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# Will New MRSA Guidelines Make a Difference in Clinical Outcomes? A Comparison of United States and United Kingdom Guidelines and Outcomes

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## Will New MRSA Guidelines Make a Difference in Clinical Outcomes? A Comparison of United States and United Kingdom Guidelines and Outcomes

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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#### **Objectives:**

After completion of this program, the reader should be able to:

- 1. Define the types of MRSA
- 2. List the medications that can be used to treat CA-MRSA
- 3. List the medications that can be used to treat HA-MRSA
- Identify how MRSA can be transmitted in the community and health care settings
- 5. Distinguish the importance of evidence-based medicine and published guidelines in helping with antibacterial resistance
- 6. State the preferred treatments of MRSA in certain clinical syndromes

#### Abstract

As of February 2011, the Infectious Disease Society of America (IDSA) published the first guidelines assessing the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections. S. aureus is present in the environment and is also located on the skin's surface. MRSA can cause a variety of clinical syndromes presenting with different symptoms that vary with the type and stage of the infection, MRSA is also classified into community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA), both of which possess different treatment options and strategies. Due to the complex treatment of MRSA, as well as the concern over the development of resistance, suggested treatment guidelines are critical for improvement in clinical outcomes. The recently published IDSA guidelines come in lieu of those previously published in 2006 by the U.K. The U.S. publication was most likely prompted due to an article published in The Journal of the American Medical Association (JAMA) suggesting MRSA was twice as common as other invasive infections and correlated with significant mortality. Although the publication of new evidence-based guidelines for the treatment of MRSA will most likely result in improved therapeutic outcomes, it is pertinent that health care providers receive adequate education regarding the use of the guidelines.

#### Background

Antibacterial resistance is problematic and continues to increase despite efforts to halt its expansion. Antibacterials have been used to treat infectious diseases over the last 70 years. The long-term and improper use of antibacterials has caused bacteria to develop resistance to specific drugs and sometimes entire drug classes.<sup>1</sup> Staphylococcus aureus (S. aureus) is a gram-positive coccus that is part of the normal skin flora and is prevalent in the environment. Staphylococcus infections normally occur due to compromised host defenses and can cause a variety of clinical syndromes with varying severity and symptomatology in both community and hospital settings.<sup>1</sup> Normally, S. aureus would be susceptible to the beta-lactam class of antibiotics with methicillin as the original treatment of choice for Staphylococcus infections. The betalactam antibiotics exert their antibacterial action by binding to penicillinbinding proteins (PBPs) located in bacterial cell walls, inhibiting cell wall biosynthesis and ultimately causing cell lysis and death.<sup>2</sup> However, S. aureus has grown resistant to methicillin treatment by a mechanism decreasing binding of beta-lactams to PBPs. Methicillin-resistant Staphylococcus aureus (MRSA) produces a different PBP known as PBP2a, binding beta-lactam antibiotics with much less affinity than PBP. PBP2a is encoded by mecA gene, which is contained in the Staphylococcal cassette chromosome (SCC). Currently, at least five types of SCC are known (I-V), and mecA IV has four subtypes (a-d), which are all used to classify MRSA strains.<sup>3</sup>

Community-acquired MRSA (CA-MRSA) is normally type IV or V, and more virulent than hospital-acquired MRSA (HA-MRSA). CA-MRSA most commonly presents as a skin infection and is usually spread through contact with another person's skin infection or personal items that have been contaminated, such as towels, razors or bandages. This transmission usually occurs through close skin-to-skin contact or open skin wounds, such as abrasions or cuts. With these conditions, locations where people are in close contact (athletic facilities, dormitories, daycare centers and correctional facilities) are at higher risk for infection spread. CA-MRSA is susceptible to a variety of non-beta-lactam antibiotics and has more treatment options.

In contrast, HA-MRSA is typically more resistant because the SCC types I, II, and III in the strains common to this setting can carry resistance genes. In the health care setting, MRSA is most commonly transmitted through unclean hands of personnel or improper use of equipment and devices. Appropriate hand-washing with hot soap and water or using an alcohol-based hand sanitizer, as well as appropriate isolation procedures with infected individuals, can help prevent the spread of MRSA. Due to the prevalence of multidrug resistance of types I, II, and III common to HA-MRSA, this type has fewer treatment options.

