Research article

A single centre experience of prosthetic joint infection outcomes with outpatient parenteral antimicrobial therapy

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ABSTRACT

Objectives: Prosthetic joint infection (PJI) is a serious complication following arthroplasties. This study assessed the clinical outcomes, readmission rates and financial impact of PJIs treated with outpatient parenteral antimicrobial therapy (OPAT).
Methods: The study used prospectively collected data from the OPAT patient database at a tertiary care Irish hospital for PJI cases managed between 2015 and 2020. Data was analyzed using IBM-SPSS.
Results: Forty-one patients with PJIs were managed via OPAT over five years, with median age of 71.6 years. Median duration of OPAT was 32 days. Hospital readmission occurred in 34% of cases. Reasons for readmission included progression of infection in 64.3%, unplanned reoperation in 21.4% and planned admission for joint revision in 14.3%. Type 2 Diabetes Mellitus (T2DM) was found to have a statistically significant association with unplanned readmission (OR 8.5, CI 95% 1.1–67.6; $p < 0.01$). OPAT saved a mean of 27.49 hospital-bed days per patient. 1,127 bed days were saved in total, estimating a total savings of 963,585 euros and median savings of 26,505 euros.
Conclusions: The readmission rate observed was comparable to international data. Most readmissions were related to primary infections rather than due to OPAT-specific complications. Our main findings were that patients with PJIs can be safely managed via OPAT, and the finding of association between T2DM and increased risk of readmission.

1. Introduction

Prosthetic joint infection (PJI) is a rare but serious complication following joint arthroplasties. The use of perioperative prophylactic antibiotics has greatly reduced the incidence of PJIs to a rate of <2% [1]. Nevertheless, the incidence of joint arthroplasties is

increasing in developed countries with an estimated projection of 4 million total hip and knee arthroplasties in the USA by 2030 [1]. This will likely result in an associated increase in PJIs and underscores the need for robust strategies to optimise their management. PJIs involve prosthesis and adjacent tissues and are often difficult to diagnose and frequently necessitate surgical intervention followed by prolonged courses of intravenous (IV) antibiotics [2,3]. Since its introduction, outpatient parenteral antimicrobial therapy (OPAT) has gained importance in the management of various infections as it facilitates the delivery of IV antimicrobial therapy in patients' homes or at the infusion centres [3,4] The safety of OPAT has been demonstrated previously and the advantages of OPAT extend to its use in the management of PJIs as well [3]. OPAT is accordingly recommended in the management of PJIs in international guidelines [2, 5].

The Infectious Diseases Society of Ireland (IDSI) has developed the national OPAT guidelines and has aided with the establishment of the national OPAT program in the country [6]. The use of OPAT follows an established referral pathway and all details of an OPAT espisode for a patient are logged on a national OPAT database facilitated by dedicated OPAT nurses and stored on a central management control centre. Depending on the type of OPAT prescribed, , either a nurse visits patient's home to administer antibiotic or a patient presents to an infusion centre or an outpatient clinic to receive the antimicrobial dose which is termed health care administered OPAT (H-OPAT) or alternately a patient self-administers OPAT to themselves (S-OPAT) As outlined by the national OPAT guidelines, management plans are established by the referring team and the OPAT team and include antimicrobial choice, dosing, and duration as well as choice and timing of oral antimicrobial switching. With regards to antimicrobial administration, the first dose is usually given in a supervised environment, with all subsequent doses documented in a logbook.

Route of administration of antimicrobials differs based on the duration of treatment; short peripheral venous catheters are used when the duration of OPAT is anticipated to be 7 days or less. Midline catheters are generally used for durations between 7 days and up to 4 weeks and peripherally inserted central catheters (PICCs) are usually used for OPAT durations of 4 or more weeks. Infusion devices can vary depending on local resources and training as well on antimicrobials used, and can be electronic infusers to elastomers and their choice depends on the individual patient training. Electronic infusers are usually used for H-OPAT while elastomers are mostly used for S-OPAT as they are easier for patients to use.

Follow up during OPAT takes place at a minimum of once per week as per the national OPAT guidelines although some patients may have more frequent follow up based on abnormal labs or if there is a clinical concern at home or during the clinic visits. Follow up includes weekly biochemical testing more specifically looking at C-reactive protein (CRP), full blood counts and renal and liver profiles. Patients are linked in with OPAT teams and are provided with emergency contact information to use if needed, this forms part of the pathway to readmission and for recording of incidences while on OPAT. Home visits generally involve recording of vital signs as well as clinical progress and patients are escalated to hospital OPAT teams if there is a clinical concern [6].

