Continuing Medical Education

MRSA in the Diabetic Foot

Here is a primer on de-escalation therapy.

Goals/Objectives

After completing this CME:

1) The reader will gain insight into the prevalence of MRSA in diabetic foot wounds and how diabetes worsens the prognosis.

2) The reader will be able to classify diabetic foot infections and choose empiric treatments for MRSA based on this classification.

3) The reader will be presented information on the most commonly used FDA approved drugs for MRSA, their dosages and adverse effects.

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*An answer sheet and full set of instructions are provided on pages 202-204.—**Editor***

By Lee C. Rogers, DPM and Nicholas J. Bevilacqua, DPM

Diabetic foot infections (DFI) are the common prequel to amputation. The destructive nature of these infections in the presence of an immunopathic process, such as diabetes, is a morbid combination. Certainly bacterial resistance worsens the outcome since the empiric therapy may be ineffective, delaying appropriate antibiotics.

Diabetes acts as an immunosuppressive process, predisposing the patient to infection, and leading to a more severe infection when one occurs. Abnormalities include granulocyte adherence, chemotaxis, and phagocytosis. Acute hyperglycemia is also associated with post-operative infection rates of up to 30%.[1]

Skin and skin structure infections (SSSI) are predominately caused by Gram positive bacteria. This, however, includes resistant Gram positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA). Approximately 30% of diabetic foot ulcers (infected and uninfected) will be colonized with MRSA. Appropriate antibiotic therapy usually involves culturing the wound and choosing an antimicrobial based on sensitivity testing. However, wound cultures are not used to diagnose an infection, just to direct therapy. This makes the initial choice of antibiotic imperative to the rapid resolution of the infection. Empiric antibiotic therapy choice is based on several factors: risk factors for MRSA, infec-

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tion severity, patient allergies and concomitant medications, and inpatient/outpatient therapy.

MRSA is increasing in prevalence in many centers. The Manchester UK group reported a near doubling in their diabetic foot ulcer MRSA prevalence between 1999 and 2003.[2,3] In our own past experience in a public county hospital, we reviewed data for the past 10 years. The number of new MRSA cases jumped from about 20 per year to over 200 per year. Ninety-five percent of the cases were from wound culture isolates. Additionally, stories of the bacteria affecting less typical populations, like young athletes, are circulating.

IDSA* Class	Description	Outcomes/Risks
Mild Infection (non-limb-threatening)	<2 cm surrounding cellulitis, no deep spread, no systemic signs	Hospitalization (11%) Amputation (4%)
Moderate Infection (limb-threatening)	>2 cm surrounding cellulitis and/or deep spread to fascia, tendon, muscle, or bone. No systemic signs	Hospitalization (54%) Amputation (47%)
Severe Infection (limb- and life-threatening)	Moderate infection with systemic signs of infection, such as systemic inflammatory response syndrome (SIRS) or sepsis	Hospitalization (89%) Amputation (78%)

*IDSA, Infectious Diseases Society of America

Figure 1: The Infectious Diseases Society of America (IDSA) classification of diabetic foot infections.

Common Resistance Patterns

While there are certainly many genotypes of MRSA, two common resistance patterns are often seen. Community-associated (formerly community acquired) and healthcare-associated (formerly hospital acquired) are the most common isolates. The newer "-associated" names are preferable since both bacterial strains can cause infections in either the community or hospital setting. Another name for healthcare-associated MRSA is resistant MRSA because it is sensitive to fewer agents. Community-acquired MRSA is generally susceptible to tetracyclines, fluoroquinolones, sulfa drugs, and rifampin. Healthcare-associated MRSA requires vancomycin, linezolid, daptomycin, tigecycline, or some other newer anti-MRSA specific drugs.

