# Organisms causing community-acquired bloodstream infection in medical department: A single centre retrospective observational study

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**ABSTRACT**

**Introduction: Community acquired bloodstream infection (CA-BSI) is positive blood culture obtained within 48 hours of hospital admission. Bloodstream infections need to be treated with antibiotics. Inappropriate choice of antibiotics will lead to antimicrobial resistance. This is an observational retrospective study to look at the antimicrobial resistance of organisms causing bloodstream infections in patients admitted to the medical wards in our centre. The aim of the study is to determine the appropriate choice of empirical antibiotics for suspected CA-BSI in our hospital.**

**Materials and Methods: All patients admitted to medical wards with blood stream infection during the period January 2021 to June 2021 were enrolled. Identification of organisms and antimicrobial susceptibility testing were obtained. Information regarding the severity of the bacteremia was collected by assessing if the patient needed inotropes, mechanical ventilation or renal replacement therapy. Data on comorbidities which were the presence of end-stage renal failure, diabetic mellitus and immunosuppression were collected.**

**Results: Total of 269 cases were screened. Out of these 104 communities acquired cases were included. The pathogens frequently isolated were gram negative organisms most commonly *Escherichia coli* (43%) and Klebsiella species (30%). *Staphylococcus aureus* accounts for the majority of gram-positive organisms. Only two out of 20 *Staphylococcus aureus* were methicillin resistant. *Bulkholderia pseudomallei* accounts for 7.8% cases. All *Burkholderia pseudomallei* isolates were sensitive to cotrimoxazole. *Escherichia coli* (46%) isolates demonstrated a higher resistance pattern to Augmentin compared to *klebsiella species* (17.4%). The overall mortality rate was 22%, with higher rates for those critically ill (39%). Patients with Enterobacteriaceae infection showed no difference in outcome between the groups of patients according to sensitivity to Augmentin and cefotaxime. These groups of patients who were critically ill did not demonstrate any significant difference in terms of resistance pattern to Augmentin (p = 0.3) and cefotaxime (p = 0.7). Patients who are aged 65 or older have a significantly more resistant pattern to Augmentin and cefotaxime.**

**Conclusion: Antibiogram serves as a guide for clinicians to choose appropriate choices of antibiotics based on local data. Empirical antibiotics of choice for patients with sepsis should be narrow-spectrum beta lactam/beta lactamase inhibitors. Broad spectrum beta lactam/beta lactamase inhibitors such as piperacillin tazobactam should be reserved for patients who are critically ill and elderly patients over 65 years. The antibiotics should be deescalated once the organisms and sensitivity of the antibiotics are known.**

## INTRODUCTION

Bloodstream infections are a common cause of morbidity and mortality in many countries in the world. The mortality rate ranges from 15.2% up to 40.8% depending on severity and clinical risk factors.[1] Bloodstream infections can be subdivided based on the timing of presentation. Based on the Centre for Disease Control and Prevention (CDC) definition, community acquired bloodstream infection (CA-BSI) is positive blood culture obtained within 48 hours of hospital admission and hospital acquired bloodstream infection (HA-BSI) is positive blood culture obtained after 48 hours of admission. It is important to differentiate CA-BSI from HA-BSI as the causative organisms and sensitivity of the bacterias are different. Bacteria such as *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Staphylococcus aureus* frequently cause bloodstream infections. Bloodstream infections are treated with antibiotics. However, inappropriate use of antibiotics has been shown to cause antimicrobial resistance.

Antimicrobial resistance is a global problem because it leads to increased morbidity and mortality.[2] Antimicrobial resistance can be attributed to many factors. Michael et al.,[3] divided these causes into microbiological and human causes.[3] Microbiological causes include the ability to acquire resistance either via mutations or plasmids. Human causes include a large and growing population, and overuse of antimicrobials either due to prescription in a clinical setting or in agriculture.[6,7] Antimicrobial overprescription may occur when the antibiotic is used in an empirical setting where tests to identify the causative organism to allow de-escalation is not done. Failure to identify the causative organisms may also lead to treatment failure necessitating more visits or a

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prolonged stay. Antibiotic overprescription may also occur when antibiotics are prescribed in conditions where they are not needed.[8,9] Multiple studies have shown that increasing antibiotic usage will increase the resistance of bacteria in the environment.[8,9]