There is limited published literature on OPAT of PJIs and the association between individual patient characteristics and OPAT outcomes. A previous US study showed a 90-day hospital readmission rate of up to 26% in patients with PJIs treated with OPAT [7] and concluded that there was a need for further studies examining the association between individual patient characteristics and high readmission rates. Such analyses may reveal specific predictors of readmission among patients with PJIs and could help guide patient selection prior to starting OPAT to achieve desirable outcomes. In this study, we therefore aimed to evaluate the management of PJIs via OPAT at our institution and to examine the association between patient characteristics and readmission rates in this population. To our knowledge, at the time of this study there were no published reports on the use of OPAT in PJIs in the Republic of Ireland or in the United Kingdom.

2. Methods

2.1. Study sample

This was a single-centre retrospective observational study of patients diagnosed with PJIs who were managed via the OPAT programme at St Vincent's University Hospital, a 614-bedded tertiary-care university hospital in Dublin, Ireland. The OPAT program at our institute commenced in 2015 and is part of a national OPAT network under the governance of the Health Service Executive (HSE) in the Republic of Ireland [6]. The OPAT patient database is prospectively maintained, and periodic reports are produced on data and outcomes which are defined per the Irish national OPAT guidelines [6]. Patients aged ≥18 years who were diagnosed with a prosthetic joint infection and received treatment with the centre's OPAT service between January 1, 2015 and December 31, 2020 were identified through the hospital's electronic OPAT database and were included in the study.

2.2. Study variables

The following data were collected for each patient:

- Patient demographics including age and gender
- Comorbidities: immunocompromising disease/on immunosuppressive medication, diabetes mellitus (DM), peripheral vascular disease (PVD), congestive cardiac failure (CCF), chronic kidney disease (CKD), chronic liver disease (CLD), Charlson comorbidity index [8], history of colonisation with multi drug-resistant organisms (Methicillin resistant staphylococcus aureus (MRSA), Vancomycin resistant enterococcus (VRE), Carbapenemase producing enterobacterales (CPE), Extended spectrum betalactamase (ESBL)), history of polypharmacy (concurrent use of 5–9 different medicines) or excessive polypharmacy (concurrent use of 10+ different medicines) [9].

- Details of prosthetic joint infection: pathogenic organism(s) and joint(s) involved, surgical or non-surgical management of PJI preceding OPAT referral (Amputation, 1 stage revision, 2 stage revision, DAIR (Debridement, Antibiotics, and Implant Retention)), antimicrobials used & their duration prior to OPAT referral, laboratory markers of inflammation (White cell count (WCC) and C-reactive protein (CRP)) levels prior to commencement of OPAT and on its completion.
- Details of OPAT intervention: Type of OPAT (H-OPAT (or S-OPAT)), antimicrobial used for OPAT, route of administration, treatment duration, change to oral antimicrobial after completion of OPAT, treatment outcome on completion of OPAT, hospital readmission (planned/unplanned), cause of readmission, adverse drug reactions, treatment failure and patient deaths.
- Number of bed days saved: Cost of average hospital bed per day was obtained from the bed management department at our institute and was placed at € 854.93, this was multiplied by the number of hospital bed days saved due to patients being discharged on OPAT to calculate the total saving.
- Details of OPAT follow up in post -OPAT outpatient infectious disease clinic.

2.3. Statistical analysis

Data analysis was performed using IBM-SPSS. Descriptive statistics were computed and presented as frequency and percentages for categorical variables and as mean, standard deviations, median, ranges and interquartile ranges for continuous variables. Multiple logistic regression model was developed to examine independent factors associated with unplanned hospital readmission including those variables significant on univariate analysis i.e.Type 2 Diabetes Mellitus (T2DM), sociodemographic variables age and gender, and other variables considered clinically important (surgery pre-OPAT, duration of IV antimicrobials both prior to and as part of OPAT). A p-value of <0.05 was considered statistically significant; 95% confidence intervals are presented for regression analysis.

2.4. Ethical approval

The study received ethical approval from the research ethics committee at St. Vincent's University Hospital, Dublin (Number RCR20-024).

