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Antibiotic Therapy of Methicillin-Resistant *Staphylococcus Aureus* in Critical Care

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Methicillin-resistant *Staphylococcus aureus (MRSA)* organisms continue to evolve to circumvent antibiotics. Between 9% and 24% of patients in intensive care units are colonized with MRSA [1]. In addition, *S aureus* was responsible for 20% of all bloodstream infections in 24,179 patients in a nationwide surveillance study with an incidence of 10.3 bloodstream infections per 10,000 patient admissions [2]. Of these *S aureus* isolates, 41% were classified as MRSA over the 7-year study period. Alarmingly, methicillin resistance increased from 22% in 1995 to 57% in 2001 ($P < .001$). In a separate study, *S aureus* accounted for 31% to 47% of ventilator-associated pneumonias (VAPs), with MRSA responsible for 11.8% to 18.3% of nosocomial pneumonias [3].

Some studies also suggest that infection with MRSA is associated with increased morbidity as compared with that of methicillin-sensitive *S aureus* (MSSA) infections. In a study of bacteremia, infection with MRSA was an independent predictor of mortality (odds ratio, 1.47; 95% CI, 0.99–2.26) [4]. In a multivariate analysis, this effect was independent of age, date of admission, previous isolation of MRSA, or specialty of care. The increase in mortality may be due to increased virulence of MRSA, suboptimal treatment options, or increased severity of illness in MRSA-infected patients.

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Vancomycin has long been the mainstay treatment for MRSA infection, but this practice has recently come under scrutiny. Not only are there strains that are frankly resistant to vancomycin, but there also appears to be an increased incidence of vancomycin-intermediate *S aureus* (VISA) [5,6]. There is also a concern of heteroresistant VISA. Such organisms may appear initially susceptible to vancomycin, but treatment with vancomycin appears to select a VISA subpopulation and clinical failure can occur [7,8]. Furthermore there is a phenomenon that has been labeled vancomycin "minimum inhibitory concentration creep" ("MIC creep") [9]. *S aureus* is defined as vancomycin susceptible when the vancomycin MIC is 4 μg/mL or less [10]. In recent years, there have been several reports of MRSA isolates with vancomycin MICs of 1 or 2 μg/mL. In a recent study of 662 MRSA isolates over a 5-year period [9], the geometric mean MIC increased from 0.62 μg/mL (range, 0.25–1 μg/mL) to 0.94 μg/mL (range, 0.5–2 μg/mL) ($P < .0001$). The MIC increase is of concern because poorer outcomes have been associated with higher vancomycin MICs [11,12]. Sakoulas and colleagues [11] performed a retrospective subgroup analysis of patients enrolled in a prospective study examining the treatment of MRSA bacteremia. Success with vancomycin was associated with vancomycin MIC levels of less than or equal to 0.5 μg/mL (55.6% cure rate) versus those with vancomycin MIC levels of 1 to 2 μg/mL (9.5% cure rate) ($P = .02$). In addition, vancomycin bactericidal activity was determined for each isolate. Bactericidal activity of vancomycin appeared to correlate with treatment outcome. No cure took place in any patient whose isolates had a $\log_{10}$ (colony forming units CFU) per milliliter [CFU/mL]) killing at 72 hours of less than 4.71, while nine isolates with a $\log_{10}$ CFU/mL of 6.27 or greater had a 50% treatment success rate ($P = .0027$). In a multivariate analysis, bactericidal activity and MIC were predictive of treatment failure (odds ratio, 10.73; 95% CI, 1.24–92.95; $P = .031$, and odds ratio, 35.46; 95% CI, 1.76–715.95; $P = .02$, respectively). Hidayat and colleagues [13] evaluated 95 patients with infection caused by MRSA treated with vancomycin targeted to attain trough levels (free drug) four to five times the vancomycin MIC. Patients were stratified by MIC of the offending MRSA pathogen. Fifty-four percent of patients were in the "high MIC" group, defined as vancomycin MIC greater than or equal to 2 μg/mL, and 46% of patients were in the "low MIC" group with a vancomycin MIC less than 2 μg/mL. Baseline demographic characteristics were well matched. In the analysis, treatment failure was associated with increased age ($P = .006$), Acute Physiology and Chronic Health Enquiry II (APACHE II) score ($P < .001$), and MIC greater than 2 μg/mL ($P = .01$). MIC greater than or equal to 2 μg/mL was associated with an increased risk of failure, despite attaining the pharmacodynamic goal of an unbound vancomycin trough of four to five times the MIC.

