

Clinical Controversy	Consensus Meeting Decision
How much dantrolene should be available in facilities where volatile agents are not available or administered, and succinylcholine is only stocked on site for emergency purposes?	Facilities that stock and have the potential to administer any triggering agent, including succinylcholine without volatile agents, should have a full dose (at least 10 mg/kg corresponding to the estimated size of their patients) of dantrolene immediately available (ie, the ability to administer dantrolene within 10 min of the first sign of MH).
What defines masseter muscle rigidity? What is its relationship to MH, and how should it be managed when it occurs?	There is no validated definition of masseter muscle rigidity, but in cases in which it has been associated with MH, it has been severe. Masseter muscle rigidity may be a clinical variant in response to succinylcholine, a harbinger of acute MH, and/or associated with clinically significant rhabdomyolysis. When severe masseter muscle rigidity occurs, especially in the absence of succinylcholine, triggering agents should be immediately discontinued, and the patient should be observed for additional signs of acute MH. Elective procedures should be postponed until further definitive analysis of the clinical situation.
What is the relationship between MH susceptibility and heat- or exercise-related rhabdomyolysis?	Sufficient evidence does not exist to predict whether patients with a history of heat- or exercise-induced rhabdomyolysis will be MH susceptible. Conversely, it is unknown whether known MH-susceptible individuals are susceptible to heat- or exercise-induced rhabdomyolysis. Patients with a history of a nonanesthesia-related MH-like illness should be considered on a case-by-case basis to estimate their likelihood of MH susceptibility or referral for contracture biopsy or MH genetic testing.
What evidence-based interventions should be recommended to alleviate hyperthermia associated with MH?	Recommended interventions include immediate administration of dantrolene, external cooling with a circulating water mattress or ice packs, and administration of refrigerated IV crystalloid.
After treatment of acute MH, how much dantrolene should be administered and for how long? What criteria should be used to determine stopping treatment with dantrolene?	A dose of 1 mg/kg or dantrolene once every 6 h should be continued for 24 h after abatement of signs of continuing MH. These include muscle rigidity, evidence of increasing rhabdomyolysis, respiratory acidosis, or hyperthermia.
Can patients with a suspected personal or family history of MH be safely anesthetized before diagnostic testing?	Yes, care of MH-susceptible patients need not be restricted by the lack of formal MH susceptibility testing, nor should care be limited to inpatient hospital facilities.

Abbreviations: IV, intravenous; MH, malignant hyperthermia.

