Guidelines

Malignant hyperthermia 2020

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Guideline from the Association of Anaesthetists

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Summary

Malignant hyperthermia is defined in the International Classification of Diseases as a progressive life-threatening hyperthermic reaction occurring during general anaesthesia. Malignant hyperthermia has an underlying genetic basis, and genetically susceptible individuals are at risk of developing malignant hyperthermia if they are exposed to any of the potent inhalational anaesthetics or suxamethonium. It can also be described as a malignant hypermetabolic syndrome. There are no specific clinical features of malignant hyperthermia and the condition may prove fatal unless it is recognised in its early stages and treatment is promptly and aggressively implemented. The Association of Anaesthetists has previously produced crisis management guidelines intended to be displayed in all anaesthetic rooms as an aide memoire should a malignant hyperthermia reaction occur. The last iteration was produced in 2011 and since then there have been some developments requiring an update. In these guidelines we will provide background information that has been used in updating the crisis management recommendations but will also provide more detailed guidance on the clinical diagnosis of malignant hyperthermia. The scope of these guidelines is extended to include practical guidance for anaesthetists dealing with a case of suspected malignant hyperthermia once the acute reaction has been reversed. This includes information on care and monitoring during and after the event; appropriate equipment and resuscitative measures within the operating theatre and ICU; the importance of communication and teamwork; guidance on counselling of the patient and their family; and how to make a referral of the patient for confirmation of the diagnosis. We also review which patients presenting for surgery may be at increased risk of developing malignant hyperthermia under anaesthesia and what precautions should be taken during the peri-operative management of the patients.

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This is a consensus statement produced by expert members of a Working Party established by the Association of Anaesthetists. It updates and replaces previous guidance published in 2011. It has been seen and approved by the Board of Directors of the Association of Anaesthetists of Great Britain and Ireland. This guideline is endorsed by the UK MH Investigation Unit, St James's University Hospital, Leeds and is supported by the Royal College of Anaesthetists.

Recommendations

- An unexplained and unexpected progressive increase in carbon dioxide production as evidenced in $ETCO_2$ should lead to a high index of suspicion for malignant hyperthermia.
- Taking a personal and family history of anaesthetic problems is a mandatory part of pre-operative assessment for all patients requiring general or regional anaesthesia.
- The principles of management of a malignant hyperthermia reaction are to immediately reverse the reaction and treat the consequences of the reaction.
- Three approaches to reversing the malignant hyperthermia process should be applied together: eliminate the trigger agent; give intravenous (i.v.) dantrolene; and start active body cooling.
- Activated charcoal filters should be available at all locations where general anaesthesia is administered.
- The initial dose of dantrolene is 2–3 $mg.kg^{-1}$ with a further 1 $mg.kg^{-1}$ every 5 min until treatment goals are reached.
- Dantrolene should be given until the $ETCO_2$ is < 6 kPa with normal minute ventilation and the core temperature is < 38.5°C.
- When a patient has a suspected malignant hyperthermia reaction it is the professional responsibility of the consultant anaesthetist in charge of the case to make a direct referral to that country's tertiary assessment unit for malignant hyperthermia (in the UK this is the Leeds Malignant Hyperthermia Unit).
- Before discharge from hospital, the patient and their GP should be informed about the suspected diagnosis of malignant hyperthermia and its implications for them and their family.
- Patients at increased risk of developing malignant hyperthermia must not be exposed to potent inhalation anaesthetics or suxamethonium.

What other guidelines and statements are available on this topic?

Since the 1980s, the Association of Anaesthetists has produced documentation relating to the management of a malignant hyperthermia (MH) crisis that was designed to be printed and laminated for display in anaesthetic rooms/theatres: the last iteration was produced in 2011 [1] and requires updating. Among numerous continuing professional development articles, there is a recent UK perspective on the diagnosis and management of MH, but this was not designed as a guideline [2]. The European Malignant Hyperthermia Group (EMHG) publishes detailed guidelines for the laboratory diagnosis of a suspected MH reaction and these were last updated in 2015 [3]. The EMHG also published guidelines on the recognition and management of an MH crisis but this was in 2010 [4]. Further afield, the MH Association of North America [5] and the Australian and New Zealand MH Group [6] have resources on their websites that include guidance on the management of an MH crisis.

