

# Evaluation of treatment options for methicillin-resistant *Staphylococcus aureus* infections in the obese patient

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Navaneeth Narayanan<sup>1,2</sup>  
Christopher D Adams<sup>1</sup>  
David W Kubiak<sup>3</sup>  
Serena Cheng<sup>4</sup>  
Robyn Stoianovici<sup>5</sup>  
Leonid Kagan<sup>1,6</sup>  
Luigi Brunetti<sup>1,6</sup>

<sup>1</sup>Department of Pharmacy Practice, Rutgers University, Ernest Mario School of Pharmacy, Piscataway, NJ, USA;

<sup>2</sup>Division of Infectious Diseases, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; <sup>3</sup>Department of Pharmacy, Brigham and Women's Hospital, Boston, MA, USA; <sup>4</sup>Department of Pharmacy, VA San Diego Healthcare System, San Diego, CA, USA;

<sup>5</sup>Department of Pharmacy, University of California, Davis Medical Center, Sacramento, CA, USA; <sup>6</sup>Department of Pharmaceutics, Rutgers University, Ernest Mario School of Pharmacy, Piscataway, NJ, USA

**Abstract:** Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major cause of infection in both the hospital and community setting. Obesity is a risk factor for infection, and the prevalence of this disease has reached epidemic proportions worldwide. Treatment of infections in this special population is a challenge given the lack of data on the optimal antibiotic choice and dosing strategies, particularly for treatment of MRSA infections. Obesity is associated with various physiological changes that may lead to altered pharmacokinetic parameters. These changes include altered drug biodistribution, elimination, and absorption. This review provides clinicians with a summary of the literature pertaining to the pharmacokinetic and pharmacodynamic considerations when selecting antibiotic therapy for the treatment of MRSA infections in obese patients.

**Keywords:** obesity, methicillin-resistant *Staphylococcus aureus*, antibiotics, pharmacokinetics

## MRSA epidemiology

Methicillin-resistant *Staphylococcus aureus* (MRSA) was identified more than 50 years ago in 1961,<sup>1</sup> shortly after the initial use of methicillin as a treatment option.<sup>2</sup> Since then MRSA has emerged as a major cause of both healthcare-associated infections such as bacteremia or pneumonia and community-associated infections such as skin and soft tissue infections or osteomyelitis. According to data reported to the National Healthcare Safety Network, *S. aureus* accounted for 16% (8.5% MRSA) of the multidrug-resistant pathogens reported.<sup>3</sup> From 1999 to 2005, the number of hospitalizations related to MRSA infections in the USA more than doubled, from approximately 127,000 to almost 280,000.<sup>4</sup> Rates of hospitalizations related to MRSA continue to increase in the USA with estimates of approximately 460,000 MRSA-related hospitalizations in 2009.<sup>5</sup> In a landmark report by the Centers for Disease Control and Prevention in 2013, MRSA is estimated to cause approximately 80,000 severe infections and over 11,000 deaths per year in the USA.<sup>2</sup> The burden of MRSA is not limited to the USA, as 13–74% of *S. aureus* infections worldwide are methicillin resistant.<sup>6</sup>

Obesity is a significant risk factor for MRSA colonization and infection although mechanisms are yet to be conclusively defined.<sup>7–9</sup> With the increased prevalence of MRSA infections and the growing presence of obesity, we need to understand the effects on treatment in this specific patient population. The estimated prevalence of overweight and obese individuals >20 years of age in the USA is 154.7 million and over 1.6 billion people are considered overweight or obese worldwide.<sup>10,11</sup> Furthermore, by 2025 the

Correspondence: Navaneeth Narayanan  
Ernest Mario School of Pharmacy,  
160 Frelinghuysen Road, Piscataway, NJ  
08854, USA  
Tel +1 848 445 6815  
Fax +1 732 445 2533  
Email navan12@pharmacy.rutgers.edu

global obesity prevalence will reach 18% in men and surpass 21% in women.<sup>12</sup> Obesity is a risk factor for infection,<sup>13</sup> antibiotic treatment failure,<sup>14</sup> and antibiotic resistance due to antibiotic underdosing. Furthermore, treatment outcome for individuals affected with MRSA infection may be worse in the obese depending on treatment selection.<sup>15</sup>

Although the mechanisms of reduced treatment efficacy in patients with obesity are unknown, one can surmise that alterations in bio-distribution patterns may influence treatment success in obesity. While the number of individuals in the USA and worldwide with obesity has reached epidemic proportions, there is no requirement for the pharmaceutical industry to perform clinical studies in this population. Boyd et al performed a review of commonly used antibacterial agents in the UK and reported no advice was included in the manufacturer information for 83% of antibacterials evaluated.<sup>16</sup> These data highlight the paucity of guidance available for drug dosing in this population. As a result, clinicians often dose therapies in obese patients without clear evidence. Much of the available literature that supports drug dosing in obesity makes the assumption that if adequate plasma concentration is achieved then this will translate into efficacy; however, this presumption does not account for adequacy at the target site. Typically, body mass index (BMI) is categorized as: underweight BMI < 18.5 kg/m<sup>2</sup>; normal BMI 18.5–24.9 kg/m<sup>2</sup>; overweight BMI 25.0–29.9 kg/m<sup>2</sup>; and obese BMI > 29.9 kg/m<sup>2</sup>. One of the challenges in the literature is that although BMI > 29.9 kg/m<sup>2</sup> is used to define obesity, many studies investigating treatment outcomes or drug pharmacokinetics use a variety of definitions. Despite widespread use of antibiotics, precise algorithms for dosing antibiotics in obese patients are not available, and the use of doses at the upper end of the approved dosage ranges is generally recommended.<sup>17</sup> However, several studies reported that current dosing strategies result in subtherapeutic concentrations in target tissues.<sup>18–21</sup> This review provides clinicians with a summary of the literature pertaining to the pharmacokinetic and pharmacodynamic considerations when selecting MRSA therapy in obese patients. In addition, recommendations for treating MRSA in the obese population are provided based on available clinical data.