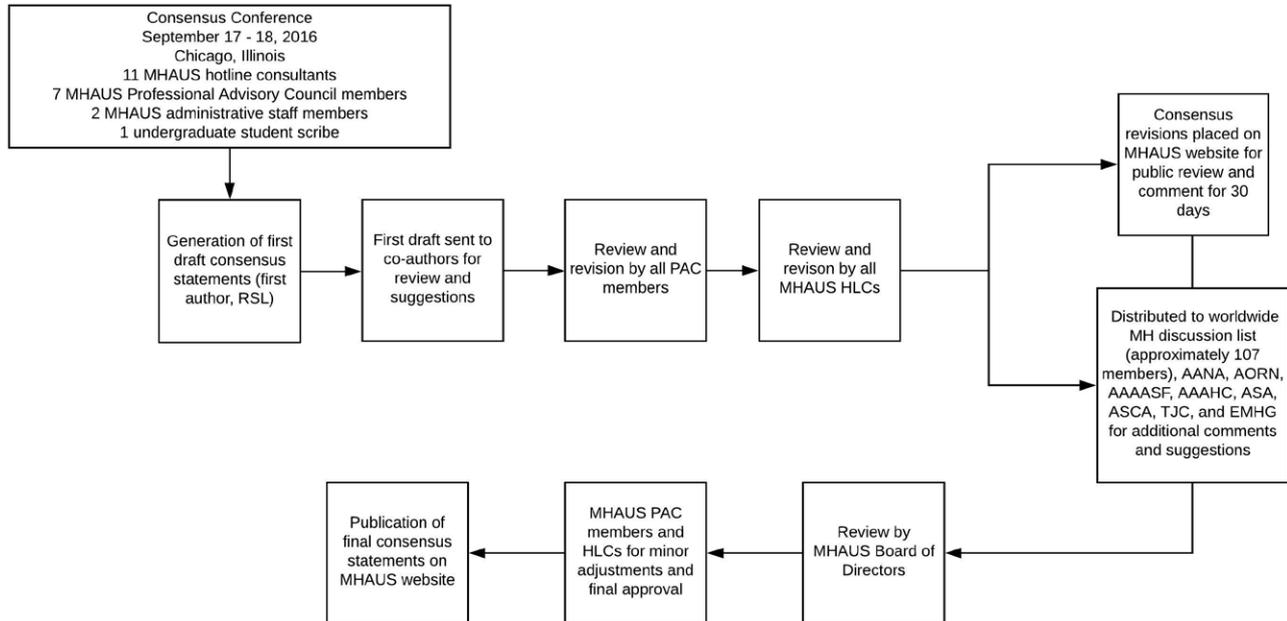


Figure. Flow diagram of the process used to establish consensus. AAAASF indicates American Association for Accreditation of Ambulatory Surgery Facilities; AAAHC, Accreditation Association for Ambulatory Health Care; AANA, American Association of Nurse Anesthetists; AORN, Association of Perioperative Registered Nurses; ASA, American Society of Anesthesiologists; ASCA, Ambulatory Surgery Center Association; EMHG, European Malignant Hyperthermia Group; HLC, Hotline Consultant; MHAUS, Malignant Hyperthermia Association of the United States; PAC, Professional Advisory Council; TJC, The Joint Commission.

HOW MUCH DANTROLENE SHOULD BE AVAILABLE IN FACILITIES WHERE VOLATILE AGENTS ARE NOT AVAILABLE OR ADMINISTERED, AND SUCCINYLCHOLINE IS ONLY STOCKED ON SITE FOR EMERGENCY PURPOSES?

Background

Most MH cases are triggered by the administration of a volatile anesthetic agent with or without succinylcholine, but in a small percentage of cases, MH appears to be triggered by succinylcholine alone in the absence of a volatile agent.^{1,2} For example, 1.4% of “very likely” or “almost certain” (terms derived from the MH clinical grading scale³) MH events reported to the North American Malignant Hyperthermia Registry were triggered by succinylcholine alone (personal communication, Michael Young M.S., North American Malignant Hyperthermia Registry, February 9, 2017).^{1,4} In a report from the University of Toronto, 20 of 129 (15.5%) biopsy-proven MH events were triggered by succinylcholine alone.² In Europe, 2 of 200 (1%) biopsy-proven MH events were due to succinylcholine alone.⁵ As a patient safety and advocacy organization, the Malignant Hyperthermia Association of the United States has recommended⁶ that “Dantrolene must be available for all anesthetizing locations where MH trigger agents are used.” Furthermore, the Malignant Hyperthermia Association of the United States recommends that centers stock a minimum of 36 20-mg vials of generic dantrolene (total dose 720 mg) or three 250-mg vials of Ryanodex (total dose 750 mg). These amounts of dantrolene were originally determined by the analysis of MH event data showing that some cases of acute MH required ≥ 10 mg/kg body weight, and therefore, these total dose amounts would suffice for the majority of average-sized patients that develop MH.¹

