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CASE SERIES

Underdiagnosis of *Borderline oxacillin-resistant Staphylococcus aureus (BORSA)* – Case series

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Abstract

Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) are *mecA*-negative strains with oxacillin minimum inhibitor concentration (MIC) close to the resistance breakpoint of ≥ 4μg/mL. Instead of producing penicillin-binding protein with low affinity to methicillin (oxacillin) mediated by *mecA* gene as in methicillin-resistant *S. aureus* (MRSA), BORSA strains are characterised by the hyperproduction of β-lactamase enzymes, thus able to break down methicillin. Common laboratory methods to detect MRSA such as cefoxitin disk diffusion alone may fail to detect methicillin resistance due to BORSA. We report five cases of BORSA blood-stream infections in a university teaching hospital. All isolates were found to be susceptible to cefoxitin using disk diffusion, resistant to oxacillin using automated MIC method, and did not harbour *mecA* gene. All patients were successfully treated with anti-MRSA antibiotics, and removal of primary sources were done if identified. A more cost-effective method for screening and diagnosis of BORSA is needed in addition to cefoxitin disk diffusion test, in order to monitor the spread, and to enable routine detection and treatment of this pathogen.

Keywords: methicillin resistance, borderline oxacillin-resistant, BORSA, *Staphylococcus aureus*, *mecA* negative

INTRODUCTION

Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) strains are still poorly understood and inadequately defined.[1] Although some authors tried to include the *mecA* positive BORSA (with oxacillin MIC 0.5–8μg/mL), the most acceptable definition is confined to *mecA* negative strains. Thus, BORSA strains are defined as *mecA* negative strains with borderline resistance to penicillin-binding proteins (PBP) with oxacillin MIC typically close to or just above the resistance breakpoint of MIC ≥ 4μg/mL.[2-4]

Although the procedures for identifying and reporting the BORSA strains are still not widely implemented, infection of BORSA strains may have clinical characteristics similar to methicillin-resistant *Staphylococcus aureus* (MRSA) infection.[1] BORSA strains can be nosocomial and community-acquired and associated with a few reported outbreaks. They have been isolated from various clinical specimens, including surgical wounds samples, respiratory samples, abscesses and blood.[4] Treatment with larger doses of cloxacillin may be ineffective for severe infection of these apparent cefoxitin susceptible strains.[1]

The prevalence of methicillin-resistant *S. aureus* (MRSA) is well described and varies according to geographical regions, ranging from 26.8% in Europe to 47.0% in North America. As most of the reference methods for the detection of methicillin (oxacillin) resistance are fixated on detecting *mecA*-mediated resistance, *S. aureus* demonstrating non-MecA mediated resistance may be under-detected or labelled as either MRSA or MSSA due to its borderline resistance.

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The lack of laboratory methods to detect and confirm the presence of BORSA, resulted in the scarce literature on the prevalence of methicillin (oxacillin) resistance due to hyperproduction of β-lactamase. The prevalence of BORSA ranges from 1.4%–to 12.5%, and varies according to different populations of studies. However, one study reported prevalence as high as 50% of all clinical isolates.[1] Therefore, we estimate that infections due to BORSA are more common than expected. Standardised methods for the detection and surveillance of BORSA infections may be needed to accurately monitor and distinguish them from MRSA.

As *mecA* mediated mechanism is the most common mechanism for methicillin (oxacillin) resistance, most guidelines recommend using of cefoxitin resistance as a surrogate for the screening of MRSA.[5] However, as stated above, cefoxitin resistance screening might fail to detect BORSA strains. Using oxacillin is more useful for detection of non-*mecA* mediated resistance, therefore more sensitive for the screening of BORSA. Nevertheless, BORSA strains with oxacillin < 4μg/mL may not be detected by this methods. BORSA strains can be confirmed by adding clavulanate to oxacillin MIC test, resulting in a 2 fold or more reduction of MIC.[6] Although the recommended method to screen for MRSA (via *mecA* mediated resistance) is cefoxitin disk diffusion, it is suggested all *Staphylococcus aureus* with oxacillin MIC ≥ 4μg/mL should be treated with an anti-MRSA antibiotic, regardless of the mechanisms of resistance.[7]

CASE SERIES

We reported five cases of *Staphylococcus aureus* bacteraemia that were suspected BORSA based on the discrepancy of cefoxitin and cloxacillin in VITEK® 2 Antibiotic Sensitivity Testing (AST) system (Table 1). Other than bacteraemia, these patient had other foci of infection including infective endocarditis (Patient 1 and Patient 5), septic arthritis (Patient 1), submental abscess (Patient 2), pneumonia (Patient 1) and possible catheter related bloodstream infection (CRBSI) (Patient 3 and Patient 4).