Why were these guidelines developed?

The Association of Anaesthetists has not previously published full MH guidelines. In the absence of any recent guidelines published in a peer reviewed journal, rather than simply updating the 2011 crisis management laminates, a Working Party was established to produce these formal comprehensive guidelines.

How does this statement differ from existing guidelines?

These guidelines describe current recommended standards of care for adult and paediatric patients in the standard Association of Anaesthetists format, incorporating recent evidence. Previous publications were either not designed specifically as guidelines, did not include information and recommendations about activated charcoal filters, included recommendations that are not applicable to practice in the UK and Ireland, or a combination of these.

Introduction

Malignant hyperthermia (MH) is a rare anaesthetic emergency. It has been estimated to occur in between 1:10,000 and 1:150,000 general anaesthetics [7,8] but these estimates are subject to error for a variety of reasons. These include incomplete reporting of suspected reactions; failure to confirm diagnosis with definitive testing; inaccurate estimates of the total number of general anaesthetics given to the relevant population (the denominator); and use of administrative databases to identify cases. In the UK, over the past few years there have been approximately 20 confirmed new cases of MH each year. If one uses the data from the Royal College of Anaesthetists' National Audit Projects (NAP5 and NAP6), which estimate the number of general anaesthetics at around 3 million per year, the incidence of MH in the UK is approximately 1:100,000 [9,10]. However, data from other countries that have systematic data collection for the number of anaesthetics, consistently put the number of general anaesthetics as around 1 for every 10 of the population per year [11,12]. Using this information to define the denominator for the incidence of MH in the UK gives a value of approximately 1:250,000 anaesthetics.

Whatever the incidence of MH, it is clear that the number of cases each year has fallen slightly, and this fall mirrors the reduction in the use of suxamethonium. The number of cases occurring during inhalational anaesthesia without suxamethonium has probably remained reasonably constant over the past 40 years. This reflects the potential for any of the potent inhalational anaesthetics to trigger an MH reaction. Indeed, the number of cases triggered by each of the inhalational anaesthetics reflects the overall usage of that particular agent [13].

The highest reported incidence of MH occurs in paediatric populations and there is also a consistently higher incidence of MH reactions in men compared with women [2,14,15]. The reasons for the age and sex distribution of MH reactions are unknown.

Malignant hyperthermia was first described in 1960 [16] and mortality was estimated to be 70–80% over the following 10 years [17]. Mortality, at least in the UK, began to decline throughout the 1970s. This was before the introduction of i.v. dantrolene and has been attributed to increased awareness of the condition and the understanding of the need to discontinue triggering anaesthetics as soon as the diagnosis is made. Despite the availability of dantrolene, deaths from MH still occur with a mortality rate of approximately 4% in the UK [2]. These data indicate that dantrolene and all symptomatic measures may be unsuccessful in preventing death from MH unless treatment is implemented early in the course of a reaction. Indeed, in North America, there are data that suggest the outcome from MH has deteriorated in recent years [18,19].

One reason that diagnosis may be delayed is if the anaesthetist incorrectly assumes that a history of uneventful anaesthesia precludes the possibility that the patient is at risk of developing MH. We know this not to be the case and there are reports of patients who have received multiple apparently uneventful anaesthetics before they have a reaction [2,20]. The reasons why susceptible individuals may not trigger when exposed to triggering agents are not fully understood.

As we learn more about the genetics of susceptibility to MH, we become increasingly aware of the discrepancy between the prevalence of genetic variants associated with an increased risk of MH and the incidence of clinical MH episodes [21,22]. With the results of large-scale gene sequencing projects available online, we now know that genetic variants associated with an increased risk of developing MH have a combined prevalence in the general population of less than 1:2000 [23]. There are likely to be genetic and non-genetic reasons for the reduced penetrance of MH susceptibility and this is an active area of research [22].

