Advanced Emergency Nursing Journal
Vol. 43, No. 2, pp. 102–110

APPLIED
PHARMACOLOGY

Column Editor: Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP

NC PD

Pathophysiology and Treatment of Malignant Hyperthermia

Haili Gregory, PharmD, BCPS
Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP

ABSTRACT
Malignant hyperthermia (MH) is caused by a genetic disorder of the skeletal muscle that induces a hypermetabolic response when patients are exposed to a triggering agent such as volatile inhaled anesthetics or depolarizing neuromuscular blockers. Symptoms of MH include increased carbon dioxide production, hyperthermia, muscle rigidity, tachypnea, tachycardia, acidosis, hyperkalemia, and rhabdomyolysis. Common scenarios for triggering agents are those used are during surgery and rapid sequence intubation. Hypermetabolic symptoms have a rapid onset; hence, prompt recognition and treatment are vital to prevent morbidity and mortality. The first-line treatment agent for an MH response is dantrolene. Further treatment includes managing complications related to a hypermetabolic response such as hyperkalemia and arrhythmias. This review is focused on the recognition and treatment considerations of MH in the emergency department to optimize therapy and improve patient morbidity and mortality. **Key words:** dantrolene, emergency medicine, hypermetabolic response, malignant hyperthermia

MALIGNANT HYPERTHERMIA (MH) occurs when a patient with a rare genetic mutation of the skeletal muscle is exposed to a triggering agent that causes the mutation to precipitate a hypermetabolic response (Larach, Brandom, Allen, Gronert, & Lehman, 2014; Rosenberg, Pollock, Schiemann, Bulger, & Stowell, 2015). Triggering agents are most commonly inhaled volatile anesthetics such as halothane, sevoflurane, isoflurane, and desflurane, or the depolarizing neuromuscular blocker succinylcholine. Rare causes include vigorous exercise and heat. The hypermetabolic response leads to prolonged muscle contraction through alterations in structure and function of calcium channels resulting in skeletal muscle hypermetabolism (Rosenberg et al., 2015). The mortality rate associated with MH in the 1970s was reported to be as high as 80%; however, with the use of dantrolene (Dantrium, Revonto, and Ryanodex), this number has been reduced to less than 5% (Rosenberg et al., 2015).

Author Affiliation: *Department of Pharmacy, University of Florida Health Shands Hospital, Gainesville, Florida (Dr Gregory) and Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, Columbia, South Carolina (Dr Weant).*

Disclosure: *The authors report no conflicts of interests.*

Corresponding Author: *Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP, Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, 715 Sumter Street, Suite 109, Columbia, SC 29208 (kweant@mailbox.sc.edu).*

DOI: 10.1097/TME.0000000000000344

EPIDEMIOLOGY

The incidence of MH during anesthesia is approximately one in every 3,000–50,000 procedures (Hirshey Dirksen, Van Wicklin, Mashman, Neiderer, & Merritt, 2013). Although it is possible for MH to present after the first exposure to an inhaled anesthetic, on average, MH occurs after exposure to three anesthetics. Malignant hyperthermia is more common in males and the mean age of reported cases is 18.3 years; however, pediatric patients younger than 15 years make up 52.1% of reported cases (Rosenberg et al., 2015). All ethnic groups may be affected, but there are reports of certain populations with higher rates of MH. These include French and Japanese populations, with a reported incidence of one in 2,000–3,000 people, and in the Manawatu region of New Zealand, one in 200 patients is either susceptible to MH or related to a susceptible individual (Rosenberg et al., 2015).

Because the genetic mutation for MH is an autosomal dominant disorder, a family history of MH is a well-known risk factor for susceptibility. Other risk factors include congenital myopathies, a history of unexplained fevers with thorough workup and no diagnosis, previous episode of rhabdomyolysis with thorough workup and no diagnosis, history of dark-colored urine, and history of heat stroke (Brislin & Theroux, 2013; Hirshey Dirksen et al., 2013).