## Pharmacokinetic and pharmacodynamic alterations in obesity

Obesity is characterized by a significant alteration of body composition (disproportional increase in fat mass) and

may affect other body functions. These physiological changes might lead to an alteration of pharmacokinetic parameters that would not be directly proportional to the increase in the actual body weight (ABW).<sup>22</sup> In addition, describing drug pharmacokinetics using only the total volume of distribution ( $V_d$ ) and total clearance (commonly derived using a non-compartmental approach from plasma data alone) may be too simplistic to describe the actual time course of exposure at the site of action. This consideration is particularly important for drugs that exhibit a time above the minimum inhibitory concentration (MIC) bactericidal effect (ie, beta-lactam antibiotics).

When considering obesity-induced changes in drug biodisposition, multiple factors should be considered. Drug physicochemical properties (such as lipophilicity and ionization state) and tissue composition (adipose vs other tissue) have been used for predicting steady-state tissue partition coefficients.<sup>23,24</sup> Obese patients have a different adipose-to-lean tissue ratio compared to normal weight subjects, which may lead to alterations in relative drug exposure in different organs. Obesity does not appear to have an effect on drug binding to albumin, and reports regarding binding to alpha-1-acid glycoprotein are contradictory.<sup>25</sup> The kinetics of tissue disposition can be also influenced by tissue blood flow, and an increase in total blood volume and cardiac output and a decrease in peripheral perfusion have been reported in obesity.<sup>26–30</sup>

Drug elimination is mostly dependent on liver and renal physiology, and obesity-induced changes of these systems including alterations in drug metabolizing enzymes and drug transporters have not been sufficiently studied. Increase in liver blood flow has been reported in obesity,<sup>30</sup> which may be important for high extraction ratio drugs. Limited data regarding changes in metabolic function have usually been deduced from comparing the pharmacokinetic profiles of certain model drugs (that are known to be specifically metabolized by those cytochrome isoforms). For example, lower CYP3A4-mediated clearance has been reported for some probes (alfentanil, triazolam) but not others (trazodone, decetaxel).<sup>31</sup> Estimated glomerular filtration rate was 62% higher in obese patients.<sup>32</sup> On the other hand, a higher incidence of renal dysfunction has been also reported and is commonly attributed to various comorbidities (diabetes, hypertension).<sup>17,31</sup>

Potential changes in the absorption process should be also taken into consideration for antibiotics delivered by extravascular routes. Delayed gastric emptying in obese

patients might affect oral bioavailability and the absorption rate.<sup>33,34</sup> Increased subcutaneous fat content in obese patients can lead to inadvertent subcutaneous delivery for drugs intended for intramuscular injection.

Taken together, there are numerous changes that occur in drug pharmacokinetics in the obese population. Currently, we do not have adequate information to make definitive conclusions as to what alterations are clinically relevant and should be considered when selecting the drug or drug dosage. When evaluating drugs and dosing strategies one should consider both pharmacokinetic and outcome data to make the most informed decisions. Ultimately, a better understanding of pathophysiological changes in obese patients and their pharmacokinetic and pharmacodynamic consequences should facilitate selection of the most appropriate drug and dose optimization, including dose level and mode of administration (route, frequency, bolus vs infusion, immediate release vs controlled release). In each of the sections that follow, the available pharmacokinetic and outcome data related to specific drugs with activity for MRSA are reviewed. In addition, recommendations related to drug and dosage selection are provided.

## Vancomycin

Vancomycin, a glycopeptide antibiotic, has been used for more than 50 years and remains the standard of care for treatment of MRSA infections.<sup>35</sup> The bactericidal activity of vancomycin results from inhibition of bacterial wall synthesis.<sup>36</sup> Vancomycin is predominantly eliminated by the kidneys, has a  $V_d$  ranging from 0.4 to 1 L/kg, and an elimination half-life ranging from 6 to 12 hours or longer depending on renal function.<sup>37</sup> The pharmacodynamic target that has been associated with clinical efficacy is the ratio of area under the concentration–time curve to a minimum inhibitory concentration (AUC:MIC) of  $\geq 400$ .<sup>36</sup> There are variable data of the effects of obesity on vancomycin pharmacokinetics and conflicting recommendations on optimal dosing of vancomycin in obese patients.

Some of the changes in the pharmacokinetics of vancomycin can be attributed to physiologic alterations. Obese patients not only have increased adipose tissue but also muscle mass. Additionally, obesity is associated with an increase in plasma proteins and since vancomycin is ~55% (range 44–82%) protein-bound there may be less active free drug in the serum.<sup>38</sup> Lastly, obesity is associated with an overall increase in cardiac output and blood volume, which leads to increases in renal blood flow and

kidney mass; these may contribute to a larger  $V_d$  and increased systemic clearance of vancomycin resulting in lower serum concentrations.<sup>38</sup>

Current national guidelines for dosing and monitoring of vancomycin recommend using ABW to calculate initial vancomycin doses (15–20 mg/kg given via an intermittent infusion every 8–12 hours with normal renal function), adjusted to achieve a target serum trough concentration of 15–20  $\mu\text{g/mL}$ .<sup>36</sup> Adjustments range from pharmacy managed pharmacokinetic protocols to dose titration based on clinician judgment. The target serum trough recommendation is based on a pharmacokinetic study performed in 1982 on six healthy morbidly obese patients who received a single 1 g dose of vancomycin infusion (1 g/h) after gastric bypass surgery. These obese patients had a significantly larger  $V_d$  (43.0 L vs 28.9 L;  $P < 0.005$ ) but no significant difference in total body clearance ( $1.112 \pm 0.160$  mL/min/kg vs  $1.085 \pm 0.071$  mL/min/kg of ABW) compared with normal weight control patients ( $n=4$ ), which correlated most closely with ABW.<sup>39</sup> However there have been several reports published after these guidelines which have challenged these recommendations and found that calculating vancomycin doses of 30–45 mg/kg/day on ABW often leads to supratherapeutic steady-state serum trough concentrations.<sup>40–45</sup> Unfortunately, no study has been able to precisely determine the optimal dosing weight of vancomycin in obese and morbidly obese patients to achieve consistent serum trough concentrations of 15–20  $\mu\text{g/mL}$  while minimizing nephrotoxicity. These efforts have been further hindered by confounding factors such as extremes of age, critical illness, and concomitantly administered nephrotoxic agents. Recent data indicate the minimal impact of serum trough concentration monitoring on clinical outcomes and in contrast, the safety advantage of AUC-based monitoring of vancomycin.<sup>44,46,47</sup> Targeting an AUC:MIC ratio of 400–600 mg h/L may help maximize efficacy while reducing toxicity; however, this has not been well tested in a robust clinical trial. Methodical therapeutic drug monitoring coupled with patient-specific pharmacokinetic calculations is likely the optimal approach for dosing and monitoring systemic vancomycin in obese and morbidly obese patients.

