Original Article

Epidemiology, risk factors and antimicrobial resistance of Escherichia coli bacteremia

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Abstract

Background: Escherichia coli is a common causative of blood stream infection having potentials to produce significant morbidity and mortality. This organism also has the ability to develop resistance against antimicrobial agents. Knowing its epidemiology, risk factors and antimicrobial resistance patterns can help preventing and managing bacteremia caused by this organism.

Materials and methods: This was across sectional observational study carried out from February 2017 to February 2018 on 64 blood culture positive Escherichia coli infected patients admitted in Medicine inpatient of a medical college hospital. Age, sex, mode of acquisition of infection, history of prior empiric antibiotic treatment, duration of hospital stay, development of complication were observed and noted. Antibiotic susceptibility test for all isolates was performed by Kirby-Bauer disc diffusion method. Pre-designed semi-structured data collection from was used and collected data were analyzed manually and expressed in descriptive statistical terms.

Results: Of the 64 enrolled patients, 47(73.43%) were female. Average age of affection was 53.48±20.65 years and increased incidence rates (51.56%) was observed at age >60 years. Infection was community-acquired in 35.84% cases and urinary tract infection was the most frequent (46.3) risk factor. More than eighty seven percent of samples showed resistance to at least one antimicrobial agent and resistance to multiple drugs was associated with complications.

Conclusion: Escherichia coli bacteremia has high incidence rates for antimicrobial resistance and mortality. Continuous surveillance and antibiotic susceptibility pattern monitoring is essential to develop regional antibiotic therapy protocols

Key words: Escherichia coli, bacteremia, septicemia, blood stream infection, epidemiology, drug resistance

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Introduction:

Bacteremia in patients is a common but challenging condition in day-to-day medical practice.

Of all bloodstream infections, Escherichia coli bacteremia (ECB) is the commonest according to many epidemiological.[1, 2]Escherichia coli is a gram-negative rod and bacteremia by a gram-negative organism is hazardous because of its potential to induce shock by a grave systemic inflammatory response.[2,3] ECB can be responsible for morbidity in the form of shock (12.8%) and severe sepsis 19.6%, and mortality can be as high as 30%.[3] This, in fact, depicts an alarming situation. Escherichia coli and Klebsiellaare two organisms that can cause both urinary tract infection and bacteremia, can produce extended-spectrum beta-lactamase rendering their affliction difficult to treat due to the development of resistance to antibiotics.[3,4,5]

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Escherichia coli (E. coli) causing urinary tract sepsis may predispose patients to concomitant bacteremia and life-threatening consequences.

In recent years, the occurrence of community-acquired E. coli infection rates has increased remarkably.[6, 7] Moreover, the development of antimicrobial resistance (AMR) produces a worsened scenario. Many health care systems of the world reported ECB and its complications as a huge burden on the system. The increasing morbidity and mortality and healthcare costs ring a concerned alarm for clinicians and health policymakers. Whether acquired from the community or from the hospital, both cases of ECB are amenable to development AMR. Precise knowledge of the epidemiological facts and risk factors can help to generate effective intervention measures to minimize ECB-related health issues.[3,8]

Aims and objectives:

This study aimed to help generate preventive measures and effective empiric antibiotic therapy protocols for Escherichia coli bacteremia. The objective was to develop precise knowledge about the epidemiological facts, risk factors and bacterial drug resistance patterns in the medicine inpatient of a tertiary care hospital in a tropical country.

Materials and method

This cross-sectional observational study was carried out in the medicine inpatient of Sylhet Women's Medical College Hospital, Sylhet, from February 2017 to February 2018. Three hundred and eleven febrile patients were enrolled primarily for the study and blood samples were sent from all of them for culture sensitivity testing. Those yielding growth of *Escherichia coli* (E. coli) and giving consent (n=64) were finally allocated for data collection (Fig. 1). After detailed history and meticulous physical examination, routine laboratory tests including blood glucose level, and chest radiograph, plain X-ray kidney-ureter-bladder region and abdominal ultrasound were done in all patients. Other investigations were guided by individual patient's specific indications. Blood and urine samples for culture sensitivity testing were done in all the enrolled patients. . Age, sex, mode of acquisition of infection, history of prior empiric antibiotic treatment, duration of hospital stay, and development of complication were observed and noted.

