it could be due to convenience of care, improved communication with OPAT providers, decreased missed workdays, and reduced travel time and costs.[32,33] High patient satisfaction may improve adherence to OPAT treatment and follow-ups,[33] allowing further cost savings. Another study in this review reported that tele-OPAT allowed equitable access to ID specialists in a geographically large area of Australia.[19] This is particularly beneficial for isolated populations including people living in rural communities, nursing home residents and socioeconomically disadvantaged patients. Increased access to OPAT care through telemedicine will allow many more patients to be managed outside of the hospital setting. In addition, direct access to specialist support via telemedicine promotes networks between OPAT and primary care clinicians, which consecutively can enhance the delivery of care and stability within healthcare systems.[19]

The studies analysed in this review clearly demonstrate that telemedicine has the potential to prevent rehospitalisation in patients receiving OPAT, even though partially different measures of readmissions were used. Rehospitalisation rates from the studies assessing readmission, when aggregated, show that telemedicine interventions significantly reduced hospital readmissions. Telemedicine provides an ideal opportunity for timely identification and appropriate management of complications and concerns before they become significant enough to warrant hospitalisation.[22] In addition, all the reviewed studies assessing the cost-effectiveness of telemedicine suggest that tele-OPAT may be more cost-effective than conventional OPAT. However, the analyses were based on projections that may not be applicable to all settings.

Although not rigorously evaluated in the reviewed articles, other potential benefits of tele-OPAT include reduced frequencies of clinic visits and late/missed appointments, and a reduction in health disparities.[9,34–36] By reducing in-person visits and travel-related emissions, tele-OPAT also offers a potential opportunity to reduce the carbon footprints of healthcare systems and thus helps in the fight against climate change.[37]

One key knowledge gap within the reviewed literature relates to patient experience and provider acceptance/perspectives on tele-OPAT. There is a limited reflection on the factors which may influence patient experience and satisfaction such as visit-related factors and degree of trust in OPAT clinician.[38] Patient and healthcare professional perceptions are crucial to the acceptability and success of telemedicine.[20] We also do not know the long-term outcomes of patients managed via tele-OPAT.

The adoption of tele-OPAT has been limited.[12] Regulatory, reimbursement, socioeconomic and technological barriers such as access to high-speed internet connections are potential obstacles to widespread use of telemedicine in OPAT.[9,35,39,40] Although, poor internet access remains an issue in some rural areas, progress has been made and video quality has improved.[9,35] Furthermore, there are concerns regarding the legal and ethical aspects of telemedicine such as data privacy, confidentiality, professional liability risk and medical malpractice.[41,42] As such, medical regulatory authorities around the world have produced practice guidelines to mitigate these risks.[43] Telemedicine in OPAT must meet the same clinical and ethical standards as traditional care in order to deliver quality treatment that safeguards the welfare and best interests of patients.

Our review has several limitations. As suggested by Scherer and Saldanha,[15] we included conference abstracts in this systematic review due to the paucity of evidence on tele-OPAT. Most conference abstracts are not peer-reviewed and reported results are often preliminary and/or based on limited analyses. Nevertheless, the inclusion of conference abstracts in systemic reviews can provide a more comprehensive overview and potentially reduce the impact of publication bias.[15] We only considered studies published in the English language due to a lack of language resources (e.g. professional translators). Relevant articles written in non-English languages could have been omitted; thus, we cannot exclude the possibility of a language bias. Although this review used a robust and iterative methodological approach, its conclusions are limited by heterogeneity in study design and outcome definitions and by lack of high-quality evidence, especially from RCTs comparing telemedicine in OPAT with conventional OPAT. Nevertheless, within its constraints, the findings of this study show that tele-OPAT offers a number of benefits to patients and OPAT service providers.

Conclusion

This study sheds light on the use of telemedicine in OPAT settings. Limited evidence suggests that tele-OPAT can be safe, clinically and cost-effective with high patient satisfaction. However, high-quality studies are required to substantiate or further investigate our findings and address gaps in knowledge, especially regarding clinician acceptance and perspectives on tele-OPAT. As telemedicine continues to grow, new and existing services should consider adopting tele-OPAT to support OPAT delivery, especially for patients residing in remote and geographically isolated locations.

