

## Introduction

One of the prominent challenges in managing acute bacterial skin and skin structure infections (ABSSSI) in today's hospital environment is the changing pattern of causative pathogens and antibiotic susceptibilities. In recent years, there has been a significant increase in the prevalence of severe ABSSSI requiring hospital intervention caused by antibiotic-resistant pathogens, in particular methicillin-resistant *Staphylococcus aureus* (MRSA) strains (ie, strains resistant to previously available  $\beta$ -lactam antibiotics).<sup>1,3</sup> Beginning in the mid-1990s, the prevalence of MRSA shifted from healthcare-associated MRSA (HA-MRSA) to community-associated MRSA (CA-MRSA) strains. CA-MRSA is now the leading identifiable cause of purulent skin and soft tissue infections (cSSTI) in emergency department (ED) patients in the United States.<sup>4</sup> Alternatively, the primary causative bacteria in nonculturable cellulitis are  $\beta$ -hemolytic streptococci (mostly *Streptococcus pyogenes* and *S. agalactiae*), which are still susceptible to  $\beta$ -lactam antibiotics, despite the MRSA epidemic.<sup>5</sup>

CA-MRSA isolates are genetically and phenotypically distinct from HA-MRSA (Table 1).<sup>6</sup> For CA-MRSA, antimicrobial resistance is typically limited to  $\beta$ -lactam antibiotics and macrolides; these strains are commonly susceptible to trimethoprim-sulfamethoxazole (TMP-

area of redness and/or induration accompanied by lymph node enlargement.<sup>9</sup>

## Infectious Diseases Society of America MRSA Management Guidelines, 2010

The Infectious Diseases Society of America (IDSA) Guidelines issued in 2010 (which do not use the ABSSSI terminology) recommend surgical debridement or drainage of SSTIs and, where appropriate, initial empiric, broad-spectrum antibiotic therapy pending culture results.<sup>10</sup> Conditions where antibiotic therapy is recommended include:<sup>10</sup>

- Large abscesses surrounded by extensive cellulitis, or accompanied by signs and symptoms of systemic illness
- Abscesses associated with severe or extensive disease (eg, multiple sites of infection) or rapid progression in presence of associated cellulitis
- Abscesses associated with comorbidities, immunosuppression, septic phlebitis, or extremes of age
- Abscesses in an area difficult to drain (eg, face, hand, genitalia)
- Lack of response to incision and drainage alone

Table 1. Microbial Profiles of CA-MRSA and HA-MRSA		
Characteristic	CA-MRSA	HA-MRSA
Antimicrobial resistance	Typically limited to $\beta$ -lactams and macrolides; usually susceptible to trimethoprim/sulfamethoxazole, doxycycline	Usually multidrug-resistant
Infection spectrum	<b>Commonly:</b> skin and soft tissue infections <b>Occasionally:</b> necrotizing fasciitis, necrotizing pneumonia	<b>Multiple sites:</b> bloodstream, respiratory tract, urinary tract infections, as well as skin and soft tissue infection
SCC mec gene	Types IV and V	Types I, II, and III
PFGE types	USA300, USA400	USA100, USA200
Toxins	More	Fewer
PVL genes	Common	Rare
Healthcare exposure	Less common	More common

Adapted from File TM Jr, 2007.<sup>4</sup>

SMX), doxycycline, and clindamycin.<sup>1,7</sup> Other distinguishing features of CA-MRSA isolates are a high prevalence of genes encoding for Panton-Valentine leukocidin (PVL) endotoxin associated with more virulent disease (such as necrosis of the skin and abscess formation) and the staphylococcal chromosome cassette (SCC) *mec* type IV for methicillin-resistance that enhances infection transmissibility.<sup>18</sup> While pulsed-field gel electrophoresis (PFGE) of CA-MRSA strains has demonstrated geographic variations, CA-MRSA genotype USA300 is the major circulating strain in most areas of the United States; it has even emerged as a nosocomial strain (HA-MRSA) in many areas.<sup>1</sup> Reflective of the increased virulence associated with PVL and other virulence factors, ABSSSIs attributable to CA-MRSA infections are associated with poorer clinical outcomes, such as a significantly greater proportion requiring hospital intervention, failure of initial therapy, and infection recurrences than seen with infections attributable to community-acquired methicillin-susceptible *S. aureus* (CA-MSSA).<sup>8</sup>

