

## ICU PEARLS

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## RESPIRATORY

### *Methemoglobinemia*

- The traditional treatment for methemoglobinemia is methylene blue IV, which reduces ferric iron to ferrous iron via an NADPH-dependent process. Treatment depends on:
  - Severity of the symptoms
  - The methemoglobin level
    - Levels <20% are generally well tolerated and can be treated conservatively
    - Levels 20% to 50% generally require treatment
  - Presence of G6PD deficiency
    - In patients with G6PD deficiency (and thus low NADPH), methylene blue is ineffective and can promote further hemolysis and worsen methemoglobinemia
    - Ascorbic acid is considered the treatment of choice when symptomatic methemoglobinemia occurs in the setting of proven or strongly suspected G6PD deficiency
      - Ascorbic acid and N-acetylcysteine are electron donors independent of NADPH and can lower methemoglobin levels

### *Smoke inhalation injury*

- Injuries to the upper airway due to thermal exposure and SIR
  - Capillary leak and airway edema, impaired ciliary function, and bronchospasm
  - Coagulation and fibrinolysis become unstable
- Carbon monoxide toxicity
  - All patients who present after inhalation injury or house fires
    - Should receive high-flow oxygen irrespective of O<sub>2</sub>Sat or PaO<sub>2</sub>
    - Carboxyhemoglobin level through a co-oximetry panel
  - Hyperbaric oxygen is reserved for patients with a level >25% or >20% if pregnant
    - Transfer to a center for hyperbaric therapy may be necessary
- Cyanide poisoning should be evaluated given the high likelihood of occurring during a fire
  - Bitter almond smell
  - Bright red venous blood should raise suspicion
  - Hydroxocobalamin is the antidote. Should be administered in severe cases (cardiac decompensation and/or arrest), even if laboratory confirmation is not yet attained

## CARDIOVASCULAR

### *Biventricular implantable cardiac defibrillator - resynchronization therapy*

- Improve symptoms, LVFx, and mortality
- Indication
  - Symptomatic pts on GDMT for heart failure
  - EF <35%
  - LBBB with QRS >120 milliseconds (optimally >150 milliseconds)

### *Electrical storm*

Greater than two to three episodes of sustained ventricular arrhythmia within 24h

- Antiarrhythmic for sustained monomorphic VT (Amiodarone, Dofetilide, Lidocaine)
- $\beta$ -blockade as an adjunct
  - Propranolol is superior to metoprolol

- Urgent ablation of the arrhythmogenic locus may be attempted

#### **Endocarditis – anticoagulation and complications**

- Anticoagulation for embolic stroke in the setting of endocarditis is typically not recommended
- Septic pulmonary emboli occur more commonly with TV involvement and often involve multiple pulmonary vessels
- Complications
  - ICH, SAH
  - Cerebral abscess from septic embolization
  - Mycotic aneurysm in the cerebral vasculature - tissue infections
    - Often present with either AIS or ICH
    - May persist even when BCs are negative, particularly in patients on antibiotics
    - Identified by angiography
      - Incidence is almost 9% markedly higher than the 1% that was previously reported

#### **Hemopericardium in the setting of acute MI**

- Stanford Type A aortic dissection with subsequent pericardial dissection
  - TEE is a very sensitive test for proximal, type A, aortic dissection
- Ventricular free-wall rupture
  - The diagnosis or even a suspicion of LV free-wall rupture is an indication for emergency cardiac surgery
  - Responders to fluid loading for cardiac tamponade derive the majority of benefit with boluses between 250 and 500 mL
  - Emergency pericardiocentesis is not a definitive solution and would lead to additional lost time

#### **Leadless pacemakers**

- Safer alternative to TVPMs for patients with bradycardia due to Afib with AV block
- Their use could be expanded in the future
  - Vasovagal syncope
  - Ablation
  - Possible dual chamber pacing through leadless coupling of two devices

#### **MI with cardiogenic shock**

- PCI is indicated for occlusive MI even several days after initial onset of symptoms (delayed presentation)
- CABG in the acute setting is generally reserved for patients with coronary lesions not amenable to PCI
- Consider MCS either before or after the PCI