Blood sample (5 ml) collected under strict aseptic measures, from the antecubital vein was instantly poured into blood culture bottles containing 40 ml Brain Heart Infusion (BHI) broth (CONDA Spain) with 0.025% of SPS as an anticoagulant; and sent to the microbiology laboratory. There it was incubated at 37^0C for up to 4 days and was examined daily for any bacterial growth. Bacterial growth was indicated by the presence of turbidity in the bottle. It was then sub-cultured on solid culture media, viz, blood agar, Mac Conkey agar, and chocolate agar. The growth of Escherichia coli was marked by the presence of bright pink colonies in Mac Conkey agar. It was confirmed by the demonstration of motility at wet film microscopy along with the presence of gram-negative rods in Gram-stained specimens during conventional microscopy. No bacterial growth on sub-culture for up to 120 hours (five days) was considered 'culture negative'.

Antibiotic susceptibility test of each isolate was performed by NCCLS recommended Kirby-Bauer disc diffusion method. The antibiotic incorporated plates were incubated at 37^0C and the zone of inhibition around the antibiotic was measured after 18 hours and within 24 hours of incubation. The used antibiotics were Amoxycillin, Amoxycillin-Clavulanic acid, Co-trimoxazole, Ciprofloxacin, Levofloxacin, Moxifloxacin, Azithromycin, Cefixime, Ceftriaxone, Cefuroxime, Gentamicin, Amikacin, Nitrofurantoin, Meropenem, Imipenem and Piperacillin- Tazobactum. The

microbiological culture was done in the same laboratory to maintain uniformity. The resistance pattern of Escherichia coli was observed and preserved in the previously mentioned data collection sheet. No growth in sub-culture for up to 120 hours (five days) was regarded as culture negative.

Data collection and analysis:

Patient's information, findings, and blood and urine culture observations were recorded in a pre-designed semi-structured data collection form. Data were analyzed manually and results were expressed in descriptive statistical terms.

Ethical clearance

Informed written consent was taken from every patient before final enrollment and data collection. Approval of the protocol was obtained from the Institutional Ethical Committee of the institution.

Operational definitions

E.coli bacteremia (ECB): Febrile patient with blood culture yielding growth of *Escherichia coli*.

Community acquired bacteremia: Infection contracted from outside a hospital or is diagnosed within 48 hours of admission without any previous health care encounter.

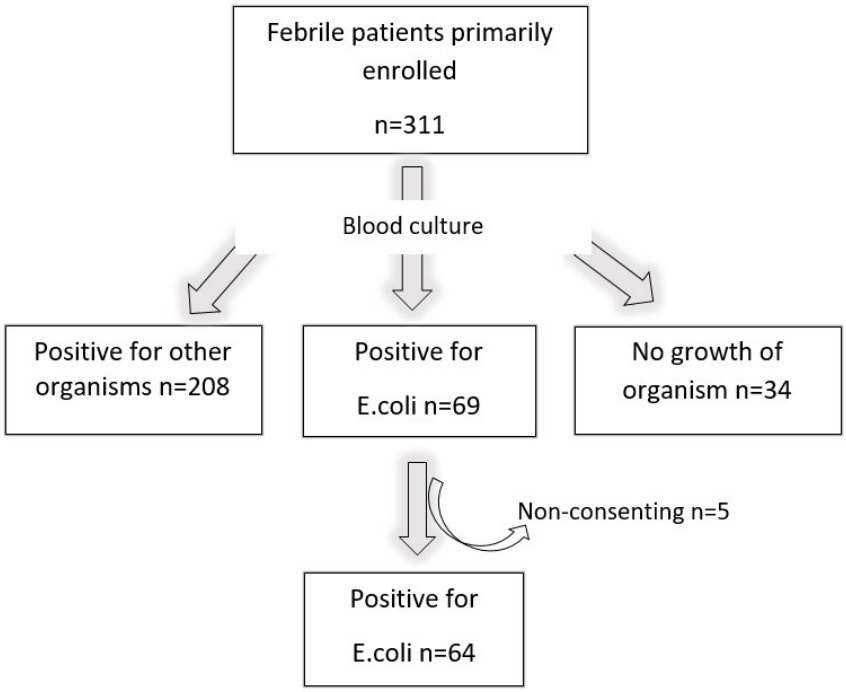
Hospital acquired bacteremia: infection contracted from the hospital and diagnosed after 48 hours of admission.

