The Utility of a Blood Culture Database to Identify Patients Suitable for Outpatient Parenteral Antibiotic Treatment

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Objective: The clinical and cost effectiveness of Outpatient Parenteral Antimicrobial Therapy (OPAT) services are well described. We used a blood culture database as a novel approach to case finding and determined its utility in identifying inpatients suitable for OPAT.

Methods and Patients: From December 2012 to November 2013, consecutive adult in-patients with bacteraemia, and those recruited to OPAT, were prospectively studied. Univariate and multivariate logistic regression analysis were used to investigate the association between bacteraemic patient characteristics and OPAT recruitment.

Results: There were 470 bacteraemic and 134 OPAT patients. The blood culture database identified 22 (16.4%; CI 10.5, 23.6) additional patients suitable for OPAT, 4.7% (95% CI 3.0, 7.0) of the total bacteraemic cohort. 20 (90.9%) of these patients had community-acquired infection, equivalent to 20/200 (10.0%; 95% CI 6.2, 15.0) of all community-acquired bacteraemic episodes. Bacteraemic patients with UTIs, 11/157 (7.0%; 95% CI 3.5, 12.2) were most commonly recruited to OPAT and the commonest blood culture isolate was *E. coli*. In the *E. coli* bacteraemic sub-group, ESBL producers were significantly higher in the OPAT group, compared to those not recruited to OPAT, 9/11 (81.8%) vs 17/192 (8.9%), p<0.001. Among OPAT patients, there were a higher proportion of upper UTIs in the bacteraemic group compared to the non-bacteraemic group, 9/22 (40.9%) vs 26/123 (21.1%), p = 0.046. There were no OPAT deaths within 30 days and no significant difference in relapse rates between bacteraemic and non-bacteraemic patients, 1/22 (4.6%) vs 5/112 (4.5%). In logistic regression analysis, there were no host factors in the bacteraemic cohort that predicted recruitment to OPAT. In a subgroup analysis of patients with gram-negative bacteraemia, ESBL production was strongly associated with OPAT recruitmentin multivariate analysis, OR 5.85 (95%CI 1.94, 17.58), p=0.002.

Conclusion: A blood culture database proved a useful adjuvant to a clinical referral system, particularly for patients with community onset infections and MDR infections. All

bacteraemic patients recruited to OPAT received treatment safely and had good clinical outcomes.

Introduction:

Outpatient parenteral antibiotic treatment (OPAT) enables patients to receive treatment with intravenous antibiotics in their home or in an ambulatory care setting rather than in hospital. It is widely used in the UK and is associated with admission avoidance, decreased length of inpatient stay, cost savings and high levels of patient satisfaction[1-5]. In carefully selected patients, outcomes are comparable with hospital based treatment[6,7] and National guidelines assist with service delivery, good clinical practice and governance. OPAT is also part of the UK government's healthcare strategy of moving services into the community so services are likely to continue to expand over the next 5 years[8].

While there is much published literature on the success of OPAT services, there is little on methods used to identify patients. Traditionally, patient identification can be passive, waiting for a referral, or active, targeting specific specialties (eg. orthopaedics or Acute Assessment units). Often referrals are unsuitable for several reasons. These include patients living outside designated postcodes, inability to attend hospital for treatment on a daily basis, being elderly with multiple co-morbidities that necessitate prolonged hospital stay, difficulty with vascular access and having conditions treatable with oral antibiotics. Bacteraemic patients feature in some OPAT populations although it is unclear what site of infection caused these bacteraemias and how these patients were recruited[7,9-11]. Overall, there is little in the literature on the value of Microbiological results in patient identification with the emphasis on clinical and risk assessment and safe delivery of treatment[7,12]. We used an existing blood culture database as a novel approach for recruitment, and determined its utility in identifying adult inpatients suitable for OPAT.

Patients and Methods:

Study Setting

This study was undertaken at the Royal London Hospital (RLH), Barts Health NHS Trust. The RLH serves a diverse population of about 250 000 patients in Tower Hamlets, East London and is a regional referral centre for the North East London sector. In addition to accident and emergency, general medicine, surgery, paediatric and maternity services, the RLH has 60 high-dependency and critical care beds (including neurosurgical, renal, and obstetric and gynaecological beds), specialist wards for renal transplant and haemodialysis patients, and a high-level intensive care unit (ICU).