## ABSSSI Nomenclature

Because the terminology used to describe bacterial infections of the skin and skin structures is often confusing, the Food and Drug Administration (FDA) recently issued guidance that standardizes the nomenclature to be used to evaluate new antimicrobial treatments for complicated skin and skin structure infections (cSSSI). The new FDA designation to replace cSSSI is acute bacterial skin and skin structure infections (ABSSSI). A primary purpose of this new terminology is to identify appropriate infections for clinical registry trials for which a reliable estimate of a treatment effect of antibacterial drug therapy can be described (eg, to avoid including patients with mild infections that would not require antimicrobial therapy).

Most of the literature to date still refers to infections requiring hospital intervention as cSSSI or cSSTI. Complicated skin and skin structure infections involve deeper tissue that may require surgical intervention (eg, extensive cellulitis/erysipelas or major cutaneous abscesses) and infected wounds, ulcers, or burns; or superficial abscesses in an anatomical site where risk of anaerobic or gram-negative pathogen involvement is higher, or are complicated by an underlying condition or comorbidity (eg, diabetes or systemic immunosuppression) that complicates response to therapy. The main clinical criterion of ABSSSI that distinguishes it from prior designation of cSSSI is the 75 cm<sup>2</sup> minimum surface

is 1 g Q 12 hrs; for very severely ill patients 15-20 mg/kg every 8-12 hrs (not to exceed 2 g/dose) should be considered. In addition, in vitro susceptibility will guide vancomycin therapy. The IDSA Guidelines make several points about this. First, the patient's response to treatment should guide the decision to continue vancomycin or switch to another antibiotic when the vancomycin minimum inhibitory concentration (MIC) is <2  $\mu$ g/mL. If the patient shows a clinical response, vancomycin treatment can continue with follow-up. Second, if clinical and microbiological responses are absent in a patient who has undergone adequate debridement, a vancomycin alternative should be considered; the MIC is irrelevant in this situation. Alternatives to vancomycin should also be used when MRSA isolates exhibit intermediate susceptibility or resistance to vancomycin (MIC>2  $\mu$ g/mL). Therapy typically continues for 7 to 14 days.<sup>10</sup>

For hospitalized patients with nonpurulent cellulitis, a  $\beta$ -hemolytic streptococci species is the more predominant pathogen. Recommendations for treatment of SSTIs attributable to streptococci include  $\beta$ -lactam agents (oxacillin) or first generation cephalosporins.<sup>10</sup> According to IDSA Guidelines, "A  $\beta$ -lactam antibiotic (eg, cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis, with modification to MRSA-active therapy if there is no clinical response."<sup>10</sup>

Although vancomycin has been a mainstay of therapy for MRSA for decades, its efficacy has come into question, with concerns over its slow bactericidal activity, the emergence of resistant strains, and possible "MIC creep" among susceptible strains. Thus, newer anti-MRSA agents such as linezolid, daptomycin, telavancin, and tigecycline have found increasing favor against gram-positive bacteria.<sup>11</sup> Use of these other recommended antimicrobials can be limited by their narrow spectrum of activity, tendency to develop antimicrobial resistance, or need for monitoring.<sup>12</sup>

Of note, although the IDSA Guidelines list several parenteral agents for MRSA, including tigecycline, the panel did not include tigecycline as a preferred agent because of a recent FDA warning indicating an increased risk in all-cause mortality with tigecycline versus comparable drugs in a pooled analysis of clinical trials. However, the greatest increase in risk of death with tigecycline was seen in patients with ventilator-associated pneumonia—an unapproved use—and there was no significant difference in mortality in complicated skin infection trials (1.4% vs 0.7%; 95% CI, -0.3-1.7). Similarly, although the novel cephalosporin ceftaroline was not yet approved by the FDA at the time of writing, the IDSA Guidelines recognized it as a potential option pending its approval.

