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Escherichia coli bloodstream infection outcomes and preventability: a six-month prospective observational study

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ABSTRACT

Background: *Escherichia coli* bloodstream infection (BSI) is a common and serious problem, and incidence and antibiotic resistance are increasing.
Aim: To understand the drivers of outcomes and factors associated with preventable cases at the study institution.
Methods: Between 1st November 2017 and 30th April 2018, cases of *E. coli* BSI in adults treated as inpatients at the study institution were included in a prospective cohort. Clinical, demographic and laboratory features were recorded, with seven-, 30- and 90-day mortality and length of hospital stay post BSI. Qualitative data on preventability were reviewed independently by two infection specialists.
Findings: In total, 195 cases in 188 patients were included in the analysis. Empirical antibiotics showed in-vitro resistance in 30.9% of cases. Thirty-day mortality was 23.6%, with a median length of hospital stay of seven days. On multi-variable analysis, 30-day mortality was associated with higher Charlson score, residential home residency, higher respiratory rate and higher serum urea, whilst prolonged length of stay was associated with hospital-acquired *E. coli* BSI. Fifty patients were felt to have avoidable BSI, all of which were health care associated; urinary catheter use, antibiotic-related and procedural complications were the areas of preventability.
Conclusions: *E. coli* BSI has an appreciable mortality, with little in the way of modifiable risk factors for mortality or prolonged hospital stay. Attention to urinary catheter use is likely to be the most useful way to reduce the incidence, but current UK reduction targets may be unachievable.

Introduction

Gram-negative bloodstream infection (GNBSI) is a common and serious cause of hospital admission and carries an appreciable mortality [1–4]. With increasing antibiotic resistance, there is a need to understand factors associated with the causes and outcomes of these infections in an attempt to reduce their incidence and severity. *Escherichia coli* is the most common GNBSI [2,3], and has been reportable to Public Health England in England since 2011 [5]. The UK Department of Health announced the aim to reduce healthcare-associated GNBSI by 50% by 2021. To elucidate the causes and management of *E. coli* BSI, a six-month prospective observational study

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of adult patients with *E. coli* BSI was conducted at the study institution. This paper reports the factors associated with 30-day mortality and length of hospital stay, and descriptive features in those cases considered to be avoidable.

Methods

Study population

The authors have previously described the bacteraemia service at the study institution and the population it serves [6]. Briefly, Hull and East Yorkshire Hospitals NHS Trust comprises two acute hospitals with 1400 inpatient beds serving a tertiary care population of approximately 1.2 million, providing all medical services apart from solid organ transplantation and allogeneic stem cell transplantation. Between 1st November 2017 and 30th April 2018, all adult patients who had a blood culture taken at any time during their admission which was positive for *E. coli* were eligible for inclusion in the cohort. They were seen at the bedside where possible. Patients who died or were discharged prior to review had their notes reviewed by an infection consultant.

Definitions

Patients who had a blood culture positive for *E. coli* taken within 48 h of admission were classified as community onset, and patients who had a positive culture from blood taken $\geq$48 h of admission were classified as hospital onset. Further classification as healthcare-associated infection (HCAI) (healthcare interaction within 28 days preceding *E. coli* BSI or presence of a prosthetic device of any type) or non-HCAI was ascertained by review of medical notes or bedside clinical review. Comorbidity was assessed using the Charlson score [7]. Empirical antibiotic therapy was considered appropriate if the *E. coli* isolated from blood culture was sensitive to one or more of the antibiotics prescribed at the time the blood culture was taken. Source of infection was assigned by the reviewing clinician, and was based on clinical features together with laboratory, radiological and further microbiological results. Cases were considered avoidable after review of the case notes by two infection consultants (PJL and PJM), who after reviewing equivocal cases independently, reviewed the infection control database with regard to recent antibiotic usage in primary care and reached consensus with regard to preventability. If there was disagreement between the reviewers, the case was designated as preventable to ensure that only those cases felt with certainty to be non-preventable were classified as such.

Laboratory data

E. coli BSI was highlighted by daily review of microbiology reports, together with a monthly list of all cases collated by the infection control team. All *E. coli* positive blood cultures were processed following laboratory standard operating procedures, and were identified using MALDI-TOF mass spectrometry. EUCAST guidelines were followed for the determination of antibiotic sensitivities [8].

Ethical approval and funding

The local clinical governance committee deemed that the project was a service evaluation, and approved the project without the need for patient consent or formal ethical committee review. No funding was needed for this study.