The causative organisms in a patient presenting with sepsis will not be known until 24 to 72 hours after cultures are taken.[10] During this time, clinicians usually initiate empirical antibiotics. The selection of empirical antibiotics is guided by clinical guidelines, antibiograms and previous microbiological results of the patient or the physician's experience. Antibiograms are created from microbiological data obtained from lab results.[11] However, the disadvantage is that the cultures are not stratified into community or hospital-acquired infections. Many organisms causing community-acquired bloodstream infections are more sensitive to narrow-spectrum antibiotics compared to hospital-acquired organisms. This may give a false appearance that empirical antibiotics selected to treat community-acquired infections appear to have a higher-than-expected resistance rate. Another limitation of this method is these calculations are made based on the culture sent rather than based on individual patients. The epidemiology of BSI and antimicrobial resistance patterns are always evolving and vary between different institutions. As such, we conducted an observational retrospective study to look at the antimicrobial resistance of organisms causing community-acquired bloodstream infections in patients admitted to the medical wards in our hospital. The aim of the study is to determine the appropriate choice of empirical antibiotics for suspected community-acquired bloodstream infections in our hospital.

## MATERIALS AND METHODS

This study was performed at Hospital Tuanku Ja'afar Seremban, a tertiary referral and teaching hospital in Negeri Sembilan. All patients admitted to medical wards in our hospital with bloodstream infections from January 2021 to June 2021 were enrolled. Exclusion criteria include patients who had positive blood cultures taken after 48 hours of admission, blood cultures growing contaminant, fungal organisms, blood cultures taken within 30 days of previous admission or the source of infection was a catheter-related bloodstream infection. Catheter-related bloodstream infections were excluded because they were more likely due to hospital-acquired organisms.

All peripheral blood culture results were collected from the microbiology laboratory using the WHONET 2022 database (expanded version of WHONET 5.6). Information about the patient identifiers, date of blood culture collection, identification of organisms, and antimicrobial susceptibility testing were obtained from this system. Organisms which were skin colonisers or yeast were removed. Reports were matched to their individual cases. Each case was assessed to determine if the bloodstream infection was community acquired. Cases that were determined to be community acquired were included in the analysis. Information regarding the severity of the bacteremia was collected by assessing if the patient needed inotropes, mechanical ventilation, or renal replacement therapy. Although the severity of bacteremia is usually assessed with more robust scores such as SOFA scores, collecting the details needed to assess these scorings were deemed difficult for the investigating team. Other data that were collected included the presence of diabetic mellitus and immunosuppression.

For this study, blood culture bottles (BACTEC Plus Aerobic/F bottles, BACTEC Anaerobic Lytic/F) were incubated in BACTEC FX system (Becton Dickinson Microbiology System, BMS Diagnostics), and flagged positive blood culture bottles were gram-stained and cultured onto blood agar, Mac Conkey agar, chocolate agar, and Sabouraud Dextrose agar. Preliminary antimicrobial susceptibility testing was done according to the microbiology laboratory standard operating protocol. All culture plates were incubated for 16-18 hours. Colony of organisms that were isolated were identified by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) Biotyper platform (Bruker Daltonics MALDI Biotyper, BMS DIagnostics). Final antimicrobial susceptibility testing was performed and interpreted according to the Clinical and Laboratory Standard Institute (CLSI) guidelines (CLSI M100 32nd Edition 2022, CLSI M45 3rd Edition 2016, CLSI M24-A2 2011) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2022 guideline. Immunocompromised status is defined as patients with haematological malignancy, human immunodeficiency virus with a CD4 less than 200, patients receiving chemotherapy within the last 30 days and patients taking immunosuppressants.

The protocol was approved by the human research ethics committee of the National Medical Research Register (NMRR ID-23-00783-TRL). The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Due to the retrospective observation nature of the study, the MREC waived the need for informed consent. Data analysis was done using the Rstudio version (2023.09.1+494). Continuous variables will be expressed as mean and standard deviation (SD) unless otherwise stated. Binary variables will be expressed as percentages. Inferential analysis of categorical data will use Chi-square or Fisher's exact test. A value of $p < 0.05$ is considered statistically significant.

