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Antibiotic Resistance Profile and Methicillin-Resistant Encoding Genes of *Staphylococcus aureus* Strains Isolated from Bloodstream Infection Patients in Northern Vietnam

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Keywords: Antibiotic resistance; Staphylococcus aureus (S. aureus); MRSA (methicillin-resistant staphylococcus aureus); MSSA (methicillin-susceptible staphylococcus aureus); MRSA encoding genes; bloodstream infections (BSIs)

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Abstract

BACKGROUND: Evaluating the antibiotic susceptibility and resistance genes is essential in the clinical management of bloodstream infections (BSIs). Nevertheless, there are still limited studies in Northern Vietnam**.**

AIM: This study aimed to determine the antibiotic resistance profile and methicillin-resistant encoding genes of *Staphylococcus aureus (S. aureus)* causing BSIs in Northern Vietnam.

METHODS: The cross-sectional study was done from December 2012 to June 2014 in two tertiary hospitals in Northern Vietnam. Tests performed at the lab of the hospital.

RESULTS: In 43 *S. aureus* strains isolating, 53.5 % were MRSA. Distribution of gene for overall, MRSA, and MSSA strains were following: *mecA* gene (58.1 %; 95.7%, and 15%), *femA* gene (48.8%, 47.8%, and 50%), *femB* gene (88.4%, 82.6%, and 95%). Antibiotic resistance was highest in penicillin (100%), followed by erythromycin (65.1%) and clindamycin (60.5%). Several antibiotics were susceptible (100%), including vancomycin, tigecycline, linezolid, quinupristin/dalfopristin. Quinolone group was highly sensitive, include ciprofloxacin (83.7%), levofloxacin (86%) and moxifloxacin (86%).

CONCLUSION: In *S. aureus* causing BSIs, antibiotic resistance was higher in penicillin, erythromycin, and clindamycin. All strains were utterly susceptible to vancomycin, tigecycline, linezolid, quinupristin/dalfopristin.

Introduction

Bloodstream infections (BSIs) became a significant concern with increasing in incidence [1]. Understanding the aetiology of BSI was essential for management. In Asian countries, *S. aureus* was one of the leading causes of bloodstream infections [2], and its incidence was increasing worldwide [3], [4]. It was responsible for many severe clinical conditions, especially in bloodstream infections [5] with rates of mortality was 50% [6]. With subtype of methicillin-resistant staphylococcus aureus (MRSA), the prevalence and mortality were higher than methicillin-susceptible staphylococcus aureus (MSSA) [7]. The burden of MRSA disease was quantifiable and substantial [8]. In European, Cassini et al. used population-level model estimating that MRSA *caused* 148 thousand infections and 32.6 thousand BSIs in 2015 [9]. In Asia, among patients with community-associated *S. aureus* infections, MRSA accounted for 25.5% [10]. Under increasing in prevalence, increasing resistance also reported, especially MRSA [11]. It caused many clinical conditions with poor outcomes [12]. Patients with MRSA in BSIs had a worse prognosis because of partially effect on correct empirical treatment [13]. It became a global concern [14] with the increasing burden of cost [15] and the

resistance to all classes of antibiotics [16]. Therefore, evaluation of the antibiotic susceptibility of bacteria is essential to decide what types of medicines and what appropriate doses that are improving treatment efficiency and minimising the antibiotic resistance rate.

In Vietnam, MRSA accounted for 67.4% of *S. aureus* healthcare-associated infections [10]. The study of causes in BSIs patients in Northern Vietnam showed 37% of methicillin-resistance among *S. aureus* [17], but there are still limited studies in Northern Vietnam. Thus, our research aims is to determine the antibiotic resistance profile and the prevalence of methicillin-resistant encoding genes in *S. aureus,* causing bloodstream infections in Northern Vietnam.

Materials and Methods

The cross-sectional study was done from 12/2012 to 6/2014 in the National Hospital of Tropical Diseases and 103 Military Hospital. Isolating blood samples from septicemia patients in two hospitals, 43 *S. aureus* strains were identified at the labs of those hospitals. The information of patients collected on the same forms.

