

TOP 10 FACTS

Top Ten Facts You Need to Know About the Perioperative Management of Malignant Hyperthermia

Vikas Chauhan, MBBS, MD, DM¹ , Lakshmi N Kurnutala, MD¹ 

¹ Anesthesiology, University of Mississippi Medical Center

Keywords: malignant hyperthermia, general anesthesia, succinylcholine, inhalational agents, genetics.

<https://doi.org/10.67225/001c.155658>

Journal of the Mississippi State Medical Association

Vol. 66, Issue 11/12, 2025

Malignant hyperthermia (MH) is a rare but life-threatening genetic disorder that can be triggered by exposure to volatile anesthetics or succinylcholine. This condition leads to a rapid and uncontrolled hypermetabolic reaction in skeletal muscle, primarily caused by mutations in the ryanodine receptor 1 (RYR1) gene. Early clinical signs include a rapid increase in end-tidal carbon dioxide (EtCO₂), tachycardia, and muscle rigidity. As condition progresses, symptoms may escalate to include hyperthermia, rhabdomyolysis, and multi-organ dysfunction. Timely recognition of MH is vital to decrease morbidity and mortality. Management requires the immediate cessation of all triggers, intravenous administration of dantrolene, and supportive care to address associated metabolic abnormalities. While diagnosis is primarily clinical, can be confirmed through contracture testing or genetic analysis. It is also important to consider differential diagnoses such as neuroleptic malignant syndrome, serotonin syndrome, and thyroid storm, especially when typical symptoms or triggers are absent. Preventive strategies, such as using non-triggering total intravenous anesthesia and implementing institutional protocols for MH, are essential for individuals at risk to minimize complications during surgery. Advances in understanding the molecular basis of MH, Malignant Hyperthermia Association of the United States (MHAUS) development of protocols, along with timely access to treatment and thorough perioperative preparation, have significantly decreased the morbidity and mortality associated with this condition.

Introduction

Malignant hyperthermia (MH) is a pharmacogenetic emergency that poses ongoing challenges for anesthesiologists, surgeons, and perioperative teams around the world.^{1,2} Despite improvements in anesthetic safety, the risk of malignant hyperthermia (MH) remains due to its unpredictable nature and potentially severe consequences. This review highlights the ten essential facts for effectively managing MH during the perioperative period.

1. Historical Insight: From Tragedy to Targeted Therapy

The first detailed account of Malignant Hyperthermia (MH) as a distinct clinical syndrome emerged in the early 1960s.² The introduction of dantrolene in the 1970s, the only specific antidote for MH, significantly improved outcomes. With proper protocols and access to the drug, mortality rates decreased from as high as 80% to less than 5%.^{1,3-5}

2. Epidemiology: A Rare Event with Global Implications

Malignant hyperthermia (MH) episodes are rare, with reported incidences ranging from 1 in 5,000 to 1 in 150,000 exposures to general anesthesia. These rates depend on factors such as population, genetic background, and the prevalence of triggering agents.^{1,4,6,7} Young males are affected more frequently than females.^{4,6} There are regional variations, and the disorder is more frequently reported in Europe, North America, and certain Asian populations.^{7,8}

3. Pathophysiology: Unchecked Calcium—The Metabolic Engine of Crisis

MH is caused by a dysregulated intracellular calcium release in skeletal muscle, most commonly due to a defective ryanodine receptor (RyR1) in the sarcoplasmic reticulum.^{1-3,9,10} When exposed to triggering agents, the RyR1 channel remains open, leading to an influx of calcium ions into the myoplasm ([Figure 1](#)). This surge of calcium activates the muscle's contractile machinery, significantly increasing metabolic rate, oxygen consumption, ATP hydrolysis, and heat production. If this process goes unchecked, it can result in lactic acidosis, rhabdomyolysis, hyperkalemia, and damage to multiple organs.^{1,2,9}

