

# Malignant Hyperthermia

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**JHP Pharmaceuticals LLC**  
**Dantrium® IV**

Presented by:  
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# **Malignant Hyperthermia**

## **Brief History:**

**1961 Proband family identified in Australia**

**1971 First international symposium on MH;  
caffeine-halothane contracture test  
developed**

**1970s Relation of masseter muscle rigidity  
to MH realized**

**1975 First treated pigs with Dantrolene,  
validated for Human use**

**1990's Genetic component identified**

**2000's DNA Testing 2000's**



## MH Defined

1

MH results in an increase in metabolism as a result of rapid and uncontrolled increase in calcium within the sarcolemma (muscle cells).

2

The increase in calcium level overwhelms the capacity of the muscle cell for active calcium reuptake.

3

This results in muscle contraction and increased breakdown of ATP, enhanced glycolysis, uncoupling of oxidative phosphorylation, & activation of actin-myosin filaments yielding significant heat production.



# Incidence vs. Mortality

## Incidence

## Mortality

General population

1-250k (1985)<sup>1</sup>

1:62k with succinylcholine

New York

1:20-100k (2005)<sup>2</sup>

Hospital less than 10%

ASC - 13.6%

Office - 19.8%<sup>3</sup>

500-800 cases of MH reported /year<sup>10</sup>



# Malignant Hyperthermia Contacts

Malignant Hyperthermia Association of the United States (MHAUS)\*\*

<http://www.mhaus.org/>

800-MH-HYPER (24/7)/800-644-9737

North American Malignant Hyperthermia Registry (NAMHR)

<http://www.mhreg.org/>

888-274-7899

Neuroleptic Malignant Syndrome Information Service (NMSIS)

<http://www.nmsis.org/>

888-667-8367



# Caffeine Halothane Contracture Test

## CHCT - Muscle Contracture Test

- **Gold Standard**
- **Requires skeletal muscle biopsy from patient's thigh**
- **Must be performed at the MH Muscle Biopsy Center.**
- **Sensitivity: close to 100% (false negatives are rare)**
- **Specificity: ~80% (~20% false positives)<sup>4</sup>**



# CHCT Testing Sites

*University of Minnesota - Minneapolis, MN*

- *Paul A. Iaizzo, PhD*
- *(612) 624-7912 or -3959*

*Uniformed Services University of the Health Sciences - Bethesda, MD (Military & Civilian)*

- *Sheila M. Muldoon, MD*
- *(301) 295-3532*

*University of California - Davis, CA*

- *Timothy Tautz, MD*
- *(530) 752-7805*

*Wake Forest University - Winston-Salem, NC*

- *Joseph R. Tobin, MD*
- *(336) 716-4498*

*The Ottawa Hospital - Civic Campus - Ottawa, Ontario*

- *Kevin Nolan, MD, FRCPC*
- *(613) 761-4169*

*Toronto General Hospital - Toronto, Ontario*

- *Julian Loke, MD, FRCPC*
- *(416) 340-3128*



# Barriers to Diagnosis

1

Lack of non-invasive screening test

2

Cost of screening test : ~\$6K  
10K

3

Not all cases are reported

4

Not all patients trigger

2/3rds manifest on their first anesthetic<sup>1</sup>



# Genetic Predisposition

## Several chromosomes:

- **19q11.2-13.2 Ryanodine (RyR1)**
  - Release of  $\text{Ca}^{2+}$  stores from sarcoplasmic reticulum
- **17q11.2-q24**
  - Altered sodium channel functioning
- **7q21.1**
  - Dihydropyridine (DHP), voltage sensor for RyR1
- **1q32**
  - CACNL1A3 gene encoding the alpha 1-subunit of the voltage-gated DHP receptor that interacts with RyR1

Genetic predisposition may be as high as 1 in 3,000 individuals<sup>8</sup>



# Genetic Testing Results

30% Autosomally inherited (not sex-linked)

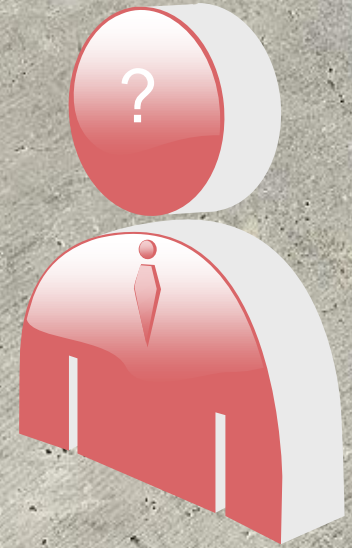
Mutations in the calcium channel receptor resulting in uncontrolled release of calcium from the sarcoplasmic reticulum. DNA testing not standardized at this time.

