MAYO CLINIC

Hospitalist Perspective on the Treatment of Skin and Soft Tissue Infections

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Abstract

The prevalence of skin and soft tissue infections (SSTIs) has been increasing in the United States. These infections are associated with an increase in hospital admissions. Hospitalists play an increasingly important role in the management of these infections and need to use hospital resources efficiently and effectively. When available, observation units are useful for treating low-risk patients who do not require hospital admission. Imaging tools may help to exclude abscesses and necrotizing soft tissue infections; however, surgical exploration remains the principal means of diagnosing necrotizing soft tissue infections. The most common pathogens that cause SSTIs are streptococci and *Staphylococcus aureus*. Methicillin-resistant *S aureus* (MRSA) is a prevalent pathogen, and concerns are increasing regarding the unclear distinctions between community-acquired and hospital-acquired MRSA. Other less frequent pathogens that cause SSTIs include *Enterococcus* species, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa*. Cephalexin and clindamycin are suitable options for infections caused by streptococcal species and methicillin-susceptible *S aureus*. The increasing resistance of *S aureus* and *Streptococcus pyogenes* to erythromycin limits its use in these infections, and better alternatives are available. Parenteral cefazolin, nafcillin, or oxacillin can be used in hospitalized patients with nonpurulent cellulitis caused by streptococci and methicillin-susceptible *S aureus*. When oral MRSA therapy is indicated, clindamycin, doxycycline, trimethoprim-sulfamethoxazole, or linezolid is appropriate. Vancomycin, linezolid, daptomycin, tigecycline, telavancin, and ceftaroline fosamil are intravenous options that should be used in MRSA infections that require patient hospitalization. In the treatment of patients with SSTIs, hospitalists are at the forefront of providing proper patient care that reduces hospital costs, duration of therapy, and therapeutic failures. This review updates guidelines on the management of SSTIs with a focus on infections caused by *S aureus*, particularly MRSA, and outlines the role of the hospitalist in the effective management of SSTIs.

 ■ Mayo Clin Proc. 2014;89(10):1436-1451

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Skin and soft tissue infections (SSTIs) are common, encompassing a wide range of clinical presentations and definitions, and have increased significantly since the mid-1990s. Ambulatory visits for abscess and cellulitis have tripled from 1993 to 2005, with visits for all SSTIs reaching 14.2 million in 2005.[1,2] Using data from the Healthcare Cost and Utilization Project National Inpatient sample, Edelsberg et al[3] found a 29% increase in hospital admissions for SSTIs during a 5-year period (2000-2004). In a study that assessed the incremental clinical and economic burden of hospitalized patients with a secondary diagnosis of SSTIs compared with matched controls without SSTIs, patients with SSTIs had a mean of 3.8 additional days of hospitalization, $14,794 excess hospital charges, and an increased risk of mortality (odds ratio, 1.32).[4] The most common organisms that cause SSTIs are *Staphylococcus aureus* and *Streptococcus* species.[5,6] Methicillin-resistant *S aureus* (MRSA) is a predominant pathogen that causes SSTIs, is associated with increased length of hospitalization, and is an independent risk factor for increased mortality and hospital charges compared with methicillin-susceptible *S aureus* (MSSA).[7,8] The increasing incidence of SSTIs in both ambulatory and hospital settings, coupled with the increase of MRSA as a causative pathogen, demands optimal management of these infections to improve outcomes.

This review outlines the role of the hospitalist in the effective management of SSTIs, with a focus on infections caused by *S aureus*, particularly MRSA. A PubMed search was performed from 2000 to the present using the search terms *SSTI*, *MRSA*, *surveillance*, *resistance*, *clinical*

Mayo Clin Proc. ■ October 2014;89(10):1436-1451 ■ http://dx.doi.org/10.1016/j.mayocp.2014.04.018
www.mayoclinicproceedings.org ■

guidelines, *antimicrobials*, and *hospitalists* and supplemented with articles under "Related citations in PubMed." Studies were selected on the basis of clinical relevance, date published, comparative trials, and standards of practice. The term *SSTIs* is used throughout to refer to skin infections; however, terms specified in published studies or approved indications are retained when appropriate.

DIAGNOSIS AND MANAGEMENT

There are a variety of SSTIs, and differentiating infection type is important in selecting appropriate treatment (Table 1).[9-16] Abscesses are collections of pus within the dermis or deeper tissues, commonly treated with incision and drainage alone.[14] Systemic antibiotics may be required for abscesses accompanied by fever or extensive surrounding cellulitis. Cellulitis and erysipelas are diffuse spreading skin infections not associated with underlying suppurative foci. Erysipelas is differentiated from cellulitis by the depth of inflammation; erysipelas affects the upper dermis, including the superficial lymphatics, whereas cellulitis affects the deeper dermis and subcutaneous fat. Antibiotics with coverage for streptococci typically provide effective therapy for erysipelas. Antibiotics with *S aureus* coverage are appropriate when cellulitis is associated with an underlying abscess or penetrating trauma.[14] Surgical site infections should be suspected in patients with postoperative fever, particularly with onset more than 48 hours after surgery. The mainstay of therapy for surgical site infections is changing of wound dressings and surgical debridement. Adjunctive antibiotic therapy should not last long if adequate source control has been achieved. Necrotizing soft tissue infections (NSTIs) are rare (500-1500 cases in the United States each year) but lethal, involving any layer of the soft tissue compartment (eg, dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle).[14,17] When there is tense edema outside the area of compromised skin, pain disproportionate to appearance, ecchymosis, bullae, significant systemic toxic effects, or presence of crepitus and/or subcutaneous gas, NSTIs should be suspected.[17] Prompt diagnosis is needed to achieve successful outcomes; thus, hospitalists should seek surgical and infectious disease consultation when NSTIs are suspected. The mainstay of therapy for NSTIs is early and complete surgical debridement, combined with antimicrobial therapy, close monitoring, and physiologic support.[17,18]