Clinical presentations and diagnosis

The definition of MH implies that the diagnosis of an MH reaction should be reserved for those patients who develop features of a hypermetabolic response during general anaesthesia. However, before describing these features, it is worthwhile highlighting that susceptible patients may have other presentations during the peri-operative period. These presentations reflect the presence of a subclinical myopathy in MH-susceptible patients that predisposes them to abnormal responses to suxamethonium. The normal response to suxamethonium before the onset of paralysis includes muscle fasciculations but suxamethonium also causes an initial increase in muscle tone most evident in the jaw muscles [24]. This is clinically apparent as resistance to mouth opening within the first 60–90 s after administration of suxamethonium. In the MH-susceptible patient, jaw muscle rigidity may be exaggerated in terms of the degree of increased muscle tone and its duration (masseter muscle spasm) and rigidity may also be apparent in other muscle groups, notably the limbs. Suxamethonium also produces rhabdomyolysis in the MH-susceptible patient [25], as well as in patients with other myopathies [26]. Very rarely, this can lead to acute hyperkalaemia severe enough to produce

cardiac arrest but more commonly it presents as myoglobinuria in the postoperative period.

Clinical features of a malignant hyperthermia reaction

Initial clinical features result from homeostatic mechanisms within the skeletal muscle cells that compensate for increased cytoplasmic calcium released by the triggering drugs. These homoeostatic mechanisms include energy-dependent ATP-ases and their turnover drives increased intermediary metabolism in an attempt to maintain adenosine triphosphate requirements [27]. Increased intermediary metabolism results in increased oxygen consumption and carbon dioxide production, which in turn causes increased sympathetic nervous system outflow. The most consistent manifestation of increased sympathetic activity is an increasing heart rate. The blood pressure response in MH is more variable as this balances the effects of sympathetic stimulation with the peripheral vasodilatory consequences of metabolic by-products.

Increased metabolic rate will also produce heat, leading to an increasing body temperature as the heat dissipates from the skeletal muscle. However, heat generation accelerates when the calcium homoeostasis mechanisms within the skeletal muscle cells fail to prevent a progressive increase in intracellular calcium that is sufficient to activate the myofilaments. Muscle contractile activity is inefficient (30–60% depending on fibre type) with the energy not used for contraction adding to the heat generation. Muscle contractile activity further exacerbates the demand for adenosine triphosphate, but also induces mechanical stresses on the skeletal muscle membrane leading initially to loss of potassium ions from the muscle cell and subsequently larger molecules, most notably myoglobin and creatine kinase. Exposed areas of skin may be hot, flushed and sweaty, while mottling of the skin appears to be more common in young children.

From the above, it can be seen that the acute sequelae of an MH reaction include acidosis (initially respiratory but subsequently mixed), hyperkalaemia and arrhythmias. Disseminated intravascular coagulopathy may develop as a consequence of the high temperature. Massive rhabdomyolysis is associated with muscle swelling giving rise to the possibility of compartment syndrome; rhabdomyolysis may also lead to acute occlusive renal injury.

The timing of MH reactions is highly variable. A reaction may become apparent within 10 min of exposure to triggering agents or the onset may be delayed for several hours, especially with the use of desflurane [28]. Once a reaction has begun, its progress is also variable with the speed of progression tending to be more rapid in those reactions that occur soon after administration of the triggering agents. The more florid reactions tend to occur when both suxamethonium and a potent inhalational anaesthetic have been administered. The diagnosis of an MH reaction has been made after the discontinuation of inhalational anaesthesia. Some of these reactions could, in retrospect, be seen to have started during the anaesthetic but in others the first signs have clearly been after the discontinuation of the inhalational agent. There are several reports suggesting that the onset of MH may be delayed for several hours after coronary artery bypass grafting, but the only one of these where the diagnosis of MH was subsequently confirmed was a patient in a Canadian series who developed an increase in temperature and hypercarbia 72 min after transfer to the cardiac ICU [15]. Aside from cardiac surgery, the longest reported interval between discontinuation of the inhalational agent and the development of a likely MH episode is 40 min [29].