#### **Passive leg raising (PLR) maneuver**

- Begins from a semi recumbent position followed by legs elevation and lowering torso, maintaining a similar angle at the hips
  - PLR is less valid when initiated from a fully supine position
- The measurement of effect is determined 1 to 3 min after the postural change
- If PetCO<sub>2</sub> increase >5% after PLR maneuver, an IVF bolus will augment cardiac output by >15% (great specificity)

### **Pericarditis – ECG**

- Diffuse upsloping ST elevation
- Negative PR segment
- The presence of deep T wave inversion reciprocal to the ST elevation indicates that is not pericarditis

### **Poor R wave progression**

- Suggest an anterior infarction with an apical thrombus
  - TTE is more sensitive for mural thrombus
  - TEE is more sensitive for LA thrombus but less for detection of mural thrombi because the cardiac apex may not always be well visualized

### **Post CABG pleural effusion**

Perioperative: within the first week

- Usually attributable to diaphragm dysfunction or internal mammary artery harvesting and are typically self-limited.

Early: within 1 month

- Usually attributable to postcardiac injury syndrome and may require treatment (NSAID, allopurinol, steroids).

Late: 2-12 months

- Can have multiple causes.

Persistent: after 6 months

- Usually attributable to trapped lung and often require decortication.

### **Post-MI mechanical complications**

#### **Ventricular septum rupture VSD**

- Most common with transmural MI involving the septum, delay presentation, or first time (no time for development of collaterals)
- High mortality next to free wall rupture
- Treatment: similar to acute MR or AR
  - Decrease afterload, optimize preload, and control rate
    - Increased afterload favors left to right shunting and risk for RV failure
    - If RV failure be cautious with positive pressure because increases RV afterload and decreases preload
  - CV surgery and interventionalist cardiology consults
    - Temporizing measures
    - MCS is usually not indicated. Consider only if patient in ventilator
      - Impella favors right to left shunt resulting in hypoxemia
      - V-A ECMO increases afterload favoring left to right shunting and risk for RV failure
    - Percutaneous closure devices in patients at high operative risk or as a temporizing measures within the first to two weeks before surgical closure
    - Surgical closure preferable after one to two weeks because when the friable tissue contract results in residual VSD

#### **LV free wall rupture**

Treatment

- IVF and inopressors
- Pericardiocentesis if evidence of hemopericardium

- Emergent surgery

#### *Acute MR*

- More common in inferior or lateral MI
- Acute large V wave in PCWP monitoring
- Treatment
  - Low threshold for NIV, avoid bradycardia
  - PCI early revascularization
    - CABG only if patient not a candidate for PCI
  - Percutaneous MR repair
    - Option at a later time if symptomatic MR despite revascularization and institution of guideline-directed medical therapy

#### *Post MI or pericardiotomy syndrome*

- Time frame: as early as one week to as late as three months prior to symptoms
- Clinical picture: supportive but not specific enough to definitively make the diagnosis
  - Pleuritic chest pain, fever and Leukocytosis
  - CXR: cardiomegaly, pleural effusion
  - EKG changes: diffuse ST-segment elevation in association with PR depression
  - Echocardiogram: pericardial effusion

#### **Treatment**

- Combination of colchicine and NSAIDs
  - Colchicine 0.5 mg twice daily for patients  $\geq 70$  kg, 0.5 mg daily for those  $< 70$  kg) for 1 month
  - Ibuprofen 600 mg q8h, with gradual tapering every week for a treatment period of 1 month
- Prednisone 20 mg/d followed by a slow taper to complete 1 month
  - For nonresponders to combination of colchicine and NSAIDs

#### *Pulse patterns*

- Pulsus paradoxus - exaggerated in cardiac tamponade
- Pulsus alternans - usually seen with severe LV dysfunction
  - It represents variable ventricular filling and SV
- Pulsus bisferiens - biphasic pulse seen in the aortic waveform as two peaks per cardiac cycle
  - Common causes include mixed aortic valve disease such as endocarditis and bicuspid AV

#### *RV Failure*

RV failure defined as RV dysfunction plus low cardiac output

- RV dysfunction defined as occurrence of at least one of the following
  - Echo findings - decreased RV function or RV dilatation
  - TAPSE
    - Normal: 1.8 – 2 cm
    - Borderline 1.6-1.8 cm
    - Decreased:  $< 1.6$  cm
  - EKG findings - complete or incomplete RBBB, anteroseptal ST elevation or depression, anteroseptal T inversion
  - Biomarkers – unexplained pro BNP elevation