## RESULTS

During the study period from January 2021 to June 2021, a total of 269 cases of bloodstream infections were screened. Out of these, 99 (36.8%) were considered clinically significant community-acquired organisms, 143 (53.1%) were hospital-acquired organisms, 5 (1.9%) were healthcare-associated bloodstream infections and the rest were classified as contaminants.

### *Patient Characteristics*

The demographics, severity, and comorbidities of patients with bloodstream infections are summarised in Table I. There were almost equal proportions of male and female patients in our study. Of note, 68 patients (69%) were diabetic. However only a small proportion of patients were immunocompromised. About 17.2% of these patients were critically ill requiring inotropic support, mechanical ventilation, and/or renal replacement therapy.

**Table I: Characteristics of patients with community acquired bacteremia at medical wards Hospital Tuanku Ja'afar Seremban, January to June 2021**

| Variables | Patients no. (%) |
|---|---|
| Age, year (mean,SD) | |
| Male | 62.2 ± 21.0 |
| Female | 64.3 ± 16.7 |
| Sex | |
| Male | 53 (54%) |
| Female | 46 (46%) |
| Comorbidities | |
| Diabetes mellitus | 68 (69%) |
| Immunocompromised | 7 (7.1%) |
| Critically ill | |
| Mechanical ventilation | 12 (12%) |
| Renal replacement therapy | 2 (2.0%) |
| Inotropic support | 15 (15%) |

**Table II: Organisms isolated from the blood of patients at medical wards Hospital Tuanku Ja'afar Seremban, January to June 2022**

| Organism | Total number (%) |
|---|---|
| *Escherichia coli* | 42 (38) |
| *Klebsiella sp.* | 22 (20) |
| *Staphylococcus aureus* | 16 (15) |
| *Burkholderia pseudomallei* | 9 (8) |
| *Streptococcus sp.* | 7 (6) |
| Others | 14 (13) |

**Table III : Outcome according to patient characteristics**

| Characteristics | Survivor | Non survivor | p-value |
|---|---|---|---|
| Sex | | | 0.3 |
| Male | 37 (50%) | 13 (62%) | |
| Female | 37 (50%) | 8 (38%) | |
| Age | 61 ± 18 | 68 ± 20 | 0.075 |
| Critically Ill | 10 (14%) | 7 (33%) | 0.052 |
| Comorbids | | | |
| Diabetes mellitus | 54 (73%) | 12 (57%) | 0.2 |
| Immunocompromised state | 5 (6.8%) | 2 (9.5%) | 0.6 |

**Table IV : Characteristics of Enterobacteriaceae bacteremia according to sensitivity of antibiotics**

| Characteristics | Augmentin | | p value |
|---|---|---|---|
| | Sensitive | Resistant | |
| Age | | | |
| < 65 years old | 23 (88%) | 3 (12%) | 0.006 |
| > 65 years old | 19 (56%) | 15 (44%) | |
| Gender | | | |
| Male | 13 (54%) | 11 (46%) | 0.029 |
| Female | 29 (81%) | 7 (19%) | |
| Diabetes mellitus | 31 (76%) | 10 (24%) | 0.2 |
| Critically Ill | 8 (89%) | 1 (11%) | 0.3 |
| Outcome | | | |
| Alive | 34 (71%) | 14 (29%) | 0.3 |
| Dead | 8 (80%) | 2 (20%) | |

