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ORIGINAL RESEARCH

Evaluation of the Negative Predictive Value of Methicillin-Resistant *Staphylococcus aureus* Nasal Swab Screening in the Medical Intensive Care Units and Its Effect on Antibiotic Duration

Chih-Hsun Tai[1,2], Wei-Ling Liu[2], Sung-Ching Pan[3], Shih-Chi Ku[3], Fang-Ju Lin[1,2,4], Chien-Chih Wu[1,2]

[1]Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence: Chien-Chih Wu, Department of Pharmacy, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan, Tel/Fax +886-2-23123456 ext. 63702; +886-2-23310930, Email 101440@ntuh.gov.tw; Fang-Ju Lin, Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, Tel/Fax +886-2-33668809; +886-2-23310930, Email fjilin@ntu.edu.tw

Background: In addition to active surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) carrier, MRSA nasal screening can be valuable for antibiotic de-escalation. This study aimed to assess the correlations between the MRSA nasal swab and subsequent culture results in patients admitted to medical intensive care units (MICU). The impact of MRSA nasal swab on the antibiotic duration was also evaluated.

Materials and Methods: This retrospective study enrolled patients who received glycopeptides in the MICU of a medical center in 2019. Patients treated with glycopeptides for over 2 days before MICU admission were excluded. The associated data were collected through the electronic medical record system. The negative predictive value (NPV) of MRSA nasal swabs for MRSA infection was calculated, and their influence on empirical glycopeptide treatment duration was analyzed.

Results: Of the 338 patients who met the inclusion criteria, 277 underwent MRSA nasal screening. The NPV of MRSA-negative nasal swab for subsequent MRSA infection was 98.4%. The glycopeptide treatment duration of the patients with and without nasal screening was not significantly different (4.2 ± 2.8 vs 4.4 ± 3.0 days, $p = 0.577$). Of the 120 patients with MRSA-negative nasal swab and no subsequent MRSA infection, 75 continued empirical glycopeptides therapy. The additional treatment time was 3 days (interquartile range: 2–6 days).

Conclusion: The MRSA nasal swabs have high NPV for MRSA infection in critically ill patients. However, it has no impact on the empirical glycopeptide treatment duration. The value of MRSA nasal swabs should be advocated to optimize antibiotic therapy.

Keywords: MRSA nasal swab, glycopeptides, antibiotic stewardship, critical care

Introduction

The *Staphylococcus* genus are gram-positive cocci and belong to the family Micrococcaceae.[1] *Staphylococci* are typically categorized as coagulase-positive staphylococci (*S. aureus*) and coagulase-negative staphylococci (*S. epidermidis*).[1,2] Both pathogens could lead to nosocomial infections, and biofilm formation further complicates clinical management.[1,2] Biofilm formation evolves in three steps, starting with nonspecific adherence of individual cells to the materials, followed by growth and biofilm formation, and ending with detachment of surface bacteria.[1] In *S. epidermidis*, biofilm formation is associated with the production of polysaccharide intercellular adhesion (PIA), and raise opsonic antibodies against PIA could be promising for the elimination of colonizing and biofilm-forming *S. epidermidis*.[3,4] Frequently, *S. aureus* is resistant to methicillin (methicillin-resistant *S. aureus* [MRSA]) and almost all β-lactam drugs (in up to 50% of hospital isolates).[1] MRSA are important bacteria in nosocomial infection and are listed by the World Health Organization as major bacteria in urgent need of new antibiotics.[5] In associated treatment guidelines, the risk of MRSA infection—including having previous

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MRSA infection or colonization, receiving parenteral antibiotic therapy or having hospitalization within 90 days, receiving dialysis, and local rate of MRSA accounting for over 20% of the *S. aureus* strain—is mostly applied to determine the use of empirical anti-MRSA agents.[6,7] Using risk assessment alone may result in overuse of anti-MRSA agents for critically ill patients. According to the internal analysis data, teicoplanin is primarily prescribed in the intensive care unit (ICU) of this hospital (with a monthly average defined daily dose per 1000 inhabitants per day of 257). Moreover, it is generally used as empirical therapy (80% of the patients stopped the treatment within 7 days). According to data from the Taiwan Nosocomial Infections Surveillance System in 2019, *S. aureus* only accounted for less than 3.5% of total isolates of the ICU of medical centers. Among all *S. aureus* isolates, MRSA accounted for 64.1%. Recent studies have indicated that MRSA nasal swabs have high negative predictive values (NPVs) in the specimen culture results of all body parts. The MRSA nasal screening can be utilized to reduce unwanted adverse drug reactions and cost by offering a high NPV and the opportunity to discontinue anti-MRSA agents.[8–11] Furthermore, the latest community-acquired pneumonia diagnosis and treatment guidelines published by the Infectious Diseases Society of America also emphasize the value of MRSA nasal swabs on antibiotic de-escalation.[12]