70% ??



# Profile of the MH Patient

- ~75% Male (Autosomal??)
- Median Age ~22 yrs
- > 2 previous GA, Any Volatile Gas
- Succinylcholine  $\sim x 2^{(5)}$





## Disease Associated or Acting Like MH under Anesthesia

King Denborough syndrome

**Caution in children with delayed motor function**

Ion channel mutations

Myopathic syndromes

Duchenne muscular dystrophy

Brody's Disease - deficient calcium, ATP (rhabdo, not MH)

McArdles Disease - glycogen storage (rhabdo, not MH)

Myotonia congenita

Pectus carinatum

Kyphoscoliosis

Osteogenesis imperfecta - temp elevation

Central Core disease



# Signs and Symptoms of MH

## 1st

### Early Signs

Hypercarbia	40%
Tachycardia	30%
Masseter Spasm	20%
Hypertension ?	

## 2nd

### Late Signs

Tachypnea  
Arterial hypoxemia  
Metabolic / Respiratory acidosis  
Hyperkalemia  
Cardiac arrhythmias  
Hypotension  
Hyperthermia  
Rhabdomyolysis  
Increased CPK – 20,000 I.U.



# Grading Scale

<b>Process</b>	<b>Indicator</b>	<b>Points</b>
1. Rigidity	Generalized muscular rigidity	15
	Masseter spasm	15
2. Muscle Breakdown		
	Creatine Kinase >20,000 IU w/ succ	15
	Creatine Kinase >10,000 IU no suc	15
	Cola colored urine perioperative	10
	Myoglobin in urine > 60 mcg/L	5
	Myoglobin in serum > 170 mcg/L	5
	Blood/plasma/serum 6 mEq/L no renal	3
3. Respiratory Acidosis		
	P <sub>ET</sub> CO <sub>2</sub> > 55 mmHg with controlled ventilation	15
	Arterial PaCO <sub>2</sub> > 60 mmHg, controlled ventilation	15
	P <sub>ET</sub> CO <sub>2</sub> > 60 mmHg with spontaneous ventilation	15
	Arterial PaCO <sub>2</sub> > 65 mmHg, spontaneous ventilation	15
	Inappropriate hypercarbia, Anesthesiologist's call	15
	Inappropriate tachypnea	10



# Grading Scale cont'

<b>Process</b>	<b>Indicator</b>	<b>Points</b>
4. Temperature Increase		
	Inappropriately rapid increase	15
	Inappropriately increased temperature > 38.8°C	10
5. Cardiac Involvement		
	Inappropriate sinus tachycardia	3
	Ventricular tachycardia or fibrillation	3
6. Family History		
	Positive family history in first degree relative	15
	Positive family history, more distant relative	5
7. Others		
	Arterial base excess more negative than -8 mEq/L	10
	Arterial pH <7.25	10
	Rapid reversal of MH signs after iv dantrolene	5
	Positive MH family history + another indicator from the	
	Patient's anesthetic experience other than increased CK	10
	Elevated CK and a family history of MH	10



# Grading Scale Scoring

## Results<sup>5</sup>

- 20 – 34 somewhat greater than likely
- 35 – 49 Very likely
- >50 Almost certain



# Differential Diagnosis

- Neuroleptic Malignant Syndrome
- Severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication
- Thyrotoxic crisis – Thyroid Storm
- Cocaine toxicity
- Heat stroke
- Serotonin syndrome - excessive serotonin usually r/t combining meds
- Status Epilepticus
- Pheochromocytoma- catecholamine surge of epi and norepi
- Lymphoma
- Contrast media in CSF

