Investigation of Gram-Negative Bacilli Bacteraemia in a Tertiary Hospital in Nigeria: Epidemiology and Antimicrobial Susceptibility Pattern

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Abstract
Background: The re-emergence of gram-negative bacilli (GNB) as the predominant cause of bacteraemia remains a major concern, given the increasing trend of antimicrobial resistance among this group of organisms. Prompt and effective empirical antibiotic treatment is vital for preventing adverse outcomes; therefore, a good knowledge of the local bacteria profile is required.

Objective: This study was designed to aid the establishment of local antibiogram and empirical treatment for GNB bacteraemia in patients referred to the University of Port Harcourt Teaching Hospital (UPTH), Nigeria.

Materials and Methods: A total of 230 blood samples were obtained from inpatients in different units/departments from December 2017 to November 2018. The blood cultures were processed using BACTEC 9060 automated blood culture system, and the isolates were identified using MICROBACT 12E identification kits (Oxoid, UK) at the microbiology laboratory of UPTH. Susceptibility and resistance tests were done according to CLSI guidelines. Relevant information was obtained from the laboratory request forms and patients’ clinical files.

Results: The prevalence of GNB in the study was 28.9% (71/246). The distribution of GNB bacteraemia was as follows: surgical unit (26.8%), special care baby unit (SCBU) (23.9%), intensive care unit (ICU) (21.1%), and paediatric ward (8.5%). The most common source of bacteraemia was pneumonia (35.2%) followed by purpural sepsis (15.1%) and urinary tract infection (UTI) (15.1%). Klebsiella pneumoniae was the most frequently isolated gram-negative bacillus (26.6%). The overall resistance rate of extended spectrum lactamase producing Enterobacteriaceae (ESBL) producers, carbapenemase producers, and multi-drug resistant (MDR) organisms was 32.4%, with Acinetobacter baumannii (50%) and Pseudomonas aeruginosa (27.3%) exhibiting the highest level of resistance to carbapenems.

Conclusion: This study showed a high MDR rate among GNB causing bacteraemia in patients at UPTH. An urgent review of the current antimicrobial prescription policy and infection control measures is recommended.

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Background
Bloodstream infections (BSI) remain a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive care.¹ Data over the past decade showed a higher prevalence of gram-positive bacteria as the predominant causative agent of nosocomial bacteraemia.² However, recent reports have shown a reversal in the trend of bacteria spectrum and antibiotic susceptibility pattern of organisms causing bacteraemia with re-emergence of gram-negative bacteria predominance.³ It is estimated that gram-negative bacilli (GNB) are the cause of approximately a quarter to half of all BSIs, with Escherichia coli and Klebsiella pneumoniae being the most predominant.³ Two broad categories of GNB are responsible for Gram-negative bacteraemia which include Enterobacteriaceae and non-fermenters.⁴ Klebsiella pneumoniae, Escherichia coli, and Serratia spp. are the prominent Enterobacteriaceae in BSIs while Pseudomonas aeruginosa and Acinetobacter baumannii are the most common non-fermenting gram-negative organisms.⁵ The type of organisms involved in BSIs is affected by several factors as follows: (i) type of health-care facility involved; whether acute or long-term care facility, (ii) initial antimicrobial therapy, (iii) presence of...
According to surviving while in other acute infections, the bacteria and their susceptibility profiles. This process is of great importance in settings such as ours where antibiotic-resistant strains with multiple resistance genes have emerged among GNB and are being increasingly recognized. The clinical and economic impacts of antibiotic-resistant GNB infections are substantial and greatly worrisome as evidence suggests that BSIs caused by these organisms are associated with increased length of hospital stay, higher costs of treatment, and increased mortality rate. As a result, this group of organisms, including multi-drug resistant (MDR) *Acinetobacter* extended spectrum lactamase producing Enterobacteriaceae (ESBL), and MDR *Pseudomonas aeruginosa*, has been classified as an urgent threat to public health.

