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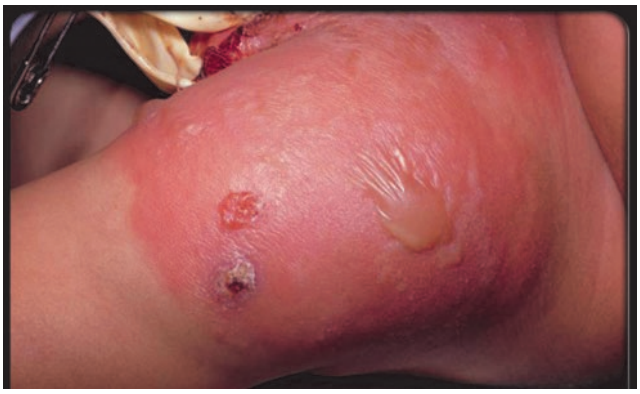
Review of Cellulitis Treatment Recommendations

Bella Mogaka, PharmD Candidate; Marcus Campbell PharmD, BC-ADM

Cellulitis is defined as an infection of the skin and soft tissue beneath the skin. The infection is usually due to bacteria that are commonly present on the skin or inner surface of the nose or mouth of otherwise normal and healthy people, most commonly staphylococci or streptococci. Cellulitis develops when there is a break in the skin such as a wound or injury, which may be minor or even go unnoticed. This break allows bacteria to pass through the outer layer of the skin and multiply, causing infection and swelling. Many cases of cellulitis are mild and heal completely with antibiotic treatment. However, some can be severe and lead to generalized infection. Thus, it is imperative to seek medical care promptly if the infection is associated with fever, rapid spreading and other signs of progression, or other medical conditions such as diabetes are present.[1]

Table 1: Risk factors for developing cellulitis

Recent injury to the skin (a wound, abrasion, cut, shaving, or injection drug use)
The presence of a fungal or viral skin infection such as athlete's foot or chicken pox
Accumulation of fluid (edema) due to poor circulation, heart failure, liver disease or past surgery to remove lymph nodes
Chronic skin conditions such as eczema
Obesity
Prior radiation therapy
Weakened immune system from conditions such as diabetes, leukemia, HIV/AIDS or medications such as corticosteroids or TNF-α inhibitor



Certain conditions increase the risk for developing cellulitis (Table 1), but it can occur in patients without known risk factors.[1] The onset of cellulitis may be gradual or sudden. The most common symptom of cellulitis is pain or tenderness. Other cellulitis symptoms include swelling, warmth, redness in a distinct area of skin, and red streaking with associated lymphadenopathy along the lymphatic pathways. Symptoms commonly worsen and the redness may expand over the course of hours or days. Itching is not a typical symptom of cellulitis. The skin is usually smooth and shiny rather than raised and bumpy. Occasionally in cases of cellulitis, blisters or small pimples form on the skin. The most common areas of the body for cellulitis to develop include the legs and the arms.[1]

Blood cultures and cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy undergoing chemotherapy, neutropenia, severe immunodeficiency, immersion injuries, and animal bites.

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Review of Cellulitis Treatment Recommendations (continued)

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Appropriate treatment of cellulitis involves selecting antibiotic therapy based on a patient's symptoms and risk factors (Table 2). Patients that do not have systemic inflammatory response syndrome (SIRS), altered mental status, or hemodynamic instability can generally be treated on an outpatient basis. Poorly adherent or severely immuno-compromised patients and those that have deep or necrotizing infections should be hospitalized and treated with IV antibiotics. In conjunction with antibiotic therapy, antiinflammatory treatment with systemic corticosteroids or ibuprofen has demonstrated more rapid clinical resolution of cellulitis and may be considered in non-diabetic adults as long as deeper infections are not present (i.e., necrotizing fasciitis). The duration of antibiotic therapy for uncomplicated cellulitis is usually 5 days but may be longer if the infection is slow to resolve. It is recommended that the affected area be elevated during treatment. It is also important to treat underlying contributing conditions such as tinea pedis, venous eczema, etc.

