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The Omnicare HealthLine

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## Inside This Issue



**Unless there is a critical need to initiate treatment, it is prudent to wait until samples for C&S are obtained before initiating empiric therapy.**

# Focus on Treatment of Osteomyelitis

*- By Carrie Allen*

Osteomyelitis (OM) is an infection within the bone. The prevalence of OM is relatively low in the general population. However, long term care residents have risk factors that may predispose them to OM. These infections are hard to treat, and they have an inflammatory component that results in destruction of bone matter and joint tissues; thereby placing an already vulnerable population at risk for immobility, decreased function, and increased mortality. It is important for caregivers to be aware of the risk factors for OM (Figure 1), as well as signs and symptoms that may indicate a resident should be evaluated to determine if OM is present (Figure 2).

**Figure 1: Common Risk Factors for Osteomyelitis**

Advanced age
Diabetes and diabetic complications (e.g., diabetic foot infection)
Hemodialysis
Immunosuppression
Infections in natural or artificial joints
Intravenous drug abuse
Peripheral arterial disease/peripheral vascular disease
Renal and/or liver insufficiency
Sickle cell disease
Surgery
Systemic infections
Trauma (e.g., puncture wound, open fracture)

**Figure 2: Common Signs and Symptoms of Osteomyelitis**

| | | |
|---|---|---|
| Pain and/or tenderness in the infected area, often exacerbated by movement | Swelling and warmth in the infected area | Fever, nausea, excessive sweating, or chills |
| Feelings of general discomfort, uneasiness, illness | Drainage of pus through the skin | Lower back pain (in osteomyelitis of the vertebrae) |
| Swelling of the ankles, feet, and legs | Changes in gait (e.g., walking pattern indicates pain) | Rash and articular symptoms in *N. gonococcal* infections |

OM may be acute or chronic (months to years), and can be the result of a reactivation of a dormant infection that has been sequestered within the bone. OM can occur when bacteria (or mycobacteria, or fungi) from a primary infection in another area of the body travel through the blood and infect the bone, such as from: the genitourinary or respiratory tract, skin or soft tissue, intravenous or urinary catheters, endocarditis, or dental infections. Alternatively, OM can be acquired through contiguous spread of an infection that is in direct contact with the bone below it [e.g., diabetic foot ulcers, other pressure injuries (ulcers)]. In adults, the vertebrae and the pelvis are more commonly infected than the long bones (e.g., femur, tibia); though infection of the long bones can occur, particularly after surgery, trauma or systemic infection. The most common pathogen involved in OM is *Staphylococcus aureus* (both methicillin-sensitive and methicillin-resistant) followed by Gram negative rods. Infection with >1 organism is more likely when infection is contiguous in nature. Though rare, fungal infections can occur. These are more common in certain areas of the country (e.g., coccidioidomycosis in desert climates) or when a patient is immunosuppressed (e.g., HIV/AIDS). Antifungal drugs are required for several months; side effects and drug-drug interactions can make management of fungal OM particularly difficult.

Depending on the severity and presentation of illness, OM may be diagnosed using a combination of the following tests:

- Blood Tests: culture and sensitivity (C&S), complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP); these tests are also often used to monitor the effectiveness of treatment
- Needle aspiration: samples from bony area(s) and/or vertebral space (if the spine is involved), bone biopsy; bone cultures are particularly critical if blood cultures are negative
- Radiography: X-ray, MRI, computed tomography (CT), and/or bone scans (choice often based on the location and acuity of infection)

The goals of OM treatment are to:

- Cure the infection (acute and chronic)
- Prevent acute progression to a chronic infection
- Prevent damage to the bone, and preserve function

Treatment is often a multimodal process that can include a combination of:

- Drainage of wounds or abcesses – ongoing wound care is crucial to promote healing
- Surgery to debride affected bone (e.g., infected, damaged, necrotic) and minimize dead space through grafts, flaps, or use of antibiotic impregnated beads
- Immobilization of bone and nearby joints in cases where movement may cause trauma or complications
- Medications (see page 3) – unless there is a critical need to intitiate treatment, it is prudent to wait until samples for C&S are obtained before initiating empiric therapy. For contiguous infection in diabetic patients with vascular insufficiency – it is imperative to obtain cultures prior to initiation of empiric therapy unless the patient is acutely ill.

Unfortunately, there are cases where cure of OM is not possible. For example, when an infection has become chronic and persists despite antimicrobial therapy, and/or the patient is not a candidate for surgery. In these cases, long-term suppressive therapy with an antimicrobial agent (6-12 months or longer) is prescribed. In rare cases, amputation of the affected area may be required.