It has been shown that the administration of inappropriate initial antimicrobial therapy might be associated with an adverse outcome in patients with gram-negative bacteraemia especially those with antibiotic-resistant strains. Hence, it is suggested that empirical antibiotics for serious infections should be recommended on the basis of the distribution of pathogens and their susceptibility patterns in the institution where the regimen is administered. The key to ameliorating the adverse outcome of BSI is prompt administration of appropriate empirical antibiotics. According to surviving sepsis campaign guidelines, the door-to-needle time for sepsis is less than one hour, while in other acute bacterial infections such as acute bacterial meningitis and community-acquired pneumonia, the door-to-needle time is less than 3-6 hours immediately after diagnosis. In selecting empiric antimicrobial therapy for infections, among important considerations are the local bacterial resistance patterns or antibiograms that are available for most pathogenic organisms at that hospital. Frequent updates of antimicrobial treatment guidelines are becoming more and more tailor-made putting into consideration the hospital and regional antimicrobial resistance situations and not neglecting the patient. This can only be effectively done with a good knowledge of the bacteria and their susceptibility profiles. This process is of great importance in settings such as ours where laboratory support for blood culture and antimicrobial surveillance are not optimal. This study was designed to aid the establishment of local antibiogram and empirical treatment for gram-negative bacteremia in patients being managed at the University of Port Harcourt Teaching Hospital (UPTH), Rivers State, Nigeria.

Materials and Methods

**Study Setting, Design and Population**

This study was a cross-sectional survey of hospitalized patients with suspected BSI whose blood samples were processed in the Department of Medical Microbiology and Parasitology, UPTH, Rivers State, Nigeria, from December 2017 to November 2018. Demographic and clinical information of each patient obtained from the laboratory request forms included age, gender, ward/clinic, and provisional diagnosis. History of co-morbidities and other relevant clinical information were obtained from the patients' case folders.

**Blood Sample Collection**

Blood samples were collected aseptically into both aerobic and anaerobic blood culture bottles using BACTEC closed system (Vacutainer). In this study, 4 mL and 16 mL of blood were collected from paediatric and adult patients, respectively. The samples were inoculated and transferred to the laboratory immediately.

**Blood Culture Processing and Isolation of Organism**

Blood cultures were processed using BACTEC 9060 automated blood culture system (BD Diagnostic Systems, Sparks, MD, USA). Blood cultures were incubated at 35-37°C in both aerobic and anaerobic conditions for a maximum incubation period of 5 days. Signal for bacterial growth was the machine’s alarm system.

**Identification of GNB Isolates and Susceptibility Testing**

All positive blood cultures were subcultured on MacConkey agar and incubated aerobically for 16-18 hours. All colonies were gram-stained and gram-negative isolates were identified using MICROBACT 12E identification kit (Oxoid, UK). Susceptibility testing was performed using the modified Kirby Bauer (disk diffusion) method, according to CLSI guidelines and interpretive criteria version 2020 (10). The following antibiotics discs (Oxoid, UK) were tested: Meropenem (10 µg), imipenem (10 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), amikacin (30 µg), gentamicin (10 µg), cefazidime (10 µg), ceftriaxone (10 µg), cefuroxime (10 µg), pipercillin/tazobactam (100/10 µg), amoxicillin/clavulanic acid (20/10 µg), and ampicillin sulbactam (10/10 µg). Isolates that showed intermediate susceptibility were also considered resistant to the antibiotic tested.

**Resistance Testing of GNB Isolates**

ESBL testing and detection of carbapenemase production were performed according to CLSI interpretive criteria using double disk synergy method and modified carbapenem inactivation method, respectively. We defined MDR as the resistance of the isolates to at least one antibiotic in three or more classes of antibiotics tested. Additionally, the associated organ dysfunction in patients was defined using sequential organ system assessment (SOFA) scores and the parameters obtained from patients’ case folders, including renal impairment.
(creatinine >170 µmol/L), hepatic impairment (bilirubin >32 µmol/L), coagulopathy (platelets <100), impaired consciousness (Glasgow Coma Scale<14), saturation abnormality; (PaO₂ <300 mm Hg), circulatory impairment (systolic blood pressure <100 mm Hg).12

**Statistical Analysis**

Data obtained was analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0. The level of significance was set at 0.0001. The chi-square test was used to estimate the possible association between the number of GNB isolated and unit/department and age groups.