Susceptible organism: E. coli strains killed by a particular antimicrobial agent during laboratory test.

Non-susceptible/resistant organism: E. coli strains not killed by a particular antimicrobial agent during laboratory test.

Multi-drug resistant E.coli: E. coli strains not killed by three or more antimicrobial agents during the laboratory test.

Fig. 1: Enrollment of study subjects



Results

In this cross-sectional study, the descriptive epidemiology, risk factors, and drug resistance pattern of bloodstream *Escherichia coli* infection were observed over a period of twelve months. Table-1 shows the major epidemiological findings of the study. Of the enrolled 64 patients, 47 (73.43%) were female and 33 (51.56%) were more than sixty years old (Fig 2). High occurrence rates were observed in young (18-39 years) and older (60-89 years) age groups of patients, around 36% and 47% respectively. Fifty-six (35.84%) patients acquired infection from the community, 07(10.93%) from the hospital, and in one patient mode of infection was could not be ascertained. History of antibiotic therapy within one year prior admission by either self-prescription or by a general practitioner was available in 41(64.0%) of the patients and inappropriate empiric therapy was associated with non-susceptible ECB in 20.31% cases (relative risk 1.45). The average duration of hospital stay among non-complicated ECB cases was 5 days whereas among the patients with infection by non-susceptible (≥1, <3 drugs) strains, or patients complicated by severe sepsis or shock due to infection with multidrug-resistant (≥3) strains, having an average duration of stay, 10 and 14 days respectively. Only one of the complicated patients died due to multi-organ failure.

Risk stratification of ECB patients showed that 29 (45.3%) of the blood culture positive patients also had concomitant positive urine cultures and 68.9% of them were females (Fig. 3). Diabetes was a common risk factor; 21(38.2%) patients were diabetic with poor glycemic control (average HbA1C level 11%). An indwelling catheter was a probable source of infection in 05 (7.81%) and all of them acquired ECB in hospital. Among the patients, 12(18.75%) had a urogenital abnormality, of them 09 were males with an enlarged prostate, and 03 were females with second or third-degree urogenital prolapse.

In the study, E. coli causing ECB, showed more than 90% susceptibility to Imipenem, Meropenem, Amikacin, Pieracillin-Tazobacaum and Moxifloxacin (Table-2). Moderate susceptibility was demonstrated with Ceftriaxone (88.9%), Levofloxacin (86.9%), Cefuroxime (80.3%), Cefixime (77.4%), Amoxycillin-Clavulanic acid (71.4%), Ciprofloxacin (69.3%), and Gentamicin (68.2%). Relatively low susceptibility rates were observed with a once-widely-used antimicrobial agent Cotrimoxazole (37.0%) and also with, Linezolid (33.9%), Amoxycillin (38.7%) Azithromycin (44.2%) and Nitrofurantoin (58.0%).The Carbapenems, though they are β-lactam antibiotics offered excellent results in the index study showing 100% susceptibility. As for the non-susceptibility rates E.coli, 15.6% of the samples showed resistance to at least one antimicrobial agent; another 12.5% showed no resistance to any of the test drugs. However, it was alarming to find out 28.1% of the samples being resistant to multiple drugs from different antimicrobial classes. Non-susceptibility rates to one or more drugs from only cephalosporins, quinolones, or aminoglycosides were 12.5%, 15.6%, and 15.6% respectively.