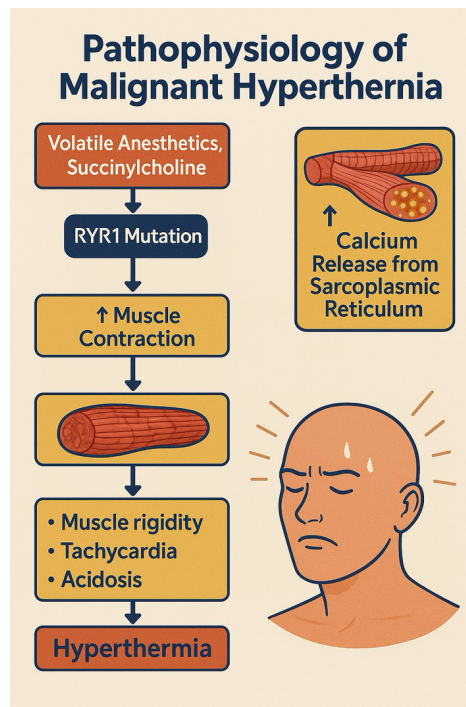


Figure 1. Pathophysiology of MH

4. Genetics: Dominant Inheritance and Heterogeneity

MH is primarily inherited in an autosomal dominant manner^{2,11}. The majority of human MH susceptibility is associated with mutations in the RYR1 gene on chromosome 19q13.1.^{1,10-12} Less commonly, mutations in CACNA1S (dihydropyridine receptor $\alpha 1\alpha 1$ -subunit) and STAC3 play a role.^{11,12} Genetic testing exists but does not capture all cases of susceptibility, and negative genetic tests do not rule out MH risk.^{12,13}

5. Triggering Agents: The Must-Know Provocateurs

MH crises are precipitated by specific anesthetic drugs—namely volatile inhalational agents (sevoflurane, desflurane, isoflurane, halothane) and the depolarizing muscle relaxant succinylcholine.^{1,4,11,14} Notably, non-depolarizing muscle relaxants, nitrous oxide, and intravenous anesthetics—including propofol, opioids, benzodiazepines, and ketamine—are safe in susceptible individuals, with extensive studies demonstrating propofol's non-triggering effects on skeletal muscle calcium regulation^{1,2,14}. Agents such as succinylcholine can also trigger MH (up to 15% of cases).⁴

6. Clinical Presentation: Early Warning Signs and Catastrophic Progression

Acute MH episodes often begin intraoperatively but may rarely present postoperatively.^{4,15,16} The earliest hallmark is a sudden, unexpected rise in end-tidal carbon dioxide (ETCO₂), out of proportion to ventilation.¹⁷ This condition may be accompanied by ([Table 1](#)):

- Sinus tachycardia
- Generalized muscle rigidity (notably masseter spasm after succinylcholine)
- Hyperthermia (often a late sign, with temperature rising precipitously)
- Metabolic and respiratory acidosis
- Hyperkalemia
- Myoglobinuria and rhabdomyolysis
- Arrhythmias progressing to cardiac arrest in severe cases

Importantly, hyperthermia is a late sign; early diagnosis hinges on recognizing unexplained hypercapnia and muscle rigidity.^{4,6,16,17}

Table 1. Signs and symptoms

System / Category	Signs and Symptoms	Temporal Pattern / Notes
Respiratory	- Rapid unexpected increase in end-tidal CO₂ (EtCO₂) - Tachypnea (may be masked by mechanical ventilation during general anesthesia) - Unexplained hypercarbia - Respiratory acidosis	Typically, the earliest and most sensitive indicator; EtCO ₂ rises despite increased ventilation
Musculoskeletal	- Generalized muscle rigidity - Masseter muscle spasm ("jaw of steel") especially after succinylcholine - Muscle breakdown/ rhabdomyolysis	Rigidity can be initial sign, especially in children; masseter spasm is notable after succinylcholine
Cardiovascular	- Tachycardia - Arrhythmias (including ventricular tachycardia/ fibrillation) - Initial hypertension - Hypotension (late, secondary to shock) - Cardiac arrest (if untreated)	Tachycardia is among the most common and early cardiovascular findings. Arrhythmias and hypotension develop with crisis progression and hyperkalemia
Thermoregulatory	- Rapid increase in core temperature - Hyperthermia (can	Hyperthermia is a late sign, often occurring after other metabolic and respiratory symptoms manifest

System / Category	Signs and Symptoms	Temporal Pattern / Notes
	exceed 40°C) - Temperature rise up to 1–2°C every 5 min	
Metabolic / Laboratory	- Mixed metabolic and respiratory acidosis ($\downarrow$ pH, $\uparrow$ PaCO ₂ , $\downarrow$ HCO ₃) - Hyperkalemia - Raised lactate - Elevated creatine kinase (CK) - Myoglobinemia/Myoglobinuria -	Laboratory evidence strongly supports the clinical diagnosis when present; reflects muscle breakdown and systemic hypermetabolism
Renal	- Myoglobinuria (cola-colored urine) - Oliguria - Acute renal failure (secondary to rhabdomyolysis and myoglobin-induced injury)	Renal complications are secondary to muscle breakdown; may progress to acute tubular necrosis if not addressed
Coagulation	- Disseminated intravascular coagulation (DIC) - Bleeding diathesis	Rare and late-stage complication, typically seen in fulminant untreated cases
Other Clinical Clues	- Rapid unexplained increase in EtCO ₂ refractory to ventilatory efforts - Failure to respond to standard anesthetic interventions	Earliest clue is often rising EtCO ₂ in the context of exposure to triggering agents; lack of response to hyperventilation is crucial