Implications for research

Large-scale and well-designed studies are needed to better evaluate the clinical efficacy, safety and cost-effectiveness of tele-OPAT. In addition, a well-validated measure to assess patient and provider acceptance and satisfaction is required for reliability and comparability of research results. Future studies should also define the type of telemedicine that is most cost-effective and adaptable to different OPAT settings. OPAT services that have already adopted telemedicine should consider publishing their existing data and experiences to further validate this model of care delivery.

Authors' contributions

OCD: Conceptualisation, Data Curation, Investigation, Methodology, Writing – original draft, Visualisation. IJ: Investigation, Writing – Review & Editing. EIK: Validation, Formal analysis, Writing – Review & Editing.

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Supplemental material

Supplemental material for this article is available online.

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Paper 10

Effectiveness and safety of a disposable elastomeric continuous infusion pump for outpatient parenteral antimicrobial therapy (OPAT) in a UK setting

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Effectiveness and safety of a disposable elastomeric continuous infusion pump for outpatient parenteral antimicrobial therapy (OPAT) in a UK setting

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ABSTRACT

We evaluated the effectiveness and safety of continuous antimicrobial infusion using a disposable elastomeric device in an outpatient parenteral antimicrobial therapy (OPAT) setting. We conducted a retrospective analysis of all patients who received either flucloxacillin ($n = 131$ episodes) or piperacillin/tazobactam ($n = 301$ episodes) as continuous infusion *via* elastomeric devices over 5 years (January 2018-December 2022) at a tertiary referral hospital in Derbyshire, UK. Overall, 81 adverse events were recorded in 77 (18%; 77/432) patient-episodes. Most adverse events were vascular access-related (59%; 4.6 events per 1000 OPAT-days), including one line-related infection (0.2%; 0.1 events per 1000 OPAT-days). 165 (38%) patient-episodes experienced at least one incident of incomplete infusion. Successful outcome (cure or improvement) occurred in 364 (84%) episodes. Our findings suggest that elastomeric infusion pumps are safe and effective for administering selected antimicrobial agents in OPAT. However, close monitoring of patients and the device are essential to ensure optimal delivery of prescribed therapy.

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Continuous infusion; elastomeric infusion pump; flucloxacillin; outpatient parenteral antimicrobial therapy; OPAT; piperacillin/tazobactam

Introduction

Outpatient parenteral antimicrobial therapy (OPAT) has been recognised to be a safe and effective alternative to inpatient care for treating a wide range of infections [1–3]. However, patients receiving OPAT are at risk of adverse events that could result in unplanned hospital readmissions [4, 5]. The choice of antimicrobial therapy in OPAT is often limited to agents that can be administered once daily or less frequently for convenience in dosing and due to staffing constraints. Infrequent dosing minimises handling of vascular access and hence reduces the risk of line-related complications such as thrombosis and infection. Furthermore, the use of relatively broad-spectrum once-daily agents such as ceftriaxone to facilitate OPAT for infections (e.g. cellulitis) that could be better treated with narrower spectrum agents with multiple daily doses (e.g. flucloxacillin) represents a major challenge to effective antimicrobial stewardship [6]. Portable continuous infusion pumps and elastomeric devices allow prolonged infusions of narrow-spectrum antimicrobial agents with time-dependent killing profiles and short half-lives such as penicillins, thereby avoiding multiple daily dosing [7]. Elastomeric pumps are increasingly used to deliver antimicrobials with documented success [8, 9]. The lack of antimicrobial stability data, however, limits the use of continuous infusions of most antibiotic agents in the OPAT setting. Recently published data from the British Society for Antimicrobial Chemotherapy (BSAC) drug stability group suggest that flucloxacillin and piperacillin/tazobactam are suitable for continuous 24-h infusion *via* an elastomeric device [10, 11].