Table 1: Epidemiological parameters of E. coli bacteremia

Epidemiological parameters		Number and percentage	Additional remarks
Age in years	18-39 years 40- 59 years 60-89 years 90+ years	23 (35.93%) 07 (10.93%) 30 (46.87%) 04 (6.25%)	Average age of occurrence 53.48±20.65 Increased incidence in old age
Sex	Males Females	17 (26.56%) 47 (73.44%)	Female preponderance
Mode of getting infected	Community- acquired Hospital- acquired Undetermined	56(35.84%) 07(10.93%) 01(1.56%)	Commonly acquired from community
History of empiric antibiotics	Within last 1 year No empiric antibiotics No history available	41 (64.0%) 20 (31.2%) 03 (4.68%)	Previous empiric antibiotics were related to multidrug resistance (RR=1.45)*
The average duration of hospital day	Susceptible organism Non-susceptible organism Multi-drug resistant organism	05±1.45 days 10±0.31 days 18±2.71 days	Longer duration of stay with non-susceptible and multi-drug resistant organism
Outcome	Uneventful course Severe sepsis and/shock Mortality	59 (92.1%) 04 (6.3%) 01 (1.6%)	Severe sepsis, shock were found among multi- drug resistant cases*
*Described in the text			

Fig. 2- Age distribution among patients with ECB

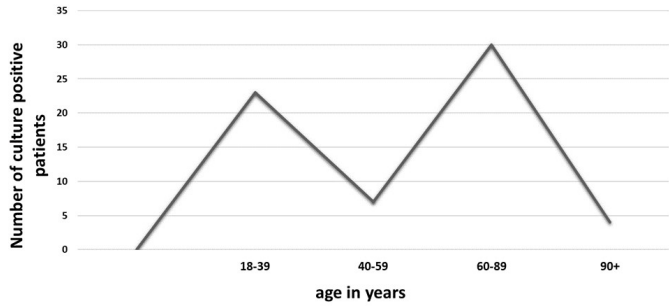


Fig.3- Risk factors of E. coli bacteremia

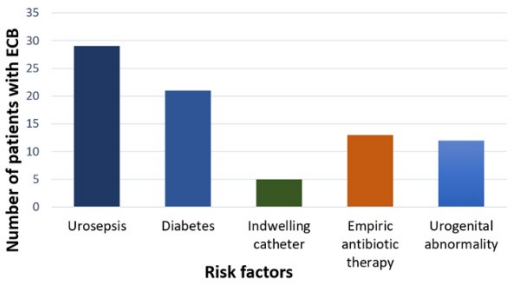
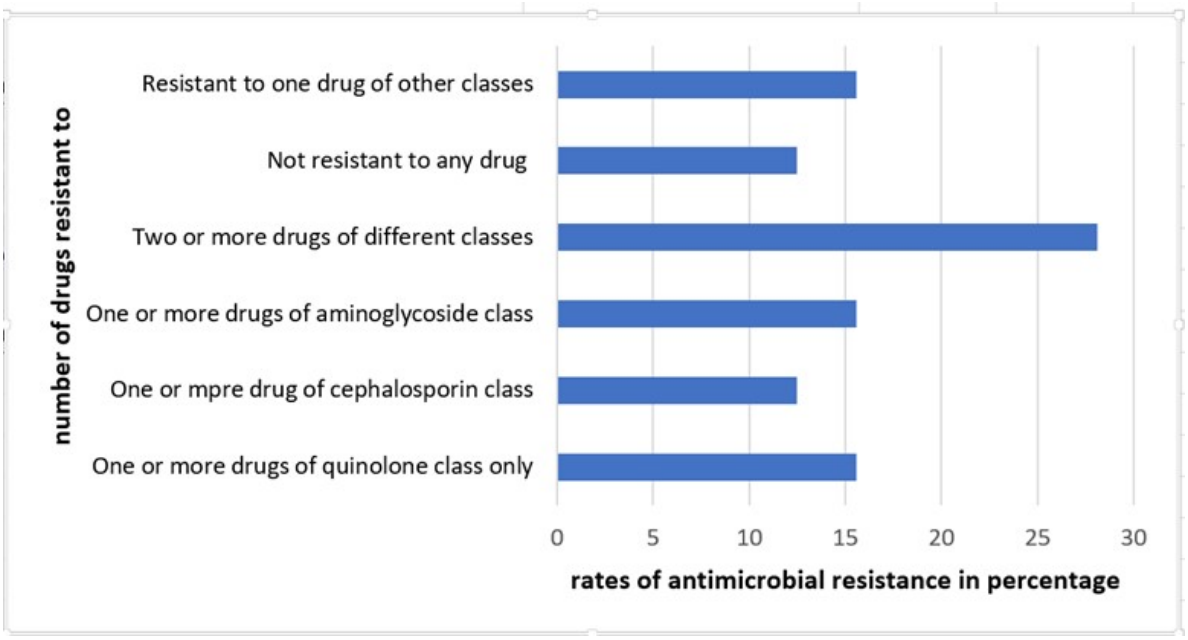