#### *Secondary hypertension*

- Renal artery stenosis
  - Sudden severe onset of more than 180/120 mm Hg and:

- Older than 55 years
- Deterioration of renal function while receiving an angiotensin-converting enzyme or an angiotensin-receptor blocker
- Radiographic evidence of renal atrophy
- Recurrent flash pulmonary edema
- Abdominal bruit
- Testing can include contrast-enhanced magnetic resonance angiography, CT angiography, or Doppler ultrasonography
- Primary hyperaldosteronism
  - Hypokalemia
  - The diagnosis can be made by evaluating the aldosterone:renin ratio
    - Aldosterone level is inappropriately high for the renin level
- Pheochromocytoma
- OSA

### ***Shock after Cardiotomy (Causes)***

#### **Ventricular failure due to primary cardiac abnormalities**

- Myocardial infarction
- Myocardial stunning
- Acute valvular obstruction or regurgitation
- Myocarditis
  - Viral
  - Eosinophilic myocarditis
    - Hypersensitivity myocarditis or acute necrotizing eosinophilic myocarditis or the DRESS syndrome (drug reaction with eosinophilia and systemic symptoms)
    - Eosinophilic granulomatosis with polyangiitis (EGPA)
    - Idiopathic Hypereosinophilic syndrome (Löffler's endocarditis)
    - Parasitic infection
    - Cancer (e.g., myeloproliferative disorder).

#### **Extrinsic obstruction**

- Pericardial tamponade
- Pulmonary embolism
- Tension pneumothorax

#### **Hypovolemia**

- Bleeding
- Inadequate volume resuscitation

#### **Vasodilatory shock**

- Systemic inflammatory response syndrome – sepsis, pancreatitis, etc.
- Anaphylaxis
- Adrenal insufficiency

#### **Neurogenic**

- Spinal cord injury

### ***Wolff-Parkinson-White (WPW) syndrome with acute Afib***

- Classically diagnosed by the presence of a short PR interval and a delta wave in NSR

- In Afib the QRS complex is wide in some beats, narrower in others, and differs from beat to beat
  - This combination of features makes the diagnosis of WPW syndrome with Afib
- Treatment
  - Urgent electrical cardioversion if hemodynamically unstable
  - Rate control with procainamide or ibutilide
    - Procainamide and ibutilide slow conduction down bypass tracts in WPW
  - Drugs to avoid: adenosine, BBs, CCBs, amiodarone, and digoxin
    - Drugs that slow AV nodal conduction increase the number of impulses that go down through the bypass tract and actually increase VR
  - Ablation for prevention of recurrent arrhythmias

## NEPHROLOGY

### *Solute diuresis*

- Common cause of polyuria with urine osmolality >300
  - Postacute tubular necrosis diuresis (urea solute diuresis)
  - Sodium diuresis from volume expansion with saline
  - Glucosuria
  - Postobstructive diuresis

### *Vasopressin withdrawal*

- Discontinuing vasopressin can result in DI (polyuria with rapid rise in serum Na level and low urine osmolality)
- Dangerous in patients who develop moderate or severe hyponatremia while on vasopressin drip

## ENDOCRINE

### *Carcinoid crises*

- Flushing, diarrhea, bronchospasm, and tachycardia
- Tumor embolization or surgical procedures in patients with neuroendocrine tumors can release large amounts of serotonin and other small-molecule neurotransmitters
- Octreotide reduces this risk and also used for treatment of diarrhea

### *Refeeding syndrome and DKA*

The treatment of malnourished patients with DKA can mimic refeeding syndrome.

- During treatment of DKA, serum phosphate levels can drop dangerously low
- Patients with uncontrolled diabetes are at increased risk of hypophosphatemia because they are typically in negative phosphate balance due to poor phosphate intake and hyperphosphaturia due to osmotic diuresis.
- Severe hypophosphatemia can cause decreased ATP production which compounded by malnutrition can cause neuromuscular respiratory failure, flaccid motor weakness, diminished deep tendon reflexes, rhabdomyolysis, confusion, seizures, and coma and occasionally associated with ventricular arrhythmias.

