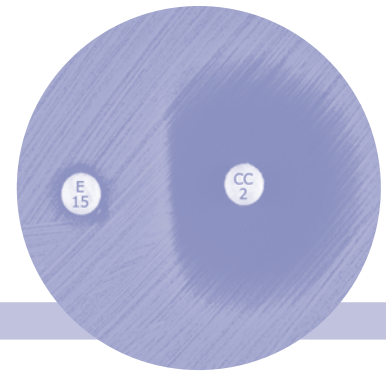


the d-zone

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New & Noteworthy

—Is it time to abandon vancomycin for MRSA? Mohr and Murray suggest how we might prolong the usefulness of this venerable antibiotic.

Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*.
Clin Infect Dis 44 (12): 1536-42, 2007.

—*S. aureus* has improved itself, but vancomycin hasn't kept pace. Deresinski asks us to be realistic about the future.

Deresinski S. Counterpoint: Vancomycin and *Staphylococcus aureus*—an antibiotic enters obsolescence.
Clin Infect Dis 44 (12): 1543-8, 2007.

Quote of the Month

"Health nuts are going to feel stupid someday, lying in hospitals dying of nothing."

—Redd Foxx

the d-zone

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Black D. Clinical practice: the story of
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Clinical Practice: The Story of Community-Acquired MRSA

Introduction

MRSA (methicillin-resistant *S. aureus*) first appeared in the UK in 1961 but not until 1968 in the US.^{1,10} Recent surveys suggest that up to 50% of strains of *S. aureus* in the United States are methicillin-resistant, with the prevalence in hospitals and intensive care units often exceeding 60%.⁷ Given the migration of penicillinase-producing *S. aureus* from the hospital to the community, the emergence of MRSA in the community was not unexpected. The majority of these community MRSA strains were presumably acquired in healthcare settings.

MRSA infection has traditionally occurred among patients exposed to healthcare settings such as hospitals, dialysis centers, and long-term care facilities, whereas the risk factors for MRSA among patients residing in the community have been injection drug use and diabetes.¹⁸ The 1999 report of four children from rural North Dakota and Minnesota who died of MRSA despite having no contact with the healthcare system or other risk factors signifies the dramatic beginning of a new chapter in the saga of *S. aureus*: community-acquired MRSA (CA-MRSA).³ Outbreaks among football players¹², Native Americans⁹, and military recruits³² have been reported. The rise in prevalence of CA-MRSA has been dramatic. In a recent study of patients presenting to the emergency department with skin and soft tissue infections, 59% were caused by CA-MRSA, 97% of which were phenotype USA300.²⁰ In some parts of the US, 60-75% of all community-acquired isolates of MRSA are methicillin-resistant.¹⁹

CA-MRSA is genetically distinct from hospital-acquired strains of *S. aureus* and thus likely represents resistance arising in a community isolate. It has successfully replaced nosocomial strains of *S. aureus* in some centers, consistent with the suggestion that CA-MRSA may be more fit than hospital-acquired strains (HA-MRSA). Possible explanations for increased fitness of CA-MRSA include its smaller staphylococcal cassette chromosome (see below) and also a faster rate of replication.⁵

Mechanism of resistance

Resistance to methicillin is predominantly conferred by the *mecA* gene, a 78-kDa protein that encodes a penicillin-binding protein with retained transpeptidase activity but reduced affinity for all β -lactam antibiotics. The origin of *mecA* is not known, although *S. sciuri* (a coagulase-negative *Staphylococcus*) has been implicated as the donor.³⁰ *MecA* is part of a mobile chromosomal element known as SCC_{mec} (staphylococcal cassette chromosome *mec*). Five main types of SCC_{mec} ranging in size from about 21 kb to 67 kb have been identified.⁶ In general, HA-MRSA carries SCC_{mec} type I, II, or III, which are large enough to harbor *mecA* as well as additional genes for encoding resistance to various non- β -lactam antibiotics. CA-MRSA carries SCC_{mec} type IV or V, which are smaller in comparison, explaining the wider range of antibiotic susceptibility characteristic of community-acquired isolates.

