**From Fever to Septic Shock**

- **SIRS**
  - Sepsis
  - Severe Sepsis
  - Septic Shock
  - Hypotension

- **Temperature**: 98°F ± 2°F (normal)
  - Fever: above 100°F

**Etiology of Fever**

- Normal human physiologic temperature ranges above and below mean of ~98°F (controversial)
- Temperature above 99.5°F considered fever (also controversial)
- Majority of research to date does not support harm from febrile state.
  - Three main exceptions:
    - Fever d/t heat stroke
    - Fever causing extreme metabolic demands in pts with underlying cardiac and pulmonary disorders
    - Fever in elderly prone to mental dysfunction
- Research to date and various guidelines:
  - Recommend only suppressing fever to provide patient comfort
  - Find an increase in viral shedding and prolonged disease states with Aspirin and Tylenol use

**Fever**

- Most common reasons for fever include:
  - Infection (to a greater extent bacterial)
  - Malignancies
  - Connective tissue/autoimmune diseases
- Other not as common reasons:
  - Post operative
  - Drugs/Medications
  - Undiagnosed illnesses
- Other factors that can cause fever:
  - Tachycardia, diurnal patterns, ovulation, exercise, digestion, trauma, psychological distress/disorders, infarction, burns, renal failure and shock, burns, tissue infarction, childbirth

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Pyrogens

- **Exogenous pyrogens:**
  - Microorganisms and toxins or other products of microbial origin, which induce mainly macrophages to produce endogenous pyrogens
- **Endogenous pyrogens:**
  - Cytokines (mainly IL-1, IL-6, TNF-alpha, interferon and prostaglandins)
  - Antigen-antibody complexes associated with complement
  - Lymphocyte derived molecules
  - Bile acids
  - Androgenic steroid metabolites (natural and synthetic)

Fever in SOAP

- **Exam:**
  - PMH
  - Medication review
  - Recent travel, exposure to pets and other animals, other exposure
  - Family hx: rare hereditary causes of fever
  - Verify fever: no research support for best location to verify (in adults)
  - Pattern: continuous, relapsing, etc...
- **Lab tests to consider:** CBC with differential, CMP. UA C&S, CXR, ECG, ESR/CRP, ANA, Monospot, TB skin test, HIV, Hep panels
- **Other imaging per exam findings or index of suspicion**
Systemic Inflammatory Response Syndrome (SIRS)

• The systemic response to a wide range of stresses
• Two or more of the following:
  – Temp: >38°C
  – HR: >90
  – RR: >20
  – PaCO2: <32
  – WBC: >12K or <4K or >10% bands

SIRS Differential Diagnosis

• Infection
• Malignant hyperthermia and heat stroke
• Burns
• Trauma
• Pulmonary embolism
• MI
• Cardiac tamponade
• Dissecting or ruptured aortic aneurysm
• Occult hemorrhage
• Adrenal insufficiency
• Thyroid storm
• Pancreatitis
• Drug overdose
• Drug hypersensitivity reactions

Other Sepsis Diagnostic Criteria

• Hypothermia <36C
• AMS
• Significant edema or + fluid balance
• Hyperglycemia >140 with DM hx
• Elevated CRP and/or ESR
• Elevated procalcitonin
• Arterial hypotension: <90 SBP, MAP <70
• Arterial hypoxemia: PaO2/FiO2 <300
• Acute oliguria: <0.5 ml/kg/hr for at least 2 hours despite adequate fluid resuscitation
• Creatinine >0.5 mg/dL
• Coagulation abnormalities: INR >1.5 or aPTT >60
• Ileus
• Thrombocytopenia: plt <100K
• Hyperbilirubinemia: TB >4
• Decreased capillary refill and/or mottling
• Lactic acid >2 mmol/L

Elevated Lactic Acid Levels

• Hyperlactatemia: >2
• Lactic acidosis: >4
• Two types
  – Type A (tissue hypoxemia)
    • Hypovolemia
      – Shock
  – Type B (without widespread tissue hypoxemia)
    • DKA
    • SaO2
    • Catecholamine release: exogenous or endogenous
    • Malignancy
    • ETOHism
    • Drugs:
      – HAART
      – Propofol
      – Linezolid
    • Mitochondrial disorders
Sepsis