Study Population

From December 2012 to November 2013, consecutive bacteraemic in-patients and patients recruited to OPAT were prospectively studied. Patients aged < 16 years were excluded.

Bacteraemia cohort and definitions

In bacteraemic adult patients, age, gender, inpatient specialty, site of infection, organism, susceptibility profile and mortality related outcomes were recorded. Bacteraemia was considered significant if a blood culture was isolated from a patient with a compatible clinical syndrome that was unlikely to be a skin or environmental contaminant. This was based upon the patient's history, examination, response to anti-microbial therapy and bacterial isolates from other body sites[13]. Specialties at the time of bacteraemia were categorised as medicine, surgery (including orthopaedics), critical care and obstetrics and gynaecology. For hospital-acquired or device related bacteraemia, the Centres for Disease Control and Prevention definitions were used to define the sites of infection[14] and for

community-onset bacteraemia, sites were defined following clinical, microbiological and radiological assessment. Bacteraemia in patients with an unknown source were classified as undefined.

Microbiology data

Blood cultures were analysed using an automated system BacT/ALERT3D (bioMerieux, Mary l'Etoile, France). Isolates were identified using either the VITEK MS system (bioMerieux, Mary l'Etoile, France, database v2.0) or Bruker Biotyper (Bruker Daltonic, Leipzig, Germany, software version 3.0) MALDI-TOF MS systems according to the manufacturer's instructions and the laboratory standard operating procedures. Susceptibility testing was performed on the Microscan walkAway system (Siemans Healthcare Diagnostics, Deerfield, IL, US).

OPAT cohort, data collection and ascertainment

Over the same period age, gender, site of infection, medical specialty, presence of bacteraemia, duration of treatment and outcomes were recorded for all patients recruited to OPAT. Where possible, patients were treated with once daily intravenous antibiotics. Patients under 16 years of age were excluded. Patients were recruited by referrals from inpatient teams or GPs or actively sought by attendance at Acute Assessment Unit board rounds or attendance at multi-disciplinary team (MDT) meetings (eg. Orthopaedics). Patients received treatment in their homes or via a fast response nursing team. A blood culture database was used to identify additional patients.

Statistical analysis

We analyzed the characteristics of bacteraemic patients (age, gender, place of acquisition, inpatient specialty, site of infection and mortality), comparing those who received and did not receive OPAT. For patients recruited to OPAT, we compared patient characteristics and duration of intravenous (IV) treatment for bacteraemic and non-bacteraemic patients. We also describe bacteraemic isolates from patients who received OPAT and compared these to patients who did not receive OPAT.

Quantitative data are presented as numbers and percentages. Associations between two categorical variables were tested using the Pearson Chi-Squared test and continuous variables using t-tests. As patients may present with more than one bacteraemic episode, we used number of patients as a denominator to calculate percentages for patient characteristics and number of bacteraemic episodes as the denominator for infection characteristics.

Univariate and multivariate logistic regression analysis were used to examine the association between age, gender, inpatient specialty and site of infection, and recruitment to OPAT in bacteraemic patients. As all bacteraemic episodes in OPAT patients were community-onset, we could not adjust for place of acquisition because there were no OPAT patients with hospital-acquired bacteraemia. In a subgroup analysis of patients with gram-negative bacteraemia, we also examined the association between E.coli infection and extended-spectrum beta-lactamases (ESBL) production and recruitment to OPAT. Generalised estimating equations (GEE) were used to account for dependency between multiple bacteraemic episodes for patients in the univariate and multivariate analysis. Data were analysed using Stata SE (Version 13.1).

Clinical governance

The clinical governance audit committee of Barts Health NHS Trust approved the study. Ethical approval was not required.

Results:

Over the 12 month period, the number of in-patients with bacteraemia and patients recruited to OPAT are illustrated in figure 1.

