Malignant Hyperthermia

- Rare genetic disorder manifests after treatment with anesthetic agents
  - Succinylcholine
  - Inhalational anesthetic agents
    - Halothane
    - Sevoflurane
    - Isoflurane
    - Desflurane
- Onset within 1 hour of the administration of “triggering agent”
  - rarely delayed more than 5 hours
- 50% of cases are inherited in as autosomal dominant

Malignant Hyperthermia

- Genetic susceptible patients have any one of several distinct mutations in the gene for the skeletal muscle (SKM) ryanodine receptor (RyR1)

- RyR1 is a homotetrameric Ca^{2+} channel in the sarcoplasmic reticulum of SKM

- In the presence of anesthetic agents, alterations occur the hydrophilic, amino-terminal portion of the ryanodine receptor → uncontrolled Ca^{2+} efflux from the SR → tetany,↑ SKM metabolism, and excessive heat production (**myocyte hypermetabolism**)

- For unclear reasons, overexpression of the wild-type ryanodine receptor does <u>not</u> ablate abnormal myocyte responses to Halothane although overexpression of a mutated ryanodine receptor can induce the malignant hyperthermia phenotype in myocytes from normal individuals

Malignant Hyperthermia

- Early clinical findings in malignant hyperthermia include muscle rigidity (especially masseter stiffness), sinus tachycardia, increased CO_2 production, and skin cyanosis with mottling.

- Marked hyperthermia (up to 45ºC [113ºF]) occurs in minutes to hours later
  - core body temperature tends to rise 1ºC every 5 to 60 min.

- Hypotension, complex dysrhythmias, rhabdomyolysis, electrolyte abnormalities, DIC, and mixed acidosis accompany the elevated temperature.

- Rarely, biochemically-proven malignant hyperthermia may present solely with rhabdomyolysis in the absence of hyperthermia.

What Do I Look For?

How Do I Diagnose?

DIAGNOSTIC EVALUATION

1. Get a rectal temperature.
2. Abnormal vital signs include sinus tachycardia, tachypnea, widened pulse pressure, and hypotension.
3. CXR may demonstrate pulmonary edema.
4. EKG may reveal dysrhythmias, conduction disturbances, nonspecific ST-T wave changes, or heat-related myocardial ischemia or infarction.
5. Labs: CBC & CMP, coagulation studies, creatine kinase, and check for hyperphosphatemia, myoglobinuria.
6. Myoglobinuria should be suspected in a patient who has a brown urine supernatant that is Heme-positive, and clear plasma.
7. Thorough toxicology screening may be indicated if a medication effect is suspected.
8. Head CT and lumbar puncture if CNS etiologies are suspected.

DIAGNOSTIC EVALUATION

- Diagnosis confirmed by in-vitro muscle contracture test following recovery from the acute hyperthermic episode.
- Abnormal augmentation of in-vitro muscle contraction subsequent to treatment with Halothane or Caffeine is diagnostic of the disorder
- Test is expensive, not widely available, and frequently not covered by insurance.
- Genetic testing for the more than 40 known mutations of the SKM ryanodine receptor (RyR1) can be used in conjunction with the in-vitro muscle contracture test to evaluate individual susceptibility in patients from families with a history of malignant hyperthermia

What Should Be Done?

Management

1. Address ABC’s
2. Initiate rapid cooling
3. Treat complications

Management

1. Vigeleo / Flotrac arterial line monitoring (and CVP) – useful for assessing volume status and determining the need for fluid resuscitation
2. Alpha-adrenergic agonists – should be **avoided,** since the resultant vasoconstriction decreases heat dissipation.
3. Continuous core temperature monitoring with a rectal or esophageal probe is mandatory, and cooling measures should be stopped once a temperature of 39ºC (102.2ºF) has been achieved in order to reduce the risk of iatrogenic hypothermia
4. In the case of NMS or malignant hyperthermia, the presumed causative agent must be discontinued immediately
5. Early adoption of **Dantrolene** treatment for sustained or escalating hyperthermia

Management

- **Cooling measures**
  - Naked patient is sprayed with a mist of lukewarm water while air is circulated with large fans. Shivering may be suppressed with intravenous benzodiazepines such as Diazepam (5 mg IV) or Lorazepam (1-2 mg IV) or, if NMS is not suspected, with Chlorpromazine (25 to 50 mg IV).
  - Immersing the patient in ice water is the most effective method of rapid cooling but complicates monitoring and access
  - Applying ice packs to the axillae, neck, and groin is effective, but is poorly tolerated in the awake patient

Management

- **Cooling Measures**
  - Cold peritoneal lavage results in rapid cooling, but it is an invasive technique that is contraindicated in pregnant patients or those with previous abdominal surgery.
  - Cold oxygen, cold gastric lavage, cooling blankets, and cold intravenous fluids may be helpful adjuncts.
  - There may be a role for antipyretic agents such as Acetaminophen (Tylenol) or ASA in the management of heat stroke (however, the underlying mechanism does not involve a change in the hypothalamic set-point)
  - Alcohol sponge baths should be avoided because large amounts of the drug may be absorbed through dilated cutaneous vessels and produce toxicity

Management:
Malignant Hyperthermia

- Dantrolene administration is the mainstay of treatment of MH and should be initiated as soon as the diagnosis is suspected.

- Since the introduction of Dantrolene, the mortality of the fulminant syndrome has fallen from 70% to less than 10%.

- Dantrolene is a non-specific SKM relaxant that acts by blocking the release of calcium from the SR → decreases the myoplasmic concentration of free calcium and diminishes the myocyte hypermetabolism that causes clinical symptoms.

Management:
Malignant Hyperthermia

- Dantrolene is most effective when given early in the illness (before hyperthermia occurs), when maximal calcium can be retained within the SR.

- Dantrolene 2.5 mg/kg IV bolus is given and should be repeated every 5 minutes until symptoms abate.
  - Until a maximum dose of 10 mg/kg

- Treatment may be repeated every 10 to 15 hours. After an initial response, the drug should be continued orally at a dose of 4 to 8 mg/kg per day, divided into 4 doses, for 1-3 days.

How is Dantrolene Preparred?

- Assistance is helpful in mixing Dantrolene, which is presented in 20 mg vials formulated with 3 g of Mannitol.

- Each vial should be mixed with 60 ml of sterile distilled water.

- Dantrolene may dissolve faster if several vials are emptied into a sterile dish and a large volume of sterile water added.

- Increasing the temperature of the diluent will also help speed the mixing process.

MH Kit with Dantrolene & Sterile Water

Hyperthermia Treatment Protocol for patients under general anesthesia

When hyperthermia develops or worsens in previously afebrile patients under general anesthesia in the absence of a therapeutic indication for hyperthermia:

- **Basic steps**:
  - Rule out malfunction of warming equipment, room thermostat, heat lamps
  - Look for signs of hypermetabolic state: high $ETCO_2$ (with normally functioning absorber and valves); tachycardia
  - Search for causes including sepsis, drug reaction, MH
  - Consider arterial blood gas analysis to establish acid base state
  - DISCUSS with staff anesthesiologist and resident / CRNA: need to consider differential diagnosis, need for invasive monitors, etc
  - NOTE: Should stop cooling measures when temperature is reduced to 38°C <u>BUT</u> continue monitoring core temperature to detect recrudescence which mandates resumption of active cooling
- **Malignant Hyperthermia 24-hr Hotline**: 1-800-644-9737 www.mhaus.org
- Interventions based on <u>core temperature</u> (nasopharyngeal, esophageal, bladder or rectal)