A CONSENSUS PARAMETER FOR THE EVALUATION AND MANAGEMENT OF ANGIOEDEMA IN THE EMERGENCY DEPARTMENT

PHILIP PAZDERKA, MD, FACEP

ANGIOEDEMA

- is a physical sign secondary to swelling of the subcutaneous or submucosal tissues and is due to enhanced vascular permeability.
- non-pitting, non-gravity-dependent, transient (lasting up to 7 days)

ANGIOEDEMA

- Bradykinin- or Histamine-mediated.
- Bradykinin-mediated
  - not mediated by IgE antibodies
  - is not associated with urticaria
  - does not respond to antihistamines or corticosteroids
  - poorly responsive to epinephrine

TYPES OF ANGIOEDEMA

BRADYKININ-MEDIATED

- more severe
- longer lasting
- involve concurrent abdominal symptoms
- lasts 2 - 5 days.

HISTAMINE-MEDIATED

- associated with urticarial
- lasts 24 - 48 hrs

ACE INHIBITOR ANGIOEDEMA

- 0.1% - 0.7% of patients develop angioedema
- edema of the lips and tongue
- African-Americans and patients on immuno-suppressants tend to be at higher risk
- highest during the first 30 days therapy
- 30% of adult ED patients with angioedema are due to ACE inhibitor

OTHER DRUGS CAUSING ANGIOEDEMA

RENIN-ANGIOTENSIN SYSTEM

- ARBs
- renin antagonists

INHIBITION OF CYCLOOXYGENASE

- NSAIDs (histamine induced)
HEREDITARY ANGIOEDEMA
• HAE type I and type II are forms of angioedema
  • overproduction of bradykinin
  • due to an abnormal C1-inhibitor (C1-INH) gene
  • begins in childhood/young adulthood and may worsen at puberty.
  • recurrent episodes of swelling or abdominal pain by the age of 10
  • prominent prodromal symptom is erythema marginatum,
  • may present with GI symptoms.

PHYSICAL
BRADYKININ-MEDIATED ANGIOEDEMA
• firm, nonpruritic swelling resulting from the accumulation of fluid in the reticular dermis and subcutaneous or submucosal tissue
• sometimes tender to palpation and are nonpitting

HISTAMINE-MEDIATED ANGIOEDEMA
• deeper dermis and tends to be more commonly associated with urticarial lesions
• lesions arise from local vasodilatation and increased vascular permeability

EVALUATION: ANCILLARY TESTING
• no ED tests available to provide immediate guidance
• C4 and tryptase levels assist in the diagnosis of HAE and angioedema associated with anaphylaxis

LAB RESULTS
C4 LEVEL
• excellent screening tool for C1-INH
• a low C4 level does not respond to anti-histamines
• C4 level need to hit the lab in a timely fashion as degradation and artificially low levels may be reported if there is a significant delay

SERUM TRYPTASE LEVELS
• Tryptase is normal in HAE
• maybe elevated in cases of anaphylaxis or other mast cell–mediated disorders manifesting with angioedema.
• elevated tryptase level can be helpful in ruling out HAE although a normal tryptase level provides no discriminatory information

ACUTE AIRWAY MANAGEMENT
• patients with involvement of the tongue, soft palate, or floor of the mouth as well as those with upper airway complaints
  • flexible fiberoptic laryngoscopy to determine the extent of involvement of the base of the tongue and the larynx
  • Tongue involvement should heighten one’s suspicion of possible airway concerns
  • while pharyngeal or laryngeal involvement definitely warrant close monitoring and consideration of early invasive airway management

ACUTE PHARMACOLOGY
• angioedema presents with signs of anaphylaxis (urticaria, asthma, hypotension), epinephrine is recommended
  • H1 and H2 antagonists and corticosteroids
  • bradykinin-mediates angioedema, these treatments are not contraindicated, and if the cause of angioedema is unknown, epinephrine followed by H1 antagonists and corticosteroids should be given.
FFP

