This supplement was supported by an independent educational grant from Paratek Pharmaceuticals, Inc. It was edited and peer reviewed by *The Journal of Family Practice*.

SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE®

VOL 71, NO 1 | JANUARY/FEBRUARY 2022 | MDEDGE.COM/FAMILYMEDICINE

EXPERT UPDATE ON ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION TREATMENT OPTIONS IN THE COMMUNITY SETTING

Preface: This article is based on a video presentation given by George Sakoulas, MD, and a panel of experts, which is housed here: https://www.medscape.org/viewarticle/959655. His presentation was adapted for print publication and peer reviewed by The Journal of Family Practice.

Expert Update on Acute Bacterial Skin and Skin Structure Infection Treatment Options in the Community Setting

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doi: 10.12788/jfp.0344

CONTINUING MEDICAL EDUCATION

GOAL STATEMENT

The goal of this activity is to improve healthcare providers' knowledge on the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) in the outpatient setting as well as how to best incorporate novel antimicrobials into patient care plans.

LEARNING OBJECTIVES

After participating in the activity, healthcare providers will:

Have increased knowledge regarding the

- Identification of patients who can be treated for ABSSSI in the outpatient setting
- Latest data on new oral antibiotics used in the treatment of ABSSSI

Have greater competence related to

- Determining a patient care strategy for ABSSSI in the community

TARGET AUDIENCE

This activity is intended for primary care physicians, infectious disease specialists, emergency medicine physicians, nurses, nurse practitioners, and physician assistants.

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- Grants for clinical research from: Octapharma
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INTRODUCTION

Skin and soft tissue infections (SSTIs) are heterogeneous and potentially life-threatening infections that involve the skin and underlying subcutaneous tissue, fascia, or muscle. A major source of morbidity and healthcare resource consumption in both the community and hospital settings, SSTIs are estimated to result in more than 800,000 hospitalizations annually in the United States.[1,2]

Commonly encountered in a wide range of healthcare settings, SSTIs are frequently seen in patients presenting to the emergency department (ED) and subsequently responsible for an increasing number of hospital admissions. The incidence of hospitalizations due to SSTIs has doubled between 1998 and 2013, with the cost increasing by 118% during this time period.[3] Treating patients in the outpatient setting is an alternative option for clinically stable patients, as it not only can reduce costs, but research shows that patient preference is to be treated outside of the hospital, or to finish treatment at home as soon as it is feasible.[4]

What is the difference between ABSSSI and SSTI?

SSTI is a broad clinically functional term that is subcategorized by the Infectious Disease Society of America (IDSA) as either nonpurulent (including cellulitis, erysipelas, and necrotizing infection) or purulent (including furuncle, carbuncle, and abscess).[5] Abscess, cellulitis, and infections of surgical or traumatic wounds are the most common.

ABSSSI defines a specific set of SSTIs used by the US Food and Drug Administration since 2013 for evaluating new SSTI antimicrobials.[6] Lesions ≥ 75 cm^2 consisting of either abscess with or without cellulitis, or cellulitis, or wound infection are included, with each antimicrobial study approximating 50% cellulitis and about 25% each of wound infections and abscess.

THE BURDEN OF ABSSSIs (OR SSTIs) TO PATIENTS AND THE HEALTHCARE SYSTEM

The 3 most common infection types requiring medical treatment are respiratory infections, SSTIs, and urinary tract infections.[7] While all infections carry a higher risk in older patients due to the presence of immunocompromising comorbidities and immunological senescence that accompanies age > 60 years, SSTIs carry considerable morbidity even in younger patient populations. Physicians see patients with necrotizing fasciitis and other severe SSTIs in younger patients who are otherwise healthy. However, younger patients with occupational and parental responsibilities are burdened by SSTIs in ways that cannot be quantified financially. SSTIs may be particularly disruptive if they require prolonged hospitalization. Therefore, creative ways to provide streamlined care of SSTIs is of great importance.