**Results**

A total of 230 blood cultures were positive for bacteremia over the study period, out of which 246 organisms were isolated. Moreover, 71 of the total isolates were GNB, indicating a prevalence of 28.9%. The prevalence of GNB isolates in intensive care unit (ICU) was reported to be the highest (65.2%), followed by medical ward (40%), while the lowest prevalence was observed in special care baby unit (SCBU) (24%), indicating a statistically significant difference ($P=0.0001$) (Table 1).

The highest percentage of GNB isolates per age group (45.3%) was found among those aged ≥18 years. The second highest percentage (24.6%) was found among those aged ≤28 days. The least percentage was found among those under 18 years of age, indicating a statistically significant difference ($P=0.0001$; Table 1).

Twenty-three (32.4%) of the GNB isolates were categorized either as ESBL, carbapenemase, or MDRO. ESBL was detected in 12 (52%) of the 23 isolates, while carbapenemase production was detected in 5 (26%) (Figure 1).

Pneumonia accounted for 35.2% of the primary source of infection among the patients, followed by puerperal sepsis and UTI, each of which accounted for 15.1%. Gram-negative bacteremia was also detected in neonates with low birth weight and patients with skin and soft tissue infections but this group had a low frequency of occurrence as it was detected in 7 (9.9%) patients (Figure 2).

Impaired consciousness, renal impairment, and coagulation abnormality were the most common organ dysfunctions recorded with prevalence rates of 91%, 87%, and 83%, respectively (Figure 3).

Overall, *Klebsiella pneumoniae* was the most frequently isolated GNB (26.6%), while *Acinetobacter baumannii* was the most frequently isolated non-fermenting GNB. Additionally, *Acinetobacter baumannii* exhibited the highest level of resistance among the isolates, while the Enterobacteriaceae and non-fermenting GNB exhibited the least susceptibility to cefuroxime (37.8%) and gentamicin (35%) (Tables 2 and 3).

**Discussion**

Bacteremia is a leading cause of life-threatening conditions and poor prognostic factor in hospitalized patients. The distribution of isolates by source and age groups was found to be statistically significant ($P=0.0001$).

**Table 1. Distributions of Blood Culture Isolates According to Source and Age Groups**

| Units/departments | Number of Organisms Isolated (n=246) | Number of GNB Isolated (n=71) | Percentage of GNB Isolated (28.9%) | Chi-square | $P$ Value |
|-------------------|--------------------------------------|--------------------------------|-----------------------------------|------------|-----------|
| ICU               | 23                                   | 15                             | 65.2                              |            |           |
| Medicine          | 35                                   | 14                             | 40.0                              |            |           |
| Pediatrics        | 71                                   | 6                              | 28.6                              | 34.61      | 0.0001    |
| SCBU              | 69                                   | 17                             | 24.6                              |            |           |
| Surgery           | 48                                   | 19                             | 35.6                              |            |           |
| Age group (y)     |                                      |                                |                                   |            |           |
| ≥18               | 106                                  | 48                             | 45.3                              |            |           |
| <18               | 71                                   | 6                              | 8.5                               | 28.93      | 0.0001    |
| ≤ 28              | 69                                   | 17                             | 24.6                              |            |           |

SCBU, special care baby unit.