• Sepsis is the presence of infection together with systemic manifestations of infection
• Apart from leukopenia and hypothermia, sepsis can be a normal manifestation of the body’s immune response and does not necessarily signify a resulting poor prognosis
• The term septic is an informal term for severe sepsis or septic shock
• Bacteremia:
  — Culturable bacteria in the bloodstream
  — May be transient and inconsequential
  — Inconsistent correlation with severe sepsis

Sepsis

• Leading cause of infectious death in U.S.
• Costs ~25 billion in hospital management
• ~20-60% mortality rate in ~750K cases in US annually
• >60% of these patients >65 years old
• ½ Gram +s, ½ Gram (-) s, Candida
• Foci of infection:
  — #1 Lungs
  — #2 “Urine”
• 100-300X greater for HD patients

Severe Sepsis

<table>
<thead>
<tr>
<th>TABLE 1. Severe Sepsis</th>
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</thead>
<tbody>
<tr>
<td>Sepsis definition—sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection):</td>
</tr>
<tr>
<td>Severe respiratory failure</td>
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<tr>
<td>Lactic acid upper limit of laboratory normal</td>
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<tr>
<td>Urine output &lt;0.5 ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation</td>
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<tr>
<td>Acute lung injury with P/F ratio &lt; 200 is the absence of pneumonia as infection source</td>
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<tr>
<td>Creatinine &gt;2 mg/dl (178 umol/L)</td>
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<tr>
<td>Bilirubin &gt;3 mg/dl (51.3 umol/L)</td>
</tr>
<tr>
<td>Thrombocytopenia &lt;100,000/mL</td>
</tr>
<tr>
<td>C-reactive protein (International normalized ratio &gt; 1.5)</td>
</tr>
</tbody>
</table>


Severe Sepsis

• Most common sites for primary infection in patients with severe sepsis are the lungs and the abdomen
• The most influential factors for progressing to severe sepsis/shock are:
  • Surface area of infection
  • Severity
  • Susceptibility to treatment
Septic Shock

• Sepsis with hypotension despite adequate fluid resuscitation with no other underlying etiology
• Hypotension: <90 systolic, <70 MAP, or >40 change from baseline
• Tachyphylaxis to catecholamines, corticosteroids and aldosterone
• Increasing lactate and H+, hyperphosphatemia
• Further depletion of ATP stores, resulting in ion pump dysfunction: intracellular decrease in K and increase in Na and Ca, leading to cellular swelling, immense ROS activity, cessation of protein synthesis, then apoptosis

PRRs, PAMPs & DAMPs

PAMPs

• LPS
• Other lipoproteins
• Peptidoglycans
• Zymosan (yeast)
• Viral coat proteins
• Bacterial flagellin
• Nucleic acids

* Small subset of variety of PAMPs represented. When binding with PRRs create inflammatory cascade via release of chemical mediators (cytokines)

Cell Signaling Molecules

http://chamberlin.med.upenn.edu/412/356/356_files/slides/mammalian_toll-like_receptors.ppt
Cell Signaling Molecules

- Cytokines:
  - Either inflammatory or inflammatory
  - Interleukins (ILs)
  - Interferons
  - Chemokines

- Histamine:
  - Vasodilation of microcirculation (capillary beds, arterioles, venules) and vasoconstriction of large vessels

- Leukotrienes:
  - Act similar to histamine

- Prostaglandins:
  - Lipids derived from cyclooxygenases (COX 1, 2)
  - Moderate contraction of smooth muscles
  - Regulate inflammation

 acute Phase Response

- The three characteristic changes in the microcirculation (arterioles, venules and capillaries) include:
  - Blood vessel dilation, increased vascular permeability and white blood cell migration to localized site of innate immune detection (leukocytosis)

- Pain: afferent signals along nociceptive neural pathways

- Fever: IL-1, IL-6, TNF-alpha, interferon and prostaglandins acting as pyrogens:
  - Alter temperature set point, and stimulate liver to synthesize bulk of initial inflammatory response proteins

- C-reactive protein:
  - Increases activity of phagocytes and facilitates the delivery of humoral (antibodies) and cellular components (T and B cells) to sites of inflammation.