Table 2: Antimicrobial susceptibility and non-susceptibility in ECB

Name of antimicrobial agent	Susceptible number(%)	Non-susceptible number (%)	Sensitivity not seen number
Cotrimoxazole	23(37.0)	39(62.9)	2
Amoxycillin	24(38.7)	38(61.2)	2
Amoxycillin-Clavulinic acid	45(71.4)	18(28.7)	1
Ciprofloxacin	43(69.3)	19(30.7)	2
Levofloxacin	53(86.9)	08(13.1)	3
Moxifloxacin	56(90.0)	06(9.7	2
Cefixime	48(77.4)	14(22.5)	2
Cefuroxime	49(80.3)	12(19.6)	3
Ceftriaxone	56(88.9)	07(11.1)	1
Imipenem	63(100)	0(0)	1
Meropenem	64(100)	0(0)	0
Gentamicin	43(68.2)	20(31.7)	1
Amikacin	59(93.7)	04(6.3)	1
Piperacillin-Tazobactum	60(100)	0(0)	4
Azithromicin	27(44.2)	34(55.7)	3
Linezolid	21(33.9)	41(66.1)	2
Nitrofurantoin	36(58.0)	26(41.9)	2

Fig 4: Antimicrobial resistance pattern



Discussion:

Escherichia coli (E. coli) is a gram-negative facultative anaerobic rod, within the Enterobacteriaceae family, prevalent throughout the globe.[2,9] It is a recognized cause of neonatal sepsis and is also a major cause of bloodstream infection (BSI) among adults.[10,11]In many parts of the world, especially in the developed countries, Escherichia coli bacteremia (ECB) is the commonest form of BSI. It confers potentials to cause significant morbidity and mortality.[12]Staphylococcus aureus and Streptococcus pneumoniae are the next common organisms causing BSI. Due to unclear pathophysiological mechanisms, gram-negative bacteremia produces more severe forms of systemic inflammatory response than gram-positive bacteremia, for which the former deserves greater attention and intervention.[13]

The overall mortality rates from bloodstream infection is 17.5%.[12,14]The incidence rates of ECB was found to be around 50% in western studies.[9,12,15] The overall incidence of ECB was found to increase with age which may be attributed to weakened body immunity, co-morbid conditions and underlying malignancy. In the present study, authors observed the highest incidence rates among patients in the 60-89 age group (46.87%) and the lowest (10.93%) in the middle age group.[16,17]

