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HealthLine

Focus on Sepsis

- by Allen Lefkovitz

As the 9th leading cause of disease-related deaths, sepsis occurs more than one million times and kills more than 258,000 Americans each year. Sepsis accounts for over 5% of all hospital costs and contributes to up to 50% of all deaths in hospital patients. While the mortality rate associated with sepsis has improved over the past 20 years, the incidence of sepsis is increasing, possibly due to the increasing age of our population.

In a January 22, 2017 *Journal of the American Medical Association* letter, researchers from the VA Pittsburgh Healthcare System and the University of Pittsburgh reminded that sepsis results in a greater length of stay in the hospital. Additionally, in examining over 1.1 million 30-day readmissions, they proposed that sepsis results in more unplanned 30-day hospital readmissions than other commonly targeted disease states (see table below).

Cause of 30 Day Readmissions	% of Index Readmissions Readmitted Within 30 Days
Sepsis	12.2%
Heart Failure	6.7%
Pneumonia	5.0%
COPD	4.6%
Acute Myocardial Infarction	1.3%

Within the past 15 months, updated international definitions, terminology, and guidelines for the management of sepsis and septic shock were published.

The new guidelines are the work of 55 international experts representing 25 international organizations. Although the new, technical definition of sepsis is a "life-threatening organ dysfunction caused by a dysregulated host response to infection", a simpler lay definition has been suggested: "Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs." Septic shock is considered a subset of sepsis that is associated with a greater risk of death (> 40%) due to "profound circulatory, cellular, and metabolic abnormalities" (e.g., severe hypotension, elevated serum lactate).

The full management of sepsis is beyond the scope of this article; however, prevention is key, and the appropriate management in the initial hours after sepsis develops improves outcomes. Therefore, the identification and prevention of sepsis, as well as treatment with antimicrobial therapy will be discussed. The full 2016 sepsis guidelines are available for free at: www.survivingsepsis.org/Guidelines/.

Although everyone is at risk, individuals at highest risk for sepsis include those who:

- have a weakened immune system;
- are infants or young children;
- are elderly;
- have a severe burn or wound; and/or
- suffer from a chronic illness (e.g., diabetes, AIDS, cancer, kidney or liver disease).

Consequences of Sepsis and Efforts to Prevent Sepsis

Beyond being a medical emergency with a high mortality rate, those who survive sepsis often have long-term

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consequences such as permanent organ damage (e.g., end-stage kidney disease), amputation(s), psychological complications (e.g., post-traumatic stress disorder), chronic pain, and worsening or new-onset cognitive impairment (especially in older adults).

It is uncontested that efforts to prevent infections are the best way of preventing sepsis. Strategies emphasized in preventing sepsis include:

Vaccinations (e.g., influenza, pneumococcal)

Clean scrapes and wounds

Practice good hygiene (e.g., hand washing)

Watchfulness if an infection develops

Approximately two-thirds of sepsis cases occur in the elderly, and the types of infections most commonly associated with sepsis include urinary tract infections and pneumonia. After infection prevention, early detection of sepsis is the most effective means of increasing the odds of survival. As the earliest signs of sepsis overlap with the symptoms of most infections, symptoms that should vigilantly be watched for are well summarized with the acronym **SEPSIS**:

Shivering, fever, very cold

Extreme Pain

Pale/discolored skin

Sleepy, difficult to wake, confused

"**I** feel like I might die!"

Short of breath

Responding to Sepsis and Choosing Empiric Antimicrobial Therapy

The Task Force responsible for the latest definition of sepsis also proposed "bedside" clinical criteria. The presence of two or more of these criteria is considered indicative of poor outcomes with sepsis:

- a respiratory rate ≥ 22 breaths per minute
- an altered mental status
- a systolic blood pressure ≤ 100 mmHg.

Sepsis generally warrants admission to the critical care unit of a hospital, but regardless of setting, any suspicion of sepsis necessitates an urgent response. In addition to recommendation changes associated with initial resuscitation methodology, the second area of significant change in the new sepsis guidelines involves the use of antibiotic therapy.

Because mortality increases with even short delays in antimicrobial therapy, urgent initiation and use of broad spectrum antibiotics are critical. However, the new sepsis guidelines also recognize and attempt to balance the increasing need for "meticulous attention to antimicrobial stewardship." Even though obtaining blood and other relevant cultures prior to initiation of antimicrobial therapy is strongly recommended, the sepsis guidelines suggest that antimicrobial therapy be initiated within 1 hour after recognition of sepsis symptoms, even if that means relevant cultures cannot be obtained prior to treatment.