Data collection and analysis

Demographic and clinical data from the time of the positive culture were recorded on a standardized pro forma and subsequently transferred to an Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet. Laboratory data; mortality at seven, 30 and 90 days; in-hospital mortality; length of hospital stay post blood culture; and relapse by 90 days were also recorded on this spreadsheet, with data collated from the pro forma, case notes and hospital electronic records where appropriate. Patient characteristics at time of blood culture positivity and potentially associated with 30-day mortality and length of hospital stay were analysed using χ^2 and Kruskal-Wallis tests, and univariate and multi-variate binary logistic regression analyses. Only predictor variables with $P \leq 0.1$ on univariate analyses were included in multi-variate binary logistic regression analyses. For length-of-stay analyses, the median length of stay was calculated initially. Patients with a length of stay below/equal and above the median were classified dichotomously into non-prolonged and prolonged length-of-stay groups for the purposes of multi-variate binary logistic regression analyses. Logistic regression models were constructed, and adjusted odds ratios and *P*-values from the models considered to be the most clinically and statistically robust are presented. *P*-values <0.05 were considered to indicate significance. Analyses were performed using Graph Pad Prism Version 6 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS Version 24 (IBM Corp., Armonk, NY, USA).

Results

Patient cohort and outcomes

In total, 207 *E. coli* BSI cases occurred during the study period, with 195 included in the study (study flow diagram available in the online supplementary material). There were seven cases of recurrent *E. coli* BSI in the study cohort, with a total of 188 patients having 195 episodes. One hundred and eleven of the 195 cases (56.9%) were reviewed by a member of the study team at the bedside. Table I shows the demographic and clinical outcomes for the entire cohort. Source of infection is shown in Figure 1, with just over half of all *E. coli* BSI originating from the urinary tract.

Patient outcomes are shown in Table I. Figure 2 shows antibiotic sensitivities to the first-line antibiotics tested. Empirical antibiotic therapy was not active against the isolated *E. coli* in 60/194 (30.9%) isolates (one isolate was not sent for antibiotic sensitivity testing as the patient had already died). Co-trimoxazole (14.4%), co-amoxiclav (10.8%) and piperacillin-tazobactam (8.2%) were the most commonly used monotherapy regimens, with gentamicin included in a combination regimen in 69 (35.4%) cases. Inclusion of gentamicin in the empirical regimen significantly increased the likelihood of empirical activity against *E. coli* (odds ratio 11.79, $P<0.0001$).

Table I
Cohort demographic and outcome data

Cohort demographics	
Age (median, interquartile range)	75 (61–83)
Male:female	99 (50.8%):96 (49.2%)
Community onset (<48 h after admission)	149 (76.4%)
Healthcare associated	114 (58.5%)
Residential care pre-admission	34 (17.4%)
Procedure within preceding 90 days	57 (27.2%)
Urinary catheter within preceding 90 days	39 (20%)
Escherichia coli isolated within preceding 90 days	45 (23.1%) [32 (16.4%) urinary isolates]
Cancer at time of bloodstream infection	51 (26.2%)
Diabetes	47 (24.1%)
Dementia	23 (11.8%)
Outcomes	
7-day mortality	26/195 (13.3%)
In-hospital mortality	43/195 (22.1%)
30-day mortality	46/195 (23.6%)
90-day mortality	63/195 (32.3%)
Relapse by 90 days	7/122 (5.7%)
Length of hospital stay, days (median, range)	7 (0–135)

Predictors of 30-day mortality and length of hospital stay

Table II shows the factors associated with mortality at 30 days after BSI. Logistic regression analyses were repeated with: (i) missing time to blood culture positivity replaced with median time; (ii) all missing data replaced with median values/best case outcome for categorical variables; and (iii) all missing data replaced with median values/worst case outcome for categorical variables. Across numerous models, pre-admission location, Charlson score, respiratory rate and serum urea remained significant (data not shown). There was no difference in 30-day mortality between community (21.5%) and hospital onset (30.4%) cases (P=0.24), or between HCAI (26.3%) and non-HCAI (19.8%) cases (P=0.31). For length-of-stay analyses (Table III), acute or community acquisition status, confusion and albumin were the only predictor variables that were consistently significantly (or with a trend towards) associated with prolonged length of stay across numerous models (data not shown), regardless of whether imputed missing data were used in best-/worse-case scenarios.