Former prevailing thought was that MRSA is no more virulent than a normal Staphylococcus aureus bacterium, just that it was resistant to many antibiotics, delaying initial effective therapy—thus causing more tissue damage. It is now known that MRSA is, in fact, more virulent than methicillin-sensitive Staphylococcus aureus (MSSA). MRSA contains vanton valentine leukocidin (VVL), and also newly discovered enzymes that can destroy white blood cells. Together, these virulence factors can be quite destructive to the body tissue, in some cases causing a true necrotizing fasciitis—otherwise rare with MSSA. We also know from animal models that untreated MRSA bacteremia leads to death about twice as fast as untreated MSSA bacteremia.[4] MRSA baceremia in diabetics with foot infections is associated with a 43% mortality rate compared with a 20% mortality rate in MSSA bacteremia.[5]

Outcomes are worse when a wound is infected with a resistant bacteria. In those with diabetic foot infections caused by MRSA undergoing amputation, the mortality rate was higher (43% MRSA vs 9% non-MRSA).[6] In another study following amputations in MRSA positive patients, post-operative stump infections occurred in 24%, over 2/3rd of which were a re-infection with MRSA.[7]

Skin and skin structure infections (SSSI) are predominantly caused by Gram positive bacteria.

There is no way to determine a sensitive from a resistant infection by physical examination. The history may help to uncover a previous resistant infection or risk factors for MRSA, such as recent antibiotic use or hospitalization. Other risk factors for MRSA infections include nursing home residence, incarceration, and locker room environments.

In some facilities, DNA probes for the MRSA Cepheid mecA gene are available. These are rapid tests with results usually within two hours and give the clinician a "positive" or "negative" result for MRSA in the wound. In situations where these advanced tests are not available, empiric therapy must be started based on the patient's risk factors and clinical suspicion. A proper tissue specimen should be taken for culture and sensitivity. The most accurate results are obtained by sending a piece of deep tissue from the ulcer/infection site. A superficial swab will usually confound the result by returning a C&S with multiple contaminants.

IDSA Classifications

The severity of the infection is important to guide empiric therapy. The Infectious Diseases Society of America (IDSA) classification stratifies diabetic foot infections into four categories (Figure 1).[8] IDSA uninfected is a wound without signs or symptoms of infection. IDSA mild infection is a wound with less than 2 cm of surrounding erythema, but no deep spread or systemic signs/symptoms of infection. IDSA moderate infection is a wound with greater than 2 cm surrounding erythema, possible deep spread, including osteomyelitis, but no systemic signs/symptoms of infection. An IDSA Severe infection is the same as a moderate, except

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there are systemic signs/symptoms of infection, such as fever, tachycardia, or bacteremia.

IDSA mild infections are predominantly caused by Gram positive bacteria, which can include MRSA. Moderate and severe infections are more polymicrobial with Gram positive, negative, aerobic, and anaerobic bacteria, usually resulting in three to six different bacterial species on culture report. As such, Mild infections can be treated with agents for Gram positive bacteria as an outpatient. If there are risk factors for MRSA, empiric therapy should be modified to use oral linezolid, minocycline/doxycycline, or trimethoprim/sulfa. Clindamycin should be avoided in suspected MRSA cases since it can rapidly become resistant. Most labs perform a D-test on MRSA isolate to determine if clindamycin can be used. But the drawback is that the D-test takes an extra 24 hours after the culture is reported, possibly creating a longer delay in appropriate treatment.

Patients with moderate and severe infections should have broad-spectrum coverage and are usually hospitalized for treatment. There is no clear consensus on whether to start anti-MRSA therapy from the beginning of treatment. Since these infections are limb-threatening, we use MRSA de-escalation therapy.

De-escalation Therapy

A recent consensus statement from a panel of experts recommends the same.[9] De-escalation therapy is a concept where broad-spectrum antibiotics with anti-MRSA coverage are started first, then narrowed, if need be, after the culture and sensitivity is reported. Tigecycline can be used as monotherapy, since it is broad-spectrum and has activity against MRSA. Other options must use combination therapy such as piperacillin/tazobactam, ertapenem, or levafloxacin plus an anti-MRSA agent like linezolid, daptomycin for injection (Cubicin), or vancomycin. See the algorithm in Figure 2 as a guide to decision-making of empiric therapy for diabetic foot infections.

MRSA is, in fact, more virulent than methicillin-sensitive Staphylococcus aureus (MSSA).

