Malignant Hyperthermia Syndrome

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Malignant Hyperthermia (MH)- Essential Characteristics

- An inherited disorder of skeletal muscle triggered in susceptibles (human or animal) in most instances by inhalation agents and/or succinylcholine, resulting in hypermetabolism, skeletal muscle damage, hyperthermia, and death if untreated.

- Underlying physiologic mechanism – abnormal handling of intracellular calcium levels
## Trigger Agents for MH

<table>
<thead>
<tr>
<th>MH Trigger Agents</th>
<th>Not MH Triggers</th>
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<tr>
<td>• Potent Volatile Anesthetics (e.g. halothane, sevoflurane, desflurane)</td>
<td>• Intravenous agents</td>
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<td>• Succinylcholine</td>
<td>• Opioids</td>
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<td>• Non-depolarizing agents</td>
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<td>• Ketamine</td>
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<td>• Propofol</td>
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<td>• Anxiolytics</td>
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Summary of Clinical Signs

Diagram:

- **Anaesthetics** → **Skeletal muscle** → **Rhabdomyolysis**
  - **Myoglobin↑**, **CK↑**, **K↑↑**, **Tachycardia**
    - **Renal failure**, **Cardiac arrhythmia**, **Cerebral damage**

- **Contracture** → **Heat**
  - **Hypermetabolism**
    - **O₂↓ CO₂↑ H↑↑**

Additional notes:

- Anaesthetics can cause skeletal muscle contracture and hypermetabolism.
- Rhabdomyolysis results in increased myoglobin, CK, and potassium levels, leading to tachycardia, renal failure, cardiac arrhythmia, and cerebral damage.
- Heat can contribute to hypermetabolism, further exacerbating the clinical signs.
Epidemiology of MH

Incidence & Prevalence

- Reported frequency of MH is 1 in 5,000 to 1 in 100,000 anesthetics
- Reported from every country and ethnic group
- Based on reports to MHAUS, there are about 600 cases of MH per year in the US.
- MH “hotspots:” Wisconsin, Michigan, West Virginia
Epidemiology of MH (continued)

**Mortality from MH**

- Per data from the North American MH Registry, of 291 events, 8 (2.7%) resulted in cardiac arrests and 4 (1.4%) resulted in death.
- The median age in cases of cardiac arrest/death was 20 yr (range, 2-31 yr).
- Factors associated with higher risk of poor outcome were muscular build and disseminated intravascular coagulation (DIC).
- Increased risk of cardiac arrest/death was related to a longer time period between anesthetic induction and maximum end-tidal carbon dioxide.

*Larach et al., 2008; Anesthesiology 108(4): 603-611.*
Epidemiology of MH (continued)

Mortality: Hospital vs. Ambulatory Settings

- During the period January 2006 through May 2008, the MHAUS MH Hotline received:
  - 503 calls from hospitals, 28 determined to be MH, with 2 deaths from MH (7% mortality)
  - 44 calls from ambulatory settings, 13 determined to be MH, with 3 deaths (21% mortality)
- A fulminant MH episode occurring outside of the hospital setting is more likely to lead to a bad outcome as compared with an episode which originates in a hospital setting.
Clinical Signs of MH

- **Specific**
  - Muscle Rigidity
  - Increased CO\(_2\) Production
  - Rhabdomyolysis
  - Marked Temperature Elevation

- **Non-Specific**
  - Tachycardia
  - Tachypnea
  - Acidosis (Respiratory/Metabolic)
  - Hyperkalemia
Spectrum of Clinical Presentations

• **Fulminant MH**: muscle rigidity, high fever, increased HR shortly after induction of anesthesia

• **Masseter muscle rigidity (MMR)**: jaw muscle rigidity after succinylcholine may be an early sign of MH (see next slide)

• **Late onset MH**: uncommon, may begin shortly after anesthesia finish time (usually within first hour)
Masseter Muscle Rigidity (MMR) and MH

- Masseter muscle rigidity (MMR) may occur after succinylcholine
- More common in children
- Presages MH in 20-30% cases
- All patients with MMR demonstrate elevated CK and often gross myoglobinuria
- With muscle breakdown and CK > 20,000IU, the likelihood of MH is very high. Generalized rigidity not always present; if it occurs, MH is almost certain.
Muscle disorders and MH-Susceptibility