Clinical Practice: The Story of CA-MRSA (continued)

Infections associated with CA-MRSA

CA-MRSA most commonly causes skin and soft-tissue infections such as abscesses and furunculosis. It has also been associated with serious necrotizing pneumonia and necrotizing fasciitis. In contrast, HA-MRSA tends to cause a broader range of infection including bacteremia, pneumonia, endocarditis, cellulitis, and infection of bones and joints.

Molecular typing

Molecular typing techniques useful for studying the dissemination and epidemiology of MRSA include pulsed-field gel electrophoresis (PGFE), multilocus sequence typing (MLST), SCCmec typing, and *S. aureus* protein A (*spa*) typing.⁶ McDougal et al. performed *Sma*I PGFE on 957 isolates of *S. aureus* submitted to the Center for Disease Control (CDC) from 1995-2000 and identified eight lineages, designated as pulsed-field types (PFTs) USA100 through USA800.¹⁷ USA300 and USA400 isolates were predominantly from community-acquired infections.

Virulence of CA-MRSA

CA-MRSA commonly harbors a number of virulence genes not usually found in hospital-acquired strains. One such gene encodes the Pantan-Valentine leukocidin (PVL) toxin, first described in 1932.²² PVL is a pore-forming exotoxin with potent cytolytic and inflammatory properties that requires the assembly of two polypeptides encoded by *lukF* and *lukS*. It is sufficient to cause necrotizing pneumonia in mice and also to cause up-regulation of certain genes of *S. aureus*, enhancing virulence.¹³ PVL is associated with necrotic skin lesions and necrotizing pneumonia in humans.

In vitro susceptibility

As previously mentioned, CA-MRSA tends to be susceptible to a much wider range of non- β -lactam antibiotics than HA-MRSA. LaPlante et al. performed susceptibility testing on 102 isolates of CA-MRSA and 115 isolates of HA-MRSA collected from patients treated at Detroit Receiving Hospital and University Health Center.¹⁴ CA-MRSA isolates met the CDC definition for community-acquired infection and also contained SCCmec type IV. According to Clinical and Laboratory Standards Institute (CLSI) breakpoints, all CA-MRSA isolates tested were susceptible to daptomycin, linezolid, and vancomycin; 99% were susceptible to Trimethoprim/sulfamethoxazole (TMP/SMX), 96% were susceptible to clindamycin, 85% were susceptible to doxycycline, and 76% were susceptible to ciprofloxacin. Only 14% were susceptible to erythromycin. MIC₅₀, MIC₉₀, and MIC range for the tested antibiotics are found in table 1. Susceptibility to rifampin was not determined in this study, but 96% of CA-MRSA were susceptible to rifampin in an earlier investigation.²¹

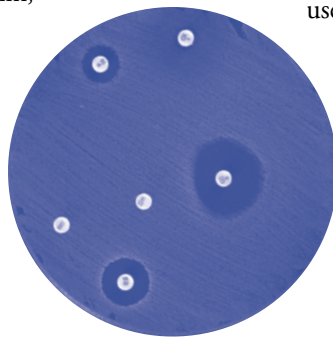
Treatment

The majority of infections due to CA-MRSA are amenable to outpatient management. This discussion will therefore focus on options for oral treatment. Treatment of seriously ill patients requiring hospital admission and parenteral drugs, including vancomycin, daptomycin, quinupristin/dalfopristin, linezolid, and tigecycline, will not be discussed further.

There are few prospective randomized trials of antibiotics for infection caused by CA-MRSA. In a recent study of patients hospitalized for *S. aureus* infection, clinical and epidemiologic risk factors did not reliably distinguish CA-MRSA from methicillin-susceptible strains (MSSA); other data suggest that nasal colonization may not precede CA-MRSA.^{18,19} These observations, coupled with evidence of increased morbidity and mortality associated with MRSA relative to MSSA,^{2,4} suggest that empiric treatment of community-dwelling patients with *S. aureus* should include antibiotics active against CA-MRSA.

