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Epidemiology of *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections in a general hospital in Singapore: a retrospective cohort study

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INTRODUCTION

Escherichia coli (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) are the predominant pathogens causing Gram-negative bloodstream infections (GNBSIs) worldwide.[1] *E. coli* and *K. pneumoniae* BSI cases show an increasing trend worldwide, with resistance to certain key antimicrobials such as ciprofloxacin, third-generation cephalosporins and carbapenems rising to alarming levels.[2-4] This is of great concern owing to the burden it places on patient safety, healthcare systems and the economy. GNBSIs have become an international concern, with some countries adopting targets and strategies over the past few years.[5]

There is conflicting evidence on the impact of empirical antibiotics and/or multidrug resistance (MDR) status on mortality related to GNBSIs. Some studies demonstrate no or weak associations, while others demonstrate significant associations.[6] Widely observed variations between study designs including statistical methods may contribute to such conflicting evidence.

The epidemiology of GNBSIs has been studied in the local context; however, it has been limited to specific subpopulations.[6,7] Despite the excellent work published over the last two decades, there are no studies investigating the epidemiology of GNBSIs in an unselected population in Singapore. This study aimed to evaluate the epidemiology of two of the most common GNBSIs, namely those caused by *E. coli* and *K. pneumoniae*, and identify the associations between 30-day all-cause mortality and inappropriate empirical antibiotic use in an unselected population at a general hospital in Singapore.

METHODS

A retrospective cohort study was conducted at a 700-bed general hospital in Singapore. The hospital provides acute medical and surgical care to patients and predominantly serves the communities in the western region of Singapore.

The study was conducted between 1 November 2015 and 31 October 2017 (two years). All patients (> 18 years) with mono-bacterial blood cultures positive for *E. coli* and *K. pneumoniae* during the study period were included. Patients with further positive blood cultures taken within 14 days from the first specimen and positive for the same organism were considered to have the same episode of bacteraemia.

The following data was collected from the Department of Medical Informatics and the electronic medical records (Epic Systems Corp, Verona, WI, USA) for all included cases: demographic data, comorbidities, onset of infection, timing of specimen collection, culture results, other investigations, treatments, devices inserted/manipulated (e.g. central venous catheters, urinary catheters) over the preceding 28 days, procedures and surgeries 28 days prior to admission, and mortality data up to 30 days. In addition, total bed days and total number of admissions were obtained for each year. All blood culture isolates included in the final data analysis were successfully linked to antibiotic susceptibility data from the laboratory information system (Epic Systems Corp).

Ethical approval was obtained from the Domain Specific Review Board of National Healthcare Group, Singapore (reference no. 2018/00253). Findings are reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

We adopted surveillance definitions from Public Health England.[8] A healthcare associated BSI was defined as a laboratory-confirmed positive blood culture for a Gram-negative pathogen in patients within 48 hours of hospital admission and who had received healthcare in either the community or the hospital in the previous 28 days (community onset, healthcare associated; HCA-BSI), whereas a BSI developed more than 48 hours after hospital admission was considered hospital-acquired BSI (HA-BSI). Patients with GNBSIs detected within 48 hours of hospital admission and who had not received healthcare in either the community or hospital in the previous 28 days were considered to have community-acquired BSIs (CA-BSIs).

MDR Gram-negative bacteria were defined as those with 'non-susceptibility to at least one agent in three or more antimicrobial classes'.[9] Empirical antibiotic therapy was defined as initiation of antibiotics for the treatment of infection before antibiotic susceptibility data was available. Antibiotic therapy was considered inappropriate if the blood culture isolate did not show *in vitro* susceptibility to any of the antibiotics administered prior to availability of susceptibility data.

The source of infection was defined as the underlying primary focus of bacteraemia, and it was determined based on the clinical notes of the attending physician or infectious diseases physician. If the source of infection was equivocal, it was determined by the researchers based on clinical notes and investigations; however, in an event of sustained ambiguity, the source of infection was classified as 'unknown'. The encounters were classified as disseminated in cases where there was objective evidence of multiple sources of infection.

