

ORIGINAL ARTICLE

**A RETROSPECTIVE STUDY OF THE PREVALENCE AND SENSITIVITY PATTERN OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN A CHONG HUA HOSPITAL, CEBU CITY, 2007-2010**

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**KEYWORDS:**

MRSA, Methicillin resistant *Staphylococcus aureus*, Methicillin sensitive *Staphylococcus aureus*, *Staphylococcus aureus*, Vancomycin

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**ABSTRACT**

**Background/Objective:** There is a deep concern about the rapid rise in resistance of bacteria to antimicrobial agents. Methicillin-resistant *Staphylococcus aureus* (MRSA) which pose challenges to the medical community. This study aimed to determine the prevalence and sensitivity pattern of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) in a tertiary hospital in Cebu City from January 1, 2007 to December 31, 2010.

**Methods:** Charts of patients with MRSA growths were reviewed upon their admission. The sensitivity pattern, demographic profile and risk factors were noted.

**Results:** Out of the 637 isolates of *Staphylococcus aureus*, MRSA had a prevalence rate of 38.6% (n=246), while Methicillin Sensitive *Staphylococcus aureus* (MSSA) had 61.4% (n=391). The prevalence rate of health-care associated MRSA was 2% (n=5). The majority of the specimens sent for culture were wound/abscess (70% of pediatric and 76% of adult patients isolates). All MRSA growths were resistant to penicillin G, ampicillin, oxacillin, cefuroxime and amikacin. Local MRSA strains were still susceptible to ciprofloxacin (82.3%), clindamycin (90.6%), erythromycin (91.5%), and sulfamethoxazole-trimethoprim (85.9%). There was no resistance to linezolid and vancomycin. Vancomycin-resistant *Staphylococcus aureus* was not isolated. The mortality rate on both pediatric and adult population was 2.1% and 4.8%, respectively.

**Conclusion:** The prevalence of MRSA is increasing. Clindamycin, erythromycin, sulfamethoxazole-trimethoprim and vancomycin are excellent treatment options treat MRSA.

**INTRODUCTION**

MRSA is an important cause of infection acquired in the community without known risk factors or in the hospital setting with underlying factors.<sup>1,2,3</sup> MRSA has become endemic worldwide. In the 1950s until 1960s, *Staphylococci* of phage type 80/81 was so widespread in hospitals that it became a pandemic.<sup>1</sup> *Staphylococcus aureus* and *Pseudomonas aeruginosa* are second only to coagulase-negative *Staphylococci* which is the most common cause of health care-associated pneumonia in adults as well as an important cause of most surgical site infections.<sup>3</sup> MRSA causes serious problems to an immunocompromised patients and it becomes especially alarming when it causes severe infection resulting in longer hospital stay, and subsequently, more toxic treatments and even death.

The rate of nasal carriage of MRSA appears to have increased in the past decade. About 20%-to-50% of individuals, both healthy adults and children, are carriers and are colonized in their anterior nose, skin or mucous membranes.<sup>1,2,3</sup> When MRSA was first reported, most cases responded poorly to  $\beta$ -lactam therapy and other commonly used antimicrobials including erythromycin, clindamycin and tetracycline. Methicillin and oxacillin are penicillinase-resistant antibiotics; however, the presence of an altered penicillin-binding protein (PBP2a) in the bacteria which is the target of the antibiotic renders *Staphylococcus aureus* resistant to these drugs.<sup>4</sup>

It was noted in an emergency center of a large children's hospital in Houston that there has been an increasing number of children with invasive disease secondary to community-acquired MRSA including severe life-threatening infections.<sup>1</sup> It is important to start with the appropriate empiric treatment when *Staphylococcus aureus* is the most likely cause of

infection based on the relative frequency of community-acquired MRSA isolates.<sup>1</sup> Intravenous vancomycin, alone or together with an aminoglycoside or rifampicin, is the drug of choice for serious MRSA infections. The addition of gentamicin should be considered for synergistic purposes.<sup>1,3</sup>