While antimicrobial stewardship efforts may focus on minimizing unnecessary use of broad-spectrum antibiotics to prevent resistance, when sepsis is suspected, "empiric regimens should err on the side of over-inclusiveness", and initial use of broad-spectrum antibiotics should not be avoided. According to the 2016 sepsis guidelines, "Survival may decrease as much as fivefold for septic shock treated with an empiric regimen that fails to cover the offending pathogen." For this reason, consideration of common pathogens based upon the infected area of the body, as well as susceptibility patterns in the local community are both important in selecting empiric treatment. Therefore, long-term care (LTC) facilities need to work with their local hospitals and laboratory service provider to develop nursing home-specific, or at least regionally-specific antibiograms on an annual basis. Other important considerations include an awareness of recent hospital or LTC admissions, concomitant underlying conditions (e.g., heart failure, chronic kidney disease), other medications (e.g., warfarin, immunosuppressants), presence of indwelling catheters or devices, recent history of infections or known colonization, and what antimicrobials have been received by the patient in the past 3 months.

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As Gram-negative bacteria (e.g., *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*) and invasive candidiasis are increasingly common causes of septic shock, general guiding principles include use of:

- broad-spectrum carbapenems (e.g., meropenem) or an extended-spectrum beta-lactam (e.g., piperacillin/tazobactam) and/or third- or higher-generation cephalosporins (e.g., cefepime) for healthcare-associated infections;
- a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., levofloxacin) if *Legionella* is suspected;
- an antifungal agent (e.g., caspofungin) if risk factors for *Candida* infection are present (e.g., neutropenia, hemodialysis catheters, central venous catheters, use of total parenteral nutrition).

Similarly, if methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, the treatment regimen should likely include vancomycin or linezolid.

Other recommendations and best practice statements from the 2016 sepsis guidelines suggest:

- "empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens";
- "empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock";
- "combination therapy [should] not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock";
- "empiric antimicrobial therapy [should] be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted."

Dosing Considerations

Treatment of sepsis almost exclusively involves intravenous antibiotics; however, in cases where rapid IV access cannot be established, and in the absence of known contraindications (e.g., a known allergy), intramuscular preparations of certain beta-lactam antibiotics (e.g., ceftriaxone, cefepime) may be considered temporarily.

While aggressive dosing is often necessary, dosing of antimicrobials should consider changes in renal function and/or volume of distribution (i.e., subsequent to aggressive fluid resuscitation) as well as the need to obtain adequate blood concentrations at the site of infection for the right amount of time. Such approaches are essential to minimizing the risk of clinical failure. Likewise, timely therapeutic drug monitoring (e.g., gentamicin, amikacin, vancomycin) can help ensure both resolution of the infection as well as avoiding potential toxicities (e.g., nephrotoxicity, ototoxicity).

"Approximately two-thirds of sepsis cases occur in the elderly, and the types of infections most commonly associated with sepsis include urinary tract infections and pneumonia. After infection prevention, early detection of sepsis is the most effective means of increasing the odds of survival."

De-escalation and Duration of Therapy

The 2016 sepsis guidelines suggest a 7- to 10-day treatment duration for most patients. Individual patients who may require a longer course of antibiotic treatment include those with a site of infection that cannot be drained, those with neutropenia or other immunocompromised conditions, or infection due to a multidrug resistant organism, fungus or virus. However, de-escalation of therapy (i.e., narrowing the spectrum of antibiotic coverage) should always be based upon identification of causative organisms, determining the susceptibility of the causative organisms, and/or upon signs of clinical improvement (e.g., normalization of blood pressure and temperature, improved white blood cell counts). The 2016 sepsis guidelines suggest that assessment for de-escalation occur "within the first few days" and every day thereafter, as prolonged use is considered "detrimental to society and to the individual patient". One-third of patients with sepsis never have the causative organism identified. In cases where multiple antibiotics are used, de-escalation to a single agent should be based upon clinical improvement.

Further discussion and consideration of preventing and appropriately responding to sepsis within long-term care facilities can help achieve one of the intents of the 2016 sepsis guidelines, that is, "improving communication among medical, pharmacy, and nursing staff".

Interventions for Select Opioid-Induced Adverse Events

- by Carrie Allen and Kori Hauersperger

Recently, opioid safety and management of opioid-induced adverse events has been a focus of initiatives from the Centers for Disease Control and Prevention, as well as other experts in the field.