Diagnosis

The key to making the diagnosis of MH in a timely manner is to be aware of its possibility whenever triggering agents are used and to have an appropriately tuned index of suspicion. Although MH has no pathognomonic features, the cardinal clinical features result from excessive carbon dioxide production (Box 1). This will manifest in the mechanically ventilated patient as increased $ETCO_2$ (even with attempts by the anaesthetist to control $ETCO_2$ by increasing minute ventilation) or in the spontaneously breathing patient as an increase in respiratory rate and subsequently increased $ETCO_2$. An unexplained, unexpected increase in carbon dioxide production should alert the anaesthetist to the possibility of an MH reaction. It is not possible to easily control $ETCO_2$ by increasing minute ventilation during an MH reaction. If the anaesthetic machine calculates oxygen consumption, this will be observed to increase in line with increased carbon dioxide production. Unless the sympathetic nervous system response is obtunded, for example, by the use of beta-blockers or remifentanil, increased carbon dioxide production will be accompanied by an otherwise unexplained and unexpected increase in

Box 1 Diagnostic features of malignant hyperthermia

- Unexplained, unexpected increase in $ETCO_2$
- Unexplained, unexpected increase in heart rate
- Unexplained, unexpected increase in temperature

heart rate – it is the upward trend in heart rate that is more useful than attainment of a specific value. The presence of increasing carbon dioxide production and heart rate and exclusion of alternative causes should be sufficient to call the diagnosis of suspected MH and instigate treatment for MH.

If the patient's temperature has been monitored during the onset of an MH reaction it will usually have started to increase by the time the diagnosis is made, but often it will not have reached beyond the upper limit of normal by the time treatment is instituted. Temperature increase that begins before any evidence of increased carbon dioxide production will not be caused by an MH reaction. However, it should be remembered that an MH reaction can occur in a patient who is already pyrexial.

Onset of generalised muscle rigidity during the course of an MH reaction (as opposed to an immediate response to suxamethonium), which may occur even in the presence of non-depolarising neuromuscular block, is a worrying development as it is likely to herald the stage of an MH reaction that will be irreversible.

Management of a malignant hyperthermia reaction

Delay in commencing treatment of MH is associated with increased mortality and the severity and number of complications [14,15]. The principles of treatment are firstly to reverse the reaction and secondly to treat the consequences of the reaction (online Supporting information Appendices S1a and b). There are three approaches to reversing the MH process and these should be applied together (Box 2): eliminate the trigger agent; give i.v. dantrolene; and start active body cooling. The first is through elimination of the triggering anaesthetics. The vaporiser should be turned off and removed from the anaesthetic machine, 100% oxygen should be delivered at maximum flow and the patient's minute ventilation should be increased to 2–3 times normal. A recent innovation is the availability of activated charcoal filters [30], which can be placed on inspiratory and expiratory limbs of the anaesthetic machine in order to adsorb inhalational anaesthetics (online Supporting information Appendix S2). Activated charcoal filters should be available in every UK hospital where general anaesthesia is administered. Dantrolene sodium is an antidote to MH in that it inhibits the excessive release of calcium into the muscle cell. The third approach to reversing the MH process is active body cooling: a raised body temperature enhances muscle cell calcium release and sensitises the myofilaments to the effects of calcium causing generalised muscle rigidity, compromising perfusion and thereby delivery of dantrolene.

Box 2 Reversing the malignant hyperthermia process

- Eliminate the agent
  - Turn off and remove vaporiser
  - Give 100% oxygen at maximum flow
  - Increase minute ventilation 2–3 x normal
  - Insert activated charcoal filters on inspiratory and expiratory limbs of circuit
- Administer dantrolene sodium
- Commence active body cooling

