Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug-Induced Hyperthermia – Acute Treatment ~

This pearl will focus on the acute treatment of drug-induced hyperthermia.

Case:

- A 24-year-old woman presented to the emergency room with altered level of consciousness after reportedly ingesting MDMA at a party 60 minutes earlier.
- The patient is a student who was out with friends celebrating her recent graduation. Her past medical history is unremarkable aside from ADHD and anxiety for which she is treated with lisdexamfetamine and venlafaxine.
- On arrival, she is diaphoretic and mildly agitated. Pupils are 6 mm, equal and reactive. She has occasional jerky movements of her limbs which appear to be involuntary. Reflexes are 3+ at the patella and ankle. Eight beats of clonus are elicited in both ankles. Vitals are as follows: Temp 39.3°C, HR 138 bpm, BP 154/92 mmHg, RR 28, SpO2 94% on room air.

Background:

- There are several important differences between hyperthermia and fever.
- Hyperthermia is due to excess heat accumulation causing body temperature to rise above the hypothalamic set point, whereas fever is caused by an increase in the hypothalamic set point which subsequently increases heat production.
- Hyperthermia is associated with multi-organ injury and a high risk of mortality. If not rapidly treated, hyperthermia often results in a constellation of altered mental status, autonomic instability, rhabdomyolysis, disseminated intravascular coagulation, and liver injury.[1]
- The traditionally described causes of hyperthermia are summarized as follows:
    1. Sympathomimetic Toxidrome
    2. Serotonin Toxicity
    3. Neuroleptic Malignant Syndrome
    4. Mitochondrial Uncoupling Toxins
    5. Malignant Hyperthermia
    6. Anti-cholinergic Toxicity
    7. GABA Withdrawal (e.g., alcohol, benzodiazepines, baclofen)
    8. Exogenous Thyroid Excess
    9. Hypersensitivity Syndromes (e.g., Drug Fever, DRESS, TEN, SJS)

Mortality Associated with Hyperthermia:

- Hyperthermia has a high mortality rate, requiring rapid recognition and management.
- In a review of published MDMA hyperthermia cases, a maximum temperature greater than 40.5°C was associated with a 45% mortality rate. If core temperature rose to greater than 42.5°C, the associated mortality rate was 78%.[2]

- Data from environmental heat stroke also suggests that taking more than 30-60 minutes to cool the patient to less than 39.0°C tripled the mortality risk.[3]

Management:

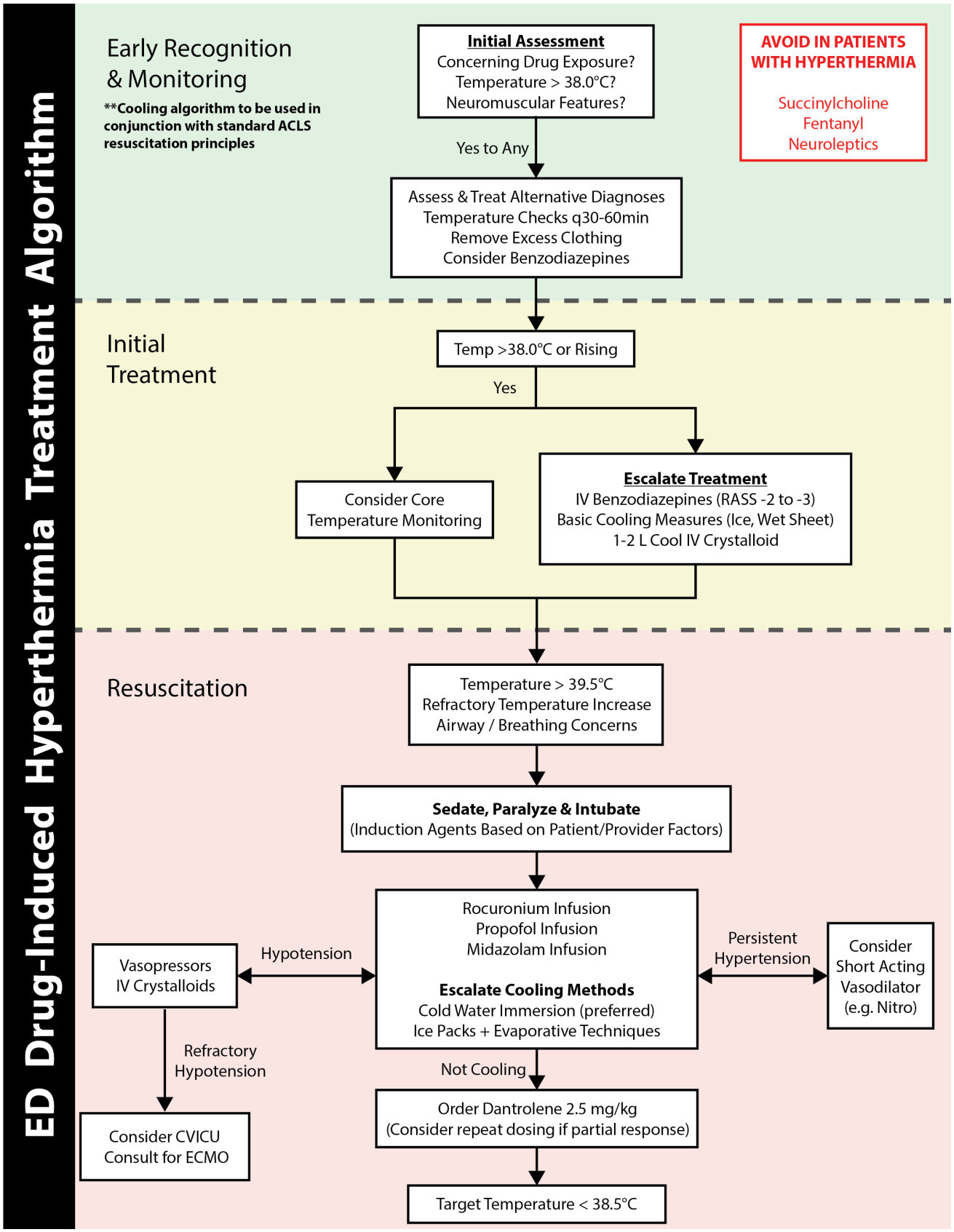
- There are three main pillars of management which should occur concurrently when treating drug-induced hyperthermia:
    1. Early Recognition & Monitoring
    2. Pharmacotherapy
    3. Cooling Measures
- An algorithm summarizing the acute treatment of hyperthermia is shown at the end of this document.