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TABLE 1. **Eron Classification System for Patients With SSTIs**[14]

Class	Patient Criteria
1	Afebrile and healthy, other than cellulitis
2	Febrile and ill appearing, but no unstable comorbidities
3	Toxic appearance, or at least one unstable comorbidity, or a limb-threatening infection
4	Sepsis syndrome or life-threatening infection

Patients with SSTIs exert a burden on hospital resources through ED visits, urgent care visits, and office visits.[8] Healthcare systems worldwide have been stretched thin over the past year and a half by the COVID-19 pandemic. Therefore, anything that can be done to lessen the healthcare burden of SSTIs while the COVID-19 pandemic rages on is highly desirable. Interestingly enough, during the COVID-19 pandemic, there seemed to be a reduction in SSTIs. This may be because of increased hand hygiene and social distancing practiced to reduce COVID-19.[9,10]

What organisms typically cause these infections?

ABSSSIs in a generally healthy population are typically caused by Gram-positive pathogens, the most common being *Staphylococcus aureus* and beta-hemolytic streptococci.[11] In nonpurulent infections, it is typically caused by beta-hemolytic streptococci, and usually by *Streptococcus pyogenes* (also known as group A *Streptococcus*).[12] This is the same organism that causes recurrent tonsillitis and "strep throat." Infections by *Streptococcus agalactiae* (group B *Streptococcus*) are more common in patients with certain chronic medical conditions such as diabetes, cirrhosis, and malignancy.[13] Purulent SSTIs are most commonly caused by *Staphylococcus aureus*, including both methicillin susceptible strains and methicillin resistant strains in about a 50-50 mix.[11] Patients with immunocompromising comorbidities can have infections with Gram-negative pathogens and even anaerobes.[8] Most commonly, these include *Escherichia coli* and other Enterobacterales. Prior antibiotic exposure and exposure to water raises the possibility of *Pseudomonas spp*.[14]

Can your patient with an ABSSSI (or SSTI) be treated in the community or outpatient setting?

The Eron classification is a very simple method of stratifying patients according to severity and determining their management setting (outpatient vs inpatient).[15] It uses a 1-to-4 scale that looks at a combination of illness severity and stability of underlying comorbidities.[15]

For example, a class 1 infection might be a patient who has simple localized symptoms with no comorbidities and no systemic symptoms. In this situation, generally, outpatient oral therapy would be most appropriate.

Patients with systemic symptoms or unstable comorbidities would be considered class 2. An example of a class 2 case would be a patient with a localized SSTI with diabetes or peripheral vascular disease. For this patient group, there may be a need to escalate to parenteral therapy or to oral therapy beyond the first line options to make sure that there is good oral bioavailability and reliable bacterial coverage.

Class 3 patients with a combination of unstable comorbidities and systemic symptoms usually warrant hospital admission for parenteral antibiotics. Class 4 patients are those with fulminant infection who have unstable vital signs and may be in need of surgical debridement (eg, necrotizing fasciitis). They may be hospitalized in an intensive care unit (ICU) setting.

But while classes 1 and 2 are treated in the outpatient setting, there is a considerable patient population (think of it as a "class 2.5" in-between group) where one might consider a newer antibiotic that might be more reliable in terms of broader spectrum of activity, or even one where a single intravenous (IV) dose provides a full course of treatment.[16]

EXPLORING THE OUTPATIENT TREATMENT OPTIONS: CONSIDERATIONS TO KEEP IN MIND

A class 1 purulent infection is typically caused by *S aureus*, and because clinicians are not likely to have a culture available at that moment, it's best to assume that it's methicillin-resistant *Staphylococcus aureus* (MRSA). The treatment of choice has to have reliable MRSA coverage.[5] In my practice, a first choice is clindamycin. This can also depend on one's geographic location, as there are some areas where MRSA resistance to clindamycin in the community is high. Trimethoprim/sulfamethoxazole (TMP-SMX) is another antimicrobial agent that is widely used.[17] However, this may not be best for older patients due to an increased risk of severe adverse reactions (eg, hyperkalemia with concomitant use of ACE inhibitor or angiotension receptor blocker, Stevens-Johnson syndrome, neutropenia).