Avoidable cases

Fifty cases (25.6%) were considered avoidable after independent review by two infection consultants, all of which were considered to be HCAI. Broadly, three major areas were found that contributed to preventable cases: (i) urinary catheter related, including insertion, manipulation or unnecessary use (21 cases); (ii) antibiotic related, including inappropriate procedural prophylaxis, delayed antibiotic treatment or insufficient treatment of a preceding infection (11 cases); and (iii) procedural related, including delay in procedures for source control, post procedural complications and line infections (18 cases). Fifteen of the 50 cases (30%) deemed to be preventable had died by 30 days post BSI. A recent audit of urinary catheter use across both hospitals in the study trust showed that 141 patients (12% of the inpatients on the audit day) had a urinary catheter in place, with urinary retention being the most common reason for insertion (data not shown). The cases considered to be preventable are described individually in the online supplementary material.

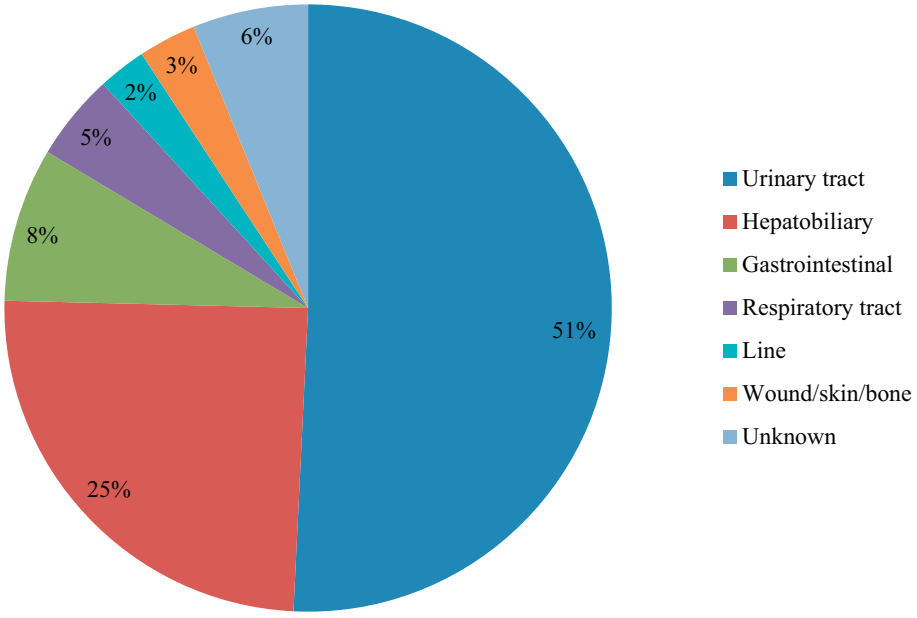

Figure 1. Source of bloodstream infection.

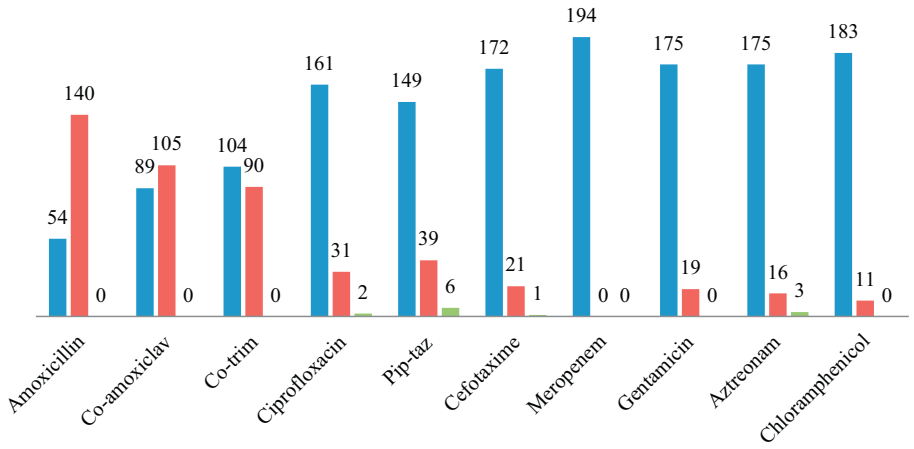

Figure 2. Antibiotic susceptibilty of *Escherichia coli* bloodstream infection isolates (*N*=194). Pip-taz, piperacillin-tazobactam. Blue bars, sensitive; red bars, resistant; green bars, intermediate.

