**ANGIOEDEMA**

**DEFINITION** – swelling of subcutaneous or submucosal tissues secondary to enhanced vascular permeability, a process that allows movement of fluid from the vascular space into the interstitial space

- Non-pitting, non-gravity dependent, can last up to 7 days

**TWO TYPES**

- Bradykinin-mediated
- Histamine-mediated

**BRADYKININ-MEDIATED**

- Bradykinin accumulation causes nonhistaminergic angioedema
- Decreased metabolism of bradykinin (ACE-I use)
- Low C1-inhibitor levels in hereditary angioedema (HAE) - type 1
- Abnormal C1-inhibitor function in hereditary angioedema (HAE) - type 2
- Acquired C1-inhibitor (C1-INH) deficiency due to consumption

- Not associated with URTICARIA
- Concurrent GI symptoms
- Typically lasts 2-5 days
- Usually unresponsive to antihistamine/corticosteroids

**ACE INHIBITOR ANGIOEDEMA**

- 30% of adult ED patients with angioedema are related to ACE-I
- 0.1-0.7% of patients on ACE-I will develop angioedema
- Most common in African American patients, or patients on immunosuppressants
- Highest risk during first 30 days of initiating med
- Other meds can cause angioedema
  - Allura, minocycline, NSAIDs (histamine induced)

**HEREDITARY ANGIOEDEMA**

- Type I and Type II
- Abnormal C1-inhibitor gene → results in over production of bradykinin
- Symptom onset → childhood/young adult
- Recurrent episodes of swelling/abdominal pain as early as age 10
- May have prodromal rash → erythema marginatum
- May present with GI symptoms
- 1 in 50,000
PHYSICAL EXAM – BRADYKININ MEDIATED

- Firm, nonpruritic swelling
- Most prominent in dermis/subcutaneous tissue
- Sometimes tender to palpation
- Non-pitting

HISTAMINE MEDIATED

- Urticarial lesions
- Most prominent in deeper dermis
- Lesions arise from local vasodilatation and increased vascular permeability
- Can manifest with or without anaphylaxis
- Often associated with urticaria
- Usually resolves within 24-48 hours
- Common causes – drugs, foods, latex, insect stings

TESTING

- No ED tests available to provide immediate guidance on etiology
- C4 and tryptase levels
  - Beneficial in diagnosis of HAE
  - Angioedema associated with anaphylaxis

C4 LEVEL

- Excellent screening for C1-inhibitor
- Most beneficial if drawn during an episode of angioedema
- Low C4 level → abnormal
- Does not respond to anti-histamines

TRYPTASE LEVEL

- Normal in HAE
- May be elevated in case of anaphylaxis or other mast-cell mediated angioedema
- Helpful in ruling out HAE

AIRWAY EVALUATION

- Little benefit in CT imaging to help determine the extent of airway involvement
- Lingual involvement, Sibilant Hoarse Voice
- Heighten concern for airway involvement
- Direct Visualization
  - FIBEROPTIC MARYNGOSCOPY or NASOPHARYNGOSCOPY
- To determine the extent of airway involvement in all patients with tongue involvement
- Consider early invasive airway management
PHARMACOLOGY

- Angioedema with anaphylaxis (urticaria, asthma, hypotension)
- Epinephrine recommended
- H1 and H2 antagonists
- Steroids
- Bradykinin-mediated angioedema
- Above interventions not contraindicated, may not help
- Should be given if cause of angioedema is unknown

PHARMACOLOGY – FFP

- Considered in ACE-I induced or bradykinin-mediated angioedema
- FFP contains variable amounts of C1-INH
- Risk of allergic reaction, volume overload
- Can worsen angioedema if underlying cause is HAE

PHARMACOLOGY – NOVEL AGENTS

- 2 purified C1-INH protein concentrates
- Ecallantide – kallikrein inhibitor (blocks bradykinin formation)
- Icatibant – bradykinin 2 receptor antagonist (blocks vascular effects of bradykinin)

- Effective in treatment of HAE attacks
- May be beneficial in ACE-I angioedema (limited data)

DISPOSITION

- Face, lip, soft palate edema
- Often can be discharged following treatment/observation
- Tongue swelling 3+ sites of edema
- Often required admission for monitoring/treatment

AORTIC DISSECTION


- Weakness/disruption of the intima layer
- Connective tissue disorders
- Hypodynamic stressors (elev HR)
- Abnormal blood flow (bicuspid aortic valve)
- Thoracic aortic dissection → in-hospital mortality upward of 27%
AORTIC DISSECTION - CLASSIFICATION

- **Type A**
  - Involves the ascending aorta and/or arch
  - Higher mortality
  - Hypotension is more common
- **Type B**
  - Involves the descending aorta/arch below the level of L subclavian artery
  - No benefit of surgical intervention
  - Back/abd pain more common

ARE THERE CLINICAL DECISION RULES THAT CAN SAFELY IDENTIFY PATIENTS AT LOW RISK FOR THORACIC AORTIC DISSECTION?