A detailed analysis was undertaken for *E. coli* and *K. pneumoniae.* Data analysis was performed using IBM SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered significant. Categorical variables were expressed as frequency and percentage, and

general associations between categorical variables were examined using the chi-square test. Logistic regression was used to determine independent predictors of 30-day all-cause mortality and the patient-level predictors of the aetiologies of BSI.

RESULTS

We identified a total of 1,699 GNBSI episodes from the database. Cases with Gram-negative organisms other than *E. coli* and *K. pneumoniae* (n = 527), duplicates (n = 162) and incomplete information on most variables (n = 3) were excluded from data analysis, leaving a total of 1,007 cases comprising 700 *E. coli* and 307 *K. pneumoniae* BSI (Fig. 1).

The overall incidences of *E. coli* and *K. pneumoniae* were 87 per 10,000 admissions (194.1/100,000 bed days) and 38.1 per 10,000 admissions (85.1/100,000 bed days), respectively. The incidence of *E. coli* HA-BSI was 11.1 per 100,000 bed days and that of *K. pneumoniae* was 9.98 per 100,000 bed days. The mean age of the study participants was 71.2 years (standard deviation 14.2). A vast majority of cases were seen in patients aged ≥ 65 years, with significant male and female preponderance in *K. pneumoniae* and *E. coli*, respectively (Fig. 2).

Overall, CA-BSI accounted for 688 (68.3%) cases, and HCA-BSI and HA-BSI accounted for 177 (17.6%) and 76 (7.5%) cases, respectively. We were unable to classify the onset of BSI in 66 (6.5%) cases owing to lack of pre-hospitalisation data from the medical records (Table I).

Table I. Summary of findings for the causative organism for BSIs stratified based on aetiology.

Characteristic	No. (%)		
	***E. coli* (n = 700)**	***K. pneumoniae* (n = 307)**	**p-value**
Incidence			
Overall admissions	87/10,000	38.1/10,000	
HA-BSI bed days	11.1/100,000	9.98/100,000	
Age* (yr)	71.5 (14.1)	68.2 (14.2)	0.68

Gender			
Female	431 (61.6)	121 (39.4)	< 0.0001
Male	269 (38.4)	186 (60.6)	< 0.0001
Onset of infection			
CA-BSI	488 (69.7)	200 (65.1)	0.341
HCA-BSI	127 (18.1)	50 (16.3)	0.611
HA-BSI	40 (5.7)	36 (11.7)	0.001
Insufficient data	45 (6.4)	21 (6.8)	
Source of infection			
Upper urinary tract	448 (64.0)	115 (37.5)	< 0.0001
Hepatobiliary	110 (15.7)	39 (12.7)	0.215
Liver abscess	5 (0.7)	61 (19.9)	< 0.0001
Gastrointestinal	32 (4.6)	13 (4.2)	0.812
Lower respiratory tract	31 (4.4)	19 (6.2)	0.236
Unknown	59 (8.4)	35 (11.4)	< 0.0001
Others	15 (2.1)	25 (8.1)	0.136
Antimicrobial susceptibility	499 (71.3)	244 (79.5)	
Non-MDR	201 (28.7)	63 (20.5)	0.007
MDR	116 (57.7)	23 (36.5)	
MDR CA-BSI	50 (24.9)	21 (33.3)	0.009
MDR HCA-BSI	25 (12.4)	14 (22.2)	0.104
MDR HA-BSI	10 (5.0)	5 (7.9)	0.056
Insufficient data on the onset of infection			
Appropriate empirical therapy			
Yes	546 (78.0)	259 (84.4)	
No	154 (22.0)	48 (15.6)	0.019
30-day all-cause mortality			
Yes	54 (7.7)	29 (9.4)	0.36
No	646 (92.3)	278 (90.6)	0.001
MDR	24/201 (11.9)	10/63 (15.9)	
Non MDR	30/499 (6.0)	19/244 (7.8)	0.003
CA-BSI	17/488 (3.5)	10/200 (5.0)	0.186
HCA-BSI	11/127 (8.7)	6/50 (12.0)	0.056
HA-BSI	13/40 (32.5)	8/36 (22.2)	
Insufficient data	13/45 (28.9)	5/21 (23.8)	0.001
Inappropriate empirical therapy	16/154 (10.4)	12/48 (25.0)	
Appropriate empirical therapy	38/546 (7.0)	17/259 (6.6)	