Several relevant specimens were submitted for culture and sensitivity test from each patient; including blood, pus and body fluids. As per standard protocol in our laboratory, all susceptibility testing of *Staphylococcus aureus* grew from sterile specimens were performed using VITEK® 2 AST system whereas the isolates from non-sterile body fluid were preformed using Kirby-Bauer disk diffusion method. Using VITEK® 2 AST method, cefoxitin screening MIC were found to be negative, but interpreted as positive MRSA by the VITEK® 2 AST system, as all the isolates from blood demonstated oxacillin MIC of ≥ 4 μg/mL, indicating resistance towards the antibiotic. These isolates were reported as MRSA despite having negative cefoxitin screen. For non-sterile samples from Patient 1 (synovial fluid and pus aspirate) and Patient 2 (pus swab and tissue), cefoxitin 30 ug disk diffusion test were performed as per protocol; all the isolates were found to be susceptible and reported as MSSA. Different result between isolates from blood samples and isolates from non-sterile samples were due to different AST methods for the detection of methicillin resistance. Further investigations were done for confirmation of BORSA strains.

IV vancomycin was started on all patients and three of them responded to the antibiotic therapy and showed improvement. Patient 3 was started on IV ceftaroline, after initial IV vancomycin due to persistent fever and bacteraemia. Patient 5 had an incomplete antibiotic treatment as he refused intravenous line and requested to be discharged at own risk.

MICROBIOLOGY METHODS

Kirby-Bauer disk diffusion of oxacillin and cefoxitin

All the isolates were further identified by determining the zone diameter using oxacillin 1 μg disk diffusion and cefoxitin 30 μg disk diffusion. The colonies of the isolate were prepared in suspension of 0.5 McFarland, and streaked using a sterile swab in three directions over the surface of Muller Hinton agar (MHA) to obtain uniform growth. Disks impregnated with antibiotic are then placed on the surface of MHA. The plates were incubated at 37^{0}C for 24 hours and the diameter of the zone of inhibition in millimetres (mm) was measured after overnight incubation.

β-lactamase test

To confirm the presence of β-lactamase, the isolates were tested using nitrocefin disks. The nitrocefin disks were moistened with normal saline and the isolates were rub onto it. Then, the disks were incubated for up to 1 hour at room temperature according to the manufacturer's recommendation. The change of colour to pink indicates the presence of β-lactamase.

TABLE 1: Clinical data of five patients with suspected BORSA infection

Patient	Gender, Age (year)	Underlying disease and risk factors	Clinical presentation	Laboratory results	Diagnosis	Antimicrobial therapy	Outcome
1	M, 58	Ex- IV drug user with Hepatitis C infection	Fever and painful left knee swelling for 1 week. While in the ward, found to have IE (tricuspid vegetation). Later complicated with right lung septic emboli.	Blood C&S: MRSA (**Isolate 1-1**). Synovial fluid C&S: MSSA (**Isolate 1-2**) Pus aspirate C&S: MSSA.	MRSA bacteraemia and IE, complicated with septic arthritis and pneumonia.	IV vancomycin 1g BD and oral TMP-SMX 1440mg BD for 42 days	Infection resolved.
2	F, 50	Diabetes mellitus, hypertension	Submental abscess with diabetic ketoacidosis. Drainage of abscess and wound debridement were done.	Blood C&S: MRSA (**Isolate 2-1**). Pus swab C&S: MSSA. Tissue C&S (intraoperative sample): MSSA (**Isolate 2-2**)	Submental abscess Diabetic ketoacidosis	IV cloxacillin 2g QID for 1 day, then IV vancomycin 1g BD for 13 days	Infection resolved.
3	M, 60	Diabetes mellitus, hypertension, chronic kidney disease	Uremic symptoms with fluid overload. Developed HAP during hospitalisation.	Paired blood C&S- Central: MRSA. Peripheral: MRSA. (**Isolate 3**) CRBSI cannot be ruled out.	HAP with MRSA bacteraemia	IV vancomycin 1g loading dose, 750mg/day (renal adjusted dosing) for 5 days, then IV ceftaroline 300mg TDS for 11 days	Infection resolved.
4	F, 61	Diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease	Fever during haemodialysis. Central catheter was removed upon diagnosis of CRBSI.	Paired blood C&S- Central: MRSA. Peripheral: MRSA (**Isolate 4**). Central grew earlier than peripheral indicating CRBSI	MRSA CRBSI	IV vancomycin 1g loading dose, then 750mg/day for 14 days	Infection resolved.
5	M, 22	IV drug user, no known medical illness	Lethargy for 1 month. Fever, loose stool and abdominal pain for 1 week. Found to have IE (tricuspid vegetation).	Blood C&S (3 sets): MRSA (**Isolate 5**).	MRSA IE Acute gastroenteritis	IV vancomycin 1g BD and IV metronidazole 500mg TDS for 4 days*	Readmitted for unresolved infection.