Although vancomycin remained as the antibiotic of choice for severe MRSA infection, its use must be monitored and controlled because there were reports regarding the emerging resistance of *Staphylococcus aureus* to vancomycin called vancomycin- or glycopeptide-resistant *Staphylococcus aureus* (VRSA).<sup>1</sup> The first documented report was isolated in June 2002 in the United States. The isolate was obtained from a catheter exit site of a forty-year old diabetic patient undergoing chronic dialysis and had high minimum inhibitory concentrations (MICs) for vancomycin and oxacillin. This was followed by six additional isolates reported from Michigan, Pennsylvania, and New York.<sup>1</sup>

Methicillin-resistant *Staphylococcus aureus* was first described after the introduction of penicillinase-resistant penicillins. Initial reports of infection appeared in England in the early 1960s and were subsequently followed by reports from other European countries. In the United States, reports of sporadic cases were observed initially but not until 1968 when the first nosocomial outbreak was described. Since then, the prevalence of MRSA in the hospital setting has increased steadily particularly in critical areas.<sup>1</sup> Worldwide, an estimated two billion people are carriers of *Staphylococcus aureus* and up to 53 million carriers or about 2.7% are thought to carry MRSA.<sup>5</sup>

In the Philippines, the first confirmed methicillin-resistant *Staphylococcus aureus* was reported in 1987 in the Philippines General Hospital (PGH) by Navarro-Almarino and Velmonte. From the study done by We, et al, at

PGH between December 1996 to April 1998, the prevalence rate of nosocomial-acquired MRSA was 53% of the total 215 cases, with a mortality rate of 69%,<sup>8</sup> while the study of Mamauag-Estrada, et al, at the same institution (2005) showed the prevalence rate of methicillin-resistant *Staphylococcus aureus* to be 37.5%, with a mortality rate of 42%.<sup>9</sup> Significant risk factors mentioned by We, et al, only included previous antibiotic use, admission to ICU and presence of burn wound,<sup>8</sup> while the study of Mamauag-Estrada, et al, included presence of co-morbidities, previous hospitalization, and devices.<sup>9</sup>

The aim of this study was to describe the clinical profile of pediatric patients with MRSA infections as well as the antimicrobial resistance patterns of the MRSA isolates.

#### **MATERIALS AND METHODS**

This descriptive study reviewed all charts of patients with culture-confirmed MRSA with sensitivity testing done admitted at Chong Hua Hospital, Cebu City from January 1, 2007 to December 31, 2010.

For patients with more than one culture studies done and more than one culture growth, only the result showing a predominant MRSA growth with sensitivity testing done were included.

Excluded in this study were culture-proven MRSA with no sensitivity testing. Isolates considered as contaminant and thus clinically not significant were also not included in the study. If a patient had two MRSA's within a month, only the first one was counted.

*Staphylococcus aureus* was isolated from various body sites of admitted patients after 24-to-48 hours of incubation From January 1, 2007 to December 31, 2010. The isolates (were identified and) were tested for susceptibility in vitro to ampicillin (AMP), oxacillin (OXA), penicillin G (PEN), cefuroxime (CEF), amikacin (AMK), ciprofloxacin (CIP), clindamycin (CLN),

erythromycin (E), sulfamethoxazole-trimethoprim (SXT), vancomycin (VA), and Linezolid (LIN).

The medical records of all MRSA culture-positive patients were reviewed. Patient's demographic profile, including the age and gender and risk factors such as the presence of underlying disease or co-morbid illnesses, previous antibiotic therapy, previous hospitalizations, presence of indwelling or invasive devices, admission to intensive care unit and presence of surgical wound/burn wound were identified. The presence of underlying disease or other co-morbidities like malignancy, diabetes mellitus, hypertension, heart disease, renal disease, liver disease, gastrointestinal disease, pulmonary disease, central nervous system disease and etc, were also reviewed thoroughly. Patient's clinical outcome and data of patient's specimen, along with sensitivity pattern were all recorded.

#### **RESULTS**

The total number of admitted patients with *Staphylococcus aureus* growth in Chong Hua Hospital, Cebu City from January 1, 2007 to December 31, 2010 was 637. Out of the 637 cases, 246 cases (38.6%) were MRSA and 391 cases (61.4%) were MSSA. The prevalence rate of MRSA among pediatric and adult population was almost the same between 38%-to-41.5% while the prevalence rate of MSSA on both population ranges from 58%-62%. In table 2, the prevalence rate of health-care-associated MRSA infection is 2% (n=5).