- Anti-inflammatory:
  - Same mechanisms causing white blood cell proliferation to infected or injured tissue also can limit ability to adhere and enter un-inflamed vascular endothelium

  - Other responses that minimize inflammation include:
    - Release of neuroendocrine hormones: cortisol, epinephrine and antioxidants

- Metabolic changes:
  - Increased TSH, vasopressin, insulin, glucagon, catabolism of muscle protein

  - Also:
    - Norepinephrine
    - Hepatic lipogenesis
    - Lipolysis in adipose tissue
Acute Phase Response

- **Constitutional**: fever, wt. loss, night sweats, chills, rigors, myalgias, arthralgias, sleep, appetite, pain, lethargy
- **HEENT**: headache, photophobia, ear congestion/drainage, diplopia, conjunctivitis, rhinitis, hoarseness, pharyngitis, lymphadenopathy
- **Cardio**: chest pain (pleuritic), palpitations, edema
- **Pulm**: dyspnea, cough (+/- productive)
- **GI**: N/V, diarrhea, hematochezia, suppurative discharge
- **GU**: dysuria, frequency, urgency, void volume, incontinence, posterior/flank pain
- **MS**: ROM, coordination, ataxia, muscle weakness
- **Neuro**: impaired mentation/consciousness, seizure, vertigo, sensation, CN impairment
- **Skin**: rash/lesions, urticaria, erythema
- **Psych**: depression, anxiety, mood lability

Pathophysiology of Severe Sepsis

- Abnormal function in microcirculatory units (arterioles, venules and capillary beds)
- Diminished access to O2 for aerobic respiration, this diminishes the ATP needed for life
- Multi-organ failure is a system-wide organ “hibernation”
- Mismatched ratio of pro-inflammatory to anti-inflammatory cytokines
- Desensitization of phagocytes to complement
- Alteration of coagulation cascades:
  - Increased tissue factors and Von Willibrand factor from increasing cellular debris and damaged endothelial tissue
  - Increased activation of platelets
  - Formation of microthrombi, leading to disseminated intravascular coagulation

Microbial Triggers for Severe Sepsis/Shock

- Majority of severe sepsis is associated with commensal bacterial and fungi
  - Enteric gram negative bacilli, coagulase negative staphylococci, enterococci, and Candida sp.
- Culture positive and culture negative cases have similar morbidity and mortality*
- Bacterial endotoxins:
  - Scant evidence these play large role in severe sepsis but they still cause significant cellular damage to areas of localized extravascular tissue
- Superantigens (toxic shock syndrome toxins):
  - Bind to broad range of TLRs via MHCII, resulting in excessive cytokines and other acute phase chemical mediators
  - *S. aureus, S. pyogenes, C. perfringens, V. vulnificus, filoviridae*
Severe Sepsis/Septic Shock Manifestations:

Nervous and Endocrine Systems

- Alterations in higher cerebral function are often early manifestations of severe sepsis, particularly in older adults
- Focal neurological signs: seizures and cranial nerve palsies are rare
- Hypothalamic-pituitary adrenal axis:
  - Blunted release of growth hormone, ACTH, prolactin
- Adrenal insufficiency:
  - Cytokine induced dysfunction, glucocorticoid tachyphylaxis, prolonged inflammatory states, hypoglycemia
- Autonomic dysfunction:
  - Abnormalities in heart rate d/t alterations in sympathetic output or tachyphylaxis

Bloodstream

- Neutrophilic leukocytosis is the normal response to bacterial or fungal infection
- Lymphocytosis in viral infections
- Thrombocytopenia
- Plasma lipids: increase in triglycerides, free fatty acid and vLDL
- Glucose: initial hyperglycemia but can progress to hypoglycemia
- Lactic acid
- Clotting:
  - DIC in ~50% of individuals with severe sepsis
  - CBC with diff and peripheral smear, aPTT/PT, D-dimer, fibrinogen