While vancomycin is still used frequently in MRSA cases, new evidence is showing reduced efficacy versus newer agents. There are poorer outcomes when treating MRSA septicemia and a higher recurrence rate. Vancomycin is probably considered the "gold standard" for MRSA since it was the only effective agent for healthcare-associated MRSA for many years.

Side-effects include renal and ototoxicity, and thus care must be used in the diabetic patient with renal impairment. For skin and skin structure infections, it is only available in IV form. With newer, more effective agents, many with fewer adverse effects and easier to dose, clinicians should migrate away from this aminoglycoside.

Linezolid

Linezolid is the first drug is a new class called oxazolidinones. It has activity for Gram positive bacteria, including MRSA, and is also active against VRE. It is FDA-approved for skin and skin structure infections (SSSI) and is the only drug with specific indication for diabetic foot infections. It is unique in that it is available in both IV and oral formulations. The oral form has just as much bio-availability as the parenteral form. It can cause bone marrow suppression resulting in pancytopenia, so a weekly CBC should be checked if linezolid is used for longer than two weeks. There have also been some reported cases of peripheral sensory neuropathy secondary to linezolid use.

Tigecycline

Tigecycline is a glycylcycline antibiotic related to the tetracycline class. It is broad-spectrum and anti-MRSA, allowing it to be used as monotherapy for de-escalation. It is only available in IV form. It has similar side-effects to tetracyclines, but also causes nausea and vomiting in approximately 18% of those who take it. It is sometime prudent to treat patients prophylactically with an anti-emetic.

Daptomycin

Daptomycin is a lipopeptide

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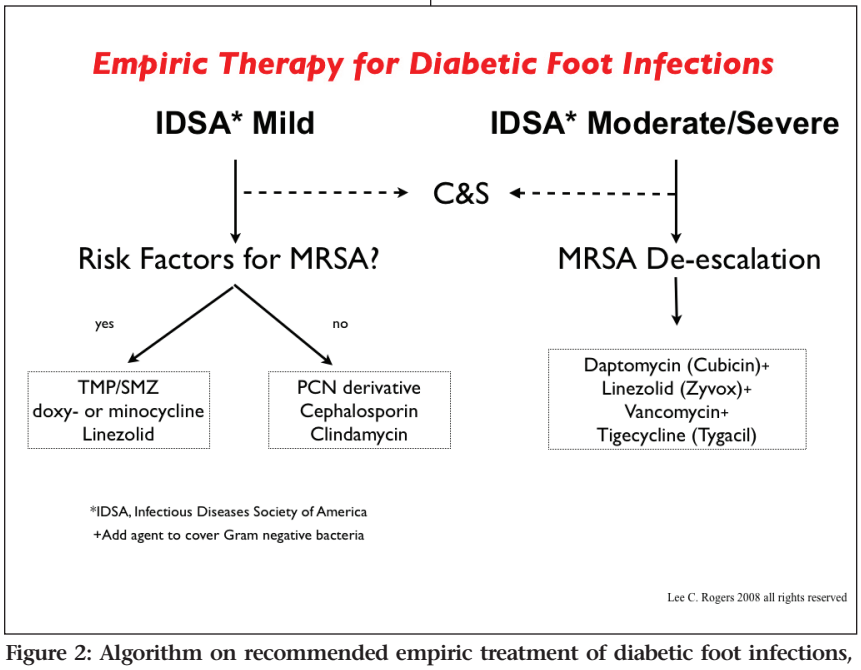

Figure 2: Algorithm on recommended empiric treatment of diabetic foot infections, based on severity.

MRSA...

with activity against MRSA and VRE. It is IV only and FDA-approved for use in SSSI. Quinupristin/dalfopristin is a parenteral streptogramin antibiotic active against MRSA, VRE, Streptococci, Clostridium, and Peptostreptococcus. It is FDA-approved for severe infections with VRE and has not been studied in the diabetic foot. Figure 3 illustrates the common antibiotics used for MRSA infections, their dosage, route, and adverse effects.