There has been a steady growth of office-based surgery facilities that use IV anesthesia techniques without inhalational agents, and stock succinylcholine only to treat life-threatening airway emergencies. The Malignant Hyperthermia Association of the United States has received requests from representatives of the Ambulatory Surgery Committee of the American Society of Anesthesiologists and the Society of Ambulatory Anesthesia to amend our recommendations for stocking dantrolene in these facilities. These requests have been based on 3 main arguments. The first is the assumption that because the incidence of MH susceptibility in the general population is low, and the need for succinylcholine to treat an airway emergency in these centers is uncommon, then the likelihood of the above 2 events happening to the same patient is so low that it renders the cost of stocking dantrolene prohibitively high when compared to its potential usefulness. The second is that accrediting agencies such as The Joint Commission have traditionally relied on the expert opinion of patient safety organizations such as the Malignant Hyperthermia Association of the United States to determine accreditation criteria. The Joint Commission has taken the stance that if a surgical facility stocks succinylcholine, it must also stock dantrolene as a requirement to become accredited by the Center for Medicare and Medicaid Services.⁷ The third is that some ambulatory surgery facilities that do not want to incur the cost of dantrolene may choose to not stock succinylcholine, thus putting their patients’ lives

at risk in the event of a life-threatening airway obstruction. (This does not take into account the recent availability of sugammadex, which may facilitate the use of high-dosed nondepolarizing muscle relaxants to treat life-threatening airway obstruction.)

Discussion

The Malignant Hyperthermia Association of the United States experts acknowledged the cost to health expenditures on a more global basis if every surgical facility was required to continuously buy and stock a dantrolene supply that is never used, and worry about the health consequences of anesthetized patients without immediate availability of succinylcholine.

However, the consensus of the group was that as a patient advocacy organization that was originally chartered by MH-susceptible patients and has MH-susceptible families on our board of directors, the primary responsibility of the Malignant Hyperthermia Association of the United States is to protect the health of our MH-susceptible patients. The cost of stocking dantrolene, even if never used, is a relatively small price to pay for the security and confidence of knowing that anesthesiologists can be free to stock and administer succinylcholine for life-threatening airway obstruction without fear of patients developing MH without the only known antidote immediately available. Furthermore, MH morbidity increases as the time between the first MH clinical sign and the first dantrolene dose increases.¹

Conclusions

The consensus of our experts was that the incidence of MH induced by succinylcholine alone is not rare enough to justify the absence of dantrolene wherever succinylcholine may potentially be administered. Facilities that stock and have the potential to administer any triggering agent, including succinylcholine without volatile agents, should have a full supply of dantrolene immediately available (ie, the ability to administer dantrolene within 10 minutes of the first sign of MH) in the event that a patient in that facility develops MH.

WHAT DEFINES MASSETER MUSCLE RIGIDITY? WHAT IS ITS RELATIONSHIP TO MH, AND HOW SHOULD IT BE MANAGED WHEN IT OCCURS?

Background

Masseter muscle rigidity is usually recognized as a difficulty in manual mouth opening that impedes direct laryngoscopy and tracheal intubation, without the presence of temporomandibular dysfunction. When masseter muscle rigidity occurs in response to administration of succinylcholine in the absence of an underlying temporomandibular joint disorder or myotonia, it may be an initial sign of MH.^{1,8–11}

Discussion

Confusion often arises when diagnosing masseter muscle rigidity due to its similarity with the normal but variable increase in masseter muscle tension that may occur after succinylcholine administration.^{12–14} This is an inherent characteristic of succinylcholine and has also been linked to the