Associated studies on MRSA nasal swabs in Taiwan has mostly examined MRSA colonization rate or the influence of decolonization on the subsequent MRSA infection rate.[13–16] Only one study targeted patients admitted to the emergency room with skin infection and analyzed the specificity of MRSA nasal swab for community-acquired MRSA infection.[17] As part of infection control policy, MRSA nasal swab screening is often conducted for patients at medical intensive care units (MICU) admission in our hospital. Patients with severe illnesses or MRSA risk factors typically receive empirical anti-MRSA therapy. Therefore, this study aimed to investigate the NPVs of MRSA nasal swabs in the MICU through retrospective analysis. The impact of MRSA nasal swab screening on the treatment duration of empirical glycopeptide therapy was also analyzed.

Materials and Methods

Study Design and Participants

This retrospective single-center study was approved by the institutional review board of National Taiwan University Hospital (202001097RIND). The informed consent was waived because of the retrospective nature of this study and all patient identification was removed. This study was conducted in accordance with the Declaration of Helsinki. The participants were patients who had MICU admission from January 1, 2019, to December 31, 2019. The inclusion criteria were as follows: (1) age $\geq$ 20 years-old and (2) receiving teicoplanin or vancomycin in the ICU (only those who had MRSA nasal screening within 7 days before or 2 days after they started using teicoplanin or vancomycin were included). Patients who had treated with teicoplanin or vancomycin for over 2 days before MICU admission were excluded. Positive MRSA culture result was defined as the specimen from blood, urine, sputum and catheter of a patient revealed MRSA within 7 days after nasal screening. When the impact of MRSA nasal screening on the treatment duration of glycopeptide was assessed, the patients who died during glycopeptide therapy and those who had other indications for glycopeptide therapy were further excluded. The patients with MRSA nasal screening comprised the experimental group, whereas those without screening formed the control group. The treatment duration of the two groups was analyzed.

Isolation and Identification of MRSA

Nasal screening samples were obtained by rotating sterile swabs (eSwab®, COPAN, Via Perotti, 10-Brescia, Italy) over the nasal vestibule. The swabs and other culture samples were then inoculated onto blood agar plates and incubated for 24 hours for colony identification via MALDI-TOF (Bruker). Identification of MRSA isolates were performed using the VITEK-2 automated antimicrobial susceptibility testing system (bioMérieux, Marcy l'Étoile, France).

Data Collection

Patient data were collected through the electronic medical system of National Taiwan University Hospital, and their demographic data were documented. The collected data were as follows: sex; age; height; kidney function; undergoing renal replacement therapy or not; Acute Physiology and Chronic Health Evaluation II score (APACHE II); risk factors of MRSA infection (previous MRSA infection/received parenteral antibiotics/prior hospitalization for over 2 days/had

dialysis within 90 days or had positive influenza test/used anti-influenza drugs in the preceding 5 days); MRSA nasal screening results; specimen culture results within 1 month; and indications, dosage, and treatment duration of teicoplanin or vancomycin.

Calculation of Predictive Value, Sensitivity and Specificity

The sensitivity, specificity, positive predictive value (PPV), and NPV of the MRSA nasal swabs were investigated in the patients who underwent screening to assess whether the swabs can predict MRSA in the subsequent culture specimens. The calculation was based on following equations:

	MRSA infection (+)	**MRSA infection (-)**
MRSA (+) nasal swab	A	C
MRSA (-) nasal swab	B	D

Sensitivity = A/(A+B), Specificity = D/(C+D).
PPV = A/(A+C), NPV = D/(B+D).