Suggested Interventions for Selected Opioid-Induced Adverse Events*†	
Opioid Overdose or Toxicity	• Discontinue opioid and any other medication that may have contributed • Administer Narcan (naloxone), doses should be individualized based on history of opioid use (generally 0.4-2 mg IV, IM or SC, up to 10 mg total dose) – Naloxone will cause cessation of pain relief and acute withdrawal in some cases – Monitor to ensure that naloxone does not wear off, as respiratory depression can recur • Maintain airway and supportive care • Send out for emergency care as directed by prescriber and facility policy
Central Nervous System (e.g., delirium, hallucinations, sedation)	• Assess medication regimen for polypharmacy/other drugs that may have an additive effect (e.g., benzodiazepines, steroids) and discontinue non-essential medications, ***and*** • Evaluate underlying cause(s) and primary diagnoses, particularly for hallucinations (e.g., change of surroundings, sleep deprivation, psychiatric diagnoses), ***and*** • Reduce dose of opioid medication, ***or*** • Consider switch to an alternative opioid (especially if using a mixed/opioid agonist/antagonist and dysphoria is present), ***or*** • Consider opioid discontinuation† (may consider an alternative agent such as an SNRI)
GI	**Nausea or delayed gastric emptying:** • Evaluate underlying cause(s) and primary diagnoses (e.g., medication timing in relation to meals, gastroparesis, chemotherapy), ***and*** • Consider a short trial of a prokinetic agent such as metoclopramide, re-evaluate as needed, ***and/or*** • Consider a short trial of premedication with meclizine, scopolamine, or ondansetron; tolerance can develop to nausea (unless caused by constipation), discontinue as soon as is possible, ***and/or*** • Consider switching the route of administration (e.g., from oral to transdermal), ***or*** • Consider switching to a different opioid or alternative agent if intolerable (e.g., oxycodone if using morphine, or an alternative agent such as an SNRI) **Opioid induced constipation (OIC):** will not resolve without intervention, nor will tolerance develop • A routine order for a stimulant laxative (e.g., senna, bisacodyl) ± PEG 3350 (Miralax) should be in place for all chronic opioid users who do not have a bowel obstruction, along with orders to hold the laxative for loose stools • Increase liquid and fiber intake as clinically appropriate • Additional laxative orders (PRN or scheduled) or enema orders may be required • Monitor closely for impaction or bowel obstruction while opioids are on the medication regimen; set goals for bowel movements that are regular and mimic stool frequency prior to opioid use • Medications approved for OIC may be tried in those who have failed other regimens such as: lubiprostone (Amitiza), methylnaltrexone (Relistor), naloxegol (Movantik)
Pruritus	• Evaluate and address underlying causes, if possible (e.g., liver or kidney disease, dialysis patient, contact dermatitis, scabies, allergies to other medications) **Tolerance to pruritus does occur; however, if intolerable consider:** • Switching to an alternative opioid or alternative agent (e.g., from a natural opioid to a semisynthetic or synthetic, or an alternative agent such as an SNRI), ***and/or*** • Switching the route of administration (e.g., from IV to PO, or PO to transdermal), ***and/or*** • A short trial of a routinely dosed H1 blocker (e.g., diphenhydramine) ± H2 blocker (e.g., ranitidine) All pruritus treatments should be reassessed and discontinued as soon as is clinically feasible

* Table is not all-inclusive, and is not a replacement for prescriber guidance and facility policies for managing of opioid related adverse events.
† When discontinuation of opioids is required, a physician should assess the need for psychiatric, and/or substance abuse consults and a plan to re-initiate pain management; in non-emergent cases the opioid should be tapered off.
GI = gastrointestinal, H1 = histamine 1 receptor, H2 = histamine 2 receptor, IM = intramuscular, IV = intravenous, PO = oral, SNRI = serotonin-norepinephrine reuptake inhibitor (e.g., duloxetine), SC = subcutaneous

Medications to be Avoided, Used with Caution, or are Contraindicated in Heart Failure (HF)

- by Kori Hauersperger

The following medications may cause or worsen heart failure. Monitor for pulmonary and/or peripheral edema, weight gain and shortness of breath.

	Brand Name (generic name)	Information
FDA Boxed Warning	**Actos (pioglitazone)** **Avandia (rosiglitazone)**	Avoid in symptomatic heart failure; initiation is contraindicated in NYHA Class III or IV HF.
	Multaq (dronedarone)	Doubles the risk for death in symptomatic HF, recent decompensated HF, or NYHA Class IV HF.
Contraindicated	**Flexeril, Amrix (cyclobenzaprine)**	Although rare, symptoms of tachycardia, arrhythmia, palpitation, and hypotension are the basis for the contraindication.
	Pletal (cilostazol)	Contraindicated in any HF severity due to tachycardia, tachyarrhythmia and hypotension. Medications in the same class caused decreased survival in severe HF.
	Calan, Isoptin (verapamil)	Contraindicated if ejection fraction < 30% or HF with moderate to severe symptoms and in any degree of HF if using a beta-blocker (e.g., carvedilol, metoprolol).
	Rythmol (propafenone)	Use is contraindicated due to negative inotropic effects and high risk of proarrhythmias.
Precaution	**Nonsteroidal anti-inflammatory drugs** *(e.g., ibuprofen, naproxen, meloxicam)*	Doubles the risk of an exacerbation of HF requiring hospitalization. Does not apply to low dose aspirin. Monitor closely.
	Betapace (sotalol) **Tambocor (flecainide)**	Associated with negative inotropic effects and high risk of proarrhythmias. Initiate / adjust dose with caution. Monitor closely. Use of sotalol is contraindicated in patients with decompensated heart failure.
	Procardia (nifedipine)	Risk of HF, especially if used with a beta-blocker. Monitor closely.