**Prolonged treatment with antimicrobial agents increases the risk for *Clostridium difficile* infection (i.e., diarrhea). It is important to monitor for signs/symptoms of *Clostridium difficile* during antimicrobial treatment and for 2-3 weeks thereafter. However, laboratory monitoring for presence of *Clostridium difficile* is not recommended unless signs/symptoms of infection have manifested.**

## Osteomyelitis: Common Causes and Treatments

**Empiric therapy for acute bacterial infections** - typically consists of Vancomycin for Gram positive coverage plus Ciprofloxacin, Ceftazidime, or Cefepime to cover Gram negative organisms and *Pseudomonas* (dosing below)

| Bacterial Pathogen | Medication* | Monitoring |
|---|---|---|
| **Methicillin-sensitive *Staphylococcus aureus* (MSSA)** | Nafcillin or Oxacillin 1-2 gm IV Q 4-6 H<br>***or***<br>Cefazolin 1-2 gm IV Q 8 H | • Routine (usually weekly) monitoring of: CBC, electrolytes, ESR, CRP, antibiotic serum concentrations (if indicated by therapy)<br>• Ongoing clinical assessment of progress is recommended; bone abscesses may recur weeks, months, or even years after treatment |
| **Methicillin-resistant *Staphylococcus aureus* (MRSA)** | Vancomycin 15-20 mg/kg IV Q 8-24 H*º<br>***or***<br>Linezolid[Ω] 600 mg IV or PO Q 12 H<br>***or***<br>Daptomycin 6 mg/kg IV Q 24 H | |
| **Mixed Gram positive and Gram negative infection (e.g., post-operative or trauma)** | Ceftazidime 2 gm IV Q 8 H<br>***or***<br>Piperacillin/tazobactam 3.375 gm IV Q 8 H (extended infusion)[¥]<br>***or***<br>Ciprofloxacin 400 mg IV Q 8-12 H<br>***PLUS***<br>Vancomycin 15-20 mg/kg IV Q 8-24 H*<br>***or***<br>Daptomycin 6 mg/kg IV Q 24 H | |
| ***Pseudomonas aeruginosa* suspected (e.g., IV drug abusers or trauma)** | Ceftazidime 2 gm IV Q 8 H<br>***or***<br>Cefepime 2 gm IV Q 12 H<br>***or***<br>Piperacillin/tazobactam 3.375 gm IV Q 8 H (extended infusion)[¥]<br>***or***<br>Ciprofloxacin 400 mg IV Q 8-12 H | |
| **Fungal Pathogen** | **Medication*** | |
| ***Candida* species** | Fluconazole 400 mg (6 mg/kg) IV daily<br>***or***<br>Lipid formulation of Amphotericin B 3–5 mg/kg IV daily for at least 2 weeks, then<br>Fluconazole 400 mg IV daily<br>***or***<br>An echinocandin** or Amphotericin B deoxycholate 0.5–1 mg/kg IV daily for at least 2 weeks, then<br>Fluconazole 400 mg IV daily | |

**Treatment Duration for Bacterial Etiologies: 4-6 weeks, depending on infection severity and response[Δ]**
**Treatment Duration for Fungal Etiologies: 6–12 months, depending on infection severity and response**
**Consultation with an infectious disease specialist is recommended**

[Δ]Some controversy exists surrounding duration of therapy. Though shorter durations are being examined for efficacy, some believe therapy should continue until skin and soft tissue defects have complete resolution.
*Dosing should be based on renal function and/or monitoring of desired serum drug concentrations, as indicated by specific therapy (e.g., vancomycin troughs); depending on regional resistance clindamycin or vancomycin can be used for beta-lactam allergic patients
ºMay add rifampin for synergy 300-450 mg IV or PO Q 12 H (caution: rifampin has extensive drug-drug interactions)
[Ω]Not FDA approved for indication/dose; compendial evidence supports use
[¥] example of extended infusion: infuse over 4 hours
**echinocandin (e.g., anidulafungin, caspofungin, micafungin) – see manufacturer's guidance for specific dosing

# Medication Safety

by Allen Lefkovitz

## FDA Suggests Further Limiting Use of Fluoroquinolones

In May 2016 the U.S. Food and Drug Administration (FDA) announced in a Drug Safety Communication that prescribers should limit use of systemic fluoroquinolone antibiotics to only situations where alternative treatment options are unavailable for certain infections.

This FDA announcement follows a safety review that showed a significant risk of "disabling and potentially permanent serious side effects" involving tendons, muscles, joints, and nerves. Individuals prescribed fluoroquinolones should be closely monitored for tendon, joint and/or muscle pain, a tingling or pricking sensation, confusion, and/or hallucinations.