Antimicrobial susceptibility assessed through MIC test by VITEK®2 Compact (BioMérieux, France and provided by DEKA *Limited Liability Company)* standardised by CLSI [18]. Antibiotics which have been used are*were (with number coding – abbreviation for Figure 3):* penicillin (1-PEN), gentamycin (2-GM), ciprofloxacin (3-CIP), levofloxacin (4-LVX), moxifloxacin (5- MXF), tetracycline (6-TE), erythromycin (7-ERY), clindamycin (8-CM), trimethoprim/sulfamethoxazole (9-SXT), vancomycin (10-VAN), rifampin (11-RIF), quinupristin/dalfopristin (12-QD), linezolid (13-LZD), oxacillin (14-OXA), tigecycline (15-TGE).

Using QIAamp DNA Mini Kit (USA) for DNA extraction (including isolation and quantification), we performed the experimental procedure according to manufacturer's instruction. PCR amplification performed in PCR master mix (Invitrogen – USA) that consisted of 200 µM of each dNTPs (dATP, dCTP, dGTP, dTTP), 100 pM primers, 1 U Taq DNA polymerase, 10 mM Tris-HCl, 1.5 mM $MgCl_2$ and 10 µl DNA template. Specific primers for *mecA*, *femA*, and *femB* genes showed in table 1. The experiments were performed using the protocol with 25 cycles that each of them consisted of 3 steps including denaturing (94^0C for 1 minute), priming (57^0C for 1 minute), synthesising of sequence (72^0C for 1 minute). PCR products were performed electrophoresis, imaged routinely and sequenced. The sequence of PCR products was compared with the original gene's sequence on GenBank to confirm *mecA, femA, and femB* genes.

Table 1: Specific primers for mecA gene

Target gene	Primer	Nucleotide sequence (5' – 3')	Size (bp)	Location
mecA	Mec-A1	5' – AAA ATC GAT GGT AAA GGT TGG C – 3'	533	1282-1303
	Mec-A2	5' – AGT TCT GCA GTA CCG GAT TTG C – 3'		1739-1814
femA	Fem-A1	5' – AGA CAA ATA GGA GTA ATG AT – 3'	509	595-614
	Fem-A2	5' – AAA TCT AAC ACT GAG TGA TA – 3'		1084-1103
femB	Fem-B1	5' – TTA CAG AGT TAA CTG TTA CC – 3'	651	1904-1923
	Fem-B2	5' – ATA CAA ATC CAG CAC GCT CT – 3'		2535-2554

Ethical considerations

The Ethics Committee of the National Hospital of Tropical Diseases and Military Hospital 103 approved the protocol of the study. The study was in line with the Declaration of Helsinki. Written informed consent has been signed by all participants after full explanation. After that, the blood samples were collected.

Statistical Analysis

The statistical analysis was conducted using the R language. Graphics also were performed by the R language. In this study, the analysis of such enormous volumes of information in the acquisition of data from 43 strains, each strain companion with genes (*mecA, femA, and femB*) and 15 antibiotics with 3 levels of resistance (susceptible, intermediate, resistance). For this reason, we used R language to analyse.

Results

Characteristics of the patient in this study showed in Table 2.

Table 2: Characteristics of patients

Characteristics		Number (Percentage)
Age (subgroup)		
	16-19	5 (11.63)
	20-29	5 (11.63)
	30-39	11 (25.58)
	40-49	7 (16.28)
	50-59	9 (20.93)
	≥ 60	6 (13.95)
Gender		
	Male	40 (93.02 %)
	Female	3 (6.98 %)
History of the medical conditions		
	Cirrhosis	4 (9.3)
	Self-report alcoholism	4 (9.3)
	Spinal cord injury	3 (6.98)
	Diabetes	2 (4.65)
	Hypertension	2 (4.65)
	Hepatitis	2 (4.65)
	Chronic arthritis	2 (4.65)
	Urinary tract stone	1 (2.33)
	Heart failure	1 (2.33)
	Deep vein thrombosis	1 (2.33)
	No	21 (48.83)
Time to hospitalization		
	< 5	17 (39.53)
	5-14	21 (48.84)
	>14	5 (11.63)

Among 43 *S. aureus* strains isolated analysed, 23 S. aureus strains were MRSA strains (53.5 %), and 20 S. aureus strains were MSSA strains (46.5%). Detail information of showed in Table 3.

