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Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Gaborone, Botswana

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Abstract

This cross sectional study at a tertiary-care hospital in Botswana describes the epidemiology of *Staphylococcus aureus* bacteremia from 2000–2007. We identified a high prevalence of methicillin-resistant *S. aureus* (MRSA) bacteremia. MRSA isolates had higher proportions of resistance to commonly-used antimicrobials, emphasizing the need to revise empiric prescribing practices in Botswana.

INTRODUCTION

In sub-Saharan Africa, *S. aureus* is a common cause of bacteremia.^{1–5} High regional prevalence rates of HIV may contribute to increased incidence and mortality rates of *S. aureus* bacteremia. In Botswana, the epidemiology of *S. aureus* bacteremia is unknown.

Knowledge of the epidemiology of *S. aureus* bloodstream isolates influences treatment decisions and has broad public health implications.⁶ Construction of empiric prescribing

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guidelines based on local susceptibility profiles may improve care delivery, optimize available resources, and decrease mortality.

Our primary objective was to describe the epidemiology of *S. aureus* bacteremia in hospitalized adults and children in Gaborone, Botswana over an eight-year period. Secondary objectives included identifying patient characteristics associated with MRSA, and describing antimicrobial susceptibilities of *S. aureus* isolates.

METHODS

Participants and setting

This cross-sectional study was performed at Princess Marina Hospital (PMH), a 530-bed hospital in Gaborone, Botswana, with approximately 25,000 annual admissions. The prevalence of HIV in Botswana's adult population is estimated at 17%, and reaches 30–40% among adults aged 25–44. The prevalence among children 1.5–4 years of age is 6.3%.⁷ The inpatient population of PMH reflects the high regional HIV prevalence. Highly active antiretroviral therapy (HAART) has been available free of charge since 2002. This study received approval from the Institutional Review Boards of the Children's Hospital of Philadelphia, and Botswana's Ministry of Health.

All patients hospitalized at PMH between January, 2000 and December, 2007 with a blood culture positive for *S. aureus* were eligible for inclusion; those with MRSA were compared to those with methicillin-sensitive *S. aureus* (MSSA) bacteremia to identify risk factors for MRSA.

Definitions

S. aureus bacteremia was defined as a blood culture yielding *S. aureus* as the sole pathogen. Polymicrobial blood cultures were not included. Multiple positive cultures on a patient within seven days of the original culture were excluded. Hospital wards were categorized by their focal population.

Microbiology methods

Blood samples were processed using a SIGNAL Blood Culture System (Oxoid, Hampshire, England). Isolation and identification of *S. aureus* was performed using Gram's stain and coagulase test. Antimicrobial susceptibility patterns were determined by the disk-diffusion method according to Clinical Laboratory Standards Institute (CLSI) guidelines. Methicillin susceptibility was determined after 24 hour incubation in Muller-Hinton agar with 4% sodium chloride. To determine MRSA status, methicillin was used from 2000–2005, whereas oxacillin was used from 2006–2007. The D-test for determining inducible resistance to clindamycin was not routinely performed.

Data Collection and Statistical Analysis

Electronic and manual records of the Botswana National Health Laboratory were reviewed to identify bacteremic patients. Demographic data available included age, sex, and ward location at the time of blood culture. Patient HIV status and outcomes were not available. Due to personnel transitions and the shift from manual to electronic records, no laboratory records were available for December, 2000 through May, 2001 and March, 2004 through October, 2005. As PMH is a resource-constrained setting blood culture bottles and antibiotics were periodically out of stock during the study period. The sporadic availability of blood culture bottles precluded may have led to an under-estimation of the burden of disease. Therefore, we report the proportion of patients with *S. aureus* bacteremia among all patients with bacteremia.

Continuous variables were described using mean, median, and range or interquartile range (IQR) values and compared using the Wilcoxon rank sum test. Categorical variables were described using counts and percentages and compared using the Fisher exact test.

RESULTS

Characteristics of the Study Population

During the study period, 2,310 (29.7%) of 7,779 blood cultures were positive for a single organism, with *S. aureus* being most commonly isolated. Antibiotic susceptibility results were available for 538 (92.4%) of 582 blood cultures in which *S. aureus* was the sole organism.

Table 1 displays the demographic characteristics of patients with *S. aureus* bacteremia and results of the univariate analysis. The cohort was 41.7% female with a median age of 0.7 years (IQR 0.02–23). Compared with neonates, children aged 1–5 years had a reduced odds of MRSA, while adult subjects had an increased odds of MRSA, both in the 15–49 and >50 years of age categories. Patients in the intensive care unit had an increased odds of MRSA bacteremia compared with patients on the general adult medical wards. After adjusting for ward type, the odds of MRSA bacteremia increased by 9% for each 5 year increase in age (adjusted OR 1.09, 95% CI: 1.04–1.16; $P=0.001$).