Dantrolene

Dantrolene is a hydantoin derivative that is poorly soluble in water. The traditional formulation is presented in 20 mg vials and each vial is reconstituted with 60 ml of sterile water, which may require 5 min of vigorous shaking. A new preparation of dantrolene is available in the USA and some other countries but it is not licensed in the UK or Europe. In this preparation (Ryanodex®), 250 mg is present in the vial and this can be rapidly dissolved in 5 ml of water for injection. In an acute MH reaction, the dose of dantrolene should be titrated against its effect. In fact, many MH reactions respond to discontinuation and elimination of the triggering agents such that the reaction has been reversed before an initial dose of dantrolene can be prepared [15]. If this is not the case, the initial dose of dantrolene is 2–3 $mg.kg^{-1}$. This dose is based on the average dose (2.3 $mg.kg^{-1}$) that is required to achieve a plasma concentration of dantrolene equivalent to the concentration that obtunds skeletal muscle preparation in vitro twitch responses [31–34]. Pragmatically, we have provided a recommendation as a dose range so that a rapid dose calculation can be made in the emergency situation for what is, after all, an initial dose of a drug that requires titration (Box 3). Indeed, from a practical point of view, due to the difficulty reconstituting dantrolene, in adults we would recommend that each syringe of dantrolene is administered as soon as it is made up rather than waiting for the complete initial dose to be ready: dantrolene can be infused in this way until the initial goals of treatment are realised. For children, we recommend the initial 2–3 $mg.kg^{-1}$ with further boluses of 1 $mg.kg^{-1}$ administered every 5 min until the treatment goals are achieved (online Supporting information Appendix S3). The recommended treatment goals are reduction of $ETCO_2$ to less than 6 kPa with normal

minute ventilation and a core temperature < 38.5°C. When these goals have been achieved, the administration of dantrolene should be paused, bearing in mind that further doses may be required should there be a rebound increase in $ETCO_2$ and temperature. When a cumulative dose of 10 $mg.kg^{-1}$ dantrolene has been administered, we would recommend a formal reappraisal of the diagnosis. If MH is still considered a likely diagnosis, administration of dantrolene should continue despite the product data sheet stipulating a maximum dose of 10 $mg.kg^{-1}$. In this situation, as well as continuing dantrolene, full attention should be made to aggressive body cooling.

Pharmacokinetic studies indicate that the disposition of dantrolene is similar in children to adults based on actual bodyweight [35]. There have been no studies of the pharmacokinetics of dantrolene in obese patients. On the basis that most lipophilic drugs require a loading dose based on actual bodyweight, or at least more than ideal bodyweight, we recommend that the initial dose of dantrolene is based on the actual bodyweight of the patient.

Recrudescence of MH can occur, and it has been reported up to 14 h after control of the initial reaction [36,37]. However, we do not recommend administration of prophylactic dantrolene after control of the initial reaction as it is not required in the majority of cases and is associated with muscle weakness and nausea [38]. If recrudescence does occur, further bolus doses of dantrolene should be administered. If they are required within 6 h of the initial reaction, 1 $mg.kg^{-1}$ should be used in the first instance but if it is more than 6 h since the previous dose of dantrolene, 2–3 $mg.kg^{-1}$ should be used. Continuous infusion of dantrolene is associated with a high incidence of thrombophlebitis due to the high osmolarity of the solution [38,39].

Box 3 Administration of dantrolene

- Titrate dose to effect
- Initial dose 2–3 $mg.kg^{-1}$
  Takes time to reconstitute so administer each syringe as it is prepared.
- Keep giving additional doses of 1 $mg.kg^{-1}$ till treatment goals achieved
- Treatment goals
  - $ETCO_2$ < 6 kPa
  - with normal minute ventilation
  - and core temp < 38.5°C

  Pause dantrolene when goals achieved but may have to give more if CO_2 or temperature rises

Management of the consequences of malignant hyperthermia

In order to facilitate further management, basic routine monitoring should be supplemented by core temperature monitoring and direct arterial blood pressure monitoring which also enables regular blood sampling (Box 4). A urinary catheter should be inserted to monitor urine output, urine pH and for myoglobinuria. Blood samples should be sent for arterial blood gas analysis, biochemistry, clotting indices, haematocrit and platelet count.