- **CCD (Central Core Disease) and MmD (Multiminicore Disease)**—disorders of muscles used for movement. Often associated with mutations in the skeletal muscle ryanodine receptor gene (RYR1), the same gene associated with MH susceptibility.
- **Duchenne's Muscular Dystrophy (DMD)**—progressive, fatal muscle wasting disorder in males, due to *absence* of dystrophin protein. Cardiac problems are common.
- **Becker’s Muscular Dystrophy (BMD)**—late onset muscular dystrophy in males, *abnormal* dystrophin protein, relatively normal life span.
- **Myotonias**—defects in various skeletal muscle ion channels leading to impaired relaxation after voluntary muscle contraction.
Muscle disorders and MH-susceptibility

Patients with occult or known myopathies such as CCD, MmD, DMD, or BMD may have a higher risk for an MH or MH-like episode upon exposure to a triggering anesthetic agent. Such patients should be evaluated by a neurologist prior to providing treatment and/or diagnostic testing recommendations.

- CCD, MmD associated with MH susceptibility.
- Patients with Duchenne’s or Becker’s muscular dystrophies are at risk for hyperkalemic cardiac arrest with succinylcholine or other MH triggering agents (but this is NOT MH).
- Individuals with any form of myotonia should not receive succinylcholine.
Immediate Therapy

- Discontinue inhalation agents, succinlycholine
- Hyperventilate with 100% O₂
- Bicarbonate 1-2 mg/kg as needed
- Get additional help
- Dantrolene 2.5 mg/kg push, repeat PRN
- Cool patient: gastic lavage, surface, wound
- Treat arrhythmias – do not use calcium channel blockers
- Arterial or venous blood gases
- Electrolytes, coagulation studies
After Crisis is controlled:

- Give dantrolene 1 mg/kg every 4-6 hours for 24 – 48 hours
- Monitor for recrudescence – rate is 25%
- Follow electrolytes, blood gases, CK, core temperature, urine output and color, coagulation studies
- **Biochemical markers**
  - Blood gases – esp pCO₂, pH
  - Myoglobin levels in serum and urine
  - PT, PTT, INR, fibrin split products
  - Liver enzymes, BUN
- Monitor for signs of myoglobinuria and rhabdomyolysis and institute therapy to prevent renal failure

**Treatment and Management of MH**
Prevention of Malignant Hyperthermia

- Avoid MH trigger agents in MH susceptibles or those suspected of being susceptible
- Preoperative personal/family history of anesthetic problems, neuromuscular disorders to identify those who may be MH-susceptible.
- Temperature/endtidal CO₂ monitoring during general anesthesia
- Recognition of masseter muscle rigidity
- Prompt investigation of unexplained tachycardia, hypercarbia, hyperthermia
- **Availability of Dantrolene**
- ORs should perform regular MH drills to be prepared.
Diagnostic Tests for MH-Susceptibility

1. Muscle Contracture Test: Caffeine Halothane Contracture Test (CHCT)
   - Gold Standard
   - Requires skeletal muscle biopsy from patient’s thigh to assess muscle contractile properties upon exposure to ryanodine receptor agonists (e.g., caffeine, halothane).
   - Must be performed at the MH Muscle Biopsy Center.
   - Abnormally high levels of contractile force indicate MH susceptibility.
   - Sensitivity: close to 100% (false negatives are rare)
   - Specificity: ~80% (~20% false positives)
2. **Genetic Testing (Ryanodine Receptor [RYR1] gene sequencing)**

- Involves isolation of DNA from patient sample (white blood, or muscle cells; or other tissue sample)
- **Primary genetic locus associated with MH susceptibility is the ryanodine receptor (RYR1) gene; a DNA variant in the gene is characterized as:**
  - a. Unrelated polymorphism (no significant functional effect)
  - b. Causative mutation* (via functional studies)
  - c. Indeterminate (variant of unknown significance)
- Presence of **causative mutation* in RYR1 gene is diagnostic for MH susceptibility.**

*Currently 29 listed MH causative RYR1 mutations (see www.emhg.org). Additional ones expected to be added to panel in near future.*
Diagnostic Tests (Continued)

2. Genetic Testing (Ryanodine Receptor [RYR1] gene sequencing)
   • At this point, not all proven MHS individuals have been found to harbor a causative mutation. The sensitivity of the genetic test depends upon several factors, including the population selected and the methodology of the testing utilized.
   • Once a causative mutation is found, family members can be tested for that specific causative mutation; if found, the individual is considered MHS and a muscle biopsy for contracture testing can be avoided.
Preparation for the MH-Susceptible Patient