In regards to empiric vancomycin dosing when patient-specific vancomycin serum concentrations are not yet available, Crass et al recently published a population pharmacokinetic study of obese patients treated with vancomycin.<sup>48</sup> The analysis provides a dosing nomogram

for empiric vancomycin dosing in obese and morbidly obese patients. The pharmacokinetic model for estimating vancomycin clearance was based on a linear combination of age, serum creatinine, sex, and weight. The targets of efficacy and toxicity in this study were developed utilizing AUC targets, and the dosing regimens were assessed using 1,000-subject Monte Carlo simulations. The nomogram, utilizing loading doses and AUC-targeted empiric dosing regimens, had a >90% probability of efficacy ( $AUC_{0-24} \geq 400$ ) for all vancomycin clearance levels analyzed and 0% probability of toxicity ( $AUC_{48-72} \geq 700$ ) for vancomycin clearance >2 L/h. Although not prospectively validated in a clinical study, the authors provide a practical empiric vancomycin dosing nomogram for obese patients that will likely maximize efficacy and minimize toxicity based on AUC targets.

## Clindamycin

Clindamycin, first available in the late 1960s,<sup>49</sup> is a bacteriostatic agent of the lincosamide class and works by blocking bacterial protein synthesis by inhibiting the peptidyltransferase reaction on the 50S subunit of the bacterial ribosome.<sup>49,50</sup> Clindamycin is lipophilic and widely distributed in many fluids and tissues that can be affected by the larger than expected  $V_d$  of obese patients, thus potentially causing plasma drug concentrations to be low.<sup>51</sup> It exhibits time-dependent killing and prolonged persistent effects, therefore maximizing the amount of drug is the most ideal approach to ensure efficacy.<sup>51</sup>

The usual dosing recommendation for clindamycin in MRSA-related infections is 300–450 mg orally three times daily for uncomplicated skin and soft tissue infection and 600 mg orally or intravenously three times daily for complicated skin and soft tissue infection, pneumonia, and osteomyelitis.<sup>35</sup> Higher doses of 2,700–4,800 mg/day divided in 2, 3, or 4 equal doses are included in the drug labeling, but doses on the upper end (>3 g) of this range are seldom used clinically.<sup>10</sup>

A retrospective study of 50 adult patients who had received oral or intravenous clindamycin for treatment of osteomyelitis utilized a population pharmacokinetic model to determine the influence of covariates, including body weight. The body weight of the patients ranged from 23 to 133 kg, and the majority received 600 mg of clindamycin orally or intravenously three times a day, except for one patient who received 600 mg four times a day and two patients who received 600 mg once a day. The results showed that clindamycin clearance increased with body

weight and concluded that 600 mg three times a day is effective for ABW less than 75 kg with the suggestion that the dose should be increased to 900 mg every 8 hours for >75 kg.<sup>50</sup>

A retrospective cohort study of 210 patients admitted for cellulitis/cutaneous abscess identified risk factors for clinical failure, including treatment with clindamycin. The population of the study was relatively obese with an average weight of 101 kg and a BMI of 34 kg/m<sup>2</sup>, including 21.9% morbidly obese patients (BMI  $\geq 40$  kg/m<sup>2</sup>). Weight over 100 kg and BMI  $\geq 40$  kg/m<sup>2</sup> were identified as independent risk factors for clinical failure. A subgroup analysis demonstrated that morbidly obese patients were at a higher risk for clinical failure if they were discharged on a low dose of clindamycin (defined as 150–300 mg orally every 6–8 hours) versus high dose (defined as >300 mg every 8 hours).<sup>52</sup> Given the findings of these two retrospective studies, it is evident that lower doses of clindamycin can place a patient at risk of treatment failure. When using higher doses of clindamycin, clinicians should be aware that gastrointestinal side effects are positively correlated to total dosage.<sup>53</sup>

## Tetracyclines

Tetracyclines interfere with protein synthesis by reversibly binding to the bacterial 30S ribosomal subunit, subsequently preventing binding of tRNA to the mRNA-ribosome complex.<sup>54</sup> Tetracycline antibiotics are highly lipophilic, and doxycycline and minocycline are approximately 3–5 times more lipophilic than tetracycline.<sup>54</sup> As such, there is reason to suspect that the disposition of these antibiotics is altered in extremely high body weight. Despite this concern, there are limited data evaluating these antibiotics in obesity. Like other tetracycline derivatives, tigecycline has a large  $V_d$  resulting in wide tissue distribution and very low plasma drug concentrations. In a study including eight obese (median BMI 43.8 kg/m<sup>2</sup>) subjects, serum and urine pharmacokinetic parameters were similar to normal weight subjects.<sup>55</sup> However, two population pharmacokinetic studies found that tigecycline clearance increased with increasing body weight.<sup>56,57</sup> One option is to increase the dosage to 100 mg twice daily following a 200 mg loading dose (compared to the standard dose of 100 mg loading dose followed by 50 mg twice daily); however, this strategy is associated with an increased risk of nausea and vomiting.<sup>58</sup> Further, evidence to support this strategy is inconclusive as different authors have reported contradicting conclusions on the influence



of obesity on pharmacokinetics. Regardless of body habitus, tigecycline carries a black box warning for increased all-cause mortality versus comparators and therefore should be limited to last line treatment option.<sup>59</sup> Further, in obese patients with invasive infections, tigecycline monotherapy is not recommended even as the last line due to rapid distribution into tissues and inadequate serum concentrations.