Hospitalization should be considered for patients with cellulitis who present with fever, pain, advancing erythema, hemodynamic instability, and failure to respond to outpatient therapy.[18] Additional factors include a compromised immune system; comorbidities, such as peripheral vascular disease, diabetes mellitus, or chronic venous insufficiency; and abnormal laboratory values, including elevated creatinine or creatine kinase (CK) level, low serum bicarbonate level, or marked left shift.[14,18] Gram stain, antimicrobial susceptibility testing, and cultures for blood,

ARTICLE HIGHLIGHTS

- Skin and soft tissue infections (SSTIs) caused by methicillin-resistant *Staphylococcus aureus* are increasing in prevalence in hospitals in the United States. Hospitalists should carefully determine appropriate antimicrobial therapy for SSTIs on the basis of severity of illness, bacterial susceptibilities, risk of adverse effects, and local resistance patterns.
- Ultrasonography can be used as initial diagnostic imaging for suspected abscesses. Computed tomography can help to exclude necrotizing infections to avoid unnecessary surgical incision and debridement; however, surgical exploration may be necessary to confirm or exclude suspected necrotizing soft tissue infections.
- When available, observation units can be used for certain patients with SSTIs to identify patients suitable for hospital admission. Good candidates for observation therapy are those who are likely to respond to empiric therapy, are expected to require a short stay, and have a low probability of infection with resistant organisms.
- Hospitalized patients with complicated SSTIs should receive empiric therapy for methicillin-resistant *S aureus* with intravenous agents, such as vancomycin, linezolid, and daptomycin. Other options include clindamycin, tigecycline, and newer agents, such as ceftaroline fosamil and telavancin.
- Oral antimicrobial agents should be considered as initial therapy in less severe infections. Patients should be switched from intravenous to oral antimicrobial therapy when they are afebrile for 24 hours or longer, improving clinically, and able to take oral medications.

TABLE 1. SSTI Types and Management Recommendations With MRSA Considerations in Hospitalized Patients[a,9-16]

Type of SSTI	Management Recommendation
Abscess	
Cutaneous abscess	Incision and drainage
Abscess associated with severe or extensive disease, rapid progression with associated cellulitis, systemic signs and symptoms, comorbidities or immunosuppression, extremes of age, area that is difficult to drain, septic phlebitis, lack of response to incision and drainage	Incision and drainage and/or antibiotic therapy
Nonpurulent (no drainage or exudate) cellulitis in hospital setting	β-Lactam antibiotic may be considered with modification for agents against MRSA if no clinical response: IV penicillinase-resistant penicillins, including nafcillin or oxacillin 1-2 g every 4 hours; first-generation cephalosporins, including cefazolin 1 g IV every 8 hours
Complicated SSTI in hospital setting, including deeper soft tissue infections, surgical or traumatic wound infections, major abscesses, cellulitis, or infected ulcers and burns	Broad-spectrum antibiotics with coverage for MRSA pending culture data: vancomycin, 15-20 mg/kg every 8-12 hours[b]; linezolid, 600 mg twice daily (oral or IV); daptomycin, 4 mg/kg per dose IV once daily[b]; telavancin, 10 mg/kg per dose IV once daily[b]; clindamycin, 600 mg 3 times daily (oral or IV)[c]; tigecycline, initial dose of 100 mg IV followed by 50 mg every 12 hours IV[d]; ceftaroline fosamil, 600 mg IV every 12 hours[b,d]; surgical debridement; 7-14 days of therapy

[a]IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; SSTI = skin and soft tissue infection.
[b]Requires dose adjustment in renally impaired patients.
[c]Per prescribing information, clindamycin can be dosed up to 2700 mg/d IV in divided doses for severe infections. For oral dosing, although 300 to 450 mg every 6 hours is recommended for severe infections, higher doses may be needed for hospitalized patients.
[d]Not included in Infectious Diseases Society of America guidelines. Tigecycline is approved for MRSA complicated skin and skin structure infections. Ceftaroline fosamil is approved for MRSA acute bacterial skin and skin structure infections. Dosing is recommended from prescribing information.

needle aspirate, or punch biopsy specimens should be performed when feasible.[14] However, for cellulitis, aspiration of the skin is not helpful in 75% to 80% of cases,[14] less than 5% of blood culture results are positive,[19] and approximately 20% of cultures from biopsy specimens yield an organism.[20] Positive needle aspiration results can vary, depending on the patient population, inclusion criteria, and identification of organisms as pathogens or contaminants, limiting its diagnostic value.[14] In a systematic MEDLINE review published in 2010, 15.7% to 16.0% of 808 patients with cellulitis had positive needle aspiration and/or punch biopsy culture results from intact skin.[21] Infectious disease consultation should be considered for patients who have immunodeficiency or severe cellulitis or who do not respond to initial antibiotic regimens.[18]

Imaging

Diagnosis of an abscess is made on the basis of history, physical examination, and imaging. For diagnosing abscesses, ultrasonography is more sensitive (sensitivity, 96.7%; specificity, 85.7%) than computed tomography (CT) (sensitivity, 76.7%; specificity, 91.4%) and is favored as the initial diagnostic imaging test.[22] Bedside ultrasonography can be performed in the emergency department to improve diagnostic accuracy during clinical examination,[23,24] with the advantages of portability, immediate availability, low costs, and increased patient comfort compared with formal ultrasonography.[24] Computed tomography should be reserved for patients in whom the ultrasonographic images are unclear or the abscess extends into deeper tissue. Studies with 16- and 64-section CT in patients with suspected NSTI reveal that CTs may be sufficiently sensitive to exclude NSTIs and prevent unnecessary surgery; however, surgical exploration with small incisions remains the principal means of confirming or excluding NSTIs whenever there is a likelihood of these infections.[14,25] Although magnetic resonance imaging has been proposed to differentiate NSTIs from non-NSTIs, its high sensitivity and low specificity can result in overdiagnoses of NSTIs that may lead to unnecessary surgery.[26,27]

Causative Pathogens

Certain pathogens are associated with specific types of infections and should be considered along with patient characteristics and predisposing risk factors. *Streptococcus* species and *S aureus*