Bacteraemic patients

There were 470 patients with bacteraemia yielding 556 positive blood cultures. Patient demographic, clinical and mortality data are summarized in table 1. 22 (4.7%; 95% confidence interval (CI) 3.0, 7.0) bacteraemic patients were recruited to OPAT. All patients recruited had community onset infection (either community-acquired or health-care associated). Of these, 20 had community-acquired bacteraemia, equivalent to 20/200 (10.0%; 95% CI 6.2, 15.0) of all community-acquired bacteraemic episodes.

Compared to surgical patients, significantly more medical patients were recruited to OPAT. Outpatient treatment episodes were most commonly for urinary tract infection (UTI), 11/157 (7.0%; 95% CI 3.5, 12.2), skin and soft tissue infection (SSTI), 3/29 (10.3%; 95% CI 2.2, 27.4), GI tract infection (all enteric fevers), 3/8 (37.5%; 95% CI 8.5, 75.5) and biliary tract infection, 3/54 (5.6%; CI 95% 1.2, 15.4). There was no significant difference between unadjusted 30-day mortality between bacteraemic patients receiving OPAT and those not receiving OPAT; 0 vs 24/470 (5.4%; 95% CI 3.3, 7.5).

OPAT patients

Of the 134 patients who received OPAT, 22 (16.4%; 95% CI 10.5, 23.6) were bacteraemic. All these patients were recruited through the blood culture database and were not referred from clinical teams. There was one patient with a bacteraemia and a non-bacteraemic episode so this information was recorded in both groups.

Demographic and clinical data of all OPAT patients are summarized in table 2. Urinary tract infection, 11/51 (21.6%; 95% CI 11.3, 35.3) was the commonest cause of bacteraemia in OPAT patients. Unadjusted data demonstrated significant differences in sites of infection, with more upper UTIs in the bacteraemic group compared to the non-bacteraemic group, 9/22 (40.9%) vs 26/123 (21.1%), p = 0.046. There were no deaths in either bacteraemic or non-bacteraemic patients and no significant difference in relapse rates at 30-days; 1/22 (4.6%) vs 5/112 (4.5%).

Total number of days on IV antibiotics received out of hospital was 1198, roughly equivalent to the number of bed days saved. The commonest drugs administered were either once daily IV ceftriaxone or ertapenem. In bacteraemic and non-bacteraemic groups, median (IQR) duration of intravenous treatment was non-significantly different, 7 (5-8) vs 6 (3-8).

Microbiology

For all bacteraemic patients, 378 (68.0%) blood culture isolates were Gram negative. The commonest organisms were *E. coli*, and *S. aureus* (Table 3). More patients with *E. coli* bacteraemia were recruited to OPAT compared to other blood cultures isolates and, among these, ESBL production was significantly higher in the OPAT group compared to the non-OPAT group, 8/9(88.9%) vs 19/192 (9.9%), p<0.001.

Bacteraemic patient characteristics and recruitment into OPAT

Univariate and multivaritate logistic regression analysis to investigate the association between bacteraemic patient characteristics and those recruited to OPAT is reported in table 4. There were no statistically significant associations in univariate or multivariate

analysis. In a sub-group analysis of patients with gram-negative bacteraemia, ESBL production was strongly associated with OPAT recruitment, OR 5.85 (95%CI 1.94, 17.58), p=0.002.

Discussion:

This is the first paper to examine the utility of a blood culture database to identify patients suitable for OPAT. An additional 16.4%, or 22 extra patients, were recruited to OPAT through the blood culture database. Although a useful adjuvant to a clinical referral system, more patients were not recruited probably due to the severity of bacteraemic infection, as bacteraemic patients often require resuscitation in hospital. Also, many patients admitted from the community can be switched to oral alternatives and, in the absence of drug resistance, do not require prolonged intravenous therapy. Our data shows that patients with community-onset and multidrug resistant (MDR) infections were most likely to be recruited to OPAT, and none of these patients were identified through the clinical referral system.