## Sulfamethoxazole-trimethoprim

Trimethoprim (TMP)/sulfamethoxazole (SMX) is a broad spectrum antimicrobial combination that has been utilized in the outpatient setting for over 50 years. TMP competitively inhibits the production of dihydro-folate reductase and SMX interferes with the production of dihydrofolate.<sup>60</sup> The co-administration of these agents are synergistic and the combination is bactericidal against most organisms *in vitro*.<sup>61</sup> Both components are well distributed (1.4–1.8 L/kg, TMP and 0.43 L/kg, SMX) after administration.<sup>62</sup> TMP is primarily cleared through the kidneys (excreted 75–85% unchanged in urine) while sulfamethoxazole is metabolized by liver microsomes (cytochrome P450 2C9).<sup>63,64</sup> The dosing of this agent has primarily been extrapolated from pediatric cohorts and has displayed significant interindividual variability in the adult population.<sup>65–68</sup> The recommended dosing, based on small pharmacokinetic studies, has been capped at 100 mg/kg/day for SMX and 20 mg/kg/day for TMP, based on patient's ABW.<sup>69,70</sup> Intravenous and oral dosing are essentially equivalent due to the high oral bioavailability of the agent. Dosing and concentrations are organism dependent, with varying target concentrations existing for each specific organism as well as the location of the infection.<sup>71,72</sup> Clinical decision-making is imperative to balance exposure versus safety profile in each patient.<sup>71</sup> Target concentrations for SMX at the site of infection have been observed to be 100–150 µg/mL with increased toxicities occurring with concentrations greater than 200 µg/mL, yet the limited data linking the relationship between target SMX concentrations and outcomes deters routine therapeutic drug monitoring.<sup>73</sup>

TMP/SMX is a lipophilic, highly protein-bound (44% for TMP, 70% for SMX) agent that is predominantly excreted through the kidneys. A pharmacokinetic study in healthy subjects determined the  $V_d$  of each agent; with TMP having a larger distribution at 1.4 L/kg versus 0.4 L/kg for SMX.<sup>65,74</sup> Data are lacking on the variables affecting the pharmacokinetics of TMP/SMX; critical illness and trauma

have been shown to increase the  $V_d$ , but other factors such as shock, fluid resuscitation and obesity are not well studied.<sup>71,75</sup> There is a concerning lack of data on the appropriate weight metrics for dosing of TMP/SMX. A small study by Garrett et al found no difference in the  $V_d$  of sulfisoxazole (a sulfonamide with similar pharmacokinetic profile) in morbidly obese patients over time after jejunal-ileal bypass surgery resulting in up to a 44% reduction in body mass.<sup>76</sup> Hall et al, on the other hand, demonstrated a decrease in maximum plasma concentration ( $C_{max}$ ) and AUCs in overweight patients.<sup>70</sup>

The lack of knowledge of target concentrations and appropriate dosing for TMP/SMX, especially in the setting of MRSA infections, is concerning, and more information is required in this arena.<sup>77–81</sup> In a recent retrospective analysis, Dao et al attempted to link therapeutic drug monitoring and dosage optimization and were unable to determine appropriate dosing regimens with target concentration attainment.<sup>73</sup> Small studies have shown that TMP/SMX is successful in eradicating MRSA infections but the heterogeneity of drug dosing and lack of available drug concentrations make determination of optimal dosing strategies difficult.<sup>79,80</sup> In conclusion, ABW should be utilized clinically to ensure adequate concentrations are being reached, while monitoring closely for adverse effects associated with higher doses.

## Linezolid/tedizolid

Linezolid (FDA approval April 2000) and tedizolid (FDA approval May 2014) are part of the oxazolidinone class of antibiotics. The mechanism of action of the oxazolidinones is through binding of the 50S bacterial ribosomal subunit.<sup>82</sup> That prevents the formation of the 70S initiation complex that leads to protein synthesis. This class is effective for the treatment of skin and soft tissue infections and lung infections caused by Gram-positive organisms, particularly MRSA.<sup>83</sup> Linezolid and tedizolid are available in intravenous and oral formulations with high bioavailability (linezolid, 100% and tedizolid, >80%).<sup>84,85</sup> Linezolid  $V_d$  approximates the total body water compartment (40–50 L), is cleared by renal and non-renal mechanisms, and elimination half-life ranges from 3.4 to 7.4 hours.<sup>85</sup> Tedizolid  $V_d$  ranges from 67 to 80 L, is predominantly eliminated hepatically although not a substrate of cytochrome P450 and half-life is approximately 9 hours.<sup>86</sup>

The first of the oxazolidinones was linezolid. It has time-dependent killing with both percentage of time

over the MIC ( $T > MIC$ ) and the AUC:MIC.<sup>82</sup>  $T > MIC$  of 82% was correlated to bacterial eradication. In a murine model, a 24-hour AUC:MIC ratio of ~83 (range of 39–167) is required for bacteriostatic activity against staphylococci.<sup>87</sup> In healthy volunteers, linezolid was found to have a  $V_d$  of 40–50 L and plasma protein binding of 31%. Its elimination half-life is 3.4–7.4 hours, and 65% is cleared by non-renal mechanisms.<sup>85</sup> In vivo, linezolid undergoes slow non-enzymatic oxidation by ubiquitous reactive species into inactive metabolites.<sup>85,88</sup> Linezolid demonstrated good penetration into bone, joints, and soft tissues, making it an attractive option for treatment of skin and soft tissue infections and staphylococcal pneumonia.<sup>85,89</sup>

