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Escherichia coli bacteremia: Clinical features, risk factors and clinical implication of antimicrobial resistance

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Escherichia coli **is an important cause of both community acquired (CA) and hospital acquired (HA) bacteremia. A prospective study was conducted at a tertiary care University Hospital from January, 2012 to July 2014, to compare the clinical features, risk factors, outcomes and antimicrobial resistance between *E. coli* bacteremia acquired from the community (CA) versus *E. coli* bacteremia acquired from the hospital (HA). Clinical and laboratory data of 171 adult patients with at least one positive blood culture of *E. coli* were analyzed. Data were collected from patients with significant blood stream infection, using medical and laboratory record files and information from treating medical staff. The overall incidence of extended spectrum beta lactamase (ESBL) infection was high, 67/171 (77.4%). Thirty-eight (40.9%) of the CA isolates were found to produce ESBL, while 28 (35.9%) of the HA isolates were ESBL producers. Patients with CA bacteremia tend to be older than those with HA bacteremia (0.003). Neoplastic diseases (hematological malignancy (<0.001), solid tumors (<0.001)), renal transplantation end stage renal disease (ESRD) (<0.006), and wound infection (<0.001) were the most commonly associated conditions in patients with HA bacteremia. Patients from the community are more likely to present with UTI (<0.001), fever and pyelonephritis (0.001). Both CA and HA *E. coli* isolates showed the highest sensitivity to imipenem, meropenem and amikacin followed by gentamicin and tazocin. The CA isolates are more susceptible to amikacin, tazocin and ciprofloxacin than the HA isolates. No significant difference in the mortality rate between patients with CA bacteremia and patients who acquire the bacteremia in a hospital setting (0.836) was observed. Clinicians need to be aware of the risk factors and changing pattern of antimicrobial resistance of this pathogen and should consider adequate empirical therapy with coverage of these pathogens for patients with risk factors**

Key words: *Escherichia coli,* community acquired, hospital acquired, bacteremia, blood stream infection.

INTRODUCTION

Escherichia coli are part of the normal gastrointestinal flora and a leading cause of Gram negative bacteremia (Tenaillon et al., 2010). Sepsis and septic shock caused by *E. coli* and other Gram-negative bacteria is due to the inflammatory response activated by endotoxin (lipopolysaccharide) present in the Gram-negative cell

wall (Johnson et al., 2006). Blood stream infection (BSI) in developing countries is a serious issue that is rarely addressed in the scientific literature (Aiken et al., 2011). Bloodstream infection (BSI) due to extended-spectrum β-lactamase (ESBL) *Enterobacteriaceae* has emerged as a major cause of in-hospital mortality (Hyle et al., 2005; Pitout and Lauplan, 2008). The spread of community-acquired and hospital-acquired (nosocomial) bacteremia cause by *E. coli* imposes a major health burden. However, only few regional information is available on the differences between hospital-acquired and community acquired *E. coli* bacteremia (Hoenigl et al., 2014). Community and hospital spread of *E. coli* producing extended-spectrum beta-lactamases has increasingly been reported, most notably *E. coli* producing CTX-M strains (Woodford et al., 2004). This poses significant challenges to clinicians caring for patients presenting to hospital with suspected sepsis as empiric antibiotic treatment is often targeting presumed, antibiotic-susceptible community organisms (Rodriguez-Bano et al., 2006; Tumbarello et al., 2008). Accordingly, this study was conducted to assess any demographic variation in the incidence, the clinical characteristics, risk factors and antimicrobial-resistance trends of community-associated (CA) and hospital associated (HA) *E. coli*-bacteremia, presenting to the hospital. To the best of the authors' knowledge, there are no other studies comparing the epidemiology and risk factors between the community-acquired and health-care associated *E. coli* bacteremia from the Gulf region.

METHODS

Patients

This study was conducted at King Khalid University Hospital, a 2500 bed major teaching hospital in Riyadh that provides both primary and tertiary medical care. From January 1, 2012 to July 30, 2014, adult patients (>14 years old) with at least one positive blood culture of ESBL-producing *E. coli* and non-ESBL-producing *E. coli* were reviewed. Only the first episode of bacteremia in each patient was included in the analysis.