3. Results

Forty-one patients aged 18 or above with PJIs were managed via OPAT at our institute between 2015 and 2020. Table 1 summarizes patient demographics, joints affected and OPAT referral details. The patients were predominantly male (n = 31, 75.6%) and the most commonly affected joints were large lower limb joints (knee: n = 23, 56.1% and hip: n = 12, 29.3%). Most of the patients received H-OPAT (n = 37, 90.2%).

Table 2 shows the patients' clinical features at the time of commencement of OPAT. Co-morbidities included coronary artery disease in 8 patients (19.5%), T2DM in 6 (14.6%), immunosuppression in 5 (12.2%), chronic kidney disease in 2 (4.9%) and congestive cardiac failure in 1 (2.4%) patient. Polypharmacy was found in 27 (65.9%) and excessive polypharmacy in 9 (22%) patients. The majority of patients underwent a 1-stage revision (n = 19, 46.3%). Pathogens were isolated in 36 patients (87.8%), the majority from tissue samples (n = 23, 56%), followed by joint/synovial fluid (n = 8, 19.5%), wound swabs (n = 3, 7.3%) and blood cultures (n = 2, 4.9%). Pathogens in all patients were isolated prior to commencing OPAT and treatment was guided by microbiological data in all patients from which pathogens were isolated (n = 36, 87.8%) (Table 2). The most common pathogen was Methicillin-susceptible *Staphylococcus aureus* (MSSA) (n = 15, 36.6%) and previous history of multidrug resistant organisms was found in 5 patients (12.2%).

Management while on OPAT and after completion of OPAT is summarised in Table 3. The median duration of OPAT was 32 days (range 5–53 days), the antimicrobials used were predominantly cefazolin (n = 15, 36.6%) followed by daptomycin (n = 10, 24.4%),

Table 1
Demographic profile and OPAT details of patients managed on OPAT program.

Age at the time of first OPAT episode, median (range), year	71.6 (24.9–91.1)
Weight, mean (SD), kg	84.30 (17.6)
	N (%)
Gender	
Male	31 (75.6)
Female	10 (24.4)
Subjects with subsequent referrals made for OPAT	14 (34.1)
Type of OPAT	
Health Care Administered OPAT (H-OPAT)	37 (90.2)
Self-administered OPAT (S-OPAT)	4 (9.8)
Joint involved	
Ankle	1 (2.4)
Knee	23 (56.1)
Hip	12 (29.3)
Multiple	0 (0)
Elbow	3 (7.3)
Shoulder	2 (4.9)

Table 2
Clinical and laboratory features at the time of commencement of OPAT.

CRP[1], median (range)	26.6 (3.0–90.0)
	N (%)
Abnormal WCC[2]	6 (14.6)
Abnormal neutrophil count	6 (14.6)
Pathogenic Microorganisms	
Unidentified	5 (12.2)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	15 (36.6)
Staphylococcus capitis	6 (14.6)
Staphylococcus epidermidis	4 (9.8)
Streptococcus agalactiae	2 (4.9)
Streptococcus dysgalactiae	3 (7.3)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	1 (2.4)
Enterococcus faecalis	1 (2.4)
Enterococcus faecium	1 (2.4)
Neisseria meningitidis	1 (2.4)
Streptococcus mitis	1 (2.4)
Treatment guided by microbiological data	36 (87.8)
Pathogens isolated before treatment (excluding samples where no pathogens isolated)	36 (87.8)
Samples from which pathogens were isolated	
Joint/Synovial Fluids	8 (19.5)
Wound Swab	3 (7.3)
Blood Culture	2 (4.9)
Tissue	23 (56)
None isolated	5 (12.2)
Surgical management prior to OPAT	
No surgical management	6 (14.6)
1-stage	19 (46.3)
2-stage	4 (9.8)
DAIR[3]	12 (29.3)
Co-morbidities	
Polypharmacy	27 (65.9)
Excessive polypharmacy	9 (22.0)
CCF[4]	1 (2.4)
CKD[5]	2 (4.9)
CLD[6]	0 (0)
CAD[7]	8 (19.5)
Immunocompromised/on immunosuppressive medication	5 (12.2)
Type 2 diabetes	6 (14.6)
Charlson Comorbidity Index (Score)	
0	3 (7.3)
1	5 (12.2)
2	11 (26.8)
3	6 (14.6)
4	8 (19.5)
5	2 (4.9)
6	5 (12.2)
7	0 (0)
8	0 (0)
9	0 (0)
10	0 (0)
11	0 (0)
12	1 (2.4)
History of drug allergies	17 (41.5)
History of multidrug resistant organisms	
None	36 (87.8)
VRE[8]	2 (4.9)
MRSA[9]	3 (7.3)
ESBL[10]	0 (0)
CPE[11]	0 (0)

