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**Review Article**

# Advances in malignant hyperthermia: pathophysiology, diagnosis and management

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## ABSTRACT

Malignant hyperthermia (MH) is a rare genetic disorder triggered by volatile anaesthestics and depolarizing muscle relaxants like sevoflurane, desflurane, and succinylcholine. It is mainly associated with pathogenic variants in the RYR1 and CACNA1S genes that disrupt calcium regulation in skeletal muscles, causing uncontrolled calcium release from the sarcoplasmic reticulum and a hypermetabolic crisis with rhabdomyolysis, muscle rigidity, hypercapnia, hyperthermia, and multiorgan failure. Since its first clinical description in the 1960s, clinical signs such as tachycardia, rising end-tidal $CO_2$ ($ETCO_2$), and sudden hyperthermia remain essential for detection. Diagnosis relies on invasive muscle contracture tests like the Caffeine-Halothane contracture test (CHCT) and *in vitro* contracture test (IVCT). Next-generation sequencing (NGS) identifies mutations in RYR1, CACNA1S, and related excitation–contraction coupling genes. Despite incomplete genotype-phenotype correlations, mechanisms including oxidative stress and sodium-calcium channel dysregulation improve understanding of MH susceptibility. Management requires immediate cessation of triggering agents, intravenous dantrolene, and supportive care including cooling, correction of acidosis, electrolyte control, and monitoring of cardiac and renal complications. Patients should be monitored for recurrence within 24 hours and receive genetic counselling, medical alert identification, and family screening due to autosomal dominant inheritance. Emerging research explores CRISPR/Cas9 correction of RYR1 mutations, antisense oligonucleotide therapy to suppress mutant transcripts, and antioxidants N-acetylcysteine and Trolox to reduce reactive oxygen species-mediated muscle injury; animal studies show improved calcium regulation but human trials are needed. Preventive measures include temperature and $ETCO_2$ monitoring, regional anaesthesia in obstetrics, and total intravenous anaesthesia, when necessary, supported by collaboration among anaesthesiologists, geneticists, intensivists, and surgeons.

**Keywords:** Malignant hyperthermia, RYR1 mutation, CACNA1S, Dantrolene, Anaesthesia, Genetic susceptibility, Calcium dysregulation, Next-generation sequencing, Antisense oligonucleotide

## INTRODUCTION

A severe type of reaction to general anaesthesia named MH was first observed in 1960.[1]

Strong volatile anaesthetics such as halothane, sevoflurane, desflurane, isoflurane, and the depolarizing muscle relaxant succinylcholine can elicit a hypermetabolic reaction in skeletal muscle and result in MH, a pharmacogenetic illness.[2]

Triggering agents cause the sarcoplasmic reticulum to release calcium uncontrollably, which allows extracellular calcium to enter myoplasm and causes skeletal muscle

contraction, glycogenolysis, and an increase in cellular metabolism.[3]

## LITERATURE REVIEW

This narrative review was conducted to synthesize current knowledge on the pathophysiology, clinical features, diagnosis, and management of MH. A comprehensive literature search was carried out using online databases including PubMed, Scopus, ScienceDirect, and Google Scholar. The search included articles published between 2000 and 2025, with a focus on high-impact reviews, clinical trials, and updated guidelines related to MH.

Search terms used were: "Malignant Hyperthermia", "RYR1 mutation", "CACNA1S", "Dantrolene therapy", "next-generation sequencing in anaesthesia", and "calcium dysregulation in skeletal muscle."

## HISTORY OF MH

A 21-year-old engineering student named Ron Evans at University of Melbourne, Australia visited Royal Melbourne hospital with compound right tibia and fibula fracture. He and his mother were worried to take general anaesthesia since there were already ten deaths happened in family due to general anaesthesia. When checked, previous records showed that ether killed those patients. He had undergone appendectomy under spinal anaesthesia when he was 12-year-old. Dr. Jim Villiers, an anaesthesiologist chose to administer him halothane. After 10 minutes of halothane inhalation, the boy's blood pressure dropped, pulse increased, he was very hot and soda lime cannister was exhausted. He stopped the anaesthetics and supplemented with 50% oxygen. Dr. Villiers believed that the blood loss effected his health and began with the transfusion, and the boy was packed in ice. One hour after starting the patient was awake and alert. He was the first known MH survivor. The research began to understand the cause and he was referred to Professor Richard Lovell Professor of medicine at Melbourne University for more valuations. After this case Dr.Villiers took good history of patient and was prepared for disaster. He seized the anaesthetics and cooled the patients. Dr. Michael Denborough took up the research and meanwhile the same patient underwent surgery for ureteric stone under spinal anaesthesia by Dr. John Forster with no complications. It was understood that these patients can undergo regional anaesthesia without any harm. Dr. Donborough found that there was variable penetration of the disease that some patient could tolerate light anaesthesia. In 1966 MH symposium was published in the Canadian Anaesthetic Society Journal. There was clarity that Some patients had inherited the condition. Muscle rigidity affected all these patients. The discovery of breed of pigs as an animal model for MH revealed that biochemistry of the disease was increased calcium in the myoplasm. Dexamethasone and procaine were the effective early treatments. Dantrolene was introduced in 1975. Ron Evans died on September 19 2006.