Table II
Multi-variable predictors of 30-day mortality

Variable	Died by day 30 (*N*=46)	Alive at day 30 (*N*=149)	Univariate *P*-value	Logistic regression *P*-value	Odds ratio (95% CI)
Age (years)	82	72	0.0005	>0.2	NA
Charlson score	7	5	<0.0001	0.024	1.342 (1.040–1.730)
Residential home resident	18 (21.9%)	16 (10.7)	<0.0001	0.037	3.977 (1.085–14.572)
Urine or biliary source vs other source	26 (17.7%)	121 (82.3%)	0.001	>0.2	NA
Respiratory rate (/min)	26	21	<0.0001	0.004	1.128 (1.039–1.225)
Systolic blood pressure (mmHg)	113.4	123.8	0.025	>0.2	NA
Temperature (°C)	37.7	38.1	0.031	>0.05	NA
Confused	31 (67.4%)	38 (25.5%)	<0.0001	>0.2	NA
Urea (mmol/L)	14.3	7.4	<0.0001	0.003	1.113 (1.036–1.1195)
Albumin (g/L)	23.5	28	<0.0001	>0.1	NA
Time to positive blood culture (h)	10.7	13.6	0.0624	>0.05	NA
Gentamicin in empiric regimen	7 (15.2%)	72 (48.3%)	<0.0001	>0.1	NA

CI, confidence interval; NA, not applicable.
Values are medians.

Table III
Multi-variable predictors of length of hospital stay

Variable	Length of stay ≤ median (days) (*N*=76)	Length of stay > median (days) (*N*=76)	Univariate *P*-value	Logistic regression *P*-value	Odds ratio (95% CI)
Age (years)	74	78	0.011	>0.1	NA
Charlson score	5	6	0.015	>0.8	NA
Haemoglobin (g/L)	121.5	105	<0.0001	>0.3	NA
Residential home resident	6 (7.9%)	16 (21.1%)	0.026	>0.3	NA
Hospital-acquired (>48 h)	3 (3.9%)	26 (34.2%)	<0.0001	0.015	5.941 (1.421–24.845)
Non-urine or biliary source	7 (9.2%)	20 (26.3%)	0.008	0.2	NA
Confused (not confused, lower risk)	13 (17.3%)	30 (39.5%)	0.003	0.062	0.413 (0.163–1.047)
Urea (mmol/L)	8.7	9.8	0.009	>0.6	NA
Creatinine	94	106	0.078	>0.9	NA
Albumin (g/L) (higher albumin, lower risk)	29	25	<0.0001	0.052	0.918 (0.842–1.001)
Gentamicin in empiric regimen	45 (59.2%)	30 (39.5%)	0.016	>0.4	NA

CI, confidence interval; NA, not applicable.

Discussion

E. coli remains a common cause of BSI, and with increasing antibiotic resistance, the range of treatment options is diminishing [9]. The mortality seen in the study cohort is higher than in other recent studies [9,10]. However, the patients in the study cohort were older and had greater physiological derangement than a recent UK wide study of GNBSI [10]; in addition, a notable proportion had cancer. The present findings are consistent with that study, however, in that comorbidity and physiological derangement were found to be significantly associated with mortality, while active empirical antibiotic treatment was not, and the use of an aminoglycoside (gentamicin) increased the likelihood of the initial regimen being active. While the use of gentamicin was significantly associated with better outcome in univariate analyses, this association was not maintained in multi-variate analyses; gentamicin was significantly more likely to be used in patients without renal impairment. As shown in the authors' previous study across a range of organisms causing BSI [11], renal dysfunction at time of positive culture is associated with mortality and is the only factor that may be clinically modifiable. The use of single-dose gentamicin as part of the empiric regimen may therefore seem counter-intuitive, but is commonly used at the study hospital, and has not been associated with prolonged renal injury [12]; in older data, renal toxicity was only evident in those receiving more than three doses of aminoglycoside [13].

Of the variables associated with mortality and prolonged length of stay, there may be little that can be targeted to improve outcomes, given that predictor variables associated with outcomes were likely markers of comorbidity and overall health status. In previous studies, age was a predictor of poor outcome [4,10,11]; however, as a Charlson score (associated with mortality) that included age as a component [7] was used, this is likely to explain why age was not associated with outcomes in the present study.