Trimethoprim/sulfamethoxazole (TMP/SMX)

Rapid bactericidal activity of TMP/SMX against CA-MRSA *in vitro* has been demonstrated,¹¹ and limited clinical data further suggest a role for TMP/SMX in the management of CA-MRSA infection. Markowitz et al. randomized injection drug users with presumed *S. aureus* infection to receive vancomycin 1 gram IV q12h or TMP/SMX 320 mg/1600 mg (equivalent to two double-strength tablets) IV q12h. In 101 patients with confirmed *S. aureus* infection, cure was achieved in 98% of patients treated with vancomycin vs. 86% of patients treated with TMP/SMX ($p < 0.02$). However, TMP/SMX failure occurred only in patients with MSSA infection.¹⁶ Stein et al. treated 39 patients with orthopedic implants infected with multidrug-resistant staphylococci (24 of which were MRSA) with 6-9 months of oral TMP/SMX (20 mg/kg/day based on the TMP component) along with appropriate surgical intervention. Twenty-six of 39 patients (66.7%) were successfully cured, including 16 of the 24 patients (66.7%) with MRSA.²⁷ Finally, Szumowski et al. retrospectively evaluated 399 cases of culture-confirmed *S. aureus* skin and soft-tissue infections, including 227 cases of MRSA, seen at an ambulatory clinic in Boston from 1998 to 2005. In the study, 48.2% of the isolates were resistant to clindamycin. At the start of the study period most patients received a β -lactam antibiotic empirically, but by 2005 76% of patients received TMP/SMX (1-2 tablets PO bid). In parallel with the increased use of TMP/SMX, the percentage of MRSA isolates susceptible to the empiric antibiotic choice increased from 0% in 1998 to 77% in 2005, and a significantly higher percentage of patients with MRSA resolved on the empiric antibiotic by 2005. No information regarding combination use of TMP/SMX plus rifampin is provided.²⁹



Clinical Practice: The Story of CA-MRSA (continued)

Table 1. *In vitro* susceptibility of CA-MRSA and HA-MRSA

ANTIBIOTIC		MIC ₅₀ ($\mu\text{g/mL}$)	MIC ₉₀ ($\mu\text{g/mL}$)	RANGE ($\mu\text{g/mL}$)
Ciprofloxacin	CA	0.25	16	0.06-16
	HA	64	128	0.25-128
Clindamycin	CA	0.125	0.25	0.06-64
	HA	64	64	0.06-64
Daptomycin	CA	0.25	0.5	0.06-1
	HA	0.25	1	0.125-1
Erythromycin	CA	32	64	0.125-128
	HA	128	512	0.06-512
Doxycycline	CA	0.25	8	0.06-8
	HA	0.5	4	0.06-32
Linezolid	CA	2	4	0.5-4
	HA	2	4	1-4
TMP	CA	0.0625	0.5	0.0625-2
	HA	0.125	2	0.125-16
SMX	CA	1.25	10	1.25-40
	HA	2.5	40	2.5-320
Vancomycin	CA	1	2	0.25-2
	HA	1	2	0.5-2

CA-MRSA (n=102; HA-MRSA (n=115)

Combination therapy with TMP/SMX and rifampin is used by some clinicians, although there is little evidence of enhanced outcome. If a patient requires empiric treatment for both *S. pyogenes* and CA-MRSA it is important to remember that the activity of TMP/SMX is not reliable for *S. pyogenes*.

Clindamycin

A role for oral clindamycin in the management of CA-MRSA is suggested by its generally favorable susceptibility. Advantages of clindamycin include its widespread tissue penetration (except the central nervous system), reliable activity against *S. pyogenes*, and possible beneficial effects on toxin synthesis. No prospective studies of clindamycin for CA-MRSA have yet been conducted.

An interesting situation is presented by strains of CA-MRSA that are clindamycin-susceptible but erythromycin-resistant. Drug efflux is one possible resistance mechanism consistent with this phenotype. A strain of CA-MRSA harboring the *msrA* gene contains an energy-dependent pump capable of extruding macrolides and type B streptogramins, but not lincosamides (clindamycin), from the bacterial cell. Clindamycin may be used for infection caused by such a strain. A second possible mechanism of resistance is ribosomal methylation (MLS_B resistance) in which a member of the *erm* gene family encodes an inducible methylase capable of modifying the 23S subunit of the bacterial ribosome, rendering the strain resistant to all macrolides, lincosamides, and type B streptogramins. If this methylase is present, the strain will exhibit the aforementioned phenotype because erythromycin (but not clindamycin) is a

strong inducer of enzyme expression. However, treatment with clindamycin may result in failure by selecting for mutants that express the methylase constitutively.²⁵ It is thus important to determine which mechanism is present.