The name MH got its name because the apparent features of the reactions were dominated by a progressive pyrexia that typically resulted in death.[1-3]

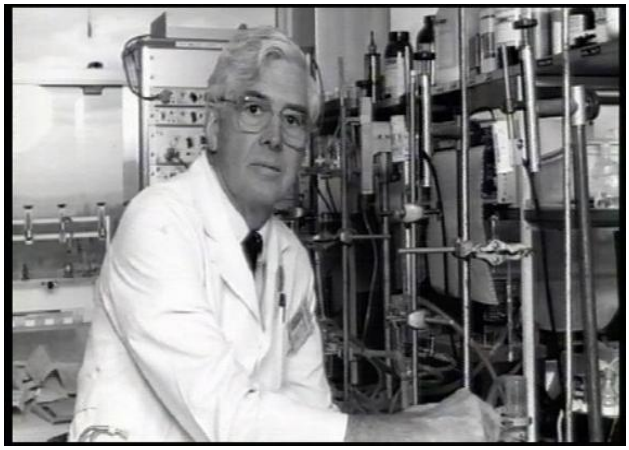

**Figure 1: Dr. Michael Donborough.[4]**

**Figure 2: Ron Evans.[2]**

### *Etiology*

Environmental stimuli such as heat, exercise, and stress induce elevated Ca2+ release in MH- Susceptible pigs and knock in mice. In humans, exposure to potent inhalation anaesthetics, with or without succinylcholine, is the predominant cause of symptomatic MH. The elevated intracellular Ca2+ induces dysregulated skeletal muscle metabolism including thermogenesis, ATP hydrolysis, augmented oxygen consumption and carbon dioxide generation, and muscular contraction. when the SR/ER Ca2+ ATPase (SERCA) can't store released Ca2+ effectively, the membrane becomes less stable which allows the potassium and creatinine kinase (CK) leakage. The cause of MH susceptibility is a malfunctioning or disordered Ca2+ channel called the ryanodine receptor

(RyR). Up to 70% of MH-susceptible families carry one of the 34 causative mutations for MH, and there are numerous more variations that have not yet been identified. Histidine rich Ca2+ proteins, plasma membrane associated proteins and integrin SR membrane proteins are the additional proteins involved in RYR1 activity.

The clinical manifestation of MH and the reaction of isolated muscle to halothane/caffeine do not exhibit strong genotype-phenotype relationships. Unsaturated fatty acids may improve halothane induced Ca2+ release due to enzymatic abnormalities. Post-translational changes that affect release of Ca2+ from SR include phosphorylation, glutathionylation, oxidation, and nitrosylation of RyR1. Mutations in sodium channels or fatty acids can affect muscle stiffness, which is a MH phenotype. Membrane proteins like STIM1, Orai1 and TRPCs are involved in Ca2+ influx across the plasma membrane which is induced by Ca2+ depletion of the SR through skeletal muscle RYR1 activity. When cultured muscle cells or myotubes with known causative mutations are exposed to substances like 4-chloro-m-cresol, halothane, or caffeine, intracellular calcium release is increased.[4,5]

**Table 1: Genetic mutations implicated in MH, their molecular functions, prevalence, and associated clinical impacts.**

| Gene | Function | Prevalence in MH | Clinical Impact |
|---|---|---|---|
| **RYR1** | Encodes ryanodine receptor 1, a calcium release channel in skeletal muscle | ~70% of MH cases | Leads to uncontrolled calcium release → muscle rigidity, hypermetabolism, rhabdomyolysis |
| **CACNA1S** | Encodes alpha-1 subunit of dihydropyridine receptor involved in excitation-contraction coupling | ~1-2% of MH cases | Alters calcium influx; modifies skeletal muscle excitability |
| **STAC3** | Stabilizes excitation-contraction coupling in skeletal muscle fibres | Rare (Native American ancestry) | Associated with native American myopathy; contributes to MH-like symptoms in specific populations |