1C-reactive protein.
2White cell count.
3Debridement, antibiotics and implant retention.
4Congestive cardiac failure.
5Chronic kidney disease.
6Chronic liver disease.
7Coronary artery disease.
8Vancomycin resistant enterococcus.
9Methicillin resistant staphylococcus aureus.

10Extended spectrum betalactamase.
11Carbapenemase producing enterobacterales.

and all patients were administered antimicrobials intravenously through a percutaneously inserted central catheter (PICC). Thirty-five (85.4%) patients were switched to oral antimicrobials after completion of OPAT. The majority of which were started on co-trimoxazole (n = 9, 22%) and cephalexin (n = 8, 19.5%).

All patients in this study were initially hospitalized and treated with IV antimicrobials prior to starting OPAT. The median duration of inpatient antimicrobial therapy prior to starting OPAT was 10 days (range 0–120 days). Patients were followed up in a designated OPAT clinic during OPAT for a median duration of 4.43 weeks (range 1–12 weeks) and then referred to the general infectious diseases clinic where they were followed up for a median duration of 68 weeks (range 3–71 weeks) (Table 3).

Inflammatory markers were recorded before starting and after completion of OPAT; 85.4% had normal white cell count (WCC) and neutrophil counts prior to OPAT compared to 95.1% post-OPAT (Table 2; 4). Table 4 outlines the OPAT outcomes of the patient cohort as defined by the national Irish OPAT portal and the national Irish OPAT guidelines [6]. The majority of patients completed the OPAT course with no complications (n = 29, 70.7%) whereas 12 patients had unplanned readmissions (29.3%). The main reason for unplanned readmissions was progression of infection (n = 9, 22%). There were 2 planned readmissions (n = 2, 4.9%) for elective revisions andd both had completed their OPAT course with no complications. T2DM was found to be independently associated with unplanned readmission on logistic regression analysis after adjusting for age, gender, prior surgery and duration of IV both prior to and as part of OPAT (adjusted OR 10.99 (95%CI 1.31–92.7)) (Table 5).

We also estimated the financial benefit to our health care system by calculating the hospital bed days saved. Per patient, a mean of 27.49 hospital bed days were saved (range 0–81), translating to a median estimated savings of 26,505 euros. This was based on the average cost of € 854.93 euros per hospital bed day in our institution at that time.

4. Discussion

To our knowledge this is the first published study in Ireland and the United Kingdom examining the readmission rate of patients with PJIs treated with OPAT and exploring associated clinical characteristics. Our results showed that the overall readmission rate was comparable to international data collected in the United States on PJIs and OPAT [7], however it was above the Irish national target of <5% for all OPAT discharges [6]. Although most readmissions were attributed to progression of infection, there were no OPAT-specific complications (such as unplanned change in antimicrobial therapy, adverse drug reactions or deaths). This indicates that PJIs can be safely managed using OPAT with minimal complications.

There are several advantages of using OPAT as compared to inpatient antimicrobial therapy such as decreased exposure to hospital acquired infections, ability to attend work/school and continue daily activities, reduced healthcare costs, improved allocation of hospital beds and increased compliance with prolonged antimicrobial therapy [10]. Possible risks associated with OPAT include

Table 3
OPAT management details.