Lungs

- Hyperventilation with respiratory alkalosis is one of the earliest manifestations of sepsis
- ALI (acute lung injury): PaO2/Fio2=<300
- ARDS (acute respiratory distress syndrome): bilat. pulm. infiltrates w/o HF or PNA with PaO2/Fio2=<200
- Diffuse alveolar epithelial injury leading to fluid spilling into interstitial and airspace compartments
- Neutrophils and monocytes aggregating in pulmonary vessels
- Pulmonary shunting
- Dead space volume increases and compliance decreases
- Intubation and mechanical ventilation

GI Tract

- Increased translocation of bacteria into the lymph system and bloodstream
- Aspiration of microbial contents into the tracheobronchial tree
- Small erosions of the gastric and duodenal mucosa which results in upper GI bleeding and ileus
Severe Sepsis/Septic Shock Manifestations:

Kidneys
- From minimal proteinuria to profound renal failure
- Oliguria
- Azotemia
- Uremia

Liver
- Cholestatic jaundice
- Complete hepatic failure is rare

Immunity
- Immune dysfunction:
  - High susceptibility to nosocomial infections and commensal infections
  - Reactivation of latent herpes simplex and CMV occurs in ~40% of severe sepsis patients

Skin
- Localized: pustules, cellulitis, eschar
- Seeding infections: pustules, cellulitis, petechiae
- Diffuse eruptions:
  - Bacterial toxins-hemorrhagic lesions
  - DIC associated peripheral gangrene-necrotic lesions
Surviving Sepsis

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate levels
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 8 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (98 mg/dL):
   - Measure central venous pressure (CVP)
   - Measure central venous oxygen saturation (Svo₂)
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Svo₂ of ≥70%, and normalization of lactate.

Continuing Sepsis Treatment

- De-escalate antibiotics: targeting both purported species and sensitivity
- Procalcitonin
- Use of crystalloids for fluid resuscitation, albumin where substantial crystalloids are needed
- Vasopressors:
  - Norepinephrine as first choice (dopamine as alternative only in highly selected patients)
  - Epinephrine as second add on or second choice
  - Vasopressin next
  - No low dose dopamine for renal protection
- Inotropic therapy:
  - Trial dose of dobutamine with signs of myocardial dysfunction: elevated cardiac filling pressures, low cardiac output
  - In some patients, hydrocortisone

Surviving Sepsis

- Obtain blood cultures x2 (aerobic and anaerobic) before administration of antimicrobial therapy if does not delay treatment for >45 minutes
- Draw cultures percutaneously and from each vascular access if not placed 48 hours prior to contact
- Cultures from urine, CSF, wounds, respiratory secretions, etc
- The administration of broad-spectrum antimicrobials within 1 hour in patients with severe sepsis and septic shock
- Source control: necrotizing soft tissue infections, peritonitis, cholangitis, intestinal infarction, intravascular access devices, etc with appropriate rapid consultation

Continuing Sepsis Treatment

- Tight glucose control
- PRBC infusion only when Hgb is below 7g/dL
- Platelets only when <10K without bleeding and <20K with active bleeding
- Continuous or intermittent hemodialysis
- Intubation and mechanical ventilation management
- Enteric nutrition
- Stress ulcer prophylaxis
- DVT prophylaxis
- Decubitus ulcer prophylaxis
Sepsis Workup

- CBC with differential, CMP, Mg, Phos., Ionized Ca
- Lactic acid (q 2 until <2)
- Procalcitonin
- ABG
- Coag. Panel, fibrinogen
- CXR, UA, BCs (PCR), Resp. Cx and gram stain (PCR)
- Legionella Ag, S. pneumoniae Ag
- C. diff. PCR
- Influenza A&B PCR

Procalcitonin (PCT)