Finally, in a study by Moise and colleagues [12] to determine predictors of prolonged bacteremia during treatment with vancomycin, 34 patients with MRSA bacteremia were studied. Vancomycin was dosed to achieve target peak serum levels of 28 to 32 μg/mL and trough levels of 8 to 12 μg/mL.

Patients with known endocarditis, central nervous system (CNS) infection, or osteomyelitis were excluded. There were 13 MRSA isolates with a vancomycin MIC of 0.5 μg/mL, 7 with an MIC of 1 μg/mL, and 14 with an MIC of 2 μg/mL. Multiple phenotypic variables were examined. These included *agr* group (type II or non–type II), delta-hemolysin expression, vancomycin MIC for each clinical isolate, bactericidal activity 16 μg/mL of vancomycin at 24 hours in an inoculum of 10^7 to 10^8 CFU/mL of each clinical isolate, and baseline characteristics. Investigators determined that higher vancomycin MIC and lower level of bactericidal activity correlated with prolonged MRSA bacteremia. Vancomycin MIC of 2 μg/mL had an odds ratio of 14.7 (95% CI, 2.26–100; $P = .005$) for failure of vancomycin to eradicate MRSA. Reduction in $\log_{10}$ CFU/mL less than 2.5 had an odds ratio of 6.7 (95% CI, 1.03–43.5; $P = .047$) for failure of vancomycin to eradicate MRSA. This led the investigators to conclude that even with the increase of the MIC to only 2 μg/mL, which is in the "susceptible" range, there was an alarmingly low rate of clearing of bacteremia. Furthermore, bactericidal activity of vancomycin was predictive of treatment failure independent of MIC. This study again underscores the need for better treatment in MRSA infections with higher MICs to vancomycin and seriously challenges the MIC breakpoints for intermediate susceptibility.

Vancomycin

Vancomycin is a glycopeptide antibiotic that is given as an intravenous infusion of 15 mg/kg twice daily in patients with normal renal function. The drug exerts its effect via inhibition of the cross-linkage of d-alanine to d-alanine in the cell wall of the bacteria, thus interfering with peptidoglycan synthesis Its pharmacodynamic bactericidal activity is best described as time-dependent killing, with area under the curve (AUC) and time above the MIC being the best predictors of activity [14]. Vancomycin distributes to most tissues well but penetration into the lung and cerebral spinal fluid is poor. The drug is 100% renally excreted and regimens need to be adjusted if renal impairment exists. Vancomycin is considered a "monitorable" drug because the laboratories of most institutions can assess serum levels. While vancomycin was initially associated with renal toxicity and ototoxicity, these are now rare with the currently available formulation [15].

It has been known for a while that vancomycin's activity against MSSA is inferior to that of antistaphylococcal beta-lactam antibiotics. In a recent prospective observational study comparing nafcillin to vancomycin for the treatment of MSSA bacteremia, risk factors for relapse of *S aureus* bacteremia included valvular heart disease, cirrhosis of the liver, deep-seated infection (ie, endocarditis), and treatment with vancomycin [16]. Vancomycin remained a risk factor for relapse on multivariate analysis with an odds ratio of 6.5 (95% CI, 1.0–52.8; $P < .048$).

