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Planning to halve Gram-negative bloodstream infection: getting to grips with healthcare-associated *Escherichia coli* bloodstream infection sources☆

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SUMMARY

Background: A thorough understanding of the local sources, risks, and antibiotic resistance for *Escherichia coli* bloodstream infection (BSI) is required to focus prevention initiatives and therapy.
Aim: To review the sources and antibiotic resistance of healthcare-associated *E. coli* BSI.
Methods: Sources and antibiotic resistance profiles of all 250 healthcare-associated (post 48 h) *E. coli* BSIs that occurred within our secondary and tertiary care hospital group from April 2014 to March 2017 were reviewed. Epidemiological associations with urinary source, gastrointestinal source, and febrile neutropenia-related BSIs were analysed using univariable and multivariable binary logistic regression models.
Findings: *E. coli* BSIs increased 9% from 4.0 to 4.4 per 10,000 admissions comparing the 2014/15 and 2016/17 financial years. Eighty-nine cases (36%) had a urinary source; 30 (34%) of these were classified as urinary catheter-associated urinary tract infections (UTIs). Forty-five (18%) were related to febrile neutropenia, and 38 (15%) had a gastrointestinal source. Cases were rarely associated with surgical procedures (11, 4%) or indwelling vascular devices (seven, 3%). Female gender (odds ratio: 2.3; 95% confidence interval: 1.2–4.6) and older age (1.02; 1.00–1.05) were significantly associated with a urinary source. No significant associations were identified for gastrointestinal source or febrile neutropenia-related BSIs. Forty-seven percent of the isolates were resistant to ciprofloxacin, 37% to third-generation cephalosporins, and 22% to gentamicin.
Conclusion: The gastrointestinal tract and febrile neutropenia together accounted for one-third of *E. coli* BSI locally but were rare associations nationally. These sources need to be targeted locally to reduce an increasing trend of *E. coli* BSIs.

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Introduction

The government in England has announced an ambition to halve Gram-negative bloodstream infections (GNBSIs) by 2021 [1]. Our hospital group has experienced an increase in *E. coli* bloodstream infections in recent years, in line with national trends [2–4]. A recent national study suggested that more than 50% of the combined hospital and community-onset *E. coli* BSIs had a urinary source [2]. Recent data published in the ESPAUR report suggest that antibiotic resistance in Gram-negative BSIs is higher in London than in other parts of England [5]. In order to focus prevention initiatives and effective therapy, a thorough understanding of the local sources, risks, and antibiotic resistance for *E. coli* BSI is required. Therefore, we reviewed the background risk and sources, and the antibiotic resistance profile of healthcare-associated *E. coli* BSIs that occurred within our hospital group.

Methods

A de-duplicated database of all *E. coli* BSI identified in patients on or after their second day of admission from April 2014 to March 2017 was analysed. Antimicrobial susceptibility was determined using EUCAST disc susceptibility testing methodology [6]. The source of the BSI was assigned during the care of the patient by a multidisciplinary approach involving the infection control nurses and clinical microbiologists. The source attribution for each case was reviewed retrospectively by the infection control doctor, modifying locally used attribution terminology to match the terms used by Abernethy *et al.* (see Figure 1) [2]. Epidemiological associations with a urinary source, gastrointestinal source, and febrile neutropenia-related BSIs were analysed using univariate and multivariate binary logistic regression models in SPSS (SPSS v23, IBM). Variables that were significant in univariate analysis ($P < 0.05$) were included in the multivariate analysis.

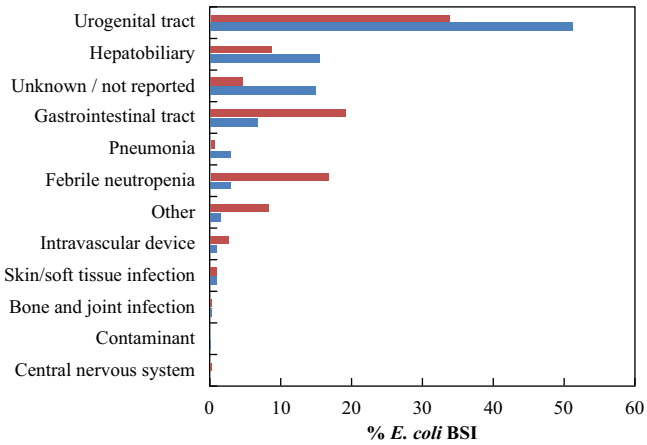

Figure 1. *Escherichia coli* bloodstream infection (BSI) sources nationally versus locally. The national dataset includes community-associated and hospital-associated cases, whereas the local dataset includes only hospital-associated cases. Red bars: data from Imperial College Healthcare NHS Trust, London, UK; blue bars: UK national data.