From January 1, 2007 to December 31, 2010, 246 patients had confirmed MRSA growth. There were 31 patients, 2 from pediatric and 29 from adult population with no sensitivity testing done that were excluded. Only 47 pediatric and 168 adult patients were included in the final population of the study

**Table 1. Prevalence rate of Methicillin-sensitive and Methicillin-resistant *Staphylococcus aureus* in the pediatric and adult age group**

	MSSA			MRSA			Total number
	Pediatric (0-18yo)	Adult	Total	Pediatric (0-18yo)	Adult	Total number	
2007	16	61	77(56.7%)	11	48	59 (43.4%)	136
2008	17	91	108 (83.1%)	6	16	22 (16.9%)	130
2009	16	84	100 (62.5%)	13	47	60 (37.5%)	160
2010	20	86	106 (50.2%)	19	86	105 (49.8%)	211
<b>Total</b>	<b>69 (17.6%)</b>	<b>322 (82.4%)</b>	<b>391 (61.4%)</b>	<b>49 (19.9%)</b>	<b>197 (80.1%)</b>	<b>246 (38.6%)</b>	<b>637</b>

Of the total number of specimens sent for culture, majority of which were wound or abscess specimens as seen in both the pediatric (n= 33; 70%) and adult (n=127; 76%) population. This was followed by blood on both (pediatric n= 10; 21% and adult n= 15; 9%) populations. Some other specimens sent included sputum, ear discharge, pericardial fluid, urine, eye discharge, cerebrospinal fluid, synovial fluid, pleural fluid, tracheal aspirate, synovial tissue, antibiotic beads, right elbow tissue and hepatic tissue.

Upon review of the sensitivity pattern of Methicillin resistant *Staphylococcus aureus*, all MRSA growths were 100% resistant to penicillin G, ampicillin, oxacillin, cefuroxime and amikacin. Local MRSA strains were still susceptible to ciprofloxacin (82.3%), clindamycin (90.6%), erythromycin (91.5%), and sulfamethoxazole-trimethoprim (85.9%). Both the pediatric and adult patients showed no resistant on vancomycin.

The presence of disease or co-morbid illnesses was analyzed. Out of the 47 pediatric subjects, only 14 (30%) patients with MRSA were found to have co-morbid conditions and 33 (70%) patients did not have an underlying disease.

On the other hand, out of 168 adult patients with MRSA growth, 92 (55%) patients had co-morbid illnesses.

Surgical interventions were also noted to patients with MRSA growth. Out of the 47 pediatric patients, 19 (40%) did not had surgical procedures done while 28 (60%) had surgical interventions done during their hospital admission. Out of the 168 adult patients, 42 (25%) had no surgical interventions done as part of the management while 126 (75%) had surgical procedures done.

The clinical outcome of pediatrics patients were recorded and noted. Out of the 47 pediatric patients, 1 (2.1%) died, 45 (95.7%) discharged improved and 1 (2.1%) discharged against medical advised. On the other hand, 8 (4.8%) out of the 168 adult patients died while 159 (94.6%) discharged improved and 1 (0.6%) discharged against medical advise.

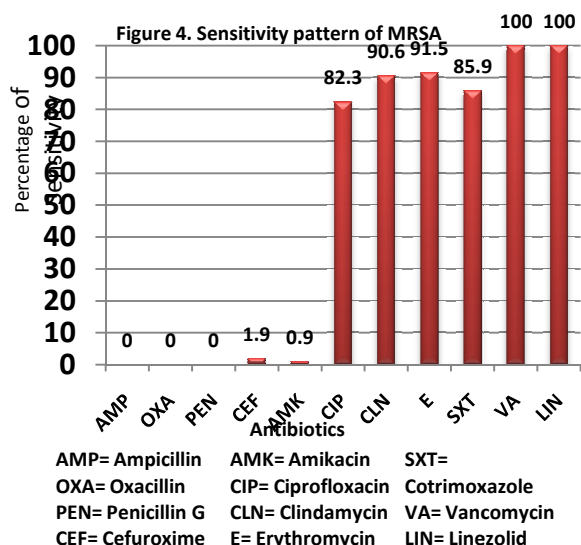
**Table 2. Prevalence rate of health-care associated MRSA infection in the pediatric and adult age group.**