- <u>Early Recognition & Monitoring</u>
    - Hyperthermia can develop rapidly, especially early after a toxin exposure.
    - Patients at risk for developing hyperthermia often display features of neuromuscular excitation including clonus, hyperreflexia, increased tone, or agitation.
    - If a patient is at risk for hyperthermia based either on the reported exposure or the presence of neuromuscular excitation on exam, temperature reassessed frequently, and core temperature monitoring may be considered.

- <u>Pharmacotherapy</u>
    - For malignant hyperthermia, first line treatment is dantrolene. Comprehensive treatment for malignant hyperthermia is beyond the scope of this review.
    - Sedation with benzodiazepines is the first line treatment for sympathomimetic toxidromes, serotonin toxicity, and neuroleptic malignant syndrome.
        - Diazepam is the preferred IV benzodiazepine due to its rapid onset of peak sedating effects (i.e., 6 minutes) and prolonged half-life.
        - IV diazepam can be repeated every 10 minutes as needed to sedate the patient to a RASS of -1 to -2 (i.e., drowsy but rouses to voice).
    - Persistent hyperthermia despite benzodiazepines should be treated with deep sedation (e.g., propofol and midazolam), paralysis, and intubation.
        - Proceeding directly to deep sedation and paralysis may be considered for patients presenting with severe hyperthermia such as temperature greater than 40.0°C.
    - If a patient continues to be hyperthermic despite sedation and continuous paralysis, dantrolene may be considered for refractory hyperthermia from any cause.
        - Animal studies support that calcium leak from the ryanodine receptor can occur in hyperadrenergic states without malignant hyperthermia susceptibility.[4]
        - Persistently increased muscle tone or heat production despite paralysis is suggestive of intrinsic myocyte activation which may respond to dantrolene.
        - Studies have supported a benefit of dantrolene treatment in both serotonin toxicity and neuroleptic malignant syndrome.[5,6]
    - Cyproheptadine is a sedating antihistamine which also causes antagonism of serotonin receptors. It has some reported efficacy in cases of serotonin toxicity. Similarly, bromocriptine is a dopamine agonist which has been used to treat neuroleptic malignant syndrome.

        - The role of both cyproheptadine in serotonin toxicity and bromocriptine in NMS is controversial. The decision to use these medications should be made on a case-by-case basis.
        - Both medications are only available in oral formulations and have delayed onset of effect, therefore there is limited utility in the acute treatment hyperthermia.
    - Anti-cholinergic toxins rarely cause severe hyperthermia. While physostigmine may be considered for anti-cholinergic delirium, it has not been shown to treat hyperthermia.