7. Rapid Recognition, Differential Diagnosis, and Laboratory Clues

The diagnosis of MH is clinical, supported by laboratory findings of hyperkalemia, acidosis, elevated creatine kinase, and myoglobinuria.^{1,4,6,9} Differential diagnoses ([Table 2](#)) include conditions like Thyroid storm, Neuroleptic malignant syndrome, and more.

Table 2. Differential Diagnosis of MH

Condition	Trigger	Onset	Key Clinical Features	Distinguishing Features	Treatment
Malignant Hyperthermia (MH)	Volatile anesthetics, Succinylcholine	Intraop. or early postop. (Minutes-Hours)	Sudden hypercapnia, muscle rigidity, tachycardia, metabolic/respiratory acidosis, hyperthermia (late), rhabdomyolysis	Exposure to anesthetic triggers; rapid progression; genetic predisposition; response to dantrolene	Immediate discontinuation of triggers, rapid IV dantrolene (2.5 mg/kg, repeat as needed), active cooling, manage acidosis/hyperkalemia, supportive care, ICU observation.
Neuroleptic Malignant Syndrome (NMS)	Antipsychotics, dopamine antagonists	Hours–days	Hyperthermia, "lead-pipe" rigidity, altered mental status, autonomic instability, elevated CK	Recent neuroleptic use; slower onset; non-anesthetic triggers	Stop causative drugs, supportive care (cooling, hydration, electrolyte correction), consider dantrolene and/or

Condition	Trigger	Onset	Key Clinical Features	Distinguishing Features	Treatment
					bromocriptine, benzodiazepines for agitation, ICU monitoring for complications (e.g., arrhythmias, renal failure).
Serotonin Syndrome	Selective serotonin reuptake inhibitors (SSRIs), Mono Amino Oxidase Inhibitors (MAOIs), serotonergic drugs	Hours	Hyperthermia, agitation, myoclonus, hyperreflexia, tremor, autonomic instability	Medication history (serotonergics), clonus/hyperreflexia common	Discontinue serotonergic agents, supportive care, benzodiazepines for agitation, cyproheptadine in moderate to severe cases, aggressive temperature management, control hypertension and tachycardia.
Thyroid Storm	Hyperthyroid state + stress (surgery, infection, & trauma)	Acute	Fever, agitation, tachycardia, hypertension, arrhythmias, tremor, delirium	Signs of thyrotoxicosis, lab confirmation (high free T4, low TSH)	Supportive care, beta-blockers (e.g., propranolol), antithyroid drugs (e.g., propylthiouracil or methimazole), corticosteroids, cooling, and definitive therapy for thyrotoxicosis.
Sepsis/Systemic Inflammatory Response	Infection, trauma, inflammation	Variable	Fever, tachycardia, hypotension, altered mental status, elevated lactate, possible DIC	Evidence/source of infection, positive cultures, inflammatory markers	Early broad-spectrum antibiotics, fluid resuscitation, vasopressors, if necessary, source control (e.g., drainage of abscess), ICU, temperature management.
Pheochromocytoma Crisis	Catecholamine-secreting tumor, stress	Sudden	Paroxysmal hypertension, headache, palpitations, diaphoresis, arrhythmias	Episodic hypertension, known/suspected adrenal tumor, catecholamine/metanephrine elevation	Immediate alpha-blockade (e.g., phenoxybenzamine), followed by beta-blockade if needed, volume resuscitation, surgical tumor removal once clinically stabilized, ICU support for complications.
Heat Stroke/Exertional Heat Illness	Environmental heat, exertion	Gradual-Rapid	Hyperthermia, confusion, collapse, (an)hidrosis, muscle cramps, possible rhabdomyolysis	History of heat/exercise exposure, no anesthetic/drug trigger; can co-exist with MH risk	Rapid whole-body cooling (e.g., immersion, evaporative), IV hydration, supportive care, monitor for and treat rhabdomyolysis, electrolyte correction. Dantrolene is generally not indicated except in suspected MH phenotype or persistent muscle

Condition	Trigger	Onset	Key Clinical Features	Distinguishing Features	Treatment
					rigidity.