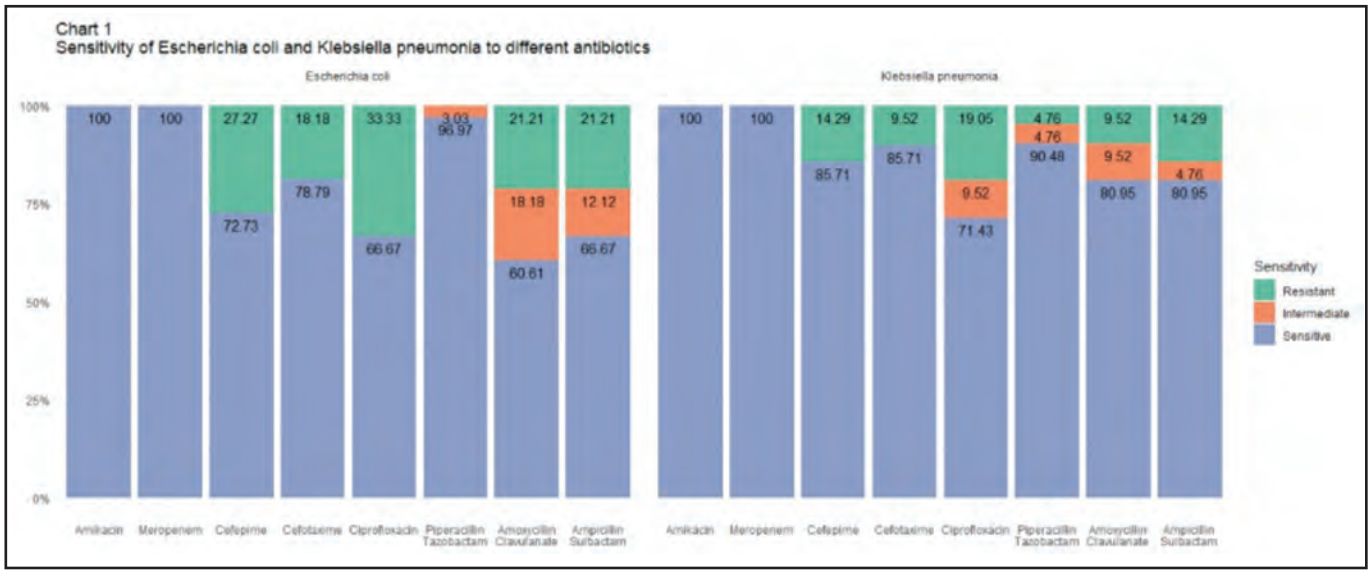


**Fig. 1:**

***Blood Culture Isolates***

Gram-negative organisms were isolated in 79% of blood cultures. The pathogens most commonly found were *Escherichia coli* and *Klebsiella species*, which accounted for 48% and 25% of gram-negative episodes respectively. Out of 21% of episodes caused by gram-positive microorganisms, two-thirds were due to *Staphylococcus aureus*. Of note, *Burkholderia pseudomallei*, the causative agent of melioidosis, was isolated in 8.2% of community-acquired bacteremias. 89% of the patients with *Burkholderia pseudomallei* bacteremia have a history of diabetes mellitus. Other organisms isolated in smaller numbers were *Streptococcus sp* (6.4%), *Salmonella sp* (3.6%), *Pseudomonas aeruginosa* (3.6%), *Enterococcus sp* (1.8%), *Enterobacter sp* (1.8%) and *Proteus sp* (1.8%).

***Antimicrobial Susceptibility Patterns***

Antibiotic sensitivity patterns of the four main organisms isolated were analysed. Antibiotic disk diffusion susceptibility testing of *Escherichia coli* isolates demonstrated that 39.4% were resistant to Augmentin, 18.2% resistant to cefotaxime and 33.3% resistant to ciprofloxacin, while 97% were sensitive to piperacillin tazobactam and none were resistant to meropenem. Comparatively, Klebsiella isolates demonstrated a less resistant pattern, 19% were resistant to Augmentin, 9.5% were resistant to cefotaxime and 28.6% were resistant to ciprofloxacin. Only 2 out of 20 *Staphylococcus aureus* were methicillin-resistant. All *Burkholderia pseudomallei* isolates were sensitive to cotrimoxazole.

***Outcome***

Of 99 patients with clinically significant community acquired bacteremia, the mortality rate is 21% (21), excluding a small proportion of 4.0% (4) unknown outcome. Critically ill patients did not demonstrate any significant difference in mortality rate. There are also no statistical differences between genders, comorbidities, and age predisposition for mortality. We did a further analysis looking into the patient groups with *Enterobacteriaceae* infection. No difference in outcome was seen between the groups of patients according to sensitivity to Augmentin and cefotaxime. The patients with *Enterobacteriaceae bacteremia* who were critically ill did not demonstrate any significant difference in terms of resistance pattern to Augmentin ($p = 0.3$) and cefotaxime ($p = 0.7$). However, our analysis has shown that patients who are aged above 65 years have significantly more resistance to Augmentin and cefotaxime.