Statistical Analysis

For the assessment of the impact of MRSA nasal swabs on the treatment duration of teicoplanin and vancomycin, the categorical variables were analyzed with the chi-square test or Fisher's exact test. The continuous variables were analyzed with the independent *t* test. Moreover, multivariable analysis was performed to examine if the patients' demographic data and characteristics influence the treatment duration of teicoplanin and vancomycin. The categorical variables were displayed by number and percentage (n, %), and the continuous variables were displayed by mean ± standard deviation (SD). A p value of <0.05 is viewed as statistically significant. The statistical analysis was conducted with SPSS 20 (IBM Corp., Armonk, NY, USA).

Results

This study included 338 patients who received teicoplanin or vancomycin treatment, and 23 patients (7%) had positive MRSA culture (Figure 1). Among them, 277 patients (82.0%) underwent MRSA nasal swab screening and 61 (18.0%) did not. Overall, 214 (63.3%) of the patients were male (Table 1). The average age was 64.9 ± 15.7 years, and the average body mass index (BMI) was 23 ± 4.6 kg/m^2. Regarding risk factors for MRSA infection, 12 patients (3.6%) had MRSA infection in the preceding 90 days, 294 (87.0%) had previous parenteral antibiotic therapy, and 289 (85.6%) had prior hospitalization for over 2 days. The number of people undergoing dialysis was 85 (25.1%), and 25 patients (7.4%)

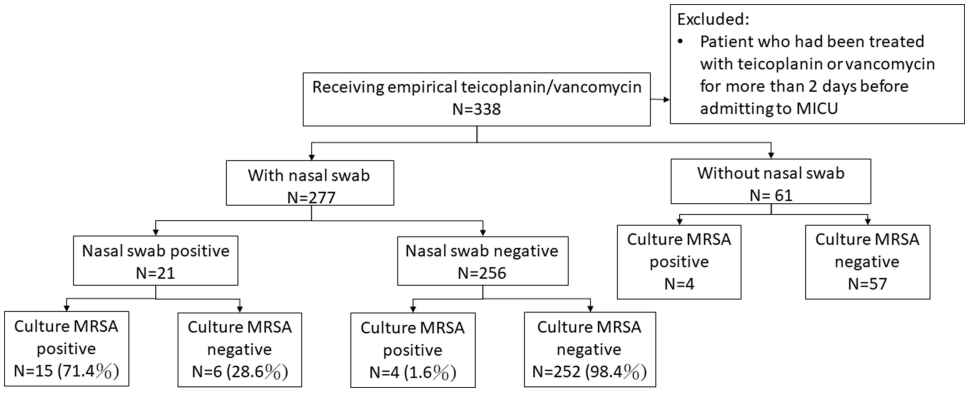

Figure 1 Flow chart.
Abbreviations: MRSA, methicillin resistant *Staphylococcus aureus*; MICU, medical intensive care unit.

Table 1 Demographic Data of Study Population

Characteristic	Teicoplanin n=280	Vancomycin n=58	All Patients n=338	P value
Male, no. (%)	175 (62.5)	39 (67.2)	214 (63.3)	0.495
Age, year (SD)	65.3±15.3	62.8±17.6	64.9±15.7	0.264
BMI, kg/m^2 (SD)$^{\#}$	23±4.7	22.9±4.4	23±4.6	0.903
APACHE II score (SD)*	26.17±9	25.3±9	26±9	0.484
Prior culture isolation of MRSA in the last 90 days, no. (%)	9 (3.2)	3 (5.2)	12 (3.6)	0.463
Receipt of parenteral antibiotics in the last 90 days, no. (%)	244 (87.1)	50 (86.2)	294 (87.0)	0.847
Recent hospitalization > 2 days in the last 90 days, no. (%)	243 (86.8)	46 (79.3)	289 (85.5)	0.141
Receipt of RRT in the last 90 days, no. (%)	54 (19.3)	31 (53.4)	85 (25.1)	<0.001
Recent influenza, no. (%)	20 (7.1)	5 (8.6)	25 (7.4)	0.695
CL_{Cr}>60 mL/min, no (%)	60 (21.4)	15 (25.9)	75 (22.2)	0.460
60≧CL_{Cr}>30 mL/min, no (%)	66 (23.6)	5 (8.6)	71 (21.0)	0.011
CL_{Cr}≦30 mL/min, no (%)	45 (16.1)	2 (3.4)	47 (13.9)	0.011
RRT, no. (%)	109 (38.9)	36 (62.1)	145 (42.9)	0.001
CVVH	65 (23.2)	18 (31.0)	83 (24.6)	
HD	33 (11.8)	18 (31.0)	51 (15.1)	
Transit to different RRT	11 (3.9)	0 (0.0)	11 (3.2)	
Treatment days	4.2±3.8	5.7±7.3	4.4±4.6	0.283
Loading dose (mg/kg)	11.2±1.1	19.7±4.3		