NYHA = New York Heart Association.
Drug information available at https://dailymed.nlm.nih.gov/

NEW Drug

Xadago® Tablet

- by Dave Pregizer

Brand Name (Generic Name)	**Xadago [ZA-da-go] (safinamide) [sa FIN a mide]**
How Supplied	50 mg and 100 mg tablets
Therapeutic Class	Monoamine oxidase type B (MAO-B) inhibitor
Approved Indication	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes
Usual Dosing	Start with 50 mg administered orally once daily at the same time of day; after two weeks, may increase to 100 mg once daily, based on individual need and tolerability. Not to exceed 50 mg once daily with moderate hepatic impairment.
Select Drug Interactions	Caution: SSRI (e.g., fluoxetine [use lowest effective dose possible]), sympathomimetic drugs (including OTC cold remedies), avoid foods containing high amounts of tyramine. Contraindicated: potent inhibitors of monoamine oxidase (e.g., linezolid), opioid drugs (e.g., tramadol), SNRI (e.g., venlafaxine); tri-or tetra-cyclic (e.g., amitriptyline) or triazolopyridine (e.g., trazodone) antidepressants, St John's wort, and dextromethorphan.
Most Common Side Effects	Dyskinesia, fall, nausea, and insomnia
Miscellaneous	Contraindicated in patients with severe hepatic impairment. May cause or exacerbate hypertension. Not shown to be effective if used as monotherapy.
Website	http://xadago.com/

OTC = over the counter, SNRI = selective norepinephrine reuptake inhibitors, SSRI = selective-serotonin reuptake inhibitors

NEW Generic Medications

Generic Name	Brand Name	Date Generic Available
Fayosim™ (levonorgestrel and ethinyl estradiol) 0.15 mg/0.02 mg, 0.15 mg/0.025 mg, and 0.15 mg/0.03 mg Tablets	Quartette® Tablet	4/10/17
Mibelas™ 24 Fe (norethindrone acetate/ ethinyl estradiol and ferrous fumarate) 1 mg/20 mcg Tablets	Minastrin® 24 Fe Tablet	3/15/17

HealthLine Quiz

– by Steve Law

1. **Which statement about sepsis is TRUE?**
   a. Sepsis results in more unplanned 30-day hospital readmissions than other commonly targeted disease states
   b. Sepsis contributes to up to 50% of all deaths in hospital patients
   c. If a patient has a severe burn or wound they are at a highest risk for sepsis
   d. Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs
   e. All of the above

2. **Which is NOT considered a long-term consequence of sepsis?**
   a. Amputation
   b. Psychological complications
   c. Weight loss
   d. Potential for new-onset cognitive impairment in older adults

3. **The presence of 2 or more of these criteria is considered indicative of poor outcomes with sepsis: a respiratory rate ≥ 22 breaths per minute, an altered mental status, a systolic blood pressure ≤ 100 mmHg:**
   a. True b. False

4. **Which statement about antimicrobial treatment for sepsis if FALSE?**
   a. Dosing of antimicrobials should consider changes in renal function and/or volume of distribution
   b. A third or higher generation cephalosporin may be a treatment option for healthcare-associated infections
   c. Empiric antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted
   d. If MRSA is suspected, an antifungal agent is warranted

5. **A routine order for a stimulant laxative +/- Miralax should be in place for all chronic opioid users who do not have a bowel obstruction, along with orders to hold laxative for loose stools:**
   a. True b. False

6. **Which statement is TRUE about the new medication Xadago® (safinamide)?**
   a. It is a monoamine oxidase type A inhibitor
   b. It may cause or exacerbate hypotension
   c. It can be given if a patient is on tramadol
   d. Levodopa/carbidopa must be given also

***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.**

Contributing Authors for This Issue

Allen L. Lefkovitz, PharmD, BCGP, FASCP
Senior Clinical Advisor, Clinical Geriatrics, CVS Health

Carrie Allen, PharmD, BCGP, BCPS, BCPP, CCHP
Clinical Advisor, Clinical Geriatrics, CVS Health

Kori Hauersperger, PharmD, BCGP
Clinical Advisor, Clinical Geriatrics, CVS Health

David Pregizer, RPh
Consultant Pharmacist, HCR-Manorcare

Steve Law, PharmD, BCGP
Clinical Services Manager for Indiana; Omnicare Pharmacies in Indiana

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