Definitions and data collection

Data were prospectively collected from patients with significant blood stream infections using daily review of blood culture results, patients' medical record files, information from treating medical staff and by a computerized method using the blood culture register numbers in the microbiology laboratory of each positive case. Standardized data forms were used to record demographic details including underlying diseases, hospital unit, and exposure to the healthcare system in the previous year, site of infection, ESBL production in organisms isolated from culture samples, clinical progress and mortality. Patients were divided into two groups based on the onset of bacteremia. Bacteremia with *E. coli* detected within the first 48 h of hospitalization was classified as "community-onset" according to the US Centers for Disease Control and Prevention definition and hospital acquired *E coli* infection was defined as an infection that occurred > 48 h after admission to the hospital, or an infection that occurred < 48 h after admission of patients that had been transferred from another hospital or nursing home (National Committee for Clinical Laboratory Standards, 1999) and were further classified into community-acquired or health care associated infections (modified from the study of Siegman-Igra et al., 2002). The former definition represents truly community-acquired infection, while the latter consists of infections in patients recently discharged (≤ 6 months), infections associated with invasive procedures performed earlier, or at the time of admission and infections in patients admitted from nursing homes. *E. coli* bacteremia was defined as the isolation of *E. coli* from ≥ 1 set of aseptically inoculated blood culture bottles. In patients with clinical features compatible with systemic inflammatory response syndrome. Patients were classified as immunosuppressed if neutropenia (defined as < 1,000 polymorphonuclear neutrophils cells/mm^3), hematologic malignancy, corticosteroid therapy (equivalent to > 20 mg prednisolone/day) for at least 2 weeks, and/or cancer chemotherapy or radiation therapy were documented within 30 days of the onset of bacteremia. Patients with serum creatinine level > 3 mg/dL, or under dialysis, before the onset of bacteremia were considered to have chronic renal insufficiency.

Identification and antimicrobial susceptibility testing

Isolates of *E. coli* were identified by standard microbiologic methods in the microbiology laboratory using an automated identification system (Vitek System; bioMe´rieux). Susceptibilities to antimicrobial agents (ampicillin, amoxicillin/clavulnate, cefradine, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, cefipem, ciprofloxacin, imipenem, meropenem, gentamicin, amikacin piperacillin/ tazobactam, trimethoprim/sulfmethoxazole) were determined by use of an automated susceptibility testing system (Vitek 2 System; bioMe´rieux). ESBL production was detected and interpreted using CLSI criteria for broth dilution in accordance with the Clinical and Laboratory Standards Institute standards (Wayne, 2005).

Statistical analysis

All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute Inc., Cary, NC, USA). For univariate analysis, categorical variables were compared using χ^2 or Fisher's exact test and continuous variables were analyzed with Student's *t* test or Mann- Whitney *U* test. A p value < 0.05 was considered to be statistically significant, and all probabilities were two-tailed.

RESULTS

During the study period, 171 adult patients with *E. coli* bacteremia were analyzed. Of these, 93 (54.4%) were community-acquired *E. coli* bacteremia and 78 (45.6%) were hospital-acquired *E. coli* bacteremia (Table 1).

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Table 1. Classification of 171 patients with *E. coli* bacteremia.

	Community acquired *E. coli*	Hospital acquired *E. coli*
ESBL	38 (40.9%)	28 (35.9%)
Non-ESBL	55 (59.1%)	50 (64.1%)
Total	93	78

Table 2. Clinical characteristics of 171 patients with *E. coli* bacteremia.