Abbreviations: IV = Intravenous, IE= Infective endocarditis, CRBSI= Catheter related bloodstream infection, HAP= Hospital acquired pneumonia, C&S = Culture and sensitivity, MRSA= Methicillin-resistant *Staphylococcus aureus*, MSSA= Methicillin-sensitive *Staphylococcus aureus*, TMP-SMX = Trimethoprim- sulfamethoxazole
* Treatment was incomplete because patient requested to be discharged at own risk.

Disk synergy with amoxicillin/clavulanate – oxacillin – piperacillin/tazobactam

Using disk diffusion test, the isolates were also tested to observe synergy with amoxicillin-clavulanate, oxacillin and piperacillin-tazobactam. The oxacillin 1 μg disk diffusion was placed in the middle of the plate and 20 mm apart from amoxicillin-clavulanate 30 μg disk and piperacillin-tazobactam 110 μg disk respectively. The plate was incubated at 37^{0}C for 24 hours. The presence of the keyhole phenomenon indicates the presence of synergy as the β-lactamase inhibitor presence in clavulanate and tazobactam inhibits the β-lactamase enzyme produced by the isolates (Figure 2).

Polymerase chain reaction (PCR) for detection of mecA gene

Bacterial lysates were prepared by vortexing one loopful of isolates in 300 μL of DNase-free distilled water, heated in a 100 ^{0}C water bath for 10 minutes then centrifuged at 12 000 rpm for 5 minutes. The resultant supernatant was used as a template for the PCR assay.

The PCR was performed by addition of PCR-grade (DNase-free) water, *Arc* gene primer (housekeeping gene), *mecA* gene primer, MyTaq Red Reaction Buffer DNA templates as per protocol. The positive control using MRSA ATCC 33591 and negative control using MSSA ATCC 25923 were included to ensure the integrity of the PCR process and a non-template control was also included to check for the presence of contaminating DNA. The PCR was done with Mastercycler Gradient (Eppendorf. Hamburg, Germany) with one cycle of initial denaturation at 94 ^{0}C for 3 minutes, 30 cycles of denaturation at 94 ^{0}C for 30 seconds, annealing for 30 seconds at 59 ^{0}C, extension at 72 ^{0}C for 30 seconds and the final extension at 72 ^{0}C for 30 minutes.

The amplicons were resolved by 2.0 % agarose gel electrophoresis, stained with ethidium bromide, visualised under UV light and photographed (Chemilmager 5500, Alpha Innotech).

RESULTS

All seven isolates from five patients were resistant to oxacillin but susceptible to cefoxitin. The representative isolate is shown in Figure 1. The reported MSSA isolates of Patient 1 (Isolate 1-2) and Patient 2 (Isolate 2-2) were also exhibit similar sensitivity pattern. These seven isolates were also positive β-lactamase test. There were presence of keyhole phenomenon that indicate clavulanate-oxacillin-tazobactam synergy in all seven isolates. The representative isolates is shown in Figure 2. All these isolates were negative *mecA* gene on PCR test (Figure 3). The investigations for the isolates are summarised in Table 2.