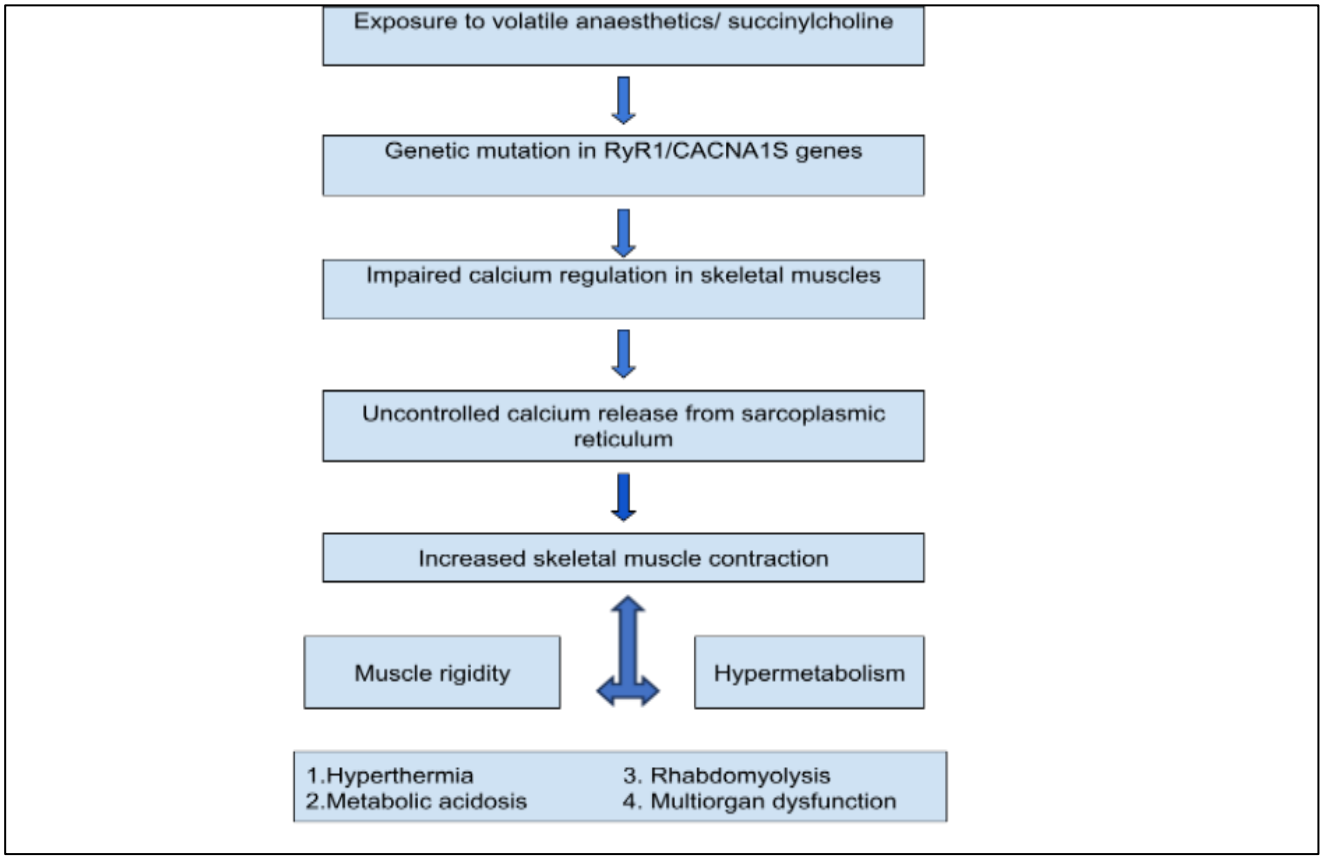


**Figure 3: Schematic representation of the pathophysiological cascade in MH, from genetic mutation to clinical complications.[5,10]**