<Click for references>

Table 2: Selection of antibiotic therapy[2]

Without systemic signs of infection (typical, uncomplicated, mild non-purulent cellulitis)	Should receive an antibiotic active against streptococci	1. monotherapy of oral beta-lactams (penicillin, amoxicillin, amoxicillin clavulanate, dicloxacillin, cephalexin) 2. oral clindamycin monotherapy
With systemic signs of infection (moderate non-purulent)	• Intravenous antibiotics indicated • Consider an antibiotic with methicillin-susceptible *S. aureus* (MSSA) coverage	1. penicillin (no MSSA coverage) 2. nafcillin, oxacillin, dicloxacillin 3. cefazolin, cephalexin 4. clindamycin 5. doxycycline, minocycline 6. sulfamethoxazole/trimethoprim
Cellulitis associated with: • Penetrating trauma • Evidence of MRSA (methicillin-resistant S. aureus) including nasal colonization • Intravenous drug use • Purulent discharge • SIRS	Antibiotic selection should provide coverage of MRSA and streptococci	**Intravenous route** vancomycin, daptomycin, linezolid, tedizolid or telavancin **Oral Route** clindamycin (monotherapy) sulfamethoxazole/trimethoprim + beta-lactam doxycycline + beta lactam
Severely immunocompromised patients	Broad-spectrum antibiotics should be considered	1. vancomycin + piperacillin/tazobactam 2. vancomycin + imipenem or meropenem
Recurrent cellulitis	• Identification and treatment of underlying conditions such as edema, obesity, venous insufficiency, etc. • Antibiotic prophylaxis: consider in patients who have had 3-4 episodes of cellulitis per year despite management of predisposing factors. Long-term prophylaxis considered if underlying conditions are chronic/persistent	Oral penicillin or erythromycin twice daily for 4-52 weeks Intramuscular benzathine penicillin every 2-4 weeks (preferred if patient has no identifiable predisposing factors)

New Antibiotics for Severe Soft Tissue Infections

Diviya Patel, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

According to the 2013 Centers for Disease Control and Prevention (CDC) report, more than 2 million people each year become infected with bacteria that are resistant to antibiotics. As a result, about 23,000 people die from these infections.[1] Bacterial drug resistance has rapidly spread in hospitals and communities worldwide, and the development of new antibiotics has faced a sharp downward trend since the early 1980s and is now minimal (Figure 1). Over the past year, the FDA has approved 3 new antibiotics to treat patients with acute bacterial skin and skin structure infections caused by gram-positive bacteria including methicillin-resistant staphylococcus aureus (MRSA). Dalbavancin, tedizolid, and oritavancin have been approved as a result of the Qualified Infectious Disease Product (QIDP) under the GAIN Act. To encourage research and development, this legislation, signed into law by President Barack Obama on July 9, 2012, gave manufacturers an additional 5 years of exclusive rights where antibiotics can be sold without generic competition.

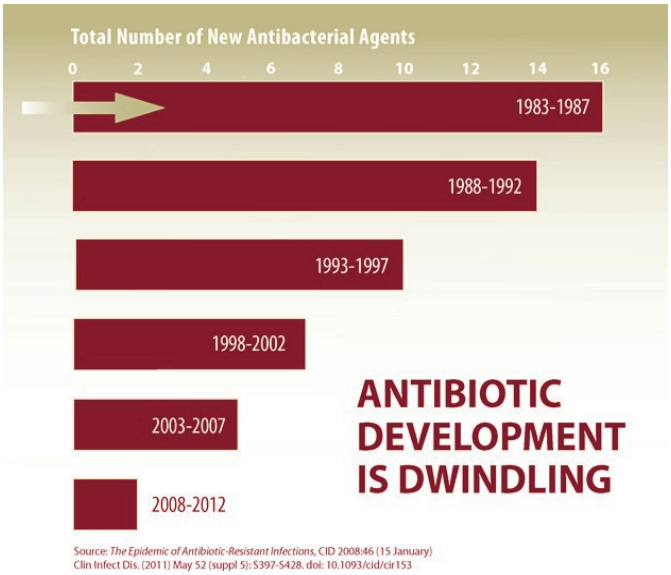

Figure 1: Total number of antibacterial agents approved by the FDA per time frame

Dalbavancin (Dalvance®)

