Artículo original

Auditing Bloodstream infection in an Intensive Care Unit in Botswana

Auditoría de infecciones del torrente sanguíneo en una Unidad de Cuidados Intensivos en Botswana

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ABSTRACT

Introduction: Nosocomial infections are a significant problem in Intensive Care units (ICUs) worldwide; however, very little research exists into their epidemiology and characteristics in subSaharan Africa. The largest public hospital ICU in Botswana underwent its first internal audit in 2017-18 and nosocomial infections were one of the defined study parameters.

Objectives: ICU admissions over 12 months were analyzed to establish the principal causative microorganisms responsible for bloodstream infection (BSI), sensitivity patterns to common antibiotics used, as well as patient outcomes.

Methods: Data from patients over the age of 14 admitted between April, 1st 2017 and March, 31st 2018 were retrospectively analyzed for the presence of BSI, BSI organisms and sensitivities and patient mortality.

Results: 182 patients were enrolled, and there were 13 BSI recorded (7.4%). There was no significant difference in mean APACHE II scores noted in the patients with BSI and without BSI (25.8±4 vs 25±5; p=0.50). The principal causative microorganism for BSI was the Klebsiella species. BSI was associated with a higher risk of dying in ICU (61.5% vs 40.1%, OR 2.38; p= 0.14) as well as a higher 30-day mortality rate of 92.3% for patients with BSI vs 46.1% without BSI (OR 13.43; 95%; p=0.01).

Conclusions: BSI impacts negatively on the ICU length of stay, ICU and 30-day mortality rate. HIV-infection is associated with a higher risk of bacteriaemia. There is a high resistance pattern to the use of β-lactams including the third-generation cephalosporins.

Keywords: Bloodstream infection; mortality rate; antimicrobial resistance.

RESUMEN

Introducción: Las infecciones nosocomiales son un problema significativo en las Unidades de Cuidado Intensivo (UCI) a escala mundial; sin embargo, existen pocas investigaciones al respecto en el África subsahariana. La UCI más grande del Hospital Público de Botswana tuvo su primera auditoría interna entre 2017-2018 y las infecciones nosocomiales eran uno de los parámetros estudiados.

Objetivos: Determinar los principales microorganismos responsables de infección del torrente sanguíneo (ITS) en los pacientes admitidos en la UCI en los últimos 12 meses, así como los patrones de sensibilidad antimicrobiana y los resultados de los pacientes.

Métodos: Se realizó un estudio retrospectivo de los datos de los pacientes mayores de 14 años de edad admitidos en la UCI entre el 1 de abril del 2017 y 31 de marzo de 2018 para determinar la presencia de ITS, organismos responsables de la infección, sensibilidad a los antibióticos y mortalidad de pacientes.

Resultados: Se incluyeron 182 pacientes, de los cuales 13 presentaron ITS (7,4 %). No hubo ninguna diferencia estadística significativa en el APACHE II, entre los pacientes con ITS y sin este (25,8±4 contra 25±5; p = 0,50). El principal microorganismo causante de ITS fue *Klebsiella* spp. La ITS se asoció con un riesgo mayor de muerte en la UCI (61,5 % contra 40,1 %, OR 2,38; p = 0,14), así como con una proporción más

alta de mortalidad a los 30 días en la UCI (92,3 %) para los pacientes con ITS contra 46,1 % sin ITS (OR 13,43; 95 %; p = 0,01).

Conclusiones: La ITS impacta negativamente en la estadía en la ICU, y en la proporción de mortalidad a los 30 días en la UCI. La infección de VIH se asoció con un riesgo más alto de bacteriemia. Hay un patrón de resistencia más alto al uso de betalactámicos, incluidas las cefalosporinas de tercera generación.

Palabras clave: infección del torrente sanguíneo; proporción de mortalidad; resistencia antimicrobiana.