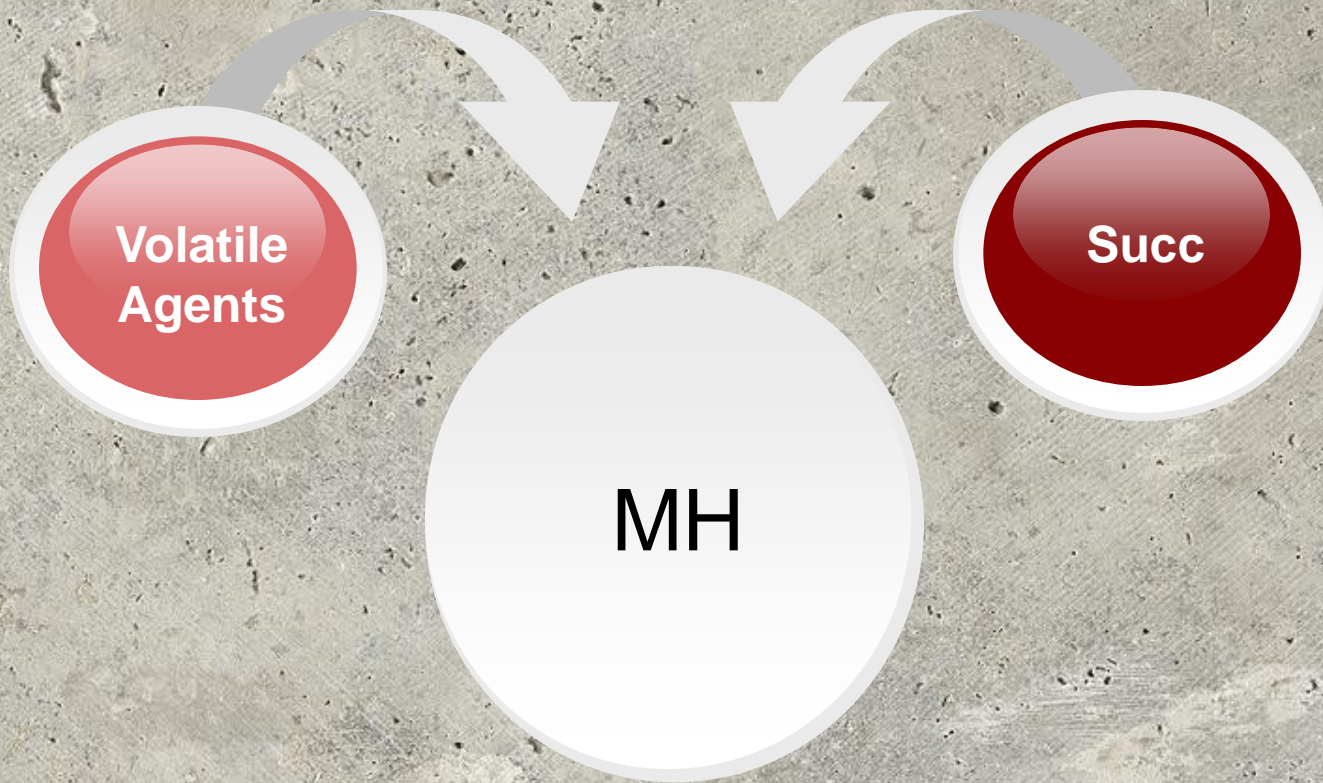


# Differential Diagnosis - example

	<b>MH</b>	<b>Thyrotoxicosis</b>	<b>Pheochromocytoma</b>
<b>↑ ETCO<sub>2</sub></b>	+++	++	++
<b>↑ HR</b>	+++	+++	+++
<b>↑ BP</b>	+	++	+++
<b>Rigidity</b>	++	+/-	-
<b>Acidosis</b>	+++	-	+