## INFECTION DISEASE

### *Abx for Urosepsis*

Piperacillin-tazobactam



- Excellent gram-negative coverage including pseudomonas
- Coverage of community-acquired enterococci (*enterococcus faecalis*)
- Adequate coverage for AmpC enterobacterales (may not be ideal for them, but emerging evidence support its efficacy)

Cefepime is an alternative option:

- Better gram-negative coverage compared to ceftriaxone (cefepime covers gram-negatives with AmpC beta-lactamase and pseudomonas).
- Lacks any enterococcal coverage.
- Can be used in patients with penicillin allergy (cefepime's side chain doesn't cross-react with penicillin).

### **Bacterial meningitis**

Three most common meningeal pathogens

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Neisseria meningitidis*

Nonsignificant reduction in mortality in adults with meningitis receiving corticosteroids except for *streptococcus pneumoniae*

### **Cefepime encephalopathy**

- Agitation, myoclonus, and seizures
- Similar to EtOH has competitive binding to GABA receptors
  - Benzodiazepines may be useful
- AKI is a key risk factor
  - Require dose adjustment for renal function if GFR <60
  - Even dose-adjusted should be used with caution
    - Excessively elevated serum concentrations of cefepime can be present in patients AKI

### **Infection prevention**

- Universal gowning and gloving have been proposed to reduce the transmission of multidrug-resistant organisms (MDRO)
  - However, a large trial did not demonstrate a reduction in MRSA or VRE acquisition
  - It was associated with reduction in health care professional entry into patients' rooms, raising concerns for unintended harms
- Daily bathing with chlorhexidine for critically ill patients in an ICU has been shown to decrease nosocomial infections and colonization with MDRO in several randomized clinical trials

### **Legionella**

- Diarrhea, hyponatremia, and aminotransferase elevation
- Macrolide, fluoroquinolones or tetracyclines
- Diagnosis
  - PCR of a lower respiratory tract sample (high-quality sputum specimen or BAL)
    - Detect all *Legionella* species and serogroups
  - The sensitivity of culture varies but the specificity is very high
  - If no high-quality lower respiratory tract sample use urinary antigen
    - Only positive for *Legionella pneumophila* serotype (most common cause)
    - Other *Legionellas* account for approximately 20% of cases

- Disinfection of the contaminated water supply is critically important to mitigate outbreaks
  - Superheating and flushing the systems
  - Copper-silver ionization
  - Ultraviolet light

Chlorination of the water

### **Strongyloidiasis**

- In the GI tract, the larvae mature into adult worms that reside in the mucosa of the duodenum and jejunum and may live for years
  - With an intact immune system, the chronic stage of strongyloidiasis is most often asymptomatic or characterized by mild GI symptoms.
- In patients with diminished cell-mediated immunity, hyperinfection with disseminated disease may develop and involve many organs
  - Fleeting lung infiltrates
  - Gram-negative bacteremia related to increased helminthic involvement of the bowel
  - Skin manifestations of migrating larvae are also common
  - Eosinophilia is present in a majority of patients during the chronic phase of the illness but often disappears during disseminated disease
- Confirmation is by demonstration of eggs or larvae in the stool, but this test, while specific, is not sensitive
- Stool examination should be accompanied by serum testing by enzyme-linked immunosorbent assay for *Strongyloides* antigens
- Ivermectin is the agent of choice
  - Since stool and serum testing may require several days or longer, patients who require immediate treatment with corticosteroids should be started on Ivermectin while further confirmation of infection is sought

### **PICC**

- Risk of bloodstream infections is similar to traditional CVCs but higher than peripheral IVs
- Catheter-related DVT higher than CVCs in the IJ, SC, or femoral veins with a NNH of 26
  - Upper extremity DVT develops in up to one-third of patients with a PICC
  - VTE prophylaxis does not seem to reduce this risk
  -

### **VAP prophylaxis in acute brain injury**

Consider using a single dose of ceftriaxone 2 gr IV within the 12 h following intubation in patients with severe brain injury expected to require mechanical ventilation for at least 48 h.

- Severe acute brain injury defined as:
  - $\leq 12$  GCS after trauma, stroke, or subarachnoid hemorrhage.

