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Review article

Empirical therapy in Methicillin-resistant *Staphylococcus Aureus* infections: An Up-To-Date approach

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be an important pathogen worldwide, with high prevalence of infection in both community and hospital settings. Timely and appropriate choice of empirical therapy in the setting of MRSA infection is imperative due to the high rate of associated morbidity and mortality with MRSA infections. Initial choices should be made based on the site and severity of the infection, most notably moderate skin and soft tissue infections which may be treated with oral antibiotics (trimethoprim-sulfamethoxazole, clindamycin, doxycycline/minocycline, linezolid) in the outpatient setting, versus choice of parenteral therapy in the inpatient setting of more invasive or severe disease. Though the current recommendations continue to strongly rely on vancomycin as a standard empiric choice in the setting of severe/invasive infections, alternative therapies exist with studies supporting their non-inferiority. This includes the use of linezolid in pneumonia and severe skin and skin structure infections (SSSI) and daptomycin for MRSA bacteremia, endocarditis, SSSIs and bone/joint infections. Additionally, concerns continue to arise in regards to vancomycin, such as increasing isolate MICs, and relatively high rates of clinical failures with vancomycin. Thus, the growing interest in vanomycin alternatives, such as ceftaroline, ceftobribole, dalbavancin, oritavancin, and tedizolid, and their potential role in treating MRSA infections.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) are those strains of *S. aureus* that possess intrinsic resistance to methicillin, oxacillin, nafcillin, carbapenems, and other beta-lactam antibiotics. This intrinsic resistance is due the presence of an abnormal low-affinity penicillin binding protein (PBP2a), which is encoded by the *mec*A gene and is not found in methicillin-susceptible strains of *S. aureus* [1,2]. While initially almost exclusively a hospital-acquired pathogen, it is now commonly acquired in community settings as well. The clinical relevance of the organism is related to multiple factors, including that infections due to MRSA are associated with significantly increased morbidity, mortality, length of hospital stay, and costs, compared with infections due to methicillin-susceptible *S. aureus*, despite adjustment for disease severity and initially appropriate antibiotic treatment [3,4]. MRSA infections have been described worldwide [5] and the prevalence continues to increase in both community and hospital settings. It is associated with a multitude of infections, most notably skin and soft tissue infection,

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blood stream infection (BSI), pneumonia (which may be severe and necrotizing), infective endocarditis, and osteomyelitis [6,7]. Thoughtful and appropriate antimicrobial selection is imperative in the setting of MRSA given its intrinsic resistance to many antimicrobials and the increased virulence with high rates of morbidity and mortality associated with the organism and its diseases processes.

There are several antibiotics that exist which have been proven effective for definitive management of MRSA infection. It is important to be familiar with these antimicrobials as well as their benefits and potential toxicities. This knowledge will guide decision making for initiation of empiric therapy for various clinical syndromes when MRSA is suspected as the primary pathogen.

Vancomycin remains the cornerstone for management of invasive MRSA infection. It is a glycopeptide antibiotic that inhibits cell wall synthesis [8]. Despite this, concerns have arisen about vancomycin. Notably, treatment failures have been observed with rising vancomycin MICs and high vancomycin MIC (>2) has been associated with a higher mortality rates in MRSA BSI [9]. At this time, isolates with an MIC $\leq$2 are considered susceptible by CLSI break points [10], though a patient's clinical response to therapy should help guide ongoing vancomycin use. Another phenomenon that has been observed in some medical centers is labeled "vancomycin MIC creep". This refers to the observation that within the populations of *S. aureus* that are considered to be susceptible, a changing pattern of vancomycin MICs has been observed, demonstrating an overall population drift in the clinical isolates of *S. aureus* towards reduced vancomycin susceptibility. Multiple studies of patients with BSIs have examined this phenomenon with varying results between institutions [11]. Careful and frequent MIC monitoring should be preformed, including use of Etest when applicable, to ensure the most accurate MIC assessments. It is still unclear if alternative therapies are superior to vancomycin when the MIC is $\leq$ 2.