Table 3: Methicillin-resistant S. aureus and methicillin-resistant encoding genes

Result	Number of strains (n = 43) Percentage (%)
MRSA	23 (53.49%)
MSSA	20 (46.51%)
mecA	25 (58.13%)
femA	21 (48.84%)
femB	38 (88.37%)
mecA + femA	11 (25.58%)
mecA + femB	23 (53.84%)
mecA + femA + femB	10 (23.25%)

And among that, 58.1 % strains were identified as producing *mecA*, and 22 of 23 MRSA strains (95.7%) proved to be having *mecA* gene when 15% strains in the MSSA group possessed this gene. The prevalence of *femB* gene of overall strains, MRSA, and MSSA was 88.4%, 82.6%, and 95%, respectively. The prevalence of *femA* gene of whole strains, MRSA, and MSSA was 48.8%, 47.8%, and 50%, respectively. More information showed in Table 4.

Table 4: Encoding genes of methicillin-resistant in S. Aureus

Gene	MRSA (n = 23)				MSSA (n = 20)			
	Positive (+)		Negative (-)		Positive (+)		Negative (-)	
	n	(%)	n	(%)	n	(%)	n	(%)
mecA	22	95.65	1	4.34	3	15	17	85
femA	11	47.83	12	52.17	10	50	10	50
femB	19	82.6	4	17.4	19	95	1	5
mecA + femA	10	43.47	13	56.53	1	5	19	95
mecA + femB	17	73.91	6	26.09	6	30	14	70
mecA + femA + femB	9	39.13	14	60.87	1	5	19	95

Figure 1 showed the highest prevalence of resistance to penicillin (PEN -100%), followed by erythromycin (ERY - 65.1%) and clindamycin (CM - 60.5%).

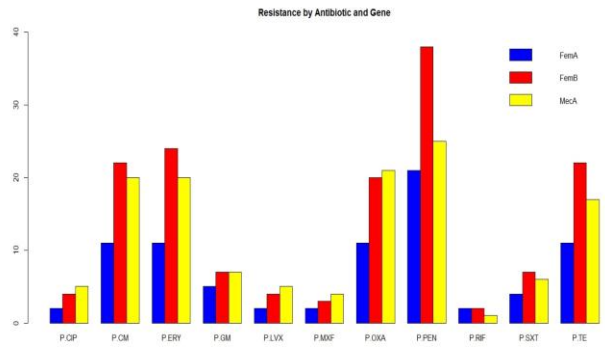

Figure 1: Antibiotic resistant profile

While Figure 2 showed highly active antibiotics in quinolone group, include ciprofloxacin (CIP - 83.7% of isolates), levofloxacin (LVX - 86.1% of isolates) and moxifloxacin (MXF - 86.1% of isolates). Several antibiotics were susceptible (100%), include vancomycin, tigecycline, linezolid, quinupristin/ dalfopristin.

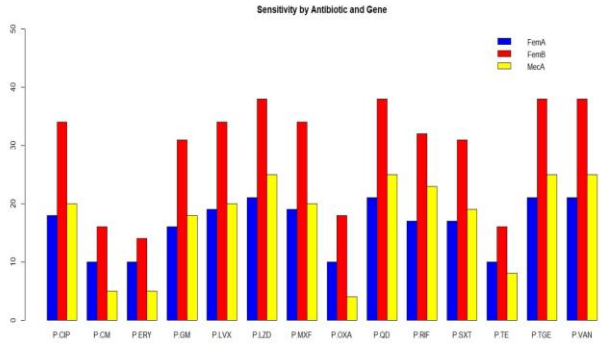

Figure 2: Antibiotic sensitivity profile

The level of resistance (MIC) in MRSA group to clindamycin, erythromycin, tetracycline, levofloxacin, ciprofloxacin, moxifloxacin was higher than MSSA group. In each antibiotic, detail information of genes showed. Figure 3 showed that the distribution of three *femA*, f*emB*, and *mecA* genes is equivalent to 15 antibiotics.