Acidosis

The primary management of acidosis is through hyperventilation, but we suggest a low threshold for the administration of sodium bicarbonate, as low pH values are associated with a poor outcome in MH. Sodium bicarbonate will aid the reuptake of potassium ions into the cells and also alkalinise the urine.

Hyperkalaemia

Treatment of hyperkalaemia should be with sodium bicarbonate and/or glucose (50 ml 50%) with insulin (10 units). Intravenous calcium 0.1 $mmol.kg^{-1}$ should only be used in extremis. Although calcium is usually a first-line treatment of hyperkalaemia, this is not the case in MH, as there is some evidence that influx of extracellular calcium contributes to the calcium overload of the myoplasm [40]. Haemofiltration should be considered if hyperkalaemia is not otherwise controlled and if the appropriate equipment and expertise is available.

Arrhythmias

The most frequent form of arrhythmia associated with MH is tachyarrhythmia. We recommend using a relevant anti-

Box 4 Managing the consequences of malignant hyperthermia

Monitor for and treat:

- Acidosis
- Hyperkalaemia
- Arrythmias
- Myoglobinurua
- Disseminated intravascular coagulation
- Compartment syndrome

arrhythmic agent with which you are most familiar such as amiodarone, a short-acting beta-blocker or magnesium.

Myoglobinuria

Should be anticipated and the aim should be a urine output of > 2 $ml.kg^{-1}.h^{-1}$. There is controversy about alkalinisation of the urine by administration of sodium bicarbonate in the prevention of acute kidney injury from myoglobinuria. Myoglobin is less likely to precipitate out of alkaline urine, and in the absence of any convincing evidence for harm in this situation we recommend sodium bicarbonate is used.

Disseminated intravascular coagulopathy

The occurrence of disseminated intravascular coagulopathy during an MH reaction is associated with poor outcome. We recommend empirical treatment using platelets, fresh frozen plasma and cryoprecipitate. Tranexamic acid is not indicated in this situation.

Compartment syndrome

Any patient who develops myoglobinuria should be monitored for the development of compartment syndrome. It should be remembered that creatine kinase levels may not peak for up to 24 h after an MH event [41]. The principal means of monitoring for compartment syndrome is therefore clinical. The awake patient is likely to complain of pain should compartment syndrome develop. In the sedated patient, regular assessment of the limbs for swelling, muscle softness and peripheral pulses or peripheral oxygen saturation should be made. If there is any suspicion that compartment syndrome has developed, the compartmental pressures should be measured. The treatment for compartment syndrome is fasciotomies.

Post-malignant hyperthermia management

If the MH reaction is successfully treated in the operating theatre, and ongoing management of its sequelae is not required, then there is no contra-indication to the continuation and completion of the surgical procedure under i.v. anaesthesia.

We recommend that the patient remains sedated after the completion of surgery until all metabolic derangements have been corrected. When this has occurred, the patient should be weaned from ventilatory support as usual. Recrudescence of MH is well described: the likelihood and severity is related to the severity of the initial MH episode [36]. If the reaction was treated in its early stages, as defined by response to discontinuation of the triggering agents without the need for dantrolene, it is reasonable to wake the patient after surgery, monitor them for at least 1 h in the post-anaesthesia care unit before returning then to the postoperative ward. It would be unwise to discharge the patient from hospital within 24 h of the end of surgery in which a suspected MH reaction has occurred. If dantrolene was required to reverse the initial MH reaction, the patient should be monitored and nursed in a high dependency unit or ICU for at least 24 h after the event. The choice between high dependency and ICU management will depend on the patient's condition, requirements for continuing mechanical ventilation and the need for invasive monitoring.

Patient and family counselling

Before discharge from hospital the patient and their family should be informed about the suspected diagnosis of MH. They should be provided with written information about the suspected diagnosis and its implications for future anaesthetic management in their family (see online Supporting information Appendix S4 for letter templates). They should be specifically advised to warn all blood relatives of the patient that can be contacted about the risk of MH and the need to mention this should any member of the family require admission to hospital. Each member of the family should be advised that this information applies to them until it is proved otherwise using definitive diagnostic tests. The patient and family should be provided with details of the UK MH Registry (www.ukmhr.ac.uk), where information for patients and relatives about all aspects of MH can be found.