Dalbavancin, developed by Durata Pharmaceuticals, is a lipoglycopeptide antibiotic. On May 23, 2014, the FDA approved dalbavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Dalbavancin provides coverage for gram-positive microorganisms, is administered intravenously (IV), and dosed 1000 mg IV x 1, then 500 mg IV 1 week later. Discover 1 and Discover 2 were identically designed randomized trials that demonstrated noninferiority of dalbavancin compared to vancomycin or linezolid for the treatment of ABSSSI. Approximately 1,300 patients were included in both studies. The primary end point was an early clinical response, defined as no spread of erythema and afebrile at 48-72 hours. For patients infected with methicillin -resistant staphylococcus aureus, clinical success was relatively high in both the dalbavancin (97.3%) and vancomycin-linezolid (98.0%) groups. Adverse events were less common in the dalbavancin group (32.8%) compared to the vancomycin-linezolid group (37.9%). The most reported adverse effects for both groups were constipation nausea, diarrhea, and pruritus.[2]

Microscopic view of staphylococcus aureus

Tedizolid (Sivextro®)

Tedizolid, developed by Cubist Pharmaceuticals, is an oxazolidinone-class antibiotic. The FDA approved tedizolid for the treatment of ABSSSI in adults on June 20, 2014. This mechanism of action involves binding to the 50S subunit of the bacterial ribosome inhibiting protein synthesis. Tedizolid is available as both IV and tablet formulations, and it has been shown to have activity against gram-positive aerobic and anaerobic bacteria. A randomized, double blind, phase-3 study demonstrated non -inferiority of once daily tedizolid compared to twice daily linezolid. 666 patients were included in the study, and the primary end-point was early clinical response 48-72 hours after start of treatment defined as ≥20% reduction in lesion area compared with baseline. The recommended duration of therapy for tedizolid is 6 days compared to 10-14 days with linezolid. The treatment-emergent adverse events were

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New Antibiotics for Severe Soft Tissue Infections (Continued)

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similar between study groups; however, nausea, diarrhea, and vomiting were less common in the tedizolid group.[3]

Oritavancin (Nuvocid®)

On August 6, 2014, the FDA approved oritavancin for the treatment of ABSSSI in adults. Oritavancin, developed by Targanta Therapeutics, is a lipoglycopeptide antibiotic that has bactericidal activity against gram-positive bacteria. Oritavancin is concentration dependent and has a longer half-life compared to dalbavancin. Oritavancin is administrated intravenously and is dosed 1200 mg IV x 1 dose. A randomized, double blind, phase-3 trial in approximately 900 patients, showed oritavancin was noninferior to vancomycin. The primary end point was no growth or reduction in the size of the baseline lesion, absence of fever, and the absence of a need for a rescue antibiotic 48-72 hours after receiving oritavancin. Efficacy of oritavancin was measured by type of pathogen, including MRSA infection and was similar in both treatment groups. Overall adverse effects for oritavancin (7.4%) and vancomycin (7.3%) were similar. However, nausea was more common with oritavancin (11%) than with vancomycin (8.9%).[4]

Managing the treatment of ABSSSI can be a difficult challenge for healthcare professionals and hospitals. The approval of new antibiotics provides additional options. Recent changes in legislation aim to open up avenues for drug manufactures to research and invest in the development of novel antibiotics to keep pace with emergence, persistence and spread of resistant bacteria in healthcare settings worldwide.

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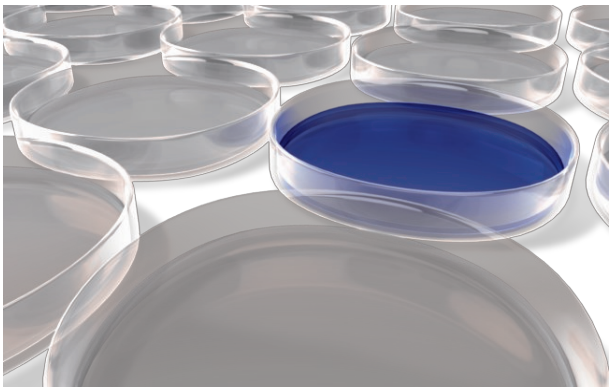

Two New Topical Antifungals for Onychomycosis

Nga Lam, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

Onychomycosis is a fungal infection of the toenails or fingernails. It is characterized by thickening of the nail, discoloring, shaping distortion, and detaching of nail plate from the nail bed. Onychomycosis is relatively common and accounts for approximately 35 million cases in the United States.[1] The major cause of onychomycosis is a dermatophyte, mostly *Trichophyton rubrum*. Other causes could be due to yeasts and non-dermatophyte molds.[2] Onychomycosis poses challenges in treatment due to a high rate of recurrence and the difficulty of achieving adequate drug penetration to affected sites. Without treatment, onychomycosis can lead to pain and discomfort while walking or wearing shoes, and it can spread to other regions of the body including feet, hands, and groin. Available treatment for onychomycosis are topical ciclopirox, oral griseofulvin, oral itraconazole and oral terbinafine. Oral antifungals are a mainstay of treatment due to the ability to penetrate the nail bed and the nail plate. However, some disadvantages that limit the use of oral therapy in patients include drug interactions and risk of liver injury.[3]