administration of subclinical doses in children.^{15,16} To differentiate between the normal increase in masseter tension versus a case of true masseter muscle rigidity, assessing masseter rigidity is helpful. The term “jaws of steel”¹⁷ aptly emphasizes the severe nature of the rigidity. When masseter muscle rigidity occurs, it may be both a harbinger of acute MH and/or associated with clinically significant rhabdomyolysis.^{1,8–10,18,19} Therefore, clinicians should seek other concomitant signs of the presence of acute MH, such as tachycardia or hypercarbia that are inappropriate for the clinical situation, generalized trunk or limb rigidity, hyperthermia, cola-colored urine indicative of myoglobinuria, and/or peaked T waves or other arrhythmias consistent with hyperkalemia. However, in some patients who have subsequently progressed to MH, those signs did not appear immediately after masseter muscle rigidity. Since sufficient evidence exists of cases in which MH ensued after muscle masseter rigidity, it may be prudent to cancel elective surgery when masseter muscle rigidity occurs.^{1,8–10} If the surgical procedure is emergent, then a non-MH triggering anesthetic should be instituted. Whether or not the case is canceled, several hours of careful observation for additional signs of MH are warranted. This approach of using a nontriggering anesthetic in emergency cases was reported by Donlon et al²⁰ and later by others.^{21,22} The anesthesia provider should obtain a blood sample to screen for metabolic acidosis, hyperkalemia, and elevated creatine kinase levels. A urine sample should also be obtained to check for heme on dipstick, which if positive without microscopic red blood cells may represent myoglobinuria. Serum creatine kinase measurements should follow immediately after and every 6–8 h (creatinine kinase may not be elevated immediately after masseter muscle rigidity), and peak levels may not appear until 12–24 h after succinylcholine administration.²³ If creatine kinase is >5 times the upper limit for normal value, appropriate treatment for rhabdomyolysis should begin, including measures to prevent damage to the kidneys from myoglobinuria.²⁴ Although cola-colored urine and elevated creatine kinase may occur after masseter muscle rigidity, development of any other additional signs of MH should prompt immediate dantrolene administration and other adjunctive therapies.⁸ In patients with myotonic muscle disorders, administration of succinylcholine may result in masseter muscle rigidity and total body rigidity.^{25,26} History of myotonia is the most helpful factor in differentiating between masseter muscle rigidity and myotonic contractures.

Conclusions

Masseter muscle rigidity may be the first sign of an acute MH event. However, no conclusive data exist for clinicians to determine the likelihood of developing MH after an episode of masseter muscle rigidity. If no other signs of MH are observed, the patient may still be at risk for developing clinically significant rhabdomyolysis and should be observed and treated as necessary. Patients who develop rhabdomyolysis without other signs of MH should be referred to a consultant that specializes in diagnosis and treatment of myopathic disorders. If no myopathies are found, evaluation for MH susceptibility may be indicated. When an anesthetic is necessary in a patient who experienced masseter muscle

rigidity during the previous anesthetic but has not had a full evaluation for malignant hyperthermia susceptibility or myopathy, such patients should receive a nontriggering anesthetic for their procedure. An important exception to these considerations is the patient with a history of temporomandibular joint disorder or the patient whose postanesthetic examination reveals an inability to open his/her mouth well. In these cases, further examination to determine MH or neurological disease is not warranted.

WHAT IS THE RELATIONSHIP BETWEEN MH SUSCEPTIBILITY AND HEAT- OR EXERCISE-RELATED RHABDOMYOLYSIS?

Background

There exists an ill-defined relationship between MH susceptibility and the development of a nonanesthetic MH-like illness during conditions of heat, exercise, stress, or viral illness.^{27,28} This nonanesthesia MH-like condition may demonstrate many of the same clinical signs as anesthetic-induced MH, such as hyperthermia, muscle rigidity, and rhabdomyolysis that may result in life-threatening hyperkalemia. Furthermore, there exist case reports of heat stroke that attest to the effectiveness of dantrolene treatment, the antidote to MH.²⁹ In the absence of previous diagnostic testing, when should patients with a history of a nonanesthetic MH-like syndrome related to external conditions such as heat or exercise exposure be considered to be MH susceptible when they present for general anesthesia? When should these patients be referred for diagnostic testing for MH susceptibility? Are patients with a suspected or proven susceptibility to MH at greater than normal risk of developing a nonanesthetic MH-like syndrome during nonextreme levels of exercise or heat exposure? If so, should their lifestyles be altered to avoid those conditions? Should competitive athletics be avoided?