Vancomycin is often used in the critical care setting for the treatment of pneumonia due to MRSA. However concern about suboptimal penetration of the lung and about the clinical implications of potentially decreased drug concentrations has led to interest in optimizing the dose of vancomycin by targeting higher trough levels. The only study looking specifically at increased trough concentrations and outcomes in pneumonia is a retrospective cohort study done by Jeffres and colleagues [17]. This study examined 102 patients with MRSA health care–associated pneumonia (HCAP) over a 6.5-year period. Neither mean trough concentrations nor mean AUC values differed significantly between the survivors and nonsurvivors. When the groups were broken into increments of 5 μg/mL (5–10 μg/mL, 10–15 μg/mL, 15–20 μg/mL, and >20 μg/mL), there was a trend toward decreased mortality in the trough of the 15- to 20-μg/mL group, though, as compared with other trough groups, it was not statistically significant. This led the investigators to conclude that there was no evidence for higher vancomycin trough levels or AUC levels to predict survival. The trial demonstrated no evidence for the value of increased trough levels. At the same time, however, because the study may have been underpowered to detect a difference in outcomes, it also did not prove the lack of correlation with trough level and treatment outcomes. Its retrospective nature and the estimation of trough levels by population kinetics models may also have weakened the validity of the conclusions. While the utility of attaining higher vancomycin trough levels in hospital-associated pneumonia (HAP), HCAP, and VAP is still unproven, the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) published guidelines for treatment of HAP, HCAP, and VAP recommend that, if vancomycin is used, it should dosed to achieve trough levels of 15 to 20 μg/mL [18].

Another attempt at improving outcomes with vancomycin has been to administer vancomycin as a continuous infusion. However, in a prospective, randomized study of 84 critically ill patients, efficacy and safety did not differ between those patients treated with continuous infusion and those with standard intermittent vancomycin therapy [19].

The most common side effect of vancomycin is an infusion-related phenomenon referred to as red-neck syndrome. Infusion of vancomycin triggers histamine release via mast cell degranulation, and patients become flushed and may become pruritic. The adverse effect can be attenuated by infusing the drug over a longer period of time. However, despite all of the concerns mentioned above, vancomycin continues to be commonly used in the treatment of MRSA infections.

Quinupristin-dalfopristin

New alternatives to vancomycin for the treatment of MRSA began to appear with the approval of quinupristin-dalfopristin in the late 1990s. Quinupristin-dalfopristin inhibits protein synthesis at the 50S ribosomal subunit

and is a bacteriostatic. The most notable adverse events associated with the drug are the development of arthalgia and myalgia during infusion of the drug.

Quinupristin-dalfopristin has been studied in the treatment of nosocomial pneumonia [20]. The study reported that clinical cure was achieved in 49 (56.3%) patients receiving quinupristin-dalfopristin and in 49 (58.3%) patients receiving vancomycin (absolute difference 2%; 95% CI, 16.8–12.8). The mortality rates were 25.3% in the quinupristin-dalfopristin group and 21.6% vancomycin group ($P = .45$). Based on the results of this study, quinupristin-dalfopristin does not appear to have a primary role in the management of MRSA pneumonia. Its high cost, increased risk of side effects, multiple drug interactions, and equivocal results greatly diminish its utility in the treatment of serious MRSA infections.

Linezolid

Linezolid is an oxazolidinone antibiotic with activity against a variety of gram-positive organisms, including MRSA. It is considered bacteriostatic against *S aureus* and exerts its effect by inhibiting bacterial protein synthesis by binding to the 70S initiation complex. It is dosed at 600 mg twice daily, and both oral and intravenous formulations are available. It distributes well into most tissues, including skin, fat, bone, lung, and cerebral spinal fluid [21]. It does not require renal or hepatic adjustment in those with impaired organ function. Caution should be used in patients taking concurrent selective serotonin re-uptake inhibitors because mild inhibition of monoamine oxidase by linezolid can cause serotonin syndrome to occur. Linezolid has also been reported to be associated with increased risk of thrombocytopenia, though one trial determined no difference as compared with treatment with vancomycin when used for short courses of therapy [22]. In addition, linezolid therapy rarely has been associated with the development of optic neuritis and peripheral neuropathy. The drug has not been well studied for long-term use (>28 days) and increased monitoring is warranted if therapy exceeds 28 days.

Linezolid has been studied head-to-head versus vancomycin for the treatment of MRSA pneumonia. Two multicenter, randomized, double-blind studies compared linezolid to vancomycin for nosocomial pneumonia [23,24]. The subset of patients treated for MRSA pneumonia has been reexamined in two retrospective subgroup analyses [25,26]. The total number of patients treated in the two nosocomial pneumonia clinical trials was 1019 with a subgroup of 160 patients with MRSA pneumonia. Baseline characteristics differed in a few important ways, though a statistical analysis was not performed as to the significance of these imbalances. There were higher percentages of patients with cardiac comorbidities (24% linezolid versus 40% vancomycin) and diabetes (17.3% linezolid versus 38.8% vancomycin) in the vancomycin-treated group. Renal comorbidities were also different in the two groups (13.3% linezolid versus 21.2% vancomycin), though patients with serum creatinine greater than 229.8 mol/L (2.6 mg/dL) was similar (4%