Drug	Dosage	Route	Adverse Effects
Linezolid (Zyvox - Pfizer) Class: oxazolidinone Activity: Gram +, MRSA, VRSA	600 mg q12h	IV or PO	pancytopenia: monitor CBC after 2 weeks
Tigecycline (Tygacil - Wyeth) Class: tetracycline Activity: Gram + and -, MRSA,VRSA	100 mg loading dose, then 50 mg q12h	IV only	GI distress, nausea and vomiting common
Daptomycin (Cubicin - Cubist) Class: cyclic lipopeptide Activity: Gram +, MRSA, VRSA	4 mg/kg q24h	IV only	emergence of Gram - infections
Vancomycin Class: aminoglycoside Activity: MSSA and MRSA	based on CrCl and adjust on peaks/ troughs	IV only	renal and ototoxicity, red man syndrome

Figure 3: Characteristics of common antibiotics used for MRSA.

Surgical Treatments

Surgical treatment is important in managing infections, resistant or sensitive. If there is an abscess, incision and drainage should be performed urgently. Systemic antibiotics will not penetrate and resolve an organized abscess. With infected ulcers, a thorough initial debridement is necessary to remove all devitalized tissue that is actively infected or harboring bacteria. Removal of undermining tissue and tunneling helps to void the wound of dead spaces for bacteria to flourish. Serial debridements are then performed to prevent recurrence of infection.

After resolution, re-infection with MRSA is common. In a study of 209 patients with MRSA infections, 29% became re-infected within 18 months.[10] Another study found that 62% of patients with a history of MRSA developed a re-infection at some point over their lifetime.[11]

MRSA and the Internet

MRSA is such a frequent problem that many patients become educated via the World Wide Web. There are several myths and unproven treatments circulating on the Internet that prey on patients' fears. Invariably, patients will ask us about them. There are websites selling "essential oils", honey, tea tree oil, and garlic preparations, none of which have been rigorously studied in MRSA infections. However, aside from the abundant misinformation on the Internet, patient-friendly web pages on the Mayo Clinic site and Wikipedia offer accurate information.

Other non-traditional treatments for MRSA that have been reported in the literature include medical maggots. The larvae can debride wounds, removing necrofibrotic tissue that leads to infection. They can also digest many types of bacteria, including MRSA.[12]

Patients with MRSA generally become colonized, usually in their nares or nasal pharynx, and they can re-infect themselves at a later date or transfer the bacteria by direct contact to family members. There was some initial consideration given to cohorting MRSA patients in hospitals to certain wings or floors.

If there is an abscess, incision and drainage should be performed urgently.

It is still general practice to isolate admitted patients to a private room or place them in a room with another known MRSA patient. Some facilities are performing MRSA decolonization. While it has not been shown to make much difference in the long-term, it might be able to reduce person-to-person transmission in the home. The recommendations for MRSA decolonization include:

1) Treat the underlying infection.

2) Prescribe mupirocin ointment in both nares three times daily.

3) Remove piercing and fake nails during decolonization.

4) Shower every other day with Hibiclens; pay extra attention to the hairline.

5) Gargle with Peridex mouthwash for 60 seconds and spit, two times daily.

6) Use clean clothes and towels daily during treatment.

7) Perform the above for two weeks.

The nares can be swabbed for MRSA screening before and after decolonization. Repeat if necessary.

For general guidelines, the CDC recommends patients wash their hands frequently, or use an alcohol-based hand sanitizer. Don't share razors, towels, or other personal items. Wipe down equipment with an antiseptic before use at a public gym.

Diabetic Foot Infections

Diabetic foot infections should be treated aggressively, since the host is immune-suppressed, the causative micro-organism can be re-

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sistant, and the infection can lead to amputation. Clinicians should classify the infection according to the IDSA and prescribe the appropriate treatment based on the class of infection. There are many agents active against MRSA, but allergies, route of administration, and adverse effects need to be considered. Patients should be cautioned about finding misinformation on the Internet and directed to reliable websites. Once the MRSA infection resolves, the doctor should be vigilant in preventing re-infections. ■

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EXAMINATION

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See instructions and answer sheet on pages 202-204.