OPAT duration, median (range) days	32 (5–42)
	N (%)
Weight-based dosing of antimicrobials	13 (31.7)
Antimicrobials on OPAT	
Cefazolin	15 (36.6)
Daptomycin	10 (24.4)
Ceftriaxone	6 (14.6)
Flucloxacillin	4 (9.8)
Ceftriaxone & Daptomycin	2 (4.9)
Vancomycin	1 (2.4)
Vancomycin & Ceftriaxone	1 (2.4)
Tigecycline	1 (2.4)
Co-amoxiclav	1 (2.4)
Oral Antimicrobial switch post OPAT	35 (85.4)
Oral Antimicrobial choice on completion of OPAT[a]	
Co-trimoxazole	9 (22.0)
Cephalexin	12 (29.3)
Doxycycline	6 (14.6)
Amoxicillin	4 (9.8)
Ciprofloxacin	1 (2.4)
Flucloxacillin	1 (2.4)
Clindamycin	1 (2.4)
Duration of IV antimicrobial treatment prior to commencing OPAT, median (range), days	10 (0–120)
OPAT duration, median (range), days	32 (5–81)
Duration of weekly reviews in OPAT clinic, median (range), weeks	4.43 (1–12)
Duration of reviews in ID clinic, median (range), weeks	68 (8–371)

[a] Missing data n = 1.

Table 4
Clinical features, laboratory results & patient outcomes at the end of OPAT (n = 41).

Parameter	N (%)
Abnormal White cell count	2 (4.9)
Abnormal neutrophil count	2 (4.9)
Abnormal CRP	31 (75.6)
OPAT outcome	
Course completed with no issue	29 (70.7)
Patient unplanned readmission	12 (29.3)
Patient had adverse drug reaction	0 (0)
Patient died	0 (0)
Course discontinued	0 (0)
Course extended	0 (0)
Reason for readmission	
Progression of infection	9 (22.0)
Unplanned reoperation	3 (7.3)
Planned (Course completed with no issues)	2 (4.9)
Hospital bed days saved, mean (range)	27.49 (0–81)
Savings in € (median)	26,505

*Missing data n = 1.

Table 5
Logistic regression: factors independently associated with readmission.

	Unadjusted OR (95%CI)	Adjusted OR ¥$ (95%CI)
Type 2 Diabetes Mellitus	6.75 (1.04–43.87)*	10.99 (1.31–92 .70)*
Age	1.02 (0.97–1.08)	1.01 (0.96–1.06)
Male Gender	0.29 (0.07–1.31)	0.26 (0.05–1.44)
Prior surgery	0.35 (0.06–2.03)	0.28 (0.04–2.07)
IV duration (pre & during OPAT)	1.0 (0.97–1.04)	1.0 (0.96–1.04)

¥adjusted for all variables listed.
*p < 0.05.
$Hosmer & Lemeshow p value = 0.797.

misuse of IV access, non-adherence with therapy and difficult social circumstances [10] which underscores the need to risk assess individual patients, decide carefully on suitability for OPAT and to follow them closely once they are commenced on OPAT. Appropriate patient selection for OPAT can ensure the efficacy and safety of treatment by taking into consideration factors at the time of assessment for OPAT such as age, clinical stability, ensuring that an adult is available to administer treatment, judicious care of intravenous access, weighing social/housing circumstances, consideration of proximity to the hospital and ability to attend OPAT outpatient clinic weekly [6]. Oral treatment is considered prior to initiation of OPAT and assessed throughout the OPAT course. Decision to switch to oral antibiotics is guided by biochemical and clinical parameters and is assessed at follow-up appointments. Switching to oral antimicrobials is guided by microbiological results as well sensitivities of initial cultured microorganisms. The choice of oral agent is based on bone penetration, culture and sensitivities as well as allergy status and other co-medications patients may be taking. Culture negative patients are usually switched to empiric oral agents that cover likely pathogens.

As illustrated by our data, the median duration of IV antimicrobials received as an inpatient was 10 days and median duration of OPAT in our study population was 32 days. The oral versus intravenous antibiotics for bone and joint infection (OVIVA) study found that oral antibiotic treatment was noninferior to IV treatment when used during the first 6 weeks in the management of bone and joint infections [11]. This suggested that earlier switching to oral agents may confer cost savings and reduced complications related to IV administration of medications [12,13]. However, the subgroup analysis in the OVIVA study shows that patients with retained metal had greater treatment failures while on oral agents when compared to intravenous agents, and in our study population 29.3% of subjects had DAIR as a surgical intervention and therefore had metal implant retention. Oral treatment of complex infections requires an organized approach that allows for supervision and monitoring of treatment, this approach requires an OPAT style framework. This has been termed as complex outpatient antimicrobial therapy (COpAT) [14] and may play a greater role in the management of PJIs in the future. It is important to establish this framework in addition to guidance on effective oral antimicrobial regiments and durations of treatment [11,14,15]. Of note, the majority of cases included in our study (spanning from 2015 to 2020) preceded the OVIVA study which was conducted in 2019 and were managed using IV antimicrobials on OPAT as per the guidelines followed by our institution at that time.