## CLINICAL PRESENTATIONS AND DIAGNOSIS

While MH can arise during anaesthesia or the first hour following surgery, it cannot happen an hour after volatile anesthetics have been discontinued. Combining succinylcholine with potent inhalation anesthetics can significantly increase the risk of MH.[6] Even if minute respiration improves, the first symptoms after a succinyl choline injection include tachycardia, muscle tightness, and an increase in end-expired carbon dioxide concentration. Body temperature elevation is one of the most common symptoms of MH.[5] Raised temperature was the initial symptom in 63.5 % of MH responses, according to Larach et al. End-tidal carbon dioxide ($ETCO_2$) is a sensitive early indicator of MH, however rather than a rapid spike, a continuous increase in CO2 has been observed in recent years along with a decrease in succinylcholine use. It is possible to conceal this rise by increasing minute ventilation. Hyperthermia occurs when the core temperature rises by 1-2 ˚C every five minutes. Severe hyperthermia (core temperature >44 °C) can result in significant increases in oxygen use, CO2 generation, widespread critical organ failure, and DIC. Because ATP and energy stores are rapidly depleted in uncontrolled hypermetabolism, respiratory and, most frequently, metabolic acidosis occur. In the absence of treatment, myoglobinuria may lead to acute renal failure, and persistent myocyte death and rhabdomyolysis may culminate in hyperkalaemia, which may be lethal. Intestinal ischemia, DIC, congestive heart failure, and compartment syndrome of the limbs caused by significant muscle oedema are all potentially fatal consequences. The primary cause of death when body temperature rises above 41˚C is DIC.[7-9]

### *Diagnostic criteria*

Large genes like RYR1 and CACNA1S can be examined with NGS because of its high rate of analysis and low cost per base-read. Researchers developed a capture-based targeted NGS sequencing framework that includes 12 additional genes linked to excitation-contraction coupling and calcium homeostasis in skeletal muscle, and genomic regions of RYR1, CACNA1S, and mitochondrial genome.

To diagnose pathogenic gene variants in MH-susceptible (MHS) individuals MHS genotyping is considered as primary method. In addition to genotyping, biopsied muscle is subjected to invasive IVCT in Europe and CHCT in North America.[11] Additionally, it was discovered that bioinformatics and NGS are relevant and helpful techniques for genetically identifying MH.[10]

**Table 2: Comparative summary of diagnostic modalities for MH, including CHCT, IVCT, and NGS, with respective advantages and limitations.**

| Diagnostic method | Description | Advantages | Limitations |
|---|---|---|---|
| **CHCT** | Muscle biopsy exposed to caffeine and halothane to detect contractures | Gold standard; high sensitivity and specificity | Invasive; requires open muscle biopsy; limited to few centers |
| **IVCT** | European version using muscle sample and standard concentrations of triggers | Validated for EU diagnosis; similar to CHCT | Invasive; limited availability; inter-laboratory variability |
| **NGS** | DNA sequencing of known MH genes (e.g., RYR1, CACNA1S) | Non-invasive; identifies genetic carriers; expanding database | May not detect all mutations; VUS (variants of uncertain significance) |

### *Potential complications if untreated*

Untreated MH can cause serious and perhaps fatal issues. Rhabdomyolysis is one such effect where in the skeletal muscle breaks down and is released into the blood stream causing acute kidney damage or renal failure due to the nephrotoxicity of higher levels of myoglobin.[5]

Unpredictable blood clotting and bleeding throughout the body are hallmarks of disseminated intravascular coagulation (DIC), a serious side effect of untreated MH. systemic inflammation and disseminated intravascular coagulation are caused by chain of events that are aggravated by hypermetabolic state associated with MH.[14]

Moreover, other organ malfunctions can result from the high heat generation and MH's metabolic imbalances such as acidosis and electrolyte imbalances can lead to arrhythmias and cardiac arrest. effect of heat and prolonged hypoxia can lead to brain injury. These outcomes could lead to mortality and irreparable organ failure if prompt treatment is not provided, such as administering dantrolene injections and supportive measures.[15]

## MANAGEMENT

### *Immediate intervention*

A suitable intravenous dose of dantrolene given as soon as possible following the diagnosis is a crucial part of treating MH.[6]

A longer time between the initial MH symptom and the first dosage of dantrolene also raised the risk of MH. With proper temperature monitoring and timely dantrolene

administration can help in early identification of MH and prevention of complications.[7]

