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Changing antibiotic resistance profile of *Staphylococcus aureus* isolated from HIV patients (2012–2017) in Southern India

Chinnambedu Ravichandran Swathirajan[a], Marimuthu Ragavan Rameshkumar[a], Sunil Suhas Solomon[a,b], Amrose Pradeep[c], Ramachandran Vignesh[a,d], Pachamuthu Balakrishnan[a,*]

[a] *Infectious Diseases Laboratory, Y. R. Gaitonde Centre for AIDS Research and Education, Voluntary Health Services Hospital Campus, Chennai, Tamil Nadu, India*
[b] *Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA*
[c] *Department of HIV Clinic, Y. R. Gaitonde Centre for AIDS Research and Education, Voluntary Health Services Hospital Campus, Chennai, India*
[d] *Preclinical Department, Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP), Ipoh, Malaysia*

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ABSTRACT

Purpose: Emergence of multidrug-resistant and methicillin-resistant *Staphylococcus aureus* (MRSA) infections in HIV patients limit the treatment options and challenge the clinical management of infections. The periodic monitoring of *S. aureus* infections and its drug resistance profile in HIV patients are of paramount importance in clinical management.
Materials and methods: A total of 7204 clinical specimens from HIV patients from 2012 to 2017 were processed for the isolation of *S. aureus* strains using conventional culture techniques and cultures were identified using standard biochemical test. Antibiotic susceptibility of *S. aureus* strains was tested by Kirby-Bauer disk diffusion method.
Results: A total of 380 (5.3%) *S. aureus* strains were isolated from HIV patients in the study period. High percentage of *S. aureus* strains were isolates from urine (69.5%) specimen and 58.4% of *S. aureus* infections were noted among hospitalized patients. Antibiotic susceptibility profile reveals *S. aureus* was highly resistant to penicillin (95.2%) followed by cephalexin (84.6%). Methicillin resistance was highly observed in the year 2017 (86%) and the rate of MRSA steadily increasing from 51.8% in 2012 to 86% in 2017. Significant increase of *S. aureus* infections (35%; $p < 0.001$) and MRSA (76%; $p = 0.0007$) were observed in the year 2016.
Conclusions: This study reports the increasing trends of *S. aureus* infections and MRSA among HIV patients from Southern India. Multidrug-resistance profile of *S. aureus* could complicate the selection of proper antibiotic regimens and time cure of HIV patients.

Introduction

Staphylococcus aureus is an important opportunistic bacterial pathogen causing significant morbidity and mortality in both immunocompetent and immunocompromised individuals such as HIV patients. *S. aureus* is a leading cause of nosocomial infections which causing bacteremia, surgical wound infections and pneumonia and it frequently acquires drug resistance to various classes of antibiotics [1–4]. Rise of drug-resistant *S. aureus* poses higher risk and burden to healthcare settings worldwide. As part of this drug resistant *S. aureus* profiles, steadily increasing rates of methicillin-resistant *S. aureus* (MRSA) over the years present serious global health issue. World Health Organization (WHO) estimated that the antibacterial drug resistance caused a total of 25,000 deaths in European Union, more than 38,000 deaths in Thailand and over 23,000 in United States until 2013 [5]. According to the suggestion of National Nosocomial Infections Surveillance system in the United States, more than 60% of the patients admitted in intensive care unit have been infected with nosocomial MRSA infections [6,7]. In India, a study conducted at 15 tertiary care centres reported that 42% and 40% of *S. aureus* strains were resistant to methicillin in 2008 and 2009, respectively [8]. Currently,

* Corresponding author.
E-mail address: bala@yrgcare.org (B. Pachamuthu).