8. Immediate Crisis Management: Dantrolene and Supportive Measures

Time is crucial in MH. Immediate steps are^{1,2,4,9}:

- **Stop all triggering agents.**
- **Call for help and mobilize MH crisis protocol.**
- **Administer dantrolene sodium IV:** initial dose 2.5 mg/kg, repeated as needed, up to 10 mg/kg total if symptoms persist.
- **Hyperventilate with 100% oxygen** (≥ 10 L/min) to address hypercapnia.
- **Actively cool** the patient.
- **Treat hyperkalemia** (with insulin/glucose, calcium, bicarbonate).
- **Manage dysrhythmias** appropriately; avoid calcium channel blockers in conjunction with dantrolene due to the risk of hyperkalemia.
- **IV fluid therapy** and **vasopressors** to support hemodynamics.
- **Insert a Foley catheter** for urine output and detection of myoglobinuria.
- **Monitor Creatine Kinase, potassium, renal function, and coagulation parameters.**
- **Prepare for transfer to ICU.**

Dantrolene acts by inhibiting abnormal calcium release from the sarcoplasmic reticulum, directly reversing the underlying metabolic derangement. Guidelines demand its ready availability in all anesthetizing areas.^{1,2,4-6,9,18}

9. Postoperative Care: Vigilance for Recurrence

After crisis control, intensive monitoring in an ICU is recommended for at least 24–48 hours, as up to 25% of patients may experience recrudescence.^{1,4,9} Dantrolene should be continued (1 mg/kg every 6 hours IV, or 0.25 mg/kg/hr infusion) as guided by symptoms. Monitoring for complications of rhabdomyolysis, hyperkalemia, hepatic dysfunction, renal dysfunction, and

DIC (Disseminated Intravascular Coagulation) is essential.^{1,4,9} The caffeine-halothane contracture test (CHCT) remains the gold standard but is not universally available.^{1,12,13} It is available in only 4 centers in North America.

10. Anesthetic Strategies for MH-Susceptible Patients

The paramount principle is strict avoidance of triggers. For elective procedures in susceptible patients:

- Use non-triggering anesthesia: total intravenous anesthesia.^{1,2,14}
- Avoid volatile anesthetics and succinylcholine.
- Prepare anesthesia equipment by removing vaporizers, flushing circuits (≥ 20 minutes with high fresh gas flow), or using charcoal filters to absorb residual inhalational agents.^{1,2}
- Maintain a high index of suspicion for any unexplained tachycardia, hypercapnia, or rigidity.
- Ensure immediate access to dantrolene and crisis protocols.^{1,9,14}
- Record clear documentation of susceptibility; advise medical alert bracelets and inform family for evaluation.^{1,4}

With such comprehensive measures, elective surgery can proceed safely in most MH-susceptible patients.^{1,2,9,14}

Conclusion

Malignant hyperthermia (MH) is a rare but critical emergency in the perioperative setting. Thanks to advancements in care, based on historical lessons, molecular understanding, Malignant Hyperthermia Association of the United States (MHAUS) development of protocols, and coordinated crisis response, the risk of death has significantly decreased. To achieve the best possible outcomes for patients at risk of this serious condition, it is essential to recognize the signs early, administer dantrolene without delay, provide strict supportive care, and maintain careful monitoring during postoperative recovery as well as in future anesthesia plans.

Submitted: May 16, 2025 CDT. Accepted: December 01, 2025 CDT. Published: January 21, 2026 CDT.