The commonest sites of infection in patients recruited to OPAT were UTIs and SSTIs. A two year retrospective review of patients treated with OPAT in one Scottish centre found the majority of infections were SSTIs, 125 (59%) of 212 episodes[5]. All were identified clinically and, in our study, we also found that these patients were predominantly recruited by clinical assessment rather than blood culture findings. In contrast, the blood culture database was particularly useful in identifying patients with MDR UTIs. One paper retrospectively reviewed the use of OPAT to facilitate early discharge of patients with UTI caused by ESBL producing Enterobacteriaceae. In this small retrospective study, there were 11 patients with 25 treatment episodes, although it is unclear whether any of these bacteraemic patients were identified through laboratory results. It concluded that OPAT administration of ertapenem was effective and decreased costs associated with MDR UTIs[15], a finding similar to ours. Our blood culture database was also useful in identifying other medical conditions not normally treated with IV antibiotics out of hospital, including

enteric fevers, biliary tract infections and central venous catheter associated infections where line salvage was being attempted.

There were no deaths in the OPAT group with bacteraemia, despite bacteraemia being a marker of severe infection. Many of these patients were recruited after hospital admission and then stabilized before discharge on an intravenous antibiotic. In addition to reducing length of inpatient stay, our data demonstrates the safety of this approach. Among bacteraemic patients recruited to OPAT, all had community onset infections. Hospital acquired infections are generally medical device or procedure related and more commonly occur in patients in critical care areas[16], so it is not surprising that the majority of patients recruited had community-acquired infection.

There were limitations to this study. Because of our proactive approach, it is possible patients were identified before clinical teams had time to refer to OPAT. The numbers of bacteraemic patients recruited to OPAT were small and as there were few deaths in the 'bacteraemic' and 'non-bacteraemic' groups, a survival analysis was not possible. In logistic regression analysis, we were unable to include place of acquisition in the model as no patients with hospital-acquired infection were recruited to OPAT. In a larger study, where patients with hospital-acquired occurred, we could have tested the association between community-onset bacteraemia and OPAT recruitment. The sample size was, however, big enough to demonstrate significant differences in unadjusted and adjusted data.

In summary, our study demonstrates that a blood culture database provided a useful adjuvant to a clinical referral system for OPAT recruitment. The blood culture database

was particularly useful for identifying patients with community-onset infections and MDR UTIs. Bacteraemic patients received treatment safely and all had good clinical outcomes.

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Figure 1: In-patients with bacteraemia and patients recruited to OPAT between December 2012 and 2013