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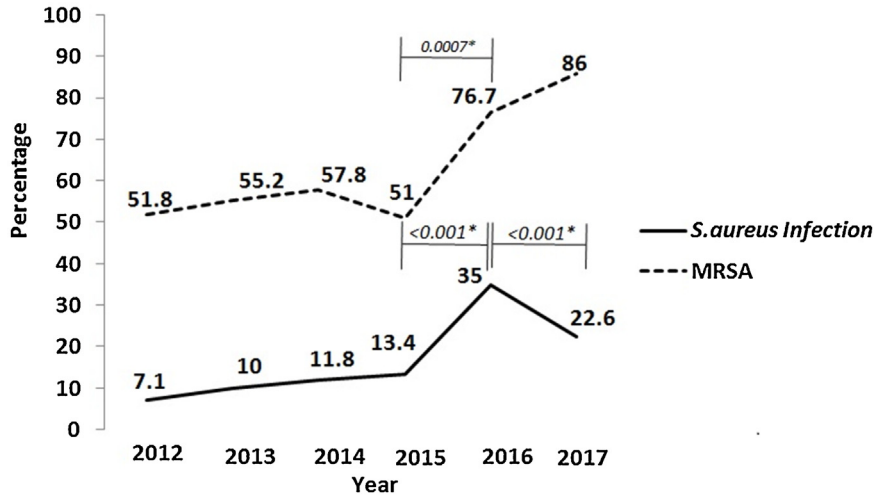

Fig. 1. Year-wise positivity of *Staphylococcus aureus* infection and methicillin-resistant *Staphylococcus aureus* in HIV patients.

S. aureus has developed resistance to several antimicrobial drugs, including second- and third-line antibiotics. Risk factors associated with MRSA infections include indiscriminate use of antibiotics, operation theatre contamination in nosocomial settings, repeated exposure in immunocompromised conditions etc. Vancomycin (a glycopeptide), daptomycin (a lipopeptide), and linezolid (an oxazolidinone) have been approved as the drug of choice for treating MRSA infections. Another drug, tigecycline (a glycylcycline), has shown good activity against MRSA strains in vitro [9]. Variations in *S. aureus* drug-resistance patterns have been observed due to constantly changing epidemiology of MRSA throughout various regions and countries. Therefore, constant surveillance of drug-resistance profile becomes essential for the clinical management of *S. aureus* infections, especially in the HIV settings in resource-limited countries.

Materials and methods

Bacterial cultures

Clinical specimens were collected from HIV patients attending YRG CARE, a tertiary HIV care center in Chennai, India, from 2012 to 2017 for routine clinical and laboratory monitoring. Specimens such as urine, pus, sputum, fine-needle aspirates, and sterile fluids were collected from symptomatic patients based on clinicians' advice. Collected specimens were immediately transported to the laboratory and cultured on MacConkey agar with 0.5% sodium taurocholate, MacConkey agar with 0.15% bile salts, blood agar (5%) and chocolate agar plates. MacConkey agar plates were incubated at 37 °C while blood and chocolate agar plates were incubated at 37 °C in a candle jar under CO_2 environment. Following incubation for 18–24 h, the plates were examined for growth. Isolated colonies suspected of *S. aureus* were identified by Gram stain, catalase and slide coagulase tests. In addition, the colonies were sub-cultured on mannitol salt agar (MSA) plates and incubated to confirm the development of golden yellow pigmented colonies, characteristic of *S. aureus*.

Antibiotic susceptibility test

Isolated *S. aureus* strains were screened for antibiotic susceptibility using Kirby-Bauer disc diffusion method according to CLSI guidelines [10]. In this method, isolated bacterial colonies were suspended in sterile saline to make culture suspensions adjusted to 0.5 McFarland standards. Lawn cultures were made from culture suspensions with sterile swab on the Mueller Hinton agar (MHA) plates. Then antibiotic discs viz. azithromycin, chloramphenicol, ciprofloxacin, clindamycin, co-trimoxazole, doxycycline, erythromycin, gentamycin, levofloxacin, nitrofurantoin, norfloxacin, ofloxacin, oxacillin, penicillin, rifampicin, tetracycline and vancomycin (HiMedia, India) were placed on the agar surface and plates were incubated at 37 °C for 18–24 h. After incubation the zone of inhibition of each antibiotic was measured and the results were interpreted as susceptible, intermediate and resistant based on the standards. Z test was performed to compare two proportions and a $p \leq 0.05$ is considered statistically significant. Statistical analyses were performed using SPSS Software version 20.0.