Available systemic fluoroquinolone antibiotics include:

| Brand Name | Generic Name |
|---|---|
| Avelox | moxifloxacin |
| Cipro | ciprofloxacin |
| Factive | gemifloxacin |
| Floxin | ofloxacin |
| Levaquin | levofloxacin |

If any of these serious side effects are detected, treatment should be immediately replaced with a non-fluoroquinolone antibiotic. Based upon these findings, the FDA has stated that if alternatives to a fluoroquinolone are available, the risk generally outweighs the benefits for patients with sinusitis, bronchitis, or uncomplicated urinary tract infections. Additional information is available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm500325.htm.

## FDA Warns of Potential Increased Risk of Amputations with Newer Diabetes Drugs

On May 18, 2016 the FDA described interim results from an ongoing clinical trial that showed an increased risk of leg and foot amputations in patients using canagliflozin-containing medications (i.e., Invokana or Invokamet). Canagliflozin, and other sodium-glucose cotransporter-2 (SGLT2) inhibitors, lower blood glucose by causing the kidneys to remove glucose from the body through the urine.

While another recent trial has not shown this increased risk, analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial showed that amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo (5 to 7 amputations per every 1,000 treated patients vs. 3 for patients receiving placebo).

> The FDA will continue to investigate this potential safety issue, but patients who continue to receive these medications should be monitored closely **for any new pain or tenderness, sores or ulcers, or infections in their legs or feet.**

Additional information is available at: http://www.fda.gov/drugs/drugsafety/ucm500965.htm

## Risk of Rare but Serious Skin Reaction with Olanzapine-Containing Products

The FDA has announced that since its approval in 1996, Zyprexa (olanzapine) and other olanzapine-containing products (e.g., Zyprexa Relprevv, Symbyax) have been associated with at least 23 cases of the severe and potentially life-threatening "Drug Reaction with Eosinophilia and Systemic Symptoms" (DRESS). While DRESS may begin as a fever, swollen lymph nodes and a rash that can proceed to spread to all parts of the body, it causes a markedly increased number of eosinophils ("infection-fighting white blood cells"), which can result in organ damage and may lead to death in up to 10% of cases.

Among the 23 reported cases of DRESS with olanzapine, 50% of cases occurred in the first 19 days of treatment, and 50% of cases occurred at doses greater than or equal to 20 mg per day; however, DRESS has been reported at doses as low as 5 mg per day.

Although olanzapine-containing products should not generally be discontinued abruptly, if symptoms of DRESS are detected, healthcare professionals are advised to stop treatment of olanzapine as soon as possible and to provide supportive care.

Additional information is available at: http://www.fda.gov/Drugs/DrugSafety/ucm499441.htm

# NEW Drug

by Dave Pregizer

## Byvalson™ Tablets

| Brand Name (Generic Name) | Byvalson [bye-VAL-son]; (nebivolol/valsartan) [ne BIV oh lole / val SAR tan] |
|---|---|
| **How Supplied** | 5 mg/80 mg tablets |
| **Therapeutic Class** | Combination beta adrenergic blocker and an angiotensin II receptor blocker (ARB) |
| **Approved Indication** | Treatment of hypertension, to lower blood pressure. |
| **Usual Dosing** | One tablet once daily. Maximum effects are attained within 2 to 4 weeks. |
| **Common Drug Interactions** | CYP2D6 enzyme inhibitors (e.g., fluoxetine), digoxin, verapamil/diltiazem, potassium sparing diuretics, potassium supplements, NSAIDs, and lithium. |
| **Most Common Side Effects** | Hypotension (low blood pressure), hyperkalemia (elevated serum potassium) |
| **Miscellaneous** | Boxed warning for fetal toxicity. Do not abruptly discontinue with coronary artery disease. |
| **Website** | www.byvalson.com |

# NEW Generic Medications

| Generic Name | Brand Name | Date Generic Available |
|---|---|---|
| **Doyxcycline Hyclate 50 mg Delayed-Release Tablet** | Doryx® Tablet DR | 5/27/16 |
| **Alogliptin/Pioglitazone 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, and 25/45 mg Tablet** | Osenia® Tablet | 5/24/16 |
| **Alogliptin/Metformin 12.5/500 mg and 12.5/1000 mg Tablet** | Kazano® Tablet | 5/24/16 |
| **Alogliptin 6.25 mg, 12.5 mg, and 25 mg Tablet** | Nesina® Tablet | 5/24/16 |

# The Clinical Capsule

by Kori Hauersperger

## The Three Beta Blockers with Proven Efficacy in Heart Failure

The American Heart Association says that long-term treatment with a beta blocker lessens the symptoms of heart failure with reduced ejection fraction (HFrEF, previously known as systolic heart failure), improves the patient's clinical status, and enhances the patient's overall sense of well-being. Beta blockers decrease the risk of death and the combined risk of hospitalization and death. With slow titration, 85% of individuals in clinical trials were able to tolerate the target doses of these three medications.