Mayo Clin Proc. ■ October 2014;89(10):1436-1451 ■ http://dx.doi.org/10.1016/j.mayocp.2014.04.018
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are the most common pathogens in SSTIs. *Streptococcus* species typically cause diffuse, nonpurulent cellulitis and erysipelas.[14] In a study of hospitalized patients with nonculturable cellulitis, acute and convalescent serologic tests for anti—streptolysin-O and anti—DNase-B antibodies along with blood cultures were used in determining β-hemolytic streptococci as the causative pathogen in 73% of this population.[5] *S aureus* is one of the most predominant organisms, causing 44.6% to 46.9% of SSTIs,[6,28] particularly cellulitis that is purulent and associated with abscesses.[9,14] Among *S aureus* isolated from SSTIs, MRSA prevalence is high (35.9%-56.8%).[6,28] In a 10-year study (1998-2007), abscess and wound isolates caused by MRSA increased nearly 8-fold (70.4%) and 4-fold (55.2%), respectively.[29] Ray et al[30] reported that the rate of MRSA stabilized or decreased slightly between 2005 and 2009; however, 80% of culture-positive skin infections were caused by *S aureus*, and half were due to MRSA. Findings of the Sentry Antimicrobial Monitoring program provide some insight into the occurrence rate of less common pathogens isolated from SSTIs during a 7-year period (1998-2004).[6] Occurrence rates of these pathogens include *Enterococcus* species (9.8%), *Pseudomonas aeruginosa* (8.2%), *Escherichia coli* (6.9%), *Enterobacter* species (4.1%), and *Klebsiella* species (4.0%).[6]

Most SSTIs are caused by gram-positive pathogens. Gram-negative organisms are more likely to be found in patients with compromised immune systems, diabetic foot infections (DFIs), NSTIs, or surgical site infections. Infected immunocompromised patients require broad-spectrum empiric coverage against resistant gram-positive organisms (eg, MRSA) and gram-negative organisms (eg, *Pseudomonas* species).[14] Many DFIs are polymicrobial, although when presenting acutely, most are caused by gram-positive cocci.[31] In diabetic patients with chronic infections or prior antibiotic therapy, aerobic gram-negative bacilli are often copathogens, and obligate anaerobes should be suspected in ischemic or necrotic wounds. In addition, NSTIs should always be suspected to be polymicrobial until proven otherwise in postsurgical patients and in patients with diabetes, peripheral vascular disease, decubitus ulcers, or spontaneous mucosal tears of the gastrointestinal or gastrourinary tract.[14] Treatment should include broad-spectrum antimicrobial coverage of gram-positive, gram-negative, and anaerobic organisms, including *Clostridium* species.[15] The NSTIs that are monomicrobial can be caused by *Streptococcus pyogenes*, *Vibrio vulnificus*, *Aeromonas hydrophilia,* anaerobic streptococci, or, occasionally, community-acquired MRSA (CA-MRSA).[14,32] Surgical site infections are usually caused by *S aureus* and streptococcal species, but those that involve colonic, vaginal, biliary, or respiratory mucosal tissues can have a combination of aerobic and anaerobic pathogens.[14]

Health Care—Associated Infections

Health care—associated infections are usually complicated skin and soft tissue infections (cSSTIs) and may increase the hospital length of stay and mortality compared with community-acquired infections.[33] Health care—associated risk factors include hospitalization within the previous year, antibiotic use within the previous 90 days, dialysis dependence, or transfer from a nursing home. Community-acquired cSSTIs are commonly caused by *S aureus*, and health care—associated cSSTIs are likely to be mixed infections that also include *Enterococcus* species and gram-negative organisms.[33] Mixed infections can increase mortality, length of stay, and hospital charges compared with gram-positive or gram-negative infections alone.[8]

Methicillin-Resistant *S aureus*

Initially, CA-MRSA was reported in specific populations (eg, intravenous [IV] drug users and athletes)[34,35] but currently is so common in the community that historically high-risk groups are no longer clinically useful. Epidemiologically, CA-MRSA infections occur in individuals in the outpatient setting or within 2 days of hospitalization and without the presence of health care—associated risk factors, whereas hospital-acquired MRSA is traditionally associated with recent hospitalization.[36,37] Typically, CA-MRSA is resistant to fewer classes of antibiotics and carries Panton-Valentine leukocidin genes, which lead to production of cytotoxins, causing necrosis and leukocyte destruction.[38,39] Despite these differences, the distinction between CA-MRSA and hospital-acquired MRSA is beginning to blur[40] as CA-MRSA is being transmitted in the health care setting.[41] In studies of bloodstream infections, the CA-MRSA USA300 genotype is a significant cause of nosocomial infections,[42]

resulting in similar risk factors and outcomes for these patients.[37] Current recommendations for the decision to treat empirically for MRSA in hospitalized patients are typically made on the basis of infection severity and progression.[9] Because empiric broad-spectrum antibiotics followed by deescalation is the standard of care for suspected serious MRSA infections,[9] there is a need for more accurate MRSA risk assessment models to tailor treatment appropriately. Zilberberg et al[43] developed a bedside risk prediction score model that used age, ethnicity, and comorbidities that more accurately identified patients with MRSA than screening with health care–associated risk factors, although both methods need improvement.

Where Should Patients Be Treated?

Observation units (OUs) are preferred places to assess and treat many patients with SSTIs.[44] Hospitalists can identify good candidates for OUs, such as those likely to respond to empiric therapy, those who require a short stay, or those who have a low probability of being infected with resistant organisms,[45] and reserve hospital resources for patients with cellulitis and tissue necrosis, severe pain, neck abscesses, or infections in specific locations (eg, periorbital, facial, and hand).[46,47] Patients in OUs who respond to therapy can be switched to home therapy within 24 hours. Those slow to respond should be evaluated for resistant pathogens or worsening infection and should be hospitalized if alternative therapy does not result in clinical improvement.[47] However, in some patients, cutaneous inflammation may worsen after initiation of effective therapy, most likely because of the release of potent enzymes caused by sudden pathogen destruction.[14] In retrospective studies of SSTIs, females and patients with fever, elevated lactate level, cellulitis of the hand, or leukocytosis (white blood cell count >15,000/μL[to convert to $\times 10^9$/L, multiply by 0.001]) were more likely to be hospitalized after being in an OU.[48,49] In these studies, 29% to 38% of patients were admitted to inpatient units after being in OUs. In addition, evidence-based decision support criteria, such as InterQual,[50] can help determine whether patients should remain in OUs or be hospitalized.