DISCUSSION

This case series illustrates the clinical presentations, diagnostic pitfalls and antimicrobial management borderline oxacillin resistant *S. aureus* (BORSA) infections. The mechanism of resistance against β-lactam antibiotics in BORSA

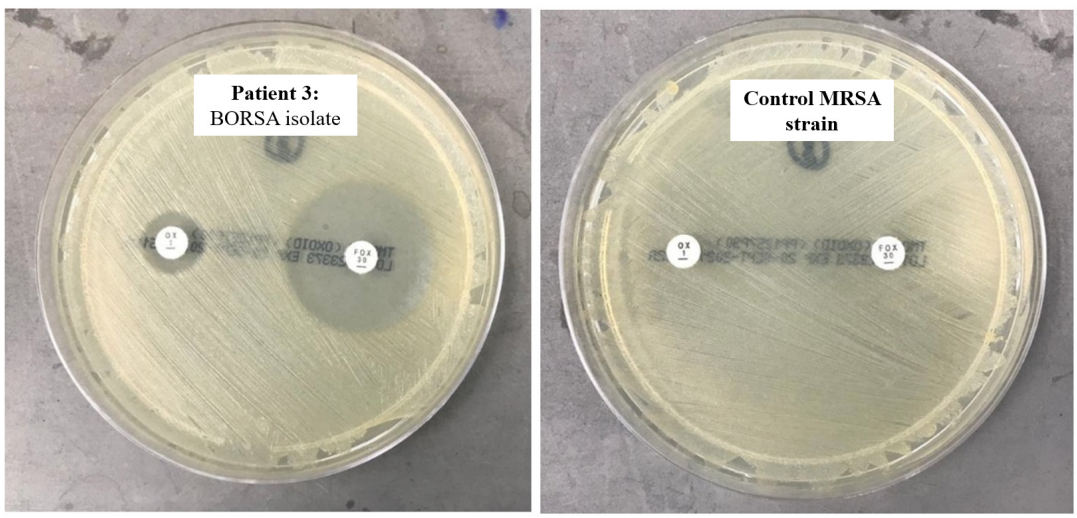

FIG. 1: Oxacillin and cefoxitin disk diffusion of suspected BORSA (Left) with oxacillin resistant but cefoxitin susceptible; and MRSA (Right) with both oxacillin and cefoxitin resistant.

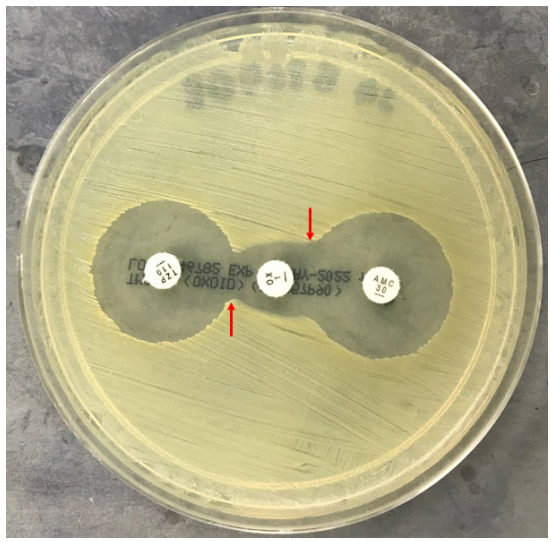

FIG. 2: Presence of keyhole phenomenon (red arrow) in disk synergy test with amoxicillin/clavulanate-oxacillin-piperacillin/tazobactam.

is due to the hyperproduction of penicillinase, a β-lactamase enzyme, occasionally encoded by *BlaZ* gene, which is plasmid-mediated and inducible.[8] BORSA usually does not have multiple drug resistance and is usually only resistant to penicillin and penicillinase-resistant penicillins such as methicillin, oxacillin, cloxacillin and nafcillin.

Resistance to methicillin or oxacillin in *S. aureus* is commonly tested using reference antimicrobial susceptibility testing methods according to Clinical Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. Such methods include disk diffusion and broth microdilution using cefoxitin as a surrogate, and broth microdilution and agar dilution using oxacillin. Recently, many clinical microbiology laboratories adopted automated or semi-automated antimicrobial susceptibility testing methods. These methods utilise modified broth microdilution with comparative analysis of growth curve for control and antimicrobial containing wells to provide rapid MIC results. For gram-positive organisms, automated methods such as VITEK® 2 utilise a card with miniature microdilution wells possessing a cefoxitin screening well, and oxacillin wells in 2-fold dilutions for the detection of methicillin resistance. Reference laboratories may also employ polymerase chain reaction methods to detect genetic determinants for methicillin (oxacillin) resistance, both for clinical diagnostic and epidemiological surveillance purposes.

