

# Applying Antimicrobial Stewardship Principles to the Treatment of CABP and ABSSSI

COMPLYING WITH CMS CRITERIA AND CLINICAL GUIDELINES

## Ask the Experts: Strategies for Optimizing Antimicrobial Use in Acute Bacterial Skin and Skin Structure Infections

The treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) is the focus of a series of learning opportunities planned by ASHP Advantage. The series began with a Midday Symposium and simultaneous webcast on December 9, 2013, during the 48th ASHP Midyear Clinical Meeting and Exhibition in Orlando, Florida. The learning opportunities are designed to build on each other to provide an evidence-based approach to managing the treatment of patients with CABP or ABSSSI according to Centers for Medicare & Medicaid Services requirements and clinical guidelines.

As a follow up to the Midyear Meeting, Initiative Chair John Esterly, Pharm.D., BCPS (AQ-ID), presented a live webinar in March that addressed questions submitted during the symposium. Those questions also serve as the basis for two e-newsletters that are part of the

educational initiative. The April 2014 issue focused on CABP. This issue addresses ABSSSI. Other learning opportunities in the series include the following:

- » On-demand web-based activity based on the Midyear symposium (2 hours continuing pharmacy education).
- » On-demand web-based activity based on the Ask the Experts webinar (1 hour continuing pharmacy education).
- » Faculty roundtable discussion available in three parts, each lasting roughly 12 minutes, on considerations in incorporating new ABSSSI and CABP treatment options into clinical practice, controversies and conundrums in the treatment of CABP, and the role of the pharmacist in treating ABSSSI and CABP.

For more information and to access other learning opportunities on this topic, go to the initiative portal. This initiative is supported by an educational grant from Forest Research Institute, a subsidiary of Forest Laboratories, Inc.

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## Why focus on ABSSSI?

There has been an epidemic of ABSSSI in the United States since the beginning of the 21st century, primarily as a result of increases in the incidence of community-acquired methicillin-resistant *Staphylo-*

*coccus aureus* (*S. aureus*) infections.<sup>1,2</sup> Cellulitis and abscesses, common types of ABSSSI, are responsible for an estimated 600,000 hospitalizations in the United States annually.<sup>3</sup> On average, the length of hospital

stay for patients with ABSSSI due to *S. aureus* exceeds 6 days at a cost of \$6,830.<sup>4</sup> The rate of hospital admissions for ABSSSI and other skin and soft tissue infections (SSTIs) increased by 29% between 2000 and 2004.<sup>3</sup> More than 11 million outpatient visits are attributed to SSTIs annually.<sup>5</sup>

Treating ABSSSI presents a challenge to clinicians because other conditions (e.g., thrombophlebitis) may mimic infections.<sup>6</sup> The severity of infection varies depending on the depth of the infection. Common pathogens (e.g., *Staphylococcus* and *Streptococcus* species) have developed antimicrobial resistance. These factors affect the challenges clinicians face in determining the need for antibiotic therapy, the choice of an agent, and route of administration.

**Q** Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is a common cause of infection in my local area, so prescribers are providing double coverage with a  $\beta$ -lactam antibiotic (e.g., piperacillin-tazobactam) plus vancomycin as empiric therapy for ABSSSI. What can I do to improve the empiric use of antibiotics for ABSSSI at my institution?

**A** *S. aureus* is the most common pathogen in complicated ABSSSI, accounting for 48% of infections.<sup>7</sup> Nearly half (43.5%) of these *S. aureus* strains are methicillin-resistant.

Table 1 lists recommended empiric treatments for various types of ABSSSI based on evidence-based guidelines.<sup>8,9</sup> Most patients (96%) with non-purulent cellulitis respond to  $\beta$ -lactam antibiotic therapy.<sup>10</sup> The use of trimethoprim-sulfamethoxazole (TMP-SMX) is associated with a higher failure rate than the use of  $\beta$ -lactam antibiotics or clindamycin for this indication.<sup>11</sup> The presence of MRSA should be considered in patients with purulent infections (presenting like “spider bites”), young patients (especially athletes), patients in areas with a high local prevalence of MRSA colonization, patients with a history of MRSA infection or antibiotic treatment failure, and patients with clinically severe infections or systemic toxicity.<sup>9</sup> Clindamycin, TMP-SMX, a tetracycline (e.g., doxycycline, minocycline), or linezolid may be used for the empiric treatment of MRSA in outpatients.<sup>9</sup> Vancomycin should be used primarily for empiric treatment of patients with complicated soft-tissue infection requiring hospitalization.