#### **CA-MRSA Treatment Options**

CA-MRSA most commonly presents as skin and soft tissue infections (SS-TIs) clinically ranging from impetigo to life-threatening necrotizing fasciitis.<sup>4</sup> This is associated with a cytotoxin, Panton-Valentine leukocidin (PVL), which causes cell lysis of the human leukocytes. PVL is also related to nectrotizing pneumonia and sepsis, although these severe conditions occur infrequently.<sup>3</sup> The primary treatment of abscesses is surgical drainage, but antibiotic therapy is recommended with certain conditions. The treatment duration is five-10 days but should be individualized based on the patient's clinical response.<sup>5</sup> Oral drug therapy options include the following: sulfamethoxazole/trimethoprim (SMX/TMP) one to two double-strength tablets twice daily to three times daily, clindamycin 300-450 mg three times daily, doxycycline 100 mg twice daily, linezolid 600 mg every 12 hours.<sup>5,6</sup> Potential clindamycin resistance exists, and a double-disc diffusion assay "D-test" should be performed to determine macrolide-lincosamide-streptogramin type B (MLS<sub>P</sub>) inducible resistance.<sup>5</sup>

#### **HA-MRSA Treatment Options**

Although CA-MRSA also would be susceptible to these antibacterials, these are not the recommended treatment options as a result of cost and resistance concerns. On the contrary, the therapies for HA-MRSA should never be used in CA-MRSA treatment strategies due to high prevalence of resistance.

#### Daptomycin (Cubicin®)

Daptomycin is a lipopeptide class antibiotic that has FDA labeled and unlabeled indications in the management of MRSA. The normal adult dose is 4-6 mg/kg once daily for one to six weeks.<sup>6</sup> This medication should not be used in MRSA presentations of pneumonia, as it is inactivated by lung surfactant.<sup>5</sup> Cases of eosinophilic pneumonia have been reported, and it is recommended to discontinue daptomycin use if this condition is suspected.<sup>6</sup>

#### Linezolid (Zyvox®)

Linezolid is an oxazolidinone class antibiotic that has 100 percent oral bioavailability and, therefore, should be used orally unless contraindicated. Long-term use is limited by hematologic toxicity, so CBC should be checked weekly.<sup>5</sup> The normal dose is 600 mg every 12 hours for two to eight weeks.<sup>6</sup>

#### Rifampin

Because of resistance, rifampin is not used as monotherapy to treat MRSA. It has been used as synergy in some situations, although its definitive role as adjunctive therapy has not been established.<sup>5</sup>

#### Telavancin (Vibativ®)

This lipoglycopeptide is active against MRSA as well as vancomycinintermediate *S. aureus* (VISA) and vancomycin resistant *S. aureus* (VRSA).<sup>5</sup> It is approved for SSTIs with a normal adult dose of 10 mg/kg IV every 24 hours for one to two weeks.<sup>6</sup> Renal adjustments are needed, and nephrotoxicity is a concern with its use.<sup>5</sup>

#### Tigecycline (Tygacil®)

A derivative of tetracyclines, tigecycline has activity against grampositive and gram-negative organisms, including MRSA. It can only be administered intravenously, with an initial dose of 100 mg followed by a maintenance dose of 50 mg every 12 hours for seven to 14 days. The most common side effects are nausea, vomiting and diarrhea. An advantage to using this medication is that it is not renally adjusted.<sup>6</sup>

#### Vancomycin (Vancocin®)

Vancomycin is a glycopeptide antibiotic that has been the drug of choice for MRSA and has been used since the 1950s. Efficacy is related to the area under the curve (AUC) and the minimal inhibitory concentration (MIC). Patient weight, renal function and the severity of the disease affect dosing requirements.<sup>7</sup> Some experts use combination therapy with rifampin and gentamicin for synergy, especially for more serious infections such as prosthetic valve endocarditis. Normal adult dosing is usually between 15-20 mg/ kg/dose every eight to 12 hours, with treatment duration depending on the clinical syndrome. Initial doses are based on actual body weight, and serum trough levels should help determine the subsequent doses. Rapid intravenous administration may cause a reaction known as "Red Man's Syndrome," which is characterized by hypotension and a rash of the upper body.<sup>6</sup>