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Introduction

Much research has been published about the burden of nosocomial infections in Intensive Care Units (ICUs) worldwide, particularly the increased patient mortality with ICU-acquired infections.[1,2] Amongst the most common ICU-acquired infections are central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP).[3,4,5]

The 2019 International Nosocomial Infection Control Consortium (INICC) report collected data from 523 ICUs worldwide from 242 hospitals, with a pooled crude mortality rate of 24.9% in adult and paediatric ICU patients with CLBSI. Only 16 data sets in this report (3%) were from African ICUs, and none of these ICUs were in sub-Saharan Africa.[6] There are very few studies in Africa and even less in sub-Saharan Africa addressing nosocomial or bloodstream infections in hospitals. An ICU study in Nigeria reported a high bloodstream infection rate among ICU patients of 48.9%, and these patients subsequently had higher mortality rates than non-infected patients of 75% vs 25%, respectively.[7]

Botswana is a middle-income country in sub-Saharan Africa, and antimicrobial resistance is seen as a growing issue, with studies in the largest public teaching

hospital recording significant gram-negative sepsis growth from blood cultures of patients and a high contaminant rate.[8] This study was performed as part of an audit of a large government hospital intensive care unit in Botswana, with BSI as one of the defined indicators.

Objectives:

1. To report on the demographic characteristic of patients admitted to ICU at Princess Marina Hospital (PMH) who developed BSI.
2. To report on the principal causative microorganisms responsible for BSI in the PMH ICU and the antibiotic susceptibility patterns.
3. To determine ICU death and 30-day hospital death rates among patients with BSI and compare these to unaffected ICU patients.

Methods

A prospective 12-month audit between April, 1st 2017 and March, 31st 2018.

Study settings: An eight-bed mixed adult and paediatric ICU in the major teaching and academic referral hospital for Botswana, Princess Marina Hospital (PMH). The ICU is staffed by three intensivist physicians during working hours and by an anaesthetist after hours. Registered nurses with no formal ICU training provide care for these patients with a nurse-patient ratio of 1:2 during the day shift and 1:3 during the night shift. There is 24/7 access to radiology and laboratory services; however, no pharmacist is assigned to the unit for consultation.

Study population: The study population for this study was adult (greater or equal to 14 years) critically ill patients admitted to PMH ICU within the audit period.

Exclusion criteria:

1. All ICU patients with burns, as APACHE II scoring, is not suitable for these types of critically ill patients, and so their data was not in the audit.[9,10]
2. ICU patients with a single positive blood culture report the following microorganisms: Coagulase-negative staphylococci, *Propionibacterium* acnes and *Corynebacterium* spp. These growths were considered contaminants of the blood sample.[11]

Data collection: Demographic data regarding age, gender, and HIV status was extracted from the ICU 24 hours paper-based observation chart, hospital password-protected Integrated Patient Management System (IPMS) pathology system and placed into ICU patient Microsoft-Access-2013 database created for a recent audit.[12] HIV status of adult patients at PMH was established by the standard HIV rapid test, confirmed by the ELISA test as per HIV national guidelines.[13]

BSI was defined as the growth of a viable organism in a blood culture taken from a patient during their ICU stay after 48 h of admission.

PMH laboratory utilised an oxoid signal blood culture system with chocolate agar, sheep blood agar and MacConkey agar plates; incubating for 5 days at 35±2°c. Antimicrobial susceptibility testing utilized the Kirby Brauer disc diffusion method and the minimum inhibitory concentration (MIC) method.

Calculations of BSI, death and infection rates were taken from recognised statistical data:[14]

$$\text{BSI rate} = \frac{\text{Number of patients with BSI in the period}}{\text{Total of patients recorded into the database in the period}} \times 100$$

Death infection-related among patients who developed BSI was established as follows:

$$\text{Death infection-related} = \frac{\text{Number of death infection-related in the period}}{\text{Total of patients with BSI in the period}} \times 100$$

Death was considered infection-related on review of the death notification form and correlated with doctor notes for each deceased.