CLINICAL PRESENTATION

The symptoms associated with MH can occur any time between anesthesia induction and continuing through the early postoperative period. One of the first symptoms commonly reported is a rise in end-tidal CO_2, but several other symptoms may or may not be present including tachycardia, arrhythmia, mixed respiratory or metabolic acidosis, muscle rigidity, myoglobinuria, and hyperthermia (Heytens, Forget, Scholtes, & Veyckemans, 2015; Mitchell-Brown, 2012; Rosenberg et al., 2015). Hyperthermia has a rapid onset, and an increase in core temperature by 1–2 °C (1.8–3.6 °F) as little as every 5 min may be seen, with temperatures reaching greater than 44 °C (111.2 °F; Rosenberg et al., 2015). Muscle rigidity, which is caused by an increased concentration of calcium ions in the myoplasmic reticulum, might be seen only in the masseter muscle in some cases, or it can be present in all skeletal muscle. Rigidity can be seen in all cases; however, it is most commonly seen when the reaction is triggered by exposure to succinylcholine (Rosenberg et al., 2015).

Following early symptom presentation, patients can develop a number of complications due to the uncontrolled hypermetabolic response that has been initiated. Complications include hypercapnia, hypoxemia, worsening metabolic acidosis, tachycardia and other cardiac arrhythmias, widespread vital organ dysfunction, and disseminated intravascular coagulation (Rosenberg et al., 2015). In some cases, patients can develop all of the above symptoms; however, there is substantial variability in the symptoms and onset after exposure to a triggering agent (Gray, 2017).

DIFFERENTIAL DIAGNOSIS

There are several conditions that may have a similar presentation to MH (Glahn et al., 2010). Because anesthesia can inhibit a febrile response, patients who develop acute-onset sepsis during anesthesia may have symptoms such as hyperthermia, tachycardia, and hypertension when anesthesia is stopped (Glahn et al., 2010; Musselman & Saely, 2013; Rosenberg et al., 2015). Patients with thyroid storm or pheochromocytoma may also have hyperthermia, tachycardia, and hypertension, which can look like MH if symptoms present following exposure to a triggering agent. Neuroleptic malignant syndrome may also have similar features to MH, including hyperthermia, muscle rigidity, acidosis, and rhabdomyolysis, which is thought to be related to the antagonism of dopamine receptors. Patients with serotonin syndrome may also present with hyperthermia,

hyperreflexia, and rhabdomyolysis, and are associated with the use of drugs that inhibit serotonin uptake or increase receptor sensitivity to serotonin (Rosenberg et al., 2015). In many cases, collecting the patients' history to determine whether they have been exposed to drugs that may be causing their symptoms is a key modality to determining a diagnosis.

PATHOPHYSIOLOGY

Malignant hyperthermia is caused by a genetic abnormality of calcium channels within skeletal muscle. Many channels are suspected to be possible locations for this abnormality; however, only the *RYR1* and *CACNA1S* subunits have been demonstrated to have alterations related to MH (Rosenberg et al., 2015). The Malignant Hyperthermia Association of the United States (MHAUS) currently lists 29 known *RYR1* causative mutations; however, more are expected to be identified with continued research and testing following reported events (MHAUS, 2018).

Exposure to Triggering Agent

The complications associated with MH are caused by a cascade of events that begins with exposure to a triggering agent, leading to the uncontrolled release of calcium from skeletal muscle. Next, the patient experiences the actin–myosis–troponin interaction that precipitates muscle contraction, ultimately leading to a hypermetabolic response (Dagestad & Hermann, 2017). Many known triggering agents for patients susceptible to MH exist. Volatile inhaled anesthetics including desflurane, enflurane, halothane, isoflurane, and sevoflurane can trigger a hypermetabolic response. In the emergency department (ED), inhaled anesthetics that can precipitate an MH response are rarely used; however, the commonly used depolarizing neuromuscular blocker succinylcholine is also a common instigator of this hypermetabolic state.

