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A study on pediatric nosocomial methicillin-resistant *Staphylococcus aureus* in Lagos, Nigeria.

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ABSTRACT

This work was undertaken to determine the incidence of nosocomial methicillin–resistant *Staphylococcus aureus* (MRSA) infections in children at a tertiary hospital and the antibiotic susceptibility profiles of MRSA compared with methicillin–sensitive (MSSA) strains. From 1994 to 1995, 4,981 admissions in the neonatal intensive care, paediatric surgical, general paediatric, and the well–baby wards of the Lagos University Teaching Hospital were prospectively monitored for nosocomial *S. aureus* infections. Antibiotic testing was performed on a total of 175 isolates of *S. aureus* obtained from 169 patients with nosocomial infections (NI) using a disk diffusion method and by E test (AB Biodisk, Sweden). In total, nosocomial MRSA infection was identified in 96 (1.9%) patients, rates recorded for patients in the various wards as stated above were 4.2%, 3.2%, 0.5% and 0% respectively. Correspondingly, the rate of nosocomial MRSA amongst all *S. aureus* infections was 63.6%, 44.7%, 41.7% and 0%, and 54.9% overall. All MRSA and MSSA were sensitive to ciprofloxacin and vancomycin. Clindamycin and rifampin (87-98%) were also highly effective against MRSA and MSSA, 78.3 % of MRSA and 91.7% MSSA were sensitive to fusidic acid. Gentamicin (70.9%) and erythromycin (65.8%) were also active on MSSA. Cotrimoxazole had low activity against all the strains. Following the high rate and multiresistant nature of nosocomial MRSA obtained in this study, there is need for intensive surveillance of such infections and initiation of stringent control measures in Nigeria and Africa at large.

Keywords: MRSA, nosocomial infections, susceptibility profiles.

INTRODUCTION

An enormous and menacing rise of antimicrobial resistance is currently being witnessed among the most common pathogens afflicting human kind. *Staphylococcus aureus* is an important pathogen implicated in both nosocomial and community–acquired infections worldwide (Van Eldene et al., 1997; Kesah et al., 2004; Denis et al., 2006). Therapy of infections, particularly hospital infections caused by *S. aureus*, has become increasingly difficult due to the emergence of strains resistant to multiple antimicrobial agents (Kesah et al., 2003; Al Sweih et al., 2005; Groppo et al., 2005; Howden et al., 2005; Sattar et al., 2005; Courvalin, 2006).

In the hospital setting, methicilin-resistant *S. aureus* (MRSA), which is also reported to be multi-resistant, has increased dramatically (Kesah et al., 1997; Cosgrove et al., 2004; Nonhoff et al., 2005). The incidence of nosocomial MRSA is however, known to vary according to geographical location, the number of beds within a hospital and with time (Schmitz and Jones, 1997). In the United States, MRSA accounted for 2.4%

of hospital isolates of *S. aureus* in 1975. By 1991, the percentage increased to 29%, and was 14.9 in hospitals of < 200 beds and 38.3% in hospitals of > 500 beds (Panililio et al., 1992). During the study period, the frequency of hospital – acquired MRSA within European countries ranged from 0.1% in Northern European countries to >30% in Spain, France and Italy (Voss et al., 1994; Voss and Doebbeling, 1995).

Nosocomial MRSA has been reported in Japan (Tobita *et al.,* 1996, Hiramatsu et al., 1997). The frequency of nosocomial MRSA in Africa is not known. However, nosocomial MRSA has been reported in Somalia (Nur et al., 1997). Methicillin resistance in clinical isolates of *S. aureus* has also been reported in some northern African countries like Morocco, Ivory Coast, Cameroon, Nigeria and Kenya (MD, 1995; Kesah et al., 1997).

We are not aware of any reports on the frequency of nosocomial MRSA in Nigeria. The aim of this study was to determine the incidence of nosocomial MRSA infections in paediatric patients at the Lagos University Teaching Hospital (LUTH) between 1994 and 1995. This study also sought to determine the susceptibility profiles of MRSA compared with methicillin-sensitive *S. aureus* (MSSA) to some commonly used antimicrobial agents.

MATERIALS AND METHODS

From 1994 to 1995, 4981 pediatric in-patients at LUTH were prospectively investigated for nosocomial infections (NI) at all body sites from admission until discharge using the methods described by the Centers for Disease Control and prevention (Emori et al., 1991, Garner et al., 1998, Horan et al., 1992). LUTH is a tertiary care hospital with over 750 beds, with the combined paediatric services having a bed complement of 232.