Early and appropriate intra venous dantrolene (IVD) treatment for active MH is advised by the expert panel. Start with 22.5 mg kg-1 and repeat every 10 min until MH symptoms diminish. With normal minute ventilation, dantrolene cessation requires lowering core body temperature and $PaCO_2$ below 6 kPa. Emergency mental health crisis management reduces respiratory acidosis and volatile anesthetic use by increasing minute breathing. MH can hyper metabolically recur within 24 hrs of remission, necessitating dantrolene. Dantrolene doses must be increased to attenuate the initial reaction, therefore more severe patients may need more doses. A loading dosage of dantrolene sustains therapeutic plasma concentrations for six hours after MH reversal. If MH symptoms return, add 2-2.5 mg kg-1 dantrolene every 10 minutes.[6]

***Long term management***

It is important to educate family members about the genetic component of MH. [8]

Long-term management of MH focuses on preventing future episodes and addressing potential complications. genetic counselling and medical alert identification should be provided to those who are at risk of MH. During any surgical procedures it is necessary to avoid the use of triggering agents.

The commonly used drug, Dantrolene is not used for long term treatment but it is advised for the patient to regularly follow up with MH centre where the status of their condition can be monitored and they can receive updated guidance on management. And even, the family can be screened for MH .[10]

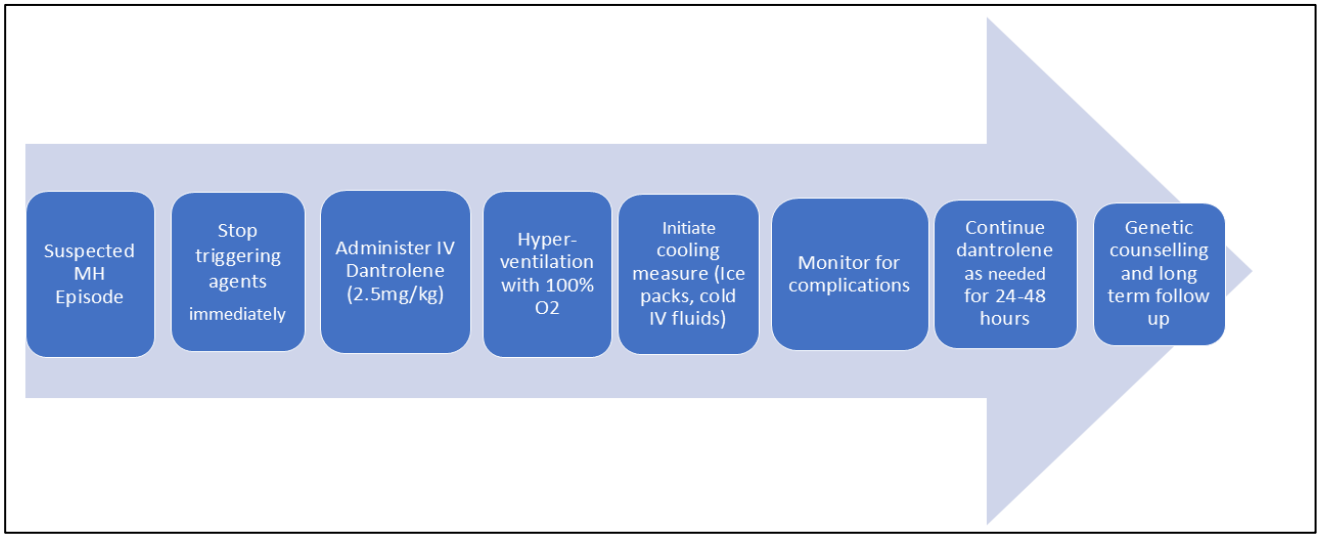


**Figure 4: Algorithm involved in managing MH from identification and cessation of trigerring agents to long term monitoring.[6]**

***Management of pregnancy***

If a pregnant woman with MHS needs non-emergent surgery, use a non-triggering anesthetic (local, nerve block, epidural, spinal, or total intravenous general). Continuous epidural anaesthesia benefits the delivery. A woman without an epidural catheter should have a caesarean under neuraxial (spinal, epidural, or combination spinal-epidural) anaesthesia unless contraindicated. Any general anesthetic should be given using a complete intravenous anaesthesia equipment designed for MH-susceptible patients.[11]

***Prevention***

Essential monitoring especially temperature and $ETCO_2$ should be used so that early warning signs can be detected in all cases where volatile anesthetic agents and other triggering agents are used.[12]