1) Which of the following is NOT a known risk factor for MRSA?
- A) Recent hospitalization
- B) Incarceration in a prison
- C) Multiple recent antibiotic usage
- D) Owning a pet

2) Which of the following drugs is NOT a good choice for MRSA?
- A) Linezolid
- B) Trimethoprim/sulfa
- C) Methicillin
- D) Minocycline

3) Healthcare-associated (formerly hospital-acquired) MRSA can be treated with all BUT which of the following?
- A) Cephalexin
- B) Linezolid
- C) Vancomycin
- D) Tigecycline

4) De-escalation therapy for diabetic foot infections is:
- A) Using a broad-spectrum anti-MRSA agent first, then narrowing the spectrum after culture and sensitivity is reported
- B) Using a broad-spectrum oral antibiotic and not checking the culture and sensitivity
- C) Using a narrow-spectrum agent and then switching to a broad-spectrum if needed
- D) Just performing an incision and drainage without antibiotics

5) The D-test is used to determine if which antibiotic can be used for MRSA?
- A) Penicillin
- B) Methicillin
- C) Clindamycin
- D) Cephalexin

6) Which of the following tests can identify MRSA in two hours or less?
- A) DNA swab for MRSA
- B) Culture and sensitivity
- C) Complete blood count (CBC)
- D) Erythrocyte sedimentation rate (ESR)

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EXAMINATION

(cont'd)

7) What is the most urgent treatment for an MRSA abscess?
- A) Warm compresses
- B) Antibiotics
- C) Heparin
- D) Incision and drainage

8) Which of the following describes an IDSA severe infection?
- A) A wound with no erythema
- B) A wound with less than 2 cm of erythema
- C) A wound with greater than 2 cm of erythema and osteomyelitis
- D) A wound with greater than 2 cm of erythema in the presence of a fever, tachycardia, and bacteremia

9) Which of the following describes an IDSA Mild infection?
- A) A wound with no erythema
- B) A wound with less than 2 cm of erythema
- C) A wound with greater than 2 cm of erythema and osteomyelitis
- D) A wound with greater than 2 cm of erythema in the presence of a fever, tachycardia, and bacteremia

10) According to this article, which describes the best treatment for an IDSA moderate infection?
- A) Incision and drainage, admission to the hospital, IV antibiotics with MRSA de-escalation
- B) Incision and drainage and discharge
- C) Oral antibiotics
- D) Tetanus prophylaxis

11) What is the proper way to culture a wound?
- A) Swab the surface
- B) Send a deep tissue specimen
- C) Send purulent drainage
- D) Do a bone biopsy

12) What is the only FDA approved antibiotic for MRSA skin infections available in oral form?
- A) Vancomycin
- B) Tigecycline
- C) Daptomycin
- D) Linezolid

13) Which antibiotic requires peaks and troughs to appropriately dose?
- A) Vancomycin
- B) Tigecycline
- C) Daptomycin
- D) Linezolid

14) Which antibiotic can cause renal or ototoxicity?
- A) Vancomycin
- B) Tigecycline
- C) Daptomycin
- D) Linezolid

15) Which recommendations can help prevent spread of MRSA colonization?
- A) Washing hands frequently
- B) Don't share razors or other personal items
- C) Wipe down gym equipment before use
- D) All of the above

16) Where is the most common site of MRSA colonization?
- A) Nares and nasopharynx
- B) Rectum
- C) Arm pit
- D) Lateral nail folds

17) Which of the following is true, regarding MRSA prevalence?
- A) MRSA is becoming controlled
- B) MRSA has been eradicated
- C) MRSA infections are steady
- D) MRSA prevalence is increasing

18) Which does NOT predispose a patient with diabetes to an infection?
- A) Immunopathy (immune suppression)
- B) Open ulcer
- C) Poor glucose control
- D) Good glucose control

19) Mild diabetic foot infections are generally caused by:
- A) Gram positive bacteria
- B) Gram negative bacteria
- C) Viruses
- D) Anaerobic bacteria

20) Which of the following treatments are available for sale to patients on the Internet without having proven efficacy for MRSA?
- A) Medical maggots
- B) Linezolid
- C) Tea tree oil and garlic preparations
- D) Vancomycin

SEE INSTRUCTIONS AND ANSWER SHEET ON PAGES 202-204.