On October 1, 2013, the Centers for Medicare and Medicaid Services implemented requirements for hospital payment of inpatient services under Medicare Part A.[51] A physician order is required for inpatient admission on the basis of factors that include patient medical history and comorbidities, severity of signs and symptoms, and risk of adverse effects. As a guideline for when to admit patients, a proposal has been made that beneficiaries who require hospital services, including OU services,[52] for more than 1 Medicare utilization day (defined as care that spans 2 midnights) are appropriate for hospital admission with Medicare Part A payment.[51] Patient hospital services that span fewer than 2 midnights should be provided in the outpatient setting, unless the physician clearly documents expectations that the patient will require care that spans 2 midnights. With the implementation of this guidance, patients with SSTIs who improve quickly and do not require care that spans 2 midnights in the OU can continue treatment in the outpatient setting, whereas those who require care that spans more than 2 midnights may need to be admitted.

ANTIMICROBIAL THERAPY

Guideline Recommendations

Appropriate initial antibiotic therapy is essential in the treatment of SSTIs to improve outcomes (Table 1).[9,14,31,53] Inappropriate initial therapy increases patient morbidity, mortality, hospital length of stay, and total treatment costs.[54] Empiric therapy should be directed against likely pathogens.[53] Penicillin is the treatment of choice for erysipelas, and first-generation cephalosporins or penicillinase-resistant semisynthetic penicillins, such as dicloxacillin, can be used when MSSA is suspected.[14] Agents that target streptococci are suggested for nonpurulent cellulitis. If the cellulitis is purulent or results from penetrating trauma, agents with additional antistaphylococcal activity, such as cephalexin, the combination of trimethoprim and sulfamethoxazole, minocycline, doxycycline, clindamycin, or dicloxacillin, should be used. If anaerobes are suspected (eg, cellulitis due to deep penetrating trauma), the use of the combination of amoxicillin and clavulanate or other agents with anaerobic activity may be beneficial. Increasing resistance of *S aureus* and *S pyogenes* to erythromycin limits its use in these infections, and better alternatives are available.[55,56] Although empiric therapy for MRSA

Mayo Clin Proc. ■ October 2014;89(10):1436-1451 ■ http://dx.doi.org/10.1016/j.mayocp.2014.04.018
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has become standard in hospitalized patients for whom *S aureus* is a significant concern, MRSA is probably not a common cause of nonpurulent cellulitis. Therefore, in circumstances in which patients are hospitalized with nonpurulent cellulitis, IV penicillinase-resistant penicillins (eg, nafcillin and oxacillin) or first-generation cephalosporins (eg, cefazolin) may be considered, with modification for therapy against MRSA if there is no clinical response.[9,14] Clindamycin or vancomycin can be used as a substitute in the presence of life-threatening penicillin allergy.[14] Uncomplicated cutaneous abscesses can often be managed with incision and drainage alone.[9,53] Antibiotics are recommended for abscesses in patients with severe or extensive disease, signs and symptoms of systemic illness, extremes of age, associated septic phlebitis, comorbidities, or immunosuppression or abscesses in an area where drainage is difficult or ineffective.[9]

Treatment choice for surgical site infections depends on the infection location.[14] Clean wounds on the trunk, head, neck, or extremities usually respond to cefazolin, oxacillin, or clindamycin. Infections that result from surgery on the perineum, gastrointestinal tract, or female genital tract require a regimen that includes antianaerobic activity. The DFIs that present acutely generally respond to narrow-spectrum agents that cover aerobic gram-positive cocci.[31] Gram-negative coverage is needed for diabetic patients who received antibiotics within the past month or have severe or chronic infections.[31] Anaerobic coverage should be added in the setting of ischemic tissue and/or systemic toxic effects. The NSTIs require empiric gram-positive and gram-negative coverage with agents active against anaerobic pathogens (eg, piperacillin-tazobactam combination or a carbapenem).[17] Parenteral clindamycin should be added to inhibit toxin production and control inflammatory responses in severe group A streptococcal and clostridial infections.[14,17] Vancomycin, daptomycin, or linezolid should be included in these regimens until MRSA is ruled out.[15]

Consistent with epidemiologic data indicating a significantly increased incidence of MRSA in SSTIs from 2000 (34%) to 2006 (77%, $P<.001$),[57] use of initial antibiotics with MRSA activity has increased for hospitalized patients with cSSTIs from 30% in 2000 to 71% in 2009.[58] In particular, MRSA should be suspected in abscesses that do not respond to oral β-lactams after adequate drainage.[14] Oral anti-MRSA agents should be used as initial therapy in patients who do not require hospitalization. The CA-MRSA can be treated with non−β-lactam antibiotics, such as doxycycline or minocycline.[14] Trimethoprim-sulfamethoxazole can also be used to treat serious staphylococcal infections, including MRSA infections, although a single trial found it slightly less effective than vancomycin in this setting.[59] Because trimethoprim-sulfamethoxazole is not active against *S pyogenes*, additional agents may be needed if *S pyogenes* is suspected. Clindamycin is available IV and orally and has anti-MRSA activity but should be used with caution because of inducible or constitutive clindamycin resistance.[9] Patients hospitalized with cSSTIs should receive empiric therapy with IV broad-spectrum antibiotics with MRSA coverage and appropriate surgical debridement.[9] Empiric IV agents against MRSA include vancomycin, linezolid, daptomycin, and ceftaroline fosamil. Stepdown to oral therapy, such as tetracycline, linezolid, clindamycin, or trimethoprim-sulfamethoxazole, should be considered on the basis of susceptibility results and after initial clinical response.[14]