**Important reminders about beta-blocker use include:**

1. Monitor vitals and HF symptoms closely when administering beta blockers
2. Tritrate cautiously, hold or reduce the dose for severe bradycardia (i.e., pulse < 55 beats/min) or symptomatic hypotension (dizziness or light-headedness).

| Medication | Initial Dose and Titration<br>*Slow titration is key to reaching the target* | Target dose | Comments |
|---|---|---|---|
| **Metoprolol succinate CR/XL (Toprol XL)** | 12.5 to 25 mg once daily, double dose every 14 days | 200 mg once daily or highest tolerated dose | Toprol XL and its generic may not be crushed but are scored. Metoprolol tartrate (may be crushed) was less effective in clinical trials. |
| **Carvedilol (Coreg)** | 3.125 mg twice daily, double dose every 14 days | 50 mg twice daily or highest tolerated dose | • Caution in COPD that is not well-controlled.*<br>• May be crushed.<br>• Coreg CR has not been studied in HF. |
| **Bisoprolol (Zebeta)** | 1.25 mg once daily x 2, then 2.5 mg once daily for the first month, then 5 mg once daily the second month and then 10 mg daily | 10 mg once daily or highest tolerated dose | • Dosing adjustment recommended with renal impairment.<br>• May be crushed. |

* The cardioselectivity of metoprolol and bisoprolol may be lost at higher doses – use caution for individuals with asthma or COPD.

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart. Journal of the American College of Cardiology. doi: 10.1016/.
2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. doi: 10.1161/CIR.0b013e31829e8776.

## Regulatory Recap – CMS Adverse Event Trigger Tool: Drug Toxicity Related to Antibiotics

- *By Carrie Allen*

**The CMS Adverse Event Trigger Tool assigns questions as "surveyor probes" to guide in an investigation of potential adverse events and/or the situations that may lead to avoidable adverse events. This month's HealthLine focus article highlighted an infection that requires relatively prolonged antibiotic therapy. In such cases, the following surveyor probes are of critical importance. Make sure you can answer the following about every antibiotic order in your facility:**

1. Is the order time-limited? (i.e., is there a stop date for the antibiotic – if not, why?)
2. Does the care plan/MAR reflect special administration instructions? (e.g., infusing IV antibiotics over a certain time period, monitoring drug concentrations and other labs as appropriate)
3. Is there evidence of additional monitoring to ensure antibiotics do not adversely affect organ function in those with liver or kidney disease?

## HealthLine Quiz

*By Steve Law*

1. **Which is a common sign and symptom of osteomyelitis?**
   a. Drainage of pus through the skin
   b. Swelling and warmth in the affected area
   c. Fever, nausea, excessive sweating, or chills
   d. Pain and/or tenderness in the infected area, often exacerbated by movement
   e. All of the above

2. **Which would NOT be considered a diagnostic test for osteomyelitis?**
   a. CBC with differential
   b. MRI
   c. Bone biopsy
   d. TSH

3. **Which statement is FALSE concerning the treatment of osteomyelitis?**
   a. Empiric therapy for acute bacterial infections typically consists of Vancomycin plus either Ciprofloxacin, Ceftazidime, or Cefepime
   b. The length of treatment of bacterial etiologies is usually 6 to 12 months
   c. A treatment option for osteomyelitis caused by MRSA could be Linezolid
   d. A treatment option for osteomyelitis caused by Candida could be Fluconazole

4. **Systemic use of the antibiotic class, Cephalosporins, may cause disabling and potentially permanent serious side effects involving tendons, muscles, joints, and nerves.**
   a. True b. False

5. **There may be an increased risk of leg and foot amputations in patients using canagliflozin-containing medications:**
   a. True b. False

6. **Olanzapine may be associated with a rare but serious skin reaction called Drug Reaction with Eosinophilia and Systemic Symptoms:**
   a. True b. False

7. **The new antihypertensive medication Byvalson™ is a combination product containing a beta blocker and ACE Inhibitor:**
   a. True b. False

***Please note, the HealthLine Quiz is designed to help readers retain information that is relevant to their care setting. It is not an approved source of continuing education credits for healthcare professionals.***



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*Answers to the HealthLine Quiz: 1) E 2) D 3) B 4) B 5) A 6) A*