- ACEI-induced or other bradykinin-mediated angioedema in the ED
- Which contains variable amounts of C1-INH, has a risk of viral transmission, allergic reactions, and volume overload and a possibility of worsening symptoms in HAE
- Antifibrinolytics and anabolic androgens
  - Taking such drugs may help identify these patients as possibly having HAE

NEWER DRUGS TREATMENT OF ACUTE HAE ATTACKS

- 2 purified C1-INH protein concentrates
- Ecallantide—kallikrein inhibitor
  - Icatibant—bradykinin 2-receptor antagonist
  - They are effective for the treatment of HAE attacks and may have benefit in ACEI-induced angioedema, but data are limited to support these treatments for non-HAE patients. No randomized comparative studies of the targeted therapies have been conducted (it won’t save the airway).

AORTIC DISSECTION

- In-hospital mortality for thoracic aortic dissection is as high as 27%
- Aortic dissection is a result of weakness and disruption of the intima:
  - Connective tissue disorders
  - Hemodynamic stressors
  - Abnormal flow caused by anatomic abnormalities such as a bicuspid aortic valve
- The disruption in the intimal layer may result in extension of the dissection, leading to external rupture if the adventitial layers of the aortic wall are weak, obstruction of coronary arteries, or chronic hematomas.

CLASSIFICATION

- Type A—Involves the ascending aorta and/or arch
  - Higher mortality
  - Hypotension is more commonly associated with a type A dissection and is also associated with a high rate of mortality in the acute setting.
- Type B—involves the descending aorta or arch (distal to the L subclavian artery)
  - No benefit shown from surgical intervention
  - Back and abdominal pain is more often described in patients with a type B dissection

ARE THERE CLINICAL DECISION RULES THAT IDENTIFY A GROUP OF PATIENTS AT VERY LOW RISK FOR THE DIAGNOSIS OF THORACIC AORTIC DISSECTION?

- Level C recommendations: 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 workup for acute nontraumatic aortic dissection should be at the discretion of the treating physician.
PRESENTATION

- Classic: tearing chest pain radiating to the back
- Most common presentation: was abrupt onset of pain described as severe and was present in 84%

3 INDEPENDENT PREDICTORS:

- Acute onset of pain and/or tearing/ripping pain
- Mediastinal widening and/or aortic widening on CXR (portal or PA and lateral)
- Pulse differential (absence of proximal extremity pulse or carotid pulse) and/or BP difference of >20 mm Hg between arms

250 patients with chest pain, back pain, or both, of which 128 had a thoracic aortic dissection

In the absence of all 3 predictors, the prevalence of an aortic dissection among the 250 patients with suspected disease was 7%; the presence of all 3 predictors had a prevalence of 100% for identification of aortic dissection.

IS A NEGATIVE SERUM D-DIMER SUFFICIENT TO IDENTIFY A GROUP OF PATIENTS AT VERY LOW RISK FOR THE DIAGNOSIS OF THORACIC AORTIC DISSECTION?

- Level C recommendations: In adult patients with suspected nontraumatic thoracic aortic dissection, do not rely on D-dimer alone to exclude the diagnosis of aortic dissection.

- The following may result in a low or false-negative D-dimer in patients with thoracic AD:
  - Chronicity
  - Time from symptom onset
  - Presence of thrombosed false lumen or intramural hematoma
  - Short length of dissection
  - Young age

- D-dimer is nonspecific; routinely obtaining this test in a large population of patients with symptoms suspicious for aortic dissection can result in harm, most notably, exposure to radiation and cost associated with advanced imaging.

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

- Level B recommendations: 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 had a sensitivity of 99%, specificity of 100%
- Alternative findings that were identified in 13% of the cases without aortic disorders
- TEE had a sensitivity of 98% and specificity of 95% (tech dependent)
- MRI had a sensitivity of 98% and specificity of 98%.

IN ADULT PATIENTS WITH SUSPECTED ACUTE NONTRAUMATIC THORACIC AORTIC DISSECTION, DOES AN ABNORMAL BEDSIDE TTE ESTABLISH THE DIAGNOSIS OF THORACIC AORTIC DISSECTION?