Note: $^{\#}$Missing data: 10 and 5 in teicoplanin and vancomycin group, respectively. *Missing data: 1 in teicoplanin group.
Abbreviations: BMI, body mass index; MRSA, methicillin-resistant *Staphylococcus aureus*; RRT, renal replacement therapy; CL_{Cr}, creatinine clearance; CVVH, continuous veno-venous hemofiltration; HD, hemodialysis; APACHE II, Acute Physiology and Chronic Health Evaluation II.

tested positive during influenza screening or used anti-influenza drugs in the preceding 5 days. In addition, 280 patients (82.8%) used teicoplanin, and the remaining 58 (17.2%) used vancomycin. Most of the patient who used teicoplanin had creatinine clearance of ≤ 60 mL/min. Most of the patients were treated empirically for pneumonia (58%), followed by intra-abdominal infections (14.2%).

Among the 277 patients who underwent MRSA nasal screening, 21 tested positive, and 15 of them had MRSA in the subsequent culture results. Among the 256 patients who tested negative in the screening, only four had MRSA in the specimen culture results. The sensitivity, specificity, PPV, and NPV of the MRSA nasal swabs for MRSA infection were 78.9%, 97.7%, 71.4%, and 98.4%, respectively (Table 2). The NPV of MRSA nasal swab for different types of infections were ranging from 93.8% to 100%. In addition, among those who tested negative in the screening with no MRSA in the subsequent culture results within 7 days, only one had MRSA in the skin pus culture 27 days after the screening.

The median time required to report the MRSA nasal screening results was 3 days (range: 2–5 days; interquartile range: 2–3 days). The median number of MRSA nasal screenings of the patients within 1 month of ICU admission was one time (range: 0–3 times; interquartile range: 1–1 time). The treatment duration of teicoplanin or vancomycin between patients with and without nasal swab screening did not differ significantly (4.2 ± 2.8 vs 4.4 ± 3.0 days, $p = 0.577$) (Table 3). The patients with no MRSA nasal swab screening were considerably more likely to have undergone dialysis in the preceding 90 days (59.4% versus 22.1%, $p < 0.001$). The two groups also differed significantly according to the two kidney function distribution populations (creatinine clearance >60 mL/min or ≤30 mL/min). Multivariable analysis revealed that the patients' characteristics including gender, age, BMI, APACHE II, and risk factors for MRSA infections had no impact on the treatment duration of teicoplanin or vancomycin. Among the 120 patients who tested negative in the MRSA nasal screening with no subsequent MRSA infection within 7 days, 75 did not stop using teicoplanin or vancomycin following the negative MRSA screening results. The total excessive usage time was 300 days, and the median was 3 days (interquartile range: 2–6 days).

Table 2 NPV, PPV, Sensitivity and Specificity of MRSA Nasal Screening by Types of Infections

	Pt, n	N+C+, n	N-C-, n	N+C-, n	N-C+, n	PPV, %	NPV, %	Sensitivity %	Specificity %
Whole screening cohort	277	15	252	6	4	71.4	98.4	78.9	97.7
Types of infections									
Pneumonia	170	12	152	3	3	80.0	98.1	80.0	98.1
Bloodstream infection	18	3	14	1	0	75.0	100.0	100.0	93.3
Sepsis	50	1	46	2	1	33.3	97.9	50.0	95.8
Intra-abdominal infection	28	0	28	0	0	–	100.0	–	100.0
Skin and soft tissue infection	18	1	15	1	1	50.0	93.8	50.0	93.8
Urinary tract infection	5	0	4	1	0	0.0	100.0	–	80.0
Head and neck infection	10	1	9	0	0	100.0	100.0	100.0	100.0

Abbreviations: N, MRSA nasal screening; C, subsequent MRSA infection; MRSA, methicillin-resistant *Staphylococcus aureus*; Pt, patient; n, numbers; PPV, positive predictive value; NPV, negative predictive value.