The standard dose for linezolid is 600 mg every 12 hours with no dose adjustment for moderate renal or hepatic dysfunction. Due to its hydrophobic properties, linezolid is less susceptible to changes of the extracellular fluid volume.<sup>83</sup> However, studies have shown that linezolid is cleared more quickly in critically ill patients, indicating other hypermetabolic factors are resulting in a lower serum concentration of linezolid.<sup>82,90,91</sup> Stein et al obtained serum samples from 7 patients with an actual body weight  $>50\%$  of their ideal body weight (IBW) after administration of linezolid 600 mg by mouth every 12 hours for treatment of cellulitis.<sup>87</sup> Although all patients had achieved clinical cure after 12 days of therapy, the serum concentrations measured were diminished compared to those in non-obese patients; the mean linezolid serum concentration at one hour was 12.3  $\mu\text{g/mL}$  compared to 16.3–24  $\mu\text{g/mL}$  in previous studies. This reduction in AUC:MIC resulted in prolonged activity in *S. aureus* with a MIC of 1.0  $\mu\text{g/mL}$  and a lack of activity to those with a MIC  $>2$   $\mu\text{g/mL}$ .<sup>87</sup> In healthy adults, linezolid reached tissue concentrations that were active against pathogens with a MIC up to 4  $\mu\text{g/mL}$ .<sup>85</sup> Additionally, the decrease in serum concentrations can be related to the variability in  $V_d$  of linezolid due to an increased amount of adipose tissue in obese patients. Adipose tissues of obese mice have also been shown to have a higher production of reactive oxygen species, thus could increase the non-enzymatic oxidation of linezolid.<sup>83</sup>

One approach is to optimize its time-dependent killing with increased dosing frequency. Corcione et al reported variability in linezolid serum concentrations of two patients with BMI  $\geq 40$   $\text{kg/m}^2$  who received linezolid

600 mg intravenously every 8 hours, suggesting that increasing the dosing frequency may not achieve desired targets. Despite an increased frequency, the patient with a BMI of 71  $\text{kg/m}^2$  could only achieve an AUC<sub>0–24</sub> of 55.05 mg h/L.<sup>83</sup> Also, in contrast to the potential pharmacodynamic benefits of increased dosing frequency, 600 mg every 8 hours is likely associated with an increased risk of toxicity (ie thrombocytopenia) due to higher trough concentrations.<sup>92</sup> De Pascale et al compared linezolid concentrations in the plasma and epithelial lining fluids when administered by intermittent or continuous infusion to 22 obese (median BMI of 33.2  $\text{kg/m}^2$ ) critically ill patients for treatment of ventilator-associated pneumonia.<sup>93</sup> Although the  $T > MIC$  was higher in the continuous infusion group, the AUC:MIC and measured penetration into the lungs were not statistically different. Additionally, there was no detectable added benefit with the use of continuous infusion and no difference in clinical improvement on day 4.<sup>93</sup>

Tedizolid was the second oxazolidinone that was FDA approved for the treatment of acute bacterial skin and skin structure infections caused by MRSA. It is administered in its prodrug form, tedizolid phosphate, requiring activation by phosphatases into the active form, tedizolid.<sup>94</sup> The standard dose is 200 mg daily without the need for dose adjustment in patients with hepatic or renal impairment. It also distributes well into the skin and soft tissue. The efficacy of tedizolid is dependent on the AUC:MIC ratio.<sup>84</sup> Few data are available evaluating this drug in obesity. One study evaluated 18 patients (9 obese and 9 normal weight-matched control subjects) with either a BMI of  $\geq 40$   $\text{kg/m}^2$  or of 18.5–29.9  $\text{kg/m}^2$ . The tedizolid median  $C_{\text{max}}$  and AUC were not significantly different compared to non-obese controls.<sup>94</sup>

Overall, caution is required as altered pharmacokinetics and pharmacodynamics in obesity has shown to affect the serum concentrations of linezolid and tedizolid. Obese patients will have a larger  $V_d$  and more reactive oxygen species, which results in lower serum concentrations of linezolid and possibly tedizolid. That can ultimately prevent linezolid and tedizolid obtaining the optimal AUC:MIC ratio to inhibit the growth of MRSA with MIC  $\geq 2$ . However, there is no clear guidance for dose adjustments as the clinical significance of these pharmacokinetic and pharmacodynamic alterations are limited due to the limited number of studies in obese patients and small sample sizes.

## Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic FDA approved (September 2003) for the treatment of complicated skin and skin structure infections caused by susceptible Gram-positive bacteria and staphylococcal bacteremia including infective endocarditis. Daptomycin exerts its bactericidal effects through various mechanisms, including insertion into and disruption of the bacterial cytoplasmic membrane.<sup>95</sup> Daptomycin also has the ability to inhibit bacterial protein, DNA, RNA, and lipoteichoic acid synthesis.<sup>95,96</sup> Unlike beta-lactams that are effective primarily during bacterial replication, daptomycin is active at all bacterial growth phases including the stationary phase.<sup>95</sup> These qualities are desirable for treating deep-seated and indolent serious infections that involve MRSA.<sup>95</sup> Pharmacokinetics of daptomycin are independent of time and linear up to doses of 12 mg/kg administered for 14 days.<sup>97</sup> Daptomycin is eliminated primarily by the kidneys and requires dose adjustment in patients with a creatinine clearance <30 mL/min. The  $V_d$  is approximately 0.1 L/kg and limited primarily to the extracellular fluid. Approximately 92% of the administered dose is protein bound.