- Usual course=cleavage into calcitonin in thyroid
- Extrathyroidal non-neuroendocrine cleavage= mainly with increased concentrations during bacterial infection but *
- DAMPs + PAMPs= increase in levels
- Sepsis vs. SIRS of noninfectious origin: Lungs and GI
- Levels peak at 6 hours, plateau at ~8-24 hours, can remain elevated for days-weeks after infection
- Different baseline and infection driven PCT levels for CKD patients

![Procalcitonin (PCT) diagram](image1.png)

![Procalcitonin (PCT) diagram](image2.png)
**Multiplex PCR**

- 1-2 days with BCs vs hours with PCR
- Amplifies DNA of large spectrum of infectious bacteria
- Decreased treatment of contaminants
- Earlier administration of directed ABXs or de-escalation of ABXs
- Minimized resistance
- ~25% reduction of # of broad spectrum days

**Antibiotic Resistance**

**Anti-infective Therapy**

- Identification of the infecting organism:
  - Cultures, immunologic assays and molecular testing (PCR) before starting drug therapy
- In most cases, offending agent will never be found:
  - Aim for most probable offending agents:
    - Cellulitis in non-immunocompromised individual (S. aureus, S. pyogenes)
    - Acute otitis media in young child (viral vs. H. influenzae, S. pneumoniae, M. catarrhalis)
- Host factors:
  - Hx of previous adverse reactions to antimicrobial agents
  - Gastric pH: absorption increases or decreases depending on pH and drug
  - Renal function:
    - Decreased in very young children and older adults
    - Most important route of elimination for antimicrobial products: adjustment needed renal function for and adequate dosing
Anti-infective Therapy

- Hepatic function: watch out for azithromycin, Zosyn, clindamycin, metronidazole, fluconazole, nitrofurantoin, isoniazid
- G6PD (glucose-6-phosphate dehydrogenase deficiency): hemolytic reactions to nitrofurantoin and Bactrim
- DMII: hypoglycemic reactions to Bactrim
- Pregnancy: increased clearance, no tetracyclines (includes breast-feeding)

- Site of infection: drug to site of infection (penetrance):
  - Bile-concentrated, blood-brain barrier, bone, etc
- Route of administration: oral vs. parenteral
- Removal of foreign material: prosthetics and implants

Gram + Aerobic Cocci

Gram + aerobic cocci:
- Coagulase positive (Staphylococcus aureus)
- Coagulase negative: S. epidermidis and other commensals

Streptococcus:
Lancefield antigen and hemolytic reaction
- S. pyogenes (strept throat and necrotizing fasciitis)
- S. pneumoniae
- S. Agalactiae
- Viridans streptococci (usually contaminants, commensals)

Treatment: Penicillins (all types), Cephalosporins, Clindamycin, Vancomycin, Daptomycin, Linezolid, Orbtaciv (oritavancin), Sivextro (tedizolid), Dalvance (dalbavancin)
**Gram + Aerobic Bacilli (Rods)**
- Listeria monocytogenes
- Bacillus anthracis

**Gram + Anaerobic Bacilli (spore forming)**
- Clostridium tetani
- C. botulinum
- C. perfringens
- C. difficile

**Other Gram +**
- Enterococcus faecalis
- E. faecium

**Gram (-) Aerobic Cocci**
- Neisseria meningitidis
- N. gonorrhoeae
- Moraxella catarrhalis
Gram (-) Aerobic Bacilli:

- Vibrio cholerae
- V. vulnificus
- H. pylori
- Pseudomonas aeruginosa

Gram (-) Aerobic Bacilli: Enterobacteriaceae

- E. coli
- Klebsiella
- Citrobacter
- Enterobacter
- Morganella
- Proteus
- Salmonella
- Yersinia pestis

Other Gram (-)

Haemophilus influenzae infections

- H. Influenzae
- Legionella pneumophila
- Captocytophaga canimorsus

Spirochetes

- Syphilis (Treponema pallidum)
- Lyme disease (B. burgdorferi)
**Antibacterials**

