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# Acute bacterial skin and soft tissue infections: new drugs in ID armamentarium

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**ABSTRACT**

Acute bacterial skin and soft tissue infections (SSTI) are among the most common reasons for hospitalization of adults in the USA today. Cellulitis or SSTI can cause significant morbidity and mortality. The 2014 IDSA guideline update for the management of skin and soft tissue infections classified skin infections as purulent cellulitis (causative pathogen – Staphylococcus aureus including MRSA) and nonpurulent cellulitis (causative pathogens include Streptococcus). Understanding the key difference and categorization will allow a physician to determine the appropriate treatment approach and antibiotic choice. In recent years, there have been several new antibiotics which received fast track approval by FDA as a Qualified Infectious Disease Product (QIDP) for the indication of SSTI. They Include Ceftaroline (Teflaro), Dalbavancin (Dalvance), Oritavancin (orbativ), Tedizolid (Sevixtro), Delafloxacin (Baxdela) and Omadacycline (Nuzyra). This article will briefly review each of these new antibiotics and summarize their roles in avoiding hospital admissions and reducing the duration of stay in patients with SSTI.

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Acute bacterial skin and soft tissue infections (SSTI) are among the most common reasons for hospitalization of adults in the USA today. Cellulitis or SSTI can cause significant morbidity and mortality. The 2014 IDSA guideline update for the management of skin and soft tissue infections classified Skin infections as purulent cellulitis (causative pathogens – Staphylococcus aureus) and nonpurulent cellulitis (causative pathogens include Streptococcus) [1]. The guidelines further subclassified these infections into mild, moderate and severe to help guide antibiotic choices. Mild and moderate infections are usually self-limited. However, severe purulent infections include patients who have failed incision and drainage plus oral antibiotics OR those with systemic signs of infection such as temperature >38°C, tachycardia (heart rate >90 beats per minute), tachypnea (respiratory rate >24 breaths per minute) or abnormal white blood cell count (>12 000 or <400 cells/μL), OR immunocompromised patients. Many of these patients could have osteoarticular involvement. These patients will need expert consultation. Understanding the key difference and categorization will allow a physician to determine the appropriate treatment approach and antibiotic choice.

The usual oral antimicrobial choices for treatment of SSTI include either penicillins, cephalosporins, clindamycin, trimethoprim-sulfamethoxazole, doxycycline or linezolid. The parenteral treatments include vancomycin, daptomycin, telavancin. In recent years, there have been several new antibiotics which received fast track approval by FDA as a Qualified Infectious Disease Product (QIDP) for the indication of SSTI [2]. They Include Ceftaroline (Teflaro), Dalbavancin (Dalvance), Oritavancin (orbativ), Tedizolid (Sevixtro), Delafloxacin (Baxdela) and Omadacycline (Nuzyra). This article will briefly review each of these new antibiotics and summarize their roles in avoiding hospital admissions and reducing the duration of stay in patients with SSTI.

Ceftaroline (Teflaro) – Allergan Pharmaceuticals. FDA approved in October 2010 [3], [4].

Ceftaroline is a novel fifth-generation cephalosporin. It is unique among FDA-approved cephalosporins in having good activity against MRSA. It also has good activity against MSSA, streptococci, including *Streptococcus pyogenes* and multidrug-resistant *Streptococcus pneumoniae*. However, it lacks good activity against enterococci. Newer studies indicate a role in patients with MRSA bacteremia. It is available as an IV formulation, administered twice a day for normal creatinine clearance. It is an alternative to vancomycin in patients needing MRSA coverage for SSTI. Ceftaroline has a side-effect profile similar to those of other cephalosporins.

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**Table 1.** Overview of newer antibiotics with activity against MRSA.