The PROPHY-VAP trial - *The Lancet respiratory*. Published online January 20, 2024

- Early single dose of ceftriaxone 2 gr IV in patients with severe brain injury
- Prevent early VAP
- Decreased antibiotic and ventilation exposure
- Decreased ICU and hospital exposure at day 60 without safety concerns
- Improve mortality at day 28

## NEUROLOGY/PSY

### **Acute disseminated encephalomyelitis (ADEM)**

- Postinfectious autoimmune encephalopathy
- MRI brain with demyelination of the white matter with typical sparing of the cortical gray matter
- There is a rare variant called *acute hemorrhagic leukoencephalitis*, which manifests primarily as multifocal hemorrhage with patchy demyelination
- Elevated CSF WBC count and elevated IgG index, which suggests production of IgG in the CSF in excess of blood
- Treatment
  - Methylprednisolone is the first line
  - Plasmapheresis in patients who fail steroids
  - IV immunoglobulins have been used

### **Cocaine**

- Bronchospasm, pneumothorax, pneumomediastinum, DAH, noncardiogenic pulmonary edema, organizing pneumonia, and eosinophilic lung disease
- Treatment
  - Benzodiazepines as first-line treatment
    - Reduce psychomotor agitation, the risk of subsequent seizures, and treat HTN and chest pain effectively
    - High doses are often required
  - Uncontrolled HTN or tachycardia
    - Either alone or combination of nitroglycerin or CCB or BBs (especially mixed  $\beta_1$ -/ $\alpha_1$  such as carvedilol and labetalol)
  - Lidocaine and sodium bicarbonate can treat tachydysrhythmias

### **Gabapentin-related hypercapnic respiratory encephalopathy**

- Dilated pupils and horizontal nystagmus are characteristic
- Impaired renal function is a risk factor

### **Local anesthetic systemic toxicity (LAST)**

- Primarily due to inadvertent intravascular injection and systemic absorption
- Bupivacaine is the more often associated
- Usually develop immediately to within 15 min after injection
- Neurologic and cardiac effects
- Treatment is IV 20% lipid emulsion
- ACLS in LAST
  - Reduced epinephrine boluses to  $\leq 1$   $\mu\text{g}/\text{kg}$ , avoidance of vasopressin, calcium channel blockers, and  $\beta$ -blockers
  - Amiodarone is the first-line antiarrhythmic

### **Physostigmine for anti-cholinergic toxicity - Diphenhydramine OD, Seroquel OD**

#### Indications

- Presence of peripheral or central antimuscarinic effects without significant QRS or QT prolongation
  - Peripheral: dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia

- Central: agitation, delirium, hallucinations, seizures, and coma

#### Contraindications

- Reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, and AV block and.
- Known or suspected TCA OD

#### Dose

- Physostigmine 1 mg IV over 5 minutes (mixed in 50 mL NS), can be repeated x 1, ~10-15 minutes after the 1st dose. **Continuous cardiac monitoring and atropine at the bedside**

## HEMATOLOGY/ONC

### *Acute hyperleukocytosis*

Defined as a total leukemia WBC >50,000 to 100,000 characterized by microvascular WBC plugs and symptoms of decreased tissue perfusion

- Most commonly seen in AML
  - Can also be seen with acute lymphoblastic, chronic lymphocytic, or chronic myeloid leukemia
- Spurious hypoxemia is a unique finding that can be seen in these patients due to increased  $VO_2$  by leukocytes
  - $SpO_2$  may be more reliable than  $PaO_2$  in this setting
- Respiratory and neurologic symptoms due to lung and brain microvascular involvement are most common
  - High risk of early mortality due to respiratory failure or intracranial bleeding
- Myocardial, bowel, renal, and limb ischemia and priapism can also be seen
- Fever is also common and can be due to inflammation from leukostasis or concurrent infection
- Overestimation of platelet count with automated blood cell counters
  - Importance of peripheral smear confirmation
  - Continued platelet support is important to reduce the risk of hemorrhage due to both thrombocytopenia and disseminated intravascular coagulation
- Risk of severe tumor lysis syndrome
- Treatment
  - Requires urgent cytoreduction with hydroxyurea or chemotherapy
  - Leukapheresis is controversial, as two meta-analyses have failed to demonstrate improvements in survival