Patient referral and follow-up

Diagnostic services for suspected MH in the UK and Ireland are provided by the MH Investigation Unit in Leeds. (Information about service provision in other countries is available from the EMHG, www.emhg.org). There is a complementary Scottish diagnostic pathway that requires the relevant consultant clinical geneticist to be informed of suspected MH cases in order to facilitate funding for testing in Leeds (Scottish Muscle Network; www.smn.scot.nhs.uk). When a patient has a suspected MH reaction, it is the professional responsibility of the consultant anaesthetist in charge of the case to make a direct referral to the Leeds MH Investigation Unit (see online Supporting information Appendix S4 for letter templates). This is because the MH consultants will need to review copies of the anaesthetic and other peri-operative records along with a narrative commentary from the attending anaesthetist to supplement

the anaesthetic record. In assessing the need for further investigation of MH risk, the MH consultants will frequently need to ask the referring anaesthetists to clarify events or provide additional information.

Not every case of suspected MH will require further investigation. It is inevitable, due to the non-specific features of MH and the vital need to treat MH in its early stages, that patients will be treated for MH when the problems encountered during the anaesthetic resulted from an alternative cause. This may be apparent to the MH Unit, which has the benefit of reviewing the case in hindsight and of considerable experience in evaluating adverse anaesthetic reactions. Such conclusions will be reached by the MH Unit if the events described in the case records and accompanying information are not compatible with an MH reaction. Added confidence to the decision that a case was not a manifestation of MH is provided if a more likely alternative explanation can be identified.

If the MH Unit is unable to exclude the possibility of an MH reaction, the patient will be offered investigation. In England, this is a nationally commissioned service, but in the rest of the UK and Republic of Ireland individual funding approval is required from the relevant health board. There are two alternatives for investigation of MH susceptibility [3]. The first is DNA screening, for which the MH Unit sends out relevant blood tubes and instructions for a blood sample to be taken by the patient's GP and returned to the MH Unit. This is relatively cheap, minimally invasive and convenient for the patient, but DNA screening has only an approximate 50% sensitivity for detecting MH susceptibility [42]. Definitive diagnosis of MH susceptibility relies on specialised tests carried out on freshly excised muscle strips taken at open biopsy (the in-vitro contracture test) [3]. Because fresh muscle specimens are required, the patient needs to travel to the MH Unit for the tests. For patients who have experienced a suspected MH reaction, DNA testing is often used in the first instance in the UK. If a genetic change associated with MH is not found, the patient will then undergo the muscle biopsy tests if they are old enough (aged> 10 y). For index cases who are < 10 y with a negative genetic test, both parents will be offered a muscle biopsy test. It should be noted that the muscle biopsy test will not be done within 4 months of an acute reaction as the response of damaged muscle in the test is unpredictable.

When a positive MH diagnosis is made by a DNA test, the patient is informed in writing, provided with information and given the opportunity to have an appointment or telephone consultation with the MH Unit. Copies of the correspondence are sent to the patient's GP and referring anaesthetist for filing in the local hospital records. When a DNA test is negative, a muscle biopsy test is needed in order to confirm or exclude MH. Patients attending for diagnostic muscle biopsy in Leeds are given the diagnosis on the day of biopsy before they return home. They are also provided with written information. Copies of the muscle biopsy report are sent to the patient's GP and referring anaesthetist. All patients who are diagnosed to be at increased risk of developing MH under anaesthesia are advised to obtain a Medic Alert or similar tag. They are also provided with warning cards from the MH Unit that may be kept in a wallet or purse.

Anaesthesia for patients with an increased risk of developing malignant hyperthermia

Patients at increased risk of developing MH must not be exposed to potent inhalational anaesthetics or suxamethonium. The easiest way to avoid these agents is to avoid general anaesthesia by substituting a regional anaesthetic technique if appropriate. In situations where general anaesthesia is required, strategies to avoid the triggering agents are essential. Nowadays, suxamethonium is invariably reserved for either a rapid sequence induction or in the rescue of a patient developing acute upper airway obstruction in the peri-operative period. The anaesthetist should have a plan to use alternative agents or techniques to replace suxamethonium or avoid the circumstances in which it would otherwise be used.