**MH CART**

The MH Association of the United States (MHAUS) and the American Society of Anaesthesiologists (ASA) recommend that the Universal MH cart should have all the drugs, supplies, and equipment needed for immediate intervention during an MH crisis. There should be at least 36 vials of dantrolene, sterile water for reconstitution, sodium bicarbonate, calcium chloride, regular insulin, 50% dextrose, furosemide, mannitol, lidocaine or amiodarone for arrhythmias, heparin, and activated charcoal filters in the cart. Ice packs, cold saline, IV catheters, syringes, temperature probes, Foley catheters, urine collection devices, and blood specimen tubes are some of the other things that are needed. The supplies are meant for quickly giving dantrolene, managing metabolism, keeping an eye on the patient all the time, and chilling them down for MH crises.[13]

## CASE REPORTS ON MH (2000-2025)

A man in his mid-20s- undergoing maxillary osteotomy developed MH after being exposed to sevoflurane, fentanyl, Propofol and furosemides (without succinyl choline). His symptoms were hypercapnia, tachycardia and hyperthermia. It was "almost certain" diagnosis with MH clinical grading score of 63. The patient recovered completely after sevoflurane discontinuation and switching to strategies like propofol administration, equipment change, cooling of body, and administering dantrolene.[14]

This case report presents the successful management of MH in an adult during orthopaedic surgery without the use of dantrolene. In this case, the successful treatment of MH in 60-year-old man undergoing orthopaedic surgery without use of dantrolene is described. The patient developed metabolic acidosis, tachycardia and pyrexia following sevoflurane exposure. Triggering agent was stopped, oxygenation, cooling, steroid administration and invasive monitoring was performed to manage the symptoms highlighting that early detection is crucial even in the absence of dantrolene.[15]

This case report describes the first reported case of potentially lethal MH following electroconvulsive therapy (ECT). Succinyl choline, a depolarizing muscle relaxant widely used in ECT. High fever (40.2°C), tachycardia, hypertension over 200 mmHg extreme muscle rigidity and altered consciousness was developed in a 79-year-old female with severe depression. It was developed after two hours of ECT, but the symptoms raised within 24 hours. Even though there was no operating room setting, dantrolene (initial dose 60 mg followed by 20 mg and 60 mg) was administered and the patient was successfully treated with reduction in muscle rigidity and fever. Keeping in mind the delayed onset of MH post ECT, this case highlights that the psychiatrist should monitor the vitals and physical presentations closely and administer dantrolene when MH is suspected.[16]

The article reports MH crisis that happened during renal transplantation, where in the diagnostic challenges in patients with chronic kidney disease is highlighted. Succinyl choline and halogenated anaesthetics trigger the MH resulting in hypermetabolism and muscular contractions, leading to sustained muscular contractions and hypermetabolism. The case refers to a 47-year-old male with end-stage CKD who developed a delayed onset MH crisis approximately 5 to 10 minutes after renal perfusion. The patient showed symptoms like rise in$ETCO_2$ to 68mmHg, rise in temperature to 37.8 °C, abdominal wall rigidity, pH being 6.92 and $PaCO_2$-79 mmHg and hyperkalaemia. After stopping the halogenated agent, TIVA was initiated with administration of dantrolene. Even though the symptoms were managed with dantrolene, patient experienced graft loss as the result of thrombosis and additional dantrolene was administered due to suspected recrudescence of MH. MHCGS score of 58 showed "almost definite" MH and the MH diagnosis was confirmed with family history of a first degree relative with pathogenic RYR1 gene mutation. The authors say that the diagnosis can be more challenging due to the similarity between physiological characteristics of CKD and symptoms of MH.[17]

A 10-year-old boy who had a family history of MH (whose uncle diagnosed by muscle biopsy) was posted for epidural abscess drainage. Since he was allergic to egg and parents' refusal on administering propofol, Total Intravenous anaesthesia was achieved using midazolam and dexmedetomidine and neuromuscular blockades used were remifentanil and rocuronium. With uneventful periop course, authors conclude that combined midazolam and dexmedetomidine can be an alternative to propofol for TIVA especially in shorter duration procedures.[18]

A 15-year-old boy undergoing scoliosis correction surgery developed MH symptoms like hyperthermia, Increased $ETCO_2$ and tachycardia with MHCGS 63 following which 40mg dantrolene was administered which improved the symptoms. In the ICU, shivering recurred with hyperthermia, increased $ETCO_2$, increased creatine kinase (CK), and other signs, leading to an increased dantrolene dose (from 40 mg to 60 mg every 6 hours). Heterozygous missense mutation of the RYR1 gene was found through genetic testing. The report notes that recurrence happened even after repeated dantrolene administration and suggests that non-C-terminal RYR1 mutations might make recurrence more likely.[19]

