orphanaesthesia

Anesthesia recommendations for

Malignant hyperthermia

Disease name: Malignant hyperthermia

ICD 10: T88.3

ORPHAcode: 423

Synonyms: Malignant hyperpyrexia

Brief disease summary: Malignant hyperthermia (MH) is an uncommon inherited, potentially lethal pharmacogenetic disorder of skeletal muscle triggered by volatile anesthetics (isoflurane, sevoflurane, halothane, desflurane) and/or the depolarizing muscle relaxant succinylcholine [1]. In rare cases, MH can also be triggered by strenuous physical exercise or heat exposure.

The clinical incidence of MH ranges between 1:5,000 and 1:100,000. However, reported frequency has increased in recent years, and in-hospital mortality remains higher than previously estimated (up to 12% of cases). Due to autosomal dominant inheritance, prevalence may be as high as 1:2,500 [2, 3].

MH results from abnormal regulation of intracellular calcium in skeletal muscle, most probably due to a defective calcium release channel or so-called ryanodine receptor (RYR1) at the sarcoplasmic reticulum (SR). Triggering initiates rapid, uncontrolled calcium release from the SR into the myoplasm [1, 4]. This results in a hypermetabolic state, leading to the typical clinical signs such as tachycardia, muscle rigidity, hypercapnia, rhabdomyolysis, hypoxemia and the name-giving hyperthermia. The skeletal muscle ryanodine receptor gene is located on chromosome 19q13.1–13.2. In up to 70% of families susceptible to MH, the RYR1 locus is linked to the phenotype. More than 400 RYR1 variants co-segregating with MH and/or central core disease have been reported. Five additional loci have been identified by linkage analysis, and mutations in CACNA1S, encoding the main subunit of the dihydropyridine receptor, have been found on chromosome 1 [4, 5]. However, the number of truly causative variants remains unclear. A list of confirmed causative mutations is published on the homepage of the European MH Group (www.emhg.org) [6].

Treatment of an MH crisis includes supportive measures and administration of dantrolene according to anesthesiology guidelines. In susceptible patients, anesthesia can be performed safely with a decontaminated anesthesia machine, avoidance of trigger substances and immediate availability of dantrolene [7].

Possible differential diagnoses of MH include insufficient anesthetic depth, hypoventilation, external overheating, CO_2 insufflation, hypoxemia, pheochromocytoma, thyroid storm, and an exhausted CO_2 absorbent [2].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.

Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.

Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

A	**AIRWAY / ANESTHETIC TECHNIQUE**	Provide trigger-free GA, strictly avoiding volatile anesthetics and succinylcholine; nitrous oxide and xenon may be used safely; if GA is required, use TIVA and appropriate non-triggering neuromuscular blocking agents. Prefer RA techniques whenever possible (although stress should be avoided).
B	**BLOOD PRODUCTS (COAGULATION)**	Not reported. Be aware of potential increased bleeding because coagulation may be impaired in MH-patients.
C	**CIRCULATION**	Cardiac arrhythmias and cardiac arrest can occur as both early and late signs* of an MH crisis.
D	**DRUGS**	Strictly avoid triggers of an MH crisis such as volatile anesthetics and succinylcholine; provide adequate premedication to minimize stress, as stress (e.g., heat or exertion) may rarely trigger MH. Ensure the availability of dantrolene and be aware of its storage location.
E	**EQUIPMENT**	Capnography and temperature monitoring, in addition to standard monitoring; ensure the availability of dantrolene and a decontaminated anesthesia machine.

*Early signs: Hypercapnia (unexpected increase in $EtCO_2$), cardiac arrhythmia (~80% of cases), muscular rigidity (30-60% of cases), hypoxemia and mixed acidosis, skin mottling

*Late signs: Hyperthermia (inadequate rise in temperature), rhabdomyolysis, cardiac arrest, disseminated intravascular coagulation, multisystem organ failure

Emergency treatment:

- Stop all triggering agents (disconnect vaporizers)
- Inform the team and consider rapid termination of the procedure
- Administer dantrolene (2.0-2.5 mg/kg, actual body weight)
- Increase ventilation to achieve normocapnia (FiO_2 1.0; high flow >10 L/min)
- Switch to TIVA
- Provide optimal management of related symptoms
- Consult with experts

Ad hoc information concerning MH and associated syndromes can be gathered through the German Hotline for MH, which is 24/7 available at +49 (0)7571-100-2828.