Potent inhalational agents can be substituted in the patient at risk of MH who requires general anaesthesia by the use of a total intravenous anaesthetic technique: guidelines for the safe practice of total intravenous anaesthesia have been published [43]. As there is the possibility that residual quantities of inhalational agents in an anaesthetic machine might trigger an MH reaction, the anaesthetic machine should be appropriately prepared so as to avoid this possibility. Most studies of the elimination of potent inhalational anaesthetics from anaesthetic machines and workstations have used a target of 5 ppm as the maximum safe concentration of inhalation agent. This probably provides for a large safety margin. Elimination of trace quantities of inhalational agent may be done by flushing the machine with 100% oxygen. The time required to achieve the target reduction in anaesthetic concentration depends on the individual anaesthetic machine. The times required have been published for several currently available machines [44], but it is our view that it is the manufacturer's responsibility to provide this information when they supply a new machine. The recent introduction of activated charcoal

Box 5 Patients at increased risk of developing malignant hyperthermia if exposed to triggering agents

1. Patients with high-risk status confirmed by the presence of a genetic variant pathogenic for MH susceptibility or by a positive *in vitro* contracture test.
2. Blood relatives of an individual with a confirmed MH susceptible diagnosis.
3. Patients with a personal or family anaesthetic history which may implicate MH.
4. Patients with clinical myopathy who have a genetic aetiology involving a gene implicated in MH susceptibility (*RYR1*, *CACNA1S*, *STAC3*).
5. Patients with a genetic variant of unknown significance in genes implicated in MH susceptibility (*RYR1*, *CACNA1S*, *STAC3*).
6. Patients with otherwise unexplained rhabdomyolysis, especially with a history of recurrent rhabdomyolysis [46,47].
7. Patients with idiopathic hyperCKaemia.
8. Patients with otherwise unexplained exertional heat illness [48,49].

filters provides an alternative means for avoiding administration of trace quantities of inhalational agents to patients at increased risk of MH [30,45].

Identification of patients at increased risk of developing malignant hyperthermia

Full evaluation of the MH risk for patients at increased risk of developing MH (Box 5), except those in group 1, is a highly specialised process and is outside the scope of this guideline. If patients meeting any of the criteria in Box 5 present for anaesthesia, we recommend the anaesthetist responsible for their management contacts the MH Unit for advice. The MH Unit will need to know as many details as possible concerning the background to the patient's history.

Ideally, in patients in whom an increased risk of developing MH cannot be excluded, we recommend deferral of surgery pending clarification of MH status if the increased risk of MH would compromise the anaesthetist's usual management of the case. We are aware of critical incidents that have resulted from a change in an anaesthetist's usual practice due to an unclarified risk of MH that subsequently proved spurious. We recommend that the anaesthetist discusses the risk of MH with the MH Unit. If the risk of MH cannot be excluded on the basis of the available history, emergency or urgent surgery will need to proceed with the patient managed as a possible MH-susceptible case. For non-urgent surgery, the consultant anaesthetist responsible for the case will need to know from the MH Unit when the results of definitive diagnostic tests could be available (in the UK, priority is given to patients waiting for surgery). They will then need to balance the inconvenience of waiting for the results against the risks of changing from their usual practice (these risks will depend on the familiarity of the anaesthetist with alternative techniques, the patient to be anaesthetised and the scheduled surgical procedure).

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1a. Emergency management of malignant hyperthermia (source: UK MH Registry; with permission).

Appendix S1b. Malignant hyperthermia treatment sequence and checklist.

Appendix S2. Guidelines for the use of activated charcoal filters (source: UK MH Registry; with permission).

Appendix S3. Malignant hyperthermia in children.

Appendix S4. Resource kit for patient information and referral, including checklist, letter templates and data form.

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