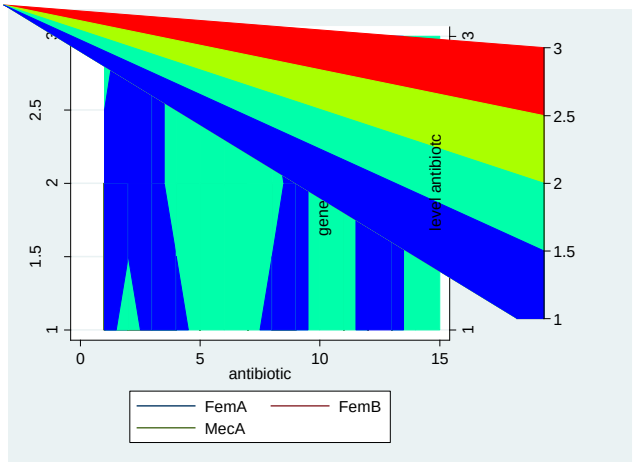

Figure 3: Distribution the antibiotic resistance level with genes. Antibiotic gene: 1.FemA; 2.FemB; 3.MecA. Antibiotic resistance level: From 1 to 3 are R, S, I, respectively; Antibiotic: From 1 to 15 is the ordinal number of 15 antibiotics

The rate of sensitivity also accounts for the majority of ciprofloxacin, levofloxacin, moxifloxacin, linezolid, quinupristin/ dalfopristin, rifampin, tigecycline, vancomycin distributed in all three genes but most in the *femB* gene. The intermediate response is concentrated in moxifloxacin and rifampin antibiotics. Antibiotic resistance focused on antibiotics clindamycin, erythromycin, oxacillin, penicillin, and tetracycline. Figure 3 supported figures 1 and 2 to visualise the association between the gene and antibiotic resistance.

Table 5 clarified the detail of antibiotic resistance with *S. aureus*. While MRSA strains were highly resistant to penicillin, erythromycin, clindamycin, and tetracycline with the rate following: 100%, 82.6%, 87%, 73.9%, respectively, MSSA strains showed a lower prevalence of resistance to these agents with the rate following: 20%, 9%, 6%, 3%, respectively. Both groups were susceptible to vancomycin, tigecycline, linezolid, quinupristin/ dalfopristine at the rate of 100%.

Table 5: The antibiotic resistance profile of S. Aureus

Antimicrobial agents	MRSA			MSSA		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Penicillin			23 (100)			20 (100)
Erythromycin	4 (17.39)		19 (82.61)	11 (55)		9 (45)
Clindamycin	3 (17.04)		20 (86.96)	14 (70)		6 (30)
Tetracycline	6 (26.09)		17 (73.91)	17 (65)		3 (35)
Gentamycin	16 (69.57)		7 (30.43)	17 (85)		3 (15)
Trimethoprim/sulfamethoxazole	17 (73.91)		6 (26.09)	16 (80)		4 (20)
Ciprofloxacin	18 (78.26)	0 (0)	5 (21.74)	18 (90)	1 (5.0)	1 (5.0)
Levofloxacin	18 (78.26)		5 (21.74)	19 (95)		1 (5.0)
Moxifloxacin	18 (78.26)	1 (4.35)	4 (17.39)	19 (95)	0 (0)	1 (5.0)
Rifampin	22 (95.65)	0 (0)	1 (4.35)	14 (70)	5 (25)	1 (5.0)
Vancomycin	23 (100)			20 (100)		
Quinupristin/dalfopristin	21 (100)			22 (100)		
Linezolid	23 (100)			20 (100)		
Tigecycline	23 (100)			20 (100)		