Characteristics	Community acquired (n=93)	Hospital acquired associated (n=78)	p Values
Age (mean + SD), years	58.8 ± 21.8	48.2 ± 24.6	0.003
Sex (M/F)	34 / 59	41 / 37	0.047
Underlying disease			
Diabetes mellitus	5 (5.3%)	3 (3.8%)	0.637
liver cirrhosis/ biliary tract disease	1 (1.1%)	4 (5.1%)	0.114
ESRD/ post-transplant	2 (2.1%)	10 (12.8%)	0.006
Solid tumor	0	15 (19.2%)	<0.001
Hematological malignancy	1 (1.1%)	11 (14.1%)	<0.001
Heart disease	2 (2.1%)	4 (5.1%)	0.286
RTA	0	1 (1.3%)	0.271
Clinical presentation			
Urinary tract infection	20 (21.3%)	2 (2.6%)	<0.001
Fever/Pyelonephritis	41 (43.6%)	16 (20.5%)	0.001
Septic shock/hypotension	9 (9.6%)	4 (5.1%)	0.272
Wound infection/diabetic foot	1 (1.1%)	11 (14.1%)	0.001
Vomiting/diarrhea	5 (5.3%)	0	0.039
ESBL	39 (41.5%)	28 (35.9%)	0.454
Mortality	24 (25.5%)	21 (26.9%)	0.836

Demographic and clinical characteristics of patients are shown in Table 2. Patients with community acquired *E coli* bacteremia tend to be older than those with hospital-acquired infection (0.003); they were more than 55 years old and were mostly female. Hematological malignancy (<0.001), solid tumors (<0.001), renal transplantation, end stage renal disease (ESRD) (<0.006), and wound infection including diabetic foot infection (<0.001) were associated with hospitalization and development of *E. coli* bacteremia. Among patients with malignancy, hematological malignancy was found to be a significant risk factor for acquisition of E coli bacteremia in hospitalized patients (14.1%) (<0.001). Patients from the community are more likely to present with urinary tract infection (<0.001), fever and pyelonephritis (0.001) or vomiting and diarrhea (0.039). Among the 78 hospitalized patients, oncology (30.8%), medicine (28.2%), and critical care (23.1%), were the commonest specialists at the onset of bacteremia (Table 3). The overall incidence of ESBL infection was high, 67/171 (77.4%). Thirty-eight (40.9%) of the community acquired isolates were found to produce ESBL, while 28 (35.9%) of the hospital acquired isolates were ESBL producers. There was no significant difference in acquiring infection with ESBL *E. coli* between patients from the community and hospitalized patients. Both community-acquired and hospital-acquired *E. coli* isolates showed the highest sensitivity to imipenem, meropenem and amikacin followed by gentamicin and piperacillin/tazobactam (Figure 1). The sensitivity pattern of ESBL producing *E. coli* of the community-acquired and hospital-acquired isolates is shown in Figure 2. Meropenem and imipenem are the most sensitive antimicrobial agents followed by the amikacin and piperacillin/tazobactam. The community-acquired isolates are more susceptible to amikacin, piperacillin/tazobactam and ciprofloxacin than the hospital-acquired isolates. No significant difference was observed in the mortality rate between patient who acquire the bacteremia from the community or those who acquire the bacteremia in a hospital setting (0.836)

Table 3. Admission characteristic of 78 hospitalized patient with *E. coli* bacteremia.

Characteristics	N (%)
Age , median years (range)	54.5
Male sex	41 (52.6%)
Hospital ward	
Medical service	22 (28.2%)
Surgical service	14 (17.9%)
Intensive care unit	18 (23.1%)
Oncology	24 (30.8%)

Table 4. Mortality among ESBL and non-ESBL patients.

	ESBL	non-ESBL	Total
Community acquired	11 (45.8%)	13 (61.9%)	24
Hospital acquired	13 (54.2%)	8 (38.1%)	21
Total	24	21	45