- Level B recommendations: In adult patients with suspected nontraumatic thoracic aortic dissection, do not rely on an abnormal bedside TTE result to definitively establish the diagnosis of thoracic aortic dissection.

- TTE was reported to have sensitivity ranging from 39% to 80% and specificity 5% to 100%

- Level C recommendations: 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. (Consensus recommendation)

IN ADULT PATIENTS WITH ACUTE NONTRAUMATIC THORACIC AORTIC DISSECTION, DOES TARGETED HEART RATE AND BLOOD PRESSURE LOWERING REDUCE MORBIDITY OR MORTALITY?

- Level C recommendations: In adults with acute nontraumatic thoracic aortic dissection, decrease BP and pulse if elevated. However, there are no specific targets that have demonstrated a reduction in morbidity and mortality.

- Specialty consensus guidelines currently present therapeutic targets of a heart rate of 60-80 beats/min and a systolic BP < 120 mm Hg; however, there is limited data to support specific BP and heart rate targets in the acute setting.
TREATMENT FOR CALCIUM CHANNEL BLOCKER POISONING: A SYSTEMATIC REVIEW.

- Calcium channel blockers were responsible for at least 11,000 exposures and 78 deaths in 2011 in the US. These numbers likely underestimation.
- This review found a low level of evidence supporting use of high-dose insulin and extracorporeal life support, and a very low level of evidence supporting use of calcium, dopamine, norepinephrine, and epinephrine for CCB poisoning.

HIGH-DOSE INSULIN

- (bolus of 1 unit/kg followed by an infusion of 0.5–2.0 units/kg/h) was associated with improved hemodynamic parameters and lower mortality, at the risks of hypoglycemia and hypokalemia (low quality of evidence).

EXTRACORPOREAL LIFE SUPPORT

- was associated with improved survival in patients with severe shock or cardiac arrest at the cost of limb ischemia, thrombosis, and bleeding (low quality of evidence).

CALCIUM, DOPAMINE, AND NOREPINEPHRINE

- These agents improved hemodynamic parameters and survival without documented severe side effects (very low quality of evidence).
- The typical calcium dose was an IV single dose of calcium chloride (1–5 g), sometimes followed by an infusion, or the equivalent dose in calcium gluconate.
- No significant ischemic complications were noted with high doses of vasopressors in a case series of 48 patients.

4-AMINOPYRIDINE

- was associated with improved hemodynamic parameters and survival in animal studies, at the risk of seizures.

LIPID EMULSION

- was associated with improved hemodynamic parameters and survival in animal models of IV verapamil poisoning but not in models of oral verapamil poisoning.
- One available human case series (5 patients) demonstrated 60% mortality when using this antidote compared to a lower mortality reported in retrospective studies of CCB poisoning, but the severity of CCB ingestions varied between observational studies and reported case series.
OTHER THERAPY

• (activated charcoal, gastric lavage, and whole-bowel irrigation), atropine, glucagon, pacemakers, levosimendan, and plasma exchange reported variable results.

• Hemodynamic improvement was observed most of the time when capture was successful with transvenous pacemakers.

RECOGNITION AND MANAGEMENT OF WITHDRAWAL DELIRIUM (DELIRIUM TREMENS).

• About 50% of persons with alcohol-use disorders have symptoms of alcohol withdrawal when they reduce or discontinue their alcohol consumption; in 3 - 5%, grand mal convulsions, severe confusion (delirium), or both develop.

STATES OF ALCOHOL WITHDRAWAL

MILD AND MODERATE

• Alcohol rapidly increases the release of GABA in the brain. With repeated exposure, the brain adapts to the effects of alcohol through changes in receptors.

• Because of the short action of ethanol (beverage alcohol), withdrawal symptoms usually begin within 8 hours after blood alcohol levels decline, peak at about 72 hours, and are markedly reduced by day 5 - 7 of abstinence.

WITHDRAWAL DELIRIUM (DELIRIUM TREMENS)

• Delirium = a rapid-onset fluctuating disturbance of attention and cognition, sometimes with hallucinations.