Discussion

The relationship between MH and this MH-like illness has been confirmed by experimental human³⁰ and animal³¹ studies, as well as human case reports and series.³² Multiple case reports exist of patients with a history of heat- or exercise-induced rhabdomyolysis who either subsequently developed MH during exposure to anesthetic triggering agents or tested positive to an MH contracture biopsy.^{32–38} These nonanesthetic episodes of rhabdomyolysis have ranged from mild symptoms such as persistent cramping during exposure to heat or exercise,³⁹ to severe muscle breakdown that resulted in clinically significant rhabdomyolysis,⁴⁰ or death due to hyperkalemia.⁴¹

Conversely, multiple case reports exist of patients known to be MH susceptible that subsequently developed a serious or fatal MH-like syndrome during exposure to heat or as a result of intense exercise, or both.^{42–46} It has been estimated that MH-related *RYR1* pathogenic variants account for approximately 20%–30% of cases of heat- or exercise-induced rhabdomyolysis.⁴⁷

Conclusions

Despite a review of the literature and extensive discussion and debate, experts in MH were unable to determine

definitive criteria to determine MH susceptibility in these patients. MH hotline consultants agreed that certain factors, mainly related to the clinical characteristics of the MH-like illness, may place the patient at a higher than normal risk for MH susceptibility. These include⁴⁸ (but may not be limited to): (1) delayed return to baseline muscle function (more than a week) after physical exercise; (2) persistent creatine kinase elevation above 5 times the upper limit of the laboratory normal range despite rest for at least 2 weeks; (3) rhabdomyolysis complicated by acute kidney injury that does not return to baseline within 2 weeks; (4) personal or family history of rhabdomyolysis; (5) personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living; (6) personal or family history of rhabdomyolysis in response to statin administration; and (7) creatine kinase peak >100,000 U/L.⁴⁸

However, if many other people experienced exercise-related heat stroke or rhabdomyolysis at the same time as the individual or family member, MH experts agreed that the event would be less suspicious for an underlying MH susceptibility. Examples would include marathons or sports-related team drills that were conducted during hot and/or humid conditions. The hotline consultants also agreed that there is insufficient evidence to determine the estimated risk of nonanesthetic MH-like illness in patients with suspected or confirmed MH susceptibility. This requires a confident risk-benefit analysis, which is currently not possible. It was agreed that, as providers, we must communicate with families, coaches, athletic trainers, and patients' physicians to ensure that signs and symptoms of an MH-like event are quickly recognized and treatment is rapidly instituted. The consultants agreed that MH-susceptible patients who have not experienced adverse effects of heat and exercise should not restrict their activity and may participate in competitive athletics. However, consultants advise patients to carry identification of their susceptibility and inform those responsible for the care of their MH status. MH-susceptible patients who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience and consult with an MH expert, expert neurologist, or sports medicine physician familiar with both MH and the adverse effects of heat and exercise. Relatives of malignant hyperthermia susceptible patients should be informed and remain aware of their family history of MH. Deciding which relatives are at risk is a matter of clinical judgement and will remain so until reliable, noninvasive tests are available.

WHAT EVIDENCE-BASED INTERVENTIONS SHOULD BE RECOMMENDED TO ALLEVIATE HYPERTHERMIA ASSOCIATED WITH MH?

Background

Treatment of MH includes discontinuing triggering agents, hyperventilation, timely dantrolene administration, and alleviation of hyperthermia. Prolonged hyperthermia worsens outcomes and should be aggressively treated. Many cooling strategies are available, but it is impossible to implement all of them simultaneously without distracting

from the key tasks of administering dantrolene and treating the patient's metabolic and respiratory abnormalities. Therefore, it is important to prioritize cooling approaches based on efficiency, ease of use, and safety.⁴

Discussion

Thermal management can be divided into 3 categories: pharmacological, noninvasive, and invasive. Pharmacological treatment of hyperthermia includes dantrolene, acetaminophen, and nonsteroidal anti-inflammatory drugs. Dantrolene is the only clinically available specific treatment for MH and, after discontinuation of triggering agents, should always be the initial treatment for any suspected MH episode. The effectiveness of acetaminophen and nonsteroidal anti-inflammatory drugs in treating hyperthermia caused by MH has not been determined.