The tetracyclines are a third option, and minocycline and doxycycline are very good choices when there is a purulent cellulitis, although they are not as reliable as clindamycin for strep infections. If one is caring for a

patient with nonpurulent cellulitis, clindamycin again becomes an option and you can also consider cephalexin since nonpurulent cellulitis is likely streptococcal.[5]

A LOOK AT NEWER AGENTS AND WHAT ADVANTAGES THEY OFFER

New agents for ABSSSIs (or SSTIs) offer advantages of activity against MRSA, are available in IV and oral formulations, and can potentially facilitate earlier hospital discharge.[16] These agents also offer an opportunity to simplify treatment in community or outpatient settings as they are oral or long-acting, single dose IV formulations.[16] All of them have been shown to be noninferior to their comparator drugs in randomized controlled trials, and additionally, newer agents offer MRSA coverage, as well as a broader spectrum of activity for ABSSSIs compared to some of the older agents in their classes.[18-22] But as with any new agent, the implications of broad-spectrum antibiotic usage and the development of drug resistance remains unknown.

While mortality among patients with ABSSSIs is relatively low, it represents a significant burden on the healthcare system. The use of newer antimicrobial therapies and their simplified dosing regimens (whether it is a once daily oral dose or a one-time single infusion) can potentially improve the efficiency of healthcare in patients with ABSSSIs by helping stable patients in the community or

TABLE 2. **Agents Approved for the Treatment of ABSSSIs in the Outpatient or Community Setting**

Drug	Class	Spectrum of activity (in ABSSSI)	Dose/Route of administration[a]	Common adverse reactions[b]
Common Oral Antibiotics for the Treatment of ABSSSIs in the Community Setting (Approved Prior to 2014)[5,16,23]				
Amoxicillin-clavulanate[24]	Penicillin	MSSA, *E coli,* and *Klebsiella* spp	PO: 875/125 mg twice daily Treatment duration: up to 14 days	Diarrhea, nausea, vomiting, mucocutaneous candidiasis
Cephalexin[25]	Cephalosporin	MSSA, *S pyogenes*	PO: 250 mg to 500 mg four times daily Treatment duration: 5 to 14 days	Diarrhea, nausea, vomiting, dyspepsia and abdominal pain
Clindamycin[26]	Lincosamide	*S aureus* (including MSSA and MRSA), *S pyogenes*	PO: 300 mg 4 times daily or 450 mg 3 times daily Treatment duration: 5 to 14 days	Nausea, vomiting, diarrhea Boxed Warning: *Clostridium difficile* associated diarrhea
Dicloxacillin[27]	Penicillin	MSSA, *S pyogenes*	PO: 250 to 500 mg four times daily Treatment duration: 5 to 14 days	Diarrhea, impetigo, nausea, vomiting
Doxycycline[28]	Tetracycline	*S aureus* (including MSSA and MRSA)	PO: 100 mg twice daily Treatment duration: 5 to 14 days	Headache, myalgia, photosensitivity
Linezolid[29]	Oxazolidinone	*S aureus* (including MSSA and MRSA), *S pyogenes*, *S agalactiae*	PO: 600 mg twice daily Treatment duration: 5 to 14 days	Diarrhea, headache, nausea, vomiting, anemia
Minocycline[30]	Tetracycline	*S aureus* (including MSSA and MRSA)	PO: 100 mg twice daily Treatment duration: 5 to 14 days	Dizziness, fatigue, myalgia, photosensitivity
TMP-SMX[31]	Folate synthesis inhibitor	*S aureus* (including MSSA and MRSA)	PO: 1 to 2 double strength tablets twice daily Treatment duration: 5 to 14 days	Anorexia, nausea, vomiting, rash, urticaria

CONTINUED

TABLE 2. **Agents Approved for the Treatment of ABSSSIs in the Outpatient or Community Setting (*cont'd*)**