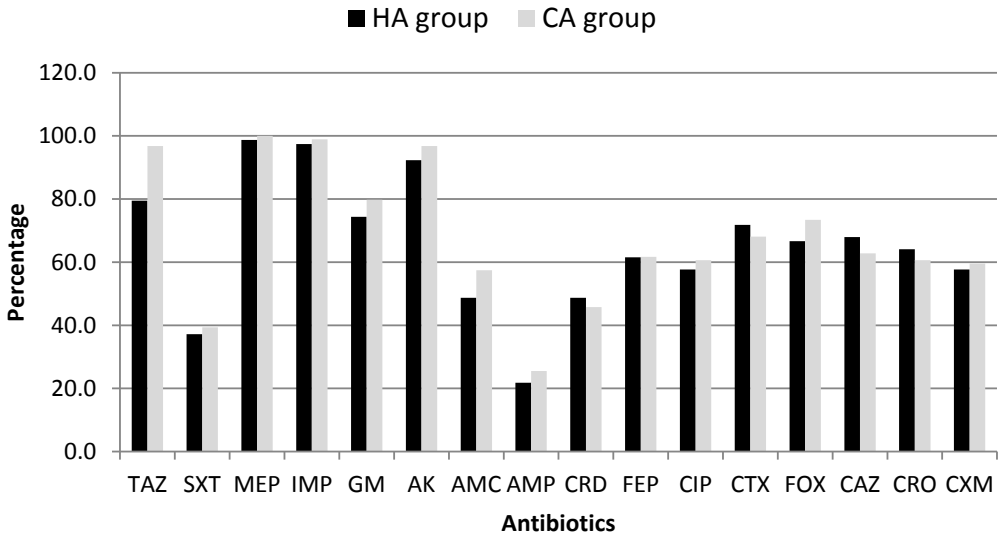

Figure 1. Percentage sensitivity of community acquired (CA) and hospital acquired (HA) *E. coli* to antimicrobial agents.

(Table 4).

DISCUSSION

E. coli-blood stream infection is a major cause of morbidity and mortality with a relatively high associated population burden (Pitout et al., 2004; Uslan et al., 2007; Williamson et al., 2013). Little data exists on the demographic variation and potential risk factors between CA and HA *E. coli* blood stream infection (Pitout et al., 2004; Rodríguez-Baño et al., 2010) such population-based demographic information is important in implementing strategies for treatment and prevention of these serious infections. There were many studies from the Saudi Arabia region that determine the prevalence of bacterial pathogens isolated from all specimen types including blood and assessed the multi-drug resistant rates of ESBLs among *Enterobacteriaceae*. The prevalence between 4.8 and 15.8% have been reported

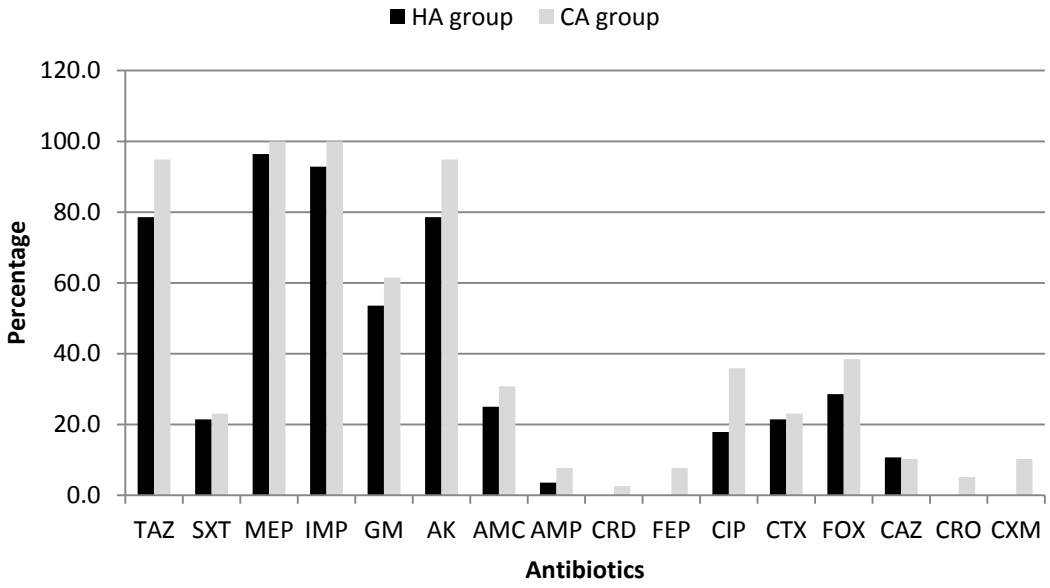

Figure 2. Percentage sensitivity of community acquired (CA) and hospital acquired (HA) ESBL producing *E. coli*.

