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ORIGINAL RESEARCH

Blood Stream Infection in Stroke Patients: Spectrum of Microbial Isolates and Antimicrobial Resistance

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Abstract

Background: Bloodstream infection (BSI) is frequent in stroke, with poorer outcomes when microbial isolates are multi-drug resistant. There is a shortage of published data on BSI amongst stroke patients in Nigeria.
Objective: To describe the microbial isolates and the antimicrobial resistance pattern among microbial isolates in BSI in stroke patients.
Methods: This retrospective study of all hospitalized stroke patients with BSI at the University of Benin Teaching Hospital, Benin City, Nigeria covered July 2018 to June 2022. The demographics, stroke type, microbial isolates and antimicrobial resistance patterns were studied.
Results: Blood culture studies were conducted among 834 stroke patients with infections; 410 (49.2%) had positive growth for microbial organisms. Amongst those with positive blood cultures, 53% (217/410) were females, while 56% had a haemorrhagic stroke. The mean age was 76.9±13.9 years, with about 80% of them aged ≥ 65. Infections of the respiratory tract (45%) and the urinary tract (33%) were the possible primary sources of BSI. The leading isolates included *Enterococcus faecalis* (18.5%), *Klebsiella oxotyca* (12.9%), *Proteus mirabilis* (12.9%), *Staphylococcus aureus* (11.5%), and *Escherichia coli* (11.2%). Approximately 88% of the isolates were multi-drug resistant, with 100% resistance to cefuroxime, ceftazidime, and co-trimoxazole, 83.3% to erythromycin and 75% resistance to ampicillin. The elderly patients were significantly more likely to acquire multi-drug resistant micro-organisms (p = 0.007).
Conclusion: Stroke patients, especially the older ones, are susceptible to bloodstream infection from multi-drug-resistant micro-organisms, contributing to increased morbidity and mortality among stroke patients.

Keywords: Antimicrobial resistance, Bloodstream infection, Microbial isolates, Stroke.

Introduction

Infections frequently accompany stroke, especially pneumonia, urinary tract infection, infected pressure ulcers and bloodstream infection. Most bloodstream infection progresses to life-threatening sepsis, the ultimate path common to these infectious conditions. Between 10% and 20% of hospital-acquired infections are due to bloodstream infection, the eighth leading cause of death. [1] The stroke patient is especially vulnerable to developing infection for reasons of

increasing age in the majority of them. Other risk factors for infections in stroke include co-existing diabetes mellitus, which is a frequent risk factor for stroke, depressed levels of consciousness, being bedridden with decubitus ulcers, dysphagia with the use of feeding nasogastric tube, aphasia, intravascular and urinary catheterization, intubation and mechanical ventilation. The increased frequency of infections following a stroke is also partly attributable to a central nervous system-mediated immune depression. This is characterized by a rapid loss and deactivation of the T-cells, a decrease in cellular immune response, sympathetic hyperactivity and a strong cytokine-mediated anti-inflammatory response which facilitates infections. [2] Bloodstream infection (BSI) during a stroke hampers optimal response to treatment, and the situation could even be fatal if blood isolates are drug resistant. Increasing antimicrobial resistance to BSI is well documented in reports worldwide. Antimicrobial resistance develops from antibiotics misuse and micro-organisms evolving many different resistance mechanisms. [1, 3] BSI caused by resistant micro-organisms frequently fail to respond to treatment, thus leading to septicaemia, prolonged hospital admission, increased costs of treatment and worsening morbidity and mortality. [1, 3]

There is accumulated evidence that BSI and sepsis are important triggers for stroke and its reoccurrence. Haemodynamic instability, atrial fibrillation, prolonged systemic inflammatory responses and coagulopathy have been the possible linkage between sepsis and stroke. [4] In many low- and middle-income countries with poor hygienic conditions and a high incidence of infections, the burden of bacteraemia and sepsis is suspected to be substantial. In Africa, infections are a widespread occurrence among hospitalized patients. A systematic review of BSI in some regions of Africa and Asia showed that the most common isolated organisms were *Salmonella enterica, Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli,* and *Mycobacterium tuberculosis.* [5]

The prompt diagnosis and speedy commencement of antimicrobial therapy in patients with BSI reduce mortality. Still, the choice of initial empirical treatment depends on the knowledge of the type of pathogens and the antibiogram pattern. To the authors' knowledge, BSI's frequency, pattern and antibiotic resistance amongst stroke patients have yet to be described in Nigeria. This study was aimed at profiling the micro-organisms responsible for BSI and their antimicrobial resistance pattern among stroke patients.