Table 1
Age group wise distribution of *Staphylococcus aureus* isolated from HIV patients.

Age group	Total number	Percentage
<15	7	1.8%
16–30	63	16.6%
31–45	207	54.5%
46–60	88	23.1%
61–75	14	3.7%
>75	1	0.3%

Results

In the study period from 2012 to 2017, a total of 7204 clinical specimens from HIV patients were processed. *S. aureus* was isolated from 380 (5.3%) specimens among which 222 (58.4%) were in-patients and remaining 158 (41.6%) were out patients. Higher positivity rates of *S. aureus* infection were observed in the age group between 31-45years (n = 207; 54.5%). Infection rates of other age groups are indicated in Table 1.

There was an increased trend of *S. aureus* infection observed from 2012 with significant increase in 2016 ($p < 0.001$) was observed. Compared to 2016, a significant decrease in *S. aureus* infection were noted in 2017 ($p < 0.001$) (Fig. 1). Infection by *S. aureus* were more often found in urine specimens (n = 264; 69.5%) causing urinary tract infections (UTI), followed by pus (n = 79; 21%), sputum (n = 34; 9%), pleural fluid, fine-needle aspiration and skin scrapings (n = 1; 0.3%). Antibiotic susceptibility testing of *S. aureus* strains revealed that higher resistance (95.2%) was shown towards penicillin while lower level of resistance was observed towards nitrofurantoin (4.2%). Detailed analyses of resistance towards individual drugs are shown in Table 2. In this study, oxacillin resistance profile was used as a marker for MRSA. An alarming upward trend in

Table 2
Percentage of antibiotic sensitivity, intermediate and resistance profile of *Staphylococcus aureus* isolated from HIV patients.