- **LEVEL C RECOMMENDATION**
  - In an attempt to identify patients at very low risk for acute nontraumatic thoracic aortic dissection, do not use existing clinical decision rules alone. The decision to pursue further work up for acute nontraumatic aortic dissection should be at the discretion of the treating physician.

PRESENTATION/PREDICTORS

- Classic – tearing chest pain, radiating to back
- Most common – abrupt onset of severe pain, present in 84% of patients

- **Predictors:**
  - Acute onset of pain (severe, ripping, and/or tearing)
  - Mediastinal widening/aortic widening on CXR
  - Pulse differential and/or BP difference of > 20 mmHg between arms

In 250 pts (128 had thoracic dissection)
- Absence of all 3 predictors, prevalence was 7%
- Presence of all 3 predictors, prevalence of 100%

IS A NEGATIVE D-DIMER SUFFICIENT TO IDENTIFY PATIENTS AT VERY LOW RISK FOR THORACIC AORTIC DISSECTION?

- **LEVEL C RECOMMENDATION**
  - In adult patients with suspected nontraumatic thoracic aortic dissection, do not rely on D-Dimer alone to exclude the diagnosis of aortic dissection.

  - Low or False-negative D-Dimer may be caused by:
    - Chronicity, time of symptom onset, presence of thrombosed false lumen, intramural hematoma, short length of dissection, young age
    - D-Dimer is nonspecific
  - Routinely ordering this may result in increased imaging/radiation

IS THE DIAGNOSTIC ACCURACY OF CTA AT LEAST EQUIVALENT TO TEE OR MRA TO EXCLUDE THORACIC AORTIC DISSECTION?

- **LEVEL B RECOMMENDATION**
  - In adults with suspected nontraumatic thoracic aortic dissection, emergency physicians may use CTA to exclude thoracic aortic dissection because it has accuracy similar to that of TEE and MRA.

  - CTA: sensitivity → 99%, specificity → 100%
  - Alternate findings identified 13% of cases
  - TEE sensitivity → 98%, specificity → 95% (tech dependent)
  - MRA: sensitivity → 98%, specificity → 98%

CAN AN ABNORMAL BEDSIDE TTE CONFIRM AN AORTIC DISSECTION DIAGNOSIS?

- **LEVEL B RECOMMENDATION**
  - In adult patients with suspected nontraumatic thoracic aortic dissection, do not rely on abnormal TTE result to definitively establish the diagnosis of thoracic aortic dissection

  - TTE sensitivity ranging from 99 – 100%
  - TTE specificity ranging from 0 – 100%

  - **LEVEL C RECOMMENDATION** (Consensus Recommendation)
  - In adult patients with suspected nontraumatic thoracic aortic dissection, immediate surgical consultation or transfer to a higher level of care should be considered if a TTE is suggestive of aortic dissection.
DOES REDUCING THE TARGETED HEART RATE AND BLOOD PRESSURE HELP MITIGATE MORBIDITY AND MORTALITY?

- **LEVEL C RECOMMENDATION**
  - In adult with acute nontraumatic thoracic aortic dissection, decrease blood pressure and pulse if elevated. However, there are no specific targets that have demonstrated a reduction in morbidity or mortality.
  - Consensus guidelines recommend HR < 60, and systolic blood pressure < 120

CALCIUM CHANNEL BLOCKER OVERDOSE


CALCIUM CHANNEL BLOCKER OVERDOSE

- At least 11,000 exposures in 2011
- At least 78 deaths in US in 2011

- Review found low level of evidence supporting the use of high-dose insulin, extracorporeal life support, and a very low level of evidence supporting the use of calcium, dopamine, norepinephrine, and epinephrine for CCB toxicity.

- Potentially life threatening toxicological emergency
  - Hypotension, conduction abnormalities, arrhythmias, bradycardia
  - Hyperglycemia, nausea, vomiting, noncardiogenic pulmonary edema

GI DECONTAMINATION

- Should be considered for large, life-threatening ingestions that occurred within 1-2 hours of evaluation.

CALCIUM

- IV Calcium is a reasonable first-line therapy
  - Appears to reduce mortality and improve hemodynamic stability
  - Adverse Effects: RARE
  - Typical Dosing: 1-5 g IV calcium chloride (or equivalents of calcium gluconate), followed by infusion

OBSERVATIONAL STUDY IN HUMANS

- The only observational study in humans examined high-dose insulin and extracorporeal life support
- Low Quality of Evidence
### HIGH-DOSE INSULIN THERAPY
- High-dose insulin was associated with improved hemodynamic parameters and lower mortality.
  - **BOLUS**: 1 unit/kg
  - **INFUSION**: 0.5 – 2.0 units/kg/h
- **RISK** → Hypoglycemia, Hypokalemia
- **LOW Quality of Evidence**

### EXTRACORPOREAL LIFE SUPPORT
- Associated with improved survival in patients with severe shock or cardiac arrest.
- Should be considered early in the above patients.
- **RISKS** → Limb ischemia, thrombosis, bleeding
- **LOW Quality of Evidence**

### GLUCAGON
- **Role of GLUCAGON in Calcium Channel Blocker toxicity** is lacking
- Optimal dosing and efficacy is unclear
- Side effects → hyperglycemia, vomiting, aspiration