There have been several pharmacokinetic studies evaluating daptomycin in obese and non-obese individuals. The importance of considering ABW when dosing daptomycin is underscored by a population pharmacokinetic analysis which included 29 extremely obese (BMI>40 kg/m<sup>2</sup>), 333 moderately obese (BMI 25–40 kg/m<sup>2</sup>), and 255 non-obese subjects (BMI<25 kg/m<sup>2</sup>).<sup>98</sup> This analysis determined that ABW was a potential factor influencing clearance and  $V_d$ . While both moderately and extremely obese subjects had a 28% and 42% higher AUC, respectively, these values were within the coefficient of variation (55%) seen in normal weight subjects. Dvorchik et al evaluated daptomycin 4 mg/kg based on ABW as a single dose in 6 morbidly obese (BMI>40 kg/m<sup>2</sup>), 6 moderately obese (BMI 25–39.9 kg/m<sup>2</sup>) and 2 non-obese healthy subjects.<sup>99</sup> Compared to the non-obese subjects,  $V_d$  was increased by 58% and 24% in the moderately and morbidly obese subjects, respectively. AUC and  $C_{max}$  were increased by 25% and 30%, respectively, compared to the non-obese subjects. Similarly, Pai et al compared the pharmacokinetics of a single daptomycin 4 mg/kg dose based on ABW in 7 morbidly obese versus 7 non-obese female subjects.<sup>100</sup> AUC was significantly increased by approximately 61% and  $C_{max}$  by 59% in the morbidly obese subjects compared to non-obese control subjects.

The difference in  $V_d$  and clearance were increased in morbidly obese subjects but failed to reach statistical significance. Furthermore, the  $V_d$  was strongly correlated to ABW and not IBW. In addition to pharmacokinetic studies, Ng et al described an institution-wide protocol that switched from an ABW to IBW dosing strategy for daptomycin.<sup>101</sup> They reported no significant differences in microbiological outcomes, length of stay, mortality, or adverse effects. Importantly, the mean body mass index in this analysis was approximately 31 kg/m<sup>2</sup> and treatment success rates range from 79% to 100% depending on the etiology of infection. While these data suggest IBW dosing may be appropriate, the external validity of the findings is limited by the small sample size (n=117), single institution, and dosing strategy of 4–6 mg/kg.

Pharmacokinetic studies completed to date suggest ABW as the appropriate descriptor to use when selecting the dosage. Although these studies used doses of 4–6 mg/kg, it is common to prescribe daptomycin doses of up to 8–10 mg/kg in the treatment of severe infections. Pharmacokinetics have been reported as linear up to 12 mg/kg in normal weight patients.<sup>95</sup> The primary safety concern with daptomycin is myositis and elevated creatinine phosphokinase. This adverse effect typically occurs after 2 weeks of exposure, and the probability of an elevated creatinine phosphokinase with a minimum plasma concentration ( $C_{min}$ ) of  $\geq 24.3$  mg/L is 50% compared to 2.9% when the  $C_{min}$  is below this value.<sup>102</sup> Based on Monte Carlo simulations, using IBW in patients weighing more than 111 kg would decrease the probability of achieving a  $C_{min}$  of  $\geq 24.3$  mg/L and therefore decrease the probability of creatinine phosphokinase elevations. Nonetheless, in patients with extreme obesity clinicians should weigh the risks and benefits of dosing based on ABW when high dose daptomycin is considered. In many cases, the risks of underdosing and treatment failure are greater than the risk of toxicity from using ABW. In obese patients treated with high dose daptomycin, it is prudent to monitor for signs of toxicity and check creatinine phosphokinase at least weekly and perhaps more frequently if the patient has other risk factors for elevated creatinine phosphokinase or muscle toxicity.<sup>103,104</sup>

Recently, a population pharmacokinetic study evaluated daptomycin exposure and safety of fixed versus weight-based dosing in morbidly obese and nonobese healthy subjects.<sup>105</sup> Monte Carlo simulations were

performed to compare pharmacokinetic parameters ( $C_{\max}$ ,  $C_{\min}$ , and AUC) of daptomycin 6 mg/kg/day or 500 mg daily. As compared to nonobese subjects, morbidly obese subjects who received 6 mg/kg/day had an approximately two times higher AUC,  $C_{\max}$ , and  $C_{\min}$ . Subjects given a fixed dose of 500 mg daily demonstrated relatively isometric exposure measures between the two groups. Also, there was a higher proportion of morbidly obese subjects given 6 mg/kg/day that had a  $C_{\min}$  associated with creatinine phosphokinase elevations ( $C_{\min} > 24.3$  mg/L) as compared to those that received 500 mg daily. Further clinical studies are needed in order to evaluate the comparative clinical effectiveness of fixed-dose regimens, particularly in patients with severe MRSA infections (ie bacteremia) where daptomycin is generally used for treatment.

## Ceftaroline

Ceftaroline fosamil, the prodrug of ceftaroline, is a broad spectrum fifth-generation cephalosporin FDA approved (October 2010) for the treatment of acute bacterial skin and skin structure infections and community-acquired pneumonia. Ceftaroline exhibits potent activity against *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, and  $\beta$ -lactamase-positive and negative isolates of *Haemophilus influenzae*.<sup>106</sup> In addition, in vitro studies support the efficacy of ceftaroline against methicillin-susceptible and methicillin-resistant isolates of *S. aureus* as well as isolates with reduced susceptibility to vancomycin or linezolid.<sup>107</sup> These data have been corroborated in randomized controlled trials where subsets of patients with MRSA skin and skin structure infections achieved clinical success with ceftaroline.<sup>108–110</sup> Ceftaroline exerts its bactericidal effect by binding to the penicillin-binding proteins (PBP) 1–3 and inhibiting bacterial cell wall synthesis.