Empiric therapy with coverage for gram-negative pathogens, including *Pseudomonas aeruginosa*, is usually not necessary for patients with ABSSSI unless they are at

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high risk for infection with these organisms, are clinically unstable, or have failed initial appropriate gram-positive therapy.<sup>9,12</sup> Risk factors for gram-negative ABSSSI include a high local prevalence of these pathogens, previous gram-negative infection, moderate or severe diabetic foot infection, necrotizing infection, and immunocompromised host status.<sup>8,13</sup> If present in a wound, *Pseudomonas aeruginosa*, can be a non-pathogenic colonizer of soft tissue infections and treatment of it does not necessarily improve patient outcomes.<sup>13,14</sup>

The empiric use of antibiotics for ABSSSI in hospitals can be improved by creating clinical pathways for treating skin infections. These pathways should facilitate stratification of patient risk based on the type of infection, anatomical site, and probable pathogen, taking into consideration local antibiogram data. The choice of antibiotic, dosage, and route of administration for empiric therapy should be outlined based on these criteria. Criteria for the use of empiric combination antibiotic therapy that provides antimicrobial coverage for gram-negative in addition to gram-positive pathogens for ABSSSI should be included in the clinical pathway.

Pharmacists should work with infectious diseases physicians and through the antimicrobial stewardship committee to develop clinical pathways. Institutional

**Table 1. Guideline-Recommended Empiric Therapy for ABSSSI<sup>8,9</sup>**

Indication	Probable Pathogen	Drug Therapy Options
Erysipelas	<i>Streptococcus pyogenes</i> , other $\beta$ -hemolytic <i>Streptococcus</i> spp.	$\beta$ -lactam antibiotic (or clindamycin if allergic to $\beta$ -lactam)
Cutaneous abscess (furuncle, carbuncle)	<i>Staphylococcus aureus</i>	None following incision and drainage <sup>a</sup>
Cellulitis (non-purulent)	<i>Streptococcus pyogenes</i> , other $\beta$ -hemolytic <i>Streptococcus</i> spp., MSSA Role of CA-MRSA unknown	$\beta$ -lactam antibiotic Clindamycin Linezolid $\beta$ -lactam + either TMP/SMX or doxycycline/ minocycline
Cellulitis (purulent or trauma-related)	<i>Staphylococcus aureus</i> including MRSA	Clindamycin TMP/SMX Doxycycline/minocycline Linezolid
Complicated soft-tissue infection requiring hospitalization	<i>Staphylococcus aureus</i> and all $\beta$ -hemolytic <i>Streptococcus</i> spp.	Vancomycin Linezolid Daptomycin Clindamycin Telavancin Ceftaroline

<sup>a</sup>Consider treatment for patients with cutaneous abscesses at multiple sites, rapid spread of infection, systemic symptoms, comorbidities, or immunosuppression; patients who are very young or very old; and patients with abscesses that are difficult to drain or fail to respond to drainage.

ABSSSI = acute bacterial skin and skin structure infections; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; SMX = sulfamethoxazole; TMP = trimethoprim

administrative buy-in should be obtained to promote acceptance of and adherence to the pathways. The potential for reduced broad-spectrum antibiotic use, collateral harm to patients, antimicrobial resistance, and health care costs can be used to justify devoting time and resources to developing clinical pathways and other antimicrobial stewardship initiatives.

**Q** What oral dosage of TMP-SMX should be used as empiric therapy in an adult with a purulent cellulitis?

**A** Trimethoprim-sulfamethoxazole is not approved by the Food and Drug Administration (FDA) for the treatment of ABSSSI. Nevertheless, the Infectious Diseases Society of America recommends TMP-SMX 160 mg/800 mg or 320 mg/1600 mg (i.e., one or two double-strength tablets) orally twice daily for patients with SSTIs.<sup>8</sup> A range of intravenous weight-based dosing (e.g., 5 mg/kg/day to 15 mg/kg/day as the trimethoprim component in divided doses) has been used for other purposes, including both FDA-approved indications and indications that have not been approved by FDA. For example, TMP-SMX 10 mg/kg/day (as the trimethoprim

component) i.v. in two divided doses has been used for adults with persistent MRSA bacteremia and vancomycin treatment failure.<sup>9</sup> Some clinicians may elect to use weight-based recommendations as a guide for determining oral doses for adults with ABSSI although no evidence exists to support this practice.

**Q** What oral dose of TMP-SMX should be used for obese patients with ABSSSI? What is the highest dosage that can be safely used in these patients?

**A** The maximum oral dosage listed in the FDA-approved prescribing information for TMP-SMX is 20 mg/kg/day (as the trimethoprim component) in divided doses for the treatment of *Pneumocystis jiroveci* pneumonia in adults and children.<sup>15</sup> Little information is available to guide TMP-SMX dosing in obese patients.