- <u>Cooling Measures</u>
    - Most patients with mild hyperthermia can be managed with removal of clothing and application of ice packs to the neck, axilla, and groin.
    - For severe hyperthermia requiring immediate and rapid cooling, cold water immersion is the fastest method of cooling in most studies.
        - Practically, the easiest way to facilitate cold water immersion in a hospital setting is to place the patient in a body bag and fill the bag with water and ice. The upper chest and arms can be left outside of the bag to facilitate IV access and monitoring.[7]
        - If ice is not readily available, cold tap water (10-15°C) still creates a large temperature gradient for rapid heat dissipation and can be used until ice becomes available.
    - Heat exchange catheters (i.e., cooling catheters) may be usefully for maintaining body temperature after initial cooling, but should not be used during acute resuscitation because they have a relative slow cooling rate (roughly 1.5°C per hour).[8]


ED Drug-Induced Hyperthermia Treatment Algorithm
Early Recognition & Monitoring
**Cooling algorithm to be used in conjunction with standard ACLS resuscitation principles
Initial Assessment
Concerning Drug Exposure?
Temperature > 38.0°C?
Neuromuscular Features?
Yes to Any
Assess & Treat Alternative Diagnoses
Temperature Checks q30-60min
Remove Excess Clothing
Consider Benzodiazepines
AVOID IN PATIENTS WITH HYPERTHERMIA
Succinylcholine
Fentanyl
Neuroleptics
Initial Treatment
Temp >38.0°C or Rising
Yes
Consider Core Temperature Monitoring
Escalate Treatment
IV Benzodiazepines (RASS -2 to -3)
Basic Cooling Measures (Ice, Wet Sheet)
1-2 L Cool IV Crystalloid
Resuscitation
Temperature > 39.5°C
Refractory Temperature Increase
Airway / Breathing Concerns
Sedate, Paralyze & Intubate
(Induction Agents Based on Patient/Provider Factors)
Rocuronium Infusion
Propofol Infusion
Midazolam Infusion
Escalate Cooling Methods
Cold Water Immersion (preferred)
Ice Packs + Evaporative Techniques
Hypotension
Vasopressors
IV Crystalloids
Refractory Hypotension
Consider CVICU Consult for ECMO
Persistent Hypertension
Consider Short Acting Vasodilator (e.g. Nitro)
Not Cooling
Order Dantrolene 2.5 mg/kg
(Consider repeat dosing if partial response)
Target Temperature < 38.5°C

Case Resolution:

- You recognize the diagnosis of serotonin toxicity and the importance of treating her hyperthermia rapidly. A thermistor foley is placed for core temperature monitoring.

- Clothing is removed and ice packs are applied to the groin and axilla. A total of 30 mg of IV diazepam is administered as well as 2 L of cool IV fluids. With this, her heart rate improves to 105 bpm and the temperature decreases to 37.8°C.

- ECG and bloodwork are unremarkable, and the patient is admitted to Internal Medicine for further observation and management. Her mental status gradually returns to baseline over the next 24 hours, and she is discharged after an uneventful hospital course.

References:

1) Dao CK, Nowinski SM, Mills EM. The heat is on: molecular mechanisms of drug-induced hyperthermia. Temperature. 2014 Nov;1(3):183-91.
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3) Shapiro Y, Seidman DS. Field and clinical observations of exertional heat stroke patients. Med Sci Sports Exerc. 1990 Feb;22(1):6-14.
4) Reiken S, Lacampagne A, Zhou H, Kherani A, Lehnart SE, Ward C, Huang F, Gaburjakova M, Gaburjakova J, Rosemblit N, Warren MS, He KI, Yi GH, Wang J, Burkhoff D, Vassort G, Marks AR. PKA phosphorylation activates the calcium release channel (ryanodine receptor) in skeletal muscle: defective regulation in heart failure. 2003 Mar;160(6):919-28.
5) Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review. CJEM. 2010 Sept;12(5):435-42.
6) Kuhlwilm L, Schonfeldt-Lecuona C, Gahr M, Connemann BJ, Keller F, Sartorius A. The neuroleptic malignant syndrome-a systematic case series analysis focusing on therapy regimes and outcome. Acta Psychiatr Scand. 2020 Sep;142(3):233-41.
7) Wang AZ, Lupov IP, Sloan BK. A novel technique for ice water immersion in severe drug-induced hyperthermia in the emergency department. J Emerg Med. 2019 Nov;57(5):713-15.
8) Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke. 2001 Nov;32(11):2550-3.

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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