Table 3 Patients with or without MRSA Nasal Screening in Medical Intensive Care Units[a]

Characteristic		Without Screening n=32	With Screening n=122	All Patients n=154	P value
Male, no. (%)		20 (62.5)	86 (70.5)	106 (68.8)	0.385
Age, year (SD)		65.3±13.1	64.6±14.9	64.7±14.5	0.972
BMI, kg/m^2 (SD)		21.5±5.3	22.9±5.9	22.6±5.8	0.135
APACHE II score (SD)		23.5±9.7	24.6±7.7	24.4±8.2	0.396
MRSA carrier		Not available	2 (1.6)		
Prior culture isolation of MRSA in the last 90 days, no. (%)		1 (3.1)	4 (3.3)	5 (3.2)	1.000
Receipt of parenteral antibiotics in the last 90 days, no. (%)		31 (96.9)	107 (87.7)	138 (89.6)	0.195
Recent hospitalization > 2 days in the last 90 days, no. (%)		31 (96.9)	103 (84.4)	134 (87.0)	0.077
Receipt of RRT in the last 90 days, no. (%)		19 (59.4)	27 (22.1)	46 (29.9)	0.001
Recent influenza, no. (%)		1 (3.1)	15 (12.3)	16 (10.4)	0.195
Subsequent MRSA infection		0 (0)	0 (0)	0 (0)	
CL_{Cr} > 60 mL/min, no (%)		4 (12.5)	41 (33.6)	45 (29.2)	0.019
60≧ CL_{Cr} >30 mL/min, no (%)		7 (21.9)	19 (15.6)	26 (16.9)	0.397
CL_{Cr} ≦ 30 mL/min, no (%)		1 (3.1)	21 (17.2)	22 (14.3)	0.047
RRT, no. (%)	CVVH	8 (25.0)	18 (14.8)	26 (16.9)	0.011
	HD	11 (34.4)	17 (13.9)	28 (18.2)	
	Transit to different RRT	1 (3.1)	6 (4.9)	7 (4.5)	
Treatment days		4.4±3.0	4.2±2.8	4.3±2.8	0.577

Note: [a]Exclude patients with indications of glycopeptides use or death.
Abbreviations: BMI, body mass index; MRSA, methicillin-resistant *Staphylococcus aureus*; RRT, renal replacement therapy; CL_{Cr}, creatinine clearance; CVVH, continuous veno-venous hemofiltration; HD, hemodialysis; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Discussion

This study verified that MRSA nasal swabs have extremely high specificity and NPV for subsequent MRSA infection (97.7% and 98.7%) under 7% prevalence rate of MRSA in this population. These test results can effectively predict whether patients who tested negative in the initial nasal swab will have MRSA culture in the subsequent 7 days or not. Thus, they can be used for antibiotic de-escalation to stop unnecessary anti-MRSA therapy. Related research in different ICU has shown the correlations between MRSA-negative nasal swab and negative MRSA culture results.[9,18–21] The swabs were not only applicable to respiratory tract specimens but also had extremely high NPVs in the bacterial culture results of specimens in other sites (eg, blood, catheters, and urinary catheters), which was compatible with our result.[11,19] When applying MRSA nasal swab for antibiotic de-escalation, the prevalence rate of MRSA in the population should take into consideration. The NPV of MRSA nasal swab would decrease when the prevalence rate increase. Sarikonda et al. reported the NPV of MRSA nasal screen

was around 85%, which was lower than that of this study due to higher MRSA prevalence rate (~16%).[18] The patients in our study were treated with teicoplanin or vancomycin empirically in the ICU (ie, the patient group deemed by doctors to have high MRSA infection risk). Thus, the NPV of MRSA nasal swabs for MRSA infection is also applicable to this high-risk group. This result is consistent with the latest community-acquired pneumonia diagnosis and treatment guidelines published by the Infectious Diseases Society of America. The guidelines recommend ceasing empirical anti-MRSA therapy upon receiving negative MRSA nasal screening results, particularly for patients with community-acquired pneumonia that is not severe.[12] However, the sensitivity and PPV of the MRSA nasal swabs are unfavorable, and they are unreliable for the prediction of MRSA infection.[18]