With the continued widespread utilisation of elastomeric devices in OPAT, it is essential to further review clinical outcomes across a range of clinical conditions, especially within the UK National Health Service [12, 13]. In the current study, we examine the clinical characteristics, safety profile and outcomes of patients who were treated with disposable elastomeric continuous infusion pumps at an OPAT service based

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in a large tertiary referral teaching hospital in Derbyshire, UK.

Patients and methods

Study design and setting

In this cohort study, we reviewed and followed up all patients who received antibiotics as continuous infusion *via* elastomeric pumps at the OPAT unit of University Hospitals of Derby and Burton (Derbyshire, England, UK) between 1 January 2018 and 31 December 2022. The number of eligible patients over the study period determined the study size and no a priori statistical calculation of sample size was performed. Patient outcomes were determined at the end of intravenous (IV) antimicrobial therapy.

The OPAT service was established in 2013 and has been previously described [14, 15]. The service is managed by a multidisciplinary team of infection specialists, specialist nurses, clinical antimicrobial pharmacists, and community nurses. The service maintains electronic databases to prospectively record patient demographics, antimicrobial agents, indication and duration of antimicrobial therapy, model of delivery, clinical outcome, and complications.

Use of flucloxacillin and piperacillin/tazobactam in disposable elastomeric infusion pumps began in late 2017. The pre-filled elastomeric pump devices were sourced from an external healthcare company and required cold chain maintenance. The selection of patients for OPAT, antimicrobial regimens, and mode of OPAT delivery were the responsibility of the OPAT infection specialists. Antimicrobials were delivered through three distinct pathways: administration in the patient's home by a district/community nurse, daily attendance at the OPAT facility, and self or care administration in the patient's home (after appropriate training). The clinical responsibility for patients during their OPAT course and follow-up was shared between the referring clinicians and the OPAT team, unless otherwise agreed upon. Patients receiving OPAT were regularly reviewed and their clinical progress was assessed during a weekly multidisciplinary meeting/virtual ward round. The residual volumes of antibiotic solution in the elastomeric devices were assessed daily using a pictorial 'infusion progress' chart provided by the healthcare company that supplied the devices as a guide.

Data collection

The OPAT databases and hospital electronic health records were reviewed. The following data were extracted: patient demographics, treatment indication, microbiological culture data, antimicrobial regimen, duration of OPAT course (bed-days saved), mode of OPAT delivery, type of vascular access device, OPAT outcome, complications, and hospital readmission. Age (in years) was determined at the time of commencing OPAT. Clinical records were anonymised at the time of data extraction. The study was approved by the local clinical audit/effectiveness team as part of ongoing commitment to clinical governance, service development, and evaluation.

Outcomes and definitions

Clinical outcomes (cure, improvement or failure) were determined at the end of IV antimicrobial therapy using the definitions provided in the BSAC National Outcomes Registry System (NORS) (see Supplementary Table S1) [16]. Adverse events included adverse drug reactions (i.e. events possibly related to study medications, including diarrhoea, rash, blood dyscrasia, renal and hepatic dysfunction), vascular access-related complications (such as infection, line migration, occlusion, thrombosis, and allergy to dressing) and infusion device-related complications (such as leaking devices and device malfunction). Major adverse events were defined as those that resulted in hospital readmissions, change in antimicrobial regimen(s), *Clostridium difficile* infection or death. Other adverse events that were not major were classified as minor. A 30-day unplanned hospitalisation was defined as unplanned inpatient admission to an acute care hospital for any reason during or within 30 days of OPAT discharge.

Statistical analysis

Categorical data were presented as frequency counts and percentages. Numerical data were summarised as medians with interquartile ranges (IQR) or means with standard deviations (SD), depending on the degree of skewness in the distributions. Categorical outcome frequencies were compared using the Chi-square test (or Mid-P exact test where required). Confidence intervals for proportions were calculated using Wilson's score method. Analyses were performed using Prism version 9.5.1 (GraphPad Software, Boston, MA, USA). A two-tailed p-value of less than 0.05 was considered statistically significant.

Sensitivity analysis

A sensitivity analysis of observed adverse event rates, restricted to the first OPAT encounter for each patient, was conducted to examine the potential for overestimating the apparent safety of the antibiotic regimens. This analysis was considered necessary since patients who tolerated their initial course of therapy might have a higher likelihood of tolerating subsequent courses of therapy.