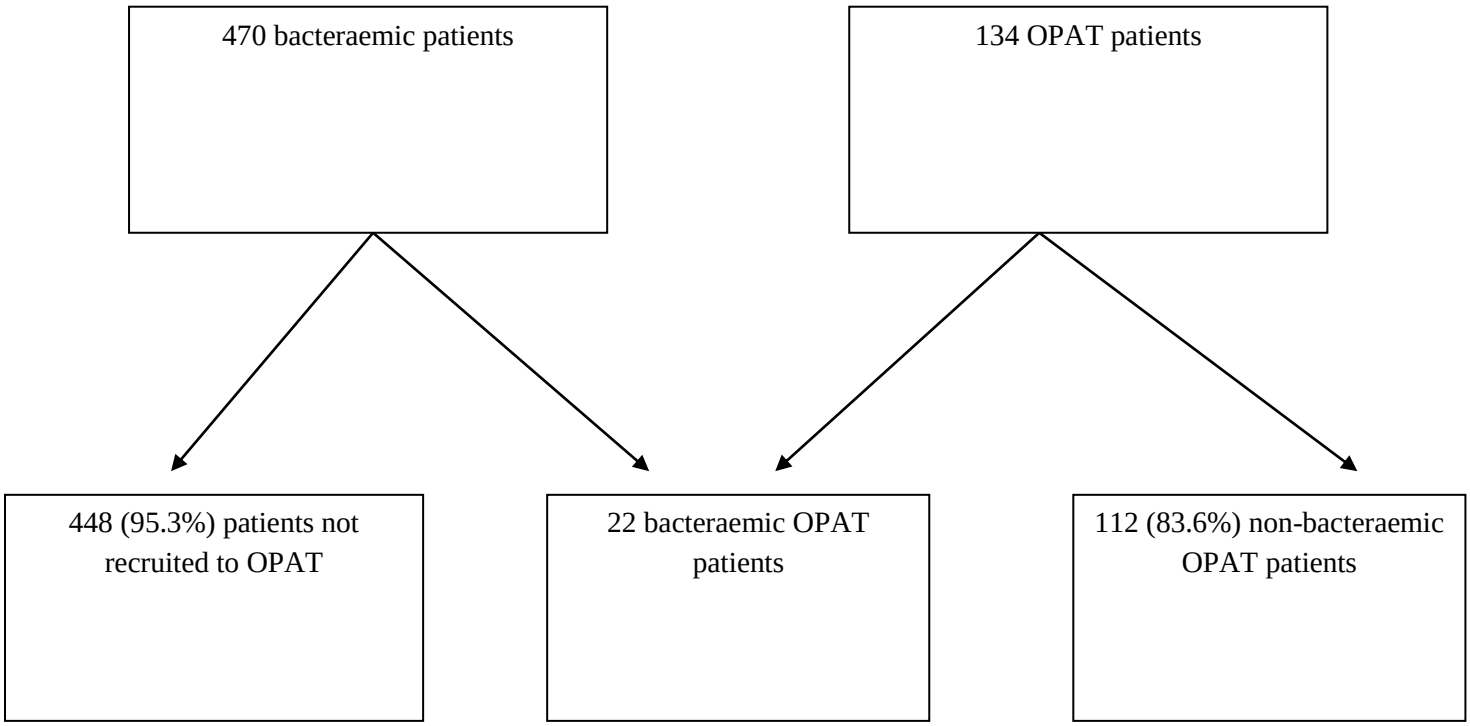

Table 1: Demographic and clinical data on 470 patients, with 556 associated bacteraemic or fungaemic episodes, who did and did not receive OPAT

		OPAT		P-value[1]
		Yes	No	
Patients		22	448	
Infections (Bacteremic / fungaemic episodes)		25	531	
Age[2] (years), n (%)	16 – 30	2 (9.1)	38 (8.5)	0.621
	31 – 50	7 (31.8)	99 (22.1)	
	51 - 70	8 (36.4)	156 (34.8)	
	> 70	5 (22.7)	155 (34.6)	
Gender[2], n (%)	Male	11 (50.0)	262 (58.5)	0.431
	Female	11 (50.0)	186 (41.5)	
Place of Acquisition, n (%)	CA	20 (90.9)	188 (35.4)	<0.001
	HCA	2 (9.1)	198 (37.3)	
	HA	0	143 (26.9)	
	Not defined	0	2 (0.4)	
Specialty, n (%)	Medicine	22 (88.0)	430 (81.0)	<0.001
	Surgery	2 (8.0)	101 (19.0)	
	O&G	1 (4.0)	0 (0.0)	
Sites of Infection, n %)	CVC (uncomplicated)			0.129
	Tunnelled	0	33 (6.2)	
	Non-tunelled	2 (8.7)	27 (5.1)	
	[3]CVC (complicated / metastatic spread)	2 (8.0)	21 (4.1)	
	Peripheral cannula		1 (0.2)	
	Urinary tract (catheter associated)		58 (10.9)	
	[4]Urinary tract (non-catheter associated)	11 (44.0)	146 (27.5)	
	Biliary tract	3 (12.0)	51 (9.6)	
	[5]GI tract	3 (12.0)	32 (6.0)	
	GU tract		9 (1.7)	
	Liver abscess		9 (1.7)	
	LRT (non-ventilator associated)		35 (7.0)	
	LRT (ventilator associated)		4 (0.8)	
	Skin and soft tissue infection	3 (12.0)	26 (4.9)	
	[6]Peripheral joints (native)	1 (4.0)	2 (0.4)	
	Peripheral joints (prosthetic)		1 (0.2)	
	Meningitis		3 (0.6)	
	Not defined		73 (13.8)	
Mortality, n (%)	Inpatient	0	22 (4.9)	0.287
	7 day	0	12 (2.7)	0.437
	30 day	0	24 (5.4)	0.265

OPAT: Outpatient parenteral antibiotic treatment O&G: obstetrics and gynecology CVC: central venous catheter CO: community-onset HA: hospital-acquired

[1]Chi[2] test

[2]patient specific variables. Age and gender were reported as a percentage of patients

[3]Complicated CVC or metastatic infections occurred only in renal haemodialysis patients. This included vertebral column, infective endocarditis and pacemaker infection.