Finally, and of high importance, the IDSA Guidelines re-emphasize the principle that MSSA should preferably be treated with a  $\beta$ -lactam agent, which has been known to be more effective than vancomycin for infections due to susceptible isolates.<sup>10</sup>

## Antibiotic Choices

In determining the appropriate antibiotic choice, one should consider the likely causative microbial(s), the site and severity of the infection, and adequate coverage based on the indicated regimen and local trends in microbial susceptibilities. Given the high and growing prevalence of CA-MRSA in ABSSSI, empirical use of agents active against CA-MRSA is now warranted.<sup>7,14</sup> and for severely ill patients with ABSSSI, broad-spectrum IV therapy with MRSA coverage is always indicated.<sup>15</sup>

While a significant portion of ABSSSI are associated with CA-MRSA, the empiric antimicrobial therapy prescribed in the past has often lacked adequate activity against CA-MRSA.<sup>2,16</sup> In a study conducted at Atlanta's Grady Memorial Hospital for 14 weeks in 2003, 389 episodes of SSTI were identified, of which 63% (244/389) were caused by CA-MRSA.<sup>7</sup> Among the isolates tested for susceptibility, the initial antibiotic prescribed was inadequate in 65% (100/157) of the MRSA infections.<sup>7</sup> In a multicity survey conducted in August 2004, infecting MRSA isolates were resistant to the antimicrobial agent (eg,  $\beta$ -lactam antibiotics such as cephalexin or dicloxacillin) prescribed for 57% (57/100) of the patients.<sup>15</sup>

The selection of empiric antibiotic therapy does appear to be improving. A more recent study that compared antibiotic choices made in a network of 12 US emergency departments in 2004 versus 2008 reported a significant improvement, from 59% of patients (182/311) treated with an inadequate antibiotic in 2004 to only 5% (27/528) in 2008 who did not receive MRSA-active antibiotic therapy.<sup>3</sup>

While vancomycin has been the mainstay of parenteral therapy for MRSA-ABSSSI infections for years, its widespread use has probably led to the emergence of MRSA strains with decreased susceptibility to glycopeptides.<sup>15,17</sup> The limited efficacy of vancomycin may also be attributable to its slow bactericidal activity and highly variable tissue penetration, dependent upon the degree of inflammation present.<sup>10</sup> Increasing vancomycin MIC<sub>90</sub> against MRSA strains (MIC<sub>90</sub> 4-8  $\mu$ g/mL) was first reported in the 1990s.<sup>17</sup> These *S. aureus* strains with reduced susceptibility to vancomycin, called vancomycin-intermediate-*S. aureus* (VISA), are associated with poor clinical outcomes.<sup>17</sup> Unfortunately, reduced susceptibility to vancomycin may not be identified by routine susceptibility testing.<sup>1</sup>

Newer antimicrobial agents have demonstrated efficacy in ABSSSI comparable to vancomycin (linezolid, daptomycin, telavancin, tigecycline, and ceftaroline).<sup>12,15,18</sup> An overview of the pros and cons of using these agents to treat ABSSSI attributable to MRSA is presented in Table 2.<sup>1,10,18-21</sup>

## New Broad-Spectrum Cephalosporin for Monotherapy of ABSSSI

Ceftaroline fosamil is a novel, broad-spectrum cephalosporin approved in October 2010 for parenteral treatment of ABSSSI in adults 18 years and older caused by:<sup>22,23</sup>

- Susceptible gram-positive *S. aureus* (MSSA and MRSA),  $\beta$ -hemolytic streptococci, *S. pyogenes*, and *S. agalactiae* bacteria
- Susceptible gram-negative *Klebsiella pneumoniae*, *K. oxytoca*, and *Escherichia coli* bacteria.

Ceftaroline is not active against gram-negative bacteria producing extended-spectrum  $\beta$ -lactamases from the TEM, SHV, or CTX-M families, 390 serine carbapenemases (such as KPC), class B metallo- $\beta$ -lactamases, or class C (AmpC) cephalosporinases.<sup>23</sup> It has variable activity against many gram-negative *Enterobacteriaceae*, and is not active against most nonfermentative gram-negative bacilli, including *Pseudomonas aeruginosa*.<sup>24</sup>