Drug	Class	Spectrum of activity (in ABSSSI)	Dose/Route of administration[a]	Common adverse reactions[b]
New Antibiotics Approved for the Treatment of ABSSSIs in the Outpatient or Community Setting				
Dalbavancin[32] (Approval: 2014)	Lipoglycopeptide	*S aureus* (including MSSA and MRSA), *S pyogenes*, *S agalactiae*, *S dysgalactiae*, *S anginosus* group, *E faecalis*	Single dose IV: 1500 mg over 30 minutes 2-dose IV: 1000 mg followed 1 week later by 500 mg	Nausea, headache, diarrhea
Oritavancin[33,34] (Approval: 2014)	Lipoglycopeptide	*S aureus* (including MSSA and MRSA), *S pyogenes*, *S agalactiae*, *S dysgalactiae*, *S anginosus* group, *E faecalis*	Single dose IV: 1200 mg once over 1 hour[33] Single dose IV: 1200 mg once over 3 hours[34]	Headache, nausea, vomiting, limb and subcutaneous abscesses, diarrhea
Tedizolid[35] (Approval: 2014)	Oxazolidinone	*S aureus* (including MSSA and MRSA), *S pyogenes*, *S agalactiae*, *S anginosus* group, *E faecalis*	IV: 200 mg once daily over 1 hour, OR PO: 200 mg once daily, OR IV to PO switch (Dosing conversions are 1:1 between IV and PO based on its high oral bioavailability of 91%) Treatment duration: 6 days	Nausea, headache, diarrhea, infusion- or injection-related adverse reactions, vomiting, dizziness
Delafloxacin[36] (Approval: 2017)	Fluoroquinolone	*S aureus* (including MSSA and MRSA), *S haemolyticus*, *S lugdunensis*, *S agalactiae*, *S anginosus* group, *S pyogenes*, *E faecalis*, *E coli*, *Enterobacter cloacae*, *K pneumoniae*, *Pseudomonas aeruginosa*	IV: 300 mg over 1 hour, every 12 hours OR PO: 450 mg every 12 hours OR IV to PO switch Treatment duration: 5 to 14 days	Nausea, diarrhea, headache, transaminase elevations, vomiting Boxed Warning: Serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, CNS effects, exacerbation of myasthenia gravis
Omadacycline[37] (Approval: 2018)	Tetracycline	*S aureus* (MSSA and MRSA), *S lugdunensis*, *S pyogenes*, *S anginosus* group, *E faecalis*, *E cloacae*, *K pneumoniae*	IV: 200 mg once or 100 mg twice on day 1 then 100 mg daily, OR PO: 450 mg once a day on day 1 and 2; then 300 mg once daily, OR IV to PO switch Treatment duration: 7 to 14 days	Nausea, vomiting, infusion site reactions, ALT increased, AST increased, GGT increased, hypertension, headache, diarrhea, insomnia, constipation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; GGT, gamma-glutamyl transferase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PO, oral administration.

[a]Treatment duration is often determined on a case by case basis.

[b]This is not a complete list of adverse effects.

outpatient setting to avoid costly hospitalization, facilitate early hospital discharge, lower rates of hospital readmissions, and improve treatment compliance.[16] Real world analyses of some of these newer agents have also shown reduced hospital length of stay, improved patient productivity, and reduced direct costs per patient.[38-41] The cost of some of these agents may be higher up-front, but at the end of the day, the overall cost may be cheaper than a 5-to-6-day hospitalization to receive IV antimicrobial treatment. As an example, in a retrospective cohort study, patients with ABSSSIs treated with dalbavancin had reduced total direct costs per patient compared to those receiving standard of care ($2758 vs $4010, respectively, $P = .105$).[41] These cost savings were ascribed mainly to reduced hospital stay.

WHAT ABOUT ANTIBIOTIC STEWARDSHIP? HOW THE NEWER DRUGS FIT IN

Now, for most clinicians, antimicrobial stewardship means that you want to use the narrowest spectrum antibiotic for the shortest duration to get the job done and treat the patient successfully. In many hospitals, antimicrobial stewardship has taken on a largely financial tone, which may supersede clinical and microbiological concerns. With that in mind, some of the new drugs have been described as not being good for antimicrobial "financial" stewardship. Some of these newer antibiotics that are focused exclusively on Gram-positive spectrum of coverage (eg, linezolid; tedizolid) actually provide a narrower spectrum than some of the less expensive older ones (eg, minocycline; doxycycline; TMP-SMX). This is particularly true for IV antibiotics used in SSTI treatment in the hospital (eg, ceftaroline vs piperacillin/tazobactam).[42,43]

FINAL THOUGHTS

Microbiologically speaking, these decisions are pretty simple, but considering a patient's personal situation is important (eg, their occupation, can they take time off from work and for how long). Also, consider how much or little room there is for error (eg, not covering the pathogen—either due to illness severity or poor patient reserve). Along with guidance from the 2014 IDSA practice guidelines for the management of ABSSSIs, we need to use the best tools that are available to us for any given situation and there are plenty of tools to choose from now, not only from the old generics, but also the newer antibiotics, some of which have been out for several years with considerable real-world experience. ●

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