Results

Cohort characteristics

Over the five-year study period, we recorded 1237 episodes of OPAT, of which 432 episodes (involving 340 individual patients) received antibiotics (flucloxacillin, 131 (30.3%) episodes; piperacillin/tazobactam, 301 (69.7%) episodes) administered as continuous infusion *via* elastomeric pumps. Respiratory infection, specifically recurrent exacerbation of bronchiectasis, was the main indication for repeated courses of OPAT. Table 1 presents the demographic, treatment characteristics, and clinical outcomes of the cohort. The median age of the patients was 71 (range, 17–98) years, and 45.4% (196/432) were female. The most frequent indications for flucloxacillin and piperacillin/tazobactam therapy were bone and joint infection (60.3%; 79/131) and respiratory infection (mostly infective exacerbation of bronchiectasis/chronic obstructive pulmonary disease (54.5%; 164/301) respectively. Antibiotic therapy was mainly administered in patient's home by visiting nurses (83.3%; 360/432). The median duration of OPAT for the cohort was 14 days (IQR, 7–33; range, 1–230 days). The longest antibiotic course was administered to control, rather than cure, chronic mandibular osteomyelitis in a patient with locally advanced oropharyngeal cancer (palliative OPAT) [14]. The median duration of piperacillin/tazobactam therapy was 14 days (IQR, 7–34; range, 1–230 days) while the mean duration of flucloxacillin therapy was 22.5 days (SD, 17; range, 2–93).

Clinical outcomes

364 (84.3%; 95% CI: 80.5–87.4%) episodes met the BSAC NORS definition of cure or clinical improvement [16]. Failures were recorded in 68 episodes (15.7%; 95% CI: 12.6–19.5%), mostly due to hospital readmission from non-OPAT related causes (Supplementary Table S2). Non-OPAT related (new) events (e.g. falls, worsening heart failure, etc.) accounted for 42.2% (27/64) of readmissions. Two patients died. One of these patients had palliative OPAT for an incurable infection [14] while the other patient died due to underlying comorbidities unrelated to OPAT. 30-day unplanned readmission was recorded in 117 episodes (27.1%; 95% CI: 23.1–31.5%). The reasons for the 30-day unplanned readmission are shown in Supplementary Table S3. The leading indication for 30-day hospitalisation was also due to non-OPAT related events (41.9%; 49/117). Compared with other models of delivery, self/carer administered OPAT was associated with a lower failure rate (6.3% vs 17.4%; $p = 0.02$) and a lower 30-day unplanned readmission rate (7.8% vs 30.4%; $p < 0.001$).

In all, 81 adverse events were recorded in 77 (17.8%; 77/432) infusions administered through elastomeric pumps (Table 1). Most of the adverse events were vascular access-related (59.3%; 48/81; 4.6 events per 1000 OPAT-days) – mainly due to line migration (52.1%; 25/48). One line-related infection (0.2%, 95% confidence interval (CI): 0.04–1.29%; 0.1 events per 1000 OPAT-days) and two catheter-related thromboses (0.5%; 95% CI: 0.12–1.67%; 0.2 events per 1000 OPAT-days) were recorded. There were no complications related to the elastomeric device (e.g. leaking device, device malfunction). In all, major adverse events were observed in 29 (6.7%; 95% CI: 4.7–9.5%) episodes. Full details of the adverse events are shown in Supplementary Table S4.

The frequencies of adverse events (i.e. line-related complications and drug reactions) were similar between the flucloxacillin and piperacillin/tazobactam groups. These findings were robust in a sensitivity analysis restricting the observed adverse event rates to the first OPAT encounter for each patient (Supplementary Table S5).

There was also no significant relationship between line-related complications and type of vascular access device (PICC vs midline; 19/145 [13.1%] vs. 29/287 [10.1%] events; $p = 0.35$); and between adverse events and mode of OPAT delivery (self/carer administered vs other modes, 23.4% vs 16.9%; $p = 0.20$). There were no adverse complications recorded in the eight patient-episodes who attended the OPAT facility daily for their antibiotic therapy. Overall, 165 (38.2%; 95% CI: 33.7–42.9%) patient-episodes experienced at least one incident of incomplete infusion (emptying) of elastomeric devices. There was no statistically significant difference in cure rates between patients with complete infusions and those who had at least one

Table 1. Characteristics of patients, treatment, and outcomes.