General guidelines for duration of therapy are recommended; however, given the considerable patient-to-patient variability in length of therapy for SSTIs, duration should be determined on the basis of clinical response. Patients treated for cellulitis in the outpatient setting should receive 5 to 10 days of therapy.[9] For hospitalized patients with cSSTIs, appropriate antimicrobial therapy of 7 to 14 days is suggested.[9] More complex infections, such as infections from hand wounds, can be complicated by nerve injury or fracture and often require prolonged courses of antimicrobial therapy for osteomyelitis (4-6 weeks) or synovitis (3-4 weeks).[14] For patients with uncomplicated orbital cellulitis, antibiotic therapy should be continued until all signs of orbital cellulitis have resolved and for a total of 2 or more to 3 weeks,[60] with a shorter course of therapy appropriate for preseptal cellulitis. In NSTIs, antimicrobial therapy must be continued until the patient is afebrile for 48 to 72 hours, has clear clinical improvement, and no longer requires repeated operative procedures.[14]

Treatment Failure

The rate of initial treatment failure is considerable for cSSTIs. In a study that reviewed data from more than 100 US hospitals, 16.6% of acute infections, 34.1% of chronic or ulcerative infections, and 26.7% of surgical site infections had initial treatment failure.[54] Failure to initiate antimicrobial therapy active against the causative pathogen within 48 hours of presentation is an independent risk factor for treatment failure.[61] Recently, the US Food and Drug Administration (FDA) revised its guidance for the evaluation of clinical response in skin infections to earlier time points of 48 to 72 hours after initiation of therapy,[62] which can be used to assess therapeutic failure. Patients whose conditions deteriorated despite empiric antibiotic therapy should be treated more aggressively on the basis of Gram stain, culture, and drug susceptibility.[14] Worsening of the SSTI may indicate the presence of resistant pathogens, and therapy should be reevaluated.[14] In hospitalized patients after initial treatment failure, MRSA should be considered and choice of agent should be made on the basis of susceptibilities. The need for source control, such as drainage or debridement, should also be carefully considered for patients not responding to antibiotic treatment.

Updates on MRSA Agents

A summary of IV and oral antimicrobial agents with activity against MRSA in SSTIs is provided in Table 2, and updates are discussed on the current and more recently approved agents since the release of the Infectious Diseases Society of America 2005 guidelines on the management and diagnosis of SSTIs.[9-12,14,63-73]

Vancomycin is effective and often used against MRSA cSSTIs in the hospital. Empiric therapy with vancomycin has increased from 2000 (18%) to 2006 (93%).[57] However, intrinsic characteristics of vancomycin that may limit its activity against MRSA, such as slow rates of bactericidal activity and poor penetration into tissues, should be considered.[74] The emergence of vancomycin-intermediate *S aureus* (VISA) and vancomycin-resistant *S aureus* has raised concerns regarding the use of vancomycin.[13] Although these strains are not common, prolonged exposure to vancomycin can increase the risk of infection with VISA or vancomycin-resistant *S aureus*.[75] Heteroresistant VISA has minimum inhibitory concentrations (MICs) within the intermediate range but reduced susceptibility.[76] Heteroresistant VISA can be inducible, potentially resulting in therapeutic failure with standard doses against strains with MICs of 0.5 to 2 μg/mL.[13,77] In 2006, after evaluating microbiological and clinical data indicating that *S aureus* isolates are less likely to respond when vancomycin MICs are 4 μg/mL or greater, the Clinical and Laboratory Standards Institute lowered susceptibility breakpoints from 4 to 2 μg/mL.[78] The clinical implications of a possible gradual increase in MICs within the susceptible range, also known as MIC creep, are not clear. Treatment failures have been reported with vancomycin-susceptible strains that have relatively high MICs,[79] and dose escalation to maintain trough levels of 15 to 20 μg/mL has been proposed to achieve therapeutic efficacy.[80] However, higher-dose regimens can increase the risk of nephrotoxicity,[81] which is associated with increasing trough levels (particularly >20 μg/mL), concomitant therapy with nephrotoxic agents, and longer durations of therapy, especially durations longer than 2 weeks.[80] Vancomycin doses of 15 to 20 mg/kg given every 8 to 12 hours are necessary for patients with normal renal function to achieve targeted serum trough levels when the MIC is 1 μg/mL or less.[13]

Linezolid, an oral and IV oxazolidinone, was approved by the FDA in 2000 for uncomplicated skin and skin structure infections and complicated skin and skin structure infections (cSSSIs).[65] Linezolid had comparable efficacy with vancomycin and oxacillin followed by dicloxacillin in pivotal trials, and linezolid can be used for the treatment of MRSA SSTIs.[82-84] Although generally well tolerated when used for a limited duration, linezolid is well known for its risk of causing reversible myelosuppression and serotonin syndrome. Complete blood cell counts should be monitored weekly to reduce the risk of myelosuppression,[65] which can often occur in patients treated for 2 weeks or longer.[65,85] Concurrent administration of linezolid and an SSRI taken in the preceding 5 weeks can precipitate a potentially life-threatening serotonin syndrome.[86] In addition, concerns about adverse events (AEs) with prolonged administration have emerged. In postmarketing surveillance studies, lactic acidosis and peripheral and optic neuropathy were

Mayo Clin Proc. ■ October 2014;89(10):1436-1451 ■ http://dx.doi.org/10.1016/j.mayocp.2014.04.018
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reported in patients receiving linezolid for durations that exceeded the recommended maximum of 28 days.[87] Because symptoms of lactic acidosis are nonspecific, monitoring of serum bicarbonate levels may be more useful for suspected lactic acidosis.[87]

Daptomycin, a lipopeptide with bactericidal activity, was approved by the FDA in 2003 for cSSSIs.[63] Daptomycin can be considered for MRSA skin infections, but hospitalists should be aware of potential adverse effects with daptomycin, specifically muscle toxic effects.[88] Daptomycin has been reported to elevate creatine kinase levels in up to 2.1% of patients,[88] which may be associated with myopathy and rhabdomyolysis. There is also a potential for cross-resistance of daptomycin with vancomycin, and susceptibility tests should be performed when feasible in the event of prior glycopeptide exposure.[71] Cell wall thickening in VISA strains is correlated with reduced susceptibility to both vancomycin and daptomycin[89]; thus, daptomycin may not be ideal to use against VISA after lack of efficacy with vancomycin. In 2010, the FDA released a safety announcement about daptomycin use and eosinophilic pneumonia, which can develop 2 to 4 weeks after initiation of therapy.[63,90] Patients receiving daptomycin should be monitored for new-onset or worsening fever, cough, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. If eosinophilic pneumonia is suspected, daptomycin therapy should be discontinued and systemic steroid therapy initiated.[63]