Year	Health-care associated MRSA infections		Total number
	Pediatric (0-18yo)	Adult (19 and above)	
2007	0	1	1
2008	0	0	0
2009	1	1	2
2010	0	2	2
Total	1	4	5

**Table 3. Source of clinical MRSA isolates**

Specimen	Pediatric (0-18yo) (N=47)	Adult (19 and above) (N=168)
Wound/abscess	33 (70%)	127 (76%)
Blood	10 (21%)	15 (9%)
Sputum/tracheal aspirate	1 (2%)	12(7%)
Ear discharge	2 (4%)	1 (1%)
Pericardial fluid	2 (4%)	0
Urine	1 (2%)	7 (4%)
Eye discharge	1 (2%)	0
CSF	1 (2%)	0
Synovial fluid	0	4 (2%)
Pleural fluid	1 (2%)	4 (2%)
Tissues (synovial, right elbow, hepatic)	0	4 (2%)
Antibiotic beads	0	1 (1%)

Gender		
Male	23 (49%)	95 (57%)
Female	24 (51%)	73 (43%)
Diseases		
Diabetes mellitus	1 (2%)	49 (29%)
Cardiovascular disease	1 (2%)	44 (26%)
Renal disease	1 (2%)	22 (13%)
Respiratory disease	8 (17%)	19 (11%)
Gastrointestinal disease	1 (2%)	12 (7%)
Neurologic disease	3 (6%)	7 (4%)
Musculoskeletal disease	2 (4%)	7 (4%)
Malignancy	1 (2%)	7 (4%)
Glucocorticoid therapy	1 (2%)	3 (2%)
Hematologic disease	2 (4%)	1 (0.6%)
Drug abuser	0	1 (0.6%)
No underlying disease	33 (70%)	76 (45%)



**Table 4. Clinical Characteristics of Pediatric and Adult Patients positive for MRSA**

	Pediatric (0-18yo) (N= 47)	Adult (19 and above) (N=168)
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**DISCUSSION**

The overall prevalence rate of MRSA shown in this study was 38.6%. Among pediatric and adult population, the prevalence rate were 41.5% and 38%, respectively. These findings were similar to the study done in PGH by Mamaug-Estrada, et al, from 1999 to 2001 (37.5%)<sup>9</sup>, the 2012 antimicrobial resistance surveillance by Carlos covering 23 hospitals in the Philippines (54.9%)<sup>10</sup>, the study in 2005 conducted by Kuehnert, et al in the United States (43.2%)<sup>13</sup>, and the study done in Northern India by Tiwari, et al, published in 2008 (38.44%)<sup>14</sup> but lower than the study in 2003 reported by Anupurba, et al (54.85%)<sup>15</sup>.

**Table 5. Identified surgical interventions and MRSA isolates.**

Surgical procedure	Pediatric (0-18yo) (N= 47)	Adult (19 and above) (N=168)
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None	19 (40%)	42 (25%)
Incision and drainage	18 (38%)	106 (63%)
CTT	3 (6%)	4 (2%)
Pericardial window and pericardial tube insertion	3 (6%)	0
Fasciotomy	0	3 (2%)
Central line	1 (2%)	2 (1%)
Arthrocentesis	0	2 (1%)
Fine needle aspiration	0	2 (1%)
Skin biopsy	1 (2%)	0
Revision of Ventriculo-peritoneal shunt	1 (2%)	0
Exploratory laparotomy	1 (2%)	0
Monaldi procedure	1 (2%)	0
Fistulotomy	0	1 (0.6%)
Dilatation & curettage	0	1 (0.6%)
Synovectomy	0	1 (0.6%)
Posterior fusion with instrumentation L2 to L4, laminectomy	0	1 (0.6%)
Revision of stump of middle finger	0	1 (0.6%)
Mitral valve replacement	0	1 (0.6%)
Removal of implant	0	1 (0.6%)
Removal of antibiotic beads	0	1 (0.6%)
Ultrasound guided subcutaneous aspiration infra-umbilical area	0	1 (0.6%)
CT scan guided hepatic abscess drainage	0	1 (0.6%)