In 2014, the United States Food and Drug Administration (FDA) approved two new topical antifungal drugs, Jublia® (efinaconazole 10%) and Kerydin® (tavaborole 5%), for the treatment of nail fungus caused by *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Efinaconazole is the first approved topical triazole, and tavaborole is the first approved oxobarole antifungals for this indication. However, they have two different mechanisms of action in treating nail fungus. Efinaconazole inhibits fungal lanosterol 14-alpha-demethylase involved in the biosynthesis of ergosterol.[4] Tavaborole inhibits protein synthesis by inhibition of aminoacyl-transfer ribonucleic acid (tRNA) synthetase.[5] Neither treatment requires nail debridement for drug penetration. Patient cost should be considered; a single 4ml vial of efinaconazole and 10 ml vial of tavaborole cost about $463 and $1240 respectively.[6,7]

Efinaconazole and tavaborole were both evaluated in clinical trials utilizing "complete cure" as the primary endpoint.

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Two New Topical Antifungals for Onychomycosis (Continued)

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Complete cure was defined as no clinical onychomycosis plus as negative results on both fungal culture and potassium hydroxide (KOH) test. The efficacy and safety of efinaconazole was studied in two multi-center, randomized, and double blinded trials, which included a total of 1651 patients. Trial 1 had 870 patients and trial 2 had 781 patients. Included, patients were aged 18 to 70 years with 20-50% clinical involvement of toenail distal subungual onychomycosis (DLSO). Patients were randomly assigned to self-apply either efinaconazole or placebo once daily for 48 weeks. The primary endpoint was assessed at week 52, 4 weeks after completing the course of treatment. In trial 1, 17.8% of patients receiving efinaconazole and 3.3% of patients receiving the placebo achieved complete cure (P< 0.001). In trial 2, patient treated with efinaconazole achieved a higher cure rate of 15.2% versus 5.5% in placebo (P <0.001). Efinaconazole was well tolerated, with the most common side effects including ingrown toe nail, application site vesicles, pain and dermatitis. [3]

The effectiveness of tavaborole was also evaluated in two multi-center, double blinded, randomized, and placebo-controlled trials. A total of 1195 patients aged 18 to 88 years with 20% to 60% clinical involvement of the target toenail fungus were recruited in the studies. Patients were randomly assigned to self-apply either tavaborole or placebo once daily for 48 weeks. The results were evaluated at week 52. For the patients treated with tavaborole, 6.5% in trial 1 and 9.1% in trial 2 reached primary endpoints comparing with 0.5% and 1.5%, respectively, for patients treated with the placebo. Tavaborole had mild side effects, such as ingrown toe nail, skin peeling, redness, itching, and swelling at the treated site.[5]

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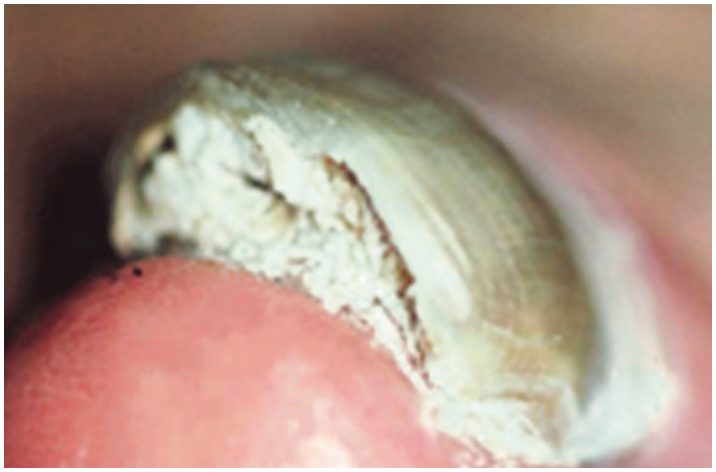

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