Methods

This was a retrospective study done at the stroke ward and the Intensive Care Unit (ICU) of the University of Benin Teaching Hospital, Benin City, spanning four years from July 2018 to June 2022. It involved the review of the medical records and microbiological laboratory results of stroke patients. Clinical assessment with a confirmatory neuroimaging study (Computerized Tomography or Magnetic Resonance Imaging of the brain with evidence of either infarction or bleeding) was used for the case definition of stroke. Adults with stroke who were admitted into the stroke ward and Intensive Care Unit (ICU) and who had blood specimens drawn for culture and sensitivity studies were included in the study.

Ethical approval was obtained from the hospital's ethics and research committee (Ethical approval certificate number: ADM/E22/A/VOL.VII/1476). A structured data capture form, self-designed based on the literature review on bloodstream infection, was used for the study. Using the data capture form, the gender, age, type of stroke, the indication for

blood culture studies, the number of patients whose blood specimens were sampled, the number of blood samples sent to the laboratory, evidence of infection, including the possible sources of bloodstream infection (BSI), from the respiratory tract (clinical and or chest radiographic evidence of pneumonia), the urinary tract (clinical and or laboratory evidence of urinary tract infection), intravenous site (evidence of phlebitis), and decubitus ulcers (wound swab). Based on their clinical manifestations, these data were extracted from the laboratory reports and case files of patients with stroke who were considered for blood culture studies at any point while on admission. Blood culture was done using the BACTEC method. Aseptic measures were ensured while drawing the blood specimens. These blood specimens (five millilitres each) were drawn from two sites into two blood culture bottles. The labelled blood specimens were transported to the medical microbiology laboratory within 15 minutes. The inoculated blood culture bottles were placed into the BACTEC machine, and within five days, the machines flagged, indicating possible yield. A blinking yellow light indicated a positive culture, while a blinking red light indicated no growth. A positive culture was after that sub-cultured. *Escherichia coli* was deployed for Gram-negative organisms for quality assurance purposes, while *Staphylococcus aureus* was used for Gram-positive micro-organisms.

The Kirby-Bauer disk diffusion method was utilized for antibiotic susceptibility testing. The antibiotics tested included ampicillin, erythromycin, ceftriaxone, co-amoxiclav (a combination of amoxicillin and clavulanic acid), levofloxacin, ceftazidime, co-trimoxazole, gentamicin, imipenem, meropenem and cefuroxime. The definition of bloodstream infection used in this study was adopted from the criteria recommended by the Centres for Disease Control and Prevention. [6] The isolation of at least one positive peripheral blood culture was defined as a bloodstream infection.

The number of blood specimens received from the subjects, positive blood culture studies and the antibiogram patterns were extracted from the microbiology laboratory records. The sources of BSI were based on the clinical diagnosis of infection: chest, urinary, skin or venous infections (i.e. bloodstream infection plus other infections) and or isolating micro-organisms similar to that cultured from BSI. Multiple drug-resistance (MDR) was defined as resistance to ≥ 3 of the following antibiotics groups: [7] (1) Cephalosporins (2) Fluoroquinolones (3) Penicillins (4) Aminoglycoside (5) Carbapenems (6) Macrolides (7) Sulphonamides.

Data management

Data entry and statistical analysis were performed using the SPSS Version 25, Inc., Chicago, Illinois, USA. Continuous variables were presented using means and standard deviations, while frequency and percentages were used to summarize categorical variables. The Chi-Squared test was used to assess the association between the variables, and statistical significance was set at the level $P \leq 0.05$.

Results

During the four years under review, blood specimens were collected from 834 stroke patients and were sent to the Microbiology Laboratory for blood culture and sensitivity. Four hundred and ten (49.2%) of these blood specimens were positive for the growth of bacterial and fungal micro-organisms. Among those with positive blood cultures, 193 (47%) were males, while 217 (53%) were females. The mean age was 76.9±13.9 years, and the age ranged from 45 years to 95 years. About 80% of the positive blood isolates were drawn from stroke patients aged ≥ 65 years. Forty-four per

cent had an ischaemic stroke, while 56% had a haemorrhagic stroke.