A 42-year-old obese female patient undergoing breast conserving oncology surgery with difficult airway who received two doses of succinyl choline and sevoflurane for general anaesthesia. There was no hyperthermia, muscle rigidity or hemodynamic instability although there were suspicious signs of mild increase in ETCO2 upto 59mmHg and restricted mouth opening. Dantrolene wasn't administered as the clinical presentation was unusual and rare but the MH crisis protocol was started with non-triggering agents and other physical strategies. The patient required haemodialysis due to prolonged rhabdomyolysis with CK levels>37,000 U/L and the patient was fully recovered. Later, pathogenic heterozygous RYR1 gene variant was confirmed, indicating MH predisposition. The authors focus on diagnostic confusions between MH and Anaesthesia induced rhabdomyolysis (AIR). After high succinyl choline administration and uneventful intraoperative radiation therapy, this is the first case which is effectively treated without dantrolene.[20]

A 67-year-old female posted for elective hysterectomy experienced MH even when there was no personal or family history of anaesthesia complications. Fentanyl, propofol, lidocaine and succinyl choline and sevoflurane was used for anaesthesia. A progressive rise in temperature to 38.3 °C peaking to 39.3 °C and rise in ETCO2 occurred around four hours after anaesthesia despite the raised minute ventilation. Jaw stiffness was also seen when

intubating. Metabolic acidosis and hyperkalaemia were confirmed with arterial blood gas analysis. Dantrolene was administered with cooling strategies and metabolic imbalance corrections after which the surgery was stopped and the patient was shifted to ICU.[21]

The case report describes a 57-year-old male with Severe acute respiratory distress syndrome (ARDS) who experienced MH following Cisatracurium-a non-depolarizing skeletal muscle relaxant administration which is usually considered safe choice for MH. About 2 hours post Cisatracurium bolus and continuous infusion the patient showed hyperthermia which gradually peaked to 108.6 °F accompanied by hyperkalaemia, muscle rigidity, elevated creatine kinase, lactic acid and $PaCO_2$. After stopping cisatracurium, loading dose of dantrolene (372.5 mg) was administered which improved the temperature little. The Naranjo score of 5 indicated that cisatracurium as the "probable culprit". He passed away after the family chose to use comfort measures.[22]

A 8-year-old male boy is successfully managed for MH without dantrolene administration due to its unavailability in Nepal. There was rapid increase in $ETCO_2$, temperature and heart rate and muscle rigidity in all limbs 15 minutes after general anaesthesia with isoflurane. MHCGS was 68. Isoflurane was stopped and patient was hyperventilated with 100% oxygen using new circuit. Anaesthesia was maintained using propofol and active physical cooling was performed. The child improved. Authors highlight that right symptomatic management with prompt diagnosis can save patients without dantrolene.[23]

**Table 3: Summary of case reports on MH (2000-2025).[14-23]**

| Age (in years)/sex | Trigger | Clinical presentation | Management | Outcome | Unique learning point |
|---|---|---|---|---|---|
| **20s/M** | Sevoflurane (no succinylcholine) | ↑$ETCO_2$, tachycardia, pyrexia | Dantrolene, cooling, monitoring | Full recovery | MH grading scale confirmed diagnosis |
| **60s/M** | Sevoflurane | ↑$ETCO_2$, hyperthermia, tachycardia | Supportive care (no dantrolene), steroids, mannitol | Recovery | Successful MH management without dantrolene |
| **79F** | Succinylcholine during ECT | Delayed onset: fever 40.2 °C, rigidity, hypertension | Dantrolene (multiple doses) | Recovery | First reported MH after ECT |
| **47M** | Desflurane (renal transplant) | ↑$ETCO_2$, hyperkalaemia, acidosis, rigidity | Stop agent, TIVA, dantrolene | Recovery, graft loss | CKD confounded MH diagnosis |
| **10M** | Epidural abscess surgery | N/A (preventive strategy) | TIVA with midazolam + dexmedetomidine (egg allergy) | Uneventful | Alternative to propofol in MHS + egg allergy |
| **15M** | Scoliosis surgery | Recurrence: fever, ↑$ETCO_2$, ↑CK | Dantrolene (large dose, repeated) | Recovery | RYR1 mutation + Central Core Disease |
| **42F** | Sevoflurane + succinylcholine | Masseter spasm, mild hypercarbia, rhabdomyolysis | Supportive (no dantrolene) | Recovery (dialysis) | MH vs AIR diagnostic dilemma |
| **67F** | Succinylcholine + sevoflurane | Hyperthermia, jaw stiffness, ↑$ETCO_2$ | Dantrolene, cooling, supportive | Recovery | Hotline assistance led to diagnosis |
| **57M** | Cisatracurium (ARDS patient) | Rapid ↑Temp (108.6 °F), rigidity, acidosis | Dantrolene, supportive | Fatal | Rare cisatracurium-associated MH |
| **8M** | Isoflurane | Classic MH (↑$ETCO_2$, 43 °C, rigidity, tachycardia) | Supportive only (no dantrolene available) | Recovery | Symptomatic management saved life |