ICU death rate of the study population was determined as follows:[14]

$$\text{ICU death rate} = \frac{\text{Number of death of patients with BSI in the period}}{\text{Total of patients with bloodstream infection in the period}} \times 100$$

The 30-day death rate of the study population was determined as follows:

$$\text{30-day death rate} = \frac{\text{No. of death with BSI at 30-day post-ICU discharge in the period}}{\text{Total of patients with BSI at 30-day post-ICU discharge in the period}} \times 100$$

Data Analysis: Data were processed using Excel 2013 and R Software version 3.5.1. For age and APACHE II score, mean values and standard deviation (SD) were calculated. For gender, HIV status, type of infection (monomicrobial or polymicrobial), BSI rate, death infection-related, ICU death rate and 30-day hospital death rate frequency and percentages were used. For comparison of means, the t-test was used, and Odds ratios and fisher exact test to investigate the association between BSI and categorical variables. Simple linear regression was used to investigate the association between BSI and continuous variables, and statistical significance was p-value less than 0.05.

Results

During the study period, 251 patients were admitted to PMH ICU. Of these, 182 were eligible to be placed into the study database, and 69 were excluded (Fig. 1). Finally, 13 patients who developed BSI were further analysed.

The characteristics of the 13 patients with acquired BSI in ICU compared to the rest of the eligible study population can be seen in Table 1. Overall, 7,4% of enrolled patients acquired BSI with the mean age of this cohort of 50,5±17,9 years and a slight non-significant female predominance. Older age was associated with a high risk of acquiring BSI but this was not significant (odds ratio= 1,03; p=0,10). 53,8% of the 13 patients with BSI, were HIV positive, and HIV was found to be associated with a higher risk of BSI (odds ratio= 1,99; p=0,22). Mean APACHE II scores at 48 hours from admission were similar in the BSI (25,8±4) and non-BSI population (25±5) without any statistical differences (p=0,50).

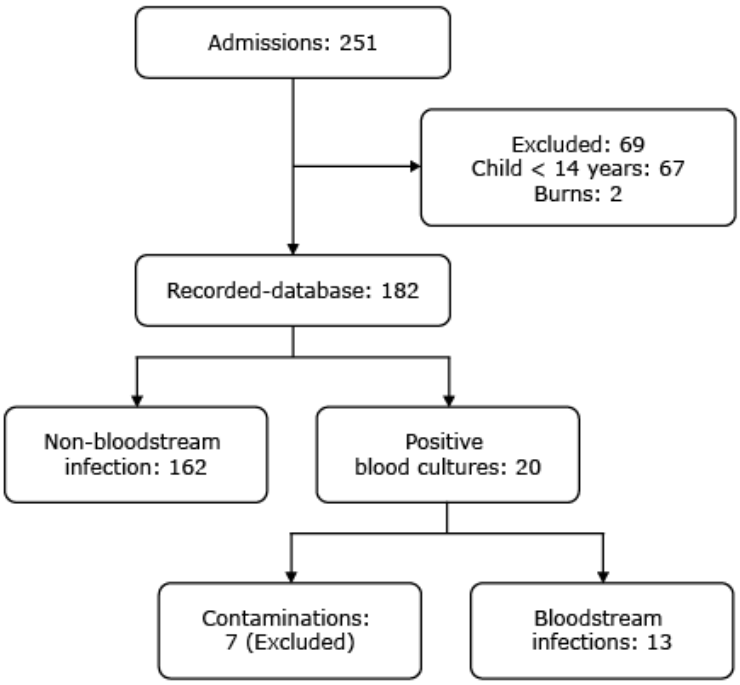

Fig. 1 - Flow chart of the enrolled population.