This study has some limitations. It was a single-centre study, performed solely during the winter months, and follow-up to date has been limited to up to nine months. Not all patients could be reviewed at the bedside due to early discharge or death. Some notes were unavailable for review, but these were few in number and unlikely to have altered the findings. There is debate about the seasonality of urinary infections due to the effect of dehydration [14,15]; as this study was carried out over the winter, this may have had an influence on relative sources of infection. The detailed review of notes by two independent reviewers to classify cases as avoidable or not should help the debate around what is an achievable target for reduction in *E. coli* BSI. It is likely that this study over-estimated HCAI infection as a proportion of the cohort, as all patients with a prosthetic device or implant, irrespective of type, anatomical site or duration were classified as HCAI, as were any patients that had *E. coli* isolated from any source in the previous 90 days. This should lead to more cases being included in the pool of those targeted for reduction, and the detailed review of all episodes erred on the side of preventability if it was felt by one of the two reviewers that there was scope to prevent that episode. The authors are analysing further data with regard to antibiotic sensitivities, and the effect that different combinations and durations of therapy may have on outcomes.

Attention should also be paid to reducing the incidence of *E. coli* BSI, and there are some common themes in this group. Half of the cases came from a urinary source, which is consistent with larger UK studies on the epidemiology of *E. coli* BSI [3]. This, along with the high level of catheter use and recent urinary isolation of *E. coli* in the study cohort, and previous findings about the role of urinary catheters in severe sepsis [16], means that reducing catheter-associated infection is an obvious area to target. Although a study of low-dose antibiotic prophylaxis in patients intermittently self-catheterizing showed a reduction in symptomatic urinary tract infection (UTI), it did not have an effect on febrile UTI [17], which is likely to be more relevant in terms of preventing BSI. Reducing the number of catheters and the duration of use is likely to be the best way to target this [18,19]. A two-year study of both infectious and non-infectious complications of urinary catheters showed a 10.5% infective complication rate within 30 days of placement [20], with little difference in the occurrence of these infective complications even if the catheter had been removed, but with increasing risk of infectious complaints with increased duration of urethral catheterization [20]. Another study has suggested that in pre-menopausal women with recurrent UTI, increasing fluid intake by up to 1.5 L/day reduced the incidence of symptomatic lower UTI and the need for antibiotic treatment [21]. Whilst this study was not powered to detect an effect on BSI, the major urinary pathogen isolated in both the intervention and control groups was *E. coli* and it is worthy of consideration as an antibiotic sparing technique that might be of use. Conversely, recent data from a UK wide primary care analysis of over 150 000 patients presenting with symptoms suggestive of UTI were suggestive that delaying or not treating UTI was associated with increased risk of subsequent BSI in the 60 days following presentation [22]. Striking the balance between antimicrobial stewardship and preventing significant infections in this group of patients is an area that requires careful study. In the future, for high-risk patients, vaccination against *E. coli* might be valuable [23], although this may be of use only for urinary tract sources of infection due to strain differences [24].

Compared with previous studies, there were fewer cases with an undefined focus of infection [3,4]. This may be due to infection consultation guiding investigations and clarifying the origin of the infection. Reducing *E. coli* BSI from non-urinary sources is likely to be more challenging and have less effect given the relative proportion of infections originating from the urinary tract, but the qualitative data suggest that improving antibiotic usage, both in terms of prophylaxis around procedures and effective treatment of pre-existing infections, may have some effect, as may improvements in procedures, line care and reducing the time to definitive procedures such as cholecystectomy. Some studies from London teaching hospitals, both pre [25] and post [26,27] announcement of Public Health England's ambition of a 50% reduction, found that well under 50% of cases were preventable [25], and in the most recent study [27], there were fewer cases with a urinary tract source of infection and therefore less amenable to intervention than in the study cohort. With other recent data from London also finding that the increasing burden of *E. coli* BSI is driven largely by community-onset infections [28], this suggests that even with a reduction in preventable cases through targeting of areas identified in this and other studies, the target of 50% reduction by 2021 in England

is unlikely to be attainable. A multi-centre prospective study across varied units would clarify the applicability of these results.

In summary, *E. coli* BSI is associated with significant mortality that is associated with few modifiable factors. There may be opportunities to reduce the incidence by targeting avoidable infections, although current national targets are likely to be unachievable.

Conflict of interest statement
None declared.

Funding sources
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.05.007.

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