Muscle Contraction

Skeletal muscle contraction starts with an action potential that leads to the release of acetylcholine, which then stimulates the release of calcium. The calcium released binds to troponin and exposes myosin-binding sites on the actin filament. The myosin head binds to the actin filament, causing the myosin head to change position resulting in actin filament movement, leading to muscle contraction. Then adenosine triphosphate (ATP) binds to the myosin head, which causes it to return to a resting position and the ATP is hydrolyzed. Muscle contraction is usually inhibited when signaling from the motor neuron stops. This leads to repolarization of the sarcolemma and closes voltage-gated calcium channels in the sarcoplasmic reticulum. Then calcium ions are pumped back into the sarcoplasmic reticulum, which blocks the binding sites from myosin (Frontera & Ochala, 2015).

When a patient is experiencing a hypermetabolic response related to MH, the process of muscle relaxation is inhibited. Muscles will contract normally; however, the release of calcium causing muscle contraction is uninhibited. Although the precise process has not been demonstrated, it is thought that because of this dysregulation, as ATP approaches to bind to the myosin head, it is hydrolyzed and the muscle filaments do not return to their resting position (Hirshey Dirksen et al., 2013).

Hypermetabolic Response

When a muscle is unable to return to a resting state due to the uninhibited release of calcium from the sarcoplasmic reticulum, the physiologic response is for ATP to continue binding to the myosin. This activity results in increased CO_2 production as a by-product of ATP generation in the mitochondria, excess heat production from the rapid consumption of ATP, and increased lactate production as the body attempts to produce energy by anaerobic metabolism. All of the consequences of the hypermetabolic response can

lead to cellular damage and destruction, resulting in the extrusion of cellular contents such as potassium and creatine kinase into the extracellular space leading to additional complications such as hyperkalemia and cardiac arrhythmias (Rosenberg et al., 2015).

DIAGNOSIS

As this is a medical emergency, if a patient has an MH response to a known triggering agent, then treatment should be initiated without testing and follow-up testing can be used to provide a definitive diagnosis later. According to MHAUS and the European Malignant Hyperthermia Group, the criterion standard to assess for malignant hyperthermia susceptibility (MHS) is muscle contracture testing. Genetic testing may also have a role in determining a patient's risk for having a response to a triggering agent (Glahn et al., 2010; MHAUS, 2018).

Screening for MHS is not recommended for the general public and should be used only in select individuals (MHAUS, 2018). To determine whether a patient has had an MH episode and warrants testing, the MH clinical grading scale can be used to determine the likelihood that MH was the cause of the event (Larach et al., 1994; MHAUS, 2018; Riazi, Kraeva, & Hopkins, 2018).

Caffeine–Halothane Contracture Testing (CHCT) is an invasive procedure that involves removal of a muscle biopsy from the vastus lateralis or vastus medialis muscle and exposing it to a ryanodine receptor agonist such as caffeine or halothane. When exposed to these agents, a muscle with a mutation causing hyperthermia will have an abnormal contraction response when exposed to lower concentrations of the testing agent than a muscle without mutation (MHAUS, 2018). Caffeine–Halothane Contracture Testing has nearly 100% sensitivity and is about 80% specific, and it is the only way to rule out MH (Hopkins et al., 2015). Caffeine–Halothane Contracture Testing is not very accessible and can be done only at four muscle biopsy testing centers in the United States. The MHAUS recommends CHCT in various situations as outlined in Table 1.

Another way to test for MH susceptibility is through genetic testing. This uses DNA isolated from the patient from blood, muscle cell, or tissue sample (MHAUS, 2018). Different DNA variations may be identified including an unrelated polymorphism that indicates no significant functional effect, a causative mutation that indicates a known mutation for MH susceptibility, or an indeterminate mutation that indicates a mutation with unknown significance. Although there are many known causative mutations that have been identified, the sensitivity of this test is still quite variable and the absence of a mutation cannot rule out MH susceptibility (MHAUS, 2018). The MHAUS recommendation for genetic testing of patients is outlined in Table 2.