### *Cytokine release syndrome (CRS) due to immunotherapy Chimeric antigen receptor (CAR)-T cell therapy*

- Acute SIR characterized by fever and potentially multiple system organ dysfunction
  - Some patients manifest a predominant neurologic syndrome called immune effector cell-associated neurotoxicity syndrome
  - Almost all patients receiving CAR-T cell therapy will develop some manifestation of inflammation and as many as 25% may require ICU
- Tend to occur 2-14 days after initiating treatment
- The severity is graded based on fever, hypotension, and hypoxemia
- Treatment
  - Mild cases
    - Supportive- symptomatic

- Need for vasopressors, HFNC, NIM, or IMV
  - Corticosteroids and tocilizumab
  - Corticosteroids alone might deplete or eradicate the infused CAR-T cells

#### **Early complications of hematopoietic stem cell transplant**

- Acute graft-vs-host disease
  - Typically manifests around the time of engraftment
  - Usually involves the skin and GI tract (diarrhea, abdominal pain, and liver function abnormalities with a cholestatic pattern)
- Engraftment syndrome
  - Systemic inflammation with fever, rash, and diffuse capillary leak with resulting pulmonary edema and end-organ dysfunction
- TMA
  - Often does not respond to plasma exchange
  - Rituximab, defibrotide, and eculizumab may be beneficial
- Diffuse alveolar hemorrhage is a rare complication

#### **Therapeutic plasma exchange Indications**

- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
- Myasthenic crisis
- Anti-glomerular basement membrane disease (Goodpasture syndrome)
- Some types of vasculitis
  - Thrombotic thrombocytopenic purpura (TTP)
  - Can be considered in GPA positive for anti-glomerular basement membrane if steroids and cyclophosphamide/rituximab have failed
- Second line after methylprednisolone in post infectious acute disseminated encephalomyelitis (ADEM)

#### **Tranexamic acid**

- Mortality benefits in postpartum hemorrhage, trauma, and selected patients with traumatic brain injury (TBI)

## **GASTROENTEROLOGY**

#### **Acetaminophen overdose**

The Rumack-Matthew nomogram is not reliable in the following conditions:

- Chronic use of acetaminophen
- Alcohol use disorder
- Preexisting liver disease

#### **Acute colonic pseudo-obstruction (Ogilvie syndrome)**

Defined as colonic dilatation of the colon (usually the cecum and the ascending colon) without evidence of a mechanical stenosis.

#### **Treatment**

- Conservative treatment if there are no signs of sepsis and if (imminent or existing) perforation and ischemia have been ruled out

- Correction of electrolyte abnormalities
- Discontinuation of constipating drugs
- Nasogastric tube
- Decompressive rectal tube
- Consider neostigmine 2 mg IV
- Endoscopic deflation and insertion of a decompressive tube in the right hemicolon if pharmacotherapy brings no improvement in 2 to 3 days
- Absolute indications for surgery
  - Imminent or existing bowel perforation or ischemia
  - Persistent dilatation of the colon with a diameter larger than 12 cm for several days

***Splanchnic vein thrombosis (portal venous system or hepatic venous outflow tract)***

In patients with primary thrombosis in the absence of cirrhosis.

- Complete work-up that considers prothrombotic factors and systemic diseases is recommended for patients with primary thrombosis in the absence of cirrhosis.
- Myeloproliferative neoplasia (MPN) should be searched for by testing for the V617F JAK2 mutation in peripheral blood.
  - In patients with no detectable JAK2 V617F mutation, consider additional investigations for MPN, including somatic calreticulin and JAK2-exon12 mutations, and next-generation sequencing.
  - In patients without an MPN driver mutation, bone marrow biopsy should be discussed to rule out MPN, irrespective of blood cell counts. Bone marrow biopsy should be considered particularly in patients without major risk factors for thrombosis.

**DERMATOLOGY**

***Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) continuum***

- Onset between 5 and 28 days but can be seen as early as 1 to 2 days
- Prodrome is typically present 1 to 3 days prior to the onset of observable cutaneous and/or mucous membrane findings
  - Early features include high fever, malaise, and myalgia. Diffuse skin pain is prominent feature
  - Symptoms attributed to early mucous membrane involvement
    - Photophobia, conjunctival dryness and burning, orodynia, and odynophagia
- Phenobarbital has a well-documented association with SJS/TEN