Our data points to increased readmissions in patients with T2DM, which is possibly related to impaired immunity in patients with T2DM leading to poorer outcomes from infectious diseases [16]. A Belgian pilot study that examined clinical characteristics and outcomes of OPAT in 218 patients similarly found that DM was associated with a higher risk of readmission while on OPAT [17]. It would be of interest to further examine the link between glycaemic control in T2DM patients and OPAT outcomes, using specific indices such as HbA1C levels. Larger studies are needed to assess the factors resulting in increased readmissions in diabetic patients and possible methods of optimizing selection of patients to decrease OPAT readmissions. This is also of relevance as the number of patients

affected by diabetes mellitus is projected to rise to 333 million globally by 2025 [18].

Patient optimisation throughout OPAT follow-up, in both clinic and home settings has the potential to minimise and prevent unplanned readmissions. This may include a multidisciplinary team approach involving care of patients' other co-morbidities such as ensuring glycaemic control in diabetic patients or assessing for fluid overload in CCF patients for example. The involvement of allied healthcare specialists such as physiotherapists and dieticians can also aid in the optimisation of patients ensuring nutritional supplementation and wound care [19]. Identifying complex patients using tools such as the Charlson co-morbidity index can allow more tailored optimisation of management before commencing OPAT and during follow-up while on OPAT. This is also important when prescribing antimicrobials that require therapeutic drug monitoring such as aminoglycosides as they require specialised follow-up, as was identified as an independent risk factor for readmission of OPAT patients in a previous study [20]. Thus careful patient selection taking into account patients' Charlson co-morbidity index, their social circumstances, coordination with public healthcare nurses and general practitioners in the community in tandem with monitoring the patient from an infectious diseases point of view may have an impact on reducing unplanned readmissions and can result in favourable outcomes.

When examining hospital bed days saved, our data points to a significant financial incentive to opt for OPAT as opposed to inpatient treatment. This cost effectiveness is reflected extensively in the literature [6,21,22]. It is important to note that the savings calculated are offset by the costs of unplanned readmissions as well as the cost of H-OPAT. Less frequent dosages of antimicrobials to reduce the frequency of nurse visits for patients on H-OPAT and antimicrobial choice before starting OPAT may further decrease costs. In this study, 90.2% of patients had received H-OPAT. A transition towards S-OPAT (Self-administered OPAT) for suitable patients should be considered whenever possible as an additional way of preserving resources. A study comparing four types of OPAT services in the UK also concluded that S-OPAT is more cost effective than OPAT administered at infusion centres. That study also indicated that OPAT administered by specialist nurses to be more cost effective than H-OPAT offered at infusion centres [23]. It is important to tailor the choice of OPAT to each patient as special patient education must be conducted for S-OPAT that includes re-constituting doses and ensuring safe sterile administration [6].

The limitation of our study includes the small sample size of 41 patients and it being a single-centre study. Including data from other centres offering OPAT can serve to increase sample size and possibly provide insight on other factors contributing to readmissions. Another limitation of the study was that we did not record or analyse the level of glycaemic control for patients with diabetes mellitus which was found to be associated with readmissions. Despite a small sample size, having a digital patient database allowed us to gather a wide range of data on each patient and to evaluate potential causes of re-admission. As the database is prospectively managed, the data is likely to be internally valid and complete.

In summary, this study points to OPAT being a safe, effective, and cost saving modality for the treatment of PJIs. Future studies are needed to further examine the link between T2DM and readmissions in PJI-OPAT patients and to highlight possible ways of optimizing patient selection to decrease readmission rates in similar patient cohorts.

Author contribution statement

Abdubadie Kutubi: Collected data; Analyzed and interpreted the data; ; Wrote the paper.
Luke O'Brien and Ben Murphy: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Deepa Rajendran: Recorded and analysed Data.
Patricia Fitzpatrick: Analyzed and interpreted the data; Wrote the paper.
Conor Hurson, Eoin Feeney and Patrick Mallon: Contributed reagents, materials, analysis tools or data.
Sarmad Waqas: Conceived and designed the study, analysed and interpreted the data, wrote the paper.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Acknowledgements

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