Results

In all, 250 cases were identified, with the numbers increasing from 75 in the 2014/15 financial year to 82 in 2015/16, and to 93 in 2016/17 (Table I). This means that there were 24% more cases in 2016/17 compared with 2014/15. The number of admissions increased from 185,922 in 2014/15 to 211,020 in 2016/17, a 13% increase. The rate of *E. coli* BSIs increased 9% from 4.0 per 10,000 admissions in the 2014/15 financial year to 4.4 per 10,000 admissions in the 2016/17 financial year. The total number of blood cultures tested by the laboratory and the rate of blood culture testing per 1000 admissions showed similar trends to the *E. coli* BSIs, with the total number increasing by 24%, and the rate increasing by 9%. The percentage of positive blood cultures that were healthcare-associated *E. coli* BSIs remained static at 0.3%. Forty-seven percent of the isolates were resistant to ciprofloxacin, 37% to third-generation cephalosporins, and 22% to gentamicin (Figure 2). Resistance to most antibiotic classes, including ciprofloxacin, third-generation cephalosporins, and gentamicin increased over the study period.

The most common BSI source was urinary (89 cases, 36%); 30 (34%) of these (12% of the total) were classified as urinary catheter-associated UTIs based on whether a urinary catheter was in place within 48 h of the positive blood culture when the source was considered to be urinary. Forty-five cases (18%) were associated with febrile neutropenia. Thirty-eight cases (15%) had a gastrointestinal source, of which 10 (26%) were associated with abdominal sepsis, seven (18%) associated with gut translocation, four (10%) associated with bowel obstruction, and two (5%) with an abdominal wound; eight cases (10%) were noted as a postoperative complication. Twenty-four cases (8.8%) were associated with hepatobiliary sources (Figure 1). This differed considerably from the national picture, where more than 50% of *E. coli* BSIs had a urinary source, and very few had a gastrointestinal source, or were associated with febrile neutropenia (Figure 1), although it is important to note that the national dataset includes community-associated and hospital-associated cases, whereas the local dataset includes only hospital-associated cases. Cases were rarely associated with surgical procedures (11 cases, 4%) or indwelling vascular devices (seven cases, 3%).

We compared the epidemiology of patients who had a BSI with a urinary source with another source. Univariate analysis suggested that female gender, older age, and being a patient in the Division of Surgery was associated with having a BSI with a urinary source (Table II). In multivariate binary logistic regression, only female gender (odds ratio: 2.3; 95% confidence interval: 1.2–4.6) and older age (1.02; 1.00–1.05) were significantly associated with a urinary source (Table II). No significant associations were identified for gastrointestinal source or febrile neutropenia-related BSIs.

Discussion

Our study provides insight into the likely preventable portion of *E. coli* BSIs, by reporting the sources of an increasing trend of healthcare-associated *E. coli* BSI in a large hospital group in London providing secondary and tertiary care, finding that the gastrointestinal tract and febrile neutropenia together accounted for one-third of all *E. coli* BSIs, that 34% had a urinary source (although two-thirds of these were not attributed

Table I
Number and rate of blood cultures and healthcare-associated *E. coli* BSIs, 2014/15 to 2016/17

Financial year	Total admissions	Total blood cultures	Blood cultures per 1000 admissions	No. of HA *E. coli* BSIs	% Blood cultures positive for HA *E. coli*	HA *E. coli* BSI per 10,000 admissions
2014/15	185,922	26,464	142	73	0.3	4.0
2015/16	202,140	27,891	138	83	0.3	4.1
2016/17	211,020	32,794	155	93	0.3	4.4
% change, 2016/17 vs 2014/15	+13.5	+23.9	+9.2	+24.0	+0.1	+9.3

HA, healthcare-associated; BSI, bloodstream infection.

to a urinary catheter), and that indwelling vascular devices and SSIs were rarely implicated. This differs considerably from the national picture of sources for community- and healthcare-associated *E. coli* BSIs, where a urinary source was more common, and the gastrointestinal tract and febrile neutropenia were considerably less common associations [2]. Older, female patients were significantly associated with a urinary BSI source, in line with other studies [3,7,8].