- Shut/disable vaporizers
- Older machines set O2 flow @ 10L/min for 20 minutes
- (through machine and ventilator)
- **OPTIONAL** - Change carbon dioxide absorbent
- Use non-trigger agents or local anesthesia
- Monitor temperature and for early signs of MH
- Have dantrolene available

**Note:** A separate, vapor-free anesthesia machine is not necessary.
Management of the MH-susceptible Patient

- MH-Susceptible individuals may undergo surgery – inpatient or outpatient; dantrolene is not necessary preoperatively
- **Avoid MH triggers** (succinylcholine and potent inhalation agents)
- **Suggested regimen:** Anxiolytic (e.g. midazolam (ketamine permissible)) → Propofol/opioid induction → Non-depolarizing relaxant → Nitrous/narcotic/propofol → Reversal of muscle relaxant → Discharge after about 1.5 hours in the recovery room if all signs are stable
Evidence for Association between Heat Stroke and MH

- 12 yr old boy with history of anesthesia-induced MH, develops fever, rigidity, rhabdomyolysis after soccer practice and dies. RYR-1 mutation detected in him and his relatives (Tobin et al., JAMA 2001; 286:169-70).

- Experiments in genetically engineered mice provide evidence for mechanism underlying heat sensitivity in some MH patients - involves leakage of Ca\(^{2+}\) through the ryanodine receptor, coupled with the production of reactive nitrogen species which bind to the ryanodine receptor, making it more porous to Ca\(^{2+}\) leak when the muscle is heated. Ca\(^{2+}\) leak may lead to typical changes of MH and at same time lead to increased Ca\(^{2+}\) release (Durham et al., Cell Apr 4 2008; 133 (1): 53-65).
MH Resources

Malignant Hyperthermia Association of the United States (MHAUS)

- Not-for-profit organization
- Over 2,000 members including MH-susceptible patients and their family, medical professionals, corporations, and other interested individuals.
- Mission of MHAUS - to promote optimum care and scientific understanding of MH and related disorders.
- Provides the best medical and scientific advice available to patients and health care providers alike.

- HOTLINE for Medical Professionals - 1-800-MH-HYPER - Available 24/7/365 to assist health providers in dealing with MH emergencies!
MH Resources (Continued)

The North American Malignant Hyperthermia Registry of MHAUS

- Database which records detailed events surrounding MH episodes as well as correlation between clinical history, genetic, and biopsy test results
- Patients and physicians can provide Registry with clinical history, thus the Registry acts as a service for patients/families and their health care professionals to communicate and store important medical histories relating to the risk for MH
- Approved by the IRB of the University of Pittsburgh Medical Center
- The Registry holds a certificate of confidentiality, reflective of its commitment to protect subject confidentiality
### MHAUS Current Services and Products

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<th>Reference and Crisis Management Materials</th>
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<td>Website/FAQs</td>
<td>MH Protocol as poster or pocket card</td>
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<td>MH Expert Consult</td>
<td>Brochures</td>
<td>Transfer Guidelines for ASCs COMING SOON!</td>
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<tr>
<td>MH Registry</td>
<td>Conferences</td>
<td>Safe/unsafe anesthetics pocket card</td>
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<td>Speaker’s Bureau</td>
<td>Slide shows, some with CME credits offered</td>
<td>Crisis Management Sheets</td>
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<td>Patient Safety Products</td>
<td>Newsletter</td>
<td>Dantrolene Dosage Chart</td>
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<td>Medical ID program and tag</td>
<td>Podcasts</td>
<td>MH Hotline Stickers</td>
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<td>MH Alert band and sticker kit</td>
<td>MH Mock Drill Kit NEW</td>
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<tr>
<td>Family health history toolkit</td>
<td>In-service kit (video/DVD with test for CEU credit)</td>
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<tr>
<td>Template letters for family and insurance companies</td>
<td>MH procedural manual for hospital, ASC, and Office-based settings</td>
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Suggested Resources/Reading


Suggested Resources/Reading (Continued)


For a more in-depth, annotated slide presentation, including:

- Historical landmarks in the discovery of MH
- Common case presentations and errors in diagnosis
- Helpful visual aides
- Recent progress in MH research

...please refer to the slide set which can be ordered through the MHAUS website.