Characteristic	Flucloxacillin ($n = 131$)	Piperacillin/tazobactam ($n = 301$)	Total ($n = 432$)
Demographics			
Age (years), median [(IQR)]	67 [58–75]	72 [66–78]	71 [63–77]
Sex (Male: Female)	1.6:1	1.1:1	1.2:1
Indication for OPAT			
Respiratory infection[a]	–	164 (54.5)	164 (38.0)
Bone and joint infection[b]	79 (60.3)	70 (23.3)	149 (34.5)
Necrotising otitis externa	–	50 (16.6)	50 (11.6)
Spinal infection[c]	31 (23.7)	5 (1.7)	36 (8.3)
Endovascular infection[d]	14 (10.7)	3 (1.0)	17 (3.9)
Intra-abdominal infection[e]	2 (1.5)	5 (1.7)	7 (1.6)
Urinary tract infection[f]	2 (1.5)	4 (1.3)	6 (1.4)
Bacteraemia	3 (2.3)	–	3 (0.7)
Main pathogen identified			
No organism identified	10 (7.6)	38 (12.6)	48 (11.1)
MSSA	116 (88.6)	–	116 (26.9)
Pseudomonas spp.	–	214 (71.1)	214 (49.5)
MSSA + *Pseudomonas spp.*	–	5 (1.7)	5 (1.2)
MSSA + other organisms	–	9 (3.0)	9 (2.1)
Pseudomonas spp. + other organisms	–	18 (6.0)	18 (4.2)
Other organisms[g]	5 (3.8)	17 (5.6)	22 (5.1)
Duration of OPAT (days), median [(IQR)]	18 [9–32]	14 [7–34]	14 [7–33]
Mode of antimicrobial (OPAT) delivery			
Visiting nurse	101 (77.1)	259 (86.1)	360 (83.3)
Self/carer administration	26 (19.8)	38 (12.6)	64 (14.8)
Daily attendance	4 (3.1)	4 (1.3)	8 (1.9)
Type of vascular access device			
Midline	61 (46.6)	226 (75.1)	287 (66.4)
PICC	70 (53.4)	75 (24.9)	145 (33.6)
Concomitant IV antimicrobial therapy	2 (1.5)	10 (3.3)	12 (2.8)
Concomitant oral antimicrobial therapy	38 (29.0)	22 (7.3)	60 (13.9)
Incomplete infusion[h]	46 (35.1)	119 (39.5)	165 (38.2)
OPAT-related adverse event	23 (17.6)	54 (17.9)	77 (17.8)
Type of adverse event[i]			
Major adverse event, *n* (%); events per 1000 OPAT-days	8 (6.1); 2.7/1000 days	21 (7.0); 2.8/1000 days	29 (6.7); 2.8/1000 days
Medication related, *n* (%); events per 1000 OPAT-days	8 (6.1); 2.7/1000 days	25 (8.3); 3.4/1000 days	33 (7.6); 3.2/1000 days
Vascular access related, *n* (%); events per 1000 OPAT-days	16 (12.2); 5.4/1000 days	32 (10.6); 4.3/1000 days	48 (11.1); 4.6/1000 days
Infection outcome			
Cured or improved	104 (79.4)	260 (86.4)	364 (84.3)
Failure	27 (20.6)	41 (13.6)	68 (15.7)
30-day unplanned hospitalisation[j]	31 (23.7)	86 (28.6)	117 (27.1)