**Data presented as mean ± standard deviation. BSI: bloodstream infection; CA-BSI: community-acquired bloodstream infection;* E. coli: Escherichia coli*; HA-BSI: hospital-acquired bloodstream infection; HCA-BSI: healthcare-associated bloodstream infection;* K. pneumoniae: Klebsiella pneumoniae*; MDR: multidrug resistance*

Upper urinary tract infections (UUTIs), collectively represented cases of pyelonephritis and renal/perinephric abscesses, were reported as the most common focus of infection, irrespective of the onset of BSI in both organisms (n = 563, 55.9%). Overall, hepatobiliary source was the second commonest cause (n = 149, 14.8%). According to the logistic regression analysis, UUTI was significantly associated with *E. coli* (adjusted odds ratio 7.12, 95% confidence interval [CI] 2.14–23.68; p = 0.001), whereas pyogenic liver abscess was associated with *K. pneumoniae* (adjusted odds ratio 0.15, 95% CI 0.03–0.67; p = 0.013). Furthermore, hepatobiliary (excluding liver abscesses) and gastrointestinal sources were significantly associated with *E. coli*.

Ciprofloxacin non-susceptibility in *E. coli* demonstrated a significant year-on-year increase from 25.9% to 33.7% (p = 0.014). No significant trends were observed for *K. pneumoniae* or MDR rates in both organisms. Regression analysis confirmed that the MDR rate was significantly associated with *E. coli* isolates (adjusted odds ratio 1.545, 95% CI 1.022–2.335; p = 0.039). Highest MDR rates were observed in HA-BSI for both *E. coli* and *K. pneumoniae* (Table I).

The sources of infection and the aetiologies of BSI did not demonstrate significant associations with 30-day all-cause mortality. However, CA-BSI was significantly associated with lower mortality (adjusted odds ratio 0.13, 95% CI 0.05–0.33; p < 0.001) (Table II). Logistic regression analysis revealed that inappropriate choice of empirical antibiotic therapy was significantly associated (adjusted odds ratio 3.38, 95% CI 1.47–7.77; p = 0.004) with higher rates of 30-day all-cause mortality (Table II).

Table II. Summary of the factors associated with 30-day all-cause mortality in patients with *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections.

Factor	Adjusted OR	SE	95% CI		p-value
			Lower	Upper	
Recurrent bacteraemia					
No	1	0.46	0.472	2.869	0.742
Yes	1.164				
Study year					
Second year	1	0.313	0.57	1.942	0.871
First year	1.052				
Gender					
Female	1	0.366	0.391	1.64	0.544
Male	0.801				
Comorbidity					
No	1				
Diabetes mellitus	1.084	0.365	0.53	2.217	0.824
Hypertension	1.059	0.396	0.487	2.304	0.884
Hypercholesterolaemia	1.378	0.366	0.673	2.824	0.381
Chronic kidney disease	1.505	0.449	0.624	3.631	0.363
Ischaemic heart disease	0.449	0.366	0.219	0.919	0.029
Cerebrovascular accident	1.959	0.422	0.856	4.482	0.111
Hepatitis	1.428	0.874	0.258	7.916	0.684
Cirrhosis	0.408	0.554	0.138	1.209	0.106
COPD	1.867	0.736	0.441	7.897	0.396
History of cancer	0.542	0.38	0.257	1.141	0.107
Onset of infection					
Insufficient data	1				
CA-BSI	0.129	0.487	0.05	0.334	< 0.001
HCA-BSI	0.618	0.521	0.223	1.715	0.355
HA-BSI	2.526	0.6	0.779	8.193	0.123
Upper urinary tract infection					
No	1				
Yes	1.812	1.141	0.194	16.952	0.602
Hepatobiliary					
No	1				
Yes	0.924	1.188	0.09	9.474	0.947
Liver abscess					
No	1				
Yes	1.536	1.606	0.066	35.778	0.789
Gastrointestinal					
No	1				
Yes	0.619	1.259	0.052	7.296	0.703
Unknown source of infection					
No	1				
Yes	0.814	1.191	0.079	8.408	0.863