Optimal dosing of vancomycin is key for effective use. The pharmacokinetic/pharmacodynamic parameter that best predicts vancomycin efficacy seems to be the ratio of AUC/MIC [12,13]. This is because vancomycin is a concentration-independent antibiotic (also referred to as a "time-dependent" antibiotic). Moise et al. completed a study of patients with lower respiratory tract infections due to *S. aureus*. The findings of this study demonstrated that an AUC/MIC threshold of >400 was associated with greater clinical response and microbiological eradication, compared with patients with an AUC/MIC ratio of <400 [14]. Optimization of vancomycin dosing based on these parameters is being further investigated. It is felt that individualization of therapy using pharmacodynamics may help achieve enhanced killing and improved patient outcomes [15]. Currently, the most widely used method to determine AUC is a surrogate measure through use of vancomycin trough levels, though recent studies have suggested that this surrogate measure may not be as accurate as previously assumed [16]. Ideally a vancomycin trough is obtained at steady state level, prior to fourth or fifth dose administration and a vancomycin trough of 15–20 μg/mL remains the goal trough [10], as this level should correspond with attaining an AUC/MIC > 400 [13]. In order to reach steady state more quickly, the use of a vancomycin loading dose has been suggested, especially in the setting of seriously ill patients [10]. This method, however, is based on initial dosing nomograms and subsequently has not been well studied while only being shown to be effective in small-scale evaluations [17,18]. Standard dosing in patients with normal renal function is weight based (actual body weight) at a dose of 15–20 mg/kg/dose every 8–12 h with trough monitoring [10]. Vancomycin is 100% renally excreted and dosing should be adjusted in the setting of renal dysfunction. Early formulations were more commonly associated with renal toxicity and ototoxicity, though these effects are now rare with currently available formulations [19]. The most common vancomycin associated side effect is the infusion-related phenomenon termed "red-man syndrome". This reaction is mediated by histamine release via mast-cell degeneration, leading to flushing and pruritus [20]. This reaction can be prevented with slow vancomycin infusion and pre-medication with anti-histamine therapy.

Doxycyline is a long-acting tetracycline derivative, along with minocycline. Both drugs are well absorbed by the gastrointestinal tract, have excellent tissue penetration, and have demonstrated sufficient antistaphylococcal activity, including against those isolates demonstrated to be MRSA [21]. Tetracycline antibiotics are bacteriostatic and should not be used in patients with bacteremia and additional data is lacking to support their use in more-invasive infections [21]. The role of doxycycline/minocycline in regards to empiric antibiotic choice in the setting of MRSA is unsettled. They are often used as oral therapy in skin and skin structure infections given their excellent bioavailability [10].

Trimethoprim-sulfamethoxazole (TMP-SMX) has demonstrated excellent activity against MRSA in in-vitro studies and has been historically used for management of infections due to *S. aureus*. Both TMP and SMX function by inhibiting bacterial folic acid synthesis at sequential enzymatic steps [22]. TMP-SMX is included in the recommendations for empiric therapy in setting of skin and skin structure infectious when MRSA is a suspected pathogen, especially important for use in the outpatient setting due to its oral bioavailability [10,23]. Consideration for TMP-SMX in more invasive infections due to *S. aureus* has been examined with demonstration of variable results [22]. Most notably, Markowitz, et al. compared TMP-SMX with vancomycin for the treatment of MSSA and MRSA bacteremia. In the case of IV drug users with MRSA bacteremia, TMP-SMX was noninferior to vancomycin for management [24]. More recently, however, a larger study involving those patients only with MRSA infection, found TMP-SMX unable to achieve noninferiority when compared with vancomycin for severe MRSA infections, particularly in those patients with bacteremia [25]. For this reason, the empirical use of TMP-SMX remains limited in the setting of severe infection.

Clindamycin is a bacteriostatic antimicrobial with excellent tissue penetration [26]. It inhibits protein synthesis by biding to 50S ribosomal subunits and interferes with transpeptidation, resulting in early chain termination. Clindamycin is unique in that its mechanism of action makes it capable of inhibiting bacterial production of toxins. Though clindamycin can be indicated for management of *S. aureus* infection including infections due to MRSA, it should not be used in the setting of endovascular infection and caution is raised against its empiric use in the setting of severe infection due to increasing rates of clindamycin resistance, which have been recognized [27]. If clindamycin is chosen in an empiric manner for management of mild to moderate MRSA skin infections, it is imperative that clinician knowledge exists regarding regional rates of drug resistance. In addition to intrinsic clindamycin resistance, there have been notably high rates of inducible clindamycin resistance in MRSA, especially strains that are erythromycin resistant [28]. In patients who have demonstrated clinical stability and there are known patterns of low regional resistance, it may be reasonable to empirically treat these patients with clindamycin and follow-up formal susceptibility testing when culture results are available. If an isolate is erythromycin resistant but clindamycin susceptible, then formal D-testing is recommended for detection of inducible clindamycin resistance [28,29]. If inducible resistance is noted, clindamycin should not be used [30] and the patient should be changed to an alternative anti-staphylococcal agent, due to concern of development of clindamycin resistance and subsequent treatment failure. See Fig. 1 below. Frequent dosing and high rates