Data are presented as *n* (%) unless otherwise indicated.
IQR, interquartile range; IV; intravenous; MSSA, methicillin-sensitive *Staphylococcus aureus*; OPAT, outpatient parenteral antimicrobial therapy; PICC, peripherally inserted central catheter; SD, standard deviation.
[a] Respiratory infection – mainly infective exacerbation of bronchiectasis/chronic obstructive pulmonary disease.
[b] Bone and joint infection – excluded spinal infection but included septic arthritis, prosthetic joint infection, non-diabetic osteomyelitis, and diabetic foot osteomyelitis.
[c] Spinal infection included discitis, vertebral osteomyelitis, and epidural abscess.
[d] Endovascular infection included infective endocarditis and vascular graft infection.
[e] Intra-abdominal infection included hepatic abscess and intrabdominal collection.
[f] Mainly complex urinary tract infection.
[g] Other organisms – *S. epidermidis* ($n = 1$), *Proteus mirabilis* ($n = 1$), *Serratia marcescens* ($n = 1$), *S. lugdunensis* ($n = 2$), *Streptococcus spp* ($n = 2$), *Klebsiella oxytoca* ($n = 2$), *Escherichia coli* ($n = 3$), and mixed culture ($n = 10$).
[h] Patient-episode who experienced at least one incident of incomplete infusion (emptying) of elastomeric device during course of OPAT.
[i] Some patient-episodes had more than one adverse event.
[j] Defined as unplanned inpatient admission for any reason during or within 30 days of OPAT discharge.

incomplete infusion (83.2% vs. 86.1%; $p = 0.42$). However, the number of incomplete infusions per patient-episode during the course of OPAT was not captured in our database.

Discussion

Portable elastomeric pump devices are increasingly used in diverse healthcare environments to intermittently or continuously infuse therapeutic medications, including chemotherapy, analgesia, diuretics, and antimicrobial agents [17, 18]. Elastomeric devices contain a stretchable balloon reservoir that contracts to deliver a continuous flow over a set time period without the need for needles, gravity, or electricity. They allow for the continuous infusion of antimicrobial agents with short half-lives that would otherwise require multiple daily dosing. Here, we report our experience with the continuous infusion of flucloxacillin and piperacillin/tazobactam *via* elastomeric devices in an OPAT setting in the UK. Similar to other OPAT-related studies [8, 9, 12, 13, 19–24], we found

a high rate of therapeutic success, low complication rates, and low OPAT-related readmission rates among our cohort.

Although 15% of antibiotic therapies were administered by patients (or their carers) in our cohort, we observed that self/carer administration of continuous infusion *via* elastomeric device was associated with equivalent adverse events but a lower risk of poor outcomes and readmission within 30 days when compared to other mode of delivery. While this may add to the growing evidence that self-administered OPAT is safe and effective [25–27], we cannot rule out the possibility that these findings were confounded by differences in underlying comorbidities between the groups. In selected patients who self-administered their antibiotics using elastomeric pumps, telemedicine could be used for remote monitoring to allow timely identification and appropriate management of complications and concerns as soon as they arise [28].

As regards time-dependent antibiotics like flucloxacillin and piperacillin/tazobactam, continuous infusion helps optimise the pharmacokinetic/pharmacodynamic ratio (percentage of the time between two injections during which the antibiotic is superior to the minimum inhibitory concentration) and reduces the risk of treatment failure and emergence of resistance [7]. As the infusion pumps are changed less frequently, either by a healthcare professional or by the patient (or their carer), they allow for patient-centred care, greater patient autonomy, and reduce the burden on the healthcare system and daily nurse visits [8]. The frequency of accessing lines is also reduced, thereby lowering the risk of vascular access-related complications such as infection and thromboembolic events.

Use of elastomeric pumps in the OPAT settings has also been associated with improved quality of life [7], high levels of patient satisfaction and acceptance [29], positive nurse evaluation [12], and cost savings when compared to inpatient care [9]. However, 'elastomeric' OPAT is more expensive compared to 'traditional' OPAT antimicrobial therapies due to significant cost relating to the devices and consumables. For example, in our hospital the elastomeric pumps pre-filled with flucloxacillin 8 g (sourced from a healthcare company) cost £99.36 per device compared to a daily drug cost of £5.09 for intermittent bolus infusion of flucloxacillin 2 g every 6 h (excluding consumables). Cost, wastage, and procurement challenges (e.g. cold chain, procurement delays which may cause delayed hospital discharge, etc.) could be minimised by in-house preparation of the elastomeric device or use of 'fresh-fill' approach without refrigerated storage (allowing for drug stability) subject to appropriate safeguards and risk assessments [12, 30]. We suggest that future analyses should assess the cost-effectiveness of elastomeric pumps compared to 'traditional' antimicrobial treatment in the OPAT setting.