## DISCUSSION

Hospital Tuanku Ja'afar Seremban(HTJS) is a 968 bedded hospital. Medical department makes up about 28% of these beds. It is located in a tropical environment in an upper middle-income nation. In our sample, the majority of bloodstream infections are caused by gram-negative organisms. The two most common organisms that were isolated are *Escherichia coli* and *Klebsiella pneumonia*. These organisms are expected to be common in our setting due to the high prevalence of diabetes mellitus.[12] In our data, female patients were more likely to develop *E. coli* bacteremia. *E. coli* is a more common pathogen in females because they are more prone to urinary tract infections.

Comparing our findings with other studies shows some interesting differences. Laos, a country from South East Asia showed that the most commonly cultured organism was Salmonella typhi.[13] The resistance rates of *E.coli* and *K. pneumonia* to ceftriaxone were 8% and 0% respectively. This was lower than the rates we encountered in our centre. Another study by Kanoksil et al.,[14] which was done in northeast Thailand showed some different findings. Here the most common organisms were *Escherichia coli* (23.1%), *Burkholderia pseudomallei* (19.3%), and *Staphylococcus aureus* (8.2%). This study was conducted from 2004 to 2010 and showed an increase in the proportion of extended spectrum beta-lactamases (ESBL) producing *E. coli* and *Klebsiella pneumoniae* over time.

In our study, resistance to narrower-spectrum antibiotics was predominant in patients above 65 years of age. Evidence for

this trend has been demonstrated by Pop-Vicas et al.[15] They have demonstrated that there is a 16-fold increase in the rates of resistant organisms for community-acquired bloodstream infections in elderly patients. The elderly are more likely to be from long-term care facilities. Hujer et al have shown that resistant organisms are more likely to colonize patients from these facilities.[16] Causes for the increase in resistant organisms colonization in this population are the presence of devices, frequent admissions, repeated courses of antibiotics, and the spread of resistant organisms from one patient to another. However, our findings show no difference in the resistance patterns and severity of the presentation.

Our study does not show an association between resistance patterns of Enterobacteriaceae and mortality. We found that there is no significant association between patients who presented with more severe disease and mortality, but this could be due to very small numbers in the subset. Older age was associated with higher mortality in our study. Similar findings were demonstrated by de Lastours et al who studied E. coli bacteremia.[17] These findings are important as they can determine the choice of empirical antibiotics for a centre.

Hence, we recommend that empirical antibiotics for patients with sepsis who are not critically ill, narrow-spectrum beta-lactam/beta-lactamase inhibitors should be selected. Broad-spectrum beta-lactam/beta-lactamase inhibitors such as piperacillin tazobactam should be selected for patients who are elderly above 65 years of age. We should consider broad spectrum antibiotics for patients who are critically ill as they tend to deteriorate rapidly. Our centre avoids the use of third-generation cephalosporins as empirical therapy except for central nervous system infections. Third-generation cephalosporins over-usage has been shown to increase rates of extended-spectrum beta-lactamase-producing organisms.[9] Third-generation cephalosporins are useful in the setting of drug-resistant *Salmonella typhi*. However, from our data, this organism is not encountered. Once the organisms and sensitivity has been identified, the antibiotics should be de-escalated to the narrowest possible spectrum.

The limitations of this study include firstly, the complete physical case notes were not reviewed. This was done to reduce the manpower needed and save time. Rather the abbreviated electronic discharge summary was reviewed. This may have caused some risk factors of resistant organisms to be underestimated, such as residence in long-term care facilities. This may explain why older patients were more likely to have resistance than younger patients. We had a lack of information on proper cultures and imaging to support clinical diagnosis for the study population. Hence, we could not be able to analyse the relationship between antibiotic sensitivity and clinical diagnosis further. The small sample size caused the lower power when subgroups were analysed. This study is the first study in Malaysia to review the antibiogram of community-acquired bloodstream infections.

## CONCLUSION

Antibiogram serves as a guide for clinicians to choose appropriate choices of antibiotics based on local data. Empirical antibiotics of choice for patients with sepsis should be narrow-spectrum beta lactam/beta lactamase inhibitors. Broader spectrum antibiotics should be selected for older or patients in critically ill. Further studies will be required to assess the relationship between antibiotic sensitivity, clinical diagnosis, and clinical outcomes.

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