#### Guidelines

In 2004, Wessex microbiologists reviewed the management of MRSA and survival rates of patients with a MRSA infection in participating British hospitals.8 Between March 1995 and December 2003, only 64 percent of patients with MRSA lived longer than 28 days, which was considered unacceptable and spurred the National Institute for Health and Clinical Excellence (NICE) to create guidelines on the management of MRSA.8 In 2006, a joint Working Party of the British Society for Antimicrobial Chemotherapy published new guidelines that focused on the prophylaxis and treatment of MRSA infections in the U.K.<sup>9</sup> The first U.S. guidelines were published five years after those in the U.K., but the Infectious Diseases Society of America (IDSA) did not provide a direct explanation for their need. It is possible the guidelines published by the IDSA were prompted by an article published by The Journal of the American Medical Association (JAMA) in October 2007, which assessed the incidence of invasive MRSA in 2005. The standardized incidence rate was revealed to be 31.8 per 100,000 persons.<sup>10</sup> Compared to other invasive infections such as S. pneumoniae or H. influenzae, MRSA was twice as common and associated with increased mortality.<sup>10</sup> Ideally, the implementation of the recently published U.S. guidelines will result in reduced drug resistance and improved patient outcomes.

#### Table 1. U.K. Practice Guidelines Strength of Evidence Categories<sup>9,11</sup>

Category	Definition
IA	Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies
IB	Strongly recommended for implementation and sup- ported by certain experimental, clinical or epidemiologi- cal studies and a strong theoretical rationale
IC	Required for implementation as mandated by federal or state regulation or standard or representing an estab- lished association standard
ll	Suggested for implementation and supported by suggestive (non-definitive) clinical or epidemiological studies or a theoretical rationale
Unresolved issue	No recommendation is offered. No consensus reached, or insufficient evidence exists regarding efficacy.

New evidence emerged shortly after the release of the first guidelines (2006), which fueled new recommendations, and an update was published in March 2009.<sup>11</sup> The initial guidelines did not provide any recommendations for treatment of impetigo and boils, but the update included a category II recommendation to treat impetigo due to MRSA with topical mupirocin or fusidic acid, if susceptible, and to not use antibiotics for small boils. The updated version also differentiates between treatment for hospitalized and non-hospitalized patients with cellulitis or surgical site infections, including step-therapy based on antibiotic susceptibility. The recommendation to use rifampin in addition to fusidic acid to treat SSTIs was removed due to adverse effects and newer, less-toxic options such as daptomycin and tigecycline. Clindamycin was designated as the antibiotic of choice, and the new guidelines emphasize the importance of patient education on diarrhea due to clindamycin-associated C. difficile. First-line treatment options for uncomplicated urinary tract infections (UTIs) due to MRSA now include oral nitrofurantoin, trimethoprim, SMX/TMP in addition to tetracycline based on in vitro susceptibility. Complicated UTIs should be treated with a glycopeptide or daptomycin. When treating bacteremia and endocarditis, the previous category IA recommendation of 14-day minimum treatment with a glycopeptide or linezolid for uncomplicated cases and longer treatment periods for high-risk patients remains, although it is now a category II recommendation with daptomycin also recognized as an alternative treatment option. The initial guidelines provided a category II suggestion to use non-glycopeptide agents to treat bronchiectasis without pneumonia, but upon review of current evidence, this is considered an unresolved issue, with linezolid as a preferred treatment option due to better penetration into lung tissue (category IC). The recommendation remains to use glycopeptides or linezolid for lower respiratory tract infections due to MRSA. Fucidic acid has been added as an appropriate option to treat susceptible superficial eye infections.

Table 2. IDSA Practice Guidelines	Strength of Evidence Categories <sup>5</sup>
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Category/grade	Definition
A	Good evidence to support a recommendation for or against use
В	Moderate evidence to support a recommenda- tion for or against use
С	Poor evidence to support a recommendation
	Evidence from ≥1 properly randomized, con- trolled trial
11	Evidence from ≥1 well-designed clinical trial without randomization; from cohort or case- controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
111	Evidence from opinions of respected authorities, based on clinical experience, descriptive stud- ies, or reports of expert committees

As of February 2011, the Infectious Diseases Society of America (IDSA) has published the first evidence-based medicine (EBM) U.S. guidelines for the treatment of MRSA. The guideline was formulated by an expert panel in the area of infectious disease as it pertains to MRSA.<sup>5</sup> The

objective of this new guideline is to provide recommendations on the management of some of the most common clinical syndromes encountered by adult and pediatric clinicians who care for patients with MRSA infections.<sup>5</sup> The guideline also addresses several issues pertaining to treatment of MRSA with vancomycin, such as dosing, monitoring and problems regarding susceptibility testing. This guideline specifically states it does not address the issues of surveillance or MRSA-prevention strategies. Several clinical questions pertaining to different clinical syndromes, such as SSTIs, bacteremia, endocarditis, pneumonia, bone and joint infections and CNS infections associated with MRSA, are answered within this guideline. Table 3 summarizes the three sets of guidelines and each of the recommendations made for each clinical syndrome. The recommendations listed are those that received the highest evidence grade for each respective syndrome.