Blood culture results					
K. pneumoniae	1				
E. coli	0.628	0.387	0.294	1.341	0.23
Multidrug resistant organisms					
No	1				
Yes	0.767	0.454	0.315	1.866	0.559
Inappropriate empirical antibiotic therapy					
No	1				
Yes	3.381	0.425	1.471	7.769	0.004
Immunocompromised host					
No	1				
Yes	0.053	1.407	0.003	0.84	0.037
Age	1.028	0.017	0.995	1.061	0.101
Absolute neutrophil count	1.064	0.019	1.026	1.105	0.001

CA-BSI: community-acquired bloodstream infection; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HA-BSI: hospital-acquired bloodstream infection; HCA-BSI: healthcare-associated bloodstream infection; OR: odds ratio; SE: standard error

DISCUSSION

To our knowledge, this is the first study to investigate the epidemiology of *E. coli* and *K. pneumoniae* BSI in an unselected population in Singapore. In keeping with other studies, *E. coli* was the commonest GNBSI.[1,10,11] Our incidence rate of *E. coli* and *K. pneumoniae* – 87 per 10,000 admissions (194.1/100,000 bed days) and 38.1 per 10,000 admissions (85.1/100,000 bed days), respectively – is much higher than that reported in other similar studies.[12-14]

The most common source of BSI in both organisms was UUTIs. Overall, 24% of patients had possible contributory factors for developing UUTIs such as urinary catheter inserted/manipulated over the preceding 28 days, UTI treatment over the preceding 28 days and recurrent UTI. Of all UUTI patients in our study, 13.8% had a urinary catheter inserted/manipulated in the 28 days prior to onset of BSI. However, what proportion of these catheters was appropriate or adequately monitored is unknown. These findings suggest that a proportion of BSI could potentially be reduced by optimal treatment of UTIs and proper

management of urinary catheters. Community-based healthcare plays an important role in reducing *E. coli* BSIs, as the majority of BSIs secondary to UUTIs are CA-BSIs (54.0%). Other sources of BSIs may offer less potential for interventions to reduce the burden of BSIs unless related to procedures or associated with devices.

Antimicrobial resistance rates were high for both organisms, with a higher MDR rate in *E. coli* (n = 201, 28.7%) compared to *K. pneumoniae* (n = 63, 20.5%). MDR rates were significantly higher in HCA-BSIs and HA-BSIs than in CA-BSIs in both organisms (Tables I & III). This was consistent with the other studies despite varying definitions of MDR used by the researchers. Although our current carbapenem resistance rate remains low, there is a risk of increasing rates owing to rising cephalosporin and piperacillin/tazobactam resistance encouraging the use of carbapenems.

Table III. Summary of the factors associated with *Escherichia coli* bloodstream infections.

Covariate	Adjusted OR	SE	95% CI		p-value
			Lower	Upper	
Recurrent bacteraemia					
No	1				
Yes	0.833	0.255	0.506	1.372	0.473
Study year					
Second year	1				
First year	1.172	0.164	0.849	1.617	0.335
Gender					
Female	1				
Male	0.542	0.19	0.373	0.787	0.001
Age category (yr)					
≥ 85	1				
15–44	1.64	0.459	0.667	4.035	0.282
45–84	1.399	0.243	0.87	2.251	0.166
Admitting ward/specialty					
Intensive care unit	1				
Medical	0.676	0.516	0.246	1.858	0.448
Surgical	0.813	0.555	0.274	2.413	0.709