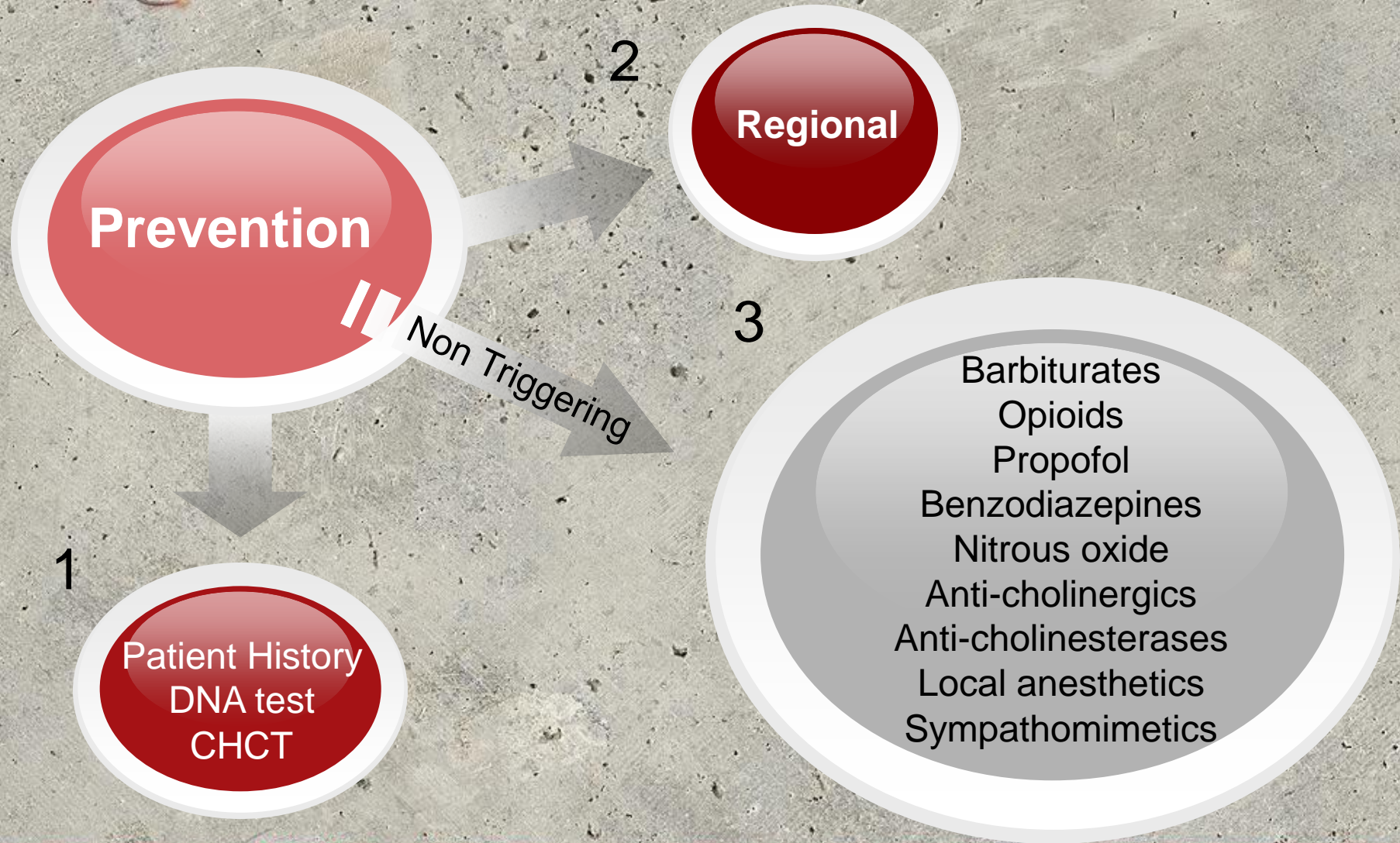


# Triggering Agents





# MH Treatment



Prevention

Regional

1  
Patient History  
DNA test  
CHCT

3  
Non Triggering

- Barbiturates
- Opioids
- Propofol
- Benzodiazepines
- Nitrous oxide
- Anti-cholinergics
- Anti-cholinesterases
- Local anesthetics
- Sympathomimetics



## Early Detection

During fulminant MH, core temperature can increase as much as 1° C every 5 minutes, so staff must be prepared to respond<sup>6</sup>

Mortality rate may be as high as 50%-70% if MH is not recognized and treated early enough<sup>7</sup>

Stabilization of an MH episode may take 30 minutes or more with multiple doses of Dantrium<sup>®</sup> IV (dantrolene sodium for injection)<sup>1</sup>