Table 1. Patients who should undergo Caffeine–Halothane Contracture Testing

- Known MHS relative that was diagnosed by positive CHCT
- MHS family member determined by a suspicious MH episode
- Past suspected MH event
- Severe MMR during anesthesia with a triggering agent
- Moderate to mild MMR with evidence of rhabdomyolysis
- Unexplained rhabdomyolysis during or after surgery
- Exercise-induced rhabdomyolysis after negative rhabdomyolysis workup
- If military service is desired, patients with suspicion of MHS are required to have CHCT

Note. CHCT = Caffeine–Halothane Contracture Testing; MH = malignant hyperthermia; MHS = malignant hyperthermia susceptible; MMR = masseter muscle rigidity.

Table 2. Patients who should undergo genetic testing

- Confirmed or highly suspicious clinical episode of MH
- Positive CHCT
- MHS relative determined by positive CHCT
- MHS relative determined by a confirmed or highly suspicious clinical episode of MH
- Relative with known causal RYR1 mutation

Note. CHCT = Caffeine–Halothane Contracture Testing; MH = malignant hyperthermia; MHS = malignant hyperthermia susceptible.

TREATMENT

The first step in treatment once MH has been identified is to discontinue the offending agent. In the ED, the most common offending agent is succinylcholine used during rapid-sequence intubation. Following an MH response if additional paralytics are required, nondepolarizing neuromuscular blocking agents such as rocuronium and vecuronium may be safely used, as they do not lead to muscle contraction or movement of calcium within the muscle. Next, the patient should be hyperventilated with 100% oxygen at 10 L/min to eliminate the inhalational agent if present and decrease the end-tidal CO_2. The MHAUS also recommends inserting an activated charcoal filter into the inspiratory and expiratory limbs of the breathing circuit if available (MHAUS, 2018). Dantrolene is the drug of choice for the treatment of MH and should be administered as quickly as possible to limit the progression of symptoms. Following dantrolene administration, there may be various hypermetabolic effects that must be managed clinically. In addition, the MHAUS hotline is available for treatment recommendations and should be contacted at 1-800-644-9737 to report each case.

Dantrolene

Dantrolene works by interfering with the release of calcium ions from the sarcoplasmic reticulum of skeletal muscle, thus decreasing the calcium ion concentration available to cause continued muscle contraction. It can be used preoperatively as a prophylactic agent for MH, or in an MH crisis. The most common adverse effects are flushing and drowsiness, as well as it being a vesicant, so patients should be monitored closely for extravasation.

When used for prophylaxis, the dose of dantrolene is 2.5 mg/kg intravenously (IV) and should be administered 75 min before anesthesia. The initial dose of dantrolene for an MH crisis is 2.5 mg/kg IV in both adult and pediatric patients and may be repeated every 10–15 min until symptoms subside. In an MH crisis, dantrolene doses do not need to be adjusted for renal or hepatic dysfunction. Once symptoms have dissipated, dantrolene should be given at a dose of 1 mg/kg every 4–6 hr or as a continuous infusion of 0.25 mg/kg for at least 24 hr. If the patient is able to tolerate oral medications, dantrolene is also available as a capsule. This formulation may be used if dantrolene is required after the patient has been treated with intravenous dantrolene for 24 hr at a dose of 1–2 mg/kg every 6 hr for 1–3 days; however, initially the intravenous formulation should be used to control the hypermetabolic response. Some institutions stock dantrolene in the ED in an automated dispensing cabinet or MH cart, so becoming familiar with your practice setting's process for dantrolene acquisition and use is important in expediting the process. Three intravenous dantrolene products are currently available, all of which require admixture before administration. Table 3 outlines admixture and administration considerations for different formulations of dantrolene (Glahn et al., 2010; MHAUS, 2018; Rosenberg et al., 2015).

Table 3. Dantrolene formulations and administration

	Ryanodex (dantrolene sodium nanosuspension)	Dantrium and Revonto (dantrolene sodium)
Dantrolene per vial	250 mg	20 mg
Volume of SWFI to reconstitute each vial	5 ml	60 ml
Final concentration of dantrolene per vial	50 mg/ml	0.33 mg/ml
MH crisis dose and administration	2.5 mg/kg iv push	2.5 mg/kg iv push
Postcrisis dose and administration	1 mg/kg every 4–6 hr iv push or 0.25 mg/kg/hr continuous iv infusion	1 mg/kg every 4–6 hr iv infusion over 1 hr or 0.25 mg/kg/hr continuous iv infusion
Prophylaxis dose and administration	2.5 mg/kg iv push 75 min before anesthesia	2.5 mg/kg iv infusion over 1 hr beginning 75 min before anesthesia

Note. iv = intravenous; MH = malignant hyperthermia; SWFI = sterile water for injection.