The distribution of the isolates by source and age groups was found to be statistically significant ($P=0.0001$).
patients. To minimize the adverse outcome associated with it, the knowledge of the most prevalent organisms and susceptibility profile is necessary to ensure the appropriateness of the initial treatment intervention. In this study, GNB represent 28.9% of the total isolates obtained from blood culture, which is similar to the findings of studies by Abebaw et al and Deku et al who reported prevalence rates of 34.7% respectively, but it is in contrast to the findings by Santoro et al who found a higher prevalence for GNB (53.19%). This could be due to the fact that most of the coagulase-negative staphylococci which form the majority of the isolates from blood culture were regarded as contaminants in the latter study. Moreover, K. pneumoniae had the highest prevalence (29.6%) among GNB, followed by E. coli (22.5%). This finding was in agreement with similar studies by Morris and Cerceo et al, where K. pneumoniae was the most common GNB isolated from blood cultures and was also MDR strain. However, this is in contrast to the findings by Santoro et al who found a higher prevalence for GNB (53.19%). This is however in contrast to findings of studies conducted by Hill et al, Fitzpatrick et al, and Santoro et al, where E. coli was the most commonly identified GNB. While among the non-fermenting GNB, Acinetobacter baumannii (16.9%) was the most common, followed by Pseudomonas aeruginosa (15.5%), Enterobacter aerogenes (5.6%) and Serratia marcescens reported in the study have also been documented with varying prevalence in different studies. The most common cause of bacteraemia in the study was pneumonia, which is consistent with the findings of Sligl et al and Wan et al. This is however not in agreement with the results of the study by Morris and Cerceo who reported that 84% of primary BSIs occur due to central venous line. The differences could be attributable to the lower number of central lines used in our settings.

Carbenpenems demonstrated the highest in vitro efficacy against GNB isolates with a susceptibility rate of 94.4% to meropenem and imipenem among the Enterobacteriaceae but a much lower rate was found among non-Enterobacteriaceae such as Acinetobacter baumannii and Pseudomonas aeruginosa (68.7% and 61.3%) for meropenem and imipenem, respectively. The pronounced resistant pattern of the non-fermenters may be related to the numerous intrinsic and acquired mechanisms for mitigating the microbicidal effect of antibiotics by this group of organisms. Generally, Enterobacteriaceae demonstrated the highest level of resistance to the second-generation cephalosporins in our study, which is at variance with the finding from similar studies by Sligl et al and Abebaw et al, where ciprofloxacin and ampicillin respectively showed the highest in vitro resistance among the antibiotics tested. The poor efficacy of cephalosporin in our study may be due to the high rate of use of these antibiotics as the last resort, especially the third generation groups, and as empirical therapy, with the lack of de-escalation protocol in place. In addition, the inappropriate use of this group of drugs as surgical prophylaxis may also have contributed.

### Table 2. Susceptibility Rate of Enterobacteriaceae Isolated from BSI

| Organisms                   | MEM (%) | IMP (%) | CRO (%) | CAZ (%) | CXM (%) | AMK (%) | CIP (%) | GM (%) | AMK (%) | TPZ (%) |
|-----------------------------|---------|---------|---------|---------|---------|---------|---------|--------|---------|---------|
| Klebsiella pneumoniae       | 19 (90) | 19 (90) | 12 (60) | 13 (62) | 7 (33.3)| 10 (47.6)| 7 (33.3)| 11 (52.3)| 17 (81) | 11 (52.3)|
| Enterobacter aerogenes      | 14 (87.5)| 14 (87.5)| 10 (62.5)| 10 (62.5)| 9 (42.8)| 7 (33.3)| 7 (33.3)| 8 (50) | 13 (81.3)| 10 (60) |
| Serratia marcescens         | 4 (100) | 4 (100) | 3 (75) | 3 (75) | 3 (75) | 4 (100) | 4 (100) | 4 (100) | 4 (100) | 3 (75) |
| Average % susceptibility    | 94.4    | 94.4    | 49.5    | 49.9    | 37.8    | 66.4    | 69.3    | 50.6   | 90.6    | 71.8    |

Abbreviations: MEM, Meropenem; IMP, Imipenem; CRO, Ceftriaxone; CAZ, Ceftazidime; CXM, Cefuroxime; AMK, Amoxicillin/Clavulanic acid; CIP, Ciprofloxacin; GM, Gentamicin; AMK, Amikacin; TPZ, Piperacillin/Tazobactam.