#### **Evidence Based Medicine (EBM)**

EBM is grounded in the idea of creating a method to effectively rank evidence according to its statistical strength and the accuracy of results.12 In most cases, EBM relies on a grading system to assess the characteristics of the methods utilized to conduct the evidence-gathering process and subsequent analysis of this gathered evidence. EBM takes into consideration study type, randomization, blinding, selection of subjects and controls, and all of the procedures associated with these events. With the ranking system EBM utilizes, evidence can be adequately assessed for strength and quality and, therefore, can be applied appropriately to therapeutic decision-making. Without the use of EBM, evidence with inadequate or potentially inaccurate conclusions has the potential to be applied and, hence, result in the generation of poor or suboptimal therapeutic outcomes. Within the 2011 IDSA guidelines, evidence was graded according to the quality of evidence (Table 2). These grades were then used to generate strength of recommendation. Strengths were A, B and C conveying good, moderate and poor evidence to support a recommendation, respectively. It is pertinent to note the IDSA guidelines follow evidence-based medicine practices when it comes to evaluating the evidence and, therefore, have the potential to influence health outcomes positively. Within the clinical guideline summary, only the highest recommendations were listed, as there are many different treatment options available.

#### Importance of and Adherence to Guidelines

The new U.K. guidelines did not prove to decrease mortality rates, according to a retrospective study completed in January 2009, three years after the initial guidelines were published.8 Data for 1,679 patients from seven hospitals was divided into three groups based on the collection date of a positive MRSA blood culture. Group A included patients through 2003 (when it was decided to create the guidelines), group B included patients from 2004 and 2005 (during the formation of the guidelines), and group C included patients from 2006 to 2008 (after publication of the guidelines). Physicians were 96 percent compliant with the guidelines. Survival rates of the different groups did not differ, but the number of MRSA bacteremias decreased from 300 in 2004 to 111 in 2008. This suggests that, although the guidelines did not improve survival rates, they were effective in decreasing the number of infections per year. The study also showed an inverse relationship between survival rates and age of the patient, implying survival rates may be more dependent on patients' co-morbidities than MRSA.

#### Table 3. Summary and Comparison of U.K. and U.S. Guidelines 5,9,11

		2006 U.K. guidelines	2008 U.K. guideline update	2011 U.S. ISDA guidelines +strength of evidence
SSTIs				
	Impetigo and Boils	No recommendation	Topical mupirocin or fusidic acid (unless small and not surrounded by cellulitis)	Simple abcesses/boils: incision and drainage (AII)
	Ulcers and Boils			<ul> <li>Purulent cellulitis: Clindamycin, SMX/</li> <li>TMP, doxycycline, minocycline, linezolid</li> </ul>
	Cellulitis/Surgical Site Infections	Tetracyclines* Glycopeptides or Linezolid**	Doxycycline or clindamycin**	All) Non-purulent cellulitis: β-lactam,
	IV infusion sites	Severe: glycopeptides or linezolid Mild: other oral agents	No change	clindamycin, linezolid (All) Complicated: Vancomycin, linezolid (Al/II)
Urinary Tract Infections		Tetracyclines or alternatively trimethoprim or nitrofurantoin	Simple: oral trimethoprim, nitrofurantoin, or SMX/TMP or tetracycline	n/a
			Severe: glycopeptides or dapto- mycin	
Bone and Joint infec- tions	Prosthetic joint infection	Vancomycin + rifampin or vancomycin + fusidic acid	No change	Osteomyelitis: Vancomycin (BII/AII) Septic arthritis: Vancomycin (BII/AII)
	Other	Rifampin + a fluoroquinolone or trimethoprim or fusidic acid	No change	
Bacteremia and endocar- ditis	Uncomplicated bacteremia	14 day minimum linezolid or glycopeptides (linezolid limitation here)	No change	Bacteremia/endocarditis/infective endocarditis with native valve: vanco- mycin (BIII)
	Complicated bacteremia or endocarditis	Longer treatment	No change	Infective endocarditis with prosthetic valve: vancomycin + gentamicin + rifampin (BIII)
Respiratory tract infec- tions	Upper Respiratory Tract Infection	See cellulitis recommenda- tions	Linezolid offers good penetration	n/a
	Lower Respiratory Tract Infection	Glycopeptides or linezolid	No change	Vancomycin, linezolid (AII)
Eye and CNS infections		Insufficient evidence for deep eye and CNS infec- tions. Superficial infections: gentamicin or chlorampheni- col	Superficial infections: gentamicin or chloramphenicol or fusidic acid	Vancomycin or linezolid (BII)
Elimination of carriage		Mupirocin in combination with a systemic agent	No change	n/a
Surgical site infection prophylaxis		Glycopeptides	No change	n/a