Disease Prevalence

Of the 538 episodes of *S. aureus* bacteremia with known susceptibilities, 44.2% ($n=239$) were caused by MRSA. The prevalence of *S. aureus* and MRSA bacteremia among all patients with confirmed bacteremia were 25.3% and 11.2%, respectively. The median yearly proportion of MRSA among *S. aureus* isolates was 44.3% (range 25.7–58.3), with the peak occurring in 2004.

Antimicrobial Susceptibility

S. aureus isolates were routinely tested for susceptibility to chloramphenicol, clindamycin, erythromycin, cephadrine, vancomycin, tetracycline, gentamicin and methicillin (Figure 1). Susceptibility testing for trimethoprim-sulfamethoxazole (TMP-SMX) was not routinely performed, and results were available for only 15 isolates. For TMP-SMX susceptibilities, there was no significant difference between the MSSA and MRSA groups. MRSA isolates were significantly less susceptible to all other antimicrobial agents. The large proportion of isolates resistant to erythromycin but susceptible to clindamycin suggests the possibility of inducible resistance to clindamycin.

DISCUSSION

Our study demonstrates several important findings about the epidemiology of *S. aureus* bacteremia in Botswana. We describe a high prevalence of bacteremia caused by *S. aureus*, and MRSA in particular, among patients at one hospital in an HIV-endemic region. Results from this study will catalyze local changes in microbiologic and clinical practices to allow better surveillance and treatment of invasive *S. aureus* infections.

One of the most striking findings of this study is the overall high proportion of *S. aureus* bacteremia. Additionally, almost half of the cases of *S. aureus* bacteremia were due to MRSA. We also identified several risk factors for MRSA among our cohort, including older age and location in the intensive care unit. This is in keeping with previous data describing these risk factors.^{8,9}

Among MRSA isolates, we describe high proportions of resistance to antimicrobials commonly used to treat *S. aureus* infections. Although more MRSA than MSSA isolates were resistant to clindamycin, the relatively high proportion of clindamycin susceptibility and erythromycin resistance among MRSA isolates raises the possibility of inducible clindamycin resistance. Although testing for TMP-SMX was uncommon, high proportions of both MRSA and MSSA isolates were resistant. Our results underscore the importance of introducing D-testing for inducible resistance and routine testing for TMP-SMX resistance in sub-Saharan Africa.

This study had several limitations. Our prevalence may have been underestimated due to the inconsistent availability of blood culture bottles. However, supply stock-outs are an unfortunate reality of medical care in the developing world. We were also unable to access patient specific data other than age, sex and ward. Therefore, we could not provide mortality data, differentiate between community-acquired and hospital-acquired infections, or group patients according to HIV status.

In summary, we report high prevalence of both MRSA and MSSA bacteremia in Gaborone, Botswana. The high prevalence of MRSA and the increased proportions of resistance to commonly-used antimicrobials among MRSA isolates emphasize the importance of revising antimicrobial susceptibility testing and empiric prescribing practices in Botswana.

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Figure 1. Antimicrobial Susceptibilities for MRSA AND MSSA Isolates

Figure 1 legend: White bars represent percent of MSSA isolates susceptible to antimicrobial; black bars represent MRSA. Overall rates of susceptibility for specific antimicrobial agents were as follows: chloramphenicol (77%), erythromycin (51.3%), clindamycin (90.8%), cephadrine (52.7%), vancomycin (99.2%), tetracycline (43%), and gentamicin (64.5%).

Table 1 Demographic Characteristics of Patients with *Staphylococcus aureus* Bacteremia* (add n=538)

Patient Characteristic	MSSA Number (Percent)	MRSA Number (Percent)	Unadjusted Odds Ratio (95% CI)	P value
Age group (n=488) ^a				
< 1 month	122 (44)	87 (41.2)	Reference	
1–11.9 months	41 (14.8)	34 (16.1)	1.2 (0.7–1.9)	0.6
1 year–4.9 years	33 (11.9)	9 (4.3)	0.4 (0.2–0.8)	0.02
5–14.9 years	25 (9)	8 (3.8)	0.4 (0.2–1)	0.06
15–49 years	42 (15.1)	50 (23.7)	1.7 (1–2.7)	0.04
>50 years	14 (5)	23 (10.9)	2.3 (1.1–4.7)	0.02
Sex (n=455)				
Female	118 (45)	104 (53.9)	1.4 (1–2.1)	0.01
Ward type (n=517)				
Medical ward	123 (42.3)	92 (40.7)	Reference	
Surgical ward	27 (9.3)	17 (7.5)	1 (0.7–1.5)	0.8
NICU	124 (42.6)	96 (42.8)	0.8 (0.4–1.6)	0.6
Adult/pediatric ICU	3 (1)	10 (4.4)	4.4 (1.2–16.6)	0.03
OB/GYN	4 (1.4)	7 (3.1)	2.3 (0.7–8.2)	0.2
Oncology	3 (1)	1 (0.4)	0.4 (0.04–4.3)	0.5
Accident & emergency	7 (2.4)	3 (1.3)	0.6 (0.1–2.3)	0.4

^a Patient-specific information not available for all cases.Abbreviations: MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; ICU, intensive care unit; OB/GYN, obstetrics and gynecology