Noninvasive treatments of hyperthermia include strategic ice packing, forced air cooling, circulating cool water blankets, cold IV fluids, and ice-water immersion. Cold IV fluid is effective: in healthy volunteers, 40 mL/kg infusion of 4°C or 20°C fluid, core temperature transiently decreased 2.5°C ± 0.4°C and 1.4°C ± 0.2°C, respectively.⁴⁹ Cold fluids should be available and should be the initial cooling measure during an MH crisis. The method is limited by the amount of IV fluid that can be safely administered, typically about 3 L in adults.

Ice packing (neck, groins, and axillae) is effective, although direct skin exposure may provoke tissue injury. Convective cooling with forced air at ambient temperature is easy to implement and essentially risk-free. However, the method is little better than simply removing all covers and exposing the patient to ambient air. Ambient air temperature should be lowered to the extent practical.

Circulating cool water blankets set to low temperatures such as 4°C absorb considerable heat,⁵⁰ but they are not available in all operating rooms, and positioning water blankets or mattresses during an MH crisis may be complicated and distracting. Efficacy is a linear function of surface area used.

Ice-water immersion is the most effective external cooling method,⁵¹ but it is limited by the equipment required and patient mobility. In practice, immersion is not an approach that can be organized and implemented safely in the midst of an MH crisis.

Invasive strategies include bladder, rectal, gastric or peritoneal lavages, esophageal heat exchangers, intravascular heat exchange devices, and cardiopulmonary bypass. Gastric lavage is neither effective nor safe due to low return of aspiration of the injected fluids.⁵¹ Bladder lavage is ineffective due to small contact surface area and a relatively low bladder perfusion.⁵¹ Although not studied, rectal lavage has similar limitations. Peritoneal lavage is effective because the peritoneum has a large contact surface area and is highly perfused. However, this method requires special apparatus and skills.

An esophageal heat exchanger is a new device that is inserted much like a standard orogastric tube. It has additional connectors designed for standard water blanket chillers/heaters. The device provides heat exchange via the blood circulation surrounding the esophagus. The system

extracts about 50 W, which is relatively small compared to potential heat production during a severe MH crisis.⁵² Furthermore, the device is not yet commonly available. Finally, cardiopulmonary bypass is the most effective cooling device, but its invasiveness and technical challenges are a deterrent to recommend its application during an MH crisis unless required to treat hyperkalemic cardiac arrest.

Conclusions

Cooling should never distract from dantrolene administration and hyperventilation. Most patients treated promptly with dantrolene and hyperventilation will not develop dangerous levels of hyperthermia or necessitate active cooling. Active cooling should be used with care because there can be a substantial after-drop, depending on the cooling technique, duration of application, and body heat distribution; cooling should be discontinued when core temperature decreases to 38°C.

External cooling methods such as circulating water mattresses or ice packs should be considered first. If external cooling is insufficient, infuse 20 mL/kg of refrigerated IV fluid. Other treatments should rarely be necessary, but peritoneal lavage is probably the safest and most effective of the invasive approaches if the peritoneum is already open.

AFTER TREATMENT OF ACUTE MH, HOW MUCH DANTROLENE SHOULD BE ADMINISTERED AND FOR HOW LONG? WHAT CRITERIA SHOULD BE USED TO DETERMINE STOPPING TREATMENT WITH DANTROLENE?