REFERENCES

1. Hopkins PM, Girard T, Dalay S, et al. Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists. *Anaesthesia*. 2021;76(5):655-664. doi:[10.1111/anae.15317](https://doi.org/10.1111/anae.15317)
2. Nelson TE, Flewellen EH. The malignant hyperthermia syndrome. *New England Journal of Medicine*. 1983;309(7):416-418. doi:[10.1056/NEJM198308183090706](https://doi.org/10.1056/NEJM198308183090706)
3. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis*. 2015;10:93. doi:[10.1186/s13023-015-0310-1](https://doi.org/10.1186/s13023-015-0310-1)
4. Kim DC. Malignant hyperthermia. *Korean J Anesthesiol*. 2012;63(5):391-401. doi:[10.4097/kjae.2012.63.5.391](https://doi.org/10.4097/kjae.2012.63.5.391). PMID:23198031
5. Riazi S, Larach MG, Hu C, Wijesundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. *Anesth Analg*. 2014;118(2):381-387. doi:[10.1213/ANE.0b013e3182937d8b](https://doi.org/10.1213/ANE.0b013e3182937d8b)
6. García-Muro C, Sáenz-Moreno I, Riaño-Méndez B, Gutiérrez-Delgado JM, Valencia-Ramos J, Esteban-Zubero E. Malignant hyperthermia syndrome: A rare entity. *Bol Med Hosp Infant Mex*. 2020;77(6):337-340. doi:[10.24875/BMHIM.20000047](https://doi.org/10.24875/BMHIM.20000047)
7. Gopalakrishnan CV, Suparna B, Arun V. A rare case of malignant hyperthermia in the Indian subcontinent. *Anaesthesia*. 2010;65(11):1141-1142. doi:[10.1111/j.1365-2044.2010.06515.x](https://doi.org/10.1111/j.1365-2044.2010.06515.x)
8. Xu ZH, Luo AL, Guo XY, et al. Malignant hyperthermia in China. *Anesth Analg*. 2006;103(4):983-985. doi:[10.1213/01.ane.0000237289.66136.cd](https://doi.org/10.1213/01.ane.0000237289.66136.cd)
9. Gregory H, Weant KA. Pathophysiology and Treatment of Malignant Hyperthermia. *Adv Emerg Nurs J*. 2021;43(2):102-110. doi:[10.1097/TME.0000000000000344](https://doi.org/10.1097/TME.0000000000000344)
10. Moolchala SM, Tan WT, Lee TL. The genetic basis of malignant hyperthermia. *Ann Acad Med Singap*. 1994;23(4):475-478. PMID:7979121
11. Broman M, Islander G, Müller CR. Malignant hyperthermia, a Scandinavian update. *Acta Anaesthesiol Scand*. 2015;59(8):951-961. doi:[10.1111/aas.12541](https://doi.org/10.1111/aas.12541)
12. Riazi S, Kraeva N, Hopkins PM. Malignant Hyperthermia in the Post-Genomics Era: New Perspectives on an Old Concept. *Anesthesiology*. 2018;128(1):168-180. doi:[10.1097/ALN.0000000000001878](https://doi.org/10.1097/ALN.0000000000001878)
13. Wallace AJ, Wooldridge W, Kingston HM, Harrison MJ, Ellis FR, Ford PM. Malignant hyperthermia--a large kindred linked to the RYR1 gene. *Anaesthesia*. 1996;51(1):16-23. doi:[10.1111/j.1365-2044.1996.tb07647.x](https://doi.org/10.1111/j.1365-2044.1996.tb07647.x)
14. Fruen BR, Mickelson JR, Roghair TJ, Litterer LA, Louis CF. Effects of propofol on Ca²⁺ regulation by malignant hyperthermia-susceptible muscle membranes. *Anesthesiology*. 1995;82(5):1274-1282. doi:[10.1097/00000542-199505000-00023](https://doi.org/10.1097/00000542-199505000-00023)
15. O'Neill SS, Smurthwaite GJ. Malignant hyperthermia presenting during laparoscopic adrenalectomy. *Anaesthesia*. 2008;63(5):540-543. doi:[10.1111/j.1365-2044.2007.05405.x](https://doi.org/10.1111/j.1365-2044.2007.05405.x)
16. Evans TJ, Parent CM, McGunigal MP. Atypical presentation of malignant hyperthermia. *Anesthesiology*. 2002;97(2):507-508. doi:[10.1097/00000542-200208000-00032](https://doi.org/10.1097/00000542-200208000-00032)
17. Kim DC, Lim H, Han Y. Early Recognition of Malignant Hyperthermia with Capnography: A case report. *Korean Journal of Anesthesiology*. 2002;43:667-672. doi:[10.4097/kjae.2002.43.5.667](https://doi.org/10.4097/kjae.2002.43.5.667)
18. Lee YS, Kim WY, Lee SH, et al. A case of malignant hyperthermia during anesthesia induction with sevoflurane -A case report-. *Korean J Anesthesiol*. 2010;59 Suppl(Suppl):S6-8. doi:[10.4097/kjae.2010.59.S.S6](https://doi.org/10.4097/kjae.2010.59.S.S6)