The possible major sources of BSI included infections in the respiratory tract (45%) and the urinary tract (33%), as shown in Table I. Approximately 78% of the bacterial isolates were Gram-negative micro-organisms, while 22% were Gram-positive. The frequency of bacterial micro-organisms isolated showed *Enterococcus faecalis* (18.5%), *Klebsiella oxotyca* (12.9%), *Proteus mirabilis* (12.9%), *Staphylococcus aureus* (11.5%), *Escherichia coli* (11.2%), *Enterobacter aerogenes* (9.3%), *Klebsiella pneumoniae* (8.5%), *Citrobacter freundii* (6.8%), *Proteus vulgaris* (6.6%), and *Candida albicans* (1.7%) as shown in Table I.

Approximately 88% of the blood isolates were multi-drug resistant (MDR). The elderly patients were significantly more likely to acquire multidrug-resistant micro-organisms than the younger patients (49.2% vs 8.5%; p = 0.007). *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli and Citrobacter fruendii* had an MDR rate of 57.1%, while *Klebsiella oxotyca, Proteus mirabilis and Enterobacter aerogenes* had MDR rate of 42.9%. The isolates were 100% resistant to cefuroxime, ceftazidime, and co-trimoxazole, 83.3% to erythromycin, 75% to ampicillin, 42.9% to co-amoxiclav, 33.3% to gentamicin, and 25% resistant to imipenem and ceftriaxone. Levofloxacin and meropenem had good sensitivities (Table II).

Table I: Demographics, types of stroke, sources of bloodstream infections and pattern of microbial isolates

Variable	*Category*	*Frequency (Percentage)*
Age (Year)	< 65	79 (19.3)
	≥ 65	331 (80.7)
Gender	Male	193 (47.1)
	Female	217 (52.9)
Type of stroke	Ischemic stroke	180 (43.9)
	Haemorrhagic stroke	230 (56.1)
Possible sources of BSI	Respiratory infection	184 (44.9)
	Urinary tract infection	136 (33.2)
	Infected decubitus ulcers	96 (23.4)
	Intravenous site infection	54 (13.2)
	Unspecified sources of infection	36 (8.9)
Microbial isolates	*Enterococcus faecalis*	76 (18.5)
	Klebsiella oxotyca	53 (12.9)
	Proteus mirabilis	53 (12.9)
	Staphylococcus aureus	47 (11.5)
	Escherichia coli	46 (11.2)
	Enterobacter aerogenes	38 (9.3)
	Klebsiella pneumoniae	35 (8.5)
	Citobacter freundii	28 (6.8)
	Proteus vulgaris	27 (6.6)
	Candida albicans	7 (1.7)

Discussion

Despite the availability of effective antimicrobial agents and improved supportive care, bloodstream infection (BSI) is a significant cause of death globally. The clinical condition becomes even more life-threatening when the critically ill stroke patient develops BSI, progressing to

sepsis. A high proportion of stroke patients had BSI in this study. This finding is similar to reports on BSI in other seriously ill patients, where up to 40% of the critically ill have been reported to acquire BSI, with a high mortality rate of nearly 50%. [8, 9]

Table II: Antibiogram pattern of microbial isolates from stroke patients with bloodstream infection

	Ko	*Ec*	*Pv*	*Sa*	*Pm*	*Ea*	*Kp*	*Cf*
Gentamicin	SS	NT	NT	NT	NT	NT	SS	RR
Levofloxacin	SS	SS	SS	NT	SS	SS	SS	SS
Imipenem	SS	SS	SS	RR	NT	NT	NT	NT
Meropenem	SS	SS	NT	NT	NT	NT	NT	NT
Ampicillin	RR	RR	SS	RR	SS	RR	RR	RR
Erythromycin	RR	RR	SS	RR	RR	NT	RR	NT
Co-amoxiclav	RR	NT	SS	RR	SS	SS	RR	SS
Ceftazidime	RR	RR	RR	RR	RR	RR	RR	RR
Co-trimoxazole	NT	RR	RR	NT	RR	RR	RR	RR
Cefuroxime	NT	RR	RR	RR	RR	RR	RR	RR
Ceftriaxone	NT	SS	NT	RR	NT	SS	NT	SS

Ko – Klebsiella oxotyca; Ec – Escherichia coli; Pv – Proteus vulgaris; Sa – Staphylococcus aureus; Pm – Proteus mirabilis; Ea – Enterobacter aerogenes; Kp – Klebsiella pneumoniae; Cf – Citrobacter freudii.
SS – Sensitive; RR - Resistance; NT - Not Tested.