We found that the number of *E. coli* BSIs increased by almost a quarter over the relatively short two-year study period, which is line with national trends [5]. For example, the recent ESPAUR report found that the number of *E. coli* BSIs in England increased by 25% over a similar period, from 32,000 cases in 2012 to 40,000 cases in 2016 [5]. The reason for this national and local increase is not clear. In our setting, the proportion of positive blood cultures that were *E. coli* BSIs did not change over the study period. However, whereas there have been no major changes in the services offered by our hospital group over this period, the number of admissions has increased by 13%, which could explain at least in part the increase in *E. coli* BSI. Also, the number of blood cultures tested in the laboratory has increased by 24%, which is in proportion to the increase in healthcare-associated *E. coli* BSIs detected. This could be driven by improved awareness around the need to take blood cultures when investigating patients who may have sepsis. The level of resistance to antimicrobial agents is higher than reported regionally in London in the latest ESPAUR report, which found ciprofloxacin resistance in 25–27% of isolates in London (compared with 47% in this study), gentamicin resistance in 14–15% (compared with 22% in this study) and third-generation cephalosporin resistance in 15–18% (compared with 37% in this study) [5]. Also, resistance to important antibiotic classes increased over the study. The ESPAUR report included all *E. coli* BSIs (rather than only those attributed to healthcare as in our study), and it covered all hospitals in London (compared with our acute teaching hospitals), which may explain the difference in these resistance profiles.

Our findings provide some insight on targeting strategies aimed at reducing *E. coli* BSI. The urinary tract was the most common source of *E. coli* BSIs identified in hospital inpatients (but only approximately a third of which were urinary catheter-associated), so improved management of hospital-onset UTI may partially reduce the rate of *E. coli* BSI. These strategies may include reducing the frequency and duration of urinary catheterization, improved hydration, and optimal antibiotic treatment of UTI [9–12]. Our findings suggest that older, female patients would benefit most from these interventions, since these patients were more likely to have a BSI with a urinary source. Interventions aimed at reducing the progression of a UTI to a BSI may be even more effective in the community setting, where a urinary source of BSI is more common [2,13]. Specifically, the use of nitrofurantoin rather than trimethoprim is now indicated based on the latest surveillance data [5,13]. However, one-third of cases were from the gastrointestinal tract or associated with febrile neutropenia, which may offer less potential for interventions aimed at reduction. The underlying reasons for *E. coli* BSIs with a gastrointestinal source were varied, including abdominal sepsis, gut translocation, bowel obstruction, wounds, and other abdominal conditions. The pathogenesis of some gastrointestinal *E. coli* BSIs and most BSIs associated with febrile neutropenia is likely to result from translocation of endogenous bacteria to usually sterile tissues as a complication of other interventions [14,15]. We identified no significant epidemiological associations for patients with a gastrointestinal source or febrile neutropenia-related BSIs, which may be due to the small sample size. Further work is necessary to understand the epidemiology of *E. coli* BSI in patients with febrile neutropenia in relation to the cause of neutropenia, and association with immunomodulating therapy [16,17]. Therefore, the preventable proportion in these cases is likely to be considerably smaller. Our findings raise important questions around whether core infection prevention and control interventions are sufficient to prevent *E. coli* BSIs in specialist patient groups, such as those with febrile neutropenia, or whether novel approaches tailored to these patient groups need to be formulated [14,15]. Only a small proportion of cases were related to indwelling vascular devices and SSIs; so, whereas these BSIs may be more preventable than those associated with the gastrointestinal tract or febrile neutropenia, the overall impact on the rate of healthcare-associated *E. coli* BSI will be minimal.

Strengths of the study include a review of consecutive cases of healthcare-associated *E. coli* BSI over a two-year period. These cases underwent detailed multidisciplinary review in order to assign a source of the BSI, which was reviewed independently by the infection control doctor. We were able to link the cases with electronic data in order to explore associations with the BSIs that had the urinary tract as a source. Limitations include difficulty in accurately assigning sources of BSIs in complex cases, especially through retrospective review. We only had source data on healthcare-associated BSI cases, so were not able to review sources for cases that were community-associated. We only included *E. coli* BSIs in our study; future studies should address sources of other Gram-negative BSIs, especially *Klebsiella pneumoniae* and