In a prospective, observational cohort study of 291 adults with ABSSSI caused by MRSA, including patients who were overweight or obese, the rate of clinical resolution of infection was not significantly different when high-dose oral TMP-SMX (320 mg/1600 mg twice daily) was used instead of standard-dose oral therapy (160 mg/800 mg twice daily) for 7 to 15 days (73% versus

75%,  $p = 0.79$ ).<sup>16</sup> The median body mass index (BMI) was similar in the two treatment groups, 28 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup>, respectively.

Treatment success rates and risk factors for treatment failure were analyzed in a 3-year retrospective cohort study of 405 adult outpatients in Hawaii with cellulitis who were empirically treated with oral cephalexin 500 mg four times daily, oral TMP-SMX 160 mg/800 mg (one double-strength tablet) twice daily, or oral clindamycin 300 mg four times daily.<sup>17</sup> Approximately half (52%) of the patients were obese (BMI 30 kg/m<sup>2</sup> or higher). The most common diagnosis was cellulitis with abscess, affecting 44% of patients. Patients with this diagnosis and obese patients were evenly distributed among the three treatment groups. A positive culture was obtained from 29% of patients, revealing the presence of MRSA (62%), methicillin-susceptible *S. aureus* (20%),  $\beta$ -hemolytic streptococci (9%), and gram-negative species (9%). The overall treatment success rate was significantly higher with TMP-SMX than cephalexin (91% versus 74%,  $p < 0.001$ ) and similar to that with clindamycin (85%). In obese patients, the treatment success rates were significantly higher with TMP-SMX and clindamycin (88% and 90% respectively) than cephalexin (68%,  $p = 0.002$  and  $0.04$ , respectively). Risk factors for treatment failure included therapy with an antibiotic that was not active against CA-MRSA (i.e., cephalexin instead of TMP-SMX or clindamycin), the severity of cellulitis, upper extremity involvement of cellulitis, and lack of drainage if an abscess was present. Of note, multivariate analysis did not identify obesity as a risk factor for treatment failure. The data from these studies suggest that large TMP-SMX dosages may not be necessary for treating ABSSSI in obese adults.

**Q** What antimicrobial agent is preferred for treating pregnant inpatients with cellulitis caused by MRSA?

**A** Antimicrobial agents with activity against MRSA and classified in FDA pregnancy category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women) are preferred for hospitalized pregnant women with cellulitis caused by MRSA. The choice of antimicrobial therapy should be made based on the severity of infection and local MRSA susceptibilities.

Clindamycin is classified in FDA pregnancy category B, and it is useful for treating purulent and non-purulent cellulitis and complicated SSTI.<sup>8,9</sup> Other antibiotics

in FDA pregnancy category B with MRSA activity include daptomycin, quinupristin-dalfopristin, and ceftaroline. Daptomycin is approved by FDA only for the treatment of complicated SSTI (and bacteremia), not cellulitis.<sup>18</sup> The use of quinupristin-dalfopristin is limited by side effects, including severe infusion reactions.<sup>19</sup> Ceftaroline is a novel/advanced-generation cephalosporin that was introduced since the release of current guidelines for treating MRSA infections and SSTIs. It is approved for the treatment of ABSSSI (and community-acquired bacterial pneumonia) but clinical data are limited.<sup>20</sup> Most  $\beta$ -lactam antibiotics are safe to use during pregnancy.

Vancomycin has been the mainstay for treating MRSA infections when intravenous therapy is warranted, but it is classified in FDA pregnancy category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Telavancin and linezolid also are classified in FDA pregnancy category C.

Trimethoprim-sulfamethoxazole is classified in FDA pregnancy category D (there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). It may interfere with folic acid metabolism and should be avoided in the third trimester.<sup>15</sup> Tetracyclines also are classified in FDA pregnancy category D and should be avoided in pregnant women because they are teratogenic.

**Q** What is the role of topical antimicrobial therapy (e.g., mupirocin topical and nasal ointments, chlorhexidine body wash) for the treatment of SSTIs caused by MRSA?

**A** There is minimal evidence supporting the use of topical antimicrobial agents for the treatment of SSTIs caused by MRSA, and available data support their use only for mild infections. Mupirocin 2% topical ointment or cream may be used to treat neonatal pustulosis and minor skin infections (e.g., impetigo) in children.<sup>9</sup>

Decolonization with topical agents can be considered in certain situations, but supporting evidence is weak. Patients sometimes develop recurrent SSTIs caused by MRSA despite wound care and hygiene measures or as a result of ongoing transmission among household or close contacts with symptomatic or asymptomatic infections. Nasal decolonization with

mupirocin 2% nasal ointment twice daily for 5-10 days and topical body decolonization with a skin antiseptic solution (e.g., chlorhexidine) for 5-14 days or a dilute bleach bath for 15 minutes twice weekly for approxi-

mately 3 months may be used for these patients.<sup>9</sup> Oral antimicrobial therapy is not routinely recommended for decolonization.

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