Ceftaroline, a prodrug rapidly converted to the active form following administration by 1-hour IV infusion, has been shown in vitro to act by inhibiting penicillin binding protein 2a (PBP2a), the form of PBP unique to MRSA strains.<sup>17</sup> In vitro, ceftaroline has demonstrated potency and coverage against multidrug-resistant gram-positive bacteria, including MRSA strains, VISA or VRSA strains, PVL-producing strains, strains resistant to other classes of antimicrobial agents (such as glycopeptides, daptomycin, clindamycin, TMP-SMX, and linezolid), and macrolide-resistant *S. pyogenes* and gram-positive anaerobes.<sup>22-24</sup> Relative MIC<sub>90</sub> values for ceftaroline and other ABSSSI antimicrobials are listed in Table 3.<sup>24,25</sup>

Table 3. In vitro MIC <sub>90</sub> for Ceftaroline and Other Agents Against Gram-Positive Bacteria				
Organism (no. isolates tested)	Ceftaroline	Vancomycin	Daptomycin	Linezolid
<b><i>Staphylococcus aureus</i></b>				
MSSA (348)	0.25	1	0.5	2
MRSA (92)	1	1	1	2
CA-MRSA (244)	0.5	—	—	—
VISA (20)	1	8	4	2
VRSA (10)	0.5	>64	1	2
<b>Coagulase-negative staphylococci</b>				
Methicillin susceptible (201)	0.12	2	4	2
Methicillin resistant (299)	0.5	2	>32	2
<b><i>Enterococcus faecalis</i></b>				
Vancomycin susceptible (157)	4	2	1	2
Vancomycin resistant (25)	4	>16	1	2
Enterococcus faecium (157)	>16	>16	4	2
<b><i>Streptococcus pyogenes</i></b>				
Erythromycin susceptible (91)	<.008	0.5	NA	1
Erythromycin resistant (10)	<.015	0.5	NA	1
<b><i>Streptococcus agalactiae</i> (59)</b>	<b>0.015</b>	<b>0.5</b>	<b>NA</b>	<b>1</b>

MIC<sub>90</sub>, minimum inhibitory concentration for 90% inhibition, values given in  $\mu$ g/mL; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CA-MRSA, community-associated MRSA; NA, not applicable; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.  
Adapted from Saravoltz LD et al, 2010<sup>23</sup> and Steed ME et al, 2010.<sup>22</sup>

Ceftaroline has demonstrated a low potential for selection of resistance in vitro for gram-positive pathogens. Spontaneous resistance, in single-step mutant selection and serial passage resistance studies were not detected for MSSA, HA-MRSA, CA-MRSA, or VISA strains.<sup>24</sup>

Two phase 3 studies of ceftaroline 600 mg BID (n=693) versus vancomycin plus aztreonam, 1 g each BID x 5-14 days (n=685) were conducted in 1378 adults with ABSSSI.<sup>12</sup> A pooled analysis of these two phase 3 studies found clinical outcomes with ceftaroline were comparable to outcomes with vancomycin plus aztreonam (Table 4).<sup>12</sup>

Table 4. Clinical Outcomes: Ceftaroline and Vancomycin Plus Aztreonam <sup>12</sup>		
	Ceftaroline (n=693)	Vancomycin + Aztreonam (n=685)
Overall clinical cure	91.6%	92.7%
Overall microbiological cure	92.3%	93.7%

A higher microbiological response was observed with vancomycin plus aztreonam against gram-negative infections. Ceftaroline efficacy was comparable to aztreonam against *E. coli* and *K. pneumoniae*, but aztreonam was more active against *Pseudomonas aeruginosa* and *Proteus mirabilis* than ceftaroline.<sup>12</sup>

Ceftaroline monotherapy is as effective and well tolerated as vancomycin plus aztreonam in the management of patients with ABSSSI,<sup>22</sup> with a clinical cure rate comparable to that of vancomycin plus aztreonam.<sup>12</sup> The most common adverse events seen with ceftaroline, occurring in  $\geq$ 2% of patients, include diarrhea, nausea, and rash.<sup>23</sup> *Clostridium difficile*-associated diarrhea has been reported with ceftaroline.<sup>24</sup> Ceftaroline represents an important addition to the armamentarium of antimicrobials active against pathogens that commonly cause ABSSSI. [\*\*R\*\*](#)