Dantrolene has been shown to significantly improve mortality in patients with MH without causing significant adverse effects since the 1980s (Kolb, Horne, & Martz, 1982). Larach et al. (2019) performed a systematic review evaluating the relationship between dantrolene administration and morbidity and mortality associated with MH. They demonstrated that each 10-min delay in treatment with dantrolene led to increased complications (Larach et al., 2019). Because of the known mortality reduction associated with dantrolene use, the MHAUS recommends that dantrolene be available within 10 min of any location where volatile anesthetics or succinylcholine is used (MHAUS, 2018).

Clinical Management of Other Hypermetabolic Effects

Initial temperature control is vital because tissue destruction begins at 41.5 °C (106.7 °F). This can be accomplished by infusing cool fluids, applying ice packs to all exposed areas, and potentially using gastric and bladder lavage with cool fluids if necessary. Additional invasive cooling equipment typically used for targeted temperature management in patients following cardiac arrest such as cooling blankets and devices with temperature feedback systems may also be used if available. The patient's temperature should be maintained at 38 °C (100.4 °F) or less, and shivering should be minimized to maintain temperature control and reduce metabolic demand (Hirshey Dirksen et al., 2013; MHAUS, 2018; Rosenberg et al., 2015). Several other complications may present that require urgent intervention. One complication that may require treatment is hyperkalemia, which can be treated with insulin and dextrose, calcium gluconate, sodium bicarbonate, albuterol, and, in some cases, hemodialysis. If hyperkalemia persists beyond the initial treatment period, additional treatment options such as loop diuretics and cation exchange resins are available (Kraft, Btaiche, Sacks, & Kudsk, 2005; MHAUS, 2018). Another complication that might require urgent treatment is arrhythmias. The MHAUS recommends treating arrhythmias in accordance with the American Heart Association's guidelines for adults and pediatric patients, with the exception of using calcium channel blockers for the treatment of tachycardia because blocking calcium channels in cardiac muscle tissue increases the risk of arrhythmia and has shown

to be ineffective in the treatment of tachycardia in MH (de Caen et al., 2015; Link et al., 2015; MHAUS, 2018; Panchal et al., 2018). Previously, the MHAUS recommended having procainamide available for the treatment of MH; however, studies did not show additional efficacy when compared with dantrolene. Procainamide works by reducing calcium transmission into the myoplasmic reticulum of cardiac muscle, thus making it a useful option for the treatment of arrhythmia in a patient with MH. Several dosing modalities have been documented, ranging from the suggestion to infuse at 0.5–1 mg/kg/min under continuous electrocardiographic monitoring until resolution of arrhythmia or presentation of secondary arrhythmia to a fixed dose of 1,000 mg infused over an hour (Britt, 1974; Stiell, Macle, & Committee, 2011). Because of risk of hypotension and arrhythmia, current recommendations are to use a dose of 15–17 mg/kg or a fixed dose of 1,000 mg for more than 60 min and then a secondary dose to complete the 15–17 mg/kg dose if the arrhythmia continues after giving 1,000 mg (Britt, 1974; MHAUS, 2018; Nelson & Flewellen, 1979).

Postcrisis Treatment

In addition to managing hypermetabolic effects, dantrolene therapy should be continued for at least 24 hr after initial symptom control at the dose outlined in Table 3. Dantrolene may be discontinued after 24 hr, or the interval between doses increased to every 8–12 hr, if the patient meets all of the following criteria: metabolic stability for 24 hr, core temperature less than 38 °C (100.4 °F), creatine kinase decreasing, no evidence of myoglobinuria, and no muscle rigidity (Hirshey Dirksen et al., 2013; MHAUS, 2018; Rosenberg et al., 2015).