The older stroke patients (aged ≥ 65 years) accounted for a majority with BSI in this study. This is a consistent finding in several studies where ageing had been reported to be a significant risk factor for BSI. [8 - 10] This is a worrisome finding, especially in stroke patients, since ageing is an essential non-modifiable risk factor for stroke. The elderly stroke patients are more vulnerable to BSI due to multiple comorbidities, impaired immunity, and a higher ICU admission with numerous devices. BSI in this group of patients is atypical in presentations and sometimes missed, but a sudden deterioration and worsening of stroke symptoms may be pointers of BSI in the aged. BSI in the elderly is likely to be more recurrent and severe. The frequent acquisition of resistant micro-organisms is characterized by repeated readmissions, poor functional recovery, and accumulated admission expenses, with increasing morbidity and mortality. [1, 3, 8 - 10] Approximately 33% of the stroke patients in this study had urinary tract infections (UTIs), while about 45% had a lung infection. These may have been the sources of BSI. Up to 40% of stroke patients have been reported to acquire UTI, and the urinary tract as a source of BSI is well documented. [11, 12] Pneumonia affects about 10 to 40% of stroke patients, and the respiratory tracts as a source of BSI have been variously reported. [13, 14]

Enterococcus faecalis was the most common isolate in the present study accounting for 18.5% of BSI, and was found resistant to three antibiotics. It is well known for widespread resistance to commonly used third-generation cephalosporins. [15 - 17] *Klebsiella oxotyca* accounted for 12.9% of BSI in this study, while *Klebsiella pneumoniae* was isolated in 8.5% of the cases. K*lebsiella oxotyca* was resistant to four antibiotics, while *Klebsiella pneumoniae* was resistant to six antibiotics. *Klebsiella pneumoniae* is well known to be resistant to commonly used antibiotics. [18, 19]

Proteus mirabilis was responsible for 12.9% of BSI, with resistance to four antibiotics. *Proteus vulgaris* accounted for 6.6% of BSI cases and was resistant to three antibiotics. The elderly patients have higher mortality from BSI caused by *Proteus spp*. [20, 21]

Staphylococcus aureus was isolated in 11.5% of BSI cases and was found to be resistant to all the antibiotics tested. The multi-drug resistant nature of this organism is well established. [22, 23] *Escherichia coli* was isolated in 11.2% of BSI cases and was resistant to five antibiotics. It is a leading cause of BSI in the aged, accounting for 40% of cases. [24, 25] The risks for infection with *E. coli* include prolonged urinary catheterization and prostatic disease in men. *Enterobacter aerogenes* was cultured in 9.3% of the BSI cases and it was resistant to four antibiotics. *Enterobacter spp* is known to cause multi-drug resistant UTI as a source for BSI. [26, 27] *Citrobacter freundii* was cultured in 6.8% of the BSI cases and was found resistant to five antibiotics. The risk for infectivity and resistance includes impaired immunity and prolonged antibiotics exposure. [28, 29] *Candida albicans* accounted for 1.7% of the BSI cases. Immune compromise, diabetes mellitus, antibiotic misuse, application of invasive gadgets in the ICU and prolonged admission are some risk factors for its occurrence. There is increasing evidence of resistance to antifungal agents in the literature. [30, 31]

Antimicrobial resistance is a worldwide phenomenon that permeates international boundaries. [32] The Centres for Disease Control and Prevention in the USA has attributed 2.8 million infections and about thirty-five thousand deaths yearly to resistant organisms. [33] Antibiotic resistance is feared to lead to about 10 million deaths every year globally, with higher figures occurring in developing countries. [33, 34] Several factors have been adduced as responsible for drug resistance; these include prolonged exposure to antibiotics, too short exposure, reduced dosing, substandard or counterfeited antibiotics and treating the wrong diagnosis. These may be related to the observations that over 90% of antimicrobials used in some developing countries are available over the counter, without prescription in many instances. [32, 34] Also, bacterial agents are evolving different forms of resistance. These mechanisms include gene mutation or horizontal gene transfer through conjugation, transformation or transduction. In addition, it could be an innate feature of the organism with the gene encoded in the chromosomes.

Limitations

The present study was limited by its retrospective nature. The authors had no access to the records of pre-hospital care or antibiotic exposure before admission and are not certain if the isolates were hospital- or community-acquired. Incomplete data precluded assessment of other relevant variables, including duration between ictus and presentation. A prospective study considering all these confounders is recommended.

Conclusion

Bloodstream infection by multidrug-resistant micro-organisms is common in strokes, especially among the elderly, and this limits treatment options, with obvious implications for the quality of care. Aggressive infection control measures, regular surveillance for emerging microbial resistance and rational use of antimicrobial drugs can mitigate microbial resistance.

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