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT OF ALCOHOL SCALE, REVISED (CIWA-AR):

• Consists of (1) 9 items scored on a scale of 0 to 7 (most severe symptoms):

  • (1). N/V, Tremor, Paroxysmal sweats, Anxiety, Tactile Disturbances, Auditory Disturbances, Visual Disturbances, Headache, Agitation; and

  • (2) 1 item scored on a scale of 0 to 4: Orientation and Clouding of Sensorium.

• Scores range from 0 to 67:

  • < 8 = mild withdrawal symptoms that rarely require the use of medications

  • 8 - 15 = moderate withdrawal that is likely to respond to modest doses of benzodiazepines

  • > 15 = severe syndromes that require close monitoring to avoid seizures and delirium tremens.

DSM-5 CRITERIA FOR WITHDRAWAL DELIRIUM

• Alcohol Withdrawal + Delirium:

  • Criteria for alcohol withdrawal: At least 2 of 8 possible symptoms after reduced use of alcohol (autonomic hyperactivity, hand tremor, insomnia, N/V, hallucinations, agitation, anxiety, generalized seizures)

  • Criteria for delirium: Disruption in attention/awareness/memory/orientation/language/perception/visuospatial ability, no evidence of coma or other evolving neurocognitive disorders

  • 3 - 5% of patients who are hospitalized for alcohol withdrawal meet the criteria for withdrawal delirium.

WITHDRAWAL DELIRIUM

• usually begins 3 days after the appearance of symptoms of alcohol withdrawal and lasts from 1 - 8 days (usually 2 or 3 days).

• 1 - 4% of hospitalized patients who have withdrawal delirium die; this rate could be reduced if a timely diagnosis were made and symptoms were adequately treated.

• Death usually results from hyperthermia, cardiac arrhythmias, complications of withdrawal seizures, or concomitant medical disorders.
DELIRIUM DURING ALCOHOL WITHDRAWAL IS PREDICTED BY THE FOLLOWING:

• CIWA-Ar scores > 15 (especially with a systolic BP >150 mm Hg or a pulse rate >100 bpm)
• Recent withdrawal seizures (seen in 20% of persons with delirium)
• Prior withdrawal delirium or seizures
• Older age
• Recent misuse of other depressant agents
• Concomitant medical problems (e.g. electrolyte abnormalities, low platelet counts, and respiratory, cardiac, or GI disease)

TREATMENT OF WITHDRAWAL DELIRIUM

• Care should be taken when administering glucose to avoid precipitating Wernicke’s encephalopathy or thiamine related cardiomyopathies and to circumvent over hydration in patients who have temporary, alcohol-related, compromised cardiac functioning

• Thiamine (500 mg once or twice IV per day for 3 days) and multivitamins are recommended, there is little support for routine administration of magnesium.

BENZODIAZEPINES

NO SINGLE DRUG OF THIS CLASS HAS BEEN SHOWN TO BE SUPERIOR TO ANOTHER.

DIAZEPAM REGIMEN

• Administer 10 - 20 mg IV or orally every 1-4 hr, as needed

LORAZEPAM REGIMENS

• Administer 8 mg IV/IM/PO every 1-3 hrs as needed. After the patient has received 16 mg, if delirium is still severe administer 8 mg every 1 hr. Then administer 10-15 mg/hr.
• Alternative Regimen: Administer 1 - 4 mg IV every 5-15 min as needed. Alternatively administer 1-40 mg IV every 20-40 min as needed. Continue dosing every hr as needed to maintain somnolence.

OTHER MEDICATIONS

• Haloperidol 0.5 - 5.0 mg IV or IM every 30 - 60 min as needed - not to exceed 20 mg;
• or 0.5 - 5.0 mg PO every 4 hr up to 30 mg. (Note that antipsychotic drugs can prolong the QT interval and can increase the likelihood of seizures).
• phenobarbital, clomethiazole, carbamazepine - data are lacking regarding their use in persons who have withdrawal delirium
• dexmedetomidine, an α2-adrenergic agonist. This drug cannot be used in patients with a heart block.