All the patients were screened on admission by collecting various clinical specimens as directed by the clinicians and follow-up specimens were also obtained. Relevant specimens were obtained from patients with NI. All collected specimens were processed, and pathogens identified according to standard microbiological methods (Balows et al., 1991). Isolates were stored frozen at – 70 °C in Brain Heart Infusion Broth supplemented with 10 % (V/V) glycerol.

Antimicrobial susceptibility testing was performed by a disk diffusion technique (Bauer et al., 1966) and by E test (AB Biodisk, Sweden) on Mueller-Hinton agar (Oxoid). Methicillin susceptibility was tested by oxacillin E test on Mueller-Hinton agar to which 2% NaCl has been added. Gram-positive Abdiscs code NZ 22P (ABTEH BIOLOGICALS LTD, LIVERPOOL) and single discs of ciproloxacin, cotrimoxazole, vancomycin, azithromycin, roxithromycin, amoxicillin-clavulanic acid (augmentin) and ampicillin-sulbactam were used in the disc diffusion testing. Pencillin G, oxacillin, augmentin, gentamicin, tetracycline, erythromycin, clindamycin, rifampin, fusidic acid, cotrimoxazole and vancomycin E test strips were used. Sensitivity plates were incubated at 35°C for 24 hours. Interpretation of results was according to the NCCLS interpretive guidelines (NCCLS, 1993) now referred to as the Clinical and Laboratory Standards Institute (CLSI, 2005). The standard reference strain *S. aureus* ATCC 29213 was included in the testing exercise.

RESULTS

A total of 175 strains of *S aureus,* isolated from swabs (80%), blood (12.6%), pus (4%) and urine (3.4%), were obtained from 169 patients with NI during the study period. *S. aureus* was isolated among 110 NI identified in 105 patients out of 1682 patients admitted in the out-born and in-born neonatal intensive care units (NICUs). There were 6 NI in 6 patients out of 1602 admissions in the well baby nurseries caused by *S. aureus.* Forty–seven nosocomial *S. aureus* infections were identified in 46 patients out of 664 paediatric surgical patients, while 12 episodes of nosocomial *S. aureus* infections were identified in 12 patients out of 1033 infants and children admitted in general paediatric wards of LUTH.

Seventy (63.6%) of the 110 nosocomial *S. aureus* infections in the NICUs were caused by methicillin-resistant strains. The percentage of nosocomial MRSA infection was 0% in the well baby nurseries, 44.7 %(21/47) in paediatric surgical patients, 41.7 % (5/12) in patients admitted in the general paediatric wards and 54.9% (96/175) in paediatric patients at LUTH during the study period. In total, nosocomial MRSA infection

was identified in 96 patients (1.9%) of the 4981 admissions in the paediatric department between 1994 and 1995, the incidence was 4.2% for patients admitted in the NICUs, 3.2% for paediatric surgical patients, 0.5% for infants and children in the general paediatric wards and 0% in the well baby nurseries.

Results of the disc diffusion testing showed 100% susceptibility to ciprofloxacin and vancomycin by all strains of both MRSA and MSSA. However, for the other antibiotics tested, percentages of susceptibility were generally lower for isolates of MRSA compared with rates obtained for MSSA strains (Table 1). Azithromycin (88.6%), cloxacillin (87.3%) and gentamicin (70.9%) were quite effective against MSSA. Percentages of susceptibility were generally low for MSSA to contrimoxazole, amoxycillin-clavulanic acid, chloramphenicol, and tetracycline.

Results of the E test are shown in Tables 2 and 3. For all the isolates E-tested, there was high susceptibility (78-97.7%) to clindamycin, rifampin and fusidic acid. The minimum inhibitory concentration (MIC) ranges of the various drugs E-tested were generally lower with MSSA compared with MRSA. The MIC_{90} values for augmentin (1.5μg/ml), clindamycin (0.5 μg/ml) and vancomycin (3 μg/ml) against MSSA were within the susceptible breakpoints, whereas only rifampin (0.19 μg/ml) and vancomycin (3 μg/ml) were effective against 90% of MRSA strains. More than 90% of MRSA isolates were resistant to gentamicin and tetracycline (MIC_{90} > 256 μg/ml), and cotrimoxazole (MIC_{90} > 32 μg/ml).