### VASOPRESSORS
- Although evidence is inconsistent...
  - **DOPAMINE, NOREPINEPHRINE, and EPINEPHRINE**
    - May improve hemodynamic instability
    - May reduce mortality
  - No significant ischemic complications noted with high dose vasopressor in case series of 48 patients
- **VERY LOW Quality of Evidence**

### LIPID EMULSION
- Limited studies suggest that lipid emulsion therapy may improve survival in patients with verapamil poisoning
- Animal models with IV verapamil but not in models of oral verapamil poisoning
- One human case series (3 patients) demonstrated 66% mortality when using lipid emulsion compared to lower mortality in retrospective studies of CCB poisoning
- Severity of CCB ingestions varied between observational and reported case series

### PACEMAKER
- Evidence for transcutaneous and transvenous pacing is mixed
- When successful capture is achieved pacemakers seem to improve hemodynamics
OTHER AGENTS

- 4-aminopyridine
  - Associated with improved hemodynamic parameters and survival in animal studies
  - Risk: increased risk of seizures
- Levosimendan
  - No high-quality evidence to support their routine use

DELIRIUM TREMENS


BASICS

WITHDRAWAL SYMPTOMS

- Agitation, insomnia, Lewy bodies, tremor, nausea/vomiting
- Tachycardia, elevated temperature, elevated blood pressure

Usually begins within 8 hours of decreased alcohol, peaks around 72 hours, and fades within 5-7 days

STATES OF ALCOHOL WITHDRAWAL

- Mild to Moderate
  - Alcohol rapidly increases the release of GABA in the brain
  - After repeated exposure, the brain adapts to the effects of alcohol through changes in receptors
- Withdrawal Delirium (Delirium Tremens)
  - A rapid onset fluctuating disturbance of attention and cognition, sometimes with hallucinations

CIWA-AR

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT OF ALCOHOL SCALE, REVISED

- Consists of 11 items scored on a scale of 0-17 (most severe symptoms):
  1) N/V
  2) Trazodone
  3) Anxiety
  4) Tachycardia
  5) Acute onset
  6) Hypertension
  7) Hypotension
  8) Tremor
  9) Fever
  10) Seizures
  11) Clouding of sensorium

CIWA-AR -- SCORING

- Scores range from 0-67
- 8 = mild withdrawal symptoms
- 8-15 = moderate withdrawal symptoms
- >15 = severe withdrawal symptoms
- Seizures
- Require close monitoring to avoid seizures and CTAs
WITHDRAWAL DELIRIUM – DSM-5

- Alcohol/Withdrawal + Delirium
- 3-5% of patients who are hospitalized for alcohol withdrawal meet the criteria for withdrawal delirium

Criteria for Withdrawal:
- At least 2 of 8 possible symptoms after reduced use of alcohol
  - Autonomic hyperactivity, hand tremor, insomnia, N/v, hallucinations, agitation, anxiety, seizures

Criteria for Delirium:
- Disturbance in attention/memorv/orientation/language/perception/visuospatial ability
- No evidence of coma or other evolving neurocognitive disorder

WITHDRAWAL DELIRIUM

- Usually begins 3 days after the appearance of symptoms of alcohol withdrawal and lasts 2-3 days (ranges 1-8 days)
- 1-4% mortality of hospitalized patients who have withdrawal delirium
- Death usually resulting from hyperthermia, cardiac arrhythmia, complications of withdrawal seizures, or concomitant medical conditions

DELIRIUM DURING ALCOHOL WITHDRAWAL

- Predicted by the following:
  - CIWA-AR scores > 15
  - Especially elevated blood pressure (SBP>150 or HR>100)
  - Recent withdrawal seizures (seen in 20% of patients with delirium)
  - Prior withdrawal delirium or seizures
  - Increased age
  - Recent misuse of other antidepressant agents
  - Concomitant medical problems

TREATMENT OF WITHDRAWAL DELIRIUM

- THIAMINE – 100 mg once or twice IV x 3 days
- MVI daily
- Caution when administering glucose
  - Avoid precipitating Wernicke’s encephalopathy or thiamine related cardiomyopathies
  - Avoid over hydration
  - Patients may have temporary, alcohol related, compromised cardiac function

BENZODIAZEPINES

- No single drug of this class has been shown superior to another

LORAZEPAM REGIMEN
- 4 mg IV/PO every 15 minutes as needed. After patient has received 16 mg,
  - If delirium is still severe, administer 8 mg IV/PO every 15-30 min
- 1-4 mg IV every 5-15 min prn

DIAZEPAM REGIMEN
- 10-20 mg IV/PO every 1-4 hours, as needed

OTHER MEDICATIONS

- HALDOL
  - 0.5 – 5 mg IV or IM every 10-60 min, as needed not to exceed 20 mg
  - 0.5 – 1.0 mg PO every 1-2 hr up to 10 mg

PHENOBARBITAL, CLOPITHIAZOLE, CARBAMAZEPINE
- Data lacking regarding their use in patients with withdrawal delirium

DEXTROMETHORPHINE
- alpha-2-adrenergic agonist
  - Cannot be used in patients with a heart block