\*Unless there is a risk of bacteremia or endocarditis

\*\*If the risk of bacteremia is high

A questionnaire assessing health care workers' awareness of the MRSA practice guidelines revealed an inadequate knowledge of current MRSA practice guidelines in 2009, three years after they were released.<sup>13</sup> The questionnaire contained 10 true-or-false questions, and the scores of physicians (6.532) and trainee surgeons (6.904) were compared to control groups of infectious control nurse practitioners (8.391) and non-clinical scientific staff (4.7). The results demonstrated room for significant improvement among physicians and trainee surgeons, although the study had a few major limitations. The study did not randomly sample the studied populations (physicians and surgeons surveyed attended a medical conference), and there was no evaluation of random answers. This study suggests health care workers must be thoroughly educated for guidelines to be maximally effective.

#### Conclusion

Development of EBM guidelines has the potential to significantly impact both CA-MRSA and HA-MRSA treatment strategies via the standardization of therapy based on graded clinical data. Education of health care providers on the usage of the guidelines has the potential to change the clinical outcomes of treatment of MRSA infection. With appropriate education, inappropriate medication usage has the potential to decrease development of resistance, patient length of stay in the hospital, and use of unnecessary treatment for the presenting syndrome. All of these factors lead not only to improved patient quality of life, but also to decreased health care costs. Overall, use of the guidelines has the potential to impact a variety of clinical and economic factors supporting its usage in the treatment of MRSA infection.

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#### **Assessment Questions**

1. *S. aureus* has become resistant to beta-lactams, such as methicillin, due to:

- a. Decreased binding to penicillin-binding proteins
- b. Production of beta-lactamases
- c. Increased activity of efflux pumps
- d. Altered metabolic pathways

2. What type of SCC characterizes CA-MRSA?

- a. I or II
- b. II or III
- c. III or IV
- d. IV or V

3. All of the following are locations with a high-risk of CA-MRSA transmission EXCEPT:

- a. Correctional facilities
- b. Daycare centers
- c. Grocery stores
- d. Athletic locker rooms

4. Which of the following is an option to treat CA-MRSA?

- a. Vancomycin 1 g IV BID
- b. Doxycycline 100 mg po BID
- c. Oxacillin 2 g IV Q6 hr
- d. Linezolid 600 mg po BID

5. Which of the following IV medications is NOT an option to treat HA-MRSA?

- a. Vancomycin
- b. Daptomycin
- c. Telavancin
- d. Ceftriaxone

6. The 2009 updated U.K. guidelines did not include the recommendation to use rifampin + fusidic acid to treat SSTIs due to:

- a. Adverse effects
- b. Improved newer drug options
- c. Increased resistance
- d. A and B

7. The recently published ISDA guidelines for the U.S. suggests treating simple abcesses/boils with:

- a. Incision and drainage only
- b. Incision and drainage with topical mupirocin
- c. Vancomycin
- d. Doxycycline

8. Recommendations backed by the strongest evidence is categorized as:

- a. IA
- b. IC
- c. IIIA
- d. IIIC

- 9. The strongest level of evidence is associated with well-designed:
  - a. Professional opinions
  - b. Multiple meta-analysis
  - c. Randomized controlled trials
  - d. Cohort studies
- 10. In order for the ISDA guidelines to be effective:
  - a. The guidelines should help determine treatment strategies
  - b. Health care workers must be knowledgeable
  - c. Health care works should be educated about MRSA transmission d. All of the above



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List the me	edications that can be used to treat HA-MRSA.	1	2	3	4	4
Identify ho	w MRSA can be transmitted in the community and health care settings.	1	2	3	4	4
	n the importance of evidence-based medicine and published guidelines with antibacterial resistance.	1	2	3	4	5
State the preferred treatments of MRSA in certain clinical syndromes.		1	2	3	4	5
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