The maximum infusion duration of an antimicrobial agent, as well as the minimum frequency of device change, depends on its stability in an infusion device [7]. However, not all antimicrobial agents are suitable for continuous infusion *via* an elastomeric device due to variable stability over the infusion period, resulting in lower effectiveness and the risk of producing potentially toxic degradation products. For example, the degradation of ceftazidime *via* hydrolysis results in the production of pyridine, which can cause neurological, liver, kidney and gastrointestinal disorders [31]. A literature review of 121 studies published between 1975 and 2015, carried out by the UK BSAC Drug Stability Working Group, found no published studies that comply with UK national standards for stability [32]. However, an updated literature review published in 2021 identified the acceptable stability of flucloxacillin and piperacillin/tazobactam for continuous infusion over 24 h, ceftolozane-tazobactam for infusion over 12 h, and the potential for acceptable stability of cefazolin, subject to adequately performed stability testing [33]. Subsequent works by the group showed that flucloxacillin [10], piperacillin/tazobactam [11], and temocillin [34] are suitable for continuous infusion *via* an elastomeric device, while meropenem is not [35]. Continuous infusion of other antimicrobial agents *via* an elastomeric device within an OPAT setting would only be appropriate if supported by robust antimicrobial stability data.

The rate of adverse events in our cohort was comparable to other similar OPAT studies [8, 19]. We did not observe any cases of *C. difficile* infection or adverse events related to the elastomeric device (e.g. leaky devices). However, we recorded a high number of patients experiencing at least one episode of incomplete infusion (failure of flow event) of the elastomeric device. The number of incomplete infusions per patient and the proportion of antibiotic dose infused/residual volume were not captured in our database. Therefore, we could not fully assess the effect of incomplete infusion on clinical outcomes. However, we did not detect any difference in cure rate between patients with and without incomplete infusion. Incomplete infusion of elastomeric devices is very common and could be due to suboptimal use of the device (e.g. temperature, position, storage), faulty

device or vascular access-related issues [12, 19, 36, 37]. Depending on the residual volume, top-up doses of antibiotics may be required to optimise antimicrobial dosing. In our OPAT centre, we often administer extra doses of antibiotics when the residual volume in the elastomeric device is more than one-quarter to one-third. Ultimately, the decision of whether or not to administer an extra dose of antibiotic should be made on a case-by-case basis, taking into account the individual patient's needs and the characteristics of the antibiotic being administered. The risks associated with elastomeric device use, thus, reinforce the need for close monitoring and escalation plans for patients receiving OPAT.

Our study is limited by a number of factors, including its retrospective design and restriction to single centre experience. We did not assess antibiotic plasma concentration and its effect on clinical outcome or adverse events since it was outside the scope of the study. Due to incomplete data, we were unable to fully assess the effect of incomplete infusion on clinical outcomes. Nevertheless, despite a high number of patients experiencing incomplete infusion, the overall clinical failure rate was relatively low. A further limitation is that patient outcomes were only determined at the end of OPAT care. Hence, the true rate of clinical failure may have been underestimated since infection relapse can occur several weeks after completion of OPAT. Nonetheless, we documented the reasons for the 30-day unplanned readmission. Lastly, we could not be entirely certain that the observed adverse events are all related to flucloxacillin and piperacillin/tazobactam because some patients received additional antimicrobial agents prior to or during their OPAT care.

In conclusion, our study adds to the growing body of evidence that elastomeric infusion pumps are a safe and effective option for administering certain antimicrobial agents *via* continuous infusion in the OPAT setting. However, it is worth noting that adverse events and incomplete infusions are not uncommon. Therefore, careful patient selection, close monitoring, and regular review of the device are essential to ensure optimal delivery of prescribed therapy and achieve favourable clinical outcomes.