This study indicated that the MRSA-negative nasal swabs do not influence the treatment duration of empirical teicoplanin or vancomycin of patients in MICU. A retrospective study reported that nasal MRSA polymerase chain reaction screening can significantly reduce the duration of empirical anti-MRSA therapy by approximately 2 days for patients with suspected MRSA pneumonia.[8] However, the MRSA nasal screening in this study employed culture-based method, which generally takes 3 days (the polymerase chain reaction test requires only 1~2 hours).[8] The turnaround time of nasal swab results were close to that of specimen culture results, which may result in similar treatment duration. In spite of the higher cost of PCR-based screening (~35 USD/time), it should be more cost effectiveness than culture-based method by shortening costly antibiotic use such as teicoplanin (~60 USD/day). Further study to demonstrate the better cost effectiveness of PCR-based screening than that of culture-based screening was needed to increase its clinical application.

A prospective observational study reported that up to 83% of the anti-gram-positive antibiotics usage is inappropriate, and 78.5% of the inappropriate use is attributable to the absence of de-escalation.[22] However, antibiotic de-escalation has been demonstrated to not increase mortality rates for hospital-acquired pneumonia. Instead, it can reduce the hospitalization duration and acute kidney injury.[23] The MRSA nasal swab is indeed a useful de-escalation tool. In many hospitals, routine MRSA nasal screening is conducted for patients at admission, and some institutions even perform weekly screening after ICU admission.[24] However, in some hospitals in the Asia-Pacific region, MRSA nasal screening is not routinely conducted because of limited medical resources.[25] The MRSA nasal swab can be used to identify carrier for contact isolation, and its additional application is also promoted in recent research. Active screening can be used as the basis for future antibiotic de-escalation when empirical glycopeptide is prescribed to patients.[26,27]

Because *Staphylococci* could lead to severe disease and are highly resistant to antibiotics, preventive strategy such as vaccine has been investigated. Vaccine could prevent or decrease the severity of *Staphylococci* infection through blocking the effect of toxins, blocking the functional surface adhesins or other relevant proteins, or stimulating phagocytosis.[28] Experimental vaccines have been developed and against constituents as diverse as the capsule or specific surface determinants such as PIA and *S.epidermidis* surface protein C (SesC).[28] Most of these vaccines conferred some protection in experimental models. For example, Mirzaei et al. have demonstrated that the conjugation of PIA with a specialized superficial protein of *S.epidermidis* as a carrier enhances the function of raised antibodies both in in-vivo and in-vitro experiments.[4] The arisen antibodies had the adequate effectiveness in biofilm inhibition so that about 90% of bacterial killing in phagocytosis and survival likelihood occurred following the intravenous challenges by *S.epidermidis*.[4] Although the data are promising in animal model, the vaccine efficacy remains controversial in clinical trial. A conjugated capsular vaccine conferred promising but transient protection in patients on hemodialysis; however, the other trial using a vaccine targeted on the iron surface determinant B to prevent deep sternal wound infections did not provide protection and paradoxically increased the mortality rate in *S. aureus*–infected patients.[29,30] It seems that vaccine targeting on different site may have distinct effect. Further studies are needed to prove the efficacy of anti-staphylococcal vaccine.

This study has several limitations. First, this was a retrospective single-center study. Thus, the NPV of our study may not be generalizable to other ICUs with different MRSA prevalence rates. Second, the time of MRSA nasal screening and administering anti-MRSA agents could not be fully controlled. Not all patients received the anti-MRSA agents on the same day as the MRSA nasal screening. The screening results or the calculation of excessive treatment duration of anti-MRSA agents may have been affected accordingly. Moreover, the judgment of MRSA infection in this study was based

on the diagnosis of clinicians and the culture results. The MRSA colonization and infection were not truly distinguished. Therefore, the true subsequent MRSA infection rate may even lower.

Conclusions

The MRSA nasal swabs have high NPV of MRSA infection for different types of infections in critically ill patients. However, it has no impact on the empirical glycopeptide treatment duration. The value of MRSA nasal swabs should be advocated to optimize antibiotic therapy.

Disclosure

The authors report no conflicts of interest in this work.

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