Discussion

The methicillin-resistant in *S. aureus* strains are encoded by mobile genes with the *mecA* and *femB* gene was the most frequently. The incidence of MRSA varies from region to region. In our study, among 43 *S. aureus* strains have been analysed in BSI patients, 53.5% strains were identified as MRSA that was higher than study in Northern Vietnam (37%) [17]. Comparing with other countries, it was higher than the Philippines (38.1%), India (22.6%) [19] but lower than that of Korea (77.6%), Taiwan (65%), Hong Kong (56.8%), Sri Lanka (86.5%) [19].

Almost cases (22/23) with MRSA had *mecA* gene and the 100% resistance to penicillin was found that in line with the present study [20]. Our results about *mecA* gene have been shown that the *mecA* gene is responsible for resistance to methicillin [21] with the mechanisms have been proved [11] and 15% strains in MSSA group possessed this gene. Mohanasoundaram et al. showed similar findings with 100% MRSA possessed *mecA* gene, and only one MSSA strain had maintained this gene [22]. The 15% rate of MSSA positive for the *mecA* gene is quite high, and field literature reported a rate of 3% for MSSA positive for *mecA* [23]. The potential explanation regarding this high number is that the resistance gene transmitted in the hospital between bacteria. Thus, this finding in our study provides useful information to determine the prevalence of *mecA* gene in MSSA patients. In our study, *femB* gene was detected in almost *S. aureus* isolates, 82.6% in MRSA and 95% in the MSSA group, respectively. This result corroborated with Kobayashi et al. [24] but the differences between two studies that needed to highlight were the expression of *femA* gene showed very high (89.4%) [24] in Kobayashi's study and lower rate in our research (48.8%). Further analysis of the expression of these genes in staphylococci will be needed.

MRSA in BSIs has been shown substantial increase in the 21 century [25]. As a result, its burden was growing not only in Europe [15], [26] but also worldwide [27]. Finding the appropriate therapy became crucial and glycopeptides had been used as an effective empirical antibiotic therapy for MRSA[28]. But in the time of antibiotics and resistance becoming popular, *S. aureus* also starts resistance to vancomycin that leading high financial burden and increased mortality [29], [30], [31]. The knowledge of antibiotic resistance profile is critical in clinical practice. In our study, some routine antibiotic agents used commonly in our area showed high resistance. The results of our study also showed that vancomycin, tigecycline, linezolid, quinupristin/dalfopristin emerged as choices for empiric therapy instead. Fan Zhang et al. showed similar findings with a high rate of resistance to penicillin (100%), erythromycin (73.3%) and clindamycin (57.3%) and the clear choice for treatment were vancomycin in these cases [20]. In our study, methicillin-resistant encoding genes showed high correlation with antibiotic resistance. Penicillin, erythromycin, clindamycin, and tetracycline showed resistant to MRSA but susceptibility to MSSA. The remarkable results in our study were that vancomycin, tigecycline, linezolid, quinupristin/dalfopristin were entirely susceptible to both groups. It guides to use antibiotics in case of suspecting bloodstream infection caused by *S. aureus.*

Limitation of study: The isolates of *S. aureus* strains included seem to be quite old (2012-2014), but it still plays an important role in the reflection of the current epidemiological situation. The isolates included were small (43 isolates) because we focused on only bloodstream infection patients and these results of our study were useful for this kind of patient.

As a conclusion, in *S. aureus* causing bloodstream infections, antibiotic resistance was higher in penicillin, erythromycin, and clindamycin. All strains were entirely susceptible to vancomycin, tigecycline, linezolid, quinupristin/dalfopristin.

Ethical approval

This study is approved by the ethics committee of National Hospital of Tropical Diseases and Military Hospital 103.

Informed consent

The consent and commitment were signed by the patients in the study.

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