# Physical Treatments

- Immediately terminate trigger drugs & conclude surgery as soon as possible
- Hyperventilate with 100% oxygen
- Initiate active cooling
- Iced saline
- Gastric lavage with iced saline
- Surface cooling



# Pharmaceutical Treatment

Dantrium<sup>®</sup> IV- 1mg/kg IV q4-8hrs repeated 24-48hrs

Dantrium<sup>®</sup> IV: Continuous rapid intravenous push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached. (regimen may be repeated)

Correct metabolic acidosis

(NaHCO<sub>3</sub> 1- 2mEq/kg IV based on arterial ph)

Maintain urine output

Hydration


Furosemide ( 1mg/ kg )

Treat electrolyte imbalances

Treatment of arrhythmias

Xylocaine infusion

**Check for IV Patency**



## Dantrium® IV - components

Dantrium® IV each vial contains

1. 20 mg dantrolene sodium
2. 3000 mg mannitol
3. Sodium Hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water (without a bacteriostatic agent) for injection





# Dantrolene Pharmacodynamics

Skeletal Muscle Relaxant

Blocks RyR1 receptors, blocking the release of Calcium

1/2 life 4-8 hrs

Side Effects

weakness grip/legs, dizziness

No apparent Cardiac depression with 1 twitch remaining

Metabolized by the liver



# Dantrium<sup>®</sup> IV vials to treat MH

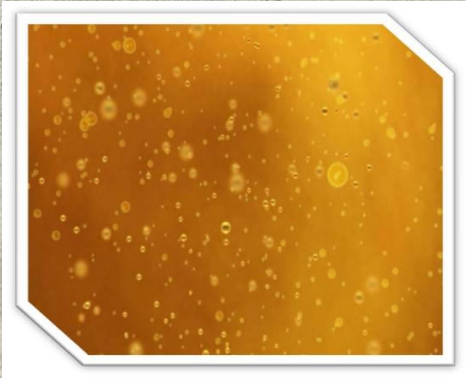
Patient Weight		Number of Vials to Achieve Dantrium <sup>®</sup> IV Dose (mg/kg)				
Kg	Lbs	1 mg/kg	2.5 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg
45	99	2.3	5.6	11.3	16.9	22.5
58	128	2.9	7.3	14.5	21.8	29.0
73	161	3.7	9.1	18.3	27.4	36.5
88	194	4.4	11.0	22.0	33.0	44.0
103	227	5.2	12.9	25.8	38.6	51.5
118	260	5.9	14.8	29.5	44.3	59.0
133	293	6.7	16.6	33.3	49.9	66.5
148	326	7.4	18.5	37.0	55.5	74.0



# New Dantrium IV

Reconstitutes  
in ~ 20sec

Less  
Shaking



New  
@ 20secs

Old  
@ 20secs



# STOP

**NO** Calcium channel blockers

Decrease myocardial contractility



## Myths about Dantrium<sup>®</sup> IV

- Myth 1** The chance of MH occurring in our facility is so remote, it makes no sense to stock it.
- Myth 2** If MH strikes, we'll have enough time to get the patient to a hospital.
- Myth 3** Our state requires stocking only 12 vials, so it must be enough
- Myth 4** Dantrium<sup>®</sup> IV costs too much, so it makes sense for facilities to share it.

**Dantrium<sup>®</sup> IV has a 36 month shelf life**



# Ordering Dantrium or Dantrolene

To order: Dantrium<sup>®</sup> IV (dantrolene sodium for injection) Vials or Capsules

Call: **JHP Pharmaceuticals**

**1.877.547.4547, or fax 1.866.923.4547.**

(Dantrium<sup>®</sup> IV is also available through your local wholesaler or distributor.)

Dantrium IV vials = 20mg

Dantrium Capsules = 25mg, 50mg, 100mg

## 24hr Emergency support

- If you have an MH episode and must have Dantrium<sup>®</sup> IV (dantrolene sodium for injection), call the JHP Dantrium<sup>®</sup> IV Emergency orders at 1.877.547.4547 and select option 1
- JHP provides notification when Dantrium vials are about to reach their expiration date



## References

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Thank You!



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