Further support is provided by the MH Association of the United States (MHAUS), also available 24/7 at 1-800-644-9737 (outside North America: +1 209 417 3722) [8].

Additional disease information

See above.

Typical surgery and procedures

Apart from muscle biopsy for in vitro contracture testing, all types of surgery can be performed.

Type of anesthesia

General as well as regional anesthesia techniques and also a combination of both can be used. Local anesthesia can also be used. However, general anesthesia must be established “trigger-free”, i.e., administration of volatile anesthetics as well as succinylcholine must be strictly avoided in patients with a history of MH. All other pharmacological preparations, such as propofol, non-depolarizing muscle relaxants, local anesthetics, nitrous oxide, xenon, etc., can be used safely [2, 7, 9-12].

Necessary additional preoperative testing (beside standard care)

Preoperative evaluation and preparation of a patient with susceptibility to MH follows standard procedures as recommended by the anesthesiologic societies, such as the European Society of Anesthesiology and Intensive Care Medicine (ESAIC). There is no indication for further examinations such as blood draws, electrocardiogram and/or X-ray of the chest in this group of patients [12-14].

In patients with undefined neuromuscular diseases a neurological status should be evaluated. Furthermore, it should be determined whether consultation with genetic, pediatric and neurological specialists is indicated in order to define the patient disease and severity. After that, it should be decided whether additional examinations (e.g., creatine kinase (CK) levels, blood gas analysis) are required in this specific group of patients [15-19].

Ad hoc information concerning MH and associated syndromes can be gathered through the German Hotline for MH, which is available at +49 (0)7571-100-2828. Further support is provided by the MH Association of the United States (MHAUS), also available 24/7 at 1-800-644-9737 (outside North America: +1 209 417 3722) [8].

Particular preparation for airway management

There is no indication for a particular preparation for airway management.

Particular preparation for transfusion or administration of blood products

Not reported. Consider the possibility of increased bleeding, as coagulation may be impaired in MH-patients [20-22].

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilization

In very rare cases MH can be triggered by stress, such as heat and exercise in humans [23-25]. Thus, it is recommended to use adequate premedication in order to avoid stress situations.

Interactions of chronic disease and anesthesia medications

Not reported.

Anesthetic procedure

Identification of patients at risk for MH is the first step for safe perioperative management. Therefore, all patients should undergo a structured interview concerning their own medical history as well as their family history. Patients reporting an MH event or complications during anesthesia should be referred to an MH investigation center for further diagnosis, if possible. For safety reasons, patients who decline MH diagnosis should be treated like those with a definitive diagnosis [5, 12-14].

Besides patients with a history of MH, patients with specific muscular diseases such as central core disease, multiminicore disease, and nemaline rod myopathy have an increased risk for MH associated with mutations in the gene encoding for the ryanodine receptor. Patients with hypokalemic periodic paralysis and those with King-Denborough syndrome may also have an increased risk for MH [12, 17, 19].

In patients with muscular dystrophies (e.g., Duchenne or Becker) clinical suspicion of MH has been reported during and after general anesthesia with MH triggering agents. The clinical presentation includes rhabdomyolysis, severe cardiac arrhythmias, acidosis, fever, and other symptoms. For a long time, it was thought that this may be “true” MH. However, despite an increased risk during anesthesia due to volatile anesthetics and/or succinylcholine, a genetic association with MH susceptibility could not be established. These adverse events are associated with marked hyperkalemia requiring emergency treatment in the usual fashion [2, 7, 17, 19].

In rare cases so-called MH episodes during emotional and physical stress situations without administration of anesthetics were reported. Some of the patients have been found to harbor RYR1 variants that are predicted to be causal for MH. However, up to now it is unknown whether these patients have also an increased risk for developing MH after administration of trigger substances. Although, there is a lack of evidence to provide clear recommendations in these cases, it may be advisable to use non-triggering anesthetics in this group of patients [15, 26, 27].