Ceftaroline has a low  $V_d$  (20.3 L) and is not extensively protein bound (approximately 20%).<sup>106</sup> Both of these attributes are favorable in the setting of obesity since ceftaroline distribution is primarily in the total body water compartment and protein binding may be altered in obesity. The primary route of elimination is through the kidneys (88%).<sup>106</sup> The pharmacokinetics of ceftaroline have been evaluated in 32 healthy normal weight and obese volunteer subjects.<sup>111</sup> Subjects were evenly assigned to one of four groups (normal to overweight; BMI, 18.5–29.9 kg/m<sup>2</sup>; obese class I; BMI, 30–34.9 kg/m<sup>2</sup>; obese class II; BMI, 35–39.9 kg/m<sup>2</sup>;

obese class III; BMI,  $>39.9$  kg/m<sup>2</sup>). Mean ceftaroline  $C_{\max}$  was 30% lower in subjects with a BMI  $\geq 40$  kg/m<sup>2</sup> compared to subjects with a BMI  $< 30$  kg/m<sup>2</sup>. Despite the lower concentration, Monte Carlo simulations performed suggested that when the MIC is  $\leq 1$   $\mu$ g/mL, the probability of target attainment is  $\geq 90\%$ . Additionally, outcomes in obese patients (defined as BMI  $\geq 30$  kg/m<sup>2</sup>) were evaluated in The Clinical Assessment Program and TEFLARO Utilization Registry (CAPTURE) multicentre retrospective cohort study.<sup>112</sup> Data were collected from 261 normal BMI patients and 690 patients with a BMI  $\geq 30$  kg/m<sup>2</sup> (of which 239 [34.6%] had a BMI  $\geq 40$  kg/m<sup>2</sup>) receiving ceftaroline for acute bacterial skin and skin structure infections. Outcomes in the obese patients were similar to normal BMI patients (clinical success rates ranging from 85.1% to 89.0%). Collectively these data suggest that no dosage adjustment is necessary for ceftaroline in obese patients and this treatment represents a viable option when there is a concern for inadequate antibiotic exposure due to extreme weight. Higher dosing (ie, every 8-hour regimen) may be considered for severe MRSA infections although further studies are needed to assess any clinical advantage to higher dosing in this scenario.<sup>113</sup>

## Telavancin/dalbavancin/oritavancin

Telavancin, dalbavancin, and oritavancin are the newest of the glycopeptide antibiotic class with the latter two FDA approved in 2014 for the treatment of acute bacterial skin and skin structure infections in adult patients. Telavancin was initially approved in 2009 for treatment of complicated skin and skin structure infections and more recently approved in 2013 for hospital-acquired and ventilator-associated bacterial pneumonia.<sup>114</sup> Compared to previously discussed antibiotics, pharmacokinetic and clinical data regarding the newer glycopeptides are limited.

Telavancin is a highly protein-bound drug (90%) that is primarily excreted in the urine ( $\sim 75\%$ ) with an elimination half-life of approximately 8 hours.<sup>114</sup> In obese patients defined as BMI  $\geq 35$  kg/m<sup>2</sup>, the mean AUC is approximately 26–35% higher in comparison to non-obese patients (BMI  $< 35$  kg/m<sup>2</sup>). Also in obese patients, the drug clearance (L/h) and  $C_{\max}$  is 20% and 10% higher, respectively, versus non-obese patients.<sup>115</sup> In a population pharmacokinetic study that included both healthy subjects and infected patients, AUC changes were minimal despite increases in doses for obese individuals. For the complicated skin and skin structure infections model, a 50% dose increase in obese (BMI  $\geq 35$  kg/m<sup>2</sup>) patients only resulted



in a 34% higher median AUC for obese compared to non-obese patients. This was similar in the hospital-acquired pneumonia model in which a 55% dose increase in obese patients resulted in an 18% increase in the median AUC.<sup>116</sup> Dosing for patients in clinical trials is based on both ABW and renal function as measured by CrCl.<sup>117</sup> Clinical data for use of telavancin in obese patients is primarily derived from post hoc analyses from two phase 3 clinical trials evaluating treatment of skin infections (ATLAS studies). Clinical cure rates were similar for telavancin versus the comparator vancomycin in the obese ( $\text{BMI} \geq 35 \text{ kg/m}^2$ ) subgroup (72% and 73%, respectively).<sup>118</sup> The specific pathogen (ie, MRSA vs other bacteria) was not delineated in the post hoc analysis. Based on limited post hoc data analysis, pharmacokinetic changes in obese patients were minimal, which is consistent with clinical findings in which clinical cure rates for skin infections were similar. Also important to note is that there is growing evidence that telavancin flat dosing at 750 mg daily performs similarly to weight-based dosing.<sup>119</sup> Recently, a study was completed assessing single-dose pharmacokinetics of weight-stratified fixed dose telavancin in obese and non-obese healthy subjects. A fixed dose in obese patients of 750 mg (ABW 90–99.9 kg) or 1,000 mg ( $\text{ABW} \geq 100 \text{ kg}$ ; maximum dose) was compared to weight-based dosing for the probability of AUC target attainment. The fixed-dose strategy resulted in more uniform AUC measures as compared to the projected AUC measures from the current standard, ABW-based dosing. The authors concluded that a fixed dose of 750 mg is a potentially safe and effective alternative to weight-based (total or adjusted) dosing for telavancin in obese patients with normal renal function.<sup>120</sup>

Dalbavancin is the first approved long-acting glycopeptide antibiotic with currently two dosing regimens. The first is a two-dose regimen of 1,000 mg followed by 500 mg one week later. More recently, a regimen of 1,500 mg as a single dose was approved for the treatment of acute bacterial skin and skin structure infections. It has a half-life of 346 hours with approximately 33% of the drug excreted unchanged in urine.<sup>121</sup> Data with dalbavancin in obese patients is limited to post hoc analyses of two phase 3 trials of the two-dose regimen versus vancomycin. Overall efficacy of dalbavancin was similar to vancomycin regardless of BMI. In patients with  $\text{BMI} \geq 30 \text{ kg/m}^2$  vs  $25 < \text{BMI} < 30 \text{ kg/m}^2$  vs  $\text{BMI} < 25 \text{ kg/m}^2$ , there were similar clinical cure rates for dalbavancin as well.<sup>122</sup> There is no available data for clinical efficacy

specifically in obese patients with MRSA infections. For acute bacterial skin and skin structure infections, cure rates seem to be unaffected by BMI and require no dose adjustments.