The so-called D-zone test is a simple way to distinguish between drug efflux and inducible methylase production. An erythromycin-containing disk is placed in close proximity to a clindamycin-containing disk on an agar plate growing the organism. If an inducible methylase is present in the strain, erythromycin diffusing from the disk will induce enzyme expression in the area between the two disks, blunting the otherwise wide zone of inhibition around the clindamycin disk and creating the appearance of a "D" on the plate. Clindamycin should not be used for treatment. If no blunting of the zone of inhibition around the clindamycin disk is observed, the mechanism of resistance is efflux and clindamycin may be safely used.^{8,15}

Long-acting tetracyclines

Doxycycline and minocycline are more potent against *S. aureus* than tetracycline.²⁶ They are well absorbed by the gastrointestinal tract, distribute into tissues well, and have prolonged half-lives (16-18 hours). Ruhe et al. reviewed the records of 24 patients with MRSA infection (mostly skin and skin-structure) who were treated with doxycycline or minocycline (both dosed at 100 mg PO bid). Thirteen patients received doxycycline and 11 patients received minocycline; 4 of the minocycline-treated patients also received rifampin. Median duration of antibiotic treatment was 19 days. Twenty of 24 patients (83%) were cured.²⁴

Linezolid

Linezolid is an expensive oxazolidinone antibiotic with broad *in vitro* activity against many resistant Gram-positive pathogens (including MRSA) and is generally well tolerated, at least in patients treated for ≤ 28 days. Optic neuropathy has recently been reported in patients receiving treatment for ≥ 5 months.²³

No prospective studies investigating the effectiveness of linezolid specifically for CA-MRSA have been conducted. However, Stevens et al. compared linezolid to vancomycin in a randomized, open-label study of hospitalized patients with known or suspected MRSA, most commonly of skin and soft tissue. The drugs were found to have equivalent microbiologic and clinical effectiveness. Rates of adverse events were similar.²⁸

Fluoroquinolones

CA-MRSA exhibits variable susceptibility to fluoroquinolones, with moxifloxacin tending to have the lowest MICs.³¹ The use of fluoroquinolones for CA-MRSA infection cannot be recommended until published evidence of effectiveness is available.

Clinical Practice: The Story of CA-MRSA (continued)