MONITORING

Patients who have experienced an MH crisis should be monitored closely. Initial laboratory test results that should be obtained includ blood gases, lactate, potassium, and creatine kinase. In addition, laboratory test results to assess for coagulopathy are recommended in patients who have a body temperature greater than 41 °C (105.8 °F) due to the risk of disseminated intravascular coagulation. Urine output should also be assessed with a goal of greater than 1 ml/kg/hr, and if there is a rise in potassium or creatine kinase, it is recommended to alkalinize the urine with a bicarbonate infusion at 1 mEq/kg/hr.

For the first 24 hr, the patient's heart rate, respiratory rate, core temperature, end-tidal CO_2 (if intubated), oxygen saturation, and muscle tone should be continuously monitored to assess for relapse of MH. After initial laboratory test results have been drawn, blood gases, lactate, potassium, and creatine kinase should be reevaluated every 8 hr, and renal function at least every 24 hr (Hirshey Dirksen et al., 2013; Rosenberg et al., 2015). Other considerations are coagulation laboratory test results if patients have evidence of bleeding. The MHAUS also recommends an infectious workup for patients who required 10 mg/kg dantrolene and greater for initial symptom control (MHAUS, 2018).

CONCLUSION

The MH is a rare but potentially fatal condition that requires prompt pharmacologic intervention. Dantrolene has been shown to significantly decrease mortality rates when treating MH and should be administered immediately following identification of an MH response. Other interventions will include monitoring for other complications associated with a hypermetabolic response that may lead to hyperkalemia, arrhythmias, and renal dysfunction. Malignant hyperthermia mock drills are recommended to prepare institutions for the acute response needed when treating a patient with MH and will help identify opportunities to improve readiness in treating MH. With proper implementation of treatment and monitoring, patient outcomes have been drastically improved.

REFERENCES

Brislin, R. P., & Theroux, M. C. (2013). Core myopathies and malignant hyperthermia susceptibility: A review. *Paediatric Anaesthesia*, *23*(9), 834–841. doi:10.1111/pan.12175

Britt, B. A. (1974). Malignant hyperthermia: A pharmacogenetic disease of skeletal and cardiac muscle. *Anesthesia Progress*, *21*(4), 108–110.

Dagestad, A., & Hermann, M. (2017). Keeping cool when things heat up during a malignant hyperthermia crisis. *Nurs Womens Health*, *21*(5), 338–347. doi:10.1016/j.nwh.2017.07.001

de Caen, A. R., Berg, M. D., Chameides, L., Gooden, C. K., Hickey, R. W., Scott, H. F., & Samson, R. A. (2015). Part 12: Pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, *132*(18 Suppl. 2), S526–S542. doi:10.1161/CIR.0000000000000266

Frontera, W. R., & Ochala, J. (2015). Skeletal muscle: A brief review of structure and function. *Calcified Tissue International*, *96*(3), 183–195. doi:10.1007/s00223-014-9915-y

Glahn, K. P., Ellis, F. R., Halsall, P. J., Muller, C. R., Snoeck, M. M., Urwyler, A., ... European Malignant Hyperthermia Group. (2010). Recognizing and managing a malignant hyperthermia crisis: Guidelines from the European Malignant Hyperthermia Group. *British Journal of Anaesthesia*, *105*(4), 417–420. doi:10.1093/bja/aeq243

Gray, R. M. (2017). Anesthesia-induced rhabdomyolysis or malignant hyperthermia: Is defining the crisis important? *Paediatric Anaesthesia*, *27*(5), 490–493. doi:10.1111/pan.13130

Heytens, L., Forget, P., Scholtes, J. L., & Veyckemans, F. (2015). The changing face of malignant hyperthermia: Less fulminant, more insidious. *Anaesthesia and Intensive Care*, *43*(4), 506–511. doi:10.1177/0310057X1504300415