Table 2. Antibiotics Commonly Employed to Treat ABSSSI

FDA Approved for MRSA ABSSSI			
<b>Daptomycin</b> <ul style="list-style-type: none"><li>• Bactericidal</li><li>• Also approved for <i>S. aureus</i> bacteremia and right-sided endocarditis</li><li>• Susceptibility breakpoint MIC <math>\leq</math>1 <math>\mu</math>g/mL</li><li>• Monitor creatine kinase for muscle toxicity<sup>1,19</sup></li><li>• May have cross-resistance with vancomycin</li><li>• Second-line agent for glycopeptide failures<sup>18</sup></li></ul>	<b>Tigecycline</b> <ul style="list-style-type: none"><li>• Bacteriostatic against MRSA, <i>Enterococcus spp.</i><sup>20</sup></li><li>• Broad spectrum, including anaerobes and many gram-negative bacilli (not <i>Pseudomonas</i>)</li><li>• Low serum levels</li><li>• Not included as preferred option for skin and soft tissue infections in recent IDSA MRSA Guideline (see text)</li></ul>	<b>Vancomycin</b> <ul style="list-style-type: none"><li>• Bactericidal activity is slower than other drugs</li><li>• Susceptibility breakpoint MIC<math>\leq</math>2 <math>\mu</math>g/mL</li><li>• MIC creep among susceptible strains (VISA)</li><li>• Emergence of resistant strains (VRSA)</li><li>• Highly variable tissue penetration</li><li>• Often requires monitoring of levels (trough)</li></ul>	<b>Not Approved for MRSA ABSSSI</b>
<b>Linezolid</b> <ul style="list-style-type: none"><li>• Bacteriostatic<sup>1,19</sup></li><li>• In vitro activity vs VISA, VRSA, <i>Enterococcus spp.</i><sup>19</sup></li><li>• Clinically superior to vancomycin in one study<sup>21</sup></li><li>• 100% oral bioavailability</li></ul>	<b>Quinupristin-dalfopristin</b> <ul style="list-style-type: none"><li>• Bactericidal</li><li>• Used as salvage therapy for invasive MRSA infections following vancomycin treatment failure</li><li>• In vitro activity vs <i>Enterococcus spp.</i><sup>20</sup></li><li>• Toxicities: phlebitis, arthralgias, myalgias, frequent need for central line</li></ul>	<b>Ceftaroline</b> <ul style="list-style-type: none"><li>• Bactericidal</li><li>• Only approved <math>\beta</math>-lactam for MRSA</li><li>• Approved for MRSA skin infections</li><li>• Effective for some <i>Enterobacteriaceae</i> infections (not for <i>Pseudomonas sp.</i>)</li><li>• IV only</li></ul>	<b>Clindamycin</b> <ul style="list-style-type: none"><li>• Bacteriostatic</li><li>• CA-MRSA susceptibility &gt; HA-MRSA susceptibility</li><li>• Geographic variation in susceptibility rates</li><li>• May develop inducible resistance (ensure that laboratory performs test—"D" test)</li></ul>
<b>Rifampin</b> <ul style="list-style-type: none"><li>• Bactericidal against CA-MRSA</li><li>• Not to be used as monotherapy to due high risk of microbial development of resistance<sup>1</sup></li><li>• Not routinely recommended for ABSSSI according to IDSA MRSA guidelines</li></ul>	<b>Telavancin</b> <ul style="list-style-type: none"><li>• Bactericidal against MRSA, VISA, VRSA</li><li>• Requires serum creatinine monitoring</li><li>• May affect results of coagulation lab results</li></ul>	<b>Doxycycline (minocycline)</b> <ul style="list-style-type: none"><li>• Bacteriostatic<sup>19</sup></li><li>• Limited clinical data</li><li>• More for mild infections as oral agent</li></ul>	<b>TMP-SMX</b> <ul style="list-style-type: none"><li>• Bacteriostatic</li><li>• Concern for allergy</li><li>• More for mild infections as oral agent</li></ul>

Adapted from Liu C et al, 2007.<sup>12</sup>



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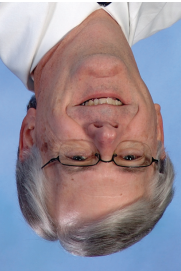
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**Released: December 26, 2011**  
**Expires: December 25, 2012**

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**Editor:** Nancy Lucas, Paradigm Medical Communications,  
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**Grant/Research Support:** Ceptra Pharmaceuticals;  
MD, MSc, MACP, FIDSA, FCCP

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