As the reference methods emphasise detecting *mecA* mediated methicillin (oxacillin) resistance i.e. MRSA, BORSA infections may not be routinely detected in clinical isolates. Cefoxitin is commonly used as a surrogate for detecting *mecA*-mediated resistance given its

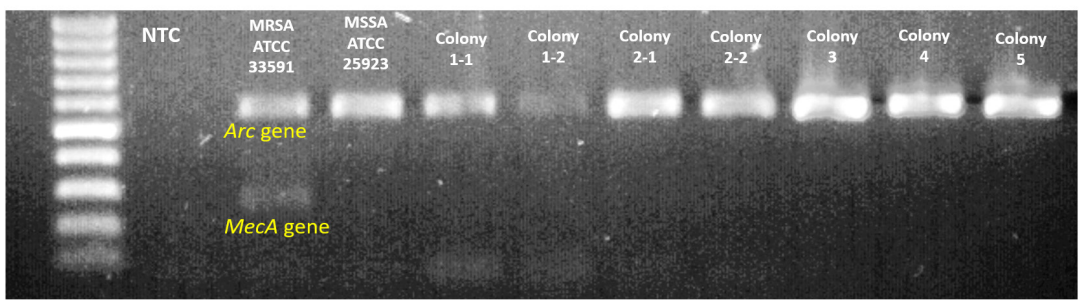

FIG. 3: Polymerase chain reaction (PCR) test of suspected BORSA isolates amplicon using *Arc* gene (housekeeping gene for *Staphylococcus aureus*) and *MecA* gene (virulence gene for MRSA). Colonies 1-1 and 1-2 were from patient 1 while colonies 2-1 and 2-2 were from patient 2 as shown in Table 1.

TABLE 2: Summary of investigations using oxacillin disk diffusion, cefoxitin disk diffusion, β-lactamase test using nitrocefin disk, disk synergy of amoxycillin/clavulanate-oxacillin-piperacillin/tazobactam and detection of mecA gene by PCR method.

Isolates*	Sample	Oxacillin inhibition-diameter (mm)**	Cefoxitin inhibition diameter (mm)***	β-lactamase test	Disk synergy (keyhole phenomenon)	mecA gene
1-1	Blood	12	27	Positive	Present	Absent
1-2	Synovial	18	29	Positive	Present	Absent
2-1	Blood	8	27	Positive	Present	Absent
2-2	Pus	6	26	Positive	Present	Absent
3	Blood	9	27	Positive	Present	Absent
4	Blood	7	28	Positive	Present	Absent
5	Blood	7	27	Positive	Present	Absent

* Colonies 1-1 and 1-2 were *Staphylococcus aureus* isolates (BORSA) from patient 1, while colonies 2-1 and 2-2 were *Staphylococcus aureus* isolates (BORSA) from patient 2 as shown in Table 1.

** No breakpoint of oxacillin disk testing as it is not reliable for *S. aureus* and *S.lugdunensis*.

*** Zone diameter breakpoint based on CLSI M100 31st edition for cefoxitin: susceptible ≥ 22 and resistant ≤ 21

superior sensitivity to detect the said resistance mechanism, as well as the less common *mecC*-mediated resistance. However, methods that utilise oxacillin for the detection of methicillin resistance are more effective in detecting non-*mecA* mediated resistance. Therefore, the laboratory that employs both antibiotics for the detection of methicillin resistance may detect borderline resistant *S.aureus* with oxacillin resistance and cefoxitin susceptibility in the susceptible range.