The anesthesia machine must be decontaminated from volatile anesthetics prior to anesthesia, as recommended in the guidelines from the European MH Group (EMHG) and the MH Association of the United States (MHAUS) [6, 8]. All parts of the anesthesia machine that might have been in contact with volatile anesthetics must be exchanged and the gas circuit washed

with a fresh gas flow of 10 L/min for at least 10 minutes. However, newer anesthetic workstations may require significantly more time for purging the machine. The use of an in-line charcoal filter apparatus will also reduce volatile gas concentration to very low levels. Additionally, the vaporizer should be removed in order to avoid an accidental administration of volatile anesthetics. Furthermore, dantrolene in adequate dosages (at least 10 mg/kg, actual body weight) must be available immediately in case of an MH event [9, 18, 28, 29].

Particular or additional monitoring

Monitoring should follow the usual standard and at least comprise ECG, blood pressure, pulse-oximetry and continuous measurement of body temperature as well as capnometry in ventilated patients.

In order to be able to examine laboratory parameters, large-bore venous lines should be placed. Invasive monitoring of vital parameters should be indicated according to the physical status of the patient and the extent of the surgical procedure.

Possible complications

Patients are at risk to develop MH if trigger substances are administered. Therefore, in patients with known disposition to MH all trigger substances must be strictly avoided. The probability for development of a severe clinical crisis is elevated in male patients and children (roughly 50% of clinical crises occur in patients under the age of 12 years). This predominance is probably caused by epigenetic factors [30, 31].

In patients with first manifestation of MH all typical signs might occur. The syndrome is characterized by hypermetabolism due to massive influx of calcium into the myoplasm. This results in tachycardia, hypercapnia, hypoxemia, muscle rigidity and masseter muscle spasm, hyperthermia, rhabdomyolysis and metabolic as well as respiratory acidosis.

Hypermetabolism induced disturbances of permeability in skeletal muscle cells may cause elevated Ca^{2+}- and K^{+}-levels, which may lead to severe cardiac arrhythmias. Blood draws might also reveal drastically elevated concentrations of CK of about more than 100,000 U/L. However, CK levels start to increase 2-4 hours after onset of MH, reaching a maximum after approximately 24-36 hours. In case of severe injury of skeletal muscle cells, myoglobin can be traced in blood and urine.

The final stage of MH might present with pulmonary edema and disseminated intravascular coagulation. Rhabdomyolysis and myoglobinuria may lead to acute renal failure. Even neurological disturbances and cerebral edema have been described. Inadequate or delayed therapeutic intervention may be lethal due to bradycardia or cardiac arrest [2, 7, 12, 16, 32].

Postoperative care

After successful treatment of MH in some patients, recurrence of symptoms can be observed. An analysis from the North American MH Registry showed that recrudescence occurred in approximately 20% of the patients. The mean time from initial reaction to recrudescence was 13 hours. On multivariate analysis muscular body type, a temperature increase and a longer

time from induction to diagnosis of initial MH reaction were associated with recrudescence [32].

Therefore, patients who experience MH crisis should be monitored for at least 24 hours on an intensive or intermediate care unit including measurement of all relevant parameters (e.g., cardiovascular, pulmonary and renal function).

In patients with disposition to MH who had undergone trigger-free and uneventful anesthesia, a postoperative monitoring of 1.5 hours is regarded as safe. In those cases, the duration of monitoring in the PACU should primarily depend on the patient's physical status and the type of surgery. Exhalation of volatile anesthetics by (neighboring) patients in the OR or PACU does not yield significant clinical concentrations. Hence, no specific considerations are necessary concerning neighboring patients in the PACU [11, 12, 29].

Disease-related acute problems and effect on anesthesia and recovery

Disease-related emergency-like situations outside an anesthetic course with trigger substances are rare. However, in rare cases MH-like symptoms and rhabdomyolysis were observed in association with heat and exercise.

Ambulatory anesthesia

Ambulatory anesthesia in patients with MH status is possible, which has been shown in several MH centers in the last decades. Furthermore, an audit showed that these patients can be safely treated in a day case setting without any MH-like reactions. However, it has to be kept in mind that this requires management in appropriate facilities, including adequate postoperative care and availability of dantrolene [2, 11, 28].

Obstetrical anesthesia

Obstetrical anesthesia follows the same concepts as presented above.

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