[4] 2 were complicated lower UTIs, one post prostatic biopsy

[5] Enteric fevers (2 x S. paratyphi and 1 x S. typhi)

[6] Metastatic complication of fistula site and catheter associated UTIs in renal haemodialysis patients.
One patient had a bacteraemic and non-bacteraemic episode, so this was recorded in both groups.

Table 2: Demographic and Clinical data on 134 patients who received OPAT (145 treatment episodes), with bacteraemia and without bacteraemia.

	Without bacteraemia	With bacteraemia	p-value[1]
Patients	112	22	
Episodes	123	22	
Age[2] (years), n (%)			0.777
16-30	20 (17.9)	2 (9.1)	
31-50	35 (31.3)	7 (31.8)	
51-70	35 (31.3)	8 (36.4)	
> 70	22 (19.6)	5 (22.7)	
Gender [2], n (%)			0.701
Male	51 (45.5)	12 (50.0)	
Female	61 (54.5)	11 (50.0)	
Specialty, n (%)			0.941
Medical	109 (88.6)	19 (86.4)	
Surgical	10 (8.1)	2 (9.1)	
O&G	4 (3.3)	1 (4.6)	
Site of infection, n (%)			0.025
Urinary tract (upper)	26 (21.1)	9 (40.9)	
Urinary tract (lower)	14 (11.4)	[3]2 (9.1)	
Biliary tract	0	2 (9.1)	
Skin and soft tissue	57 (46.3)	2 (9.1)	
Central venous catheter	0	2 (9.1)	
GI tract	2 (1.6)	3 (13.6)	
Infective endocarditis	0	1 (4.6)	
LRT	1 (0.8)	0	
Meninges	2 (1.6)	0	
Orthopaedic infections	6 (4.9)	1 (4.6)	
Vertebral column (VC)	2	0	
Osteomyelitis (non-VC)	0	0	
Peripheral joints	3	1	
Sternal wound	1	0	
Other	[4]15 (12.2)	0	
Outcome[2], n (%)			0.987
Recovered / anticipated outcome	107 (95.5)	21 (95.5)	
Relapse	5 (4.5)	1 (4.6)	
Death within 30 days of treatment completion, N (%)	0	0	N/a
Duration of IV treatment (days)			0.207
Mean (SD)	8.6 (9.5)	6.2 (4.0)	
Median (max-min)	7.0 (0.0 – 64.0)	6.0 (0.0 – 14.0)	

OPAT: Outpatient parenteral antibiotic treatment O&G: obstetrics and gynecology; SSTI: skin and soft tissue infection; GI: Gastrointestinal; LRT: lower respiratory tract; SD: standard deviation

[1]Chi[2] test for categorical variables, t-test for continuous variables

[2] Patient specific variables so reported as a percentage of patients. One patient is in both columns because they had one episode without bacteraemia and one with bacteraemia.

[3] One post prostatic biopsy

[4] Other included liver abscesses, malignant otitis externa, meningitis, leptospirosis, infected ovarian cysts, pre-patella bursitis, fistula infection, TB, bronchiectasis and community-acquired pneumonia with empyema.

Table 3
Bacteremia isolates on 470 patients, with 556 associated bacteraemic or fungaemic episodes, receiving or not receiving OPAT

	OPAT		p-value[1]
	Yes (N=25)	**No (N=531)**	
E. coli, n (%)	11 (44.0)	192 (36.2)	0.426
ESBL +ve	9	19	<0.001[3]
ESBL -ve	2	173	
K. pneumonia, n (%)	2 (8.0)	51 (9.7)	0.812
ESBL +ve	0	14	0.388[3]
ESBL -ve	2	37	
P. aeruginosa, n (%)	0	24 (4.5)	0.277
MSSA, n (%)	2 (8.0)	51 (9.7)	0.789
MRSA, n (%)	0	3 (0.6)	0.706
Candida species, n (%)	1 (4.0)	9 (1.7)	0.397
Other[2], n (%)	9 (36.0)	202 (38.0)	0.837