| | Ceftaroline | Dalbavancin | Oritavancin | Delafloxacin | Omadacycline | Tedizolid |
|---|---|---|---|---|---|---|
| Brand name | Teflaro | Dalvance | Orbativ | Baxdela | Nuzyra | Sevixtro |
| Generic available | No | No | No | No | No | No |
| Antibiotic class | Cephalosporin | Lipoglycopeptide | Lipoglycopeptide | Quinolone | Tetracycline | Oxalizolidine |
| FDA approval | 2010 | 2014 | 2014 | 2017 | 2018 | 2014 |
| Type of activity | Bactericidal | Bactericidal | Bactericidal | Bactericidal | Bacteriostatic | Bacteriostatic |
| Mechanism of action | Inhibition of cell wall synthesis by binding to penicillin-binding proteins (PBPs) | Interferes with the carboxyl terminal D-alanyl-D-alanine residue terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. | 1. Inhibits transglycosylation (polymerization) by binding to stem peptides of peptidoglycan precursors;<br>2. Inhibits cell wall transpeptidation (crosslinking) by binding to the peptide bridging segments of the cell wall;<br>3. Disruption of bacterial cell membrane integrity, leading to depolarization, permeabilization, and cell death. | 1. Inhibits the activity of bacterial DNA topoisomerase IV and DNA gyrase (topoisomerase II) 2. In contrast to other quinolones, delafloxacin is anionic leading to increased accumulation in bacteria allowing for enhanced bactericidal activity. | Inhibition of the 30S ribosomal subunit, which blocks bacterial protein synthesis. Active against bacteria expressing tetracycline resistance via efflux pumps tetK and tetL, as well as ribosomal protection protein tetM. | Binding to the 50S ribosomal subunit in bacteria, which inhibits protein synthesis. |
| Half life | 2h 36m | 14 | 10 | About 8 hours | 17–21hours | 10h |
| FDA approval for SSTI | Yes | Yes | Yes | Yes | Yes | Yes |
| FDA approval for other indications | CABP | | | | CABP | |
| Streptococcal coverage | Yes | Yes | Yes | Yes | Yes | Yes |
| Staphylococcal coverage | Yes | Yes | Yes | Yes | Yes | Yes |
| VISA/VRSA coverage | | Yes | | | | |
| Gram negative coverage | No | No | No | Yes(Antipseudomonal) | Yes(Acinetobacter, Stenotrophomonas) | No |
| Formulation | IV | IV | IV | IV/PO | IV/PO | IV/PO |
| Advantages | Used in patients with complicated SSTI w bacteremia. | One dose, minimal drug drug interactions, can be administered in ER in 30 minutes w potential for discharge from ER if close followup at PCP or ID office can be established. | One dose, can be used in pts w renal impairment.Potential for use in patients with osteomyelitis. | Potential single oral option for polymicrobial diabetic foot infections and osteoarticular infection due to good anaerobic and gram negative coverage. | Potential step-down therapy for polymicrobial infections. | Once daily oxalizolidine. Minimal interaction with SSRI/SNRI. Activity against VRE |
| Adverse effects | Neutropenia, Rash. | Infusion reactions, red man syndrome. | Infusion reactions, red man syndrome. | Clostridium difficile-associated diarrhea, tendonitis and tendon rupture, QTc prolongation and torsades de pointes, central nervous system effects, dysglycemia, and photosensitivity. | nausea, vomiting, infusion reactions, AST/ALT increase, hypertension, headache, constipation, diarrhea, and insomnia. | headache, thrombocytopenia (low platelets), peripheral neuropathy, paresthesia, and visual impairment. |

CABP – Community-Acquired Bacterial Pneumonia; SSTI – Skin and soft tissue infection.

Ceftaroline is used off-label for the treatment of other severe infections, e.g., endocarditis or osteomyelitis. Neutropenia is a possible adverse effect with prolonged usage.

Dalbavancin (Dalvance) – Allergan Pharmaceuticals. FDA approved in May 2014 [5,6].

Dalbavancin is a novel lipoglycopeptide antibiotic similar to vancomycin. Its primary mechanism of action is inhibition of cell wall peptidoglycan cross-linking and hence could be bactericidal. The drug has a long plasma half-life of 8 – 14 days. This allows for a single-dose regimen of 1500 mg administered intravenously. The duration of infusion should be over 30 min. The spectrum of coverage includes susceptible isolates of the following gram-positive microorganisms: *S. aureus* (including MRSA and methicillin-susceptible *S. aureus*, or MSSA), *Streptococcus pyogenes, S. agalactiae* and *S. anginosus* group. Renal impairment with creatinine clearance below 30 will need a dose adjustment.

Oritavancin (Orbativ) – Melinta Pharmaceuticals. FDA approved in August 2014 [7]

Oritavancin is also a lipoglycopeptide antibiotic. This antibiotic has multiple mechanisms of action including inhibiting peptidoglycan cell wall synthesis and disrupting the bacterial cell membrane, leading to cell death and hence has bactericidal activity. Oritavancin is active against common gram-positive pathogens including methicillin-resistant *Staphylococcus aureus*, MSSA and strep species. The drug is administered as a single intravenous dose of 1200 mg over 3 h in adult patients, and because of its terminal half-life of 393 h, repeat dosing is not required in the treatment of SSTIs. There is a very slow elimination from tissue sites, and no dosing adjustments are required for renal or hepatic insufficiency. Two clinical trials (SOLO 1 and 2) have demonstrated noninferiority compared with vancomycin in the treatment of SSTIs [8,9]. Side effects are similar to vancomycin and include liver enzyme elevation occasionally.