Tigecycline, a glycylcycline with activity against anaerobic, gram-negative, and gram-positive organisms, including MRSA, was approved by the FDA in 2005 for the treatment of cSSSIs.[11] It had efficacy similar to that of vancomycin plus aztreonam in 2 phase 3, double-blind pivotal studies in 1116 hospitalized adults with cSSSIs.[91] Tigecycline had a safety profile similar to that of vancomycin-aztreonam, but nausea and vomiting were more common (46% and 21%, respectively; $P<.001$). Recently, the FDA issued a boxed warning for increased all-cause mortality with tigecycline treatment when used in approved indications.[92] Analysis of 10 clinical trials revealed a higher risk of death among patients taking tigecycline (2.5%) compared with other antibiotics (1.8%; adjusted risk difference, 0.6%; 95% CI, 0.0%-1.2%). Tigecycline should be reserved for clinical situations in which alternative therapies are not available.[11]

Telavancin, a lipoglycopeptide approved by the FDA in 2009 for the treatment of gram-positive cSSSIs, had cure rates similar to vancomycin in 2 randomized, double-blind, phase 3 studies to assess its safety and efficacy in 928 patients with cSSSIs.[72] Cure rates for MRSA were also similar (telavancin, 91%; vancomycin, 86%). In a meta-analysis published in 2012 of 6 randomized controlled trials that compared telavancin and vancomycin in cSSTIs and hospital-acquired pneumonia,[93] telavancin had similar efficacy in treating cSSTIs (odds ratio, 1.10; 95% CI, 0.82-1.48), better clinical response, and higher eradication rates in MRSA infections. Telavancin was associated with clinically significant increases in serum creatinine levels compared with vancomycin (10% and 5%, respectively), higher rates of AEs, and AE-related withdrawals, with most withdrawals being related to nausea, vomiting, and renal AEs.[93] The FDA has issued a boxed warning regarding the use of telavancin in renally impaired patients after determining higher all-cause mortality for telavancin (39%) compared with vancomycin (30%).[12] Monitoring of renal function is recommended for all patients, and use should be considered only when the benefits of therapy outweigh the risks in patients with a baseline creatinine clearance of 50 mL/min/1.73 m^2 or less (to convert to mL/s/1.73 m^2, multiply by 0.0167).

Ceftaroline fosamil is the prodrug of ceftaroline, a cephalosporin that exhibits broad-spectrum bactericidal activity against gram-positive pathogens, including MRSA and multidrug-resistant *Streptococcus pneumoniae*, and gram-negative organisms. It was approved in 2010 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs).[10] Ceftaroline fosamil therapy resulted in similar clinical cure rates compared with vancomycin-aztreonam in 2 phase 3 clinical trials in patients with cSSSIs.[94] Ceftaroline fosamil was also as effective against MRSA cSSSIs (clinical cure rate, 93.4%) as vancomycin-aztreonam (94.3%). In 2012, a retrospective study was published on the results of an analysis of clinical response at earlier time points in a population of 400 patients who had ABSSSIs consistent with the definition provided by the FDA guidance for ABSSSI trials.[95] Clinical

TABLE 2. Summary of IV and Oral Antibiotics With Activity Against MRSA Skin Infections[a,10-12,63-65]

Agent	Advantages	Disadvantages	Dosing for Skin Infections	Adverse Events	Resistance
Oral agents					
Doxycycline[9,14]	Activity against gram-positive and gram-negative organisms	Pregnancy category D Tooth enamel discoloration in children younger than 8 years Data on use for MRSA infections are limited Not recommended for streptococcal infections	100 mg orally twice daily for 5-10 days in outpatient purulent cellulitis	Gastrointestinal intolerance, anorexia, rash	Tetracycline resistance and inducible doxycycline resistance have been reported
Trimethoprim-sulfamethoxazole[9,66]	95%-100% of CA-MRSA strains are susceptible in vitro Effective for purulent SSTI in children	Not FDA approved for any staphylococcal infections Pregnancy category D Contraindicated in patients younger than 2 months Not recommended for streptococcal infections	1-2 double-strength tablets orally twice daily for 5-10 days in outpatient purulent cellulitis	Gastrointestinal intolerance, anorexia, rash	Resistance in CA-MRSA isolates is low
Clindamycin[9]	Excellent penetration into abscesses Pregnancy category B IV formulation available	Not FDA approved for MRSA infections	300-450 mg orally 3 times per day for outpatient purulent cellulitis	Gastrointestinal intolerance (particularly *Clostridium difficile*—associated diarrhea), rash, pruritus	Inducible or constitutive resistance in 50% of MRSA isolates with clindamycin resistance
IV agents					
Vancomycin[9,67-71]	Vast clinical experience Inexpensive	Active against only gram-positive pathogens Only available in parenteral form Risk of nephrotoxicity Monitoring of blood levels required Slow bactericidal activity	15-20 mg/kg per dose every 8-12 hours, not to exceed 2 g per dose Adjust dosage for CrCL	Hypotension, gastrointestinal intolerance, stomatitis, chills, drug fever, rash, eosinophilia, reversible neutropenia	Possible MIC creep Vancomycin-intermediate and -resistant *Staphylococcus aureus* has been seen but remains uncommon
Linezolid[67,68,70,71]	Oral and IV formulations available	Active against only gram-positive pathogens Serious adverse effects, including bone marrow toxicity, serotonin syndrome, lactic acidosis, and peripheral neuropathy	600 mg IV or oral every 12 hours for 10-14 days in cSSSIs (adults and adolescents ≥12 years old) 400 mg orally every 12 h for 10-14 days for uSSSIs (adults) 600 mg orally every 12h for 10-14 days for uSSSIs (adolescents ≥12 years old)	Gastrointestinal intolerance, headache, insomnia, rash, dizziness, fever (in adults), reversible myelosuppression; optic neuritis and irreversible peripheral neuropathy have been reported in postmarketing surveillance reports	Resistance is uncommon but can be associated with drug target site mutation and chloramphenicol and florfenicol resistance