OPAT: Outpatient parenteral antibiotic treatment; MSSA; methicillin-susceptible Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; ESBL: extended-spectrum beta-lactamases
[1]Pearsons chi[2] test. Tests each bacteraemic isolate verses all other bacteraemic isolate
[2]These include 2 S. paratyphi, 1 S. typhi, 1 P. mirabilis, 1 E. aerogenes, 1 Group G streptococcus, 1 Viridans Streptococcus, 1 Acinetobacter and 1 Candida haemulonii.
[3]ESBL +ve verses ESBL –ve for each bacteraemic isolate
.One patient had a bacteraemic and non-bacteraemic episode, so this was recorded in both groups.

Table 4: Univariate and multivariate logistic regression analysis for all bacteraemic patients to investigate association between patient characteristics and recruitment to OPAT

(469 patients, 555 bacteraemic patients)

		Univariate analysis		Multivariate analysis	
		Odds Ratio (95% CI)	**p-value[1]**	**Odds Ratio (95% CI)**	**p-value[1]**
Age (years)	16 – 30	Reference	0.733	Reference	0.633
	31 – 50	1.18 (0.23, 6.06)		1.12 (0.22, 5.80)	
	51 - 70	1.02 (0.21, 4.98)		0.91 (0.18, 4.45)	
	> 70	0.61 (0.12, 3.28)		0.51 (0.09, 2.79)	
Gender	Female	Reference	0.593	Reference	0.799
	Male	0.79 (0.34, 1.86)		0.89 (0.37, 2.12)	
Speciality	Medicine	Reference	0.254	Reference	0.237
	Surgery	0.43 (0.10, 1.83)		0.42 (0.10, 1.78)	
Site of infection	Urinary tract	Reference	0.415	Reference	0.349
	Skin and soft tissue	1.64 (0.40, 6.77)		1.54 (0.36, 6.67)	
	Other	0.67 (0.27, 1.62)		0.61 (0.24, 1.52)	

1 patient with obstetrics and gynecology speciality was excluded
Generalised estimating equations were used to adjust for multiple episodes for some patients
OPAT: Outpatient parenteral antibiotic treatment ; CI: confidence interval
[1]Joint wald test

Table 5: Univariate and multivariate logistic regression analysis for gram-negative bacteraemic patients to investigate association between blood culture isolate and recruitment to OPAT

(332 patients, 377 bacteraemic patients)

		Univariate analysis		Multivariate analysis	
		Odds Ratio (95% CI)	**p-value[1]**	**Odds Ratio (95% CI)**	**p-value[1]**
Age (years)	16 – 30	Reference	0.464	Reference	0.544
	31 – 50	1.56 (0.17, 14.11)		1.67 (0.17, 16.42)	
	51 - 70	1.03 (0.12, 8.94)		0.97 (0.10, 9.12)	
	> 70	0.47 (0.05, 4.77)		0.53 (0.05, 5.76)	
Gender	Female	Reference	0.442	Reference	0.614
	Male	0.67 (0.24, 1.88)		0.76 (0.25, 2.25)	
Speciality	Medicine	Reference	0.242	Reference	0.228
	Surgery	0.30 (0.04, 2.28)		0.28 (0.03, 2.23)	
Site of infection	Urinary tract	Reference	0.341	Reference	0.296
	Skin and soft tissue	4.69 (0.49, 44.82)		5.94 (0.39, 89.49)	
	Other	0.85 (0.29, 2.49)		0.73 (0.22, 2.41)	
E.coli	No	Reference	0.987	Reference	0.756
	Yes	1.01 (0.36, 2.83)		1.21 (0.37, 3.95)	
ESBL production	negative	Reference	0.001	Reference	0.002
	positive	6.15 (2.13, 17.75)		5.85 (1.94, 17.62)	

1 patient with obstetrics and gynecology speciality was excluded

Generalised estimating equations were used to adjust for multiple episodes for some patients

OPAT: Outpatient parenteral antibiotic treatment ; CI: confidence interval; ESBL: extended-spectrum beta-lactamases

[1]Joint wald test