Females are more prone to develop urinary tract infections by E. coli due to anatomical and behavioral reasons. Around half of ECB is the sequel of urosepsis with the same organism. As a result, a female preponderance of ECB is observed in most epidemiological studies.[18]Structural urogenital abnormalities in both genders are associated with increased incidence rates.[6,18,19,20] In the study, males with enlarged prostate and females with urogenital prolapse had both urosepsis and ECB. The overall incidence rates of urinary tract infection in this study was 45.3%. And 38.2% of the patients had diabetes mellitus. This metabolic condition induces compromised immune systems, and thus renders patients vulnerable to ECB and other infections as observed in the study. [21,22]

Development of antimicrobial resistance (AMR) predominantly by β-lactamases production renders this organism capable of surviving against a wide range of antibiotics. This factor, combined with the complications arising from ECB has made treatment of the condition challenging. Mortality from ECB is significantly reduced with definitive antibiotics rather than empiric therapy even with carbapenems.[23]Injudicious and inappropriate antibiotic prescribing is a major cause of AMR. The practice of empiric antibiotic administration, though warranted in different critical clinical scenarios, can increase incidence rates of multi-drug resistance. The index study demonstrates a relative risk of 1.45, for acquiring infection with multi-drug resistant strains among patients with a history of empiric antibiotic therapy within the previous year.[12,13,23]

About 75% of ECB is community-acquired, and hospital-acquired infections are attributed to cross infectivity among patients, debility due to other medical conditions, indwelling urinary catheter, and contaminated environment.[24] Seven (10.93%) of the enrolled patients in this study had hospital-acquired ECB, were non-susceptible to multiple antimicrobials and 4 of them developed shock and required treatment in the intensive care and one died. But the mortality rates due to ECB complications in other studies are found to be 5%-30%.[25]This study failed to provide objective results on prognosis and mortality-morbidity indices. Mean Charlson Comorbidity Index (CCI) is a popularly used and effective tool for assessing and guiding interventions for patients during a hospital stay, has been worked out in some studies.[4]

Extended Spectrum β-lactamases (ESBL), induce AMR in E. coli and Klebsiella especially against third-generation cephalosporins which may influence morbidity and mortality. Acquisition of infection through the pulmonary portal was an independent risk factor for death in one study. Other factors related to increased mortality were the presence of iha_17 virulence gene, the STc88, healthcare-associated infections, and a high CCI.[13,23]

Effective vaccination against E.coli, if it were available could prevent and minimize to a great extent all the hazards related to ECB. Considering all these issues, prevention through addressing risk factors still remains in focus.[26] The overall prevalence of bacteremia 19.4% and ECB incidence rates of 21% among culture positive blood samples were found in a separate laboratory based study in the same institute done a couple of years later. However, 11.3% and 17% resistance to Meropenem and Piperacillin-Tazobactum respectively were observed in thisstudy. This also implies anincreasing and worsening burden of ECB on health systems.[27]
The index study showed a strikingly lower (1.5%) mortality rates than other studies. Apart from this, the authors presume that other findings of epidemiological parameters and risk factors may not have been revealing to the full extent for several reasons. Firstly, the sample size was small; secondly, patients with ECB admitted into other specialties were excluded; and thirdly, this study did not enroll the very critically ill ECB patients primarily admitted into intensive care units.

Conclusion

Escherichia coli bacteremia is a common but potentially fatal form of bloodstream infection. Knowing its epidemiological characteristics, risk factors, and antimicrobial resistance pattern will help to advocate beneficial preventive measures and also to generate cost-effective intervention protocols. This is a small-scale study but can serve as a useful template for designing larger research works.

Limitations: The study includes patients from Medicine inpatient only and population size is small. Bacteriological culture was not done by modern automated machines. Objective measurement of comorbidity of the patients during hospital stay was not done. Bacterial genetics and molecular risk factors were not assessed.

Conflict of interest: It is a self-funded study and the authors declare no conflict of interest.

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