Class of antibiotics	Antibiotics	2012 (n = 27)			2013 (n = 38)			2014 (n = 45)			2015 (n = 51)			2016 (n = 133)			2017 (n = 86)			Total (n = 380)		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Aminoglycosides	Gentamicin	48.1	7.5	44.4	47.4	13.1	39.5	44.4	17.8	37.8	33.3	17.7	49.0	52.6	15.1	32.3	40.7	46.3	13.0	45.5	22.1	32.4
	Netilmicin	92.5	0.0	7.5	89.5	7.9	2.6	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	15.5	83.7	4.6
Ansamycins	Rifampicin	59.2	37.1	3.7	52.6	15.8	31.6	57.7	0.0	42.3	51.0	2.0	47.0	45.1	0.0	54.9	57.0	2.0	41.0	53.4	3.5	43.1
Phenicols	Chloramphenicol	48.1	44.5	7.4	65.8	2.6	31.6	40.0	51.1	8.9	21.6	70.1	8.3	15.8	84.2	0.0	21	77.8	1.2	27.9	66.8	5.3
First Generation Cephalosporins	Cephalexin	7.4	7.4	85.2	15.8	0.0	84.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.1	13.3	84.6
Fluoroquinolones	Ciprofloxacin	18.5	26.0	55.5	5.3	36.8	57.9	15.5	20.0	64.5	1.9	27.5	70.6	12.0	15.0	73.0	8.1	18.6	73.3	10.0	21.0	69.0
	Levofloxacin	NS	NS	NS	NS	NS	NS	NS	NS	NS	23.5	27.5	49.0	14.3	8.3	77.4	15.1	19.8	65.1	11.6	20.3	68.1
	Norfloxacin	11.1	7.5	81.4	7.9	5.3	86.8	11.1	31.1	57.8	5.9	12.1	82.0	6.0	22.6	71.4	8.1	32.6	59.3	7.6	24.3	68.1
	Ofloxacin	22.2	33.4	44.4	15.8	23.7	60.5	17.7	4.5	77.8	5.9	0.0	94.1	8.3	2.3	89.4	12.8	3.5	83.7	11.8	6.9	81.3
Folate pathway inhibitors	Co-trimoxazole	29.6	7.4	63.0	21.1	5.2	73.7	17.6	4.4	78.0	19.6	3.9	76.5	18.0	3.8	78.2	28.0	1.0	71.0	21.6	3.7	74.7
Glycopeptides	Vancomycin	96.3	0.0	3.7	86.8	0.0	13.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	24.4	58.2	17.4	14.7	71.3	14.0
	Teicoplanin	77.7	18.6	3.7	42.1	50.0	7.9	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	9.7	89.3	1.0
Lincosamides	Clindamycin	NS	NS	NS	NS	NS	NS	NS	NS	NS	62.7	9.8	27.5	57.1	8.3	34.6	72.0	9.4	18.6	44.7	27.2	28.1
Macrolides	Azithromycin	NS	NS	NS	NS	NS	NS	NS	NS	NS	9.8	9.8	80.4	13.5	3.1	83.4	17.2	12.8	70.0	10.0	11.5	78.5
	Erythromycin	40.7	18.6	40.7	29.0	28.9	42.1	15.5	31.2	53.3	5.9	35.3	58.8	12.8	21.8	65.4	15.1	36.1	48.8	16.3	28.5	55.2
Nitrofurans	Nitrofurantoin	NS	NS	NS	NS	NS	NS	NS	NS	NS	66.7	23.1	10.2	76.7	15.0	8.3	64.0	34.8	1.2	50.3	45.5	4.2
Penicillins	Penicillin	NS	NS	NS	NS	NS	NS	NS	NS	NS	8.0	0.0	92.0	3.0	0.0	97.0	5.8	0.0	94.2	3.4	1.4	95.2
Anti-staphylococcal b-lactams	Oxacillin	44.4	3.8	51.8	44.7	0.0	55.3	33.3	8.9	57.8	47.0	2.0	51.0	21.8	1.5	76.7	12.8	1.2	86.0	29.2	2.6	68.2
Tetracyclines	Doxycycline	NS	NS	NS	NS	NS	NS	NS	NS	NS	66.7	5.9	27.4	64.0	10.4	25.6	76.7	3.5	19.8	48.7	27.2	24.1
	Tetracycline	77.8	0.0	22.2	63.1	10.6	26.3	48.8	11.2	40.0	64.7	0.0	35.3	57.1	5.3	37.6	74.4	1.2	24.4	63.1	4.5	32.4

Note: S-Sensitive; I-Intermediate; R- Resistant.

the prevalence of MRSA strains were observed from 2012 (51.8%) with 2016 (76.6%) showing a significant rise in MRSA incidence ($p < 0.0007$). It must be noted that, while there were lesser number of *S. aureus* infections noted in 2017, the proportion of MRSA incidence was still on the rise (86%), though not statistically significant (Fig. 1). It was also noted that the MRSA strains were highly isolated from male HIV patients (65.3%) compared to female HIV patients (34.7%) and high positivity of MRSA was noted among hospitalized patients (66.8%) than non-hospitalized patients (31.2%). This emphasizes the widespread dissemination of MRSA strains into the environment. *S. aureus* strains showed high level of susceptibility against tetracycline (63.1%) followed by rifampicin (53.4%), nitrofurantoin (50.3%), doxycycline (48.7%), gentamycin (45.5%) and clindamycin (44.7%). Susceptibility patterns of *S. aureus* against various antibiotics during the study period were given in table 3.

Discussion

Antibacterial drugs have been misused in humans in several decades, thereby creating ways for selection and spread of drug resistant bacteria. Consequently, antibacterial drugs have become less effective or even ineffective, resulting in an accelerating global health security emergency that is rapidly outpacing the available of treatment options. WHO reports identify *Staphylococcus aureus* resistance to beta-lactam antibacterial drug methicillin as an international concern [5]. Excess usage of antibiotics has expedited the development of methicillin resistance in *S. aureus* [11]. Risk of death in patients infected with MRSA is as high as 26.3%. Antibacterial resistance by MRSA also causes additional medical costs for antibacterial therapy, medical care and additional cost variable [5].