Hirshey Dirksen, S. J., Van Wicklin, S. A., Mashman, D. L., Neiderer, P., & Merritt, D. R. (2013). Developing effective drills in preparation for a malignant hyperthermia crisis. *Aorn Journal*, *97*(3), 329–353. doi:10.1016/j.aorn.2012.12.009

Hopkins, P. M., Ruffert, H., Snoeck, M. M., Girard, T., Glahn, K. P., Ellis, F. R., ... European Malignant Hyperthermia Group. (2015). European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *British Journal of Anaesthesia*, *115*(4), 531–539. doi:10.1093/bja/aev225

Kolb, M. E., Horne, M. L., & Martz, R. (1982). Dantrolene in human malignant hyperthermia. *Anesthesiology*, *56*(4), 254–262.

Kraft, M. D., Btaiche, I. F., Sacks, G. S., & Kudsk, K. A. (2005). Treatment of electrolyte disorders in adult patients in the intensive care unit. *American Journal of Health-System Pharmacy*, *62*(16), 1663–1682. doi:10.2146/ajhp040300

Larach, M. G., Brandom, B. W., Allen, G. C., Gronert, G. A., & Lehman, E. B. (2014). Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: A report from the North American malignant hyperthermia registry of the Malignant Hyperthermia Association of the United States. *Anesthesia and Analgesia*, *119*(6), 1359–1366. doi:10.1213/ANE.0000000000000421

Larach, M. G., Klumpner, T. T., Brandom, B. W., Vaughn, M. T., Belani, K. G., Herlich, A., ... Multicenter Perioperative Outcomes Group. (2019). Succinylcholine use and dantrolene availability for malignant hyperthermia treatment: Database analyses and systematic review. *Anesthesiology*, *130*(1), 41–54. doi:10.1097/ALN.0000000000002490

Larach, M. G., Localio, A. R., Allen, G. C., Denborough, M. A., Ellis, F. R., Gronert, G. A., & Ording, H. (1994). A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology*, *80*(4), 771–779.

Link, M. S., Berkow, L. C., Kudenchuk, P. J., Halperin, H. R., Hess, E. P., Moitra, V. K., & Donnino, M. W. (2015). Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, *132*(18 Suppl. 2), S444–S464. doi:10.1161/CIR.0000000000000261

MHAUS. (2018). *Malignant Hyperthermia Association of the United States*. Retrieved from http://www.mhaus.org

Mitchell-Brown, F. (2012). Malignant hyperthermia: Turn down the heat. *Nursing*, *42*(5), 38–44; quiz 44–35. doi:10.1097/01.NURSE.0000413609.98565.96

Musselman, M. E., & Saely, S. (2013). Diagnosis and treatment of drug-induced hyperthermia. *American Journal of Health System Pharmacy*, *70*(1), 34–42. doi:10.2146/ajhp110543

Nelson, T. E., & Flewellen, E. H. (1979). Rationale for dantrolene vs. procainamide for treatment of malignant hyperthermia. *Anesthesiology*, *50*(2), 118–122.

Panchal, A. R., Berg, K. M., Kudenchuk, P. J., Del Rios, M., Hirsch, K. G., Link, M. S., & Donnino, M. W. (2018). 2018 American Heart Association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: An update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, *138*(23), e740–e749. doi:10.1161/CIR.0000000000000613

Riazi, S., Kraeva, N., & Hopkins, P. M. (2018). Malignant hyperthermia in the post-genomics era: New perspectives on an old concept. *Anesthesiology*, *128*(1), 168–180. doi:10.1097/ALN.0000000000001878

Rosenberg, H., Pollock, N., Schiemann, A., Bulger, T., & Stowell, K. (2015). Malignant hyperthermia: A review. *Orphanet Journal of Rare Diseases*, *10*, 93. doi:10.1186/s13023-015-0310-1

Stiell, I. G., Macle, L., & Committee, C. A. F. G. (2011). Canadian Cardiovascular Society atrial fibrillation guidelines 2010: Management of recent-onset atrial fibrillation and flutter in the emergency department. *Canadian Journal of Cardiology*, *27*(1), 38–46. doi:10.1016/j.cjca.2010.11.014