Continued on next page

TABLE 2. Continued

Agent	Advantages	Disadvantages	Dosing for Skin Infections	Adverse Events	Resistance
IV agents, continued					
Daptomycin[67,69-71]	Once-daily dosing Rapidly bactericidal	Active against only gram-positive pathogens Only available in parenteral form Serious adverse effects, such as eosinophilic pneumonia	4 mg/kg IV every 24 hours for 0.5 hour in 0.9% sodium chloride for 7-14 days in cSSSI Adjust dosage for CrCL	Gastrointestinal intolerance, headache, rash, abnormal liver function tests, pruritus, elevated CK level, urinary tract infection, hypotension, renal failure, dizziness, anemia, dyspnea	Cross-resistance with vancomycin seen Associated with sequential mutations and various changes in membrane structure and function
Tigecycline[70,71]	Activity against gram-positive and gram-negative organisms	Boxed warning for increased all-cause mortality Only available in parenteral form	100 mg IV, followed by 50 mg every 12 hours IV for approximately 30-60 minutes for 5-14 days Adjust for severe liver impairment	Gastrointestinal intolerance, headache, increased SGPT	Resistance in MRSA rarely described
Telavancin[71,72]	Once-daily dosing Bactericidal	Active against only gram-positive pathogens Only available in parenteral form May have higher risk of renal dysfunction compared with vancomycin	10 mg/kg IV every 24 hours infused for 1 hour for 7-14 days Adjust dosage for CrCL	Taste disturbance, gastrointestinal intolerance, foamy urine, dizziness, pruritus, rash, infusion-site pain, rigors, decreased appetite, infusion site erythema	Currently resistance in MRSA rarely described
Ceftaroline fosamil[73]	First cephalosporin with activity against MRSA Activity against gram-positive and gram-negative organisms Generally well tolerated Bactericidal	Only available in parenteral form	600 mg IV every 12 hours infused for 1 hour for 5-14 days in ABSSSIs Adjust dosage for CrCL	Gastrointestinal intolerance, increased levels of transaminases, hypokalemia, rash, phlebitis	Low potential for developing ceftaroline resistance in vitro

[a]ABSSSI = acute bacterial skin and skin structure infection; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus;* CK = creatine kinase; CrCL = creatinine clearance; cSSSI = complicated skin and skin structure infection; FDA = Food and Drug Administration; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; SGPT = serum glutamic pyruvate transaminase; SSTI = skin and soft tissue infection; uSSSI = uncomplicated skin and skin structure infection.

response at 48 to 72 hours was 74.0% (296 of 400 patients) for patients taking ceftaroline fosamil and 66.2% (263 of 397 patients) for patients taking vancomycin-aztreonam (difference, 7.8%; 95% CI, 1.3-14.0). In pivotal trials, ceftaroline fosamil was well tolerated and had a safety profile consistent with the cephalosporin class of antibiotics.[94] The most common treatment-emergent AEs were nausea (5.9%), headache (5.2%), diarrhea (4.9%), and pruritus (3.5%).[96]

New IV drugs are in development for MRSA ABSSSIs. The FDA has recently accepted the new drug application with priority review for the new oxazolidinone tedizolid.[97] Tedizolid was reported to be statistically noninferior to linezolid in patients with ABSSSIs at early clinical response evaluated 48 to 72 hours after initiating therapy.[98] Dalbavancin and oritavancin have the potential to be dosed less frequently. Dalbavancin has a prolonged half-life of 6 to 10 days and can potentially be administered as 2 doses 1 week apart.[99] It is currently being studied in phase 3 trials for the treatment of ABSSSIs.[100] Another lipoglycopeptide, oritavancin, is being investigated for ABSSSIs and has the potential to be used as single-dose therapy. The SOLO II trial (Oritavancin Versus IV Vancomycin for the Treatment of Patients With Acute Bacterial Skin and Skin Structure Infection) evaluated oritavancin efficacy in patients with ABSSSIs and recently released results reporting similar efficacy between the single-dose oritavancin regimen and twice-daily vancomycin at early clinical and end-of-therapy time points.[101]

Multidisciplinary Management and Transitions in Care

A multidisciplinary team approach may improve management of SSTIs in some instances, such as in DFIs. In the management of DFIs, hospitalists will often optimally serve as key members of a team that includes surgeons who perform debridement and revascularization procedures and wound care specialists who perform pressure off-loading and special dressing techniques.[31] Antimicrobial stewardship teams with members from infectious disease, clinical pharmacy, clinical microbiology, infection control, and hospital epidemiology can collaborate to ensure proper antibiotic use and reduce antimicrobial resistance and cost.[102]

There are several improvements that hospitalists can implement at key transition points to enhance patient care and outcomes while reducing hospital costs. Appropriately identifying patients for outpatient therapy or observation is vital to reserving hospital resources for more severely infected patients.[102] Patients with cellulitis who have no uncontrolled comorbidities or systemic signs and symptoms of infection can usually be treated as outpatients with oral or topical antimicrobials.[45] Good candidates for observation should also be identified, as previously discussed, to prevent unnecessary hospital admission.[45] Timely consultation with the primary care physician, specialized physicians, and social services is required for successfully treating and discharging patients from the OU, especially when observing the new guidance of care that spans 2 midnights. Those who are afebrile with stabilized vital signs, comorbidities, and nonprogressive infection and who require daily IV therapy but do not need 24-hour acute care nursing are candidates for outpatient parenteral antimicrobial therapy.[103,104] Outpatient parenteral antimicrobial therapy is an important consideration for patients because it can improve patients' quality of life, reduce readmission, decrease risk of nosocomial complications, reduce costs, and help patients transition to care outside the hospital.[104,105]