Monomicrobial infection was recorded in 61,5% of BSI patients and polymicrobial infections in 38,5%. ICU death rate amongst patients with BSI was 61,5%, and BSI was associated with a higher risk of death in ICU (odds ratio= 2,38; p=0,14). Of all the BSI patients who died, 38,5% of their hospital records listed the death as a direct consequence of the BSI. Patients with BSI had a 30-day hospital death rate of 92,3% and had a statistically significant higher risk for 30-day mortality (odds ratio=13,43; p = 0,01). BSI was also associated with a statistically significant longer length of stay in ICU than those without BSI (odds ratio of 38,58; p= 0,01).

Table 1 - Characteristic of the ICU patients by bloodstream infections (BSI) status

	BSI (no. 13, 7.4%)	**Non-BSI (no. 162, 92.6%)**	**Odds Ratio (OR)**	**95% Confidence interval (95% CI)**	**P value**
Age-Mean(SD)	50,8(17,6)	41,9(17,7)	1,03		0,10
Gender- no. %					0,55
Male	6(46,2)	93(57,4)	0,64	0,17 to 2,32	
Female	7(53,8)	69(42,6)	1		
HIV status*- no. %					0,22
Negative	6(46,2)	98(60,5)	1		
Positive	7(53,8)	42(25,9)	1,99	0,52 to 7,39	
APACHE II-Mean(SD)	25,8(4)	25(5)		-3,25 to 1,70	0,50
Monomicrobial infection- no.%	8(61,5)	-	-		-
Polymicrobial infection-no.%	5(38,5)	-			-
Bloodstream infection rate- no.(%)	13(7,4)	-	-		-
Death BSI-related -no.%.	5(38,5)				
Outcome at ICU-no.(%)					
Died	8(61,5)	65(40,1)	2,38	0,64 to 9,66	0,14
Alive	5(48,5)	97(59,9)	-		-
30-day hospital death rate				1,90 to 585,44	0,01
Died	12(92,3)	76(46,1)	13,43		
Alive	1(7,8)	86(53,1)	-		
ICU LOS in days- Mean(SD), coefficient	44,6(48,8)	6,7(10,4)	38,58		0,01

* 22 patients with non-BSI (13.6%) had unknown HIV status; BSI: bloodstream infection; ICU: Intensive Care Unit; LOS: Length of Stay.

Ten species of organisms were found in this BSI population with *Klebsiella pneumoniae* the most prevalent microorganism; representing 39,3%. Other microorganisms recorded include *Klebsiella* species (10,7%), *Enterobacter* species (7%) and *Enterococcus* species (7%), as listed in table 2.

Table 2 - Frequency of causative microorganisms for bloodstream infection in patients admitted to ICU-PMH during the study period

Microorganisms	**no. (%)**
Klebsiella pneumoniae	11(39,3)
Klebsiella species	3(10,7)
Enterobacter specie	2(7,0)
Enterococcus species	2(7,0)
Candida species	1(3,6)
Enterobacter cloacae	1(3,6)
Escherichia coli	1(3,6)
Klebsiella oxyboca	1(3,6)
Lactosa fermenting colony	1(3,6)
Non-Lactose fermenting colony	1(3,6)
Proteus mirabilis	1(3,6)
Pseudomonas aeruginosa	1(3,6)
Streptococcus Group A	1(3,6)
Streptococcus Group D	1(3,6)

Antimicrobial susceptibility was performed in the PMH laboratory for all 13 BSI patients, as Figure 2 shows. All antimicrobials tested apart from Vancomycin and Amikacin had a resistance rating of 60% or greater. Four antimicrobials– ampicillin, amoxicillin plus clavulanic acid (Augmentin), erythromycin and trimethoprim recorded a 100% resistance rate.