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Author contributions

Conceptualization, O.C.D.; methodology, O.C.D.; software, O.C.D.; validation, E.I.K. and J.C.; formal analysis, E.I.K. and O.C.D.; investigation, O.C.D.; data curation, O.C.D.; writing—original draft preparation, O.C.D.; writing—review and editing, E.I.K. and J.C.; visualization, O.C.D. All authors have read and agreed to the final version of the manuscript.

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Appendix 3: Presentations

A.3.1 National/International Oral Presentations

1. **Title:** Clinical efficacy, cost-analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of Sheffield OPAT service
   Meeting: BSAC National OPAT Conference 2016; 8-9 December 2016.
   Location: International Convention Centre (ICC), Birmingham, UK.

2. **Title:** Developing a risk prediction model for 30-day unplanned hospitalisation in patients receiving outpatient parenteral antibiotic therapy
   Meeting: BSAC National OPAT Conference; 13-14 December 2018.
   Location: Queen Elizabeth (QE) II Conference Centre, London, UK.

3. **Title:** Evolving role of clinical pharmacists within the OPAT setting: the Derby Experience.
   Meeting: BSAC OPAT Regional Workshops 2024, Birmingham; 21 June 2024.
   Location: IET Birmingham: Austin Court, Birmingham, UK.

A.3.2 National/International Poster Presentations

1. **Title:** Outpatient parenteral antibiotic therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards.
   Meeting: BSAC National OPAT Conference 2017; 11-12 December 2017.
   Location: International Convention Centre (ICC), Birmingham, UK.

2. **Title:** Incidence of venous thromboembolism among patients receiving outpatient parenteral antimicrobial therapy at Sheffield Teaching Hospitals NHS Foundation Trust, UK: an observational study.
   Meeting: 30th ECCMID Conference (2020).

3. **Title:** Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antimicrobial therapy.
   Meeting: BSAC National OPAT Conference 2020; 2 December 2020.
   Location: Conference webinar (virtual event).

4. **Title:** Validation of a predictive risk model for 30-day unplanned hospitalisation in patients receiving outpatient parenteral antimicrobial therapy.
   Meeting: BSAC National OPAT Conference 2020; 2 December 2020.
   Location: Conference webinar (virtual event).

5. **Title:** Palliative outpatient parenteral antimicrobial therapy (OPAT): a single centre experience and systematic scoping review.
   Meeting: FIS/HIS International Conference 2022; 22 – 26 September 2022.
   Location: Business Design Centre, London, UK.

6. **Title:** Systematic review: effectiveness of telemedicine in OPAT (Tele-OPAT).
   Meeting: BSAC National OPAT Conference 2022; 4 November 2022.
   Location: Royal College of Physicians (RCP), London, UK.

7. **Title:** Evaluation of health-related quality of life (HRQoL) in patients receiving outpatient parenteral antimicrobial therapy (OPAT).
   Meeting: BSAC National OPAT Conference 2023; 9 November 2023.
   Location: Royal College of Physicians (RCP), London, UK.

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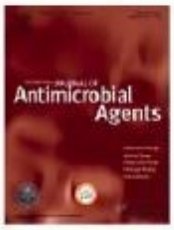

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Author:
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Clinical predictors of outcome in patients with infective endocarditis receiving outpatient parenteral antibiotic therapy (OPAT)

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Paper 4

Retrospective analysis of outcomes of outpatient parenteral antimicrobial therapy (OPAT) for necrotising otitis externa

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Paper 6

External validity and clinical usefulness of a risk prediction model for 30 day unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy

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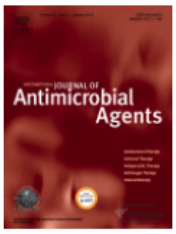

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Author: Oyewole Christopher Durojaiye,Joby Cole,Evangelos I. Kritsotakis

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Outpatient parenteral antimicrobial therapy (OPAT) in the UK: a cross-sectional survey of acute hospital trusts and health boards

Author: Oyewole Christopher Durojaiye,Katharine Cartwright,Fotinie Ntziora

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