Once a patient is admitted, hospitalists play a key role in optimizing length of stay by determining appropriate antimicrobial regimens and evaluating the need for surgical intervention. After antibiotic treatment has been initiated, it is imperative that hospitalists assess antimicrobial therapy when available culture results return, usually within 48 hours.[106] The need for antibiotics and the effectiveness of the specific regimen should be evaluated at this time with the additional microbiologic, radiologic, and clinical information that has become available since the patient was admitted. If continued antimicrobial treatment is warranted, hospitalists should try to narrow therapy and identify opportunities for switching to outpatient parenteral antimicrobial therapy or oral therapy and determine a final duration of therapy.[106] Infectious disease specialists can be consulted on optimal empiric and deescalation therapy on the basis of susceptibility results[102] and provide recommendations for the transition to outpatient parenteral antimicrobial

Mayo Clin Proc. ■ October 2014;89(10):1436-1451 ■ http://dx.doi.org/10.1016/j.mayocp.2014.04.018
www.mayoclinicproceedings.org

therapy or oral therapy. A switch to oral therapy is recommended for patients with no fever for 24 hours or more, a normalizing white blood cell count, no unexplained tachycardia, and the ability to take oral medications.[107-109] Once oral therapy is initiated, patient discharge should be planned. Typically, patients who are afebrile for 48 hours, can tolerate a normal diet, require IV access only for glycopeptides, and are physically independent for outpatient care are ready for discharge from the hospital.[107] Using these criteria in a prospective study of 211 patients, Desai et al[107] found that 62 patients (29%) fulfilled both IV to oral switch and discharge criteria while they were receiving an IV glycopeptide. An estimated 649 inpatient days were saved with an appropriate IV to oral antibiotic switch and then discharge.[107] Although these are the conventional criteria for discharge, it may be possible to discharge patients even earlier. One study reported favorable outcomes when patients were discharged while still febrile early in their clinical course, before clinical improvement of all signs of infection.[109] Patients who were discharged early did not have an increased rate of readmission to the hospital and had increased patient satisfaction compared with a matched case-control study of 112 patients discharged with conventional methods.

Hospitalists' commitment to patient care requires working with the case management team to ensure proper transition of care. Table 3 provides a checklist of important factors to consider.[31,45] Discontinuity in the process of transition can result in patient harm.[104] Although medication reconciliation is routine practice for patient discharge, 1 study reported that 23% of patients experience AEs at discharge that are often drug related.[110] Hospitalists must work with the hospital pharmacy team to resolve discrepancies between hospital and home medication lists. Hospitalists also have the responsibility of sending accurate and timely discharge summaries to patients' primary care physicians. In a survey of 4000 physicians, only 20% reported that they were always notified about discharges.[111] Communication with the primary care physician should include the diagnoses, medications, procedure results, pending tests, follow-up appointments, and recommended next steps.[112] Home health or skilled nursing facility services should be considered for patients who qualify so that an excessive responsibility for providing proper care does not fall on the family.[104] Prevention of readmission is an important goal, and a variety of interventions and strategies must be implemented to have an effect on readmission. Use of a readmission prediction model can assist in determining patients who are less likely to be rehospitalized if discharged and help target transitional care for these patients.[113] More important, well-organized discharge planning and appropriate follow-up are required to improve patient communication and reduce the rate of readmission. Often there are delays between patient discharge and the patient's next appointment with the primary care physician.[112] As a result, before hospital discharge, patients must be educated about how to take their new medication and assess their own progress. This situation emphasizes the importance of patient education and arrangement of discharge counseling. Counseling should include diagnosis, medication instruction or changes, follow-up appointments, self-care instructions, and an appropriate contact for concerns and questions.[112] Follow-up evaluations with a hospitalist instead of a primary care physician can maintain continuity of care and reduce the likelihood of readmission in the first 30 days after discharge.[114] Several studies have found reduced rehospitalization rates when health care professionals, such as advanced practice nurses, are designated to coordinate patient education, assess patient adherence, and schedule discharge follow-up appointments.[115-117]

TABLE 3. Hospital Discharge Checklist for Patients With Acute Bacterial Skin and Skin Structure Infection[31,45]

Discharge Checklist
Review results of blood cultures and other tests
Switch to oral therapy or plan for outpatient parenteral antibiotic therapy
Plan for length of antibiotic therapy after discharge
All comorbidities stable
Appropriate follow-up arranged
Wound care education
Glycemic control in patients with diabetes
Safe environment for continued care
Home care evaluation when appropriate

CONCLUSION

The prevalence of SSTIs, including those caused by MRSA, is increasing in both ambulatory care and hospital settings. Hospitalists play a key role in providing care for patients with SSTIs by

selecting appropriate initial empiric therapy and obtaining timely surgical consultation when appropriate. Antimicrobial treatment choices and duration of therapy should be individualized on the basis of patient risk factors and response to therapy. The use of OUs, drug susceptibility tests, decision support criteria, and imaging techniques can be integrated for more effective diagnosis and management of SSTIs. Hospitalists play an integral part in efficiently using hospital resources to manage SSTIs and improve patient outcomes while reducing therapeutic failures.

ACKNOWLEDGMENTS

Scientific Therapeutics Information Inc provided editorial assistance on the manuscript.

Abbreviations and Acronyms: **ABSSSI** = acute bacterial skin and skin structure infection; **AE** = adverse event; **CA-MRSA** = community-acquired methicillin-resistant *Staphylococcus aureus*; **cSSSI** = complicated skin and skin structure infection; **cSSTI** = complicated skin and soft tissue infection; **CT** = computed tomography; **DFI** = diabetic foot infection; **FDA** = Food and Drug Administration; **IV** = intravenous; **MIC** = minimum inhibitory concentration; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **MSSA** = methicillin-susceptible *Staphylococcus aureus*; **NSTI** = necrotizing soft tissue infection; **OU** = observation unit; **SSTI** = skin and soft tissue infection; **VISA** = vancomycin-intermediate *Staphylococcus aureus*

Grant support: Funding for editorial assistance was provided by Forest Research Institute Inc.

Potential competing interests: Dr Amin serves on the Speakers' Bureau, served as a consultant, and received research and grant funding from Forest Research Institute Inc. Drs Cerceo, Deitelzweig, Rosenberg, and Sherman have served as consultants for Forest Research Institute Inc.

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