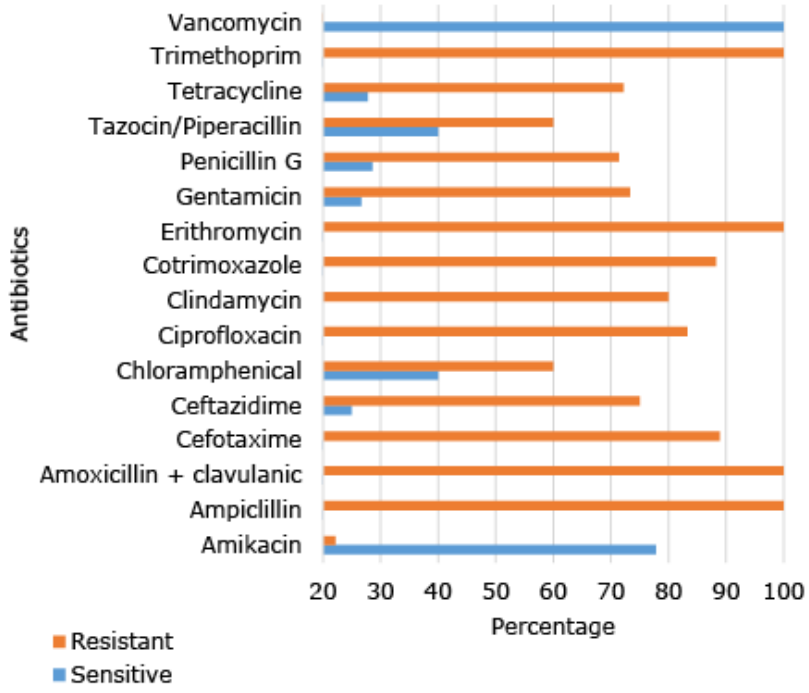

Fig 2 - Sensitivity testing results of the patients enrolled in the study.

Klebsiella pneumoniae, the most prevalent pathogen in BSI in this study population was further analyzed and was noted to have high resistance to β-lactams and other classes of antimicrobials. Of the antimicrobials used, amikacin yielded the highest overall sensitivity to *Klebsiella* of 72,7%.

Three other significant pathogens (*Klebsiella* species, *Enterobacter* species and *Enterococcus* species) showed high resistance to all classes of antimicrobials apart from amikacin and vancomycin.