References

- Barrett FF, McGehee RF, Jr., Finland M. Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital. Bacteriologic and epidemiologic observations. *N Engl J Med* 279 (9): 441-8, 1968.
- Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med* 162 (19): 2229-35, 2002.
- CDC. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997-1999. *MMWR Morb Mortal Wkly Rep* 48 (32): 707-710, 1999.
- Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 36 (1): 53-9, 2003.
- Deresinski S. Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic, and therapeutic odyssey. *Clin Infect Dis* 40 (4): 562-73, 2005.
- Deurenberg RH, Vink C, Kalenic S, Friedrich AW, Bruggeman CA, Stobberingh EE. The molecular evolution of methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect* 13 (3): 222-35, 2007.
- Drew RH. Emerging options for treatment of invasive, multidrug-resistant *Staphylococcus aureus* infections. *Pharmacotherapy* 27 (2): 227-49, 2007.
- Fiebelkorn KR, Crawford SA, McElmeel ML, Jorgensen JH. Practical disk diffusion method for detection of inducible clindamycin resistance in *Staphylococcus aureus* and coagulase-negative staphylococci. *J Clin Microbiol* 41 (10): 4740-4, 2003.
- Groom AV, Wolsey DH, Naimi TS, Smith K, Johnson S, Boxrud D, Moore KA, Cheek JE. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. *Jama* 286 (10): 1201-5, 2001.
- Jevons MP. "Celbenin" -resistant staphylococci. *Br Med J* 1: 124-5, 1961.
- Kaka AS, Rueda AM, Shelburne SA, 3rd, Hulten K, Hamill RJ, Musher DM. Bactericidal activity of orally available agents against methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 58 (3): 680-3, 2006.
- Kazakova SV, Hageman JC, Matava M, Srinivasan A, Phelan L, Garfinkel B, Boo T, McAllister S, Anderson J, Jensen B, Dodson D, Lonsway D, McDougal LK, Arduino M, Fraser VJ, Killgore G, Tenover FC, Cody S, Jernigan DB. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. *N Engl J Med* 352 (5): 468-75, 2005.
- Labandeira-Rey M, Couzon F, Boisset S, Brown EL, Bes M, Benito Y, Barbu EM, Vazquez V, Hook M, Etienne J, Vandenesch F, Bowden MG. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. *Science* 315 (5815): 1130-3, 2007.
- LaPlante KL, Rybak MJ, Amjad M, Kaatz GW. Antimicrobial susceptibility and staphylococcal chromosomal cassette mec type in community- and hospital-associated methicillin-resistant *Staphylococcus aureus*. *Pharmacotherapy* 27 (1): 3-10, 2007.
- Lewis JS, 2nd, Jorgensen JH. Inducible clindamycin resistance in Staphylococci: should clinicians and microbiologists be concerned? *Clin Infect Dis* 40 (2): 280-5, 2005.
- Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* 117 (5): 390-8, 1992.
- McDougal LK, Steward CD, Killgore GE, Chaitram JM, McAllister SK, Tenover FC. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. *J Clin Microbiol* 41 (11): 5113-20, 2003.
- Miller LG, Perdreau-Remington F, Bayer AS, Diep B, Tan N, Bharadwa K, Tsui J, Perlroth J, Shay A, Tagudar G, Ibebuogu U, Spellberg B. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: a prospective investigation. *Clin Infect Dis* 44 (4): 471-82, 2007.
- Moellering RC, Jr. The growing menace of community-acquired methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 144 (5): 368-70, 2006.
- Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 355 (7): 666-74, 2006.
- Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, Johnson SK, Vandenesch F, Fridkin S, O'Boyle C, Danila RN, Lynfield R. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 290 (22): 2976-84, 2003.
- Panton PE, Valentine FCO. Staphylococcal toxin. *Lancet* 222: 506-8, 1932.
- Rucker JC, Hamilton SR, Bardenstein D, Isada CM, Lee MS. Linezolid-associated toxic optic neuropathy. *Neurology* 66 (4): 595-8, 2006.
- Ruhe JJ, Monson T, Bradsher RW, Menon A. Use of long-acting tetracyclines for methicillin-resistant *Staphylococcus aureus* infections: case series and review of the literature. *Clin Infect Dis* 40 (10): 1429-34, 2005.
- Siberry GK, Tekle T, Carroll K, Dick J. Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance *in vitro*. *Clin Infect Dis* 37 (9): 1257-60, 2003.
- Smilack JD. The tetracyclines. *Mayo Clin Proc* 74 (7): 727-9, 1999.
- Stein A, Bataille JF, Drancourt M, Curvale G, Argenson JN, Groulier P, Raoult D. Ambulatory treatment of multidrug-resistant *Staphylococcus*-infected orthopedic implants with high-dose oral co-trimoxazole (trimethoprim-sulfamethoxazole). *Antimicrob Agents Chemother* 42 (12): 3086-91, 1998.
- Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis* 34 (11): 1481-90, 2002.
- Szumowski JD, Cohen DE, Kanaya F, Mayer KH. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. *Antimicrob Agents Chemother* 51 (2): 423-8, 2007.
- Wu SW, de Lencastre H, Tomasz A. Recruitment of the *mecA* gene homologue of *Staphylococcus sciuri* into a resistance determinant and expression of the resistant phenotype in *Staphylococcus aureus*. *J Bacteriol* 183 (8): 2417-24, 2001.
- Zhanell GG, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, Smith H, Hoban DJ. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 62 (1): 13-59, 2002.
- Zinderman CE, Conner B, Malakooti MA, LaMar JE, Armstrong A, Bohnker BK. Community-acquired methicillin-resistant *Staphylococcus aureus* among military recruits. *Emerg Infect Dis* 10 (5): 941-4, 2004.