### Table 3. Susceptibility Rate of Gram-Negative Non-enterobacteriaceae Isolated From BSI

| Organism                  | MEM | IMP | CAZ | TPZ | GM | AMK | SAM | LVX | CIP |
|---------------------------|-----|-----|-----|-----|----|-----|-----|-----|-----|
| Pseudomonas aeruginosa    | 8 (72.7) | 8 (72.7) | 4 (55.5) | 3 (33.3) | 3 (25) | 5 (41.7) | 6 (50) | 5 (41.7) | 4 (33.3) |
| Acinetobacter baumannii   | 6 (50) | 6 (50) | 4 (41.7) | 4 (33.3) | 3 (25) | 5 (41.7) | 6 (50) | 5 (41.7) | 4 (33.3) |
| Burkholderia cepacia      | 5 (83.3) | - | 2 (33.3) | - | - | - | - | 4 (66.7) | - |
| Average % susceptibility  | 68.7 | 61.3 | 40.2 | 48.5 | 35 | 52.7 | 50 | 54.3 | 43.9 |

Abbreviations: MEM, Meropenem; IMP, Imipenem; CAZ, Ceftazidime; CIP, Ciprofloxacin; GM, Gentamicin; AMK, Amikacin; TPZ, Piperacillin/Tazobactam; LVX, Levofloxacin; SAM, Ampicillin/sulbactam.
Acinetobacter baumannii was the most notorious of all the isolates with regard to antimicrobial resistance and accounted for the high percentage of MDR in the study. In the present study, the highest number of GNB per unit (65.2%) was found in the ICU even though the lowest number of positive bacteraemia was also observed in this unit. This may be due to the fact that most cases of bacteraemia in the ICU are healthcare associated and the majority of these organisms are GNB. This view is supported by the report of Karakoc et al reporting that ICU poses a significant risk for the development of nosocomial bacteraemia and that ratio of GNB bacteraemia in the ICU and non-ICU patients is as high as 1.5:1.21

Within the paediatric age group, the prevalence of GNB bacteraemia in neonates (24.6%) was three times higher compared to other age groups (8.5%), which is somewhat in agreement with the findings of studies conducted by Meremikwu et al22 in Calabar and Nwadioha et al23 in Kano State, Nigeria, where GNB bacteraemia was also reported to be higher in neonates than in other paediatric age groups. This may be due to the routine use of blood culture as part of the investigative tool for fever in the neonatal ICU. Evidence from this study indicates that a significant number of GNB isolates (23/71, 32.4%) were resistant to a number of antibiotics tested, including ESBL and carbapenemase producing Enterobacteriaceae, while some were MDRO. This is far higher than the 13.7% resistance rate reported by Gudiol et al13 and 17% by Sligl et al.14 Possibly explained by the high rate of inappropriate use of antibiotics in our settings, suboptimal infection control and prevention together facilitate the spread of health care associated infections and resistance.2

Using the SOFA scoring system, the most common organ dysfunction reported in the study was impaired level of consciousness in 91% of cases, closely followed by impaired renal function (87%). This may be as a result of the ease with which Glasgow coma scale can be assessed both in the emergency department and in the ward. The renal function is assessed by electrolytes, urea, and creatinine levels which are routine investigations done in the emergency unit as they are readily available.

**Conclusion**

This study showed that there are a significant number of MDR strains among GNB causing bacteraemia in patients at the UPTH, with the highest resistance to the third-generation cephalosporins. There is a need for an urgent review of the current antimicrobial policy with the aim of recommending carbapenems as the empirical therapy for patients with proven bacteraemia.

**Authors’ Contributions**

JAI conceptualized the study, sample collection and processing was done by JAI, and ATO. FAO and AU collected and analyzed data. All authors read and approved the final manuscript.

**Ethical Approval**

Ethical approval was obtained from the University of Port Harcourt teaching Hospital ethical review committee.

**Conflict of Interest Disclosures**

The authors declare that they have no conflict of interests.

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