Onset of infection					
No sufficient data	1				
CA-BSI	0.796	0.328	0.419	1.512	0.485
HCA-BSI	0.699	0.367	0.341	1.435	0.33
HA-BSI	1.548	0.399	0.708	3.385	0.273
MDR					
No	1				
Yes	1.545	0.211	1.022	2.335	0.039
Comorbidity					
No	1				
Diabetes mellitus	0.556	0.189	0.383	0.806	0.002
Hypertension	0.862	0.215	0.565	1.314	0.49
Hypercholesterolaemia	1.294	0.187	0.897	1.868	0.168
Chronic kidney disease	0.617	0.218	0.402	0.947	0.027
Ischaemic heart disease	1.341	0.203	0.9	1.998	0.149
Cerebrovascular accident	1.345	0.215	0.883	2.047	0.168
Hepatitis	0.718	0.352	0.36	1.43	0.345
Cirrhosis	0.865	0.367	0.421	1.777	0.693
COPD	2.395	0.483	0.929	6.169	0.071
History of cancer	0.791	0.242	0.492	1.27	0.331
Upper urinary tract infection					
No	1				
Yes	7.121	0.613	2.142	23.677	0.001
Hepatobiliary					
No	1				
Yes	5.401	0.625	1.586	18.393	0.007
Liver abscess					
No	1				
Yes	0.152	0.761	0.034	0.675	0.013
Gastrointestinal					
No	1				
Yes	6.272	0.699	1.593	24.703	0.009
Lower respiratory tract infection					
No	1				
Yes	3.061	0.694	0.785	11.932	0.107
Unknown source of infection					
No	1				
Yes	3.394	0.642	0.964	11.947	0.057

CA-BSI: community-acquired bloodstream infection; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HA-BSI: hospital-acquired bloodstream infection; HCA-BSI: healthcare-associated bloodstream infection; OR: odds ratio; SE: standard error

Our mortality rates are lower than those reported in other studies, where *E. coli* mortality ranged from 11% to > 30%. This variation is likely due to some studies examining specific patient populations.[2,10,15] Similarly, the mortality in *K. pneumoniae* demonstrates a wide variation.[10,15-17] Our low mortality rate may be attributable to the higher proportion of patients with UUTIs (n = 563, 55.9%), higher rates of appropriate empirical antibiotic therapy (n = 805, 79.9%), and the lack of severely immunocompromised patients or low severity of sepsis. Mortality rates were higher in HA-BSIs and HCA-BSIs as opposed to CA-BSIs for both organisms, and the latter was significantly associated with a lower mortality, which was consistent with the previous studies.[10,15,17] Logistic regression analysis demonstrated that inappropriate empirical antibiotic therapy was significantly associated with increased 30-day all-cause mortality (adjusted odds ratio 3.38, 95% CI 1.47–7.77; p = 0.004).

Our study has several limitations. Firstly, it was a retrospective study carried out in a single acute hospital. Thus, it is not representative of the overall epidemiology in Singapore. Secondly, we did not evaluate the severity of BSIs/sepsis at the time of specimen collection, and therefore, this was not included in the regression analysis as a confounder. It is possible that a lower proportion of patients who had organ dysfunction or septic shock in our study may have underestimated our mortality rates. Thirdly, we were unable to study long-term trends as our hospital was opened in mid-2015. Finally, we did not have access to all healthcare services received in the community, and therefore, a proportion of patients categorised as CA-BSIs may actually have HCA-BSIs.

We identified relatively high incidence rates and high MDR rates of GNBSI in our healthcare setting. Our study adds to existing evidence that the inappropriate empirical antibiotic therapy is significantly associated with higher 30-day all-cause mortality. Moreover, we recognise

optimal treatment of urinary tract infections and proper management of urinary catheters, in particular, in the community setting as a potential intervention to reduce the incidence of GNBSIs. Given the current incidence rates and MDR rates of GNBSIs, we recommend concerted and streamlined efforts to bring various elements of existing surveillance mechanisms and interventions together.