Methicillin-resistant strains of *Staphylococcus aureus* have been responsible for many nosocomial epidemics. The prevalence rate of health-care-associated MRSA infection in this study was low at 2% compared to the study done at PGH by We, et al, in 1999 and at St. Luke’s Medical Center by Atilano, et al, in 2001 which was 53% and 11.7%, respectively.<sup>8,12</sup> According to the study by Klevens, et al, from 2004 to 2005, 26.6% of invasive MRSA infections in the United States were hospital in onset or healthcare associated.<sup>19</sup>

The hallmark of a staphylococcal lesion is abscess formation and *Staphylococcus aureus* is the most common cause of pyogenic infection of

the skin and soft tissue.<sup>2</sup> 70%-76% of the clinical specimens sent for culture was from wound or abscesses. Blood culture only 9%-21%. This was consistent with the findings of the study done at St. Luke’s Medical Center by Atilano, et al where wound discharge and abscess aspirates accounted for 79% of the source of MRSA.<sup>12</sup> The study conducted by Ontengco, et al (2004), revealed that majority of the MRSA isolates came from skin and soft tissue (34.6%) while blood accounted for 9.7%.<sup>4</sup> In India, Anupurba, et al, (2003) also stated that majority of MRSA were isolated from pus and wound swabs.<sup>15</sup> Center for Disease Control and Prevention also mentioned that in 2004, 78% of the purulent skin and soft tissue infections were caused by MRSA in 11 emergency departments in the United States.<sup>6</sup> Approximately 25% of MRSA were isolated in the blood as mentioned in the study by Linden.<sup>16</sup>

In the last 3 decades, MRSA strains have gradually evolved. Antibiotic sensitivity results in this study showed resistance to penicillin, oxacillin, ampicillin, and cephalosporins. These results were consistent with MRSA resistance patterns of isolates in three hospitals in Manila by Ontengco, et al from 1999 to 2003<sup>4</sup>, by Tahnkiwale, et al (2002)<sup>7</sup> and Anupurba, et al (2003) in India.<sup>15</sup>

Local MRSA strains in this study were 98-100% resistant to  $\beta$ -lactams such as ampicillin, oxacillin, penicillin, and cefuroxime. These results were consistent with the study done by Ontengco, et al in 1999-2003.<sup>4</sup> There was almost 100% resistant to aminoglycoside using amikacin in this study compared to the study done by Ontengco, et al which was only 19% with gentamicin.<sup>4</sup> This study and the study done by Ontengco, et al had almost the same resistance rate with cotrimoxazole (13-14%).<sup>4</sup> High resistance rate to cotrimoxazole was noted in the study done by Tahnkiwale, et al (97%)<sup>7</sup> and by Tiwari, et al (95.68%).<sup>14</sup> Lower resistance rates

were seen to other antibiotics in this study such as ciprofloxacin (17.7%), clindamycin (9.4%), and erythromycin (8.5%). However, these results were in contrast to the study done by Tiwari, et al in Northern India wherein the MRSA isolated there were highly resistant to ciprofloxacin (75.75%).<sup>14</sup> Higher resistance rate was also noted to ciprofloxacin (31%), clindamycin (24%) and erythromycin (25%) in the study of Ontengco et al in Manila.<sup>4</sup>

Intravenous vancomycin is recommended for the treatment of serious infections caused particularly by MRSA. Vancomycin can be administered intermittently or in a continuous fashion.<sup>1,3</sup> MRSA isolated in this study was still 100% sensitive to vancomycin. Therefore, vancomycin-resistant *Staphylococcus aureus* was not isolated within the four-year duration of this study. This finding was consistent with the study done in PGH by We, et al,<sup>8</sup> in St. Luke's Medical Center by Atilano, et al,<sup>12</sup> the 2009 antimicrobial surveillance done by Celia Carlos,<sup>10</sup> and the many studies done in India.<sup>7,14,15</sup> In St. Luke's Medical Center, Pasumbal and Peña (2004) reported no vancomycin-resistant *Staphylococcus aureus* isolated in bloodstream infection.<sup>18</sup>