linezolid versus 4.7% vancomycin). Otherwise, the groups were well matched in terms of APACHE II score, age, and concomitant bacteremia. The overall mortality rate was 20% for the linezolid group as compared with 36.5% for the vancomycin group ($P = .03$). The clinical cure rate was 59% in the linezolid-treated group versus 35.5% in the vancomycin-treated group ($P < .01$). The investigators concluded that linezolid is superior to vancomycin for the treatment of MRSA pneumonia. This conclusion has been challenged because of the perceived suboptimal treatment in the vancomycin-treated group, because of the imbalance in cardiac comorbidities, and because this was a subgroup analysis. A study sponsored by Pfizer (NCT00037050) is underway to resolve this issue.

The utility of linezolid in the treatment of bacteremia is limited to one retrospective study of pooled results of five studies [27]. Of 144 patients with infection due to *S aureus,* 53 had MRSA bacteremia. Clinical cure rate for MRSA infections was 56% in patients treated with linezolid and 46% in patients treated with vancomycin, (odds ratio 1.47; 95% CI, 0.5–4.34). Survival was 74% in both treatment groups. Neither treatment was associated with increased rate of clinical cure or survival in the multivariate analysis. A recently completed, yet unpublished, trial (NCT00037050) compared linezolid to either vancomycin or oxacillin-dicloxacillin for the treatment of catheter-related bacteremia. Overall mortality was higher in the linezolid-treated patients, leading the Food and Drug Administration to add a warning to linezolid packaging about the risk of mortality in linezolid-treated catheter-related bloodstream infections.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic with activity against MRSA. It exerts its effect by rapidly depolarizing the bacterial cell membrane via the formation of potassium efflux channels. Pharmacodynamically, the drug is bactericidal and its killing effect is best predicted by concentration-to-MIC ratio. It is dosed at 4 mg/kg intravously every 24 hours in skin and skin-structure infections and at 6 mg/kg every 24 hours for *S aureus* bacteremia [28]. It is renally excreted and must be dose-adjusted in the setting of renal impairment. Daptomycin has a limited volume of distribution. However, at standard doses, it can achieve therapeutic levels in the blood and soft tissues. Treatment with daptomycin may cause elevations in the creatine kinase and the development of myalgia [28]. Patients should be monitored for symptoms of muscle pain and creatine kinase should be monitored at baseline and weekly during therapy.

Daptomycin's role in the critically ill patient is primarily in the treatment of bacteremia. The drug should not be used to treat pneumonia because it has been shown to be inferior to ceftriaxone in the treatment of community acquired pneumonia in an unpublished study (NCT00538694). These inferior results are likely because daptomycin penetrates the lung poorly and binds to surfactant [29].

In a study by Fowler and colleagues [30], 246 patients were randomized to either daptomycin or standard treatment for the treatment of *S aureus* bacteremia. Patients were excluded if pneumonia was present or estimated creatinine clearance was less than 30 mL per minute. The standard therapy treatment arm consisted of vancomycin for MRSA isolates and an antistaphylococcal penicillin, such as oxacillin, for the MSSA isolates. Gentamicin dosed 1 mg/kg intravenously three times daily was added to the treatment regimen in all patients with standard treatment and in patients in the daptomycin group with left-sided endocarditis for the first 4 days of therapy. Treatment success was defined as absence of clinical failure, microbiological failure, death, failure to obtain blood culture, receipt of potentially effective study antibiotics, or premature discontinuation of the drug. Treatment success occurred in 53 of 120 patients (44.2%) in the daptomycin group versus 48 of 115 patients (41.7%) in the standard therapy group (absolute difference of 2.4%; 95% CI, 10.2–15.1). In the subgroup of patients with MRSA bacteremia, no statistically significant differences in success were observed. As a result, daptomycin met the noninferiority criteria for treatment of bacteremia. The two antibiotic regimens exhibited similar safety and tolerability with the exception of a statistically significant increased incidence of renal failure in those in the standard treatment group. This was postulated to be a result of the addition of gentamicin, a known nephrotoxic agent, to this treatment group. Daptomycin has been associated with elevations of creatine kinase and, accordingly, this study showed a statistically significant increased incidence of creatinine kinase elevations in daptomycin-treated patients (6.7% versus 0.9% in the standard treatment group). Of those patients with elevated levels, 4 had a level greater than 10 times the upper limit of normal, and 3 discontinued treatment as a result. Lastly, this trial demonstrated a tolerance or acquired resistance to both daptomycin and vancomycin while on therapy. In the daptomycin group, 6 of 120 isolates became resistant to daptomycin while on therapy and led to subsequent treatment failure. In the vancomycin group, frank resistance did not occur. However, in 4 of the 53 patients who received vancomycin for MRSA, the MIC increased to 2 μg/mL from a baseline of 0.5 μg/mL or 1 μg/mL. These patients also failed treatment.