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FIGURES

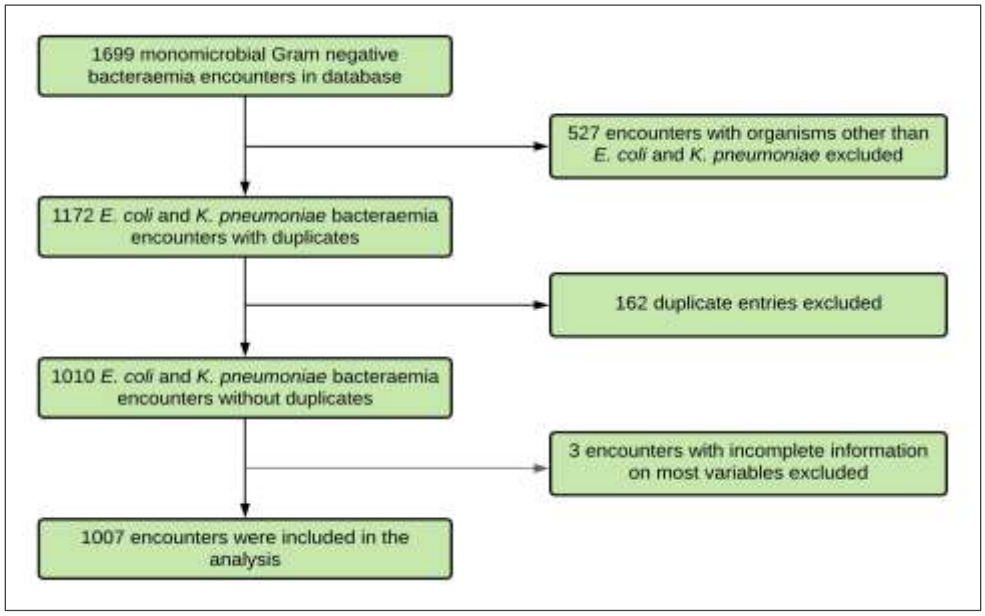

Fig. 1 Case-selection flowchart shows selection process, with 1,007 encounters included in the analysis after the initial exclusions.

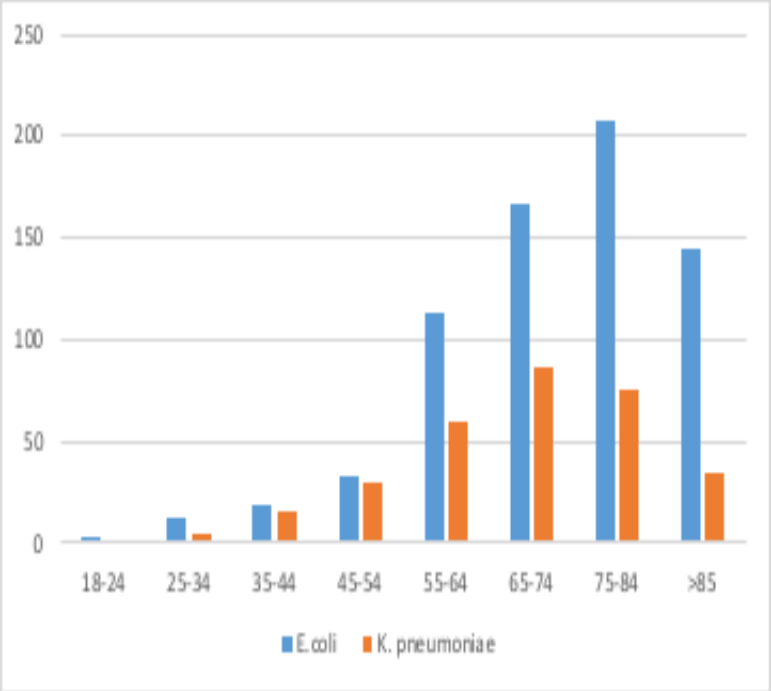

Fig. 2 Chart shows distribution of age categories across the two aetiologies, *Escherichia coli* and *Klebsiella pneumoniae.*