Aminoglycoside such as amikacin or gentamicin is also added for synergistic purposes especially in severe life threatening infection.<sup>1</sup> This study reported almost 100% resistance to amikacin compared to the low resistance in the study in India by Anupurba, et al (60.5%)<sup>15</sup>, the study done by Tahniwale, et al using gentamicin (6.66%)<sup>7</sup> and Ontengco, et al using gentamicin in three hospitals in Manila between 1999 to 2003 (19%).<sup>4</sup>

Review of patient sex distribution was done. In this study, both pediatric and adult population had almost equal distribution of males and females. The mean ages of both the pediatric and adult population were 4.5 years and 44.3 years, respectively. We, et al, reported that age was the

only confirmed confounder in their study. Infants and those greater than 60 years had a higher risk of acquiring MRSA infection due to their vulnerability to infection. There was no statistical difference between male and female sex in acquiring MRSA infection.<sup>8</sup> On the other hand, Mamaug-Estrada, et al, mentioned in their study done at the PGH that the demographic profile was not statistically significant. Sex and age of patient were not associated with increased risk of MRSA infection. Their study failed to demonstrate an association of increased MRSA infection with a younger age group because of limited study population.<sup>9</sup>

Many risk factors have been implicated in MRSA infection. In this study, 58%-60% had previous antibiotic therapy, 9%-12% was admitted to an intensive care unit, 10%-11% had previous hospitalizations, 30%-55% had co-morbid illnesses, 2%-16% had indwelling catheters or devices and 2%-4% had glucocorticoid therapy. Risk factors that were statistically significant in the study done by Mamaug-Estrada, et al, when MRSA and MSSA were compared included the following: presence of co-morbidities, admission to intensive care or burn units, previous antibiotic therapy, previous hospitalizations, presence of surgical wound/burn wound and presence of 3 or more indwelling devices.<sup>9</sup> The study of We, et al, mentioned (1999) that only previous history of antibiotic therapy was the only statistically significant risk factor identified. Risk factors other than previous antibiotic therapy were not independent risk factors by themselves.<sup>8</sup>

Several studies showed susceptibility to MRSA infection particularly among patients with underlying disease since these individuals will require prolong hospitalization and multiple drug therapy.<sup>9</sup> This study showed thirty percent of pediatric population had co-morbid illnesses with respiratory disease among the highest followed

by neurologic, musculoskeletal and hematologic diseases. About 55% of the adult population also had underlying diseases. Topping the list was diabetes mellitus followed by cardiovascular, renal, respiratory and gastrointestinal diseases.

Surgical interventions may be needed if the infection is complicated. In this study, the most frequent surgical procedure performed during admission was incision and drainage since majority of patients had skin or wound abscesses.

Mortality rate had been reduced due to effective antibiotic treatment. Untreated staphylococcal septicemia is associated with high mortality rate ( $\geq 80\%$ ).<sup>2</sup> In this study, the mortality rate of the pediatric age group as well as the adult population was 2.1% and 4.8%, respectively. The overall mortality rate due to MRSA infection during the four-year study period was not as high (4.2%) as to that reported by Mamauag-Estrada, et al, (42%) in 2005 and by We, et al, (69%) in 1999.<sup>9</sup> In the United States, the standardized mortality rate was 6.3 per 100,000 (interval estimate, 3.3-7.5 per 100,000) among patients with invasive MRSA in nine United States communities participating in the Active Bacterial Core Surveillance (ABCs) or Emerging Infections Program Network from July 2004 until December 2005.<sup>19</sup>

## CONCLUSION

The present study showed a high prevalence rate of MRSA infection at 38.6%. However, health-care-associated MRSA infection was low (2%) compared to other studies conducted here in the Philippines and among other countries. The mortality rate of MRSA infection (4.1%) in this institution was also lower compared to other institution. The most common surgical intervention was incision and drainage. About 58-60% of patients had previous history of antibiotic treatment. Only 30% of the pediatric

and 55% of the adult population had underlying illnesses documented. Local MRSA was still sensitive to ciprofloxacin, clindamycin, erythromycin and cotrimoxazole. There was no vancomycin-resistant *Staphylococcus aureus* isolated during the four-year study period. Due to continuously increasing incidence of methicillin resistance among *Staphylococci* from 2007 until 2010, there may be an indication to shift empiric treatment from oxacillin to other alternatives especially in severe staphylococci infections.

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