from Saudi Arabia with the finding of the lowest frequency rates of ESBL producers in the eastern region and the highest frequency was observed in the central region (El-Khizzi and Bakheshwain, 2006; Kader and Kumar, 2004; Masoud et al., 2011; Rodríguez-Bano et al., 2009). In two studies (El-Khizzi and Bakheshwain, 2006; Khanfar et al, 2009) from the Arabian Gulf region, ESBL detection in *Enterobacteriaceae* was described. In the first study (El-Khizzi and Bakheshwain, 2006), different patient populations with nosocomial and community-acquired infections were assessed, the majority (83%) of the ESBL-producing isolates were *E. coli*. ESBL producers were significantly higher among isolates from in-patients, 15.4% as compared to those from out-patients, 4.5%. Urine was the most common specimen for the isolation of ESBL pathogens among in-patients and out-patients. In the second study from Qatar, Khan et al., 2010 reported the occurrence of resistant Gram-negative organisms in 63.1% of bacteremia patients with the following prevalence: ESBL-producing *p0ki9* (34%), followed by *Klebsiella* spp. (13.7%) and finally *Pseudomonas aeruginosa* (7.4%). A recent study on the characteristics of hospital-acquired and community-onset blood stream infections from Austria (Hoenigl et al., 2014), *E. coli* followed by *Staphylococcus aureus* were the most frequently isolated pathogens. This study has shown that, ESBL producing *E. coli* is an important cause of bloodstream infection presenting from both, the community and the hospital settings (40.9 and 35.9%, respectively). The overall incidence of *E. coli* ESBL bacteremia in this study is high, higher than the rate reported by Memom et al., 2009 and Kang et al., 2013**,** from the eastern region of Saudi Arabia (31%), and from Korea (33%), respectively. In another retrospective study from Taiwan [6], of 404 episodes of community-onset *E. coli* bacteremia, the frequency of ESBL producers was 4.7%. This rate is considerably lower than the rate found in our study. The differences in risk factors between CA and HA bacteremia was also identified. Patients with community acquired *E coli* bacteremia tend to be older than those with hospital-acquired infection and are mostly females. This finding is in agreement with a population-based incidence and comparative study (Williamson et al., 20113) of community-associated and healthcare-associated *E. coli* bloodstream infection from New Zealand, which revealed that, the incidence of *E. coli* bacteremia was highest in the under one year and over 56 year-old age groups. Previous population-based studies have documented the association of all bloodstream infections with old age (Hyle et al., 2005; Johnson et al., 2006). Uslan et al., 2007 identified an increased risk of *E. coli* bacteremia in females across all age ranges which contrasts the finding of an increase risk in only those above 55-year-old of age. In contrast, Kang et al., 2013 found that elderly males were at highest risk. The study showed that, solid tumors (19.2%), hematological malignancy (14.1%) and end-stage renal disease/post renal transplant (12.8%), are the most common underlying diseases and were identified as significant risk factors for health-care associated *E. coli* bacteremia.

Comparably, Kang et al., 2013 has found that, solid tumors, diabetes mellitus and liver diseases were the most common underlying diseases and predisposing factors for community onset bacteremia caused by ESBL producing *E. coli*. In a case controlled study from Spain of

96 patients with nosocomial blood stream infections (BSI) due to ESBL producing *E. coli*, the risk factors were found to be organ transplant, previous use of oxyimino-β-lactams, unknown BSI source and duration of hospital stay (Rodrguez-Bano et al., 2008). In addition, a population-based surveillance involving a total of 2368 episodes of *E. coli* bacteremia conducted in the Calgary Health Region has found that, the very young and the elderly were at highest risk for *E. coli* bacteremia. Additionally, dialysis, solid organ transplantation and neoplastic disease were identified to be the most important risk factors for acquiring *E. coli* bacteremia (Laupland et al., 2008). Among the 422 patients with neoplastic disease, 270 (64%) had malignant tumors, 96 (23%) had hematological malignancies, one patient had both a tumor and a hematological malignancy, and 55 (13%) patients had neoplastic disease in remission.