DISCUSSION

S. aureus is one of the most important pathogens in the hospital environment and has been recognized in Nigeria since the inception of NI surveillance in the 1970s. Between 1994 and 1995, *S. aureus* was the second most frequently isolated nosocomial pathogen from all infection sites at LUTH, and occurred in 16.7% of the infections. It came after *K. pneumoniae* which accounted for 21.9% of all the infections and preceded *P. aeruginosa* which had a frequency of 11.9% (Kesah et al., 1998).

Table 1: Antimicrobial susceptibility patterns of nosocomial MSRA: results of disc diffusion testing

Antibiotic discs (concentration)	No(%) sensitive	
	MSRA (n=96)	MSSA (n=79)
Ciprofloxacin(15 μg)	96(100)	79(100)
Ofloxacin (5 μg)	95(99.0)	79(100)
Vancomycin (30 μg)	96(100)	79(100)
Azithromycin (15 μg)	-[a]	70(88.6)
Cloxacillin(5 μg)	-	69(87.3)
Roxithromycin (15 μg)	-	62(78.5)
Gentamicin (10 μg)	32(33.3)	56(70.9)
Erythromycin (5 μg)	-	52(65.8)
Cotrimoxazole (5 μg)	45(46.9)	47(59.5)
Streptomycin (10 μg)	21(21.9)	35(44.3)
Chloramphenicol (10μg)	-	31(39.2)
Ampicillin-Sulbactam (20μg)	-	30(38.0)
Amoxicillin-Clavulanic acid (30 μg)	-	30(38.0)
Tetracycline (10 μg)	18(18.8)	30(38.0)
Penicillin G (1 unit)	-	2(2.5)
Ampicillin (10 μg)	-	2(2.5)

[a] Not tested

Table 2: Antimicrobial susceptibility patterns of nosocomial MRSA and MSSA determined by E test.

Antimicrobial Agents	MRSA		MSSA	
	No. tested	No(%) susceptible	No. tested	No(%) susceptible
Penicillin G	52	0(0)	43	2(4.7)
Oxacillin	52	0(0)	43	43(100)
Amoxicillin-Clavulanic acid	-	-	35	35(100)
Gentamicin	41	4(9.8)	38	32(84.2)
Tetracycline	41	10(21.7)	39	13(33.3)
Erythromycin	-	-	43	39(90.7)
Clindamycin	52	45(86.5)	43	42(97.7)
Rifampin	52	49(94.2)	43	42(97.7)
Fusidic acid	52	36(78.3)	36	36(91.7)
Vancomycin	46	46(100)	43	43(100)
Trimethoprim-Sulphamethoxazole	46	20(43.48)	43	37(86.0)

Table 3: Minimum inhibitory concentration ranges of antimicrobial agents E-tested against nosocomial MRSA and MSSA.

Antibiotic	Susceptible Breakpoint	MRSA (µg/ml)			MSSA (µg/ml)		
		MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	MIC Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Penicillin G	≤ 0.12	0.9 ->32	> 32	> 32	0.023 - >32	2	>32
Oxacillin	≤ 2	3 - >32	>32	> 32	0.016 – 2	0.75	2
Amoxicillin-Clavulanic acid	≤ 4	-	_	-	0.0125 – 2	0.50	1.5
Gentamicin	≤ 4	0.064 - > 256	48	> 256	0.016 – 4	0.38	48
Tetracycline	≤ 4	0.5 -> 256	128	> 256	0.125 - > 256	48	>256
Erythromycin	≤ 0.5	-	_	_	<0.016-> 256	0.19	2
Clindamycin	≤ 0.5	0.016- >256	0.125	8	0.016-4	0.125	0.25
Rifampin	≤ 1	0.002 - > 32	0.008	0.19	< 0.002 -4	0.008	0.016
Fusidic acid	≤ 2	<0.016 - >256	0.094	4	0.032 – 3	0.125	0.50
Vanconmycin	≤ 4	1 – 4	2	3	1 - 4	2	3
Trimethoprim-Sulphamethoxazole	≤ 2/38	0.032 - >32	6	>32	0.002 – 12	0.064	3