MRSA strains identified four decades ago have become more problematic due to the evolutionary mechanisms adapted by the bacteria to evade antibiotics which are supported by environmental changes which aid the bacterial spread beyond the restrictions of health care facilities. Virulence conferred by these factors rendered the bacterium dominant resulting in making significant changes in the choice of antibiotics for the management of community-acquired infections [12]. In addition, HIV infection serves as mutualistic co-factor for *S. aureus* in establishing infections. Increase in the number of infections proportionally increases the usage of antibiotics for treatment. High exposure of antibiotics resulted in evolutionary changes in the genetic makeup of the bacterium which in turn lead to the development of drug resistant strains.

In this present study, 7 year data of *S. aureus* infections in HIV patients and antibiotic susceptibility of the isolated strains were analyzed. Higher number of infections was observed in male population compared to female population which might be due to more HIV infections in males which could have been a proportional reflection of this observation. HIV-infected patients have reported to be having 6 times higher risk of community-associated MRSA infections than HIV-negative patients [13] and increased odds of having community-acquired *S. aureus* bacteremia [14]. *S. aureus* is known to be a common cause of UTI infections [15]. Likewise, here, a 3-fold increase in UTI infections caused by *S. aureus* was observed in this study.

MRSA was observed in 68.3% of the *S. aureus* strains which is much higher when compared to other reports, where it is 13–15% [16] and 32% [17] in HIV patients. There was an ascending scenario seen in this study in terms of MRSA incidence which is similar to other studies involving HIV cohorts. Individual exposure to β-lactams, in association with a history of multiple hospitalizations, low CD4+ T-cell counts, injecting drug use, and same sex practices might have contributed as risk factors of increasing incidence of MRSA infections in HIV infected patients [18–25]. Recent antibiotic use is a known risk factor for MRSA infection in the general population and may also be a risk factor among HIV patients. In particular, fluoroquinolones and β-lactams have been shown to increase risk for MRSA colonization and infection, whereas trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be protective, even against community-acquired strains [26–32]. Possibility of *S. aureus* infections causing illnesses and morbidity rates similar to pre-antibiotic era cannot be ruled out due to constant decline in drug effectiveness against *S. aureus* infections [32]. The β-lactamase producing bacteria in HIV patients will certainly make their treatment to bacterial infections more complicate [33]. Preventions strategies are highly recommended for the need and development of various prevention strategies to bring down

S. aureus infection rates in HIV patients in order to control both community-associated and hospital-associated MRSA infections. Prevention strategies include keeping cuts and scrapes clean and covered, practicing good hand hygiene, periodical MRSA screening of healthcare workers; avoiding shared personal items, such as towels and razors; and decolonization in certain situations [34].

It is well established that the potential of currently approved antimicrobials are reduced by the constant emergence of multidrug-resistant pathogens. Novel approaches in drug development to manage multi-drug resistant strains should be entertained but involves limitations such as efficacy, prolonged time taken for development and cost. Cost-efficient methods such as repurposing of FDA-approved drugs were proven to be beneficial in tackling drug-resistance and such strategies should be widely entertained [35].

Conclusions

Expanding drug resistance profiles among *S. aureus* could complicate and limit the treatment options with antibiotics that are currently available. The increase level of antibiotic resistant bacterial infections in HIV patients might be due to high level use of antibiotics for their treatment or transfer of drug resistant bacteria from the environmental settings. It must be clearly noticed from this study that the level of antibiotic resistance among *S. aureus* from HIV patients has been constantly changing and for most of the antibiotics it is increasing steadily. Hence, it is mandatory to constantly screen for *S. aureus* infections and analyze its antibiotic profile to update the clinicians for more effective clinical management of *S. aureus* infection by choosing the right drug especially in a setting where immunocompromised patients are treated.

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Conflict of interest

None Declared.

Ethical statement

Not required.

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