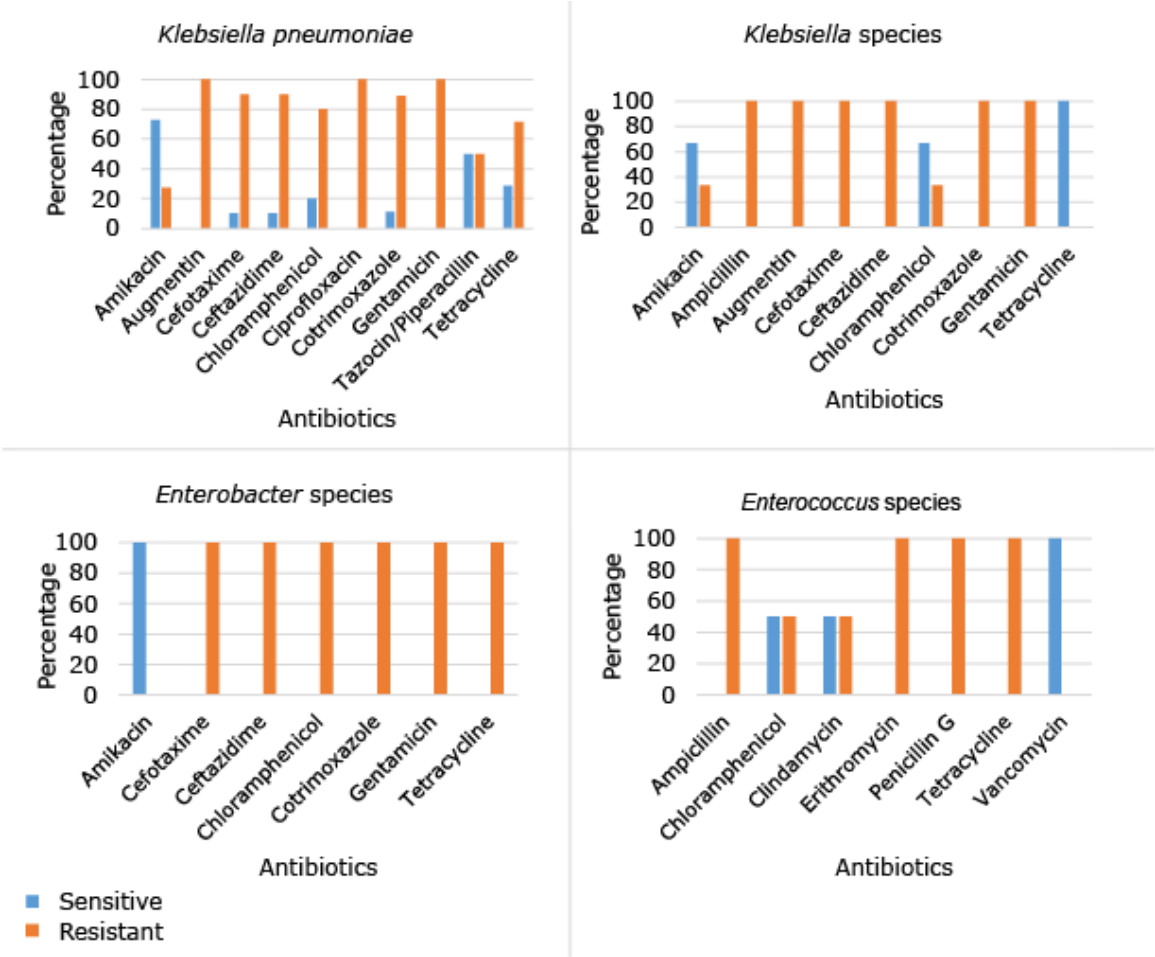

Fig 3 - Sensitivity/Resistance pattern of the more prevalent microorganisms cultured in the blood of the ICU patients in the study period.

Discussion

In this audit, the BSI rate (7.4%) amongst PMH ICU patients was far lower than expected and much lower than similar data from developed country settings.[11,15] Regional data has reported higher BSI rates and mortality similar to our findings;[7,8,16] however, one of these with a higher frequency measured BSI associated with other healthcare-acquired infections, whereas our study determined the frequency of BSI in the entire enrolled population.[7] In the Cape Town study, data was recorded from an entire hospital population, not just the ICU.[16]

Neonatal sepsis studies conducted in our same hospital setting reported laboratory-confirmed BSI in their patient cohorts of 8,5% and 6,4%.[17,18,19]

Several studies have reported similar high mortality rates amongst patients with BSI during ICU admissions.[1,20,21] One Nigerian study published a mortality rate amongst ICU patients

with BSI of 75% compared with 25% without BSI.[7] Their 30-day mortality was also statistically significantly higher in patients with BSI (92,3% vs 46,1%; OR of 13,43; 95% CI of 1,905391 to 585,438874; p=0,0024).

Our findings also showed BSI patients in PMH ICU had a statistically significant longer mean admission time of 44,6 vs 6,7 days without BSI (OR of 38,58; p=0,014). This finding is similar to the BASIC study.[21]

Klebsiella species predominated in our setting, with Klebsiella pneumoniae representing 39,3% of all microorganisms isolated. Multiple ICU studies have reported a high prevalence of gram-negative microorganisms,[17,20,22,23] including studies conducted in Africa.[16,24,25] A study conducted in neonatal ICU, also at PMH reported a predominance of gram-negative over gram-positive micro-organisms of 67,4% vs 32,6%, respectively.[19] Our findings are comparable with developed countries ICUs, with the BASIC study reporting a higher percentage of gram-positive rods cultured in the blood of the patients and amongst gram-negatives *Pseudomonas* spp., *Klebsiella* spp. and *Escherichia coli* having the highest prevalence.[21] A study conducted amongst HIV/AIDS patients reported *Klebsiella pneumoniae* as the second most prevalent pathogen (13%) comparable with our study with 16% (4/25).[26]