Dalbavancin and Oritavancin are attractive antibiotics to consider in the outpatient arena due to their long half-life and one-time dosing strategy conferring ideal administration in the ambulatory setting and emergency room to facilitate ED discharges avoiding admissions for appropriate patients with uncomplicated cellulitis if close followup with Primary care physician or the Infectious Diseases service could be established [10]. They are also good antibiotics to consider at discharge for patients with SSTI who failed oral antibiotics. The infusion does not require a peripherally inserted central catheter and has no need to maintain vascular access for daily administrations of antibiotic therapy. These factors will enhance compliance as well as limit noninfectious complications of long-term intravenous catheter use especially in people who inject drugs (PWID) [11]. In contrast to vancomycin, no monitoring of blood concentrations is required with either antibiotic. In addition, there is no need to use an oral agent to complete a course of therapy due to the long duration of activity. Finally, adherence to multiple-dose regimens would be eliminated by a single-dose parenteral agent. The use of Dalbavancin and Oritavancin for treatment of SSTIs can reduce costs associated with outpatient infusion services and home care, as well as improve patient satisfaction, but the acquisition cost of these antibiotics may limit its use. In addition, we need to be mindful that these drugs to date have not been thoroughly assessed in serious infections including bacteremia or bone and joint infections. Curbside or official consultation with Infectious Diseases specialists is recommended while prescribing these antibiotics.

Tedizolid (Sevixtro) Merck FDA approved in June 2014 [12]

Second-generation oxazolidinone with activity against Gram-positive bacteria, including MRSA isolates resistant to linezolid and VRE. Tedizolid is available in intravenous and oral formulations and has high oral bioavailability. The most common adverse effects in clinical trials were nausea, headache, diarrhea, and vomiting. Interactions with SSRIs are less likely. Tedizolid may be less likely than linezolid to cause optic and peripheral neuropathy and may have a lower potential for the development of myelosuppression/thrombocytopenia. It appears to offer advantages over linezolid with respect to side effects and drug interactions. In addition, the cost of tedizolid is somewhat less than that of linezolid and considerably less than that of dalbavancin.

Delafloxacin (Baxdela) Melinta pharm. FDA approved in June 2017 [13]

New-generation anionic quinolone with spectrum of activity against various gram-positive and gram-negative pathogens, including *Staphylococcus aureus* (methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] strains), *S. haemolyticus, S. lugdunensis, Streptococcus pyogenes, S. agalactiae, S. anginosus* group, *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae*, and *Pseudomonas aeruginosa*. Baxdela exerts antibacterial activity through inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes. The drug is available in both IV and oral formulations and has 60% oral bioavailability. No dose adjustments are needed for body weight, hepatic impairment, or mild-to-moderate renal impairment. It can be used as a step-down therapy at discharge. The gram-negative and anti-pseudomonal coverage makes it attractive as a single agent option for diabetic foot and other poly-microbial infections. FDA black box warnings for quinolone apply to Delafloxacin with adverse effects including *C. difficile* infection, tendon

rupture, QT prolongation, and effects on glucose homeostasis [14–16]. However, most common side effects include nausea, vomiting and diarrhea.

Omadacycline (Nuzyra) FDA approved in Oct 2018 [17]

Omadacycline is a new-generation tetracycline for treatment of SSTI. It overcomes common tetracycline resistance mechanisms, including efflux and ribosomal protection. It exhibits excellent in vitro activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, vancomycin-susceptible and vancomycin-resistant enterococci, and beta-hemolytic streptococci. It is dosed once daily in both oral and intravenous forms. Nuzyra offers clinicians the ability to treat patients with the IV and transition them home to complete treatment with the oral formulation.

## Conclusion

There are newer antimicrobial options to treat acute bacterial skin and soft tissue infections caused by MRSA. Awareness of their mechanisms of action, pharmacokinetic/pharmacodynamic properties including bioavailability and their role in the treatment of various patient populations and treatment settings is vital to optimize care for these infections.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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