- **Lungs**
  - Non-Pseudomonas
    - Rocephin + Azithromycin
    - Levaquin
  - Pseudomonas
    - Cefepime or Aztreonam + Levaquin or Carbapenem
    - Pseudomonas + MRSA Risk
      - Cefepime or Aztreonam + Levaquin or Carbapenem + Vancomycin
- **Meningitis**
  - Rocephin or ID consult + Vancomycin
- **Intra-abdominal**
  - Zosyn or Levaquin or Flagyl

**Antibacterials**

- **Skin**
  - Vancomycin + Clindamycin + Zosyn or Aztreonam
- **Line sepsis**
  - Vancomycin + Cefepime or Levaquin
- **Urine**
  - Cefepime or Aztreonam + Levaquin
- **Neutropenic fevers**
  - Vancomycin + Cefepime or Aztreonam or Levaquin
### Antibacterials

**Zosyn:**
- Coag. abnormalities
- Thrombocytopenia
- Jarisch-Herxheimer reaction
- Seizures (renal failure)

**Levaquin:**
- QT prolongation
- Caution with electrolyte abnormalities
- Hypoglycemia
- Tendon rupture
- Caution in Sz d/o

### Antifungals

- Azoles (voriconazole, etc)
- Echinocandins (caspofungin, micafungin)
- Amphotericin B
- Bactrim

### Antivirals

- Acyclovir

**Reactivation**
- HSV
- CMV
- EBV
- Hepatitis B
Fluid Resuscitation

- +Fluid balance → steady state fluid balance → (-) fluid balance
- CHF and CKD
- Crystalloids
  - 30ml/kg bolus
  - maintenance fluids
  - NS vs LR
- Colloids
  - Albumin (no definitive answer from research)
  - Starches=AKI

Corticosteroids

- Greater dendritic cell response= greater magnitude and time of sepsis presentation
- Glucocorticoids mute dendritic cell response
- During sepsis increased chemical mediator concentrations=blunted adrenal corticosteroid production
- Addition of exogenous corticosteroids decreases magnitude and truncates length of presentation but increases risk of recurrent infection
- Hydrocortisone

Sodium Bicarbonate

- No current research supported recommendations but in practice
- Indicated for ESRD or renal tubular acidosis patients with concurrent sepsis
- pH < 7.2
- Issues
  - Na overload thus fluid overload also
  - Increases lactate and pCO2 levels
  - Decreases ionized Ca levels which results in decreased CO

Dysglycemia and Sepsis

- Hyperglycemic variability s/t proinflammatory mediators (cortisol, catecholamines, cytokines)
- Prothrombotic effects
- Decreased endothelial vascular reactivity
- Decreased function of neutrophils
- Insulin gtt-short acting
  - Goal BG 140-180
Metabolism and Sepsis

- Net catabolic state
  - Decreased carbs, protein, and lipids
- Anorexia
- Encephalopathy
- Mechanical ventilation
- ~6 day delay in nutritional supplementation
  - Enteral first!

<table>
<thead>
<tr>
<th>Table 1: Summary of major metabolic changes in sepsis</th>
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<tbody>
<tr>
<td>Physiologic Change in Sepsis</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Gluconeogenesis, Hyperglycemia glycosis</td>
</tr>
<tr>
<td>Protein catabolism</td>
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<tr>
<td>Lipolysis</td>
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<tr>
<td>Micronutrients</td>
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<tr>
<td>Neuroendocrine activation</td>
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<tr>
<td>Cortisol</td>
</tr>
<tr>
<td>Catecholamine release</td>
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<tr>
<td>Cytokine release</td>
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<tr>
<td>Impaired oxygen utilization</td>
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</tbody>
</table>

ETOH use and sepsis

- Associated with CAP
  - Extended duration of febrile state
  - Increased length of hospital stay
  - Increased likelihood of empyema and ARDS
- Minimizes immune function
  - Neutrophil and Macrophage activity
- Increased proinflammatory cytokines
- Increased intestinal permeability and bacterial translocation
- Decreased cilia and surfactant function
- Increases risk of aspiration
- Poor dental hygiene
- Minimizes cough reflex
- Malnutrition

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CDC

IDSA

WHO