Tigecycline

Tigecycline is the first agent in the class of antibiotics known as the glyclcyclines. It shares structural similarities to minocycline and can be thought of as a broad-spectrum tetracycline antibiotic. It acts by inhibiting the 30S ribosomal subunit in a way unique to current tetracyclines. Therefore it is often effective against pathogens that demonstrate tetracycline resistance. It exerts a bacteriostatic effect on a wide range of gram-positive and gram-negative agents, including MRSA. It is considered to exhibit time-dependent killing

with AUC/MIC being the primary determinant of activity [31]. It is dosed as a 100-mg intravenous loading dose and 50 mg intravenously twice daily thereafter. It does not require dose adjustment in renal impairment, though severe hepatic impairment (Child Pugh classification) requires a maintenance dose adjustment to 25 mg twice daily. The drug is extensively distributed throughout the body. The distribution is such that maximum steady-state concentrations in serum are only 0.6 μg/mL [32]. Treatment of infections with concurrent bacteremia due to *S aureus* is cautioned as MICs vary between 0.03 and 0.5 μg/mL [33]. The side effect profile of the drug is similar to that of minocycline, with gastrointestinal intolerance being the most common treatment-limiting adverse event.

The drug has been extensively studied in skin and skin-structure infections as well as in intra-abdominal infections [34,35]. In the studies of intra-abdominal infections, MRSA was not identified as a significant pathogen, and the comparator drug imipenem has no activity against MRSA. Therefore, the only clinically relevant data to this discussion is pertaining to treatment of MRSA as presented in two double-blind phase 3 trials comparing tigecycline to a combination of vancomycin and aztreonam for the treatment of skin and skin-structure infection [35]. Microbiological success, defined as eradication of MRSA in 65 patients suitable for evaluation, occurred in 78% of patients treated with tigecycline versus 75.8% of those treated with the vancomycin-aztreonam regimen. These data come with the caveat that extensive exclusion criteria were implemented to select out severely ill patients. Patients with necrotizing fasciitis, neutropenia, or "any condition or medication that would impair the ability to eradicate infections" were excluded. The last measure would exclude many severely ill patients who frequently receive their care in intensive care units.

The drug has been used with limited success in gram-negative pneumonia with multidrug-resistant pathogens and, until recently, data consisted only in case reports and series [36,37]. A study by Maroko and colleagues [38] was presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy and compared tigecycline to imipenem as part of an empiric treatment regimen for HAP. Vancomycin could be added to the patients receiving imipenem, and ceftazidime and amikacin could be added to tigecycline for coverage of *Pseudomonas aeruginosa*. The mean APACHE II score in the study population was 12.3, indicating a relatively less severe patient population. Tigecycline treatment was associated with poorer cure rates in the population that could be clinically evaluated. Cure rates for the tigecycline group were 67.9% as compared with 78.2% cure rates for the imipenem group, with an absolute difference of −10.4% (95% CI, −17.8, –3.0). The safety of tigecycline was also less favorable with a discontinuation rate of 10.9% versus a discontinuation rate of 6.6% for imipenem. The pharmacokinetics favor the delivery of drug to the lung. However, in light of the recent data, tigecycline should be used with caution to treat HAP, VAP, and HCAP. Therefore, until further studies examine

tigecycline's usefulness, the agent falls to the role of salvage therapy for the treatment of MRSA in the critically ill patient. In less severe patients with intra-abdominal infections or skin and skin-structure infections due to MRSA, tigecycline can be used interchangeably with vancomycin, especially if the extended spectrum of tigecycline is needed for polymicrobial etiology.