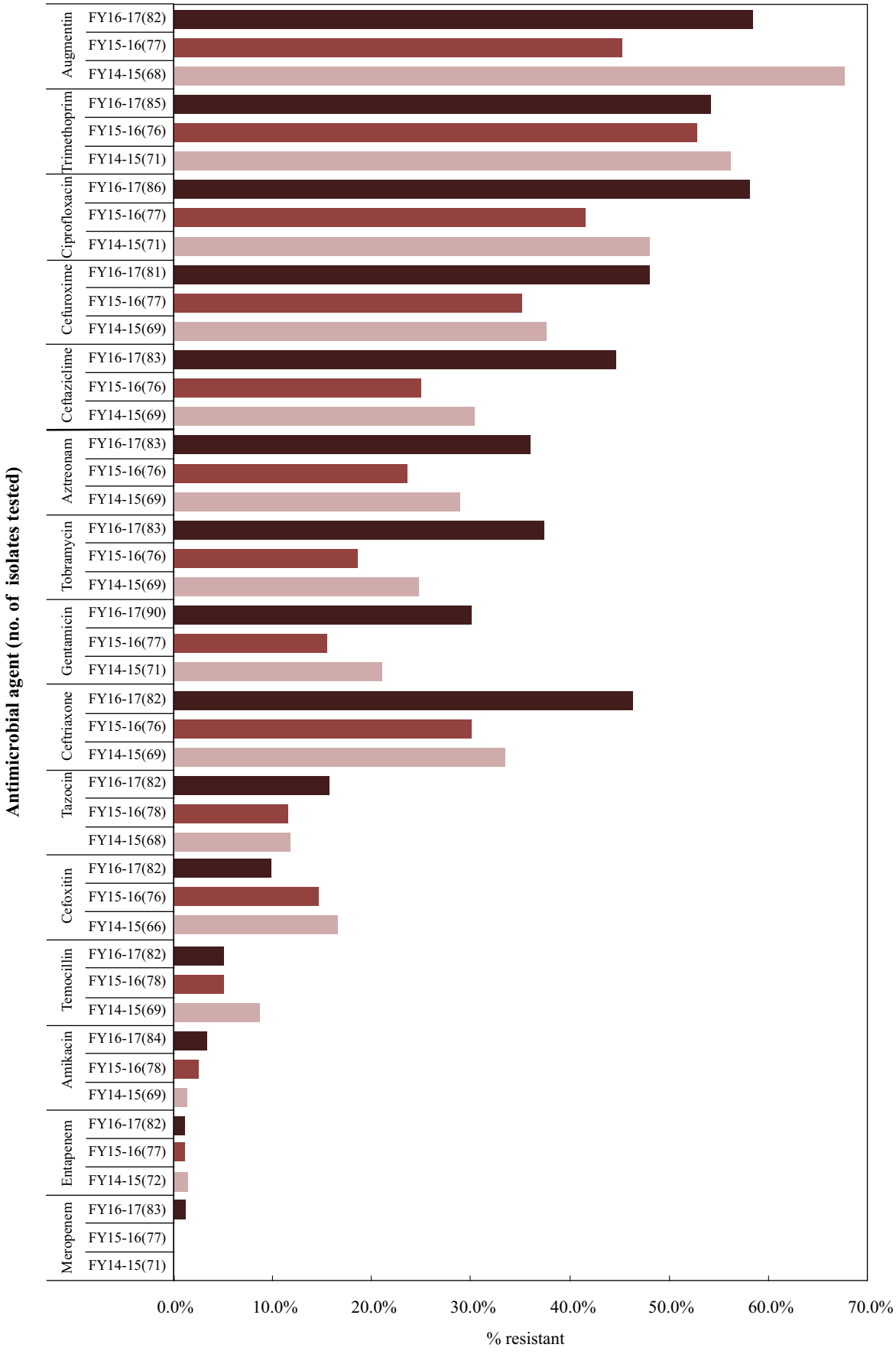

Figure 2. Antimicrobial resistance in the isolates included in the study.

Table II
Risk factors for bloodstream infection with a urinary source

Variable	Not urinary source ($N = 153$)	Urinary source ($N = 85$)	Univariate		Multivariate	
			P	OR (95% CI)	*P*	OR (95% CI)
Median age (range)	62 (0–95)	70 (0–96)	0.007	1.02 (1.00–1.03)	0.030	1.02 (1.00–1.05)
Median duration of hospitalization (range)	11 (2–293)	12 (2–193)	0.238	1.01 (1.00–1.01)	–	–
Female gender	36 (46.2%)	42 (53.8%)	0.006	2.4 (1.3–4.6)	0.016	2.3 (1.2–4.6)
Specialty			0.005		0.481	
Medicine	39 (50.0%)	39 (50.0%)	Ref.			
Private patients	1 (20.0%)	4 (80.0%)	0.224	4.0 (0.4–37.4)	–	–
Surgery	86 (72.3%)	33 (27.7%)	0.002	0.4 (0.2–0.7)	0.199	0.6 (0.3–1.3)
Women and children	23 (63.9%)	13 (36.1%)	0.169	0.6 (0.3–1.3)	0.825	1.2 (0.3–4.5)

OR, odds ratio; CI, confidence interval.

Pseudomonas aeruginosa. The data available for the risk factor analysis for BSIs with a urinary source were limited, and did not include a history of exposure to antibiotics, which should be a focus of future studies.

The first step in achieving a sustained reduction in healthcare-associated Gram-negative BSIs is an accurate understanding of the likely source of these serious infections. Our study highlights a local increase in the number of healthcare-associated *E. coli* BSIs, emphasizing that within secondary and tertiary care a deeper understanding of BSIs related to the gastrointestinal tract and febrile neutropenia will be needed to achieve reductions in these settings.

Conflict of interest statement
J.A.O. is a consultant to Gama Healthcare and has been a consultant to Pfizer. All other authors have no conflicts to declare.

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