In another study by Chen et al., 2010, on the epidemiology of bloodstream infections in patients with haematological malignancies with and without neutropenia, the authors found that *E. coli* (12%) predominated the Gram-negative isolates causing BSI in neutropenic patients (Chen et al., 2010). Over the past two decades, treatment of *E. coli* bacteremia has become increasingly complicated by the emergence of antimicrobial-resistant *E. coli* strains, particularly those strains possessing acquired resistance genes encoding extended-spectrum beta-lactamases (ESBLs) and carbapenemases. Bloodstream infections with these resistant organisms have been associated with adverse clinical consequences and significant therapeutic challenge to treating physicians. The initiation of an antimicrobial agent is usually empirical, requiring knowledge of the likely pathogen and usual antimicrobial susceptibility patterns. This work has highlighted concerning trends towards greater antimicrobial resistance in *E. coli* causing bacteremia. However, in this study, both community-acquired and hospital-acquired *E. coli* isolates showed the highest sensitivity to carbepenem and amikacin followed by gentamicin and tazocin. The community-acquired isolates are more susceptible to amikacin, tazocin and ciprofloxacin than the hospital-acquired isolates. Similar to this study, Khanfar et al., 2009 found in his study, none of the strains isolated were resistant to carbapenems. In addition, recent studies showed that previous use of oxyimino-β-lactams or fluoroquinolones is a risk factor for ESBL-producing isolates in patients with bacteremia caused by E. *coli* (Quirante et al., 2011; Rodrguez-Bano et al., 2010). A retrospective cohort analysis (Rodriguez-Bano et al., 2006) has shown that, when compared with β-lactam/β-lactamase-inhibitor and carbapenem-based regimens, empirical therapy of ESBL-producing *E. coli* bacteremia with cephalosporins or fluoroquinolones were associated with a higher mortality rate. Resistance to drugs other than penicillins and cephalosporins was associated with increased mortality (Rodrguez-Bano et al., 2010). The mortality rate in this study (25%) is higher than previously (11.4 %) reported [6]. In a recent prospective cohort studies, carried out in hospitals from 31 countries that participated in the European Antimicrobial Resistance Surveillance System (EARSS), excess mortality associated with BSIs caused by MRSA and third-generation cephalosporin-resistant *E. coli* (G3CREC) is significant, and the prolongation of hospital stay imposes a considerable burden on health care systems.

These studies are essential to assist with the challenges of empiric antibiotic prescribed for those presenting to hospitals with suspected sepsis. As both community-acquired and hospital-acquired *E coli* isolates showed the highest sensitivity to imipenem, meropenem, in this study, it is believed in view of their excellent *in vitro* activity, carbapenems along with amikacin should be the initial empiric choice for serious life threatening infections caused by ESBL producing *Enterobacteriaceae*, with prompt de-escalation when culture and susceptibility results become available. In this study, there was no significant difference in the mortality rate between community and nosocomial bacteremia. Identification of risk factors for MDR organisms in patients presenting from the community with sepsis is necessary to help optimize patient outcomes and minimize the use of broad-spectrum antibiotics. To the authors' knowledge, this is the first report presenting data differentiating between nosocomial and community acquired ESBL *E. coli* bacteremia in Saudi Arabia. Continued surveillance, appropriate use of antibiotics and implementation of strict infection control measures are recommended to reduce ESBL frequency.

Conflict of interests

The authors declare that they have no conflict of interests.

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Abbreviations

CA, Community acquired; **HA,** hospital acquired; **ESBL,** extended spectrum beta lactamase; **ESRD,** end stage renal disease.

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