Trimethoprim-sulfamethoxazole and clindamycin

Many strains of MRSA are susceptible to trimethoprim-sulfamethoxazole. This drug exerts its effect by interfering with bacterial folic acid synthesis. It has been studied in comparison with vancomycin in only one randomized double-blind study on efficacy of treatment for *S aureus* infections in 101 intravenous drug users [32]. MRSA caused infections in 47% of these patients. Vancomycin was shown to be superior in terms of treatment and safety. Therefore, trimethoprim-sulfamethoxazole's role in critical settings is severely limited and treatment should be confined to less severe infections, such as outpatient treatment of laboratory-proven trimethoprim-sulfamethoxazole–susceptible MRSA infections.

Clindamycin is an agent that in some cases can be considered for treatment of MRSA infections. It is a lincosamide antibiotic and acts on the 50S ribosome inhibiting bacterial protein synthesis. Clindamycin resistance can be constitutive or inducible. Inducible resistance is determined in the microbiology laboratory during routine susceptibility testing. MRSA isolates with the clindamycin-susceptible phenotype are commonly identified as community-acquired MRSA (CA-MRSA) [39]. CA-MRSA can be involved in serious infections as it can be associated with production of the Panton-Valentine leukocidin exotoxin. Clindamycin is thought to decrease the production of this exotoxin through its effects on bacterial protein synthesis. In the critical care setting, however, with more serious infections, it should not be given as a sole agent. In the case of necrotizing-type infections due to Panton-Valentine leukocidin–positive MRSA, it may be prudent to add clindamycin to the regimen for the duration of treatment [40]. Beyond this use, clindamycin has not been studied for the treatment of severe infections due to MRSA, nor compared with any MRSA-active drugs in the setting of a serious MRSA infection.

Summary

The treatment of MRSA in the critically ill patient is complicated. Data for treatment of critically ill patients are often lacking due to the exclusion of patients with high mortality risk in larger clinical trials. In the setting of nosocomial pneumonia, the evidence-based critical care practitioner must choose vancomycin or linezolid for treatment of MRSA. Tigecycline should

only be thought of as a salvage therapy at this time. Daptomycin should not be considered because it is sequestered in lung secretions. The choice of linezolid or vancomycin should take into account patient-specific factors, such as allergies, organ function, concomitant medications, MIC for each agent as applied to the pathogen in question, and susceptibility trends from the local antibiogram. It is prudent to consider the use of linezolid, especially in patients with MRSA isolates with elevated vancomycin MICs and in patients for whom limited lung penetration is a concern. If vancomycin is used, it is unclear if higher trough concentrations aimed at 15 to 20 μg/mL are necessary for efficacy, or will effectively treat the higher susceptible MIC pathogens. Because vancomycin is well tolerated, many practitioners will target higher troughs despite the absence of data supporting the decision. A prospective trial of MRSA pneumonia patients is underway to investigate the issue of vancomycin versus linezolid in greater detail. This trial will, it is hoped, settle the controversy.

In the patient with bacteremia, the primary concern is the source of the bacteremia. In a patient with concurrent pneumonia, the options are again linezolid and vancomycin. In a patient with a skin or skin-structure infection or intra-abdominal infection with a secondary bacteremia, there are more options. Vancomycin can be used and is the standard by which other agents are judged. Daptomycin is effective in treating primary bacteremia due to MRSA as well as bacteremia secondary to skin and skin-structure infections. Tigecycline can be considered in select instances as well, though blood levels are likely not sufficient for treating a primary bacteremia. As with pneumonia, treatment choice should be made after careful consideration of patient characteristics and local trends of antibiotic resistance.

In the event a patient presents with a severe CA-MRSA infection, the same reasoning discussed previously applies. However, addition of an agent with a mechanism of action related to decreasing protein synthesis, such as linezolid or clindamycin, should be considered as part of the regimen to attenuate potential toxin production. If clindamycin is used in the critically ill patient, it should be in combination with another drug active against MRSA, such as vancomycin, until the patient is stabilized and susceptibilities are known.

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