Background

After initial successful treatment of acute MH, the Malignant Hyperthermia Association of the United States currently recommends continuing dantrolene therapy for at least 24 h and sometimes longer as clinically indicated. We recommend that dantrolene can be stopped, or the interval between doses increased to every 8–12 h if the following criteria are met: metabolic stability for 24 h, core temperature <38°C, creatine kinase continues to decrease, no evidence of ongoing myoglobinuria, and muscle rigidity has abated. The hotline consultants discussed these criteria and searched for evidence that they should change or remain the same.

Discussion

The most pertinent published data in this area concerns the possibility of recrudescence—the recurrence of MH signs after successful initial treatment of the acute event.⁵³ Recrudescence of MH occurred in 20% of 308 patients examined. Half of the patients showed signs or symptoms of recrudescence within 9 h of the initial event (median time 8.7 h), and 80% did so within 16 h. Signs included muscle rigidity, evidence of increasing rhabdomyolysis, respiratory acidosis, and hyperthermia.

Conclusions

After initial bolus dosing to treat the acute MH crisis, maintenance dantrolene should be continued at a 1 mg/kg/dose every 4–6 h while monitoring the patient for signs of recrudescence. No evidence exists to refute or change the current guidelines that continue this maintenance regimen

until the above criteria are met. Current evidence does not suggest that administering the maintenance dose as a bolus or infusion is superior. Bolus administration may serve to remind clinicians to evaluate the patient at regular intervals. The package insert for dantrolene indicates that it should be used within 6 h of reconstitution; bolus dosing may make compliance with this directive easier.

CAN PATIENTS WITH A SUSPECTED PERSONAL OR FAMILY HISTORY OF MH BE SAFELY ANESTHETIZED BEFORE DIAGNOSTIC TESTING?

Background

Patients with a known or suspected personal or family history of MH are often denied access to general anesthesia before diagnostic testing for MH susceptibility, resulting in cancellation and postponement of necessary surgical procedures. Also, MH-susceptible patients may be told they cannot have surgery in ambulatory surgery centers but must have surgery at inpatient hospitals.

Discussion

A suspected personal or family history of possible MH is not uncommon in patients requiring general anesthesia for medical or surgical procedures.⁵⁴ The details of the presumed episode may be unclear, and in many instances, it is impossible to determine these details because medical records cannot be accessed in a timely manner. However, some patients suspected of being MH susceptible may require surgical management before formal MH susceptibility testing has been performed. In addition, for many patients, diagnostic testing for MH susceptibility is not feasible because of the geographical distance to an MH biopsy-testing center or their lack of insurance coverage for muscle contracture or genetic testing.

Conclusions

Care of MH-susceptible patients need not be restricted by the lack of formal MH susceptibility testing nor should care be limited to inpatient hospital facilities. MH-susceptible patients can be safely cared for in most anesthetizing locations, including appropriately staffed and resourced ambulatory surgery centers, provided non-MH triggering agents are used, and the facilities are prepared to recognize and treat an MH crisis^{1,4,55–57} according to the established guidelines of the Malignant Hyperthermia Association of the United States and accrediting organizations.^{58–60} ■■

APPENDIX

Attendees at the September 17–18, 2016 Malignant Hyperthermia Association of the United States Consensus Meeting in Chicago, IL:

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Malignant Hyperthermia Association of the United States Professional Advisory Council (PAC):

Chair: Robert T. Dirksen, PhD; Paul Allen, MD, PhD; Barbara W. Bandom, MD; Thierry Girard, MD; Steven K. Howard, MD; Paul A. Iaizzo, PhD, Richard F. Kaplan, MD, Marilyn Green Larach, MD; Stuart E. Lieblich, DMD, FACD, FICD; Sheila M. Muldoon, MD; Sheila Riazi, MSc, MD, FRCPC; Harvey K. Rosenbaum, MD, Henry Rosenberg, MD, Henrik Rueffert, MD, Daniel I. Sessler, MD, Nicholas J. Silvestri, MD, Deanna P. Steele, CGC, Albert Urwyler, MD, Charles B. Watson, MD, Stacey Watt, MD.

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