Botswana study encountered coagulase-negative staphylococci as the commonest pathogen isolated with 31,9%, probably due to specimen contamination and followed by *Enterococci* spp. (18%).[18] These findings contrast with the USA ICU study reporting that coagulase-negative staphylococci (35,9%), *Staphylococcus aureus* (16,8%), *Candida* species (10,1%) and enterococcus species (9,8%) as the most prevalent pathogens in ICU.[27]

Susceptibility to many antimicrobials was recorded; however, vancomycin and amikacin had the highest sensitivity to all exposures. Only two microorganisms (*Enterococcus* spp. and *Streptococcus* Group D) were exposed to vancomycin during this audit. Of note, there was a high resistance found with the use of β-Lactams including third-generation cephalosporins and other groups of antimicrobials (Fig. 2). The neonatal PMH study also reported a low susceptibility of *Klebsiella* to gentamicin and cefotaxime of less than 50% and high susceptibility of gram-negative microorganisms to amikacin.[19]

These results differ from a BSI study at Cape Town, where *Enterobacteriaceae* healthcare-acquired BSI had higher susceptibility to β-Lactamic based antibiotics.[16] However, unlike our smaller ICU study, their study included blood samples from the entire hospital

population. Another South African study found that *Klebsiella pneumoniae* had 20% resistance to amikacin, which is similar. However, the same study reported high resistance rates to β-lactams for *Klebsiella pneumoniae*, as blood cultures were sent to private facilities and hospital-associated infections were not separated from community-associated infections.[28] There have been reports from another South Africa ICU study of high frequencies of *Klebsiella pneumoniae* producing extended-spectrum β-lactamase (ESBL).[29] INICC report has found resistance to *Klebsiella pneumoniae* amongst ICU patients of 67,5% to some of the third-generation cephalosporins and carbapenems.[6]

There was no BSI associated with *S. aureus* in our study, probably influenced by the fact of low rate of sample collections due to the frequent lack of culture bottles in our unit.

Study limitations

Firstly, this study was conducted in a single eight-bed ICU at the major tertiary and teaching hospital in Botswana, not reflecting the standard hospitalized patients in the country. The previous audit of PMH ICU reported a higher proportion of surgical patients compared with medical patients and when all eight beds are full, patients requiring ICU are transferred to the private sector for their management.[12] Our exclusion of burns patients may have affected the overall data, as burns patients are known to have higher infection rates however, in the entire study period, there were only two patients admitted to the ICU with burns. The mixed nature of PMH-ICU also makes international comparisons challenging, as many ICU International studies do not include patients aged between 14-18 years, as occurred in our study.

Finally, blood culture bottles were frequently unavailable, with patients unable to have blood cultures performed despite having indications for this investigation. The number of stock limitations was not able to be calculated but almost certainly led to an underestimation of the real prevalence of BSI in our study population.

Conclusions

There is no difference in demographic characteristics (age, gender, APACHE II score) among patients with and without BSI. BSI negatively impacts in the ICU length of stay, ICU and 30-day mortality rate. In our setting, HIV infection is associated with a higher risk of bacteriaemia. *Klebsiella* species including *Klebsiella pneumoniae, Enterobacter* species,

and *Enterococcus* species are the principal microorganisms associated with BSI in PMH-ICU.

Recommendation

Effective infection, prevention and control measures should be implemented to reduce the incidence of BIS, mostly caused by gram-negative microorganisms. Escalate in the capacity of performing blood cultures ensuring the availability of culture bottles at all times is required which will increase the microbiological surveillance in the unit.

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