BORSA can be differentiated from *mecA*-mediated resistance and other mechanisms such as modification of intrinsic PBPs (MOD-SA) by adding β-lactamase inhibitors such as clavulanic acid to the oxacillin MIC test. This will lower the MIC by 2-fold dilutions or more.[6] However, such a method of detection is not employed routinely in the clinical microbiology laboratory and most international guidelines do not provide a standardised method for the detection of BORSA. In our series, we used double disk synergy test with amoxicillin/clavulanate-cloxacillin-piperacillin/tazobactam to detect phenotypic appearance of β-lactamases producer. The presence of the keyhole phenomenon indicates the presence β-lactamases enzyme produced by the isolates as the β-lactamase inhibitor properties in clavulanate and tazobactam inhibits the growth of these BORSA isolates.

According to Hryniewicz & Garbacz[1], the clinical characteristics of BORSA strains seem to mimic the MRSA strains as the infection is commonly more severe and invasive than the infection caused by MSSA. However, in BORSA infections, there is less propensity to cause acute kidney injury and the in-hospital mortality among patients with BORSA bacteraemia (24.6%) is lower compared to MRSA (38.5 %).[9] In this case series, all five patients presented with invasive infections, and two of the patient had pyogenic features requiring removal of the sources of infection. Except for Patient 4 who presented with acute on chronic kidney disease, none of the patients required haemodialysis for acute kidney injury.

As isolates of BORSA frequently display borderline resistance to methicillin (oxacillin) by reference laboratory testing methods, treatment with β-lactam antibiotics with or without the addition of a β-lactamase inhibitor is considered controversial. Both the MIC of the oxacillin and the severity of the disease play an important role in deciding the antibiotic of choice for its treatment. An earlier study[10] showed no treatment failure with B-lactam antibiotics but another study showed the failure of cloxacillin in the treatment of infective endocarditis with BORSA strain.[2]

As we reported all the BORSA strains as methicillin-resistant, all the patients were treated with anti-MRSA antibiotics vancomycin and ceftaroline, with successful clinical response and microbiological clearance. This indicate

that these anti-MRSA antibiotics, which are able to inhibit bacterial cell wall synthesis despite mutation in MRSA that results in low affinity PBP2, are also effective in inhibiting cell wall synthesis of BORSA strains that hyperproduce beta lactamase.[7] Vancomycin binds to a different target, D-alanyl-D-alanine tail of muramyl pentapeptide, thereby preventing its incoperation into cell wall peptidoglycan chain.[11] Ceftaroline possesses strong affinity to PBP2A due to its ethoxyimino side chain.[12] These mechanisms that able to bypass or overcome the low affinity PBP2 of MRSA, appear to be also effective in overcoming the hyperproduction of penicillinase in BORSA, possibly due to the borderline nature of oxacillin resistance and the stability of these antibiotics against the action of pencillinase. It is likely that other anti-MRSAs, such as linezolid and daptomycin, are also effective for the treatment of BORSA, due to their mechanisms of action that do not target cell wall synthesis.

According to Nomura *et al*.[8], the *blaZ* gene in BORSA strains is plasmid-mediated and the encoded enzyme is categorised as Type A β-l*actamase*. This may have a significant impact on the role of infection control in preventing the spread of the BORSA, particularly in the hospital setting. There is evidence suggesting that the BORSA strain may spread from patient to patient. The clonal spread of BORSA in a dermatology unit was found to be of the same spa type, t230 by Thomsen *et al*.[13] Although all isolates were borderline oxacillin resistant, all the patients were successfully treated with high dose cloxacillin. This may demonstrate the use of β-lactam antibiotics with or without β-lactamase inhibitor combinations, may have a role in treating non-invasive BORSA infections.

CONCLUSION

This case series highlights the importance of recognising BORSA by routine susceptibility testing in a clinical microbiology laboratory, and the need to distinguish it from MSSA, as the definitive therapy used for MSSA may be ineffective in treating invasive or severe BORSA infections. As BORSA strains typically demonstrate borderline oxacillin (methicillin) resistance, a higher than usual dosing regime of penicillinase-resistant penicillins may be required. Nevertheless, glycopeptides such as vancomycin should be used for the treatment of *S. aureus* infections with oxacillin MIC of 4 μg/ml or higher. The role of infection control measures to prevent the transmission of BORSA strains should also be explored. The use of oxacillin to screen for BORSA, in addition to the routine use of cefoxitin as a surrogate for methicillin resistance, may not be cost effective. Further study is necessary to explore the mechanism of resistance, prevalence, clinical characteristics and as well as a standardised routine detection method of BORSA strains.

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