Oritavancin is the second FDA approved long-acting glycopeptide antibiotic given as a single dose regimen (1,200 mg). It has a long half-life of approximately 245 hours.<sup>123</sup> In an efficacy analysis of subgroups from two pivotal phase 3 clinical trials, there were similar rates of the primary efficacy outcome in patients with  $\text{BMI} \geq 30 \text{ kg/m}^2$  in the oritavancin and vancomycin treatment arms (77.3% and 74.9%, respectively).<sup>124</sup> In a separate analysis of the same acute bacterial skin and skin structure infections clinical trial data, there was not a statistically significant difference of clinical success for  $\text{BMI} \geq 29.1 \text{ kg/m}^2$  in comparison to  $\text{BMI} < 24.8 \text{ kg/m}^2$  specifically for patients with *S. aureus* (odds ratio 0.377 [95% CI, 0.087–1.63]).<sup>125</sup> Additionally, in a population pharmacokinetic analyses of the same phase 3 clinical trial patients (mean weight 79.9 kg, range 42.7–178 kg), covariate analyses concluded no dose adjustment is needed for weight or BMI given the lack of relation to the interindividual variability in oritavancin pharmacokinetics. The standard dose (1,200 mg) is appropriate regardless of variations in body size based on this pharmacokinetic analysis.<sup>126</sup> Based on limited pharmacokinetic and clinical data in the context of acute bacterial skin and skin structure infections, there appears to be no significant difference in outcomes for oritavancin in subgroups of obese patients although conclusions must be drawn cautiously, given the absence of high-quality evidence.

## Summary and conclusions

There are a variety of agents available to treat MRSA infections. As the obesity epidemic continues to reach new heights, clinicians are frequently faced with decisions related to drug selection and dosing strategy when managing these infections. The general recommendation is to dose at the higher end of the dosing range and use therapeutic drug monitoring if available. Another important consideration is the source of infection as different antibiotics may be preferred depending on the setting. Table 1 provides a summary of the anti-MRSA antibiotics discussed in this manuscript and includes pertinent antibiotic information to help clinicians select optimal therapy and choose the most appropriate dose.

**Table 1** Summary of antibiotic characteristics for agents used to treat methicillin-resistant *Staphylococcus aureus* infections

| Drug class          | Drug        | Pharmacodynamic target         | Typical adult dosage  | Dosage in obesity  | Evidence to support altered dosing strategy* |
|---------------------|-------------|--------------------------------|---|--|--|
| Cephalosporin       | Ceftaroline | T>MIC                          | 600 mg IV every 12 hours  | Consider 600 mg every 8 hours dosing if there is concern of inadequate exposure in severe MRSA infections  | +  |
| Lincosamide         | Clindamycin | T>MIC                          | 300–900 IV every 6–8 hours (maximum; 2,700 mg/day)<br>150–600 mg PO every 6 hours | Consider 900 mg every 8 hours or at least 10 mg/kg/day depending on infection severity   | +  |
| Glycopeptide        | Vancomycin  | AUC:MIC; T>MIC                 | Maintenance dose: 15–20 mg/kg IV every 8–12 hours                                 | Consider 20–25 mg/kg loading dose, then 10–15 mg/kg IV every 12 hours (maximum single dose of 2 g and maximum total daily dose of 4.5 g); adjusted by TDM for AUC targets<br>Consider empiric dosing nomogram by Crass et al followed by TDM for AUC targets <sup>48</sup> | +++  |
| Lipoglycopeptide    | Dalbavancin | AUC:MIC                        | 1,000 mg IV followed by 500 mg IV one week later<br>OR<br>1,500 mg IV once        | No dosage adjustment   | +  |
|                     | Oritavancin | AUC:MIC                        | 1,200 mg IV once  | No dosage adjustment   | ++   |
|                     | Telavancin  | AUC:MIC, C <sub>max</sub> :MIC | 10 mg/kg IV every 24 hours  | No dosage adjustment; consider dose cap of 750–1,000 mg  | ++   |
| Cyclic lipopeptides | Daptomycin  | AUC:MIC, C <sub>max</sub> :MIC | 4–10 mg/kg IV every 24 hours  | Consider dosing based on adjusted body weight or capping at 1 g<br>Clinicians should weigh the risk/benefit of potential underdosage when using adjusted body weight or dose capping   | ++   |
| Tetracycline        | Doxycycline | AUC:MIC                        | 100–200 mg IV/PO twice daily  | No dosage adjustment   | ND   |
| Glycylcycline       | Tigecycline | AUC:MIC                        | 100 mg IV loading dose followed by 50 mg IV twice daily                           | Consider higher dose; 200 mg IV loading dose followed by 100 mg twice daily; however, may have increased nausea and vomiting or other toxicities   | +  |
| Oxazolidinone       | Linezolid   | AUC:MIC, T>MIC                 | 600 mg IV/PO every 12 hours   | No dosage adjustment   | +  |

(Continued)

Table I (Continued).

| Drug class  | Drug                          | Pharmacodynamic target | Typical adult dosage                    | Dosage in obesity   | Evidence to support altered dosing strategy* |
|-------------|-------------------------------|------------------------|---|---|--|
|             | Tedezolid                     | AUC:MIC                | 200 mg IV/PO every 24 hours             | No dosage adjustment  | +  |
| Sulfonamide | Trimethoprim-sulfamethoxazole | AUC:MIC                | 1–2 double strength tablets twice daily | Consider higher end of the typical dosing; aim for at least 5 mg/kg/day for skin and skin structure infections <sup>a</sup> | +  |

**Notes:** \*+Pharmacokinetic studies OR observational studies. ++Pharmacokinetic studies PLUS observational studies. +++Pharmacokinetic studies plus several observational/outcome studies. <sup>a</sup>More serious MRSA infections such as bacteremia should not be treated with trimethoprim/sulfamethoxazole. Limit use to skin and skin structure infections.

**Abbreviations:** AUC, area under the curve; AUC:MIC, area under the curve to minimum inhibitory concentration ratio;  $C_{max}$ :MIC, maximum drug concentration to minimum inhibitory concentration ratio; TDM, therapeutic drug monitoring; IV, intravenous; PO, by mouth; ND, no data; T>MIC, time above the minimum inhibitory concentration.

## Disclosure

The authors report no conflicts of interest in this work.

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