## EMERGING THERAPIES IN MH

Research into alternative and supplemental treatments has been spurred by dantrolene's shortcomings, which include poor water solubility, delayed onset due to complex reconstitution, and possible hepatotoxicity, despite the drug's effectiveness as the current standard therapy for MH.[24,25] New therapeutic approaches that seek to address these deficiencies and possibly offer curative methods

have been made possible by recent developments in molecular genetics, pharmacology, and bioengineering.

***Gene editing using CRISPR***

One promising method for addressing the RYR1 gene mutations that cause MH susceptibility is the CRISPR/Cas9 genome editing tool. In the study performed in France, The CRISPR-Cas9 components were introduced into immortalised patient muscle precursor cells. The study successfully induced the specific deletion of the mutant RYR1 allele at the DNA level, reducing the amount of mutant RYR1 transcript (mRNA) in the edited cells which showed functional improvement in calcium release, reversing at least partially, the abnormal calcium handling observed in the patient's original muscle cell.[26]

***Treatment with ASO***

Antisense oligonucleotide (ASO) therapies are a good fit for monogenic disorders that have dominant-negative mutations or gain-of-function. Since MH is a gain-of-function disorder, Gamper ASOs are a possible treatment. These gapmer ASOs can break down target RNA in a way that favours one allele over the other or doesn't favour any allele at all. The initial outcomes of ASO and siRNA strategies for RYR1-related myopathies have been promising; however, their advancement for these conditions has not occurred as rapidly as for other genetic disorders. According to the general principles of ASO therapy, this treatment may be still beneficial, especially for disorders like MH.[27,28]

***Focusing on secondary routes***

Antioxidants and mitochondrial defence Michelucci et al used calsequestrin-1 knockout mice as a model for MH, imitating sudden death induced by heat and anaesthesia. The mice exhibit lethal hypermetabolic episodes similar to MH in humans, characterized by elevated serum markers, rhabdomyolysis, hypermetabolism and increased body temperature. The study states that one of the main reasons for this crisis is because of too many reactive oxygen and nitrogen species. Trolox and N-acetylcysteine are two examples of antioxidant treatments that have reduced the death rate from 80% to 20-33%. The study's results suggest antioxidant pre-treatment may offer viable, cost-effective preventive measures to reduce patients' risk of developing MH. Future research is required on other animal models and also to know the safe doses for humans.[29]

These developments could lead to future MH treatments that are more accurate, efficient, and widely available. The majority, however, are still in the preclinical phase and need thorough safety profiling and clinical validation.

## CONCLUSION

MH is a intra operative emergency that usually happens during anaesthesia which causes significant risk. The research on genetics and molecular mechanisms has established the essential roles of RYR1 and CACNA1S mutations for disease development and revealed the complex genetic patterns and variable disease expression. The introduction of NGS alongside contracture testing enabled healthcare providers to detect susceptible patients before exposure which led to improved prevention measures and lowered risk factors.

The early signs of unexplained hypercapnia along with tachycardia and rising core body temperature must be detected quickly in clinical practice to reduce patient morbidity and mortality. Rapid administration of dantrolene, active colling to reduce the temperature and stabilizing the metabolic fluctuations are the treatment of acute MH. Continuous education, genetic counselling and continuous screening in both patient and their family can reduce the risk and improve the outcome.

Research in gene therapies with antisense oligonucleotides and antioxidant-based treatments shows promising future directions for developing specific or curative therapies but requires further clinical trial validation. Patient safety and treatment outcomes improve when multiple teams including anaesthesiologists and geneticists and critical care professionals work together.

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