In this study, the frequency of nosocomial MRSA infection was 4.2% in patients admitted to the NICUs, 3.2% in paediatric surgical patients, 0.5% in patients in general paediatric wards, and 1.9% in all paediatric patients studied. Patients admitted in tertiary-care hospitals and in intensive care units, burn patients and patients with surgical wounds or intravenous lines are known to be at very high risk for MRSA infection (Emmerson and Garau, 1992; Hiramatsu et al., 1997; Schmitz and Jones, 1997). In some areas, MRSA is an important pathogen among intravenous drug users. Duration of hospitalization, previous antibiotic treatment and proximity to a patient colonised or

infected with the organism are also predisposing factors to MRSA infection. In acute care and nursing facilities, the major MRSA reservoirs are colonised and infected patients. Person to person transmission of MRSA usually occurs via the hands of healthcare staff (Levine et al., 1982). In this study, patients in the NICUs where there is a high usage of intravenous lines, and paediatric surgical patients had the highest rates of MRSA infection, and patients with MRSA infection, were noted to have had previous antimicrobial therapy and prolonged hospitalization ($\geq$ 3 weeks).

Nosocomial infections caused by multiply resistant strains of S. aureus remain a special problem. The principal concern with *S. aureus* has been resistance to methicillin, recognized since 1961 by Jevons (Jevons, 1961). Three kinds of mechanisms have been reported to give rise to methicillin resistance in staphylococci. Firstly, there is intrinsic resistance which is a classical type of methicillin resistance caused by a novel penicillin-binding protein PBP_{2a}. Secondly there is beta-lactamase-mediated resistance which occurs in strains that are hyper-producers of beta-lactamase thereby inactivating the drug. Thirdly, there is intermediate resistance which is due to alterations of the "regular" PBPs i.e. not PBP_{2a}.

Methicillin resistance mediates clinically inadequate susceptibility to all currently available beta-lactam antibiotics, and MRSA are typically resistant to several other antimicrobial agents including aminoglycosides, chloramphenicol, macrolides and flouroquinolones. However, since multiple resistance varies greatly geographically, susceptibility testing has become imperative in planning of therapy (Schmitz and Jones, 1997)

In this study, the incidence of nosocomial MRSA among all *S. aureus* infections was 63.6% in the NICUs, 44.7% in paediatric surgical patients, 41.7% in general paediatric wards, and 54.9% in all paediatric patients. In the European prevalence of infection in intensive care (EPIC) study, 60% of all *S. aureus* infections (overall rate across Europe) were caused by methicillin resistant strains, the percentage varied considerably between countries. Rates due to MRSA were, between 50 and 80% in Italy, France, Greece, Belgium, Portugal, Spain and Austria, and below 50% in Germany, Switzerland and the UK. Nosocomial MRSA was not reported in the Netherlands, Sweden, Denmark and Norway (Vincent, 1993, Vandenbroucke – Grauls, 1994). The prevalence of nosocomial MRSA infection for all hospitalized patients is 17.5% in the USA (Thornsberry, 1994), 40% in Italy, 34% in France, 31% in Spain, 24% in Belgium, 17% in Austria, 40% in Germany, 24% in Switzerland, 2 % in the Netherlands and 0 % in Sweden and Denmark (Voss et al., 1992). The higher rate of nosocomial MRSA infection obtained in this study compared with the EPIC study is not surprising as there are no adequate and consistent control measures yet in Nigeria for MRSA.

In European countries, majority of hospital strains of *S. aureus* are resistant to gentamicin (62-100%) and ciprofloxacin (50-90%), while relatively lower resistance rates are recorded to rifampin (2-52%) (Voss et al., 1992). In the US, 18.3% of all hospital *S. aureus* are resistant to ciprofloxacin, and 12.8% are resistant to imipenem. Approximately 82% of MRSA are resistant to ciprofloxacin and 68.4% to imipenem, whereas for MSSA, only 4.8% are resistant to ciprofloxacin and 0.3% to imipenem (Thornsberry, 1994). In this study, all the hospital strains of *S. aureus* were sensitive to ciprofloxacin, 49.7% were resistant to gentamicin and 4.2% were resistant to rifampin. The lack of resistance to ciprofloxacin by *S. aureus* in this study may be due to non-usage of this drug in children at LUTH during the study period. Fusidic acid and clindamycin were also highly effective against both MRSA and MSSA. The glycopeptides, vancomycin and teicoplanin are still considered the drugs of choice for infections caused by MRSA in the study area, although reduced susceptibility to glycopeptides has been reported the world over (Hiramatsu et al., 1997; Van Eldene et al., 1997; Cosgrove et al., 2004; Howden et al., 2005; Nonhoff et al., 2005; Courvalin, 2006; Denis et al., 2006). There is need for intensive surveillance of MRSA infection and initiation of stringent infection control measures in Nigeria and Africa at large.

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